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Review

Endogenous opiates and behavior: 2004

Richard J. Bodnar*, Gad E. Klein

Department of Psychology and Neuropsychology Doctoral Sub-Program, Queens College, City University of New York, Flushing, NY 11367, USA

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Abstract

This paper is the 27th consecutive installment of the annual review of research concerning the endogenous opioid system, now spanning over 30 years of research. It summarizes papers published during 2004 that studied the behavioral effects of molecular, pharmacological and genetic manipulation of opioid peptides, opioid receptors, opioid agonists and opioid antagonists. The particular topics that continue to be covered include the molecular-biochemical effects and neurochemical localization studies of endogenous opioids and their receptors related to behavior, and the roles of these opioid peptides and receptors in pain and analgesia; stress and social status; tolerance and dependence; learning and memory; eating and drinking; alcohol and drugs of abuse; sexual activity and hormones, pregnancy, development and endocrinology; mental illness and mood; seizures and neurologic disorders; electrical-related activity and neurophysiology; general activity and locomotion; gastrointestinal, renal and hepatic functions; cardiovascular responses; respiration and thermoregulation; and immunological responses.

Keywords: Enk ephalins; Endorphin; Dynorphin; Mu opioid receptor; Delta opioid receptor; Kappa opioid receptor

Abbreviations: Ach, acetylcholine; ACTH, adrenocorticotrophic hormone; AGRP, agouti gene-related peptide; AMSH, alpha-melanocyte-stimulating hormone; AS, antisense; ATP, adenosine triphosphate; BEND, beta-endorphin; BFNA, beta-funaltrexamine; BNST, bed nucleus of the stria terminalis; Ca(2+), calcium; CART, cocaine and amphetamine-regulated transcript; CB, cannabinoid; CCK, cholecystokinin; cDNA, complementary deoxyribonucleic acid; CFA, complete Freund's adjuvant; CGRP, calcitonin gene-related peptide; COX, cyclooxygenase; C/P, caudate/putamen; CREB, Ca(2+)/cAMP responsive element binding protein; CRF, corticotropin factor; CSF, cerebrospinal fluid; CWS, cold-water swims; DA, dopamine; DADL, D-Ala(2); D-Leu(5)-enkephalin; DALDA, D-Arg-Phe-Lys-NH2; DAMGO, D-Ala(2); Nme(4); Gly-ol(5)-enkephalin; Delt, deltorphin; 5,7-DHT, 5,7-dihydroxytryptamine; DOR, delta opioid receptor gene; DPDPE, D-Pen(2); D-Pen(5)-enkephalin; DREAM, downstream regulatory element antagonistic modulator; DRG, dorsal root ganglion; DRN, dorsal raphe nucleus; DYN, Dynorphin; Enk, enkephalin; EPSC, excitatory post-synaptic currents; ERK, extracellular regulated signal kinases; FMRI, functional magnetic resonance imaging; GAD, glutamic acid decarboxylase; GI, gastrointestinal; GIRK, G-protein inwardly rectifying K+ channel subunit; GnRH, gonadotropin-releasing hormone; GP, globus pallidus; HIV, human immunodeficiency virus; HR, heart rate; ICSS, intracranial self-stimultion; IPSC, inhibitory post-synaptic currents; K(+), potassium; KO, knockout; KOR, kappa opioid receptor gene; Lenk, leu-enkephalin; LH, leutinizing hormone; LI, like immunoreactivity; LiCl, lithium chloride; L-NAME, N(omega)-nito-l-arginine methyl ester; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; MAP, mean arterial pressure; MAPK, mitogen-activated protein kinase; MBH, medial-basal hypothalamus; Menk, met-enkephalin; MOR-1, mu opioid receptor gene; MPOA, medial preoptic area; MRI, magnetic resonance imaging; mRNA, messenger ribonucleic acid; NAC, nucleus accumbens; NalBzOH, naloxone benzoylhydrazone; NBNI, nor-binaltorphamine; NE, norepinephrine; NGF, nerve growth factor; NO, nitric oxide; NOS, nitric oxide synthase; NPY, neuropeptide Y; NRM, nucleus raphe magnus; NSAID, non-steroidal anti-inflammatory drug; NTI, naltrindole; NTS, nucleus tractus solitarius; OFC, orbitofrontal cortex; OFQ/N, nociceptin; ORL-1, orphan receptor like receptor; 6-OHDA, 6-hydroxydopamine; PAG, periaqueductal gray; PBN, parabrachial nucleus; PET, positron emission tomography; PKA, protein kinase A; PKC, protein kinase C; POMC, pro-opiomelanocortin; PVN, paraventricular nucleus; RSNA, renal sympathetic nerve activity; RVM, rostral ventromedial medulla; SN, substantia nigra; SON, supraoptic nucleus; SP, substance P; SSRI, selective serotonin reuptake inhibitor; STZ, streptozotocin; THC, tetrohydrocannibinol; TRH, thyrotropin releasing hormone; VP, vasopressin; VTA, ventral tegmental area

* Corresponding author. Tel.: +1 718 997 3543; fax: +1 178 997 3257.
E-mail address: richard_bodnar@qc.edu (R.J. Bodnar).

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Contents

1. Introduction

This 27th installment of the annual review of research concerning the endogenous opioid system summarizes published papers during 2004 that studied the behavioral effects of molecular, pharmacological and genetic manipulation of opioid peptides, opioid receptors, opioid agonists and opioid antagonists. This review continues the excellent tradition initiated by Drs. Abba Kastin, Gayle Olson, Richard Olson, David Coy and Anthony Vaccarino in the reviews

spanning from 1978 through 2000. As begun in the summaries of papers published over the past three years (2001, 2002 and 2003 papers), two major sections of the review have been added because of the rapid and large expansion of the field. The first is the molecular-biochemical effects and neurochemical localization studies of endogenous opioids and their receptors especially as they may eventually relate to behavior (Section 2). The second is the examination of the roles of these opioid peptides and receptors in their most studied aspect, pain and analgesia (Section 3). As with the previous reviews, subsequent sections will cover the roles of opioid peptides and receptors in the areas of stress and social status (Section 4); tolerance and dependence (Section 5); learning and memory (Section 6); eating and drinking (Section 7); alcohol and drugs of abuse (Section 8); sexual activity and hormones, pregnancy, development and endocrinology (Section 9); mental illness and mood (Section 10); seizures and neurologic disorders (Section 11); electrical-related activity and neurophysiology (Section 12); general activity and locomotion (Section 13); gastrointestinal, renal and hepatic functions (Section 14); cardiovascular responses (Section 15); respiration and thermoregulation (Section 16); and immunological responses (Section 17). To accommodate these additional large sections, only published articles are covered in this review; published abstracts from scientific meetings are not covered, but will be added as they are published in the scientific literature. Given the scope of this review, a paper may be inadvertently overlooked. If this is the case, please accept my apologies, and send the citation and abstract to richard_bodnar@qc.edu, and I will include it in the next yearly review.

2. Endogenous opioids and receptors

This section examines the molecular-biochemical effects (Section 2.1) and neuroanatomical localization (Section 2.2) of opioid peptides and receptors.

2.1. Molecular-biochemical effects

This sub-section will review current developments in the molecular and biochemical characteristics of opioid peptides and receptors by subtypes: mu agonists and receptors (Section 2.1.1), delta agonists and receptors (Section 2.1.2), kappa agonists and receptors (Section 2.1.3), and OFQ/N and the ORL-1 receptor (Section 2.1.4).

2.1.1. Mu agonists and receptors

A review [869] summarizes recent studies identifying splice variants of the MOR-1 clone in explaining the pharmacology of opioids. Another review [1081] indicates that the order of opioid receptor type evolution is kappa, delta and most recently, mu receptors. There are high correlations in the binding and analgesic effects of mu, delta and kappa opioids in mammals and amphibians [1081]. Endogenous morphine can be formed in human cells [900]. Splice variants of MOR-1produced differential [35S]gammaS binding with the MOR-1E variant binding BEND to a greater degree than DAMGO, and the MOR-1C variant binding BEND to a lesser degree than DAMGO. Whereas DYN, BEND and morphine were most effective in stimulating this binding in the MOR-1E variant, M6G and fentanyl were most effective in stimulating this binding in MOR-1 [125]. Three new alternatively spliced varaints of MOR-1C (MOR-1C1, MOR-1C2, MOR-1C3) were obtained using RT-PCR with these variants differing in their responses to agonist-stimulated [(35)S]GTPgammaS binding assays [868]. Identification of 11 of the 17 proposed exons as well as the majority of exon combinations used to make 21 differentially spliced mu opioid receptor genes was accomplished using specific polymerase chain reaction conditions [637]. Morphine, but not fentanyl or methadone produces impairments in the mitochondrial membrane potential in desimipramine-treated human glioma cells, an effect prevented by naloxone and L-NAME [737]. Morphine induces terminal MOR desensitization by sustained phosphorylation of the carboxy-terminal residue, serine-375 [1003]. Opioids block the ability of epidermal growth factor to rapidly internalize its receptor, and thereby alter its ability to phosphorylate ERK [1002]. Both the human MOR gene and the N40D mutation showed similar binding affinities to morphine, M6G and BEND, similar robust receptor internalization following DAMGO and BEND, but not morphine and M6G, and similar desensitization to prolonged morphine, M6G and BEND [98]. CXBK mice display less morphine expression because of an A-to-C change at the MOR 5′-untranslated region that decreases Sp1 binding and MOR gene transcription [654]. MOR, but not DOR mRNA in the DRG was ipsilaterally up-regulated 1–2 h and at 96 h after ipsilateral paw inflammation that corresponded with increased DAMGO binding in the DRG [907]. Activation of MOR by saturating concentrations of DAMGO, methdone or fentanyl, but not morphine reduced robust internalization of a tagged MOR [186]. Heterodimerization and cross-sensitization occur between the MOR and chemokine CCR-5 receptor such that DAMGO enhances phosphorylation of the chemokine receptor and reduces chemokine CCR-5 agonist-induced [35S]GTPgammaS binding [198]. Phospholipase D2 is a modulator of mu agonist-induced endocytosis as well as desensitization and resensitization of MOR [611]. MOR activation increased transcription of STAT-3 through an ERK-dependent and Raf-1-independent mechanism [1255]. DAMGO-induced super-sensitization of adenylate cyclase acts through G-alpha-o that is modulated by regulator of G protein signaling proteins [226]. Mu opioid-induced stimulation of c-jun N-terminal kinase was dependent upon phosphatidylinositol-3-kinase given effective inhibition by wotmannin or coexpression of a dominant negative mutant [557]. Morphine and fentanyl decrease and increase local blood flow and partial pressure of oxygen in the fronto-parietal cortex and NAC respectively [830]. The 7,8-saturated codeine congeners were more efficacious

in activating MOR, but only dihydrocodeine was more effective than codeine in activating DOR. Hydrocodone and oxycodone in turn were more effective than either agonist in activating MOR and DOR. The 3-hydroxy related compounds were more effective than the 3-methoxy related compounds of morphine in activating MOR [1120]. Neuron-restrictive silencer factor can repress MOR transcription in NS20Y and HeLa cells through a mechanism dependent on the MOR neuron-restrictive silencer element [589]. A new series of fentanyl derivatives were found to have very high affinity for both MOR and I(2) imidazoline binding sites [267]. Mu receptor antagonists developed from 3,4-dimethyl-4-(3-hydroxyphenyl)piperidine appear to act biochemically as inverse agonists [315]. *N*-demethylation of 3-deoxymorphine(1) alters mu, delta and kappa opioid binding affinity [254]. Compound 2 of an *N*-alkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene)-phenylmethyl]-benzamide acted as a selective mu receptor agonist [179]. The thiosaccharide compounds in the morphine series 5b, 5e, 6a and 6a had higher affinity, but less selectivity for MOR than M6G [709]. The transport inhibitor, probenecid decreased the clearance of plasma M6G, and increased the area under the miotic effect versus time curve [1033]. Meningitis increased the passive diffusion of morphine over the blood-brain barrier [1138]. Morphine pharmacokinetics were found to be worse in brain tissue damaged by trauma with shorter *T*(max) and relative recovery measures [309]. Endogenous morphine was found in the amygdala and could stimulate hippocampal and amygdala NO release in a naloxone- and L-NAME-sensitive manner [1295]. Reticuline, a morphine precursor in plants increased endogenous morphine levels in the pedal ganglion of *Mytilus edulis* [1296]. Morphine stimulated NO release from muscles of *Ascaris suum* in a naloxone- and L-NAME-sensitive and CTOP-insensitive manner. In contrast, CTOP, but not naloxone blocked M6G-induced NO muscle release [1298]. Sublingual buprenorphine administered alone or in combination with naloxone fails to display dose proportionality in pharmacokinetic analyses [448]. Intravenous morphine and codeine decreased pupil diameter by 26% in volunteers; whereas tramadol had slower-acting effects [608]. An admixture of morphine, bupivacaine and clonidine in implantable pumps retained their stability at room and refrigerator temperatures over 90 days [227]. Drug incorporation, during rather than after, synthesis was more effective in controlling release rate of morphine in an ethylcellulose polymeric suspension [785].

BEND-induced [(35)S]-GTPgammaS binding was observed in wild type mice, but not in mice with triple KO of MOR, DOR and KOR [236]. Whereas PC2 and 7B2 null mice lack pituitary AMSH, the latter, but not the former group is still capable of producing BEND from beta-lipotropin [644]. Acrylamide-induced neuropathy increases BEND and AMSH immunoreactivity in spinal motorneurones [503]. Nonopioid BEND receptors insensitive to naloxone and Menk were characterized on mouse macrophages and rat myocardium, spleen, adrenal and brain membranes [819]. HEK293 cells joining human BEND to part of the NL1 gene secreted BEND in a dose-dependent manner following doxycycline administration [974]. Endomorphin-2 was more effective than endomorphin-1 in dose-dependently increasing DYN(1–17) in spinal perfusates of rats, an effect blocked by naloxone or 3-methoxynaltrexone [659]. Mice with triple KO of MOR, DOR and KOR displayed increases in NPFF(2) receptor binding in the amygdala, nucleus of the vertical limb of the diagonal band, SN, vestibular nucleus and spinal cord, and decreases in NPFF(1) receptor binding in the nucleus of the vertical limb of the diagonal band, SN and spinal cord [404]. Methadone was more effective than morphine in inhibiting NMDA receptors expressed in *Xenopus oocytes*, particularly the NR1/2A and NR1/2B subtypes relative to the NR1/2C and NR1/2D subtypes [168]. Intrathecal morphine and fentanyl increased spinal adenosine in healthy human volunteers [311]. Loperamide-stimulated uptake of radiolabeled glucose into C2C12 cells was decreased by concentrations of U73122 which inhibits both phospholipase C and PKC [684]. Endomorphin-1 and -2 display flux in cerebral endothelial cells from the basolateral to apical direction with self-inhibition induced by excess treatment. Transport was unaffected by P-glycoprotein inhibition, DAMGO or DPDPE treatment [1059]. An opioid agonist, DiPOA potently inhibited diprenorphine binding and had mu > kappa ~ ORL-1 > delta activity in human MOR and human guanosine 5′-*O*-(3-[35)S]thio)triphosphate assays [1150]. A chimeric peptide, H-Dmt → D-Arg → Phe → Lys-NH-CH2-CH2-NH-Phe ← Cha[NH-CH2]PsiTic ← Tyr-H displayed a mu agonist-delta antagonist action on the guinea-pig ileum and mouse vas deferens assays [1202]. Endomorphin-1 and morphine exposure to SH-SY5Y cells down-regulated mu receptors and produced rapid internalization, effects blocked by hypertonic sucrose [492]. A peptide, c-[Tyr-d-Pro-d-Trp-Phe-Gly-], structurally related to endomorphin-1, displayed affintity towards MOR [172]. Every oxygenated functional group of naltrexone (1) is necessary for binding to MOR [1148]. The pharmacokinetics of intravenous, buccal, intramuscular and gastric administration of oxycodone in children aged 6–93 months were similar to that of adults [617]. A series of 6-amino acid conjugates of 14-*O*-methyloxymorphone were agonists in the mouse vas deferens assay with the alpha-amino acid epimers favored by MOR and the beta-epimers showing increased interaction with DOR [1067]. Whereas the *N*-2-phenylethyl analogue 18 of the 10-ketomorphinans exhibited good affinity and selectivity at MOR, the *N*-cyclobutylmethyl analogue 13 gave high affinity and selectivity at KOR [1269]. The mu binding affinity of cyprodime was reduced following prolongation of the 4-alkoxy group of cyprodime and its 4-butoxy analogue [1068]. Mutant H297Q MOR Chinese hamster ovary cells show diminished (50%) kinetic rate constants for [3H]-BFNA and associated rate constants for [3H]-naloxone [1070]. Naloxone-induced cAMP overshoot in insect Sf9-mu cells was differentially induced by different ohmefentanyl stereotisomers [691].

2.1.2. Delta agonists and receptors

A review [1159] indicates that since chemically-different agonists differ in their ability to phosphorylate, internalize and/or down-regulate DOR, and because homologous regulation of opioid receptor signaling is thought to play an important role in opioid tolerance, potential DOR-selective opioid analgesics should be developed with a reduced propensity for analgesic tolerance [1159]. Another review [1049] examines the development of understanding intracellular signaling systems of Enk including the IP3 receptor, immunophilins, NO and D-serine [1049]. Whereas Enk expression is increased during the day in the frontal cortex, DYN expression is lower in the SN during the day relative to the night [1197]. Intrathecal injection of Fluo-Delt labels DOR-internalizing neurons in the dorsal and ventral horn that are increased by either morphine exposure for 48 h or dorsal rhizotomy. However, rhizotomy blocked the ability of morphine to increase Fluo-Delt DOR internalization [791]. Binding of Delt II to the human DOR was interrupted by systematic alterations and deletions in the third extracellular loop, particularly in positions 279–299. Alterations in Trp(284) and Leu(286) produced the largest effects [327]. A mutation in position S363A of the human DOR attenuates DPDPE-induced, but not SNC80-induced down-regulation of DOR [820]. ERK/mitogen-activated protein kinase activity prevents DOR internalization, desensitization and sequestration by blocking arrestin 2 and DOR interactions [313]. SNC-80 was more effective than Enk in producing stronger and faster desensitization, loss of opioid DOR binding sites and downregulation and redistribution of the receptors from the cell surface to intracellular compartments [649]. DOR, but not MOR opioid-stimulated [35S]GTPgammaS binding was decreased in the spinal cord of polyarthritic rats treated with CFA [223]. Substitution of 2′,6′-dimethylphenylalanine for the N-terminus, tyrosine, retains DOR binding activity for Delt and Enk [987]. A Cys2-containing Enk analogue was seven times more selective for DOR than DPDPE because it increases the efficacy, but not the affinity of the analogues to DOR, increases their peptidase resistance and thereby attaches resistance to enzyme degradation [882]. A methylated cyclic analogue of Enk showed higher mu, delta and kappa antagonist potencies and greater affinity for MOR, DOR and KOR [1203]. P-glycoprotein KO mice displayed an eight-fold increase in uptake of the delta agonists, DPDPE and SNC121 and the mu agonist, loperamide relative to wild type P-glycoprotein-competent mice [259]. Interactions between the different agonist-bound states of the DOR with different G-protein subtypes indicated cooperativity between separated alpha and beta-gamma subunits, and pointed to the independent promotion of specific signaling events [24]. A rank-order of delta agonist analogues of SNC86, SNC80 and SNC162 was demonstrated in their ability to elicit convulsions, produce anti-depressant effects and induce locomotor activity [552]. The ability of Delt to increase extracellular DA in the NAC was unaffected by pretreatment with general, delta-1, delta-2 or mu opioid antagonists [799]. DOR and alpha2A-adrenoceptors are in close proximity and form interacting complexes in heterologous cells. Alpha2A-adrenoceptor expression promotes DOR-mediated neurite outgrowth [942]. The circulating short-chain fatty acids, proprionate and butyrate increased Enk and tyrosine hydroxylase mRNA levels in PC12 rat pheochromocytoma cells [716]. Affinity labels for [D-Ala(2)]-Delt I were identified by incorporation at the para position of Phe(3) ('message' sequence) or Phe(5) ('address' sequence) of an electrophilic group [15]. A fluorescent analogue of the delta opioid agonist, Dmt-Tic was identified [65]. A delta receptor antagonist and delta receptor inverse agonist [+]-KF4.{+}-4, was created from the 5-phenylmorphan class of opioids [176]. Compound 15a and 15c of an *N*-alkyl-4-[(8-azabicyclo[3.2.1]-oct-3-ylidene)-phenylmethyl]-benzamide acted as a selective delta receptor agonist [178]. Menk absorption into the human nasal epithelium was markedly increased by protease inhibitors and absorption enhancers [7]. A bivalent ligand, KDN-21, revealed that spinal delta and kappa opioid receptors are organized as heterodimers that in turn give rise to delta(1) and kappa(2) phenotypes [102].

2.1.3. Kappa agonists and receptors

A review [692] of regulation and trafficking of KOR include biochemical mechanisms of desensitization, internalization and down-regulation, species differences and structural basis for species variations. The number of haplotypes of the KOR gene varied across racial categories including African-Americans (9), Caucasians (6) and Hispanics (5) [1256]. The kappa agonists, U50488H, U69593 and TRK-820 increased [35S]GTPgammaS binding in lower midbrain, straiturm and limbic forebrain in a NBNI-sensitive manner [777]. The kappa agonist, U69593 administered over 5 days increased kappa receptor density in the hypothalamus, but not in frontal cortex or C/P 3 days later, whereas kappa receptor density was decreased in the frontal cortex and C/P, but not hypothalamus two weeks later. DYN levels were increased in the frontal cortex at 3 and 14 days and in the C/P at 14 days after U69593 treatment [258]. An anti-endothelin antiserum increased kappa, but not mu or delta receptors in the C/P, and decreased C/P DAMGO efficacy, but not potency [1194]. GTPgammaS potently inhibited U69593 binding and affinity, but not bremazocine binding and affinity. NBNI had a four-fold higher affinity for U69593-labeled receptors relative to bremazocine-labeled receptors. U69593 activated more G-protein receptors than bremazocine [966]. Salvinorin A, a non-nitrogenous naturally-occurring compound acts as a full agonist at kappa receptors with similar efficacy to DYN and greater efficacy than U50488H or U69593 [196], and is reviewed in terms of its chemistry, pharmacology and biology relevant to KOR [1235]. The ability of kappa opioid receptors to activate c-Jun N-terminal kinase is dependent upon Gbetagamma, Src, FAK, Sos, Rac and Cdc42 signals [558]. DYN A(1-17) and DYN A(2-17) evoked spinal prostaglandin release that was blocked by the NMDA antagonist, AP-V, the COX inhibitor, ibuprofen and the COX-2 inhibitor, SC58560,

suggesting that the nonopioid actions of spinal DYN in producing hyperalgesia acts through a combined NMDA and COX cascade [613]. Multiple transcription initiation sites for pro-DYN were identified with one possessing an additional 19 nt at the 5′ end [638]. The SSRI, fluoxetine delivered over 1 week increased pro-DYN gene expression in the hypothalamus, and decreased this expression in the C/P and NAC [287]. Cloning of pro-DYN cDNA revealed the encoding of alpha-neoendorphin, DYN-A, DYN-B and two Lenk sequences in the lungfish brain [300]. The selective norepinephrine reuptake inhibitor, nisoxetine, increased pro-DYN gene expression in the hypothalamus, NAC and hippocampus, and decreased pro-DYN gene expression in the C/P [288]. The putative kappa-3 agonist and ORL-1 antagonist, NalBzOH stimulated [35S]GTPgammaS binding and basal adenylyl cyclase activity in the olfactory bulb that was unaffected by ORL-1 or kappa antagonists, but reduced by delta and mu antagonists [850]. Piperidine-derived kappa antagonists (e.g., JDTic) rely more on their phenol address groups in producing kappa activity than naltrexone-derived antagonists (e.g., NBNI) [1118]. Potent 10-oxo, 10-alpha-hydroxy and 10-beta-hydroxy derivatives of the kappa agonist, TRK-820 were synthesized [490] as well as metabolites of TRK-820 [573].

2.1.4. OFQ/N and ORL-1 receptor

Pairing the C-terminus of ORL-1 with green fluorescent protein revealed that 80% of the protein was internalized in periplasmic membrane in the presence of OFQ/N [241]. OFQ/N and other ORL-1 receptor ligands inhibited K(+)-induced serotonin overflow in mouse neocortex, an effect blocked by peptide and non-peptide ORL-1 receptor antagonists, and absent in ORL-1 KO mice [756]. OFQ/N antagonists that also act at the mu receptor were designed using octahydrobenzimidazol-2-ones 14 and 23 [208]. The OFQ/N-ORL-1 receptor system functionally coupled with G-protein regulated inwardly rectifying K(+) channels is antagonized by NOX2149, a Spiegelmer L-enantiomeric oligonucleotide ligand [331]. An ORL-1 peptide antagonist, Ac-Arg-Tyr-Tyr-Arg-Ile-lysinol, displayed inhibition using the mouse vas deferns assay, and competed at the ORL-1, but not delta opioid receptor [612]. Substitution of the 3-quinoline ring was very critical for affinity of the ORL-1 antagonist, JTC-801 [1010]. OFQ/N suppresses basal DA release from midbrain primary cultures that is blocked by an ORL-1 antagonist, but fails to alter DA release evoked by direct depolarization of terminals with elevated extracellular K+ [801]. Functional coupling characteristics of the ORL-1 receptor are similar in dog brain membranes as they are in other species [541]. A selective ORL-1 petide analogue antagonist, Ac-Cit-D-Cha-Qaa-D-Arg-D-*p*-ClPhe-NH2 displayed highly potent and selective effects [1156]. A series of *N*-(4-piperidinyl)-2-indolinones have been identified as ORL-1 ligands [1266]. A chimeric OFQ/N ligand, NNC 63-053 showed lower potency than OFQ/N in inhibiting electrically-induced twitches of the guinea pig ileum, and moreover was blocked by naloxone but not an ORL-1 antagonist [419]. Novel quinolizidine templates have facilitated the design and synthesis of ORL-1 receptor and OFQ/N ligands [545].

2.2. Neuroanatomical localization

This sub-section will review current neuroanatomical studies indicating localization of opioid peptides and receptors by subtypes: mu agonists and receptors (Section 2.2.1), delta agonists and receptors (Section 2.2.2), kappa agonists and receptors (Section 2.2.3) and OFQ/N and the ORL-1 receptor (Section 2.2.4).

2.2.1. Mu agonists and receptors

MOR-labeled somatodendritic processes were co-localized with D2 dopamine receptors half of the time in the dorsolateral striatum [27]. MOR mRNA was co-contained with GAD mRNA in almost all neurons of the hippocampus, whereas GAD-DOR mRNA co-localization was restricted to the hippocampal principal layers, oriens layer and hilus. Finally, somatostatinergic oriens layer, but not hilar neurons expressed DOR and MOR in the hippocampus [1089]. MOR and CB-1 receptors were co-localized approximately 20% of the time in dendrites in the NAC shell, and to a lesser extent in the NAC core [893]. MOR-1 immunoreactivity had axonal appositions with vesicular Ach transporter immunoreactivity in the hippocampal dentate gyrus [566]. MOR immunoreactivity is co-localized with activity-regulated cytoskeleton-associated protein in dendritic shafts and also spines of the C/P with increased co-localization occurring during post-natal development [1186]. Antisera directed against exon 11 of the MOR-1 splice variant indicated immunoreactivity in the olfactory tubercule, GP, SN and C/P with the latter site demonstrating co-expression of exon 4- and exon 11-LI in cells apposed to dopaminergic terminals [1]. Using a RNA probe directed against the MOR(1C) splice variant, autoradiographic labeling was detected over much of the telencephalon, diencephalon, mesencephalon, cerebellum, spinal cord and DRG [997]. The PKC antagonist, NPC 15437 blocked morphine-induced increases in c-fos expression in the striatum, cortex, but not in the thalamus. Morphine increased [14C]-2-deoxy-D-glucose-measured cerebral glucose utilization in the C/P, primary somatosesnory cortex, thalamus, superior colliculus, pontine reticular formation and spinal cord, and when paired with neuropeptide FF, morphine also increased glucose utilization in the auditory cortex, inferior colliculus and dorsomedial PAG [911]. Morphine translocates PKC beta-II, but not beta-I from perinuclear areas to the plasma membrane in cortical and striatal neurons [445]. MOR KO mice displayed increases in D1 and D2 DA receptor autoradiography across all cerebral brain regions, but no one particular brain region displayed significance [660]. Endomorphin-1 and endomorphin-2 immunoreactive neurons originating in the PBN innervate predominantly the dorsomedial, centromedial and arcuate hypothalamic

areas [205]. Endomorphin-2 immunoreactivity co-localized with SP in lumbar DRG, and persisted in mice lacking the preprotachykinin A gene that codes SP [982]. Ultra-low (10(-14)M), but not low (10(-6)M) doses of morphine increased neurite growth in cultured spinal cord and cortical neurons [140]. Beta-galactosidase, a gene reporter molecule for NPY Y2R and Y5R receptors, was found in arcuate neurons that co-expressed NPY and BEND in Y2R-KO and Y-5R KO mice [342]. MOR are detected in vestibular afferents in the Scarpa's ganglion and cristae ampullare epithelia in the inner ear, particularly in calyx, dimorphic and bouton vestibular afferents [902]. Mu opiate receptors are expressed in keratinocytes and unmyelinated nerve fibers in the dermis and epidermis that co-express BEND [107].

