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Review article

Endogenous opiates: 1998☆

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Abstract

This paper is the twenty-first installment of our annual review of research concerning the opiate system. It summarizes papers published during 1998 that studied the behavioral effects of the opiate peptides and antagonists, excluding the purely analgesic effects, although stress-induced analgesia is included. The specific topics covered this year include stress; tolerance and dependence; eating and drinking; alcohol; gastrointestinal, renal, and hepatic function; mental illness and mood; learning, memory, and reward; cardiovascular responses; respiration and thermoregulation; seizures and other neurologic disorders; electrical-related activity; general activity and locomotion; sex, pregnancy, and development; immunologic responses; and other behaviors.

Keywords: Stress; Tolerance; Dependence; Eating; Drinking; Alcohol; Depression; Learning Memory; Cardiovascular responses; Temperature; Respiration; Epilepsy; Activity; Mental illness; Aggression; Sex; Immunology; Opiate; Peptide

1. Introduction

In 1998, as in previous years, interest in the role of endogenous opiates in mediating behavior remained high. Although much of the research focused on characterizing the role of opiate receptor types, there was a great deal of interest in the interactions between opiate and nonopiate systems. Furthermore, besides the typical use of opiate agonists and antagonist, antisense techniques were increasingly used in 1998 to 'knock out' specific receptor types, allowing researchers further to delineate the relationships between opiate systems and behavior. This paper will review work published in 1998 that studied the behavioral and nonanalgesic activity (except stress-induced analgesia) of endogenous opiate systems. This represents the twenty-first installment of our series of reviews that attempts to summarize the developments in the field during the past year.

Stress-induced activation of endogenous opiate systems, and the changes that occurred because of stress, continued to be of interest in1998. As had been reported in previous years, the parameters of the stressor influenced both its behavioral effects and physiological consequences. Research continued to be strong in the field of opiate dependence and tolerance. Chronic administration of opiates produced many changes within opiate systems, and particular attention was paid to long-lasting molecular and cellular adaptions. Clinically, the benefits derived from various pharmacological treatments were evaluated, including rapid detoxification with opiate antagonists given under general anesthesia and methadone-maintenance. Research in the role of endogenous opiates in eating and drinking remained high, and made use of antisense techniques to help identify the opiate receptor subtypes involved. There was some confusion, however, in the role of opiate systems in the modulation of alcohol consumption, as opiate antagonist tended to decrease consumption in general. Although this debate remains to be clarified, research examining of the motivational properties alcohol indicated opiate involvement.

Research on the opiate modulation of gastrointestinal function focused primarily on the opiate receptor subtypes involved in transit. However, their involvement in renal and hepatic functions is still not entirely clear. Although attempts were made to link opiate systems to mental illness, their role was obscured because no clear benefits were found from naltrexone treatment. Interest in the role of

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endogenous opiates in learning and memory was high, emphasizing the role of endogenous opiates in brain reward systems and thus had enormous clinical relevance for understanding opiate abuse. The role of endogenous opiates in mediating cardiovascular function continued to be studied, including the opiate receptor subtypes that mediate heart rate and blood pressure. In addition, there were increased attempts examining the role of endogenous opiates in cardiovascular disease, in particular their possible protective effects against infarct after ischemia. Research continued to address opiate modulation of respiratory functions, and there seemed to be more interest this year than last in assessing the clinical safety of combining opiates with nonopiates, in particular benzodiazepines. However, continuing a trend observed in previous years, interest in opiate involvement in thermoregulation was low.

The role of opiates in mediating seizure activity was examined, and it was generally accepted that μ-agonists were proconvulsive and κ-agonists were anticonvulsive. Animal models were used to also examine opiate modulation of other neurologic disorders, including traumatic brain injury, Parkinson's disease, and Alzheimer's disease. Interest in opiate involvement in electrical-related activity remained high in 1998. It included mostly the use of in vitro preparations but also some in vivo. Although locomotor activity was influenced by opiate agonists, the results were inconsistent making any generalizations difficult. Studies of endogenous opiates in sex and development remained high, with particular interest this year in the ontogeny of opiate systems during embryonic development. However, there was little interest in the changes that occur during the aging process. There was research on the effects of prenatal exposure to opiates on development that should not only be of concern for opiate abuse during pregnancy but also for opiate pain control during pregnancy and labor. Although there were exception, exogenous opiates were immunosuppressive, whereas endogenous opiates enhanced immune function, indicating that they probably have different mechanisms of action. Opiate involvements in other behaviors were also addressed, including scratching and smoking behavior.