2.2.2. *Delta agonists and receptors*

Decreased DOR expression is observed ipsilaterally in the spinal cord of rats undergoing sciatic nerve transaction, chronic constriction injury of the sciatic nerve and L5/L6 spinal nerve ligation [1084]. Enk and SP are co-localized in boutons in the pre-Botzinger complex that is related to respiratory rhythmogenesis; this colocalization is accompanied by glutamate, but not GABA or glycine [689]. Menk and DYN have somatodendritic profiles in cells projecting from the VTA to the medial prefronrtal cortex [377]. Enk KO mice display increases in adenosine A1 receptor autoradiographic binding, but not in adenosine A2 receptors or transporters [61]. Enk is found in small neurons in Area X, and is co-localized with GABA in large cells projecting from Area X to the thalamus in songbirds [175]. Whereas Enk immunoreactivity was almost absent in Area X of the male zebra finch, SP fibers, but not perikarya were present [931]. Menk distributions in the lateral septum, the septohippocampal and septofimbrial pathways are highly homologous in songbirds and mammals [402]. Grafts of immortalized rat chromaffin cells over-expressing Menk significantly reduced the number of formalin-evoked c-fos immunoreactive spinal neurons [305]. In the hamster brain, Menk and Lenk are consistent with that of the rat with notable exceptions in the lateral septum, ventromedial hypothalamus and cingulate. Menk is more abundant than Lenk in most nuclei except for the postero-intermediate BNST [479]. Enk and SP fibers, but not stained cells are found in the human paraventricular thalamus [1146]. The reciprocal commissural fibers in the lateral aspect of lamina III-IV of the dorsal horn projecting to the contraletal gray matter immunostained for glutamic acid decarboxylase and/or the glycine transporter, but not for Menk [888]. Menk-Arg(6)-Gly(7)-Leu(8)-LI is found in both cells and fibers of the entire rat auditory system with the exception of the medial superior olive and ventral division of the medial geniculate body [8]. It is also found in widespread fashion in the human medullary reticular formation, NTS, hypoglossal nucleus, spinal vestibular nuclei, lateral cuneate nucleus, nucleus prepositus, inferior and superior colliculi, SN and pontine and midbrain central gray [247]. Methylphenidate administration fails to affect striatal Menk and DYN while robustly increasing SP levels [1241]. Both Enk and ACTH immunoreactivity are detected in the sea bass gut at an early larval stage four days after hatching [780].

2.2.3. *Kappa agonists and receptors*

Pro-DYN mRNA decreased significantly with age in the arcuate nucleus and amygdala, increased significantly with age in the hippocampus, and failed to produce age-related changesin the NTS, cortex, C/P or PVN [625].

2.2.4. *OFQ/N and the ORL-1 receptor*

OFQ/N was found in its highest concentrations in the dorsal PAG, LC, ventromedial hypothalamus and spinal dorsal horn, and in high concentrations in other hypothalamic nuclei, the ventral PAG, pontine tegmentum, amygdala, reticular formation and spinal trigeminal nucleus of adult human brains [1216].

3. Pain and analgesia

This section has four major parts examining recent advances in: (a) pain responses especially as they may relate to opioid function, (b) opioid analgesia organized as a function of receptor subtypes, (c) sex, age and genetic differences in opioid analgesic responses, and (d) opioid mediation of other analgesic responses.

3.1. *Pain responses*

The following sub-sections examine work done on spinal (Section 3.1.1) and supraspinal (Section 3.1.2) circuits, respectively.

3.1.1. *Spinal circuits*

Intrathecal administration of nuclear factor B inhibitors significantly reduced mechanical allodynia and thermal hyperalgesia following unilateral hindpaw inflammation evoked by CFA that was accompanied by increases in spinal COX-2 mRNA [653]. Like spermine and DYN, intrathecal poly-L-lysine induces biting, licking and scratching of the hindpaw, tail and flank, effects blocked by morphine and competitive NMDA antagonists [1113]. Whereas, neurokinin or NMDA receptor antagonists attenuated the inhibition of bradykinin-induced plasma extravasation induced by intrathecal nicotine or intraplantar capsaicin, intrathecal naloxone or phentolamine enhanced nicotine's and capsaicin's effects [762].

3.1.2. *Supraspinal circuits*

Anesthetized rats with a retractor placed between the right fourth and fifth ribs for 1 h displayed mechanical and cold allodynia within 14 days after surgery with axon loss noted in the intercostals nerves of the retracted ribs; this effect was blocked by systemic and intrathecal morphine and clonidine [164]. Avulsion of the rat brachial plexus produces a

neuropathy at distant sites of the injury including the ipsilateral and contralateral hindpaws. The resultant mechanical and cold allodynia are reversed by morphine, clonidine, ketamine and gabapentin [946]. Acidic saline administered into the lateral gastrocnemius muscle bilaterally reduces withdrawal thresholds to tactile stimulation of the hindpaws; this allodynia is reduced by morphine, NMDA antagonists (NS1209, ketamine), KCNQ K(+) channel openers (retigabine, flupirtine) and Na(+)-channel blockade (mexiletine) [829]. Post-incisional surgery of the plantar surface of the rat hindpaw produced mechanical hyperalgesia, tactile allodynia and decreases in weight bearing with systemic morphine and gabapentin more effective in blocking mechanical hyperalgesia than tactile allodynia [1206]. Intraplantar interleukin-18 produced mechanical hyper-nocicption that was inhibited by dexamethasone, morphine and an endothelin-1 inhibitor, but not by indomethacin or a lipoxygenase inhibitor [1169]. Two models of osteoarthritis, using partial medial meniscectomy and iodoacetate, produced minor changes in the amount of weight borne by the limb, but produced marked mechanical hyperalgesia and tactile allodynia that were sensitive to opiate treatment [339]. Rats treated with an intra-articular injection of monosodium iodoacetate to induce osteoarthritis developed mechanical allodynia and a weight-bearing deficit on that foot for up to 10 weeks; these effects were blocked by morphine and tramadol [231]. Adrenalectomy decreased pain behaviors in both phases of the formalin test, and increased plasma BEND above the detection limit [1174]. Physiological manipulations that block analgesia eliminate inhibition of the tail-flick reflex and restore vocalization to thermal stimulation, but also produce concurrent sensitization that generally heightens behavioral reactivity [252]. Formalin administered in the tail produce licking responses similar to that of the hindpaw. Systemic morphine, MK-801 and aspirin produce analgesia on this measure similar to that of the second phase of the formalin hindpaw response, whereas topical morphine exerts a shorter time course of action [618]. An animal model of bone cancer pain consisting of injections of the mouse femur with NCTC2472 cells produced tumor growth. Spontaneous lifting and movement-evoked lifting were sensitive to morphine treatment, although stress-induced analgesia cannot be ruled out [1168].

3.2. Opioid analgesia

The following sub-sections examine advances in our understanding of opioid-mediated analgesia in the past year especially as they pertain to the opioid receptor subtypes and their genes: (i) mu agonists and receptors, (ii) delta agonists and receptors, (iii) kappa agonists and receptors, and (iv) OFQ/N and the ORL-1 receptor. A large number of studies examine either knockout or knockdown techniques to indicate roles of the receptors, and potential splice variants in opioid analgesic function. Separate paragraphs are devoted to studies in which other transmitter and peptide systems affect opioid analgesia; the effects of opioid manipulations upon analgesia induced by other peptides and transmitters are covered in Section 3.4. Finally, human studies related to opioid and particularly mu receptor-mediated analgesia are covered in Section 3.2.5.

3.2.1. Mu agonists and receptors

3.2.1.1. Morphine. Chronic perfusion of morphine into the OFC depressed tactile and cold allodynias and thermal hyperalgesia in mononeuropathic rats in a naloxone-reversible manner. In contrast, it increased acute nociceptive thresholds in control rats in a naloxone-insensitive manner [14]. Administration of morphine, endomorphin-1 or DADL, but not U50488H into the ventrolateral orbital cortex decreased nociceptive behaviors on the formalin test, effects blocked by naloxone and BFNA, but not NTI [1226]. Morphine administered into the basolateral amygdala produces analgesia and altered RVM cell activity, effects interrupted by PAG lesions [746]. Intrathecal morphine decreased mechanical hyperalgesia caused by both spared nerve injury and spinal nerve ligation models in a naloxone-reversible manner [1283]. The mechanical allodynia induced by unilateral spinal nerve injury was more pronounced ipsilaterally and present contralterally in MOR KO mice; U50488H, but not morphine inhibited these allodynic effects in the KO animals [721]. Morphine reversed and prevented stimulus-induced progressive tactile hypersensitivity following sciatic nerve crush in rats, but not stimulus-induced hypersensitivity in spared nerve injury [280]. Morphine produced more potent analgesia in neurpathic mouse models involving STZ-induced diabetes than with sciatic nerve ligation. Morphine failed to affect NRM 5HT reductions induced by both models [1062]. Using the Hargreaves thermal test and bradykinin-induced nociception, the reduction in morphine analgesia in a neuropathic pain models was most pronounced for intraplantar morphine, was shifted rightward for systemic morphine, and was unaffected for supraspinal morphine. This corresponded with a drastic decrease in MOR expression in DRG neurons of nerve-injured mice [919]. Unilateral hindpaw CFA produced up-regulation of MOR and DAMGO-induced G protein coupling in the ipsilateral, but not contralateral DRG, and failed to affect spinal cord and hypothalamic MOR levels [1013]. The suppression of morphine analgesia in mice with sciatic nerve ligation was accompanied by an up-regulation of MOR on the ipsilateral side of the superficial lumbar dorsal horn laminae [812]. The Bennett's model of neuropathic pain was significantly reduced by intraplantar, but not subcutaneous administration of morphine, DAMGO, endomorphin-1 and endomorphin-2, and reversed by the peripheral antagonist, naloxone methiodide and the mu antagonist, cyprodime administered into the site of injury [836]. Writhing responses induced by acetic acid administration in gerbils were reduced by mu (morphine, fentanyl) and kappa (U50488H), and to a lesser degree by delta (SNC80) agonists [368]. The dose-dependent pattern of morphine analgesia was shifted to the right in NMRInu/nu mice relative to NMRI mice, presumably because of lower baseline thermal latencies

[1167]. Morphine analgesia and morphine tolerance were enhanced in mice lacking expression of the PKC-interacting protein gene, and this interactive protein reduced agonist-induced inhibition of adenylyl cyclase and suppressed human MOR at the G-protein level [417]. AS probes directed against G-protein signaling proteins belonging to the Rz subfamily significantly increased the antinociceptive potency of morphine, heroin, DAMGO and endomorphin-1 without altering analgesia elicited by endomorphin-2, DPDPE or Delt II [376]. Intrathecal morphine analgesia was blocked by intrathecal naloxone, but not BFNA or NTI. Intrathecal NBNI blocked intrathecal morphine analgesia on a shock, but not tail-flick measure [400]. Intraplantar administration of XC *Rous sarcoma*-virus transformed rat fibroblasts produces both short-term and long-term thermal hyperalgesia. Whereas both phases are blocked by morphine and the endothelin type A antagonist, BQ-123, only the short-term phase is blocked by the endothelin type B antagonist, BQ-788 [54]. Lipopolysaccharide administration decreases forelimb grip force in mice that displays tolerance with repeated treatment and is reversed by either systemic or intrathecal morphine [577]. The flexor paw response induced by intra-arterial capsaicin or pinch was inhibited by morphine and reinstated by naloxone [35]. Higher doses of morphine were needed to induce analgesia on the hot-plate and tail withdrawal tests in rats with partial tail amputations [594]. Morphine decreased the rabbit jaw depressor reflex in spinalized and non-spinalized rabbits in a naloxone-sensitive manner, and decreased the ankle flexor tibialis anterior reflex induced by toe stimulation more in intact than spinalized animals [528]. Mechanical and cold allodynia induced by the vinca alkaloid, vincristine, was blocked by morphine and clonidine [706]. Morphine attenuated the amplified visceral nociception in the external oblique muscle induced by either glycerol or colorectal distension [788]. Animals with unilateral stab wounds showed an increase in percent of paw withdrawal (secondary mechanical hyperalgesia) without thermal hyperalgesia with the former effect reversed by morphine administration [81]. Intrathecal morphine, DAMGO and fentanyl each induced scratching that was blocked by intravenous naltrexone or the mu antagonist, clocinnamox, but not by quaternary naltrexone, histamine antagonism or kappa or delta antagonism [610]. Morphine produced analgesia in mice sensitized to the intraplantar administration of ovalbumin [896]. Whereas B&K Sprague–Dawley rats had stronger morphine and methadone analgesia than the Mollegard strain, the latter had stronger buprenorphine-induced analgesia. Mollegard rats metabolized morphine to M3G to a greater degree than B&K Sprague–Dawley rats [158]. Morphine caused mild histopathological changes in rabbit knee joints marked by synovial membrane inflammatory hyperplasia and hypertrophy [295]. Single nucleotide polymorphism 118G of the MOR gene has been associated with decreased potency of morphine and M6G analgesia in carriers of the mutated G118 allele [696]. Such changes can be detected by a flexible computer simulation to visualize pharmacokinetic-pharmacodynamic models [697]. Topical application of morphine to cutaneous ulcers generally failed to alter morphine or M6G plasma levels [939].

3.2.1.2. Mu opioid agonists. DAMGO was more effective in blocking formalin-induced responses in non-diabetic than in STZ-treated diabetic rats. Whereas a NOS inhibitor blocked DAMGO-induced analgesia in both groups, a NO donor only enhanced DAMGO-induced analgesia in non-diabetic rats [1114]. The dermorphin tetrapeptide analogue, TAPA produced naloxonazine-sensitive analgesia on the tail-pressure and formalin tests whereas TAPA(NH2) produced naloxonazine-insensitive analgesia on both measures [776]. Tyr-D-Ala-Gly-Phe-D-Nle-Arg-Phe displays high affinity for MOR and stimulates regulatory G-proteins, and following intrathecal administration, produces naloxone-sensitive analgesia that is basically insensitive to either NTI or NBNI [1128]. The peripherally-restricted, small molecule mu agonist, DiPOA blocked CFA-induced mechanical hyperalgesia and incisional-induced mechanical hyperalgesia, but failed to affect neuropathic pain or alter basal tail-flick latencies [1207]. Mu-delta interacting complexes exist because delta receptor occupancy by antagonists enhances mu opioid binding and signaling activity as well as intrathecal morphine analgesia [395]. The slower onset of analgesia induced by mu-1-selective dermorphin analogues appears to be due to slower transport across the blood–brain barrier [281]. D-Nal3-morphiceptin displayed increased MOR affinity and potency on the hot-plate test than morphiceptin itself [343]. The morphinan derivative, BU72 showed high affinity and efficacy for MOR, was a partial DOR agonist and a full KOR agonist. Its analgesic effects were blocked by mu, but kappa and delta receptors, and after these effects subsided, it blocked morphine analgesia [824]. Endogenous opioids are found in the brain and spinal cord of teleost fish, block avoidance learning using electric shock, and reduce nociceptive behavioral and physiological responses [1046].

3.2.1.3. Mu opiate agonists. Dihydromorphine, 6-acetyldihydromorphine and dihydroheroin produced analgesic profiles similar to M6G and heroin, and not morphine. They were blocked by 3-*O*-methylnaltrexone and by AS probes directed against exon 2, but not exon 1 of the MOR clone, but were intact in morphine-tolerant mice [387]. Codeine was effective in blocking lambda-carragenan-induced thermal hyperalgesia because of increased brain uptake of the codeine in the presence of chronic pain [456]. Codeine was less effective in producing analgesia in 3-day old rats relative those aged 10 and 21 days or relative to adults [1212]. Fentanyl produces analgesia that is followed by prolonged hyperalgesia on the formalin and paw pressure tests as well as allodynia in wild-type, but not PKC-gamma KO mice. Naloxone further precipitated the hyperalgesic and allodynic symptoms following fentanyl in wild-type but not PKC-gamma KO mice [185]. Whereas fentanyl produced naltrexone-reversible anti-allodynic effects in capsaicin and VR-1 agonist models

as well as analgesia, peripherally-acting loperamide only prevented the expression of capsaicin-induced allodynia, an effect reversed by peripherally-acting methylnaltrexone in anesthetized primates [163]. Tramadol decreases the second phase of formalin pain following systemic and local administration with the two routes producing self-synergism according to isobolographic analyses [275]. Tramadol and bupivacaine produced comparable analgesic and anti-inflammatory responses induced by formalin as morphine [384]. Norhydromorphone and hydromorphone-3-glucuronide, metabolites of hydromorphone, displayed limited analgesic effects on the formalin test [1289]. 7-Hydroxymitragynine has high affinity for mu receptors, inhibits contractions of the guinea pig ileum, and produces thermal analgesia greater than morphine following subcutaneous and oral administration [738]. AA501, a chimeric peptide with opioid receptor agonist and SP receptor antagonist properties, produced analgesia following spinal administration [126]. Hydromorphone and butorphanol administered alone or together produced long-lasting increased thermal thresholds in cats [643]. Hydrocodone administered intrathecally for pain in sheep elicited gating deficits and biting behavior over the infusion site [539]. Remifentanil-induced analgesia was markedly potentiated by transcutaneous electrical stimulation [553]. Mu agonists with 3,6-bis[Dmt-NH-(CH(2))(n)]-2(1H)-pyrazinones produce selective mu, but not delta affinity and potent analgesia following oral delivery [537]; similar effects are found with novel 2′,6′-dimethyl-L-tyrosine-containing pyrazinone opioid mimetics [538].

3.2.1.4. Endomorphins. Both central endomorphin-1 and -2 suppress cold-water allodynia in a naloxone-reversible and naloxonazine-reversible manner in rats with sciatic nerve damage. Continuous intrathecal endomorphin-1 infusions blocked thermal hyperalgesia in carrageenan-treated rats, effects augmented by adenosine or agmatine co-treatment [578]. Endomorphin-1 dose-dependently increases synovial vascular resistance that is blocked by CTOP, and eliminated by adjuvant inflammation [744]. Synovial inflammation by kaolin and carrageenan induced endomorphin-1 immunoreactivity in the synovium, and exogenous endomorphin-1 reduced synovial vascular permeability, an effect blocked by the mu antagonist, CTOP [743]. Endomorphin-2, but not endomorphin-1 induced a CPP [501]. Analogues of endomorphin-2 incorporating 2′6′-dimethyl-L-tyrosine at the hydrophobic C-terminal extension produced MOR affinity and potent analgesic effects [363].

3.2.1.5. BEND. POMC gene transfer using intramuscular electroporation decreased the thermal hypersensitivity and paw swelling observed in rats receiving CFA, and markedly increased both plasma BEND and ACTH levels [217]. Likewise, electroporation of a transrepressor system (pTRE2-POMC) increased spinal BEND and increased pain thresholds in lims suffering chronic constriction injury; these effects were blocked by doxycycline [1219]. BEND-like proteins drawn from the ciliate, Tetrahymena blocked the mechanical response of the ciliate Stentor and inhibited phagocytosis in murine peritoneal macrophages in a naloxone-reversible fashion [947]. Burn wound healing induced by diphoterine was associated with higher concentrations of BEND [181].

3.2.1.6. Manipulations affecting Mu analgesia. A review [852] discusses the upregulation of the pro-nociceptive and anti-opioid peptide, CCK in the RVM during persistent opiate exposure. CCK activates descending pain facilitation mechanisms from the RVM enhancing nociceptive transmission at the spinal cord and promoting hyperalgesia. PAG DA depletion with 6-OHDA affected only large multipolar neurons but not small rounded cells, and decreased heroin and morphine analgesia on the hot-plate, but not tail immersion tests. D1, but not D2 DA receptor antagonism in the PAG produced a similar pattern of effects [352]. The protein kinase G inhibitor, KT5823 blocked analgesia induced by morphine and dipyrone, and produced an acute hypernociception [969]. Both intrathecal dextromethorphan and MK-801 potentiated morphine analgesia, but their combined treatment did not produce any further enhancements [215]. The ability of dextromethorphan to potentiate morphine analgesia following intrathecal and ventricular administration failed to be affected by alpha-2 adrenergic or 5HT2 receptor antagonism [216]. Intrathecal CART enhanced morphine analgesia on the tail-flick test without altering basal thresholds [262]. Although intrathecal administration of the 5HT(1A) agonist, 8-OH-DPAT induced analgesia on the formalin and paw pressure tests, it antagonized morphine analgesia, an effect blocked by intrathecal pretreatment with the 5HT(1A) antagonist, WAY-100635. In turn, WAY-100365 potentiated morphine analgesia in acutely-treated and morphine-tolerant rats [73]. The SSRI sertraline respectively increased and decreased morphine analgesia on the hot-plate test after acute and chronic (2 weeks) administration [862]. Whereas subcutaneous morphine analgesia was blocked by intrathecal administration of the muscarinic antagonist, atropine and M1/M4 antagonist, pirenzipine, but not by M2 or M3 antagonists, intrathecal pirenzipine blocked ventricular, but not intrathecal morphine analgesia [486]. GIRK and GIRK-2 KO mice exhibited thermal hyperalgesia, and displayed lower levels of intrathecal morphine analgesia at higher, but not lower doses [727]. Morphine analgesia on the paw pressure and tail-flick tests was reduced by pretreatment with MIF-1, Tyr-MIF-1, Tyr-W-MIF-1 or Tyr-K-MIF-1 [120]. The potentiation of morphine analgesia by the L-type calcium channel blocker, verapamil, was blocked by the peripherally-acting opioid anatagonist, naloxone methiodide [1017]. L-type calcium channel blockade-induced potentiations of morphine analgesia are accompanied by increased serum, and to a lesser extent, brain levels of morphine [1018]. KO mice lacking the R-type, but not the N-type, Ca2+ channel displayed greater analgesic responses to moprphine and opioid-mediated warm water swim stress as well as resistance to morphine tolerance [1248]. Whereas acute morphine increases phospho-

inositide 3-kinase in the PAG, inhibition of this kinase shifts the dose–response curve of morphine analgesia to the right [811]. Whereas morphine produces analgesia on both thermal and mechanical nociceptive tests, sodium channel blocking agents are preferentially effective on thermal thresholds [975]. The neuraminidase inhibitor, oseltamivir, enhances morphine analgesia, and prevents the hyperalgesic effects of either ultra-low morphine doses or repeated morphine tolerance [251]. The mechanical allodynia and thermal hyperalgesia caused by the chronic constriction model of the sciatic nerve was markedly reduced by morphine, THC and the CB-1 agonist, CP55940, weakly reduced by gabapentin, carbamazepine and baclofen, and unaffected by ketamine and dizocilpine [278]. The endothelin B antagonist, IRL 1620 failed to alter the magnitude or duration of morphine-induced analgesia or hyperthermia [99]. Those opiate agonists that induce robust beta-arrestin protein translocation produce similar types of analgesia in wild-type and beta-arrestin KO mice, whereas morphine and heroin that do not promote beta-arrestin recruitment display enhanced analgesia in beta-arrestin KO mice [124]. An extract of roasted coffee, 4-caffeoyl-1,5-quinide reduced morphine analgesia and inhibited [3H]-naloxone binding in mice [274].

3.2.2. *Delta agonists and receptors*

Both DPDPE and Delt produced analgesia in DOR KO mice, but produced either absent (tail immersion test) or reduced (hot-plate test) responses in MOR KO mice. Moreover, DPDPE analgesia in DOR KO mice was blocked by the mu antagonist, CTOP [992]. CFA treatment increased both the membrane density of DOR as well as the ratio of plasma membrane to intracellular DOR in wild type mice, but not in MOR KO mice [792]. An Enk-encoding herpesvirus reversed the thermal A-delta and C fiber-mediated hyperalgesia induced by pertussis toxin with the C-fiber-mediated actions blocked by mu and delta antagonists, and the A-delta-fiber-mediated actions blocked by delta antagonists [1243]. Enk-based opioid glycopeptides all produced analgesic activity on the tail-flick test with disaccharides producing greater potency than a tri-saccharide or bis- and tris-monosaccharides [314]. Crotalus durissus terrificus venom produces analgesia on a prostaglandin-induced mechanical hyperalgesia model sensitive to delta and kappa antagonists; this effect is reduced by inhibitors of neuronal, but not inducible forms of NOS as well as by an inhibitor of guanylate cyclase [895].

3.2.3. *Kappa agonists and receptors*

KOR immunoreactivity in the lumbar spinal cord was increased following sciatic nerve ligation in wild-type mice, but not NBNI-treated mice or KO mice lacking DYN or G-protein receptor kinase 3. The NBNI and KO mice displayed greater tactile allodynia and thermal hyperalgesia than wild-type animals after the lesion, and failed to display U50488H-induced tolerance after the lesion [1231]. CFA produced more intense hyperalgesia and spinal PDYN mRNA up-regulation in adrenalectomized relative to normal rats [1275]. Repeated systemic or central U50488H treatment enhanced analgesia and agonist-stimulated thalmic [35S]GTPgammaS binding induced by morphine or delta agonists, whereas repeated mu and delta agonist treatments failed to alter these measures induced by U50488H [583]. The kappa receptor agonist, bremazocine reduced carrageenan- and prostaglandin E(2)-induced hyperalgesia of the rat paw, effects reversed by NBNI, but not by ATP-sensitive K(+) channel blockers, Ca(2+)-activated K(+) channel blockers or non-selective K(+) channel blockers [25]. U50488H administration into the contralateral hindpaw 6–10 days after mononeuropathy reduced mechanical allodynia and autonomy, but not thermal hyperalgesia, an effect in turn blocked by peripherally-acting naloxone methiodide [109]. The kappa agonist, TRK-820, blocked tactile allodynia and mechanical hyperalgesia induced by herpes simplex virus type-1, effects blocked by NBNI, but not naltrexone, and not subject to tolerance or cross-tolerance with morphine [1110]. A highly potent kappa opioid agonist, D-Phe-Phe-D-Nle-D-Arg-NH2 (FE200041) produced peripheral hindpaw analgesia as well as analgesia on the acetic acid writhing and formalin tests, effects blocked by general and kappa, but not mu opiate antagonists [1157]. Chloroquine-induced scratching is abolished by the kappa agonists, TRK-820 or ICI204,448 [513], whereas TRK-820 inhibits morphine-induced scratching in rhesus monkeys [1180]. Whereas PKC-gamma wild-type and outbred mice displayed mechanical allodynia, thermal hyperalgesia and increased spinal DYN levels after spinal nerve ligation, neither PKC-gamma KO nor inbred 129S6 mice displayed any of these symptoms following spinal nerve ligation [375]. Two DYN derivatives, N-MT DYN A and N-MT DYN A amide, produced greater analgesia in morphine-tolerant rats [153]. Spiradoline, a kappa agonist produced more pronounced analgesic effects in sedentary than exercising rats, whereas exercising rats were more sensitive to spiradoline's locomotor and rewarding effects [1042]. A long-acting kappa antagonist, JDTic blocked kappa-mediated (enadoline), but not mu-mediated (sufentanil) analgesia in mice, and was more effective than NBNI in shifting the dose–response curve of U50488H-mediated analgesia and diuresis to the right in squirrel monkeys [177].

3.2.4. *OFQ/N and ORL-1 receptor*

OFQ/N continues to present a complex picture concerning its role in pain responses producing both "pro-nociceptive" and "anti-nociceptive" actions depending on such factors as site of administration, dose and time course. This section therefore presents these data separately.

3.2.4.1. Pro-nociceptive actions. OFQ/N administered into the hypothalamic arcuate nucleus decreased thermal and mechanical nociceptive thresholds and reduced systemic and intra-arcuate morphine analgesia. The hyperalgesic effect was blocked by an ORL-1 peptide antagonist [669]. The enhanced hyperalgesia induced by OFQ/N in a rat car-

rageenan inflammatory pain model is reduced by the ORL-1 antagonist, SB-612111 with the latter reversing morphine-induced tolerance as well [1261]. Long-term treatment (26 days) with AS directed against the ORL-1 receptor increased tail-flick latencies, body temperature, water intake and alcohol-induced locomotor activity, and decreased corticosterone levels, grooming in the open field and time spent in open arms of an elevated plus maze [116]. Intrathecal morphine, but not endomorphin-1 increased pro-OFQ/N and ORL-1 mRNA in neuropathic rats, and intrathecal pretreatment with the ORL-1 antagonist, PhePsi potentiated morphine analgesia in this neuropathic pain model [764]. OFQ/N-induced pain responses were blocked by intrathecal H1 histamine antagonists, unaffected by H2 antagonism, and augmented by H3 antagonists. The OFQ/N nociceptive responses were reduced in H1 receptor KO mice and in mice receiving histamine antisera or histidine decarboxylase inhibitors [977]. Intradermal OFQ/N induced scratching in wild-type, but not ORL-1 KO mice, effects blocked by naloxone and leukotrine B(4) antagonists [36]. An analogue substituting sarcosine (N-Me-Gly) for glycine in the third but not second position of OFQ/N produced hyperalgesia and inhibition of electrically-induced contractions of the mouse vas deferens in a naloxone-sensitive and ORL-1 antagonist-sensitive manner [203].

3.2.4.2. Antinociceptive actions. Intrathecal OFQ/N suppressed mechanical hyperalgesia in both diabetic and mononeuropathic rats in a naloxone-sensitive manner, and displayed synergy with systemic morphine for both analgesic effects [246]. Intrathecal OFQ/N produced an ORL-1 receptor-sensitive analgesia on bee-venom-induced persistent spontaneous nociception, but failed to affect the primary thermal and mechanical hyperalgesia and inflammation [1096]. OFQ/N immunoreactivity increased and ppOFQ/N mRNA decreased in the NRM after electroacupuncture in neuropathic rats [707].

3.2.5. Human studies

This section examines opioid analgesic effects in studies involving volunteers, dental pain, chronic pain, cancer pain, surgical pain, and pain related to cesarean section and labor.

3.2.5.1. Volunteers. Morphine produced analgesia, but not sedation, according to electroencephalographic power spectra and behavioral measures in volunteer subjects [909]. Gender, ethnicity and temperament contribute to individual variation in thermal and cold pain sensitivity by interactions with the vanilloid receptor subtype 1 and delta opioid receptor subtype I genes [592]. Adult volunteers displayed linear and dose-proportional effects following oxymorphone under both single-dose and steady state conditions for the parent compound and its meatbolites [5]. Oxycodone and morphine analgesia on the cold-pressor test fail to display synergistic analgesic effects [406]. Combinations of ketamine and morphine were more effective than either drug alone in reducing wind-up pain in both primary and secondary hyperalgesic areas elicited by a skin burn injury [1000]. Intranasal hydromorphone demonstrated nasal drug absorption and predictable accumulation after repeated treatment in human volunteers [965]. Naloxone increased fMRI activation in the insula, orbitofrontal cortex, thalamus and hippocampus of healthy human volunteers exposed to a 46 °C heat stimulus to the back of the hand [129].

3.2.5.2. Dental pain. Combinations of hydrocodone and ibuprofen were more effective in controlling pain after peridontal surgery than ibuprofen alone [96]. Paracetamol was as effective as morphine in acute and repeated administration paradigms for postoperative dental pain [1155]. Etoricoxib was more effective than an oxycodone-acetaminophen combination in analgesic duration, pain relief and use of rescue opioids following extraction of two or more molars [192]. A single dose of rofecoxib was as effective an analgesic as an oxycodone–acetaminophen combination for oral surgery [191] and removal of the third molars [621]. A COX-2 inhibitor, etoricoxib was more effective than combined acetaminophen-codeine in relieving pain following removal of the third molars [717]. Pain associated with removal of impacted third molars was equivalently affected by preoperative ibuprofen (600 mg), diclofenac (100 mg), and paracetamol (1 g) with codeine (60 mg) [546]. A combination of codeine, acetaminaphen and ibuprofen appeared to have longer post-operative analgesic effects than a combination of tramadol and acetaminophen following dental surgery [550].

3.2.5.3. Chronic pain. A review [831] discusses the use of a combination of nonopioid and moderate opioids (oxycodone, codeine, tramadol) for moderate pain and a combination of nonopioid and a potent opioid (morphine) for strong pain in older patients with chronic non-malignant pain. Although morphine use increased in Oregon and the United States from 1997 to 1999, the use of morphine in the last week of life for dying patients did not increase correspondingly [1124]. Central neuropathic pain patients displayed significant decreases in opioid receptor binding in the dorsolateral and anterior cingulate cortex, insular cortex, thalamus and inferior parietal cortex using PET imaging [544]. Increases in the use of more potent opioids for the treatment of chronic musculoskeletal pain were observed between 1980 (8%) and 2000 (16%) [180]. Use of opioid anagesics for pain treatment remains very low in Slovakia relative to use in Denmark, Canada and Austria [502]. In contrast, strong opioids were used in 68% of patients receiving palliative care in Germany [817]. Morphine is generally effective in affording pain relief in patients with non-malignant musculoskeletal disease with adjustments in dose and regimen following any adverse effects [210]. Both fibromyalgia and low back pain increased CSF Menk-Arg6-Phe7, and these levels were inversely correlated to systemic pain thresholds [72]. Nebulized morphine was effective in the management of chronic chest pain from sickle cell painful episodes [69]. Patient-controlled intra-nasal fentanyl was

similar to oral morphine for relief of procedural wound care pain in burn patients [347]. African patients treated for malaria fever with chloroquine develop severe generalized pruritus that can be reduced by treatment with naltrexone or the anti-histaminergic, promethazine [12]. Remifentanil was more effective than morphine in providing analgesia and sedation in mechanically-ventilated and critically-ill patients [260]. Sufentanil was 7.5 times more effective than fentanyl for treating chronic pain in patients receiving prior long-term opioid treatment [936]. Patients with chronic non-cancer pain who receive controlled release oxycodone or transdermal fentanyl are less likely to switch pain therapy than those receiving controlled release morphine [93]. Sustained release oxycodone was prescribed more than twice daily (every 8 h) in 67% of chronic pain patients [724]. Valdecoxib was as effective as oxycodone and acetaminophen in treating emergency room patients with acute musculoskeletal pain [698]. Patients with chronic back pain displayed the greatest intensity when there was an absence of endogenous opioid analgesia to acute pain and in a High Disability group [151]. The Mulligan Mobilization with Movement treatment technique produced naloxone-insensitive hypoalgesia in patients with chronic lateral epicondylalgia [874]. Patients with cluster headaches displayed lower plasma OFQ/N levels during the headache than before or after it, an effect that acted independently of sex, age or episode duration [320]. Patients with chronic critical limb ischemia and treated with spinal cord stimulation displayed higher plasma BEND, DYN and Menk levels after the system was switched off, and higher Menk levels when the system was re-initiated [353]. Fractures of both arms produce immediate increases in plasma BEND that dissipates with healing [540]. Patients removed from life support in an intensive care unit showed similar temporal patterns of death regardless of whether they were treated with narcotics or benzodiazepines for discomfort [190]. Naltrexone displayed effectiveness for the treatment of uremic pruritus in a subset of patients [656]. Family physicians are more comfortable in prescribing NSAIDs, tylenol + codeine, morphine + MS contin or percocet than prescribing dilaudid, hydromorphone contin, fentanyl patches or methadone for chronic non-cancer pain [990].

3.2.5.4. Cancer pain. Intrathecal and epidural administration of opioids produced similar degrees of pain relief in the treatment of refractory cancer pain [160]. Cancer pain and morphine requirements appear to be increased in patients with the 118 A>G polymorphism of the MOR gene [607]. Day-to-day variation of morphine and its metabolites was lower in cancer patients receiving subcutaneous morphine than for oral morphine [606]. Delivery of sustained release morphine doses correlated with plasma morphine, M6G and M3G levels in cancer patients, but only correlated with plasma M6G and M3G in non-cancer patients. However, correlations between the pain score and plasma morphine, M6G and M3G levels were weak in both patient groups [33]. An intravenous dose of morphine that is 20% of the basal oral dosage is very effective in treating episodic breakthrough pain in cancer patients [758]. Indeed, the intensity of incident pain in bone cancer may be reduced by increasing the opioid dose above that effective for controlling pain at rest [759], particularly by administering a second opioid [760]. Administration of controlled release oxycodone preoperatively reduced by half the amount of postoperative intravenous patient controlled opioid consumption in breast cancer surgery [563], and was effective in opioid-naïve cancer patients [616]. Cancer patients maintained on controlled-release oxycodone could be switched to extended-release oxycodone needing half the effective dose to stabilize pain [366]. Oral transmucosal fentanyl citrate was found to be effective in the treatment of breakthrough cancer pain [441]. Transdermal fentanyl produced superior pain relief and increased global quality of life in patients receiving radiotherapy for metastatic bone pain [897]. Cancer patients could be switched from transdermal fentanyl to oral methadone for the treatment of somatic, but not neuropathic pain [91]. Patients with metastatic cancer pain initiated long-acting opioid therapy 3–4 months before death, and 50% received less than 60 days of long-acting opioid therapy [94]. Methadone was less effective than morphine in the treatment of cancer pain over a 4-week period [152]. Transdermal fentanyl was more effective than sustained release oral morphine in chronic pain patients, whereas both were equally effective in chronic cancer patients [225], and this treatment produced satisfaction in a large cohort with cancer [802]. Hospice patients treated for cancer pain with higher morphine doses showed longer survival times than patients with lower morphine doses; the former patients had higher incidences of gastrointestinal, lung, ovarian and brain carcinomas [92]. Opioid rotation was effective in treating pediatric cancer pain by reducing dose-limiting side effects and maintaining analgesia [301]. Switching from morphine to another opioid for treatment in cancer pain occurred in older patients, those with a high white cell or platelet count, or with severe organ impairment [941]. A survey of veterans receiving combined oxycodone-acetaminaphen prescriptions indicated that this regimen was given more often for those with cancer, and a higher dose regimen was related to duration, older age and diagnosis with HIV/AIDS [471]. Radiotherapy is ineffective in altering the necessary morphine doses in patients with bone metastasis from lung cancer [515].

3.2.5.5. Surgical pain. Caucasian and Hispanic patients failed to differ in either the amount of morphine prescribed or self-administered following surgery [6]. Elderly Australian caridiac surgery patients received less morphine and were refused morphine more often than younger patients, and females indicated less satisfaction with pain relief than males [1253]. Opioid consumption in hospitals increased from 56 to 100 mg per surgical procedure between 1990 and 1999 [312]. The addition of background morphine infusions enhanced analgesia and consumption of patient-controlled morphine after cardiac surgery [421] and elective spine surgery [84].

The need for rescue analgesia in post-operative patients was associated with the initial visual analog score for pain and the degree of sedation [49]. Patients undergoing extracorporeal shockwave lithotripsy for urinary calculi displayed less post-operative pain and greater satisfaction with analgesia after receiving dexmedetomidine and morphine relative to tramadol and midazolam [19]. Dexmedetomide treatment before completion of surgery reduced by 66% the early postoperative need for morphine to maintain analgesia [43]. Diabetic patients undergoing abdominal hysterectomy had higher short-term and long-term morphine consumption, and reported higher pain scores than non-diabetic controls [567]. Short-term post-operative pain control was observed with morphine in the absence of hemodynamic factors with greater analgesia in men and greater satisfaction in women [642]. An iontophoretic PCA transdermal system indicated that fentanyl and morphine were equally effective for post-operative pain [1173]. A dose–response relationship exists between morphine's effective dose and the incidence of clinically meaningful events after ambulatory laparoscopic cholecystomy [1286]. Combination of ultra-low doses of naloxone with morphine in surgical patient controlled analgesia does not affect analgesia or opioid requirements, but decreased the incidence of nausea and pruritus [187]. Post-operative controlled release oxycodone was more effective than tramadol and metamizol combinations following retinal surgery [571]. Controlled-release oxycodone was as effective as morphine in a pediatric spinal fusion population [257] as well as for knee arthroplasty [10]. Continuous post-operative subcutaneous morphine produced pain relief and lower analgesic consumption in patients undergoing spinal fusion for idiopathic scoliosis [712]. Intrathecal morphine provided superior analgesia and lung volume in patients receiving off-pump coronary artery bypass grafting [754] as well as producing analgesia in children receiving cardiac surgery [1097]. Intrathecal morphine during radical prostatectomy decreased pain and supplemental intravenous morphine, but increased pruritus during the first post-operative day [148]. Transcutaneous electrical nerve stimulation during total knee arthroplasty failed to change the need for patient controlled morphine analgesia after surgery [141]. Combined femoral and sciatic blocks were more effective than epidural analgesia for unilateral knee arthroplasty [271]. A pump containing combinations of acetaminophen, rofecoxib, tramadol, dexamerthsone and bupivacaine decreased opioid use and hospital stay in patients receiving total hip or knee arthroplasty [1034]. Narcotic use and pain reports were quite similar for four groups of patients undergoing different levels of anterior cruciate ligament surgery [78]. Intra-articular administration of kertolac [169] or sufetanil [574] provided better pain relief than bupivacaine or morphine during knee arthroscopy. Combined intra-articular morphine and ropivacaine increased knee flexion, reduced hospital stay and reduced the number of days before the patient was walking on crutches in patients with total knee replacement [922]. Intra-articular morphine was superior to intramuscular morphine for post-operative pain after knee arthroscopy [918]. Intrathecal morphine during spinal anesthesia in arthroscopic knee surgery severely prolongs post-surgical latencies to urinate [427]. Increased BEND expression elicited by inflammation of synoival tissue failed to shift the dose–response curve of intra-articular morphine [675]. Subachromial ropivacaine PCA after arthroscopic shoulder surgery provided effective postoperative pain relief [452]. Patient-controlled analgesia with morphine was found to be safer and better than either femoral nerve block or psoas compartment block after total-hip arthroplasty surgery [106].

Continuous sciatic peripheral nerve blocks with ropivacaine reduced pain from total knee arthroplasty [90]. Ropivacaine infusions into the wound after spinal fusion surgery decreased pain scores and rescue medication requirements to a greater degree than morphine infusions [105]. Intercostal block with bupivacaine and intravenous morphine PCA is very effective in post-thoracotomy pain management [233] as well as after loin incision [53]. Levobupivacaine and ropivacaine were equally effective when paired with morphine for pain relief following abdominal surgery [1008]. Continuous subacromial bupivacaine failed to alter the incidence of morphine consumption or subjective pain in patients undergoing acromiplasty and rotator cuff repair [131]. Subcutaneous bupivacaine in the wound after open appendectomy failed to affect post-operative pain and morphine consumption in children [530], but decreased post-operative opioid requirements in adult patients receiving transperitoneal laparoscopic renal and adrenal surgery [581] as well as adult appendectomy [694]. Clonidine administered systemically or caudally was equally effective in enhancing bupivacaine-induced caudal blocks in pediatric hypospadias repair [444] and for orthopedic surgery [1087]. Perioperative administration of lidocaine [620] and rofecoxib [1024] during abdominal surgery reduced surgical pain and post-operative morphine consumption [620]. Pre-operative, low-dose ketamine failed to alter post-operative morphine consumption or pain scores in patients undergoing radical prostatectomy [570], but was effective in reducing post-operative oxycodone consumption following cardiac surgery [639] and was effective in combination with morphine in patients undergoing prostatectomy [1047]. A similar pattern of interactive analgesic effects was observed following oral administration of the non-competitive NMDA antagonist, amantadine and morphine in prostatectomy patients [1048]. Oral dextromethorphan reduced the need for perioperative administration of fentanyl in children undergoing typanomastoid surgery [453] that was related to treatment of post-operative nausea and vomiting associated with high pain ands opiate administration [454]. In children undergoing tonsillectomy, acetaminophen and codieine did not provide adequate pain relief in either around-the-clock or as needed dosing regimens [1099], but morphine was more effective than tramadol and ketamine for pain relief [1145]. COX-2 inhibitors were more effective than opioid-containing analgesics and similar to NSAIDs in post-operative pain

management [202]. The use of intra-operative magnesium sulphate with morphine produced greater short-term pain relief in open cholecystectomy patients, but did not decrease the post-operative morphine requirement [101]; controlled-release codeine was as effective as controlled-release codeine and acetaminophen for this type of surgery [219]. Combinations of diclofenac and paracetamol decreased post-operative morphine consumption and lowered pain scores in patients undergoing cardiac surgery [332]. Early extubation failed to alter postoperative pain control or use of opioid analgesics after cardiopulmonary bypass surgery [890]. The factors involved in cholecystomy patient satisfaction with pain relief included treatment regimen, age, worst pain experienced, pain interference with functioning, morphine equivalent dose and opioid-related side effects [529]. Remifentanil infusion during abdominal surgery modified intraoperative hemodynamic stability, and had little influence on postoperative morphine consumption [111]. Remifentanil was as effective as morphine and fentanyl in cardiac surgery with fewer bouts of nausea or vomiting [426]. Oral rofecoxib was better than intravenous ketoprofen in reducing pain and requiring PCA morphine in patients with urologic surgery [165], and was similar to ketorolac in controlling post-operative pain following orthopedic surgery [554]. Combinations of parecoxib and valdecoxib were more effective than placebo in reducing symptoms of distress and post-operative morphine use in patients undergoing laparoscopic cholecystomy surgery [370]. Gabapentin administered before and during abdominal hysterectomy reduced post-operative morphine consumption without affecting pain scores [291]; a similar pattern of results were observed in patients undergoing spinal surgery [1139]. Combinations of the beta-blocker, esmolol and fentanyl during perioperative hysterectomy reduced anesthetic and fentanyl use as well as subsequent PCA morphine [211]. Combination of nefopam and morphine for post-operative minor surgical pain failed to be greater than the analgesic effects of each compound alone [85]. Tissue oxygen tension was higher and pain scores were lower after breast reconstuction surgery using paravertebral levobupivacaine relative to intravenous morphine [156]. Chronic pancreatitis patients who had previous opioid use displayed more advanced disease symptoms than opioid non-users [16]. Nerve stimulation guidance was effective in placing epidural catheters fro pain relief during pediatric surgical procedures [1135].

3.2.5.6. Cesarean and labor pain. PCA applied epidurally was superior to PCA applied intravenously for pain relief during labor with no increased incidence of obstetrical intervention [436]. Combined sub-arachnoid morphine and clonidine increased postcesarean analgesia, reduced opioid requirements and increased intraoperative sedation than the agents applied individually [860]. Intrathecal bupivcaine paired with morphine was as effective as intrathecal ropivacaine paired with morphine for pain relief during cesarean delivery [265]. The ED50 and ED95 were determined for intrathecal bupivacaine analgesia coadministered with opioids during cesarean delivery, and it was determined that delivery should be made by a catheter-based technique [389]. Intrathecal sufentanil for labor analgesia showed a chronopharmacological rhythm with 12 h peaks at midnight and noon [279]. Subarachnoid anesthesia produced greater sensory block in pregnant women relative to patients receiving total abdominal hysterectomy, but the pregnant group required more intravenous morphine after the operation [329]. PCA diamorphine offered no increased pain relief during labor than the intramuscular route of administration [747]. Ondansetron failed to alter the incidence or severity of intrathecal fentanyl-induced pruritus during labor [1201]. Listening to music under anesthesia did not reduce perioperative stress hormone release or post-operative opioid consumption in patients undergoing gynecological surgery [763].

3.3. Sex, age and genetic differences

So-called organismic variables play vital roles in the mediation of opioid analgesic responses, and continue to attract a great deal of attention; therefore, this section summarizes sex (Section 3.3.1), aging (Section 3.3.2) and genetic (Section 3.3.3) differences.

3.3.1. Sex

A review [250] summarizes the gonadal steroid modulation of pain and analgesia in animals and humans, describing mechanisms by which 'males' and 'females' biology may differentially predispose them to pain and the analgesic effects of drugs and stress in terms of both quality and quantity. Another review [345] indicates that whereas human sex differences in opioid analgesia in clinical oral surgery settings demonstrate greater kappa agonist-induced analgesia in women, laboratory models using human volunteers demonstrate greater mu agonist-induced analgesia in women. The differences in human (women with greater analgesia) and animal (males with greater analgesia) models suggest that the models themselves may be mechanistically different, and could be due to such factors as pharmacokinetics, pharmacodynamics, gonadal hormone effects, genetic influences, balancing of analgesic and anti-analgesic processes and psychological factors. Long-term (2 week) exposure to the essential oil extracted from citrus lemon induced female-specific decreases in formalin-induced pain while both sexes displayed increases in tail-flick latencies [184]. Estradiol increased formalin-induced licking behaviors in male rats, an effect blocked by BFNA and the estradiol antagonist, ICI 182780. Formalin also produces an estradiol-reversible reduction in interferon-gamma production [183]. Formalin administered into the temporo-mandibular joint produced greater pain behaviors in diestrous females than in males or proestrous females; U50488H produced NBNI-reversible analgesia with greater effects in diestrous females [228]. Pairing ultra-low doses of naltrexone with morphine enhanced morphine analgesia in mature female rats, an effect inversely correlated to the antagonist dose. Ultra-low doses of nal-

trexone paired with morphine dose-dependently and linearly decreased morphine analgesia in mature male rats [437]. Castration produces analgesia on the formalin test that is potentiated by the SSRI, fluoxetine and the TP antagonist, flutamide; these effects are reversed by naloxone or the 5HT nerotoxin, 5,7-DHT [821]. Male, but not female mice display potentiations in morphine analgesia on the tail withdrawal test following non-competitive NMDA antagonists (dextromethorphan, dextorphan, MK-801) at low, but not high morphine doses, and following competitive NMDA antagonists (LY235959, L-701324) at both doses of morphine [825]. Assessment of naltrexone effects on the cold-pressor test revealed similar increases in ACTH, BEND, prolactin and cortisol in men and women with the latter displaying greater pain, less pain tolerance and finally, lower pain ratings following naltrexone [13]. Although the general pattern of KOR immunoreactivity in the lumbo-sacral dorsal horn was similar in males and females, it was denser in estrous and proestrous females relative to males, particularly a greater proportion of cytoplasmic KOR labeling within axon terminals [450]. Sex differences were not observed in the pharmacokinetic and pharmacodynamic analgesic effects of M6G in human volunteers [954]. Female patients treated for pain in an emergency room experienced better pain relief scores following butorphanol than morphine [768].

3.3.2. Aging

Aged rats display more pronounced CFA-induced hyperalgesia and up-regulation of spinal DYN expression relative to young animals [1276]. Consistent with human autoradiographic data, mu opioid binding increased at a rate of 0.9% per year in the left temporal cortex after MRI-based partial-volume correction using PET [88]. Senescent female mice display reduced levels of U50488H-induced analgesia, but unlike younger intact females, display sensitivity to MK801-induced reversal of U50488H analgesia [1078]. Whereas 1-day-old mice show enhanced pain behavior relative to 1-week-old animals, the latter show enhanced morphine analgesia relative to the latter. Male neonates show greater morphine analgesia than females [1079].

3.3.3. Genetic differences

A review [440] proposes that variances in the 3′ untranslated region (39-UTR) of the MOR gene might participate in the variability of the opioid responses observed individually in humans and interstrain differences in non-human subjects.

3.4. Opioid mediation of other analgesic responses

This section summarizes studies that indicate that analgesia elicited by a wide range of peptides and transmitters can alternatively and respectively be sensitive (Section 3.4.1) or insensitive (Section 3.4.2) to opioid manipulations using agonists, antagonists and transgenic knockouts.

3.4.1. Opioid-sensitive analgesic responses

The amount of electrical stimulation of the NRM to suppress A-delta-mediated nociceptive responses was twice as high as that needed for C-fiber- mediated nociceptive responses. Whereas intrathcal administration of general and delta-1 antagonists blocked NRM stimulation-produced analgesia mediated by both fiber populations, mu-1 and delta-2 antagonists preferentially reduced C-fiber-mediated NRM stimulation [702]. CCK(2) receptor KO mice displayed naloxone-reversible mechanical hyposensitivity and expressed higher levels of lumbar delta and kappa receptors. When experimental neuropathy was induced, CCK(2) receptor KO mice failed to display mechanical hyperalgesia and showed increases in POMC and delta opioid receptors [634]. Acetaminophen produced analgesia that was effectively blocked by general, mu and kappa, and to a lesser degree, delta opioid antagonists [157]. Analgesic self-synergy between combined supraspinal and spinal administration of acetaminophen was blocked by mu, delta and kappa antagonists [914]. Synergistic analgesic interactions between morphine and NSAIDs were blocked by mu, but not delta or kappa antagonists [771]. Naloxone-reversible synergistic interactions were noted for systemic and intrathecal administration of tramadol and the NSAID, naproxen, but not rofecoxib [988]. Both carbachol and morphine administered into the central nucleus of the amygdala produced analgesia on the vocalization test in guinea pigs that were both blocked by naloxone pretreatment in the same site [658]. C-fiber EMG activity in hindlimb flexor muscles was similarly reduced by morphine, the NMDA antagonist, MK-801 and following systemic and NRM administration of the nicotinic agoinist, epibatidine [913]. Placentophagia during parturition significantly enhanced analgesia induced by delta (DPDPE) and kappa (U62066, spiradoline) agonists, but decreased analgesia induced by mu (DAMGO) agonists [293]. A soy diet ameliorated secondary mechanical hyperalgesia induced by sarcoma cells introduced to the femur, but had no effect on primary mechanical hyperalgesia in the calcaneus model or on movement-induced hyperalgesia in the humorus model; morphine dose-dependently reversed the three hyperalgesic models in all diet groups [1284]. Oxytocin-induced analgesia was blocked by general, mu and kappa, but not delta opioid antagonists in thermal and mechanical pain withdrawal tests [372]. SP administered into the ventrolateral PAG produced analgesia blocked by a NK-1 receptor antagonist. Systemic morphine increased SP release in the ventrolateral PAG [957]. The prokinetic compound, domperidone reduced both the first and second phases of formalin pain in a naloxone-reversible manner [1030]. THC, like morphine produces analgesia in both arthritic and non-arthritic rats with NBNI-induced antagonism of THC analgesia observed only in arthritic rats. THC increases DYN in non-arthritic rats and decreases DYN in arthritic rats [248]. THC and morphine enhanced each other's reductions of formalin-induced pain, increased thalamic 5-HT and reduced locomotor activity [346]. NE administered

directly into inflamed hindpaws produces analgesia that is blocked by alpha(1), alpha(2) and beta(2) adrenergic antagonists, by mu and delta antagonists, by antisera raised against BEND, and by chemical sympathectomy [113]. Acute or chronic administration of clonidine elicited a subsequent delayed tactile hypersensitivity that increased DYN content in the lumbar spinal cord and that could be reversed by either MK-801 or DYN antiserum [910]. The GABA-A antagonist, bicuculline administered into the thalamic nucleus submedius produced naloxone-reversible analgesia and enhanced morphine-induced analgesic actions with the latter effect blocked by the GABA-A agonist, muscimol [534]. The activation of spinal and supraspinal NPFF and NPFF2 by inflammation and neuropathic pain was further activated by acute, but not chronic morphine [835]. The SSRI, fluoxetine decreased the inflammatory response to subplantar carageenan in a partial naloxone-sensitive manner [2]. Likewise, the SSRI, paroxetine increased hot-plate latencies in mice, effects blocked by naloxone and ondansteron, but not by ketamine [304]. Amytriptaline produced a synergistic interaction with morphine in producing analgesia on the cutaneous orofacial formalin pain test [704]. Chronic administration of the antidepressant, nefazodone increased tail-flick latencies and decreased immobility on the Porsolt swim test, while increasing the density of MOR in the frontal and cingulate cortices, DRN and PAG [851]. Selective adenosine-2B, but not adenosine-1 or -2A, antagonists produced analgesia, that when paired with morphine, enhanced the latter's effect. In contrast, adenosine-3 antagonism produced thermal hyperalgesia [3]. Intracisternal NMDA induced scratching and blocked the late phase of the formalin-induced hyperalgesic response, effects reversed by naloxone [650]. The AMPA/GluR5 antagonist, NS1209 produced comparable responses to systemic morphine on the hot-plate and formalin analgesic assays, on mechanical allodynia and hyperalgesia following chronic constriction injury, and reduced cold hypersensitivity to ethyl chloride [114]. NPY administered into the PAG increased paw withdrawal latencies in mononeuropathic rats, an effect blocked by Y1 and opiate receptor antagonists [1188]. Intracisternal administration of interleukin-1 beta blocked NMDA-induced scratching responses in a naloxone-sensitive manner [593]. Intrathecal galanin produced analgesia on the formalin test through activation of the GalR1 rerceptor, and isobolographic analyses demonstrated synergy between galanin and either morphine or AP5 [499]. Intrathecal melatonin increased mechanical nociceptive thresholds that were reversed by naloxone and the melatonin antagonist, luzindole [849]. Melatonin-induced analgesia on the formalin test was blocked by the ML2 antagonist, prazosin, but not the ML1 antagonist, luzindole. This analgesic effect was naloxone-insensitive, but enhanced by cotreatment with morphine [926]. LiCl administered 24 h prior to morphine reduces the latter's analgesic effects, an effect reversed by central and peripheral naloxone and peripheral naloxone methiodide administered before LiCl. Naloxone methiodide administered after LiCl, but before morphine failed to block the reduced analgesic effect [543]. Trans-resveratol, a polyphenolic compound with antioxidant properties, produced naloxone-reversible analgesia following acute treatment and tolerance following chronic treatment [425]. Low-frequency transcutaneous electrical stimulation of a carrageenan-treated inflammed paw blocked hyperalgesia in a naltrexone-reversible fashion [935]. Whereas naloxone in the thalamic submedius blocked analgesia induced by high-, but not low-frequency acupuncture, naloxone in the anterior pretectal nucleus blocked analgesia induced by low-, but not high-frequency acupuncture [1294]. Both acute and chronic electroacupuncture treatment significantly reduced mechanical allodynia, but not thermal hyperalgesia induced by CFA in a naloxone-sensitive manner [500]. Electoracupuncture significantly reduced mechanical allodynia induced by a neuropathic model of inferior caudal trunk injury; this effect was blocked by spinal mu and delta, but not kappa antagonists [596]; a similar pattern of effects was noted for the hyperalgesia induced by CFA [1277]. Peripheral electrical stimulation relieved neuropathic pain induced by lumbar spinal ligations in a naloxone-reversible manner for up to 12 h. Repeated exposure failed to display tolerance [1094]. Exposure to weak (1 μT) complex magnetic fields produced thermal analgesia that was enhanced by morphine and blocked by naloxone [732]. Intraplantar, but not subcutaneous injection of CRF produced naloxone-reversible analgesia in CFA-treated rats, an effect reduced by depletion of polymorphonuclear cells expressing CXCR2, MIP-2 and keratinocyte-derived chemokines [137]. CRF-induced immune-derived analgesia is decreased in rats undergoing cyclosporin-induced immunosuppression that destroy BEND-containing immune cells [470]. Both isomers of meptazinol blocked the thermal hyperalgesia induced by carrageenan in a naloxone-sensitive manner [1190]; the same pattern of effects was observed after intrathecal meptazinol administration [1271]. Bovine milk-derived lactoferrin suppressed the development of arthritis and hyperalgesia induced by CFA in a naloxone-reversible manner [458]. Lactoferrin produced analgesia and potentiated morphine analgesia on both phases of the formalin test, effects that were blocked by mu receptor antagonism and NOS inhibition [460]. The 1-substituted methyl and pohenyl analogues of pyrazolines each produced analgesia on the tail immersion test with the latter, but not the former blocked by naloxone [1107]. Sub-analgesic doses of nefopam, a monoamine uptake inhibitor and morphine blocked the thermal hyperalgesic and mechanical allodynic responses induced by carrageenan or incisions [391]. Insulin produced antinociception that was potentiated by morphine and blocked by naloxone [40]. ACTH produced analgesia on the tail-withdrawal test that was blocked by naltrexone, but unaffected by deficient glucocorticoid production [123]. A naturally-occurring enantiomer in essential oils, (−)-linalool produced naloxone-reversible analgesia on the hot-plate and formalin tests [875]. Access to a 32% sucrose solution produced significantly greater analgesic effects to morphine across a

dose–response curve in a naltrexone-reversible manner [264].

3.4.2. Opioid-insensitive analgesic responses

Ultra-low doses of morphine reduce the analgesic effects of mu (morphine, DAMGO), delta (Delt) and kappa (U50488H) agonists, effects in turn blocked by naloxone and (+)-naloxone, but not 3-methoxynaltrexone. This anti-analgesic response was unaffected by delta, kappa or NMDA antagonists as well as antisera directed against DYN, Lenk, Menk, BEND, CCK or SP [1221]. Clonidine-induced analgesia on the formalin test was reduced by NOS and guanyl cyclase inhibition, but not by naloxone [273]. CRF produced lesser magnitudes of analgesia than morphine in rats given a thermal injury. The D2 receptor antagonist, prochlorperazine increased hotplate latencies that were blocked by D2 receptor agonists and M1 muscarinic antagonism and AS probes, but not by naloxone [386]. Mesh chambers used to accumulate fluid showed that corticosterone and BEND levels in CRF-treated rats were similar to controls [188]. Analgesia elicited by the NSAID, *S*-(+)-ketoprofen was blocked by ventricular 5-HT(1)/5-HT(2)/5-HT(7) antagonism with methiothepin and intrathecal 5-HT(3)/5-HT(4) antagonism with tropisetron, but not by naloxone or NO agents [286]. Paclitaxel, a chemotherapeutic for treatment of solid tumors, produces pain that is blocked by the selective T-type Ca(+)-channel blocker, ethosuximide, but not by morphine or the NMDA antagonist, MK-801 [350]. Both diazoxide and diclofenac, ATP-sensitive K+ channel openers produced naloxone-insensitive blockade of hyperalgesia induced by prostaglandin E2 [22,23]. Riboflavin (Vitamin B2) produced naloxone-insensitive analgesia on the formalin test, but failed to affect tactile allodynia in a spinal nerve ligation model [407]. Acupoint stimulation with diluted bee venom reduced the thermal hyperalgesia, but not the mechanical allodynia induced by chronic constrictive injury, an effect blocked by intrathecal administration of the alpha2-adrenoceptor antagonist, idazoxan, but not naloxone [950]. Whereas morphine's analgesic actions are decreased in STZ-induced diabetic rats, the reversal of carrageenan-induced thermal and mechanical hyperalgesia by oxcarbazepine, carbazepine and mexiletine was enhanced in STZ-induced diabetic rats [587]. The superoxide dismutase mimetic, M40403 blocked carrageenan-induced inflammation and hyperalgesia in a naloxone-insensitive manner [1196]. Low-frequency electroacupuncture decreases carrageenan-induced hyperalgesia and enhanced dorsal horn c-fos expression in a naloxone-insensitive manner [1278]. Platycodin D, a triterpene saponin, produces analgesia on the tail-flick, formalin and writhing tests following systemic, ventricular and intrathecal administration in a naltrexone-insensitive manner [214]. Bovine adrenal medulla 22 peptide produces analgesia on both pahases of the formalin test following intrathecal administration that is partially blocked by naloxone, but produces analgesia on the tail-withdrawal test that is insensitive to naloxone, indicating mixed opioid-nonopioid activity [488].

4. Stress and social status

This section examines the phenomenon of stress-induced analgesia (Section 4.1), emotional responses in opioid-mediated behaviors (Section 4.2), and opioid involvement in stress response regulation (Section 4.3).

4.1. Stress-induced analgesia

One major theme of stress-induced analgesia is to examine its role vis a vis the opioid system, particularly considering parametric (Section 4.1.1), molecular (Section 4.1.2) and sex/age (Section 4.1.3) factors.

4.1.1. Parametric factors

The anti-opiate peptide family, Tyr-MIF-1 potentiated immobilization-induced analgesia when administered prior to stress, but reduced this response when administered after immobilization. Immobilization reduced the analgesic effects of Tyr-MIF-1 [121]. Swim stress-induced analgesia was potentiated by the anorectic drug, mazindol, an effect blocked by sulpiride and MK-801, but not naloxone [1166].

4.1.2. Molecular factors

Pre-Enk KO mice with a genetic mutation on the DBA/2J, but not the C57BL/6J background displayed increased levels of opioid-dependent stress-induced analgesia. Moreover, while C57BL/6J-pre-Enk KO mice displayed elevated anxiety on only the light–dark and startle response tests, DBA/2J-pre-Enk KO mice showed elevated anxiety on the zero maze and social interactions tests. [110]. Swim stress-induced analgesia in tissue inflamed by CFA was reduced by blockade of L- and P-selectins or by monoclonal antibodies raised against alpha(4) and beta(2) integrins, but not by blockade of platelet-endothelial cell adhesion molecule-1. This effect coincided with a 40% decrease in migration of opioid-containing leucocytes to the inflamed tissue [711]. CWS and intraplantar injection of CRF and opioid peptides produced similar analgesic profiles in rats injected with CFA and macrophage inflammatory protein-2. This early inflammatory response did not alter MOR or DOR nerve fibers or MOR binding sites in the DRG [136]. Granulocyte colony-stimulating factor mobilized opioid-containing polymorphonuclear cells, but had a minor influence on cell migration and peripheral analgesia in response to inflammatory pain induced by CFA [138].

4.1.3. Sex/age differences

Whereas female spontaneously hypertensive, Lewis and Wistar rats exhibited swim stress-induced analgesia with the latter group displaying a NMDA receptor-sensitive response, swim stress-induced analgesia was observed in male Lewis and Wistar rats, but not spontaneously hypertensive rats

[1165]. Insulin hypoglycemic stress increased analgesia induced by morphine, buprenorphine and pentazocine and decreased responses to noxious stimuli in ovariectomized rats with or without steroid-induced LH surge [1071]. MOR-expressing cells in the anterior distalis of the pituitary gland were more numerous in male than female rats except in the pre-pubertal and old periods; aging decreased the number of MOR cells from the first postnatal week through 24 months in both sexes [173]. The insensitivity of females to NMDA antagonism of cold-water swim and U50488H analgesia is blocked by ovariectomy and reinstated by progesterone treatment [1077].

4.2. Emotional responses in opioid-mediated behaviors

A review [622] analyzes the roles of brain stimulation reward, morphine-induced oral stereotypy and sensitization in terms of implications for drug abuse. Monkeys with dysfunction of a single nucleotide polymorphism of the C77G site of MOR displayed lower basal and ACTH plasma cortisol levels, and increased aggressive threat scores [766]. MOR KO mice with deletions of exons 2 and 3 show less anxiety on the elevated plus maze and emergence tests, reduced responses to novel stimuli, and less depressive activity in the forced-swim test. These effects were accompanied by decreased M1 muscarinic mRNA in cortex, C/P, NAC and hippocampus, and increased 5HT-1A levels in cerebral cortex and hypothalamus of MOR KO mice [1251]. Mice exposed to predator odor displayed freezing and less time in the light, effects associated with increased Fos-related antigen in the prelimbic cortex and NAC shell and decreased Enk-positive neurons in the NAC core. High anxiety in these mice was associated with increased Enk-positive neurons in the baso-lateral, central and medial amygdala [465]. The increases in BEND by acoustic startle were blunted in plasminogen-deficient mice, and central administration of BEND or AMSH increased the acoustic startle reflex in plasminogen KO mice [1189]. Morphine lowered the threshold for lateral hypothalamic brain stimulation reward in aged and young rats that showed baseline threshold differences [532]. The kappa agonist, U69593 increased lateral hypothalamic intracranial self-stimulation thresholds in a kappa antagonist-sensitive manner [1123]. Low and high central doses of OFQ/N produce respective anxiolytic and angiogenic nocistatin-sensitive effects on the hole board test. The anxiolytic effect was accompanied by increased hippocampal 5HT turnover and was blocked by the 5HT1A antagonist, WAY100635. The angiogenic effect was accompanied by decreased amydala 5HT turnover and was blocked by the 5HT1A agonist, 8-OH-DPAT [560]. Ventricular OFQ/N increased anxiety-like behaviors and corticosterone levels in the open field, elevated plus maze and dark–light neophobic tests [336]. Acoustic startle magnitude was increased in animals undergoing spontaneous or naloxone-precipitated withdrawal from acute morphine, effects blocked by clonidine or chlordiazepoxide [446], and exacerbated by multiple opiate exposures and withdrawals [447]. High-aggression pigeons treated with naloxone showed less offensive aggression and more emotional responses, whereas naloxone-treated low-aggression pigeons showed greater offensive aggression during food competition [326]. Human volunteers that displayed greater ACTH responses to psychological stress showed a similar pattern to naloxone administration with personality characteristics related to high scores of Extraversion Openness predicting higher ACTH responses [853]. Subjects with the methionine/methionine genotype polymorphism of the catechol-*O*-methyltransferase gene displayed augmented ACTH responses to naloxone [854].

4.3. Opioid involvement in stress response regulation

Whereas acute and chronic morphine administered in a familiar environment increases c-fos expression in striato-nigral and cingulate cortex cells, acute, but not chronic morphine administered in a novel environment increases c-fos expression in striato-nigral cells, but decreases c-fos expression in striato-pallidal cells [337]. Delt and hibernation induction, but not DADL, reduce total polyubiquitin transcript expression in a caridiac ischemic model [1060]. Immobilization stress and learned helplessness increased DYN A and B levels in the NAC and hippocampus. Learned helplessness in turn was reduced by NBNI microinjections into the CA 3 region of the hippocampus and the NAC shell, and to a lesser degree, in to the hippocampal dentate and NAC core [1020]. Immobilization stress increased subsequent rapid eye movement and slow-wave sleep that was blocked by naltrexone pretreatment [1163]. Whereas tail-pinch enhanced BEND release from the arcuate nucleus and the NAC, arcuate nucleus BEND was only enhanced by fox odor, and NAC BEND was enhanced by systemic alcohol administration [726]. Naloxone blocked the increases in ACTH and corticosterone induced by the opioid agonist, levorphanol, but not by its dextrorotary enantiomer, dextrophan, a non-competitive NMDA antagonist [880]. Inescapable, but not escapable tail-shock stress potentiated morphine-induced dopamine, but not serotonin efflux in the NAC, but not the VTA with the potentiations blocked by either naltrexone or 8-OHDPAT administration into the DRN [118]. Neurotoxic 5,7-DHT lesions placed in the medial prefrontal cortex completely blocked the ability of morphine to enhance the release of NAC DA in uncontrollably-stressed rats [117]. Menk decreased resistance to oxidative stress earlier in life in male relative to female mice [70]. Immobilization stress increased hippocampal Enk and DYN mRNA levels with the latter effect increased further by increased stress duration [201]. Social stress induced by a visible burrow significantly reduced Enk mRNA levels in the NAC in both stress-responsive (acute and chronic) and non-responsive subordinate (chronic) rats [703]. CRF KO mice displayed reductions in pain stress and a higher molecular weight form of BEND [364]. Bovine lactoferrin reduced stressful behaviors in a conditioned fear-induced freezing test and an elevated plus maze; these effects were

reduced by naloxone or L-NAME, and potentiated by electric foot shock [561]. Dogs fearful of gunshots displayed higher plasma concentrations of BEND, cortisol, progesterone and VP during the gunshot test than dogs fearless of gunshots [508]. Morphine administration produces a rapid and transient increase in Hsp70 and other heat shock genes [28]. Intraoperative increases in ACTH during major abdominal surgery were prevented by intrathecal, but not intravenous sufentanil [127].

5. Tolerance and dependence

The most-often studied variables in the functional analysis of opioid-mediated responses next to analgesic processes are the underlying neurobiological roles of tolerance and dependence. This has continued unabated through the years, and continues to be a focus in this review. Developments will be reviewed for animal models in tolerance (Section 5.1), and animal models in dependence and withdrawal responses (Section 5.2).

5.1. Animal models in tolerance

This section will be divided into the following subsections: (i) cellular effects, (ii) organismic effects, (iii) opioid effects and (iv) peptide-transmitter effects on morphine tolerance, as well as (v) other forms of opioid tolerance.

5.1.1. Cellular effects on morphine tolerance

A review [390] indicates the emerging evidence for up-regulation, augmented phosphorylation and altered expression of adenylyl cyclase type II isoforms, underlying the ability of chronic morphine to shift opioid receptor G-protein signaling from Gi-alpha inhibitory to G-beta-gamma stimulatory. A review [646] proposes that cellular modulation of opioid receptor signaling, either through transcriptional or post-translational control of the receptor, is the basis for morphine tolerance and dependence. Another review [235] indicates that suggestions that clinically-relevant mu-opioid receptor agonists may have different propensities to produce tolerance and dependence that arise from their differential recruitment of regulatory mechanisms are premature, have not been appropriately assessed, and lack a thoroughly established regulatory scheme.

Recovery from desensitization of LC neurons was increased with chronic morphine or M6G treatment. PKC inhibition also increased LC desensitization in control tissue [266]. Chronic morphine sensitized LC NE neurons to CRF, and was also expressed as hyperresponsivity to physiological swim stress such that NE-mediated hyperactive responses predominated [1228]. Morphine analgesia induced from the vlPAG developed tolerance after 2 h of continuous infusions, and this tolerant state resulted in naloxone-precipitated increases in RVM ON-cell activity and cessation of RVM OFF-cell activity 3 days thereafter [641]. Morphine dose escalation over five days produced tolerance and upregulation (18%) of [3H]DAMGO autoradiography in the superficial layers of the spinal cord [927]. Chronic morphine inhibited SNAP-25 phosphorylation and down-regulation of neuronal SNARE complex formation in the hippocampus [1232]. The ability of MK-801 to ameliorate morphine tolerance appears to correlate with its ability to block the CSF release of glutamate and aspartate by repeated morphine administration [1204]. Deletion of the G-alpha(z) subunit increased morphine tolerance in mice through pharmacodynamic and not pharmacokinetic mechanisms [648]. AS probes directed against RGS proteins significantly inhibited chronic morphine-induced up-regulation of adenylyl cyclase activity and reversed chronic morphine-induced actions on DAMGO-stimulated [35S]GTPgammaS binding [1229]. Whereas acute morphine respectively decreased and increased phosphorylated ERK and protein kinase B in the NAC in a naltrexone-sensitive manner, chronic morphine decreased protein kinase B, but not ERK levels in the same nucleus [798]. Morphine tolerance increases PKC-gamma activity and glial fibrillary acidic protein in the dorsal horn. Mice with enhanced green flourescent protein display even greater expression after morphine tolerance, whereas PKC-gamma KO mice fail to display astroglial hypertrophy or proliferation after repeated morphine [816]. Chronic morphine decreased the affinity of glycine for the NMDA receptor, but not glutamate, homoquinolinic acid and NMDA. Its alterations of the antagonist actions of 7-chloro-kynuernic acid and idenprodil suggest increases in NR2A NMDA subunit expression or function after chronic morphine [731]. Chronic morphine resulting in behavioral sensitization decreased levels of phospho-Thr34 DARPP and phosphorylation of GluR1 and NR1 subunits, suggestive that morphine challenges decrease PKA activity in morphine-sensitized rats [991]. Chronic morphine pellets increased Ca(2+)-calmodulin-dependent kinase II mRNA, protein and phosphorylation in the spinal cord [673] as well as the CO/NO-cGMP signaling pathway [672]. DAMGO-induced inhibition of Chinese hamster ovary cells expressing MOR develops tolerance that is attenuated by cholera toxin. Pertussis toxin unmasks DAMGO's ability to facilitate forskolin activation of adenylate cyclase. Interestingly, the mu antagonist, CTAP produces similar cholera toxin- and pertussis toxin-sensitive effects [1106]. The ability of vasoactive intestinal polypeptide and the delta agonist, DPDPE to facilitate cAMP formation was abolished by chronic morphione exposure and re-established by in vitro PKC inhibition [688]. An AS, but not a missense, probe directed against post-synaptic density protein-95 reduced this protein's binding to NMDA receptors and prevented the development of morphine tolerance [674]. A single morphine treatment blunted the ability of morphine 1 week later to elevate the HVA/DA level in the C/P, but had no effect on the second morphine treatment to increase the DOPAC/DA ratio in the C/P [884]. Acute and chronic morphine produced respective naloxone-sensitive decreases and increases in NO synthesis activity in

rat cervical nucleus neurons [306]. Chronic morphine infusions upregulated caspace 9, NF-kappaB, NF-H, tau, GABA-A delta sub-unit, FGFFR1, Ggamma2, synuclein 1, syntaxin 5 and 13, GRK5 and c-fos mRNA gene expression in the NAC shell, down-regulated v\caspace 1, D2 dopamine receptor, GABA-A alpha1 subunit, GRIA 1/3/4, Galpha2, PSD-95 and CREB gene expression in the NAC shell, upregulated NAIP, GABA-A alpha1 subunit, GRIN2C, GRIA1, mGuR1, D4 dopmine receptor and PSD-95 gene expression in the NAC core, and down-regulated bax, bcl-x, cox-1 and MAP2 gene expression in the NAC core [469]. Chronic morphine produced up-regulation of such cytoskeletal genes as glial fibrillary acidic protein and activity-regulated cytoskeleton-associated protein, and down-regulation of growth-associated protein, calthrin heavy chain, alpha-tubulin, Tau and stathmin [725].

5.1.2. Organismic effects on morphine tolerance

Following continuous morphine, weekly challenges with morphine produced greater and more sensitized biting responses in aged relative to younger rats [609]. Whereas acute stress enables long-term depression induced by hippocampal low-frequency stimulation, acute morphine causes synaptic potentiation that is reversed to long-term depression by combined stress-morphine exposure in a glucocorticoid and NMDA receptor antagonist-sensitive fashion. Chronic morphine attenuates each of these acute morphine responses [1239]. The magnitude of tolerance was found to be greater in female rats relative to male rats following intrathecal morphine administration [489]. Moreover, in a short (6 h) morphine tolerance paradigm, tolerance was observed in male and proestrus female rats, but not in ovariectomized, estrus, metestrus or diestrus females [1014]. However, although male rats display greater analgesia than female rats following acute systemic morphine, males and females developed similar rates of acquistion for systemic morphine tolerance [480]. Neuropathic animals with sciatic nerve ligations were more sensitive to the ability of U50488H to produce greater analgesic and anti-allodynic effects than morphine; repeated administration of morphine or U50488H failed to produce tolerance to either response [1063].

5.1.3. Opioid effects on morphine tolerance

Morphine-tolerant rats display analgesic cross-tolerance to intrathecal DAMGO without changing the magnitude of DAMGO-induced internalization of MOR in lamina II of the dorsal horn [1130]. Both endomorphin-1 and -2 produced analgesic tolerance following repeated injections that were in turn cross-tolerant with each other and with morphine [1054]. Chronic intrathecal treatment with [Dmt1]-DALDA more potently shifted the AD50 dose of morphine and DAMGO than the agonists themselves, yet was ineffective in shifting DAMGO AD50 doses following ventricular [Dmt1]-DALDA administration [86]. Morphine-tolerant rats displayed analgesic activity following administration of the metabolically-stable analogue [N-Met-Tyr1]-DYN A(1-13) on the tail-flick test [18]. Morphine tolerance and dependence are markedly attenuated in mice lacking the ORL-1 receptor gene or the NMDA receptor epsilon-1 subunit, and chronic morphine increases spinal and supraspinal ORL-1 gene or epsilon-1 subunit protein expression. Rescue of the epsilon-1 sub-unit gene in specific nuclei of KO mice reinstated morphine tolerance and dependence [1141]. An electroporation technique that delivers the receptor into the brain of KO mice revealed that the ORL-1 KO mouse deficits in morphine tolerance acted through the GluR-epsilon-1 or NR2A NMDA receptors [1142]. The decreases in neurofilament-L protein immunodensity in the cerebral cortex following chronic morphine in wild-type mice was abolished in MOR, KOR and DOR KO mice, whereas the marked increases in phosphorylated neurofilament-H protein density in wild-type mice following chronic morphine were abolished in MOR KO mice [374].

5.1.4. Peptide-transmitter effects on morphine tolerance

Chronic morphine dose-dependently increased NO production that coincided with tolerance development. The ability of L-arginine to initially enhance morphine-induced analgesia dissipated rapidly due to a NO-associated loss of antinociception [467]. Mice deficient in neuronal NOS, but not in endothelial NOS displayed less morphine antinociceptive tolerance than wild type mice; prolonged L-arginine administration mimicked morphine tolerance in wild-type and endothelial NOS KO mice [468]. G-protein receptor kinase KO mice display normal analgesic responses to morphine and fentanyl, but these animals fail to exhibit analgesic or electrophysiological tolerance to fentanyl. Morphine tolerance to the analgesic response is unaffected while morphine tolerance to electrophysiological responses is slowed in these KO mice [1117]. Both PKC and PKA inhibitors reverse morphine tolerance in both analgesic and hyperthermic assays [526]. Co-treatment of the cyclin-dependent kinase 5 inhibitor, roscovitine with morphine inhibited morphine-induced analgesic tolerance by shifting morphine's analgesic dose–response curve to the left [1184]. Chronic cotreatment of gabapentin with morphine blocked the latter's analgesic tolerance on the tail-flick and paw pressure tests by possibly reducing the ED(50) for morphine analgesia [443]. Dipyrone potentiates morphine-induced analgesia in both dipyrone-treated as well as morphine-tolerant rats [472]. Whereas chronic administration of the glycine(B) site antagonist, L-701.324 decreased morphine analgesia and increased the development of morphine tolerance, the NMDA antagonist, MK-801 potentiated morphine analgesia and reduced morphine tolerance [623]. Whereas combined treatment with mGlu(1) (CPCCOEt) and mGlu(5) (MPEP) antagonists blocked morphine tolerance, single treatments produced partial effects [1039]. The injectable form of aspirin, lysine-acetylsalicylate, produced naloxone-reversible analgesia following acute systemic and PAG administration, and tolerance following repeated systemic and PAG administration that was cross-tolerant with repeated systemic and PAG morphine [885]. Continuous infusion of the 5HT1A agonist,

F13640 with morphine enhanced the latter's analgesic effect after 1 week in a rat model of trigeminal neuropathic pain [284]. Lipoxygenase inhibitors prevent the development of chronic morphine-induced analgesic tolerance, whereas a leukotriene agonist augments formalin-induced pain [1131]. Intrathecal morphine analgesic tolerance was blocked by co-treatment with either an interleukin-1beta antagonist or an antibody against the fractalkine receptor. These co-treatments enhanced the ability of acute morphine to produce analgesia and reverse the development of hyperalgesia and allodynia induced by chronic intrathecal morphine [542]. Whereas chronic bupropion treatment delayed the development of morphine tolerance and blocked naloxone-precipitated morphine withdrawal, acute bupropion reduced morphine dependence, but not tolerance [547].

5.1.5. Other forms of opioid tolerance

Whereas chronic naltrexone infusions upregulated MOR density, and down-regulated the trafficking protein, dynamin-2, chronic etorphine infusions decreased immunoreactive MOR and increased dynamin-2 [1246]. Analgesic tolerance to the kappa agonist, U50488H was reduced in GIRK-3 KO mice, and U50488H produced increases in the labeling intensity of a KOR-P antibody that relates phosphorylation of serine 369 within KOR by GIRK-3 [748]. Tolerance to acetic acid-induced writhing as well as sedation was noted following the kappa agonists, U50488H, TRK-820 and ICI199441. Repeated treatment with U50488H, but not TRK-820 produced decreases in KOR number [1100]. Development of the hydromorphone- derived 4-chlorophenylpyridomorphinan-7h, produced mu agonist-delta antagonist in vivo and in vitro activity, and produced analgesia with no observable tolerance [32]. The NSAID, dipyrone which produces tolerance and cross-tolerance with morphine in the PAG has its analgesic effect blocked by CCK. The CCK antagonist, proglumide in the PAG prevented the development of dipyrone-induced tolerance and cross-tolerance with morphine as well as reinstating both morphine and dipyrone-induced analgesia in the PAG [1127].

5.2. Animal models in dependence and withdrawal responses

This section will be divided into the following subsections: (i) cellular effects, (ii) organismic effects (iii) opioid effects and (iv) peptide-transmitter effects on morphine dependence and withdrawal as well as (v) other forms of opioid dependence and withdrawal.

5.2.1. Cellular effects on morphine dependence and withdrawal responses

A review [147] demonstrates that hypothalamic oxytocin neurons robustly develop morphine tolerance and serve as a model to study the cellular mechanisms underlying morphine dependence and withdrawal excitation. Spontaneous morphine withdrawal mediates a persistent repression of genes involved in neural outgrowth and re-wiring [1069]. Morphine's ability to enhance guanosine 5′-*O*-(3-[(35)*S*]thio)triphosphate binding and adenylyl cyclase activity causes persistent changes in naloxone's and naltrexone's effects upon these responses such that these antagonists suppress these responses in morphine-treated and not naïve animals. The time course of inverse opiate antagonist effects was similar to the degree of antagonist-precipitated withdrawal actions [1185]. The increase in ERK in glial, but not neuronal cell lines by acute morphine was not observed following naloxone-precipitated morphine withdrawal [795]. Whereas chronic morphine decreased brain concentrations of pregnenolone, progesterone and pregnenolone sulfate, but not allopregnanolone, dihydroepiandrosterone and dihydroepiandosterone, naloxone-precipitated morphine withdrawal increased all of these steroid concentrations [1234]. Naloxone-precipitated morphine withdrawal increases c-fos in CRF-positive PVN neurons as well as in CRF-negative neurons in the central amygdala and BNST [439]. Naloxone-precipitated morphine withdrawal increases the number and degranulation of mast cells in the mouse thalamus [1108]. Naloxone-precipitated morphine withdrawal increased MOR density in male and female mouse striatum and male mouse cortex with the B(max) increased in male relative to female withdrawn mice. The GABA-B agonist re-established MOR by significantly decreasing B(max) in both sexes [285]. Local overexpression of the glial glutamate transporter, GLT-1 within the bilateral LC by recombinant adenoviruses before morphine treatment inhibited subsequent naloxone-precipitated morphine withdrawal [858]. Naloxone-precipitated morphine withdrawal increased NAC glutamate and aspartate for up to 48 h after the last opiate administration; NAC glutamate and aspartate increases persisted up to 96 h in morphine withdrawn rats [1009]. Naloxone-precipitated morphine withdrawal increases c-fos expression in cortex and thalamus, effects prevented by pairing morphine and the NMDA antagonist, dizocilpine, but not by dizocilpine alone. Naloxone-precipitated withdrawl-induced increases in c-fos expression in the central and medial amygdaloid nuclei, but not the NAC shell occurred 24 h following a single morphine exposure [536]. Naloxone-induced increases in cAMP in morphine-treated rat brain slices were reduced by adding morphine or the endogenous amine, agmatine. TH-induction by morphine in the LC was also reduced by agmatine [45]. This paired effect also prevented withdrawal-induced phosphorylation of Ca2+/calmodulin kinase II in the cortex, but not thalamus [438]. Transcranial magnetic stimulation increased DA concentrations in the NAC shell more in morphine-sensitized rats during abstinence than in control animals [317]. In addition to transient transcriptional activation of the Fos, Jun and Krox families, microarray studies identified transcriptional repressors as the cAMP response element modulator, IkappaB, silencer factor B, helix-loop-helix proteins or the glucocorticoid-induced leucine zipper in withdrawal in opioid-dependent animals [29]. Increased phosphorylated

CREB levels were observed in Neuro2a MOR neuroblastoma cells following acute and withdrawal-administered opioids with PKC responsible for transcription following acute administration and cAMP triggering the mechanisms during withdrawal [108]. Morphine dependence up-regulates Fas receptor aggregates and receptor homodimerization in rat brain [373]. Butorphanol dependence is associated with increased densities of p-Tyr protein spots in the rat frontal cortex [600].

5.2.2. *Organismic effects on morphine dependence and withdrawal responses*

A discrete population of GABA-A receptors in the VTA serves as a potential addiction switching mechanism by gating reward transmission through either a dopamine-independent (opiate-naïve) or a dopaminergic-dependent (opiate-dependent or opiate-withdrawn) system [645]. Rats undergoing naloxone-precipitated morphine withdrawal displayed marked deficits in lateral hypothalamic brain stimulation reward thresholds relative to naloxone alone, morphine alone or vehicle treatment [686]. Administration of naloxone after each morphine treatment increased the potency of naloxone to induced morphine-precipitated withdrawal responses 4–8 h, but not 22 h after administration [1001]. Intermittent morphine withdrawal paired with restraint stress produced decreased weight gain, food intake and caloric efficiency with short-term reductions in leptin, insulin and testosterone that were associated with and over-response of CRF mRNA [495]. Quantitative trait locus analyses of C57BL/6 and 129P3 F2 hybrids revealed that a 28cM-wide region of chromosome 1 accounted for 20% of the overall phenotypic variance for naloxone-precipitated withdrawal jumping responses, and that 43% of the variance could be accounted for loci on chromosomes 5 and 10 [579]. Somatic signs of naloxone-precipitated morphine withdrawal in water-deprived rats were markedly reduced by sucrose intake in a concentration-dependent manner [522]. Morphine-dependent rats display more marked and potent opioid antagonist-induced suppressions of lateral hypothalamic ICSS behavior than naïve control rats [307]. The most common adverse effects of naloxone-precipitated withdrawal during heroin overdose were gastrointestinal disorders, aggressivensess, tachycardia, shivering, sweating and tremor [155]. Cats decerebrated by a midbrain transection displayed all typical naloxone-precipitated withdrawal signs, suggesting brainstem mechanisms of opiate dependence and withdrawal [272].

5.2.3. *Opioid effects on morphine dependence and withdrawal responses*

A low dose of morphine elicited behavioral and thermal withdrawal symptoms in rats made dependent to higher morphine doses, and drug-onset cue-elicited withdrawal symptoms are not a sensitized response to the opiate but rather an associative phenomenon [742]. Both acute and chronic buprenorphine treatment blocked the behavioral signs of spontaneous morphine withdrawal in rat pups [1083]. Administration of chronic very low doses of naltrexone attenuates naltrexone-precipitated withdrawal in morphine-dependent rats as well as decreased levels of c-fos, PKA and p-CREB in the LC and NTS [720]. Acute opioid physical dependence can be elicited by acute morphine or hydromorphone treatment followed 2 or 6 h by naloxone in healthy volunteer subjects [232]. OFQ/N fragments of 1–11 and 1–6 attenuate naloxone-precipitated morphine-induced withdrawal signs [624].

5.2.4. *Peptide-transmitter effects on morphine dependence and withdrawal responses*

A review [806] indicates that mRNA of the glial glutamate transporter, GLT-1 is decreased in NAC and C/P of morphine-dependent rats. Whereas a glutmate transporter activator suppressed development of both morphine dependence and morphine-induced CPP, a glutamate transporter inhibitor facilitated naloxone-precipitated withdrawal and conditioned place aversion [806]. Another review [833] indicates that AS directed against the NMDA NR1 receptor blocks the development, expression and/or maintenance of opiate physical dependence in adult, but not neonatal animals. NMDA NR2 KO mice failed to show naloxone-precipitated abstinence that can be recovered by the rescue of NR2A protein by electroporation into the NAC.

Naltrexone-precipitated withdrawal and discriminative stimulus effects in morphine-dependent rhesus monkeys is attenuated by morphine, cocaine, amphetamine and imipramine, but not by drugs (ketamine and triazolam) lacking affinity for monoamine transporters [751]. Naloxone-precipitated morphine withdrawal responses and increased cAMP levels were reduced by the selective DA D4 receptor antagonist, L-745,870 administered prior to naloxone [718]. SP (1–7) administration into the VTA prior to naloxone-precipitated morphine withdrawal decreased D1 DA binding in the C/P, NAC, SN and medial GP, decreased D2 DA binding in the VTA, and increased D2 DA binding in the SN and frontal cortex [1291]. Alpha(2A)-adrenoreceptor KO mice displayed reductions in naloxone-precipitated morphine withdrawal with no changes in morphine analgesia or tolerance [859]. Naloxone-precipitated morphine withdrawal was significantly reduced by chronic treatment with the putative Enk-ase A inhibitor, HLDF-6 [680]. Although acute and chronic agmatine reduced all naloxone-precipitated withdrawal signs in morphine-dependent wild-type mice, it only blocked peripheral, but not central withdrawal signs in neuronal NOS-KO morphine-dependent mice [46]. KO mice lacking the GluR-epsilon1 NMDA receptor subunit displayed attenuations of naloxone-preceipitated morphine withdrawal, morphine analgesic tolerance and morphine-induced CPP [775]. Ionotropic NMDA and DNQX antagonism in the VTA significantly reduced naloxone-precipitated morphine withdrawal signs [1187]. Cotreatment with the dihydropyridine calcium channel blocker, nifedipine blocked spontaneous morphine withdrawal signs and blocked morphine-induced increases in neural NOS activ-

ity [1175]. The metabotropic Glu2/3 antagonist, LY341495 increased naloxone-precipitated behavioral withdrawal signs and activation of LC neurons in rats withdrawing from high (strong), but not low (mild) doses of morphine [921]. The metabotropic Glu5 receptor antagonist, MTEP inhibited naloxone-precipitated morphine withdrawal responses without affecting locomotor activity [864]. Naloxone-precipitated withdrawal was significantly reduced by intraperitoneal, ventricular or intracerebral administration of repeated ketamine into the NAC, but not amygdala [533]. Morphine-dependent animals receiving the hallucinogenic indole alkaloid, ibogaine, displayed decreases in local cerebral glucose utilization in the MPOA, nucleus of the diagonal band, NAC shell, inferior colliculus, LC and cerebellar flocculus [663]. Alpha-CGRP KO mice display decreases in both morphine and nicotine withdrawal signs [979]. CREB KO mice displayed marked attenuations in the behavioral and LC electrophysiological signs of morphine dependence, and displayed increased anxiogenic behaviors in stress paradigms [1154]. Adenosine 2A receptor KO mice show enhanced morphine withdrawal responses and increases in mu receptor-stimulated [35S]GTPgammaS binding in the NAC, but not overall changes in either mu or dopamine 2 receptor binding [60]. Lesions placed in the anterior cingulate gyrus attenuated behavioral responses induced by morphine dependence, but no changes in morphine analgesia or morphine tolerance [1092]. The neuroactive steroid, dehydroepiandrosterone prevented the development of both morphine dependence and tolerance through c-fos expression linked to ERK [934]. Magnesium cotreatment with morphine decreased the subsequent physical signs of naloxone-precipitated morphine withdrawal [822].

5.2.5. *Other forms of opioid dependence and withdrawal responses*

Withdrawal responses from U50488H and cocaine in Planaria were significantly attenuated by co-treatment with either D-glucose or 2-deoxy-D-glucose, but not L-glucose [1144].

6. Learning and memory

Learning and memory effects of endogenous opioid peptides, their receptors, their agonists and their antagonists, as well as genetically altered animals continue to be studied extensively. Recent developments will be reviewed for animal models in conditioned place preferences (CPP: Section 6.1), conditioned aversion paradigms (Section 6.2), drug discrimination and spatial learning (Section 6.3), as well as memory and amnesia (Section 6.4).

6.1. *Opiates and conditioned place preferences*

The following sections examine opioid CPP (Section 6.1.1), non-opioid effects upon opioid CPP (Section 6.1.2), and opioid effects upon non-opioid CPP (Section 6.1.3) respectively.

6.1.1. *Opioid CPP*

Prior morphine infusions followed by 10–30 days of morphine withdrawal enhanced the development of subsequent morphine-induced CPP; the infusions also decreased amphetamine-induced increases in NAC DA [464]. Brief electric shock enhanced morphine-induced CPP and motor activation, while producing a conditioned place aversion by itself [335]. In contrast, peripheral electrical stimulation at 2 or 100 Hz suppressed the expression and reinstatement of morphine-induced CPP, and increased PEnk (2 Hz) and PDYN (100 Hz) mRNA levels in the NAC [1016]. Morphine-induced CPP was observed in non-aggressive, but not highly-aggressive mice, whereas the latter group self-administered morphine at a higher rate [1164]. Morphine-induced CPP was more pronounced in rats with a high response to novelty or an open field relative to low responses for these measures [1290]. Ventricular endomorphin-1 and endomorphin-2 produced respective CPP and conditioned place aversions with the former blocked by mu antagonists and the latter blocked by mu and kappa antagonists [1220]. Endomorphin-1 and -2 produced respective CPP and conditioned place aversion following posterior NAC shell administration with both effects blocked by CTOP and the latter effect blocked by DYN antisera. Whereas endomorphin-1, but not endomorphin-2 produced CPP after VTA treatment, neither agonist altered place preferences following injection into the SN [1116]. Whereas buprenorphine-induced analgesia is eliminated in MOR KO mice, buprenorphine-induced CPP is attenuated as a function of the number of copies of wild-type genes that were reduced. The remaining buprenorphine-induced CPP is abolished by naloxone, but only partially blocked by delta (NTI) or kappa (NBNI) antagonists [511]. The ability of buprenorphine to produce CPP at high doses is dependent upon the interval used between drug and vehicle conditioning [1140]. Two ohmfentanyl stereoisomers, F9202 and F9204, like morphine, induced CPP and enhanced CREB phosphorylation and Ca2+/calmodulin-dependent protein kinase IV expression in the hippocampus [371]. OFQ/N blocked the acquisition of CPP induced by either morphine or cocaine, but weakly reduced the conditioned aversion induced by naloxone [976]. Compound B, an OFQ/N antagonist, produced a CPP at doses that increased mesolimbic DA release in wild type and ORL-1 KO mice [615]. TRK-820, a kappa agonist, suppressed the rewarding and discriminative stimulus effects of morphine and cocaine, and attenuated mecamylamine-precipitated nicotine withdrawal aversion [455]. A review [800] indicates the ability of OFQ/N to block the acquisition of CPP to rewarding drugs as well as self-administration of the same drugs without possessing hedonic properties itself.

6.1.2. *Non-opioid effects on opioid CPP*

The enhancements in morphine-induced CPP were blocked by DRN lesions or administration of the 5HT-1A

agonist, 8-OH-DPAT into the DRN [1210]. A single exposure to cocaine significantly enhanced morphine-induced CPP and U69593-induced conditioned place aversion with both effects blocked by NMDA antagonists placed in the VTA prior to cocaine [595]. The cannabinoid agonist, WIN55,212-2 enhanced morphine-induced CPP, an effect blocked by the cannibinoid antagonist, SR141716A [722]. Moreover, SR141716 blcoked the expression of morphine-induced CPP without affecting the locomotor sensitization induced by repeated morphine [1026]. The NOS inhibitor, 7-nitroindazole, produced conditioned place aversion by itself and blocked morphine-induced CPP without affecting activity or morphine-induced hyperactivity [723]. The development and expression of morphine-induced CPP occurred following VTA administration of NMDA (APV), AMPA (CNQX) or PKA (Rp-cAMPS) antagonists [449]. The GABA-A agonist (muscimol) and antagonist (bicuculline) administered into the basolateral amygdala respectively decreased and increased the acquisition of a morphine-induced CPP. Yet bicuculline, but not muscimol in the basolateral amygdala decreased the expression of a morphine-induced CPP [1262]. The calmodulin inhibitor, trifluoperazine suppressed the acquisition and expression of morphine-induced CPP, an effect unaltered by apomorphine, but suppressed further by verapamil [1242]. The phosphodiesterase Type IV inhibitor rolipram blocked the development of CPP induced by morphine or cocaine without affecting the expression of already-established CPP [1119]. The glutamate transporter inhibitor, DL-threo-beta-benzyloxyaspartate, facilitated the expression of morphine-induced CPP and the somatic signs of naloxone-precipitated morphine withdrawal without affecting morphine analgesia [1006]. The NMDA antagonist, memantine blocked morphine-induced CPP without producing place preferences or aversions by itself [940]. The mGlu(5) receptor antagonist, MPEP, attenuated morphine-induced, but not cocaine-induced CPP [473] by inhibiting up-regulation of the PKCgamma isoform in the murine limbic forebrain [41]. Whereas D3 DA receptor agonists (7-OH-DPAT, quinelorane, BP897) enhanced the development of morphine-induced CPP, the D3 DA receptor antagonist, PNU99194A impaired morphine-induced CPP while producing a CPP itself [359]. DA D3 receptor KO mice showed greater sensitivity to development of a morphine-induced CPP, the D3 partial agonist, BP897, impaired the expression of an already acquired morphine-induced CPP in heterozygous, but not homozygous DA D3 receptor KO mice [358]. Whereas alpha-1 (phenylephrine) and alpha-2 (clonidine) adrenoreceptor agonists decreased the expression of morphine CPP, alpha-1 (prazosin) and alpha-2 (yohimbine) adrenoreceptor antagonists increased the expression of morphine CPP [971]. Intrathecal administration of the PKC activator, PDBu abolished morphine-induced CPP without affecting morphine-induced hyperlocomotion or analgesia; concomitant administration of the PKC inhibitor, RO-32-0432 reinstated morphine-induced CPP [839]. Sciatic nerve ligation significantly attenuates morphine-induced CPP, an effect reversed by intrathecal RO-32-0432, a PKC inhibitor [814]. Sciatic nerve injury inhibited MOR-mediated G-protein activation onto GABAergic neurons and a reduction of ERK activity on DA VTA neurons. ERK cascade inhibitors suppressed morphine-induced CPP in normal mice [815]. Sciatic nerve injury affected both ERK and p38 in the VTA. However, the ERK inhibitors, PD98059 or U0126, but not the p38 inhibitor, SB203580 blocked morphine-induced CPP [857]. Inhibition of calcium/calmodulin-dependent protein kinase II attenuates morphine-induced CPP, but not morphine's analgesic or locomotor actions; morphine CPP increases this kinase's levels in the limbic forebrain, but not the cortex or lower midbrain [813]. Mice lacking either tissue plasminogen activator or plasminogen itself display attenuated morphine-induced CPP or hyperlocomotion that is accompanied by reduced morphine-induced DA release from the NAC [803].

6.1.3. Opioid effects on non-opioid CPP

MDMA produced CPP, increases in NAC DA and decreases in NAC homovanillic acid in both wild-type and MOR KO mice [944].

6.2. Opiates and conditioned aversion paradigms

Whereas Fisher 344 rat strains display greater morphine-induced conditioned taste aversions than the Lewis strain, the Lewis strain showed some greater aversive qualities to lithium chloride than the Fisher 344 strain [357]. Naloxone potently elicited place avoidance behavior 24 h after morphine administration, an effect attenuated by nicotine and apomorphine. The nicotine effect was reversed by mecamylamine, haloperidol, SCH23390, raclopride and eticlopride, but not hexamethonium, indicating nicotinic and dopaminergic interactions [44]. Naloxone facilitated acquisition of fear to contextual and auditory conditioned stimuli, and also blocked the ability of prior conditioning to a distinctive context to interfere with fear conditioning to an auditory stimulus [753]. Conditioned place aversions and physical signs induced by naloxone-precipitated morphine withdrawal were blocked by the naturally-occurring central substance, gamma-hydroxybutyric acid [715]. KO mice lacking the D1 or D2 DA receptor continued to display normal naloxone-induced conditioned place aversions [810]. Naloxone administered into the ventrolateral, but not dorsolateral PAG dose-dependently impaired development of extinction of Pavlovian fear conditioning [752]. Although morphine increased conditioned avoidance responses, its combination with the neuroleptics, haloperidol, sulpiride and risperidone impaired acquisition and performance of these responses [9]. Morphine was ineffective in altering the decreased pattern of responding induced by shock during 10 min punishment periods [1215]. Patterns of morphine-and cocaine-induced cFos within conditioned taste aversion-associated, but not reward-or locomotion-associated brain regions paralleled the differential behavioral sensitivities of Lewis and F344

rats to these drugs within conditioned taste aversion learning [405].

6.3. Opiates and drug discrimination and spatial learning

Morphine disrupted the production and discrimination of interresponse times in pigeons by flattening the distribution and reducing the accuracy of categorizing their accuracy, particularly at long intervals without producing overestimation of time [838]. In substitution tests in pigeons capable of discriminating among saline, morphine and nalbuphine, naltrexone and CTAP substituted for nalbuphine, fentanyl and etorphine substituted for morphine, and spiradoline and U50488H substituted for saline [1182]. In monkeys trained to discriminate heroin, morphine and M6G substituted in all cases, but 3-*O*-methylnaltrexone substituted for heroin in only half of them. In those positive monkeys, this effect was naltrexone-reversible and 3-*O*-methylnaltrexone enhanced heroin, morphine and M6G discriminative effects. In the negative monkeys, 3-*O*-methylnaltrexone antagonized the discriminative effects of heroin, morphine and M6G [899]. Monkeys trained to discriminate the kappa agonist, U69593 generalized to bremazocine to a greater degree than DYN or its analog, E-2078 with all kappa agonists producing enhanced prolactin release that was blocked by naloxone and its quartenary derivative [161]. Monkeys trained to discriminate to heroin generalized with oxycodone that also acted as an analgesic, rewarding stimulus and a suppressor of dependence signs [77]. Conditioned stimuli paired with heroin, cocaine or sucrose elicited lever pressing that was not due to an over-riding Pavlovian approach response to lever location with extinction occurring only when the CS-US association was devalued prior to and not after lever press acquisition [289]. Rats trained to discriminate tramadol from saline also displayed substitutions for morphine in a naloxone-sensitive manner; antidepressant drugs sensitive for serotonin, norepinephrine and/or dopamine reuptake were ineffective [344]. The two kappa agonists, U50488H and TRK-820 produced discriminative stimulus effects in which the former substituted for the latter, but the latter failed to substitute for the former. The kappa agonist, E-2078 substituted for both U50488H and TRK-820, whereas the kappa agonists, KT-90, CI-977 and ICI-199441 substituted for U50488H, but not TRK-820 [790]. Whereas low OFQ/N doses in the dorsal hippocampus improved spatial learning, higher doses in the same site impaired spatial learning with both effects blocked by ORL-1 receptor antagonism [983]. The ORL-1 agonist, Ro64-6198 produced a slow, but reliable discrimination in a two-choice food reinforced operant procedure that was blocked by the ORL-1 antagonist, J-113397, but not naloxone. Morphine poorly substituted for Ro64-6198, and kappa and delta agonists were ineffective. Animals trained for morphine discriminations were sensitive to naloxone, but not J-113397 antagonism, and Ro64-6198 substituted poorly in this condition [930]. Morphine-induced discriminative effects were respectively reduced and potentiated by central histamine H2 receptor antagonism and histamine precursor administration, but unaffected by either central H1 or peripheral H2 receptor antagonists [789]. The D2/3 antagonists, nafadotride and eticlopride attenuated the heroin-like discriminative effects of nalbuphine, heroin, methadone and morphine [237]. The D2/3 agonists, quinpirole, 7-OH-DPAT and quinelorane, attenuated the heroin-like discriminative stimulus effects of morphine, methadone and nalbuphine, whereas the first two agonists attenuated the discriminative effects of heroin itself [238]. Hippocampal CA3 microinjections of BFNA significantly impaired the acquisition of spatial learning only for those periods that it blocked mu receptors without affecting sensory or motor function [755]. Rats exposed to low level microwave radiation exposure took longer to complete a radial arm maze following naltrexone, but not naloxone methodide, indicating a central mechanism of action [229]. The hallucinagen, salvinorin-A, but not ketamine, produced generalization to the discriminative effects of the kappa agonist, U69,593 in rhesus monkeys, an effect blocked by the opioid antagonist, quadazocine, but not by the kappa antagonist, GNTI [162]. Rats with experimentally-induced colitis displayed attentional deficits, but no changes in locomotor activity, environmental interactions or memory encoding with the attentional deficit ameliorated by morphine [765]. Methadone-maintained human participants trained to discriminate naloxone from placebo displayed reductions in this task following cotreatment with either the Ca(2+)-channel blocker, isradipine or the NMDA antagonist, dextromethorphan [846].

6.4. Opiates and memory

Morphine-induced memory retrieval in a passive avoidance task was enhanced by glucose co-treatment, and impaired by insulin co-treatment [520]. Morphine's state-dependent effects of impairing memory of a passive avoidance task are naloxone-reversible. The K(ATP) blocker glibenclamide produced similar effects to morphine in a scopolamine-reversible manner and glibenclamide potentiated morphine's effects [1263,1264]. Whereas administration of D1 (SKF38393) or D2 (quinpirole) agonists decreased the amnesia induced by pre-training morphine on a passive avoidance task, administration of D1 (SCH23390) or D2 (sulpiride) antagonists increased this amnestic effect [1265]. Previous exposure to morphine decreases the apparent reinforcing effect of morphine or remifentanil in a runway procedure, whereas previous exposure to morphine or remifenitanil increases responding to saline [1181]. Morphine and/or the CB1 agonist, anandamide impaired memory consolidation of a one-trial inhibitory avoidance task immediately, but not 2 h after training, effects blocked by D1 and D2 DA agonists [245]. Morphine administered during training impaired passive avoidance during testing unless morphine or ethanol was administered before the test. These opiate and ethanol effects were blocked by naloxone, bicucucculine, atropine or meca-

muylamine [1149]. Repeated morphine or cocaine in a novel drug-cue environment decreased ICSS thresholds initially in the presence of the drug, and then in the absence of the drug; lesions placed in the basolateral complex of the amygdala abolished the ability of cocaine-associated cues to lower ICSS thresholds [461]. Spinally-transected rats learn to maintain a flexion response when they receive legshock in response to leg extension. Delivery of noncontingent shock disrupts this form of learning, and the acquisition and expression of this deficit is blocked by systemic and central naltrexone and kappa, but no mu or delta antagonism [548]. Immunodepletion of endogenous morphine decreased entry latency into the dark chamber during the retention session of a passive avoidance task [418]. Whereas naltrexone prevented memory impairment induced by pentylenetetrazol, it failed to alter the enhancements of retention of an inhibitory avoidance task induced by the anti-convulsant, gabapentin [115]. Naloxone improved Morris water maze performance in aged rats and prolonged the maintenance of LTP of EPSP's from Schaffer collaterals to the CA1 field of isolated hippocampal slices [1285]. The impairments in retention of an inhibitory avoidance task induced by acute restraint stress or dexamethasone were blocked by naloxone treatment [920]. Scopolamine-induced impairment of spontaneous alternation behavior was prevented by the kappa agonist, U50488H, an effect in turn blocked by AS probes directed against exons 2 or 3, but not 1 of the KOR gene [475]. Beta-amyloid-induced impairments of Y-maze behavior were blocked by pretreatment, but not post-treatment with U50488H that concurrently decreased pro-DYN mRNA and the alpha7-type nicotinic acetylcholine receptor [476]. Abstinent heroin addicts exhibited significant reduction in P300 amplitude during the anticipatory period of a short memory task in the central frontal region [866].

7. Eating and drinking

This section will review ingestive effects as functions of opioid agonists (Section 7.1), opioid antagonists (Section 7.2), and the interaction of POMC-derived peptides (Section 7.3).

7.1. Opioid agonists and ingestive behavior

A review [122] summarizes a 30-year historical perspective of the roles of endogenous opioids in feeding behavior. Another review [848] compares feeding elicited by OFQ/N with that of other opiate agonists, and suggests that OFQ/N may not only promote feeding initiation but rather inhibit signaling responsible for inhibition of consummatory behavior by influencing such inhibitory systems as oxytocin, AMSH and CRF. Chronic intermittent binging of a sucrose solution decreases PEnk, protachykinin and D2 mRNA levels more in the NAC than in the C/P with the former site showing identified cooperativity among these genes [1065]. Whereas DAMGO, muscimol or amphetamine administration into the NAC increased free feeding, they failed to alter acquisition of lever pressing for food in the manner observed for food deprivation [442]. DAMGO administered into the central nucleus of the amygdala produced feeding and mu opioid receptor internalization into the nucleus as well as selective c-fos activation of the NAC shell [664]. In turn, the ability of DAMGO administered into the NAC to robustly increase fat intake was blocked by inactivation of the basolateral or central nucleus of the amygdala with muscimol [1211]. A bi-directional mu opioid-opioid connection between the central nucleus of the amygdala and the NAC shell was established such that naltrexone pretreatment in one site reduced the ability of DAMGO to elicit feeding from the other site [591]. DAMGO administered into either the NAC shell or the VTA induced feeding that was significantly reduced when the D1 DA antagonist, SCH23390, but not the D2 DA antagonist, raclopride was administered into the other site, indicating regional interactions between opioids and DA in mediating opioid-induced feeding [708]. Both OFQ/N and a selective ORL-1 agonist, Ro 64-6198, reversed the anorectic effect of CRF in an ORL-1 antagonist-sensitive manner particularly in the BNST [220]. An injection of intralipid increased circulating triglyceride, but not glucose, insulin or leptin levels, and was accompanied by increased expression of Enk in the PVN, periformical and arcuate hypothalamic nuclei; similar increases were observed for galanin and orexin, but not for NPY or AGRP [193]. Methadone-treated opioid-addicted patients preferred sweet taste particularly early in the program, and mono-and di-saccharides provided far more than the 10% recommendation for energy [995].

7.2. Opioid antagonists and ingestive behavior

Food-restricted MOR KO mice displayed alterations in food-anticipatory activity as evidenced by equal amounts of running wheel activity before and after feeding rather than increased running wheel activity just before feeding time observed in restricted wild-type mice; these changes were not accompanied by any changes in arcuate BEND gene expression [568]. Whereas mu, kappa, but not delta receptor antagonists decrease food deprivation-induced feeding in rats, all three antagonists are effective in reducing deprivation-induced feeding in mice. AS probes directed against the KOR and DOR genes significantly reduced deprivation-induced feeding to the same degree as corresponding antagonists in mice, but AS probes directed against individual exons of MOR-1 and its splice variants produced significant, but modest effects, suggesting a role for multiple mu-mediated mechanisms [430]. Naltrexone failed to alter the acquisition or expression of a flavor preference conditioned by fructose despite producing dose-dependent reductions in fructose intake during training and testing [64]. Rats highly reactive to a novel environment display greater sensitivity to naltrexone-induced decreases in sweetened condensed milk intake and less sensitivity to morphine analgesia than low-reactivity rats [1205]. Increased saccharin consumption after

a saccharin deprivation period was inhibited by naltrexone and the NMDA antagonist, memantine, but not by naloxone or acamprosate [1260]. Either naloxone or a NPY antagonist augmented and potentiated the feeding suppressive effects of glucagons-like peptide or xenin-2 with combined antagonist treatment producing greater effects [1004]. Combinations of nalmefene and the cannabinoid CB-1 inverse agonist, AM251 decreased food intake in both lean and diet-induced obese mice [204]. Whereas muscimol-induced feeding elicited from the NAC shell was significantly reduced by mu, delta or kappa antagonists, muscimol-induced feeding elicited from the VTA was significantly enhanced by mu or delta antagonists and reduced by kappa antagonists. Whereas baclofen-induced feeding elicited from the NAC shell was significantly reduced by delta or kappa, but not mu antagonists, baclofen-induced feeding elicited from the VTA was significantly enhanced by mu or kappa, but not delta antagonists [580]. Feeding elicited by lateral hypothalamic administration of orexin-A was blocked by systemic and ventricular naltrexone as well as following NAC, but not lateral hypothalamic pretreatment [1101]. Exposure to 90 dB of white noise elevated the response function for food intake under a cyclic-ratio schedule of reinforcement in a naloxone-sensitive manner [841]. A patient with respiratory failure became intolerant to gastric feeding, an effect reversed by intragastric administration of naloxone [774].

7.3. POMC-derived peptides and ingestion

A review [699] examines transgenic mouse strains with expression of enhanced green fluorescent protein in POMC neurons together with KO strains with selective absence of BEND or all POMC peptides and discusses the hormonal, metabolic and transsynaptic signals that converge on the arucate hypothalamus and NTS to regulate POMC neuron activity. NPY hyperpolarizes POMC neurons through a Y1 receptor mechanism that is unaffected by the AMSH analogue, MTII. Ob/ob mice display an increased desensitization of NPY-induced currents in POMC neurons, whereas mu agonists failed to produce further desensitization [956].

8. Alcohol and drugs of abuse

The interaction between opiates and other drugs of abuse, particularly alcohol, continues to be a vigorous area of investigation. This section is organized into a consideration of how the opioid system works in the general area of drugs of abuse (Section 8.1), in opiate self-administration (Section 8.2) and in interactions with ethanol (Section 8.3), THC (Section 8.4), stimulants such as cocaine and amphetamine (Section 8.5) and other abused drug classes (Section 8.6).

8.1. Opiates and drugs of abuse: reviews

A review [827] summarizes the 30-years of research sponsored by the National Institute of Drug Abuse in characterizing animal models that replicate the key features of addiction and the brain areas responsible for addiction and dependence. A review [58] indicates that environmental context and prior drug history interact to modulate the effects of morphine, cocaine and amphetamine on behavior, gene expression and structural plasticity. A review [629] summarizes the role of the endogenous opioid peptide/receptor system in addictive states and their treatment as well as how the atypical responsivity to stress plays a role in vulnerability and relapse to specific addictive diseases. A review [855] summarizes the ability of opioid antagonists to reduce ethanol consumption and ethanol-induced DA release, the relationship of opioid activity in predicting ethanol-preferring and ethanol-nonpreferring rats as well as human alcoholism, and the ability of opiate antagonists to reduce alcohol consumption in relapsing alcoholics. A review [451] indicates that although naltrexone is widely covered on public and private health plan formularies, its use in alcohol dependence is restricted by quantity limits and prior authorization.

8.2. Opiates and self-administration studies

This section examines animal (Section 8.2.1) and human (Section 8.2.2) studies.

8.2.1. Animal studies

Heroin self-administration in rats produces an immediate (10 min) and sustained reduction in GABA dialysates and a delayed (1 h) increase in glutamate dialysates from the ventral GP [167]. Whereas acute heroin produced positive blood oxygen level-dependent signals in the prefrontal, cingulate and olfactory cortices and negative signals in the C/P, NAC, thalamus and hypothalamus, previous heroin self-administration attenuated the pattern in the prefrontal cortex, NAC and thalamus [1225]. Reinstatement of heroin-seeking behavior in heroin self-administrating rats was associated with attenuated blood-oxygen level-dependent responses in the prefrontal and parietal cortices, the hippocampus and the NAC [705]. Morphine self-administration was respectively increased and decreased by the NOS synthase inhibitor, L-NAME and the NO precursor, L-arginine. In turn L-arginine induced self-administration behavior that was blocked by L-NAME [972]. Morphine, cocaine, nicotine and THC increased ERK phosphorylation in NAC, lateral BNST, central amygdala and deep layers of the prefrontal cortex [1151]. Whereas a low dose of heroin enhanced cue responding for heroin reinstatement at an early stage of withdrawal, this low dose of heroin actually suppressed responding induced by contextual or conditioned cues after one month of withdrawal [1292]. Heroin administration to pregnant mice yielded offspring with upregulated hippocampal presynaptic Ach activity and Ach post-synaptic receptors [1162]. Prenatal heroin exposure in mice decreases hippocampal Ach-mediated behaviors, reducing PKC isoforms betaII and gamma, and decreasing desensitization to Ach receptor-induced activation. A similar pattern of effects was observed in chicks receiving heroin in

the eggs [1237]. Prenatal heroin exposure also disrupts Ach receptor-induced PKC translocation and activation acting through PKC-gamma and PKC-betaII, but not PKC-alpha sensitive mechanisms [1240]. Animals exposed neonatally to lead responded for heroin at significantly lower rates, and exhibited a decrease in progressive ratio responding for heroin as adults [945]. Methadone maintenance blocked heroin-induced and cocaine-induced reinstatement, but not stress-induced reinstatement of lever pressing following extinction [661]. Morphine self-administration increased amygdala gene expression of gamma PKC, upstream binding factor 2, lysozyme, noggin and heat shock protein 70 [948]. THC pre-exposure increased heroin self-administration behavior with shorter pauses between reinforcements and at short schedules of reinforcement. This potentiation did not extend to increased behavior on leaner progressive and fixed ratio schedules [1057]. Rats made tolerant to delta9-THC self-administered morphine to a similar extent to controls even though such animals were more sensitive to CB-1 antagonism [396]. The CB1 antagonist, SR141716A, suppressed heroin self-administration in opiate-dependent rats, but not in non-dependent animals [818]. NMDA NR1 receptor subunit-labeled dendrites in the NTS displayed fewer plasmalemmal gold particles and more intracellular gold particles in rats self-administering morphine than those self-administering saline [392]. Two gene transcripts that were down-regulated in the NAC shell after heroin self-administration are up-regulated in the NAC core independent of heroin response contingency [519].

8.2.2. *Human studies*

Naltrexone-treated patients (44%) showed significantly greater retention in treatment and less relapse over a 6-month period than placebo-treated patients receiving counseling (16%) [630]. Heroin-dependent patients showed a 34% history of attempted suicide, particularly female and residential rehabilitation entrants [269]. Injectable diamorphine was preferred over injectable methadone in young male British opiate-dependent patients, and were used to improve family relationships and avoid trouble with the police [1007]. Decreases in heroin purity correlated with declines in heroin-related ambulance callouts, increase in enrollment in methadone programs, reductions in robberies and burglaries, but little change in increased use of other illicit drugs in Australia [1045]. Emergency room patients in Maine treated for poisoning or overdoses accounted for 1.7% of all encounters with 0.2% treated with naloxone. Of the overdose patients, about 8% were treated with naloxome because of respiratory depression [17]. Heroin overdoses in young people were associated with high rates of feelings of hopelessness, depression, anti-social behavior, self-harm and diagnosed mental illness [159]. Users that smoked or inhaled heroin were typically younger, better-educated, more employed, had less criminal charges, and showed fewer signs of dependence or overdoses than users who injected heroin [268]. Heroin use in adolescent females was mostly through the inhalation method, but also subsequent heroin injection with introduction to injections by a male friend or boyfriend [308]. Heroin diffusion in New York State appears due to the purchase of cheaper heroin by irregular users in urban areas, and the selling of premium-priced heroin to mid-Hudson users who do not have access to cheaper heroin [365]. Methadone and heroin overdose deaths increased similarly through the 1990s in New York City [154]. A heroin drought in Australia increased the use of amphetamines and alcohol during that time period [63]. Heroin was prescribed most often for treatment of heavily opioid addicted individuals in Switzerland with doses markedly higher than those used in the United Kingdom [415]. Concordance between self-report of drug use and urine test results had an 85% concordance in India [521]. Although a majority of heroin addicts maintained their route of drug administration over a 1-year period, those who switched from injection to "chasing the dragon" showed improvements in other substance use behaviors [403]. Driver characteristics testing positive for heroin (32 years, 78%) were older and arrested more often for drunken-drugged driving than those testing positive for ecstacy (24 years, 47%) with common levels of multi-drug use in both groups [457]. Mention of opioid use and abuse accounted for only 2% of total drug mentions during the period from 1997 to 2002, but the mention of fentanyl, morphine and oxcodone increased by 161–267% during this period [834]. Opioid analgesics, including oxycodone, fentanyl, hydromorphone and meperidine accounted for almost 10% of all drug abuse in 2002, up from about 6% in 1997 [388]. Patient characteristics for development of dependence on hydrocodone and oxycodone are described [767]. The vitreous humor appeared to be a better predictor than femoral blood and cerebrospinal fluid for the detection of 6-monoacetylmorphine in deceased individuals [1224]. Codeine intoxication in a patient appeared to be due to ultrarapid CYP2D6 metabolism which bioactivates codeine into morphine [378]. Slow-release oral morphine transition from methadone was associated with improved social functioning, weight loss, fewer side effects and less craving, and an enhanced feeling of normalcy [773]. The anti-epileptic agent, gabapentin reduced reliance on symptomatic medication and an overall beneficial effect of heroin withdrawal [734]. Opiate-dependent patients receiving naltrexone implants displayed marked individual and intra-individual variations in naltrexone concentrations [847]. Thirty percent of a naltrexone-treated group was retained in treatment in an Australian naltrexone maintenance program for heroin dependence [1137]; the presence or absence of counseling did not change the rate [1136]. Low-dose naltrexone treatment produced no discernible advantage in treatment of heroin dependence, and patients preferred a 50 mg relative to 0.05–0.5 mg doses [929]. Buprenorphine maintainance is as effective as methadone maintainance in retaining patients in substance abuse treatment, and sublingual buprenorphine is more effective than clonidine and/or naltrexone in short-term opioid detoxification [1082]. Sublingual buprenorphine reduced urine morphine levels in opiate-dependent individu-

als [784], and depot buprenorphine provided effective relief from opioid withdrawal with no need for additional medication [1052]. A combination of buprenorphine and naloxone (Suboxone) was as effective as buprenorphine itself in promoting abstinence from heroin [83]. Buprenorphine-naloxone combinations in opioid-dependent volunteers was effective in relapse without affecting psychomotor speed, time perception, conceptual flexibility, focused attention and memory tasks [770]. The LEEDS project will compare the open use of buprenorphine with dihydrocodeine for illicit opiate detoxification in UK primary care facilities [845]. Buprenorphine is more bioavailable in the solution relative to the tablet form [1086]. Unlike morphine and lorazepam, propoxyphene failed to elicit reliable subjective effects in non-drug taking volunteers, and did not impair psychomotor or cognitive performance [1257]. Rapid opiate detoxification with naltrexone produces gabapentin-reversed post-inhibitory somatosensory evoked potentials, increases in nociceptive afferent volleys, and decreased nociceptive thresholds associated with back pain, limb thrashing and a restless-leg syndrome [361]. Rapid opiate detoxification with naltrexone also produces a higher than expected incidence of delirium [394]. Serious adverse events appear to occur more frequently and with shorter latency in heroin and methadone users who leave treatment with naltrexone than those who leave treatment with opiate agonists [292]. Blood naltrexone and 6-beta-naltrexol levels can be maintained above therapeutic levels following sequential 3.4 g naltrexone implants in recovering heroin addicts [504]; this was superior to a 1.7 g naltrexone implant [505]. Electroencephalographic spectral power analyses recorded frequency shifts in the alpha2 range in frontal and central areas related to duration of daily heroin consumption and slowing of alpha1 frequency related to heroin doses consumed [901]. Subjects who died of an opiate overdose displayed down-regulation of brain mu-opioid receptors but also GRK 2/6 and beta-arrestin-2 proteins [341]. The prefrontal cortex of human heroin addicts also displayed pronounced down-regulation of the MAPK cascade including MEK and ERK1/2 phosphorylation [340]. Oxycontin in combination with other centrally-acting drugs is more toxic than oxycontin alone as measured by lower oxycontin blood levels in drug-induced fatalities [234]. Substance abuse usage among Iranian nursing students showed increased prevalence of opium and tobacco use in males than in females with pleasure, habit and need as the major reasons [11]. Young heroin users before a fatal overdose accessed medical services six times more frequently than the general population and over half of the prescribed drugs were prone to misuse [736]. A combination of buprenorphine and naloxone was successful in detoxification of 68% of intravenous heroin users by community treatment providers in the NIDA Clinical Trials Network field experience [26]. Morphine and cocaine are more concentrated in toenails than in hair in autopsies of drug abusers [224]. The mu receptor mRNA levels of three drug-induced fatalities were 10,000% higher than measured housekeeping gene levels in the thalamus [79]. The use of buprenorphine for heroin detoxification appears equally cost-effective in clinic and shared care facilities [299]. Critically-ill children maintained on opiate medications over four days display significant withdrawal symptoms even with the use of a standardized assessment tool and a tapering management protocol [360].

8.3. Opiates and ethanol

This section examines animal studies (Section 8.3.1), ethanol-induced changes in opioid systems (Section 8.3.2) and human (Section 8.3.3) studies.

8.3.1. Animal behavioral models

Deprivation initially increased ethanol intake in high ethanol-preferring rats, an effect respectively enhanced and reduced by morphine or naltrexone pretreatment [793]. Although naltrexone reduced ethanol intake in both Alko alcohol-accepting and alcohol-preferring rat lines, it reduced ethanol's palatability on the taste reactivity test in the former, but not latter strain [240]. Nalmefene microinjections into the NAC and to a lesser degree the VTA potently and selectively reduced operant responding for alcohol relative to saccharin; the same injections in the hippocampus non-selectively reduced both reinforcers [549]. Alcohol intake in alcohol-preferring rats was potentiated by morphine and the CB-1 agonist, WIN55,212-2 with the latter effects blocked by the GABA-B antagonist, baclofen [230]. Mice lacking expression of BEND, Enk or both peptides learned to self-administer ethanol and maintain responding for ethanol similar to wild-type mice, indicating that endogenous MOR agonists are not necessary to shape or perpetuate ethanol-induced responding [462]. The catalase inhibitor, AT enhanced the corticosterone-induced increases by ethanol, but not by morphine or cocaine [870]. The social memory deficit caused by ethanol consumption in ethanol-preferring and non-preferring rats was unaffected by naltrexone, although naltrexone facilitated social memory in non-ethanol-treated animals [844]. Whereas acute naltrexone dose-dependently reduced ethanol-induced locomotion in mice, repeated naltrexone treatment transiently increased ethanol-induced locomotion [981]. Naloxone and the CB-1 antagonist, SR141716 had greater effects both alone and in combination in reducing the break points for responding of rats for beer than for near-beer [369]. Naltrexone decreased intravenous ethanol self-administration, whereas contingent or noncontingent ethanol attenuated naltrexone-induced increases in plasma ACTH [1213]. Naltrexone in the presence and absence of acamprosate significantly reduced alcohol intake in a murine limited access paradigm [598]. Both acute and chronic ethanol administration increased NAC DA, but not Ach; naloxone-precipitated withdrawal decreased NAC DA and increased NAC Ach [912]. Single and combined treatment with naltrexone and the 5HT-3 receptor antagonist, ICS205-930 potently suppressed ethanol intake [761]. Naltrexone and the GABA-B receptor antagonist, baclofen suppressed ethanol

intake to a greater degree than either drug alone [1088]. Both naltrexone and a mixed benzodiazepine agonist-antagonist, betaCCt reduced ethanol-induced behavior following injection into the central nucleus of the amygdala, but not the C/P [355]. Naltrexone modestly reduced a CPP for the cocaine metabolite, cocaethylene, without affecting its locomotor effects. Naltrexone failed to alter either CPP or locomotor activity induced by co-administration of cocaine and ethanol [968]. Reinstatement of ethanol-seeking behavior by both cue-induced and ethanol priming was inhibited by naltrexone and by antagonism of NMDA-glycine and AMPA-kainate receptors [57]. OFQ/N reduced alcohol self-administration, but not sucrose self-administration, and inhibited the reinstatement of extinguished ethanol responding under positive odor-light pairing conditions in alcohol-preferring rats [221]. Rat pups (Days 12–16) exposed to intoxicated siblings increased ethanol intake; expression, but not acquisition of this effect was blocked by general, mu and delta antagonism [435].

8.3.2. *Ethanol-induced changes in opioid systems*

Acute ethanol initially decreased [3H]DPDPE binding in the posterior C/P after 30 min, followed by increased binding in the SN, pars reticulata after 1 h, and increased binding in the frontal and prefrontal cortics, the core and shell of the NAC, and the anterior-medial and medial-posterior regions of the C/P after 2 h [757]. Ethanol consumption over 2 weeks abolished the circadian rhythm of POMC mRNA expression in BEND-containing arcuate neurons by altering rat period-1 and -2 mRNA in the arcuate nucleus [199]. Chronic ethanol also suppresses BEND-induced natural killer cytolitic activity as well as granzyme B and interferon-gamma actions [297]. Chronic alcohol consumption blocked the stimulatory effects upon [35S]-GTPgammaS binding by DAMGO and DPDPE in the hippocampal dentate gyrus, CA1 field and inferior colliculus [978]. Long-term (56 days) of ethanol ingestion decreased serum endomorphin-1, but not Menk levels, whereas AS probes directed against Menk decreased Menk levels in ethanol-treated rats yet increased endomorphin-1 levels [71]. In alcoholic subjects, increased craving correlated with lower mu-opioid receptor binding potentials in the right doro-lateral prefomtal cortex, the right anterior frontal cortex and the right parietal cortex [89].

8.3.3. *Human studies*

Individuals with the G allele of the A118G polymorphism of MOR reported higher subjective feelings of intoxication, stimulation, sedation and happiness to alcohol consumption than participants with the A allele, and also reported a higher incidence of family history of alcoholism [925]. Koreans having one or two copies of the A118G allele of the mu opioid receptor gene may possess an important genetic factor in the etiology of alcohol dependence and frequency of alcohol consumption [599]. However, Taiwanese Han alcoholic-dependent subjects failed to show any differences in 20 single nucleotide polymorphisms across the MOR, DOR and KOR genes relative to controls [693]. Combined treatment with acamprosate and naltrexone produced less alcohol relapse in clinical than pre-clinical studies with diarrhoea and nausea the most common side effects [585]; patients with acamprosate alone also showed improvement in the alcohol-related problems questionnaire [603]. Alcoholic subjects displayed similar drinking patterns when given immediate access to alcohol following naltrexone and placebo. In contrast, naltrexone-treated subjects consumed fewer drinks and had a slower progression of drinking when access to alcohol was delayed [38]. Naltrexone was of particular benefit to alcoholic entry drinker patients who began to drink during two weeks before commencement of medication [588]. Disulfiram was superior to naltrexone in preventing relapse among alcohol-dependent men with family support [276]. Cognitive behavior therapy was effective in improving self-reported health status and well-being in alcohol-dependent subjects with or without the adjunctive use of naltrexone [333]. Heavy drinking was associated with higher levels of positive or negative mood states with naltrexone attenuating the positive association between heavy drinking and both positive and negative mood [627]. Alcoholic subjects treated with a long-acting naltrexone depot had significantly fewer drinking days during treatment, greater abstinence and a longer latency to the first drinking day than placebo-treated subjects [628]. However, the opiate antagonist, nalmefene failed to differ from placebo treatment in the number of heavy drinking days, craving and concentrations of gamma-glutamyl-transferase and carbohydrate-deficient transferrin in alcohol-dependent individuals [39]. Naltrexone performed more poorly than placebo on craving and consumption measures in profoundly alcoholic subjects [270]. However, both naltrexone and nalmefene reduced craving and alcohol-induced stimulation in non-treatment seeking alcoholics and social drinkers [302].

8.4. *Opiates and THC*

The following sections review animal behavioral (Section 8.4.1) and anatomical, molecular and neurochemical (Section 8.4.2) studies.

8.4.1. *Animal behavioral studies*

A review [330] indicates that THC and opioids display functional crosstalk in the mutual modulation of addicitve and reward behaviors. THC produced CPP that was blocked by the CB-1 antagonist, SR141716A or naloxone [139]. THC increases BEND in the VTA, but not the NAC shell. Morphine and naloxone respectively potentiate and reduced THC-induced drug discrimination, and VTA, but not NAC BEND potentiates the discriminative effects of THC [1058]. THC enhances the analgesic potency of opioids through the mediation of delta and kappa receptors [222]. Wild-type, but not CB-1 KO mice decreased operant lever pressing following delta(9)-THC and the endocannabinoid analog, O-1812, effects blocked by the CB-1 antagonist, SR141716A.

Both wild-type and CB-1 KO mice displayed decreased lever pressing to the stable endocannainoid metabolite, methanandamide, and morphine and ethanol produced greater lever pressing decreases in the CB-1 KO relative to the wild-type mice [75]. The CB-1 antagonist, SR141716A blocked the expression, but not the induction of the behavioral sensitization effects of repeated morphine [1172]. The discriminative stimulus effects of THC were completely substituted with methanandamide, but not with morphine or phencyclidine [20]. The discriminative effects of the CB-1 agonist, BAY59-3074 blocked by the CB-1 antagonist, SR141716A, did not generalize to morphine [277]. Analgesia elicited by the CB-1 agonist, WIN55212-2 was unaffected by chronic morphine pellet or injection pretreatment [1245]. Naltrexone pretreatment repeatedly reduced self-administration for THC, but not for cocaine in monkeys trained on a FR-10 schedule with a 60 s timeout between injections [551]. Rats extinguished for THC self-administration display reinstatement of this response when administered the CB1 agonist, WIN55212-2 or heroin, but not cocaine. These effects were blocked by either SR141716A or naloxone [1066]. DREAM KO mice display potentiations in the aversive effects of THC, but fail to show changes in either cocaine or morphine reward, or naloxone or LiCl aversion [209]. The discriminative effects of the CB1 antagonist, SR-14716 in a taste aversion paradigm were completely substituted by its analogue, AM-251, but not by morphine or naloxone [524].

8.4.2. Anatomical, molecular and neurochemical studies

Repeated THC exposure in rats increased MOR density over 1–3 days in the C/P, NAC, amygdala, hippocampus, SN and VTA [243] that further supports the concept of crosstalk between cannabinoid and opioid systems [242]. Repeated exposure to WIN55212-2 during adolescence, but not adulthood produced cross-tolerance to morphine, cocaine and amphetamine even though WIN55212-2 treatment during adolescence or adulthood reduced midbrain DA responsiveness [898].

8.5. Opiates and stimulants

The following sections review animal behavioral (Section 8.5.1), anatomical, molecular and neurochemical (Section 8.5.2) and human (Section 8.5.3) studies.

8.5.1. Animal behavioral studies

The background strain of MOR KO mice interacted with their effects upon cocaine-induced sensitization. MOR KO mice maintained on a mixed 129S6*x*C57BL/6J background failed to display cocaine-induced locomotor activation or sensitization. In contrast MOR KO mice developed on a C57BL/6J background displayed aumentation of cocaine-induced sensitization and locomotor activation, an effect also observed in F1 hybrid 129S6*x*C57BL/6J wild type and KO mice [506]. The effect of heroin priming on reinstatement of cocaine seeking was time-dependent with higher responding occurring after 1–3 months than after 1 day [701]. Heroin engendered full or partial substitution for cocaine in a discrimination task in primates; this effect was enhanced by the dopamine transport inhibitor, GBR12909, but unaffected by noradrenergic transport inhibition, alpha1-adrenergic antagonism or SSRI treatment [961]. Chronic morphine treatment and subsequent immediate withdrawal failed to alter cocaine self-administration under a continuous reinforcement schedule, but markedly enhanced cocaine self-administration under a progressive ratio-5 schedule, including increased responding during initial extinction [463]. Bilateral NAC administration of BEND antibodies during the maintenance phase of cocaine self-administration increased the number of active and inactive lever responses, reminscent of behavior during extinction of cocaine self-administration [958]. Rhesus monkeys choosing between cocaine and food increased their cocaine responding following the kappa agonist, U50488H, an effect blocked by NBNI [823]. The kappa agonist, R84760 [1279] and DYN [1280] blocked cocaine-induced increases in striatal DA levels, cocaine-induced CPP and cocaine-induced locomotor activity in a NBNI-sensitive fashion. Striatal DYN is stimulated by D1 receptor activation and decreased by D3 receptor activation after repeated exposure to cocaine [1272]. Co-administration of heroin or ethanol with cocaine diminishes the development and occurrence of the retreat behaviors induced by cocaine alone in a runway task, suggesting that ethanol and opioids alleviate some of the negative side effects of cocaine [323]. Cocaine-induced locomotor activity was enhanced in DOR KO mice and reduced in MOR KO mice with the former producing smaller cocaine-induced increases in DA levels [197]. Further, MOR KO mice displayed reductions in cocaine-induced CPP, but enhanced sensitization of cocaine-induced locomotion [434]. The DA transporter blocker, PTT, reduced self-administration of cacaine alone and cocaine-heroin combinations while minimally affecting heroin self-administration [1031]. The ORL-1 antagonist, Compound B enhanced the progressive locomotor sensitization to methamphetamine during the early stages of the process [842]. Naltrexone attenuated reinstatement of methamphetamine drug-seeking behaviors when it was administered prior to re-exposure to methamphetamine-associated cues, but not when drug-seeking behaviors were reinstated with methamphetamine priming [37].

8.5.2. Anatomical, molecular and neurochemical studies

The NR1 sub-unit of the NMDA receptor that is expressed in 55% of DYN-positive striato-nigral and in 90% of Enk-positive striato-pallidal neurons was increased by amphetamine treatment in the DYN-expressing cells [690].

8.5.3. Human studies

Novel polymorphisms in intron 1 and the 5′-untranslated region of MOR were found in patients with methamphetamine dependence and psychosis, and that A118G of MOR shows a significant association with methamphetamine

abuse [510]. Vesicular Ach transporter activity was increased in the C/P, but not hippocampus of methamphetamine, but not in heroin or cocaine users [1022]. Naltrexone reduced subjective arousal, but not other behavioral and physiological signs induced by amphetamine in healthy volunteers [527]. A daily dose of 50 mg of naltrexone failed to reduce cocaine or alcohol use or interact with the form of therapy provided [996]. The mild kappa-like agonist, cyclazocine produced only modest effects upon the physiological, subjective and behavioral responses to cocaine in cocaine users [906].

8.6. Opiates and other drug abuse classes

Naltrexone inhibits alpha-7 nicotine acetylcholine receptors up-regulated by nicotine in hippocampal cultures [21]. Naloxone dose-dependently blocked an anticipatory food-seeking conditioned response developed during nicotine versus saline discrimination [863]. MOR KO mice fail to display locomotor sensitization induced by either chronic nicotine administration or reinstatement of nicotine behaviors in withdrawn animals [1252]. Naloxone-precipitated nicotine withdrawal and its conditioned aversive effects were blocked by acute THC [67]. Naltrexone decreased cigarette smoking by increasing sedative effects, increasing negative affect and decreasing positive affect after smoking [316]. Methadone-maintained tobacco smokers performed more poorly on a gambling task and had more treatment failures for heroin relapse than maethadone-maintained non-smokers [959]. Smokers carrying the mu opioid receptor Asp40 variant displayed greater abstinence, less mood disturbance and weight gain following smoking cessation especially when using transdermal nicotine patches [662]. The kappa agonist, cyclazocine, but not hydromorphone, decreased spontaneous smoking 5–8 h after drug administration in residential polydrug users [894].

9. Sexual activity and hormones, pregnancy, development and endocrinology

This section will examine developments in the last year relating the endogenous opioid system to sexual activity (Section 9.1), pregnancy (Section 9.2), development (Section 9.3), and general endocrinology (Section 9.4).

9.1. Sexual activity and hormones

Mating that included one ejaculation in male rats induced naloxone-sensitive increases in MOR immunoreactivity and receptor internalization in the MPOA within 0.5 h and lasted for 6 h to the same degree as DAMGO. Corresponding mating-induced increases in MPOA Fos expression was not blocked by naloxone [239]. Genital stimulation of male dogs produced semen ejaculation, penile erction and pelvic thrusting behavior that was biphasically altered by yohimbine, dose-dependently decreased by 8-OH-DPAT, but unaffected by naloxone [1250]. Copulation or exposure to sex-related environmental cues in male rats increased MOR internalization in the VTA and activated both dopaminergic and nondopaminergic neurons in the nucleus as well as the core and shell of the NAC [68]. Penile erections elicited by PVN administration of VGF(588–617) were reduced by morphine, muscimol and L-NAME, but not by the MK-801 inhibitor dizocilpine [1091]. Lordosis induced by estradiol benzoate priming of ovariectomized rats was inhibitied by MPOA administration of DPDPE, and reversed by NTI [1025]. An Enk analogue blocked estradiol-induced increases in hypothalamic Akt protein in a naloxone-reversible manner in ovariectomized rats. The Enk analogue decreased expression of the estrogen receptor-alpha and [3H]-estradiol binding in hypothalamus [1170]. Cocaine-induced increases in penile erections and ejaculations in paradoxical sleep-deprived rats were reduced by morphine and reinstated by naloxone [34]. BEND- and LHRH-immunoreactivity appears to be juxtaposed in the human MPOA and in the infindibulum-median eminence regions of the diencephalon [303]. BEND levels were lower in aged relative to control and ovariectomized female rats, an effect reversed by conjugated equine estrogen administration [383]. BEND expression increases in the corpus lutea and perivascular stroma of the ovaries of superovulated rats, and prolactin treatment produced greater immunostaining in the granulosa cells of antral follicles, corpus luteum and stroma [932]. Porcine basal androstenedione, testosterone and estradiol release were reduced by mu, delta and kappa agonists [562]. The inhibitory effects of testosterone on corticotrope responses to stress appear to be linked to decrements in plasma and pituitary corticosteroid-binding globulin, allowing greater access of corticosterone to its receptors and thereby enhancing glucocorticoid feeding regulation of ACTH and/or POMC processing [1171]. Naloxone increased LH concentrations and amplitude of LH pulses in mid-anestrous ewes that is not appreciably affected by melatonin [772]. Naloxone decreased the enhanced plasma prolactin levels observed in Klinefelter subjects, but did not alter the increased levels of follicle stimulating hormone or estradiol and the decreased testosterone levels noted in these subjects [1209]. Whereas kappa antagonists selectively inhibited LH secretion in the ewe MBH, kappa and mu antagonists increased LH pulse frequency in the MPOA. MBH GnRH neurons had close associations by DYN-and BEND-containing varicosities [401]. Bicuculline, but not naltrexone prevented anandamide-induced inhibition on NMDA-induced LHRH release. Fourth ventricular administration of the glucoprivic agent, 5-thioglucose inhibited plasma LH levels and colabeling of rostral GnRH neurons for c-fos, effects blocked by the mu antagonist, CTOP. CTOP also inhibited the glucoprivation-induced increases in c-fos activity in septal and MPOA sites [1028]. Anandamide increased GABA, but not BEND release from medial hypothalamic explants [338]. Central naloxone in male Japanese quail decreases appetitive responding during extinction test trials for sexual behavior [478]. The reduction of sexual behavior and

lowered testosterone concentrations in morphine-dependent male rats are recovered faster by electroacupuncture treatment during morphine withdrawal [256]. BEND administration to female rats at 3 weeks of age increased adult lordosis activity, and decreased serotonin and uterine estrogen receptor affinity [253]. A peptide Y1 NPY agonist inhibited estrogen + progesterone-induced lordosis in ovariectomized female rats, an effect blocked by the mu antagonist, CTOP. Estradiol or NPY internalizes MOR in the MPOA of ovariectomized rats that are blocked by a Y1R NPY antagonist [769]. Naloxone delayed and dampended the peak of the prolactin response to suckling, an effect accompanied by increased tyrosine hydroxylase in the arcuate nucleus [1270].

9.2. Pregnancy

Parturition increased oxytocin levels and decreased BEND and progesterone levels relative to late pregnancy. Whereas DAMGO and BEND increased prolactin secretion at the end of pregnancy, kappa (U50488H) or delta (DPDPE) agonists did not. The mu-1 antagonist, naloxonazine was more effective than NBNI in increasing mifepristone-induced prolactine release [1051]. Prolactin secretion noted at the end of pregnancy was increased by DAMGO and BEND that also increased related DA activity. This effect was potentiated by 5HT2 antagonism with ketanserin, prevented by SR95531, and was unaffected by phaclofen [1050]. The mu agonist, clocinnamox increased oxytocin and PVN and SON NE levels, whereas U50488H decreased oxytocin levels in parturient rats [635]. In investigating anesthetic preparations for the production of transgenic rats, it was found that an isoflurane-morphine combination increased the incidence of pregnancy relative to ketamine-xylazine combinations, and yielded comparable numbers of live births [1040]. Women in fear of labor displayed increased NE, but not ACTH or BEND levels before and during the cold-pressor test [973].

9.3. Development

Both MOR and DOR mRNA are detected in fetal (E16), neonatal (P6) and adult rat cerebellum in both the granular and Purkinje layers [797]. MOR KO mouse pups produced fewer ultrasonic vocalizations following maternal separation, but normal responses to cold or male mouse odors, and also fail to display a preference to maternal cues or produce ultrasonic calls after brief maternal exposure [781]. Whereas brainstem MOR expression was low in the late fetal and early postnatal period and increased in the juvenile and adult, brainstem DOR expression was high in the fetal and postnatal period, and decreased thereafter [604]. MOR mRNA in the brainstem in neonatal guinea pigs was unchanged by chronic intermittent morphine administered during fetal development [1044]. Cultured cells from rat brainstem indicate expression and co-expression of MOR and DOR with the former showing more intense immunoreactivity postnatally than in late fetal development [605]. Using [3H]DAMGO autoradiography, more MOR was detected on post-natal Days 7 and 14 relative to post-natal Day 30 [928]. Significantly more neonatal DRG neurons expressed functional MOR than in adults in large neurofilament positive sensory neurons, but not small nociceptive neurofilament-negative neurons. Correspondingly, morphine analgesia was higher in the neonate for mechanical stimulation, but not thermal stimulation [808]. Prenatal morphine respectively decreased and increased POMC mRNA in the arcuate nucleus in males and females, and respectively increased and decreased PEnk mRNA in the ventromedial hypothalamus. Ovariectomy and hormone replacement produced further differential effects in females [1035]. Prenatal morphine suppressed stress-induced ACTH, but not corticosterone levels in diestrus and proestrus females, attenuated the ability of dexamethasone to suppress stress-induced corticosterone levels [1036]. Morphine and naloxone exposure in neonatal piglets respectively increased and decreased endothelin-1 production and endothelin A, but not endothelin-B receptor mRNA expression in vascular endothelial cells [1158]. Although chronic morphine tolerance did not affect endothelin receptor affinity and density in the neonatal rat, it reduced endothelin's ability to stimulate [35S]GTPgammaS binding, and induced higher stimulation of G proteins by endothelin-A, but not endothelin-B antagonists [908]. Spontaneous and precipitated withdrawal from a single dose of morphine produced mechanical allodynia in 7-day and 21-day old rats, and produced thermal hyperalgesia in 7-day old rats [1102]. Whereas AMPA receptor antagonists and Group II MGluR agonists interfere with morphine withdrawal in rat pups at 7, 14 and 21 days of age, NMDA antagonists are ineffective at 7 days, partially effective at 14 days and fully effective at 21 days of age [1293]. PKC modulates the exaggerated spinal ventral root response and withdrawal-associated thermal hyperalgesia produced by morphine administration in 7-day old rats [1103]. Neonatal BEND increased adult rat nocistatin levels with females displaying greater CSF levels of nocistatin in both groups [1115]. Buprenorphine or methadone during gestation attenuated DAMGO, but not OFQ/N GTPgammaS binding in mesolimbic areas of the dam and male pups in a naloxone-sensitive fashion. Chicken eggs injected with heroin, nicotine or chlorpyrifos yielded subsequent deficits in imprinting behavior that were associated with deficits in cholinergic synaptic signaling involving the muscarinic receptor-mediated membrane translocation of PKC-gamma and in the basal levels of PKCgamma and PKCbetaII [516]. Buprenorphine stimulated OFQ/N-induced GTPgammaS binding in the NAC and lateral septum in males on P2 [494]. Although maternal separation for 4 h daily increases subsequent maternal behavior by the dams, it failed to change opioid peptide levels in male or female offspring [728]. Capsaicin treatment to rat pups produced hyperalgesia, forebrain mu opioid receptor uncoupling, and increased basal and forskolin-stimulated adenylyl cyclase activity that proved to be quite impervious to DAMGO treatment [687]. Although pre-emptive morphine infusions

did not reduce the frequency of severe intraventricular hemorrhage, periventricular leucomalacia or death in ventilated pre-term neonates, intermittent boluses of open-label morphine were associated with an increased rate of the composite outcome [31]. Lenk half-life induced by breast and formula feeding in infants correlated with temperament, but not psychomotor development [1055]. In neonatal abstinence syndrome of infants born to opiate-dependent mothers, morphine was more effective than phenobarbitone in shortening pharmacological treatment, requiring second line treatment or need for the special care baby unit [518]. M3G is the predominant metabolite of morphine in young (0–3 years) children with total body morphine clearance 80% of that of adult values [133].

9.4. Endocrinology

DAMGO and DPDPE, but not U69593 stimulated *N*-acetyltransferase activity and increased melatonin in bovine pinealocytes through the induction of adenylate cyclase [218]. In anestrus, ovariectomized estradiol-treated ewes, the caudal continuation of the arcuate nucleus contained DYN, tyrosine hydroxylase, estrogen receptor alpha, NOS and CART, whereas the premamillary nucleus contained only NOS and CART [1038]. The pattern and magnitude of naloxone-induced changes in endocrine function with prediction accuracy of 69–85% facilitates identification of sexually-active and sexually-inactive rams [1075]. Recombinant adeno-associated viral vectors encoding the human leptin-receptor gene decreased hypothalamic BEND, NPY levels and expression and increased LH levels in fatty Zucker rats [576].

10. Mental illness and mood

This section summarizes the few studies examining opioid involvement in mental illness (Section 10.1) and mood (Section 10.2).

10.1. Mental illness

A review [1015] examines the role of endogenous opioids in mediating placebo effects upon post-traumatic stress disorder, particularly the symptom clusters or re-experiencing of symptoms, avoidance and numbing, and physiological arousal. Another review [1104] indicates that naltrexone successfully reduced self-injurious behavior in 80% of people with mental retardation with males more likely to respond than females [1104]. The Pro-Enk gene located at 8q12.1 is one of a few genes that have been identified using a convergent approach in the etiology of bipolar (manic-depressive) and related disorders [840]. The allelic + G of the A118G polymorphism tended to be higher in patients with obsessive-compulsive disorder and tics than in controls [1147]. High-dose opioid treatment in a woman with terminal ovarian cancer produced delirium that was ameliorated by acetylcholinesterase inhibition with phystostigmine and then donepezil [1037]. Naltrexone augmented neuroleptic treatment in alcohol-abusing patients with schizophrenia [889] and augmented the GABA agonist, clonazepam in the treatment of tardive dyskinesia in schizophrenic patients [1217]. Naloxone at doses of 100–200 mg per day over four months decreased sexual fantasies and masturbation in a subset of adolescent sex offenders [967]. However, naloxone did not differ from placebo treatment in reducing symptoms during acute dissociative states in female patients with borderline personality disorder [892].

10.2. Mood

Morphine produced naloxone-reversible increases in the discounting of the value of delayed rewards, an animal model of impulsivity [586]. The delta agonist, BW373U86 at doses that produce antidepressant activity, increases BDNF mRNA expression in frontal piriform and olfactory cortices, amygdala and hippocampus in a NTI-sensitive manner [1126]. The ORL-1 antagonist, UFP-101 demonstrated anti-depressant properties by reducing immobility on the forced swim test, an effect blocked by OFQ/N. ORL-1 KO mice displayed far less immobility than wild-type mice [380]. The anti-depressant actions of venlafaxine on the forced swimming test in mice were blocked by naloxone, but not BFNA, naloxonazine, NTI or NBNI, suggesting a need for overall blockade of the opioid system for effectiveness [95]. Chronic desipramine and sertraline treatment both decreased mu-opioid binding in many brain areas, but only decreased functional coupling to G proteins in the amygdala [200]. Suicide victims displayed elevations in the expression of MOR, alpha-2 adrenoreceptors and both 5HT1A and 5HT2A receptors relative to matched controls [321].

11. Seizures and neurologic disorders

This section summarizes the research examining the role of the endogenous opioid system in the mediation of seizures (Section 11.1) and neurological disorders (Section 11.2).

11.1. Seizures

A review [1056] summarizes the modulatory role of DYN in hippocampal slices and its anti-ictal effects in animals and humans, suggesting the DYN dysregulation is involved in refractory encephalitic seizures. MOR KO mice display enhanced kindling development induced by pentylenetetrazol, an effect further enhanced by NTI treatment [408]. Analgesia produced by post-ictal electroconvulsive shock seizures was blocked by naloxone as well as V1 and V2 vasopressin antagonists [903]. Hippocampal penicillin-induced seizures were blocked by ventrciular OFQ/N, an effect reversed by an ORL-1 antagonist [334]. Prenatal morphine

exposure reversed the increased latency induced by naloxone to bicuculline-induced seizures. This treatment decreased PEnk mRNA and Menk in the hippocampal dentate gyrus, and correspondingly increased PDYN and DYN in hippocampal areas [993]. Bicuculline-induced seizures were reduced in adult rats receiving cholera toxin, and that were exposed prenatally to morphine or saline. Chronic saline injections prior to bicuculline reversed the seizure latency in morphine-exposed adult males, suggesting interactions with stress [994]. Diestrus females displayed a higher threshold for pentylenetetrazole-induced seizures relative to males and estrus females. Morphine produced anticonvulsant effects at all doses in males, at lower doses in estrous females, and at higher doses in diestrus females [938]. Naltrexone, but not NBNI reversed the anticonvulsive effects of the CB1 agonist, ACPA, whereas the CB1 antragonist, AM251 blocked the proconvulsive and anticonvulsant actions of high and low doses of morphine in pentylenetetrazole-treated mice [1011]. Intestinal inflammation induced by croton oil administration lowered the threshold of pentylenetetrazole-induced sezures, an effect blocked by chronic, but not acute naltrexone and unaffected by NOS manipulations [937]. Kainate-induced seizures in the hippocampus produced two-fold increases in OFQ/N for up to 3 h [42]. Kainic acid-induced seizures were enhanced by intra-hippocampal infusions of the mu opioid agonist, PL017 and inhibited by intra-hippocampal infusions of BFNA [682]. Low frequency stimulation during amygdala kindling increased mu receptor binding in the ipsilateral basolateral amygdala and thalamus and in the contralateral temporal cortex, but decreased binding in the ipsilateral frontal cortex [695]. The CCK antagonist, proglumide inhibited the anticonvulsant effects of morphine, opioid-mediated prolonged, intermittent footshock and opioid-mediated immobilization stress, while potentiating the analgesic effects of each manipulation [482]. Ultra-low doses of naltrexone potentiated the anticonvulsant effects of morphine by lowering the effective morphine dose, but not be increasing maximal anticonvulsant effects of higher morphine doses. As naltrexone doses increased, they then blocked morphine's anticonvulsant effect [484]. Both acute and chronic lithium chloride inhibited the respective anticonvulsant (1 mg/kg) and proconvulsant (30 mg/kg) actions of morphine in a pentylenetetrazole-induced clonic seizure model. Lithium's effect was potentiated by the NOS inhibitor, L-NAME and reversed by the NOS substrate, L-arginine [483]. Naltrexone and lithium respectively worsened and lessened cocaine-induced seizures [710]. Seizures produced by lithium chloride and pilocarpine combinations are reduced by exposure to a 10 min swim stress between the two drugs; this effect was reversed by yohimbine, but not by naloxone or mifepristone [367].

11.2. Neurological disorders

Intrathecal morphine, but not buprenorphine or pentazocine induces spasic paraparesis after a noninjurious interval of spinal cord ischemia [807]. Morphine reduced the dyskinesias induced by L-DOPA, D1 agonists and D2 agonists in MPTP-treated cymologous monkeys without affecting their anti-Parkinsonian efficacy [980]. Striatal MPTP treatment in primates resulted in increased Enk levels in the striaturm and external GP, but not the SN [97]. Ibotenate-induced lesions of intralaminar thalamic nuclei prevented the increased striatal Menk mRNA levels observed in rats receiving SN 6-OHDA without affecting striatal SP down-regulation [56]. Striatal pro-Enk mRNA levels were significantly elevated in 6-OHDA lesioned rats by repeated administration of L-DOPA, but not by the D2/D3 receptor agonist, ropinrole [923]. High-frequency stimulation of the sub-thalamic nucleus increased striatal Enk mRNA expression, an effect blocked by sub-thalamic nucleus excitotoxic lesions [55]. Haloperidol-induced catalepsy and increases in striatal enkephalin mRNA are abolished in mice with nerve growth factor inducible gene B deletions; striatal DYN mRNA is preserved [322]. Tremors induced by the anti-Ach esterase, diisopropylfluorophosphate were increased in MOR KO mice, and striatal Ach esterase activity was higher in MOR KO mice [1121]. Increased Ach esterase activity was noted in C/P and NAC, but not cortex or hippocampus of MOR KO mice. MOR KO mice displayed lower binding of nonselective and M2 muscarinic agonists in the C/P and NAC, but unchanged binding of M1 muscarinic agonists [1122]. DOR sensitive to BEND were found in higher densities in the fast extensor digitorium longus muscles and slow soleus muscles of dystrophic mice [324]. Mutant hamsters with dystonic symptoms display higher basal ventro-striatal pro-DYN and lower Pro-Enk in hippocampus and hypothalamus. Following stress, mutant hamsters with dystonia exhibit lower Pro-DYN levels in the limbic system and lower Pro-Enk levels in anterior and doral straitum and NAC [832].

However, 11C-diprenorphine binding failed to differ in patients carrying the DYT1 primary torsion dystonia gene and controls [1208]. Moreover, P-Enk mRNA was not changed in the striatum or NAC of mice with defective tetrahydrobiopterin biosynthesis, and an animal model of l-DOPA-responsive dystonia [1267]. Male and female Alzheimers patients show greater estrogen receptor alpha in nuclei than in cytoplasm in the infindibular nucleus of the hypothalamus which produce BEND that inhibits GnRH release [474]. Severely demented Alzheimer's patients have higher cortisol levels upon death than less demented Alzheimer's patients or controls; morphine treatment does not alter this cortisol rise [319]. Dysautonomic patients following traumatic brain injury are more likely to receive neurologically-active medications including morphine and midazolam with cessation resulting in increased heart and respiratory rates [59]. Naloxone failed to reduce levodopa-induced dyskinesia in Parkinson's patients [356]. Whereas early stages of Huntington's disease result in Enk, SP and GAD depletions in the striatal projection to the external GP, later stages of Huntington's disease show profound losses in all striatal projection systems [283]. Intrathecal administration of the delta agonist, SNC80 attenuates hindlimb motor dysfunction and neuronal

injury after spinal cord ischemia [491]. Intrathecal morphine infusions ameliorated spasticity in patients refractory to clinical treatment [949]. Both PKC and PKA activation augment lactate dehydrogenase in normoxic and hypoxic cortical neurons, whereas PKC, but not PKA inhibition decreased this activity in both normoxic and hypoxic cortical neurons. DOR inhibition reduced lactate dehydrogenase in mormoxic cortical neurons, but failed to affect hypoxic neurons [487]. Mu and kappa opioids suppress the hypoxic response of adrenal chromaffin cells through their action on SK channels and voltage-dependent Ca(2+) channels [575]. Patients with strokes display reduced opioid receptor binding using [11C]-diprenorphine PET-imaging independent of the lesion site [1214].

12. Electrical-related activity and neurophysiology

The following section will review neurophysiological effects described over the past year for mu (Section 12.1), delta and kappa (Section 12.2) as well as ORL-1 (Section 12.3) agonists and their receptors.

12.1. Mu agonists and receptors

A review [195] indicates that opioids can directly excite individual cells when opioid receptors interact with other G-protein coupled receptors, when different subtypes of opioid receptors interact, or when opioids transactivate other receptors such as receptor tyrosine kinases. Morphine inhibited the increase of free intracellular Ca2+ concentration evoked by depolarization of small neurons in adult dorsal root ganglion, effects blocked by L-, N-and P/Q-type voltage-dependent Ca2+ channel inhibitors and mu and delta, but not kappa antagonists [582]. Morphine-induced suppression of the Ca2+-dependent release of glutamate by exposing cerebro-cortical synaptosomes to the K+ channel blocker, 4-aminopyridine appeared to act through presynaptic mechanisms [1238]. Morphine-induced inhibition of the nocieptive flexor reflex in the rat toe was attributable to a preferential reduction of A-delta-mediated short-latency components relative to long-latency C-fiber-mediated components [601]. The apparent entropy of persistent discharge of lumbar dorsal horn wide dynamic range neurons following bee venom injection into the receptive field of a rat correlated strongly with the ability of morphine to depress the activity of individual neurons [1288]. Morphine produces rapid desensitization of LC MOR cells when PKC is also activated [62]. Dose–response and isobolographic analyses of MOR and alpha(2A)-adrenergic receptor agonist-induced hyperpolarization in individual LC neurons revealed an additive and not a synergistic interaction for this in vitro response [1085]. Endogenous morphine and codeine, detected in primates by gas chromatography–mass spectrometry, could be released by high potassium concentrations depolarizing neurons through a Ca2+ dependent mechanism [826]. DAMGO hyperpolarized tonic-firing substantia gelatinosa neurons through activation of G protein-coupled inward-rectifier K+ conductance without affecting adapting- or delayed-firing neurons [986]. DAMGO inhibits voltage-dependent Ca(2+) channels in rat spinal dorsal horn neurons, an effect dependent upon PKC-dependent phosphorylation [652]. DAMGO inhibited high voltage-activated calcium currents in DRG neurons in wild-type and MOR KO mice receiving virally-expressed MOR. However, desensitization was less in wild-type mice indicating that a higher density of receptor resulted in less desensitization [1183]. Moreover, DAMGO's inhibitory effects upon DRG neurons were more potent in isolectin B4-negative cells than in isolectin B4-positive cells, and acted upon the N-type and P/Q-type Ca2+ currents in these cells [1223]. DAMGO increased discharge activity in about half of LC neurons in a bicuculline-dependent fashion, and decreased discharge activity in the remainder. DAMGO decreased the frequency and amplitude of GABA-mediated miniature IPSCs in LC neurons without affecting glutamate-mediated miniature EPSCs [865]. Menk and DAMGO, but not DPDPE decreased the amplitude of raphe pallidus-evoked EPSCs, increased the amplitude ratio of pairs of these evoked EPSC's, while decreasing the frequency, but not the amplitude of miniature EPSC's in the hypoglossal motoneurones [132]. DAMGO increased the transient I(A) and sustained I(K) components of the K+ current components as well as hyperpolarized the membrane potential of trigeminal root ganglion neurons in a selective (CTOP) mu antagonist-sensitive manner [1111]. DAMGO reduced the frequency of bicuculline-sensitive miniature IPSCs in isolated PAG neurons, and effect reversed by *N*-ethylmaleimide, but not by cadmium, depletion of extracellular Ca(2+) or K+ channel blockade [432]. DAMGO decreased the amplitude of both EPSC's and IPSC's as well as the frequency of both miniature EPSC's and IPSC's in spinally-projecting RVM neurons [348]. Morphine and DAMGO, but not DADL or U69593 inhibited KCl-induced release of [3H]GABA from rat inferior colliculus slices [1125]. DAMGO was more effective than DPDPE or DYN in decreasing the amplitude of EPSC's and IPSC's as well as the frequency of miniature EPSC's and IPSC's in the mouse SON, effects blocked by naloxone and selective mu antagonism [485]. DAMGO potentiates spike frequency adaptation in lateral amygdala pyramidal neurons, effects blocked by G-protein inhibition with *N*-ethylmaleimide or by blocking phospholipase A(2) [325]. Mu agonists hyperpolarized a subset of central amygdala neurons through opening inwardly rectifying K+ channels that had no spike accommodation, whereas kappa agonists hyperpolarized central amygdala neurons that displayed a characteristic accommodating response [1297]. Morphine attenuated the long-latency, but not the short-latency component of laser-evoked potentials and ensemble neuronal activity in the tail region of the primary somatosensory cortex [1133]. Morphine-induced inhibition of medial prefrontal cortex neurons triggered both nociceptive specific neurons using their response as a sensory transduction code, and wide

dynamic range neurons using duration more than frequency in defining stimulus intensity [1274]. Although Menk and DAMGO failed to alter the amplitude of evoked IPSC's in the dorsal vagus motor nucleus, brief incubation the adenylate cyclase inhibitor forskolin, TRH or CCK facilitated Menk or DAMGO-induced inhibition that was blocked by mu-selective antagonism. NGF selectively attenuated fentanyl-mediated inhibition of voltage-activated Ba2+ currents in rats' sensory neurons through TrkA receptor activation [745]. The partial mu opioid agonist, buprenorphine depressed the baseline flexor reflex and reduced C-fiber conditioned stimulus-induced reflex facilitation at lower doses than morphine [626]. BFNA enhanced NMDA-evoked release of Ach in striosome-rich areas but not in the striatal matrix, effects more pronounced in the afternoon than in the morning. Alpha-methyl-para-tyrosine administration that interfered with DA transmission elicited similar NMDA-evoked release of Ach in the morning and the afternoon, whereas the BFNA-induced facilitation was suppressed. DAMGO failed to affect NMDA-evoked release of Ach, but abolished both DA-dependent and DA-independent responses of BFNA [517]. Forskolin-induced facilitations were in turn blocked by adenylate cyclase inhibition of PKA inhibition [150]. Morphine and DAMGO enhance ciliary beating in the marine mussel *M. edulis*, effects blocked by naloxone and NOS inhibitor, L-NAME [166]. Both endomorphin-1 and OFQ/N inhibited the electrically-evoked outflow of glutamate and GABA by 50 and 30%, respectively in primary cultures of rat cortical neurons with the former, but not the latter also inhibiting electrically-evoked Ca2+ influx [104]. The ability of CGRP8-37 to inhibit wide dynamic range neurons in the dorsal horn was attenuated by naloxone, BFNA and NBNI, but not by NTI [1236]. The ability of CCK to reduce morphine-induced analgesia elicited from the RVM appears due to CCK's ability to selectively activate RVM on-cells and produce behavioral hyperalgesia [466]. Like morphine, NPY acts through presynaptic Y2 receptors to attenuate EPSC's and through presynaptic Y1 receptors to attenuate glycinergic and GABAergic IPSC's in the rat substantia gelatinosa [786].

12.2. Delta and kappa agonists and receptors

Lenk inhibited Ca2+ channel currents in *X. oocytes* that were blocked by the nootropic agent, nefiracetam [1254]. DADL decreased the amplitude and the conduction velocity of the sciatic nerve of Rana ridibunda in a naloxone-dependent manner [170]. Lesions placed in the frontal cortex eliminated the ability of the delta agonist, DPDPE to enhance striatal glutamate and DA in dialysate, and to reduce [3H]-DPDPE binding by 18% in the striatum [112]. Menk decreased GABA post-synaptic currents in GnRH neurons in fed, but not fasted mice, whereas opioid receptor blockade increased this frequency in fasted, but not fed mice [1093]. Bovine adrenal medulla 22, a cleaved product of PEnk A decreased heat-induced and formalin-induced fos-like immunoreactivity in the dorsal horn laminae in a naloxone-reversible manner [1268]. The nonpeptide delta agonist, SNC80, but not DPDPE blocked Na+ current amplitude and increased slow inactivation processes in isolated rat hippocampal neurons, effects unaffected by naloxone or NTI treatment [933]. Mechanically-induced and spontaneous discharges following injury to the inferior alveolar or lingual nerves of the trigeminal complex are reduced by Enk and increased by SP, CGRP and vasoactive intesinal polypeptide [943]. The delta antagonists, NTI and naltriben reversibly inhibited 5HT-induced GIRK currents in the DRN that was unaffected by delta agonist administration [1019].

SON VP cells exhibiting spontaneous phasic activity had their firing rates elevated by the VP-1 receptor antagonist, OPC21268, while the kappa antagonist, NBNI produced an emerging excitation over the course of each burst [146]. Inhibition of high-voltage-activated Ca2+ currents in medium-to-small GP cells occurred following DAMGO, DYN and U50488H with the kappa responses blocked by the PKC inhibitor, cehlerythrine. Reserpine dramatically reduced kappa, but not mu-sensitive fractions in principal striatal cells [1064]. Changing the pH of the external solution affects the ability of DYN to inhibit NMDA receptor-mediated currents in *X. oocytes* with decreased pH enhancing inhibtion and increased pH blocking inhibiton [856]. Somatodendritic DYN release terminates phasic bursts by autocrine inhibition of plateau potentials in SON magnocellular neurosecretory cells in hypothalamic explants, an effect blocked by NBNI [145]. DYN appears to be the autocrine messenger in the ability of VP to discharge lengthy repeating bursts of action potentials in the SON following stress [955]. DYN suppresses GABA inputs, thereby disinhibiting tuberomammillary neurons. Whereas orexin A and B increased the frequency of GABAergic potentials, their combination with DYN produced the same effect as DYN alone [318].

12.3. ORL-1 agonists and receptors

A review [213] summarizes the neurophysiological activity in the ventrolateral PAG of several ORL-1 receptor ligands, including [Phe1-Psi(CH2-NH)Gly2]-OFQ/N(1-13)NH2, [Nphe1]-OFQ/N(1-13)NH2, J-113397 and NalBzOH. In tsA-201 cells, expression of N-type channels with huiman ORL-1 resulted in voltage-dependent G-protein inhibition of the channel that occurred in the absence of OFQ/N, the ORL-1 receptor agonist [80]. OFQ/N inhibited the spinal C-fiber evoked response, post-discharge, wind-up and input in neuropathic rats, but facilitated post-discharge and wind-up in sham-operated rats; neither effect was appreciably altered by CCK [714]. The inhibition of voltage-dependent Ca current in heterologous sensoty neurons by OFQ/N was blocked by *N*-ethylmaleimide and an ORL-1 antagonist, but not naloxone [1244]. OFQ/N also reduced in a naloxone-insensitive manner the spontaneous and stimulus-evoked activity in wide dynamic range neurons in neuropathic rats with chronic constriction injury, but not in sham or intact rats [1061]. OFQ/N infused into the

basolateral nucleus of the amygdala decreased both basal and systemic OFQ/N antagonist-induced increases in NE release from the same nucleus [572]. The ORL-1 agonist, Ro64-6198, activated GIRK in ventrolateral PAG neurons, though not to the same degree, potency or selectivity as OFQ/N [212].

13. General activity and locomotion

Contralateral turning behavior was induced by DAMGO and Delt, but not by DPDPE administered into the NAC shell and core, effects respectively reduced by CTOP and naltriben, and all blocked by combined D1/D2 DA antagonism. In turn, turning induced by combined D1/D2 DA agonists in the NAC shell was blocked by naltriben, but not CTOP [740]. Inbred mice showing high and normal wheel running each displayed longer tail-flick latencies at night, equal naloxone-induced reductions in daytime tail-flick latencies, and equal naltrexone-induced decreases in wheel running activity [666]. The ability of repeated morphine and fentanyl to induce locomotor sensitization occurred independent of intermittent administration and/or environmental specificity [1132]. Wheel running in spontaneously hypertensive rats increased hippocampal levels of Menk-Arg-Phe and a five-fold increase in newly-generated hippocampal cells, an effect reduced by naltrexone, but not NTI. Naltrexone and NTI decreased hippocampal proliferation in non-running rats [886]. Laparotomy in rats reduced ambulation rearing and sterotypy as well as reduced responding for sucrose. Single or combined administration of morphine and ketorolac reversed all but the surgery-induced rearing deficits [733]. The increased locomotor activity induced by morphine, cocaine and amphetamine in Roman high-avoidance relative to Roman low-avoidance rat strains was accompanied by greater basal DA and drug-induced DA release in the NAC shell relative to the NAC core in the Roman high-avoidance rat strain [647]. The psychomotor-sensitizing actions of morphine were enhanced by social crowding in rats that displayed higher motor activity in novel environments, but not in rats that showed low levels of novel activity [1227]. Animals with low reactivity to a novel environment displayed more robust and persistent context-specific increases in morphine-induced locomotor sensitization than animals with high reactivity to a novel environment even though the latter group displayed greater locomotor increases following acute morphine [556]. A buprenorphine analogue, thenorphine, inhibited the development of behavioral locomotor sensitization to repeated morphine and reduced acute morphine-induced hyperactivity [1287]. Morphine-induced increases in activity and body temperature were inhibited by the CB1 antagonist, SR141716. Moreover morphine-induced increases in c-fos in the C/P, cortex, NAC, lateral spectrum, MPOA, PVN and dorsomedial hypothalamus, paraventricular thalamus, amygdala, VTA and Edinger-Westphal nuclei were also inhibited by SR 141716 [1027]. Morphine-induced locomotor sensitization was blocked by the 5HT2A antagonist, SR46349B in alpha-1 beta-adrenergic receptor KO mice, and by SR46349B and prazocin in wild-type mice. DA release in the ventral striatum by morphine was blocked by prazocin in both wild-type and alpha-1 beta-adrenergic receptor KO mice [50]. Morphine-induced motor stimulation and sensitization following chronic morphine treatment was blocked by intra-VTA administration of the GABA-B agonist, baclofen, an effect reversed by GABA-B antagonism. This sensitization was accompanied by increased c-fos in the NAC shell, but not core, and effect blocked by VTA baclofen [657]. The induction, but not the expression of morphine-induced motor sensitization was dose-dependently inhibited by the GABA transaminase inhibitor, valproate [667]. Whereas carbamazepine failed to alter the induction or expression of morphine-induced motor sensitization, it dose-dependently potentiated the transfer of morphine-induced sensitization [668]. Both the locomotor and CPP effects of morphine were sensitized in mice previously exposed to nicotine; these cross-sensitization effects were attenuated by L-type voltage-dependent Ca(2+)-channel antagonists [103]. Whereas low doses of morphine and psychstimulants (cocaine, methamphetamine) increase locomotion in synergistic fashion, higher doses act in an additive fashion [787]. Behavioral locomotor sensitization to repeated intermittent morphine is accompanied by a blunted ACTH response after drug injection [531]. Morphine-induced hyperlocomotion and reward were each enhanced by prenatal and perinatal exposure to the environmental endocrine dirupter, bisphenol-A [778]. Morphine-induced increases in locomotor activity in the snail were blocked by specific pulsed magnetic fields [1021].

OFQ/N and the ORL-1 antagonist, UFP-101administered into the SN, pars reticulata respectively impaired and enhanced rotorod performance, respectively relaxed and contracted triceps muscle tone, and respectively reduced and stimulated striatal DA release [730]. UFP-101 in the SN reduced haloperidol-induced akinesia and stabilized the haloperidol-induced increases in nigral glutamate release [729]. OFQ/N suppressed locomotion and NAC DA release in wild-type but not ORL-1 KO mice, effects blocked by the ORL-1 antagonist, UFP-101. In turn, UFP-101 alone suppressed locomotion and NAC DA in both genotypes [614]. Suppression of motor activity was most pronounced following OFQ/N administration into the VTA, to a lesser degree in the NAC, but failed to occur following SN or CP administration; these effects were reduced by J-113397 [809]. OFQ/N produced biphasic increases (high doses) and decreases (low doses) in locomotor activity which was blocked by both peptide and synthetic ORL-1 antagonists and NalBzOH, but not naloxone. The ORL-1 agonist, Ro 64–6198 monophasically inhibited locomotor activity which was reversed by a peptide ORL-1 antagonist and NalBzOH [636]. Repeated naloxone blocked the acquisition, but not the expression of increased wheel running in dopamine D2L KO mice [1160]. The ability of liposaccharide to increase

locomotor activity and alter nigrostriatal catecholamine levels was blocked by post-treatment but not by pretreatment with a combination of naloxone and indomethacin [1191]. Whereas ginsenoside Re increased morphine-induced hyperactivity, but not morphine-induced CPP, ginsenosides Rd, Rb2 and Rgl antagonized morphine-induced CPP without affecting morphine-induced hyperactivity [423]. Administration of pituitary adenylate cyclase activating polypeptide 38 produced naloxone-sensitive short-term (0.5 h) increases and longer-term (3–6 h) decreases in locomotion and rearing [4]. Muscimol markedly increased locomotor activity in mice lacking dopamine D2 receptors that was associated with striatal Enk gene expression [30].

14. Gastrointestinal, renal and hepatic functions

The following section will review opioid effects described over the past year for gastric function (Section 14.1), intestinal function (Section 14.2), nausea and emesis (Section 14.3), hepatic function (Section 14.4), glucose function (Section 14.5) and renal function (Section 14.6).

14.1. Gastric function

A review [1218] summarizes opiate inhibition upon gastric emptying, intestinal transit, intestinal secretion of water and electrolytes, and suppression bile transport into the duodenum in terms of the overall function of the enteric nervous system. MOR in the guinea pig is confined to the muscle and dep muscle plexus of the myenteric plexus mostly in the small intestine, stomach and proximal colon respectively. In human gut, MOR and DOR are found in myenteric and submucossal neurons, whereas KOR is confined to the myenteric plexus [1080]. Morphine-induced inhibition of GI transit and gastric emptying was observed using fluorescent polysterene microbeads and flow cytometry rather than radiolabeled markers [512]. Morphine stimulates cNO in the mouse stomach, small intestine and large intestine, effects reversed by naloxone and L-NAME [1073]. Intrathecal diamorphine delayed gastric emptying that occurs immediately following elective spinal Caesarean section [602]. Central OFQ/N delayed gastric emptying, inhibited GI transit, and delayed expulsion in an OFQ/N antagonist-sensitive, but naloxone-insensitive manner. However, the decreases in gastric secretion by OFQ/N were blocked by naloxone [144]. Ingestion of placenta blocked the inhibition of GI transit induced by central, but not systemic morphine [244]. Decreased weight gain induced by experimental stress was blocked by the arginine-containing mu and delta opioid agonist, sedatin, presumably by increasing DNA synthesis in the epithelium of the gastric fundus [351]. An imidazole, Compound 4a, with good binding affinities for the DOR and MOR reduced GI propulsive motility, but failed to produce analgesia [142].

14.2. Intestinal function

A review [481] examines the ability of peripherally-acting opioid antagonists (*N*-methylnaltrexone, alvimopan) to normalize opioid-induced bowel dysfunction without compromising central opioid analgesia. A review [410] indicates that central (naloxone) and peripheral (alvimopan, methylnaltrexone) reverse morphine-induced GI transit in mice and can produce viscero-motor hypersensitivity in the absence of opioids, suggesting a constitutive function. In contrast, naltrexone, but not alvimopan fails to hypersensitivity to the visceromotor response induced by colorectal distension. In vitro modeling indicates that the prokinetic activity of naloxone is apparent where peristalsis is compromised by drug-induced suppression of motor nerve activity or by modulation of endogenous processes using receptor antagonists or inappropriate intraluminal distension [984]. Morphine decreased gastric contractions during pressure-controlled and volume-controlled gastric distensions, but decreased the rate of lower oesophageal sphincter relaxations during only pressure-controlled distensions [881]. Antral activity is inhibited by DAMGO, but not by DADL or U50488H; this inhibitory effect was reversed by either guanethidine or propranolol [1134]. Laporectomy in the presence and absence of intestinal manipulation increased MOR endocytosis in cholinergic and nitergic neurons that parallelled the manipulation's delay of GI transit [873]. Heroin decreased both basal and vagal-electrically stimulated acid and pepsin secretions in intact, but not vagotomized animals [915]. DAMGO stimulated whole nerve mesenteric afferent discharge that was blocked by alvimopan. Alvimopan also attenuated the low-threshold, but not high threshold response in chronically vagotomized animals [414]. Diprenorphine binds to a single high-affinity site in myenteric neural membranes that is displaced by naloxone. Delta and kappa antagonists displace diprenorphine from two distinct sites, whereas DPDPE, SNC-80 and U69593 display diprenorphine from three distinct myenteric sites [1129]. The putative kappa agonist, asimadoline decreased short-circuited currents in the colon epithelium and trachea airways in a concentration-dependent manner that was insensitive to either naloxone or NBNI [998]. Inhibition of GI transit by either peptide YY or serotonin was blocked by naloxone administered into the proximal, but not the distal gut [677]. Bile-duct-ligated animals displayed naltrexone-reversible decreases in GI trnasit relative to controls, and failed to display morphine-induced slowing of GI transit [385]. Electrically-stimulated contractions of strips of the rat cathartic colon were respectively inhibited by mu and kappa agonists and stimulated by mu antagonists [681]. The inhibitory action of ginger on rat ileal motility as produced by Ach or electrical stimulation was blocked by naloxone as well as alpha-2 adrenergic, CB-1, or NOS antagonism [130]. Transdermal fentanyl had lower incidences of constipation in patients treated for chronic pain than oxycodone or morphine [1072]. Intravenous pentoxifylline increased recovery of bowel function in patients undergoing colorectal cancer

surgery, and reduced morphine consumption and the perioperative cytokine response [700]. The use of peripherally-acting opioid antagonists and opioid rotation are the most effective treatments in managing opioid-induced bowel dysfunction in cancer patients [1112].

14.3. Nausea and emesis

Methylnaltrexone and ondansetron each decreased kaolin consumption in a rodent model of emesis [51]. Dexamethasone at a dose of 8 mg was effective in reducing emetic episodes in surgical patients receiving patient-controlled morphine delivery [655]. Pretreatment, but not co-treatment or post-treatment of acepromazine prior to morphine significantly lowered vomiting in dogs [1153]. Morphine produced less nausea than meperidine in an emergency room population following parenteral administration [1023]. Haloperidol reduced the incidence of postoperative nausea and vomiting after spinal anesthesia and morphine in surgical patients [867].

14.4. Hepatic function

Morphine induced hepatic oxidative damage including 8-OHdG, protein carbonyl group and malondialdehyde, effects reversed by the antioxidants, glutathione and ascorbic acid [1282]. Hepatitis induced by agonisitc anti-Fas antibodies was reduced and survival time was increased by prior or simultaneous naltrexone or naloxone methiodide treatment. Morphine treatment enhanced anti-Fas antibody-induced mortality [525]. Mice with a sickle cell transgene KO displayed higher morphine and M3G formation in liver microsomes [805]. Naltrexone does not appear to produce clinically significant liver disease or exacerbates serious pre-existing liver disease in the treatment of heroin and alcohol abuse [143]. In liver transplant patients, those on methadone maintenance required more intraoperative analgesia and postoperative opioids, had greater hepatitis virus infection and lower survival [1200]. Plasma OFQ/N progressively elevates up to 17-fold during the development of hepatocellular carcinoma [493]. DPDPE clearance did not differ in livers of control and multi-drug resistance associated protein-deficient rats, but biliary excretion of DPDPE was lower in these deficient animals and lowered further by the P-gp inhibitor, GF120918 [477]. A 10-fold increase in plasma OFQ/N was noted in patients with hepatocellular carcinoma with smaller increases noted in patients with Wilson disease or primary biliary cirrhosis [1105]. Opioid growth factor resulted in resolution of liver metasteses and regression of a pancreatic tumor in cancer patients [1041].

14.5. Glucose function

BEND improves insulin resistance in fructose-fed rats [1090]. Cerulein-induced pancreatitis measured by increased serum amylase and spinal c-fos activation of T9 and T10 was reduced by buprenorphine administration [590]. Electroacupuncture-induced hypoglycemia is blocked by naloxone, but not in either MOR KO or adrenalectomized mice [678]. The isoflavone, puerarin, lowers blood glucose and increases plasma BEND in STZ-diabetic rats, effects blocked by the alpha-1 adrenergic antagonist, prazosin, the opioid antagonists, naloxone and naloxonazine, and in MOR KO mice [207]. Tetrandrine increased BEND immunoreactivity parallel to its glucose-lowering effects in STZ-diabetic rats with the lowered plasma glucose effect prevented by naloxone, naloxonazine, bilateral adrenalectomy and nicotinic receptor blockade, and absent in MOR KO mice [496]. Epidural analgesia with ropivacaine and morphine did not suppress catabolic responses to surgery as glucose administration decreased protein breakdown, protein synthesis and glucose production to the same degree as the control group [999]. Hyperinsulinemic post-menopausal women treated with naltrexone reduced fasting and stimulated the insulin response to a glucose load, and correspondingly improved hepatic extraction [255]. Remifentanil increased blood glucose in cardiac patients relative to fentanyl and morphine without showing differences in blood pressure, heart rate or cortisol measures [82]. Twenty-nine percent of young adults with Type I diabetes admitted to using street drugs with 68% taking them more than once a month and 72% unaware of the adverse effects on their diabetic symptoms [828].

14.6. Renal function

Morphine increased renal plasma, creatinine and urea clearance as well as urine potassium concentration [1098]. DAMGO, but not DPDPE or U69593 into the ventrolateral, but not lateral or dorsolateral PAG suppressed volume-evoked bladder contractions and increased arterial pressure [739]. An enkephalinamide analogue and mu receptor agonist, cUENK6, stimulated excretion of urine, sodium, potassium, cGMP and urinary atrial natriuretic peptide activity, effects blocked by naloxone, but not by the mu-1 antagonist, naloxonazine or the peripherally-acting antagonist, naloxone methiodide [428]. [Dmt]-DALDA increased urine volume and excretion and produced mild hypertension, effects fully reversed by naloxone, partially reversed by naloxone methiodide, and unaffected by either naloxonazine or L-NAME [429]. Low doses of U50488H to increase voiding efficiency without changing bladder capacity were effective in rats with spinal cord injury in a NBNI-sensitive manner [1249]. Administration of the kappa-2 agonist, GR-89,696, but not the kappa-1 agonist, U50488H decreased the number of bursts, but not the frequency during micturition in female rats in a naloxone-sensitive manner [416]. An ORL-1 receptor analogue, ZP120C induced aquaresis, the excretion of solute-free urine by indirectly inhibiting VP-2 receptor mediated stimulation in collecting duct water reabsorption in the kidney [431]. Intrathecal morphine and sufentanil each reduced bladder function by dose-dependently suppressing detrusor contractibility and decreasing sensation to urge [631].

Naltrexone plasma levels were not markedly affected by hemodialysis in patients with impaired renal function [559].

15. Cardiovascular responses

This section will review the work done in the last year on the role of opioids upon heart rate (Section 15.1), cardioprotection and ischemic preconditioning (Section 15.2) and blood pressure (Section 15.3).

15.1. Heart rate

Morphine produced greater hypotension and bradycardia in spontaneously hypertensive than in Wistar–Kyoto and Sprague–Dawley rats as well as enhanced Phase I and Phase II analgesic responses on the foramlin test [713]. Combined treatment with morphine and fentanyl decreased heart rate, diastolic and MAP and total peripheral resistance in dogs anesthetized with sevoflurane [804]. Morphine reduced isoflurane-induced minimal alveolar concentration to the same degree in the presence and absence of the COX-2 inhibitor, meloxicam [985]. The mu agonist, DAMGO increased MAP, HR and RSNA to a greater degree in obese animals maintained on a high-fat diet relative to controls, whereas the mu antagonist, BFNA produced greater decreases in these responses in obese high-fat diet rats. Normal, but not obese rats showed respective decreases and increases in MAP following the kappa agonist, DYN and the kappa antagonist, NBNI [74]. The kappa agonist, spiradoline inhibited glycinergic, but not GABA-ergic synaptic inputs to cardiac vagal neurons without altering voltage gated calcium currents in cardiac vagal neurons; the delta agonist, DPDPE was without effect on any of these measures [1192]. Kappa agonists were most effective in blocking dysrhythmia in which U50488H acted like the beta-blocker, propranolol, and was blocked by glibenclamide or chelerythrine, but not calcium channel blocker pretreatment [1152]. HR and blood pressure were decreased by administration of endomorphin-2 into the NTS, an effect blocked by naloxonazine as well as competitive and non-competitive NMDA antagonism [569]. Although fentanyl itself increased HR and blood flow in the ovine fetus, it did not alter the increased HR induced by cutaneous electrical stimulation [1043]. Acetic acid or formalin injection depresses HR and MAP, an effect prevented by either lidocaine or NTI pretreatment in the ventro-lateral, but not dorso-lateral PAG; mu and kappa antagonists were ineffective [182]. Naloxone caused concentration-dependent depressions of peak force, maximal rate of force development and rapid cooling contracture of guinea pig right ventricular papillary muscles [597]. Bile duct-ligated rats displayed lower HR and MAP, an effect reversed by chronic naloxone. Chronic naloxone failed to affect the resistance of these rats to epinephrine-induced arrhythmia [433]. Anandamide-induced relaxation was significantly potentiated in mesenteric vascular beds in bile duct-ligated rats, an effect blocked by L-NAME and aminoguanidine, and potentiated further by chronic naltrexone [779]. Administration of naloxone and peripherally-acting naloxone methiodide to morphine-tolerant rats increased c-Fos immunoreactivity in the left and right ventricles of cardiomyocyte nuclei, and the former, but not latter antagonist increased PVN Fos expression [398]. Naloxone-precipitated morphine withdrawal increases c-fos expression in cardiomyocyte nuclei in the right and left ventricles as well as increased NE turnover, effects blocked by alpha-2, but not alpha-1 or beta adrenergic antagonists [397]. Naloxone-precipitated morphine withdrawal also increased c-fos activity, tyrosine hydroxylase activity and NE turnover in the left and right ventricles [399]. In selegiline-treated dogs, butorphanol and medetomidine, but not oxymorphone decreased HR [294]. Intravenous BEND increased left ventricular ejection fraction and stroke volume, and reduced vascular resistance in patients with mild to moderate chronic heart failure [249]. Oxycodone in combination with enflurane anesthesia provided hemodynamic stability during and after coronary bypass grafting [905]. Adenosine infusions produced chest pain without hemodynamic changes in the presence and absence of naloxone and BEND in human volunteers [970]. Patients with cardiogenic pulmonary oedema suffer high in-hospital mortality, and patients treated with catecholamines, corticosteroids and/or morphine have a greater probability of mortality [349]. Dexmedetomidine administered during caridac surgery requiring mechanical ventilation reduced the necessity for rescue opiate analgesics, maintained HR and blood pressure, and produced effective sedation and analgesia [509]. Neither naloxone nor codeine altered HR, blood pressure or muscle sympathetic nerve activity during head-down rotation in either young or old subjects [924].

15.2. Cardioprotection and ischemic preconditioning

A review [883] examines cross-talk between opioid and beta-adrenergic receptors in terms of the attenuation by opioid receptor agonists to attenuate beta-adrenergic receptor-mediated positive inotropic effects and cAMP increases through heterodimerization of these receptors, counterbalancing of functional G-protein signalling and interfaces at downstram signalling events. Chronic morphine treatment was more effective than acute morphine in improving functional recovery during an ischemia-reperfusion paradigm [876]. Whereas acute morphine produced functional recovery from ischemia-reperfusion in young, but not senescent hearts, chronic morphine treatment produced effects in both young and aged animals [877]. Morphine protected cerebellar Purkinje cells against cell death under in vitro-simulated ischemia-reperfusion conditions [676]. The ability of morphine to reduce infarct size and protection during the ischemia-reperfusion paradigm was inhibited by the phosphatidylinositol-3 kinase inhibitors, wortmannin and LY294002 [412]. Morphine-induced reductions in infarct size were mimicked by ibuprofen, and their combined effects

were blocked by the 12-lipoxygenase inhibitor, baicalein. Aspirin co-treatment abolished morphine-induced reductions in infarct size [413]. The abilities of morphine and ischemic preconditioning to protect against infarct size produced by ischemia-reperfusion injury were blocked by both naloxone and the delta antagonist, NTI with the latter also reversing the ameliorative actions of morphine on apoptosis [843]. Morphine-induced reductions in infarct size were abolished in inducible NOS KO mice, and following the inducible NOS blocker, methylthiourea sulfate [535]. Intrathecal morphine was as effective as systemic morphine in reducing infarct size induced by ischemia, and protected heart rate better than systemic morphine during ischemia-reperfusion treatment [411]. Antecedent apnea reduced infarct size of subsequent sustained ischemia in a naloxone-insensitive manner [290]. In a hypothermic myocardial ischemia model, functional recovery at 45 min of reperfusion was increased by the delta agonist, DADL and the kappa agonist, U50488H, but not fentanyl. Naltriben and NBNI respectively reversed the delta and kappa agonist effects [952]. In turn, naltriben and NBNI alone resulted in imapired functional recovery in a return of isovolumetric-developed pressure in this hypothermic myocardial ischemia model [953]. Moreover, both cold exposure and restraint stress attenuated infarct size induced by myocardial ischemia and reperfusion, effects blocked by general, mu, delta and kappa antagonists [1222]. The delta-1 receptor antagonist, BNTX blocked the protective ability of remote ischemic preconditioning to reduce infarct size, but did not change infarct size per se [1199]. BRL 52537, a kappa receptor agonist significantly attenuated infarct volume in cortex and striatum following middle cerebral artery occlusion in rats [206]. The cardioprotective effect of the delta agonist, SNC-121 in the rat ischemia model was unaffected by opioid antagonism or pretreatment with pertussis toxin, but was reduced by a free radical scavenger [872]. The cardioprotective effects of the delta agonists, BW373U86 and SNC-121 in the rat ischemia model were also attenuated by the COX-2 inhibitor, NS-398 and the inductible NOS inhibitors SMT or AG [871]. Like morphine, the delta agonist, BW373U86 and the kappa agonist, U50488H each produced cardioprotection in post-ischemic hearts that was respectively blocked by the delta antagonist, BNTX and the kappa antagonist, NBNI [878]. Moreover, the kappa agonists, ICI204448 and BRL52537 also produced cardioprotection with the former, but not the latter blocked by NBNI [879]. Remifentanil, a potent and short-acting phenylpiperidine opioid dose-dependently reduced infarct size in a manner similar to ischemic preconditioning; this effect was blocked by mu, delta and kappa antagonists [1281]. The ability of interleukin-2 to reduce infarct size and lactate dehydrogenase in response to ischemia and reperfusion was blocked by the kappa antagonist, NBNI, but not the delta antagonist, NTI [171]. Left vagal stimulation increased DYN release and inhibited SP release from rat thoracic spinal cord during cardiac ischemia [498]. OFQ/N relaxed porcine arterial rings and inhibited PGF2alpha-induced vasoconstriction, responses blocked by removal of endothelium, ORL-1 receptor antagonism and the presence of L-NNA and cGMP, but not naloxone [1233]. NMDA cerebrovascular dilation was impaired following fluid percussion brain injury in pigs with OFQ/N contributing to this impairment through a cycooxygenase-dependent generation of superoxide [47]. High, but not low frequency femoral nerve electrostimulation significantly reduced in a naloxone-reversible manner myocardial infarct size produced by myocardial ischemia and reperfusion [298]. Hemoragghic shock effects of vascular smooth muscle cells as measured by decreases in intracellular Ca2+ concentration were decreased by mu, delta and kappa antagonists as well as NE administration [555]. Patients with coronary artery disease following myocardial ischemia and reperfusion displayed augmented myocardial and peripheral BEND concentrations [194]. Patients undergoing thoracoabdominal aortic surgery are at risk for ischemic spinal cord injury with elevated CSF glutamate an excellent indicator; naloxone is effective in reducing CSF glutamate during this procedure [633].

15.3. Blood pressure

Morphine impaired MAP-induced increases by lactated Ringer's fluid resuscitation in animals exposed to trauma and hemorrhage, and increased both mortality and lipopolysaccharide-induced lung and spleen TNF expression [782]. Electroacupuncture decreased blood pressure in cats, and increased c-fos in the ventro-lateral medulla and PAG in close proximity to BEND and Menk fibers using both single- and double-labeling [424]. Rats with sinoaortic dennervation display tachycardia and hypertension accompanied by increased NE and decreased hypothalamic BEND and Lenk after 1 week, but not after 18 weeks. Chronic stress reinstates these deficiencies [1012]. Fentanyl attenuated Ach-induced vasorelaxation in the aortic smooth muscle rings in the presence of naloxone and pirenzepine, but not 4-diphenylacetoxyl-*N*-methylpiperidine methiodide [1053]. Animals subjected to myocardial ventricular fibrillation and administered cardiopulmonary resuscitation displayed improved blood pressure, cardiac indexes and survival times following the delta antagonist, pentazocine [1095]. Naloxone enhanced cardiovascular reactivity to cold pain without affecting diffuse noxious inhibitory controls. Further, the greater cardiovascular responses to noxious cold were associated with enhanced diffuse noxious inhibitory control [310]. Bovine-derived lactoferrin decreased MAP, but not HR, effects blocked by centrally-acting, but not peripherally-acting forms of naloxone as well as NOS synthase inhibition with L-NAME [459]. Vasodilation was blunted by fluid percussion injury in pigs, and effect restored by an OFQ/N antagonist [354]. Morphine produced a naloxone-sensitive synergy with dextromethorphan in relaxing mesenteric artery rings preconstricted with phenylephrine [514]. Opioid-based anesthesia during carotid endarterectomy produced more episodes of intraoperative hypotension and hypertension, but fewer epsidodes of tachycardia than hypnotic-based anes-

thesia with equal pain scores [393]. Preferential selection of combined epidural and general anesthesia with fentanyl and propofol is recommended in subjects with high risk for venous thromboembolism [282].

16. Respiration and thermoregulation

16.1. Respiration

A review [1161] indicates that resistive breathing produced by cytokine-induced increases in BEND decreases the activation of the respiratory muscles and change the pattern of breathing to rapid and shallow, possibly to reduce further injury to respiratory muscles. Fentanyl decreased phrenic nerve and vagus nerve respiratory discharges and firing of post-inspiratory neurons, an effect prevented by the D1 DA agonist, SKF-38393 which in turn was reversed by the D1 DA antagonist, SCH23390 [640]. Chronic methadone in rats decreased respiratory rate and HR with partial tolerance developing during active nocturnal periods [665]. Naloxone blocked the decreased respiratory rate and minute volume induced by DAMGO, but not by the cannabinoid agonist, WIN 55212-2 [891]. Morphine decreased isofluane minimum alveolar concentration in goats, an effect unaltered by flunixin meglumine co-administration [296]. Children with obstructive sleep apnea and hypoxemia appear to need less morphine following adeno-tonsillectomy as they display oxygen desaturation [149]. Exposure to high single doses of morphine or M6G production by slow-release morphine increases the risk of acute chest syndrome as a complication of sickle cell disease [619]. OFQ/N inhibited the ability of feoterol, a beta-2-adrenergic agonist to sensitize human isolated bronchi, an effect insensitive to naloxone pretreatment [328]. The ORL-1 agonist, Ro-64-6198 inhibited capsaicin-induced cough in the guinea pig, and significantly reduced capsaicin-induced Ca2+ responses in nodose ganglion cells [750]. Intra-oesophageal HCl infusions increased plasma extravasation in the bronchi and trachea, an effect reversed by vagotomy. OFQ/N and a petide agonist inhibited airway microvascular leakage that was blocked by an ORL-1 antagonist, but not naloxone. Morphine produced similar effects blocked by naloxone, but not by the ORL-1 antagonist [960]. Naloxone was effective in reversing deep anesthesia with fentanyl allowing quick tracheal extubation for ventilatory support after abdominal surgery [1109]. Normal human volunteers receiving morphine displayed similar pharmacodynamic responses for simultaneously-collected respiratory (breathing, arterial blood measures) and analgesic variables [261]. Morphine was prescribed in 41% of Taiwanese cancer patients for the control of dyspnea [497].

16.2. Thermoregulation

Microinjection of delta-2 (Delt), but not delta-1 (DPDPE) agonists into the anterior MPOA produced immediate hyperthermia that was blocked by the delta-2 antagonist, naltriben [87]. Racemic tramadol and its levo-isomer reversed reserpine-induced alterations in body temperature and ptosis in a manner similar to that of the anti-depressants, desimpramine and venlafaxine [951]. ORL-1 KO mice display higher core body temperatures, but no changes in either spontaneous activity or plasma cortisol levels [1143]. The increases in tail skin temperature induced by naloxone-precipitated morphine withdrawal in ovariectomized mice were blocked by the 5HT-2A/2C agonist, DOI [1029]. Inthethecal meperidine when paired with bupivacaine and morphine decreased shivering in patients undergoing cesarean section [962].

17. Immunological responses

A review [362] describes the immune deficiencies, hypothalamic-pituitary axis activation and activation of proinflammatory cytokines like TNF-alpha following heroin and cocaine self-administration. Proinflammatory chemokines, especially C–C chemokine ligand 3 induced internalization of MOR in MOR/HEK293 cells, impaired MOR-mediated inhibition of cAMP accumulation and DAMGO-elicited Ca2+ responses [1273]. Sustained exposure to morphine and HIV Tat(1-72) viral protein preferentially decreases glial precursors and astrocytes through a MOR-mediated mechanism together with caspase 3 activation [584]. Music increased MOR expression in peripheral blood mononuclear cells [1074]. Chronic morphine decreased exogenous phase S markers as well as proliferating cell nuclear antigen and phosphorylated histone, suggesting that chronic morphine treatment results in shorter Gap2/mitosis [719]. Morphine displays dose-dependent antioxidant properties inhibiting the peroxidation of lineolic acid emulsion [420]. Morphine protects against glutamate-induced toxicity of primary rat neonatal astrocytes, an effect that is not blocked by naloxone or altered by mu, kappa or delta agonists [651]. Morphine and tramadol each increase the amount of red neuron apoptosis in cortical and hippocampal regions with higher incidences in the occipital and temporal lobes following tramadol [48]. Morphine increased the sensitivity of NIH-3T3 cells to vinblastine, but not colchicine, but failed to alter P-glycoprotein expression in any cancer cell lines [861]. Morphine and DAMGO enhanced NF-kappaB promoter-directed luciferase activity and induces SP expression in NT2-N neurons that was blocked by general and mu antagonism and the non-peptide SP antagonist, CP-96,345 [1193]. Morphine activates the accumulation of SIV-infected cells in the G1 phase of the cell cycle through increases in Ca(2+), PKC and phosphorlyated ERK1/2 [670]. The *S*(+) isomer of methadone produced far greater immunosuppression thatn the potent analgesic *R*(−) isomer of methadone [507]. A similar pattern of SIV cell effects are also observed following Menk [671]. DADL slows down the synthetic activity of PC3 prostatic cancer cells by interfering with nuclear functions [66]. Morphine decreases

blood leukocyte expression of the major histocompatability complex class II and its protein expression on B lymphocytes, as well as inhibit interleukin-4-induced up-regulation of the latter [76]. Morphine promoted macrophage apoptosis through the production of superoxide and NO, effects blocked by antioxidants and diphenyleneiodonium chloride [100]. Combined administration of morphine and lipopolysaccharide induced greater vascular endothelial cell-induced apoptosis and permeability than either agent alone [683]. This combination also produced hypothermia, decreased MAP, increased plasma thrombin-anti-thrombin complex and accelerated progressive intramicrovascular coagulation and leukocyte-endothelial adhesion [837]. Morphine enhanced the effect of HIV gp160 protein on macrophage apoptosis, effects blocked by NOS inhibition [565]. The ability of morphine to stimulate HIV-infected CD4(+) cells was inhibited by the cannabinoid agonist, WIN55,212-2 [887]. Morphine induces greater loss of CD4(+) T cells and a higher viral load in HIV and simian-HIV-infected rhesus macaques [632], and aggravates the apoptosis of simian HIV infected cultured CEM × 174 cells [1230]. Morphine triggers apoptosis in mesangial cells of mice with control and HIV-1 genes [783]. Morphine reverses retinoic acid receptor-induced TNF-alpha suppression in activated U937 cells [794]. Morphine also reverses TNF-alpha suppression induced by LG101305 and ciglitazone in phytohemaggutinin-stimulated U937 cells [964]. NE augmented intrathecal morphine's decrease in natural killer cell activity in female patients undergoing hysterectomy [1247]. Monocytes and macrophages produced by inflammation were the predominant producers of opioid peptides [135]. Morphine tolerance development induced glial activation and enhanced pro-inflammatory cytokine levels in the lumbar spinal cord that was temporally correlated with hyperalgesia. The glial modulator, propentofylline administered during the induction of morphine tolerance attenuated both inflammatory and hyperalgesic responses [916]. Chronic morphine also decreases IFNgamma and interleukin-2 mRNA and increases interleukin-4 and -5 mRNA accumulation in murine splenocytes [963]. Fever, decreased cAMP production and increased hypothalamic PGE2 release were elicited in a naloxone-sensitive manner by interferon N-alpha and 129-Ser-interferon N-alpha, but not 38-Leu-interferon N-alpha [1195]. Morphine withdrawal produced deficits in macrophage function in spleen cells that depended upon the ratio of co-cultured intact and withdrawn cells [917]. Inflamed paw tissue elicited BEND and POMC release colocalized with prohormone convertase-1 and -2, carboxypeptidase E and 7B2 in macrophages and monocytes [796]. Morphine dose-dependently and naloxone-reversibly produced anti-inflammatory effects upon carrageenan-induced oedema in the mouse paw that corresponded in increases in interleukin-1 serum levels [904]. Short-term (24 h) withdrawal from both morphine and cocaine administered over 7 days suppressed proliferation responses of peripheral blood T-lymphocytes stimulated by concanavalin A, and elevated plasma corticosterone levels [52]. Morphine-induced immunosuppression was blocked by systemic and central administration of the D2 DA receptor agonist, 7-OH-DPAT [989]. Epidural opiate treatment with anesthesia preserves lymphocyte, but not monocyte immune function after major spinal surgery [1176], and post-operative pain treatments using oxycodone or diclofenac also alters the phytohaemagglutind-induced leucocyte proliferative response in children receiving surgery [1178].

Endomorphin 1 and 2 are found predominantly in macrophages and B cells, but not in T cells of the spleen [1005]. Endomorphins increased apoptosis in human leukemia HL-60 cells by down-regulating Bcl-2 and up-regulating Bax, Fas and FasL expression [679]. Migrations of peripheral blood nonadherent mononuclear cell and neuropil chemotaxis toward BEND, angiotensin II, somatostatin and interleukin-8 were deactivated by naloxone [564]. Menk and its metabolites enhanced and accelerated the ability of a purified derivative of tuberculin to induce delayed-type hypersensitive inflammatory reactions when injected together with CFA [1032]. Menk stimulated hydrogen peroxide and NO production in rat peritoneal macrophages, effects enhanced by combined mu and kappa antagonism or kappa antagonism alone [1177]. Menk administered intraperitoneally, but not by either osmotic minipump or intratumoral administration reduced human squamous cell carcinoma in the head and neck of nude mice, delaying tumor appearance by 3 days and reducing tumor volume [749]. The autoimmune diseases of polymyositis and dermatomyositis induce increased plasma NPY levels and decreased BEND, ACTH and CGRP levels [685]. Whereas acute OFQ/N upregulates activation marker expression (CD28) and causes proliferation of TNF-alpha secretion, re-stimulation inhibits proliferation presumably by upregulating CTLA-4 expression [1179]. Repeated electroacupuncture in estrdiol valerate-injected rats increased hypothalamic BEND and then altering CD4+ T and CD8+ T cells [1076]. Migrations of leukocytes to L15 medium in mice, fish and frogs, and to zymosan-activated serum in mouse and fish were respectively increased and decreased by pretreatment with mu and delta, but kappa agonists, effects blocked by appropriate mu and delta antagonists [189]. Fentanyl, but not buprenorphine decreased lymphoproliferation measures of natural killer cell activity and interleukin-2 and interferon gamma production at doses that produced similar analgesic profiles [735]. Interleukin-6 induces MOR, but not DOR mRNA in the human neurobalstoma cell line SH SY5Y [128]. Buprenorphine suppressed splenic natural killer cell activated lymphocyte proliferation and IFN-gamma production in a naltrexone-sensitive manner [174]. Codeine and meperidine induced mast cell activation with the release of histamine and tryptase in a naloxone-independent manner [119]. Opiate growth factor inhibited anchorage-independent growth in human cancer cells [1258], and is present in whole brain by embryonic Day 20 with levels increasing during the first post-natal week, and persisting at these levels into adulthood [1259]. Whereas DPDPE promotes superantigen-induced clonal deletion during T-cell develop-

ment, this response is significantly impaired in DOR KO mice [741]. Animals lacking KOR displayed higher antibody titers for a series of immune subtype responses. Although two morphiceptin analogues bound with greater affinity than endomorphins or morphiceptin itself to human breast cancer MCF-7 cells, neither analogue decreased cell proliferation [523]. Heroin self-administration suppresses immune function, increasing infection and susceptibility to disease [1198]. Rotation stress suppressed in a naloxone-reversible manner immune inflammation in delayed-type hypersensitivity, increased antibody-forming cells and nucleated cells in regional lymph nodes [381].

Naltrexone blocks mu-opioid receptor negative feedback function upon delta opioid receptors thereby allowing delta agonists to stimulate the cytolic activity of splenic NK cells [134]. Naltrexone protected mice from septic shock induced by lipopolysaccharide and D-galactosamine, but not the same symptoms produced by pairing staphlococcal eneterotoxin B with D-galactosamine or an agonistic anti-Fas antibody [409]. Pertussis toxin blocks cyanide generation in pheochromocytoma cells induced by muscarinic agonists, but fails to affect nalxone-induced cyanide generation [422]. NTI-induced inhibition of the allogenic mixed lymphocyte reaction was observed in both wild-type and triple MOR-KOR-DOR KO mice, indicating that NTI is not acting through a classic opioid receptor [379]. Cocaine-induced increases in HIV-1 expression in microglial cells were reduced by both kappa agonists and the kappa antagonist, NBNI [382]. Compounds structurally related to the delta antagonist, NTI produced immunosuppression as demonstrated by interleukin-2 release in mitogen-activated peripheral blood mononuclear cells [263].

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