2. Stress

Many stressors are known to interact with endogenous opiate systems. In 1998, the physiological and behavioral effects of a variety of stressors were elucidated, which included forced swim [9,30,31,155,183,189,191], social conflict and threat [184,410], foot-shock [199,248,368,442], restraint [117,186,204,240,359,407], asphyxiation [424], insulin-induced hypoglycemia [424], confinement and crowding [271], wheel running [176], electroconvulsive shock [120], hypertonic saline injections [119], formalin injections [387], physical exercise [147], mental arithmetic [107], emotional stress [251], cold-air exposure [13], and childbirth/pregnancy [34,92].

As in previous years, there was continued interest in the analgesic effects of stress. Some stressors are known to activate endogenous opiate systems as defined by sensitivity to opiate agonists and antagonists. Other stressors are nonopiate as defined by the same criteria. The differential activation of opiate and nonopiate systems depended on the duration of stress exposure, as deer mice exposed to biting flies for 30 min showed naloxone-sensitive opiate analgesia, but a 5-min exposure elicited nonopiate analgesia that was insensitive to both naloxone and the κ-opiate antagonist, nor-BNI [184]. However, there were sex differences in the expression of opiate analgesia because the magnitude of naloxone-sensitive analgesia elicited by exposure to biting flies was greater in male than female deer mice [184]. Opiate-mediated analgesia was produced in rats exposed to a continuous forced swim for 3-min in 2°C water, whereas 18 10-s swims in 2°C water at 10 s intervals produced nonopiate analgesia, suggesting that the activation of opiate systems by forced swim also depends on the pattern of exposure [155]. The activation of endogenous opiate systems by forced swim also differed as a function of water temperature, as mice exposed to a 3-min forced swim in 32°C water showed opiate-mediated analgesia, but a 3-min swim in 20°C water produced nonopiate analgesia [30]. Chronic wheel running also activated endogenous opiate mechanisms because male and female rats exposed to running activity wheels for 20 days showed subsequent cross-tolerance to morphine analgesia [176].

Not all stressors produce analgesia, however, as immobilization in Bolman cages did not produce analgesia and did not modify morphine analgesia [407]. Furthermore, although a single restraint stress produced analgesia in both male and female rats, 40 daily exposures produced a gender–specific hyperalgesic response in males [117]. Exposure to low frequency electromagnetic fields was found to inhibit opiate-mediated analgesia in snails, which was shown to depend on the presence of light as the inhibitory effects of low frequency electromagnetic fields on opiate analgesia was reduced in the absence of light [312]. In contrast, exposure to ultra-wideband electromagnetic pulses in rats did not modify morphine analgesia [350].

The opiate receptor subtypes that mediate stress-induced analgesia also were elucidated. Mice selectively bred to display high levels of swim stress-induced analgesia showed greater analgesic effects to the selective μ-opiate receptor agonist DAMGO, the δ_1 agonist DPDPE, and the δ_2 agonist DELT, as compared with mice bred for low levels of swim stress-induced analgesia [189]. However, despite these differences between mouse lines in μ and δ analgesia, in vitro assays only revealed differences for δ_1 receptor binding, and μ-opiate receptor mRNA levels in the nucleus raphe magnus, suggesting that the differences in analgesia are not related to simple genetic alterations in opiate receptor density or regional mRNA levels [189]. On

the other hand, deficiencies in δ_1 and δ_2 analgesia in CKBK mice were correlated with reductions in whole-brain δ_2 receptor binding [188].

The opiate receptor subtypes that mediate swim stress-induced analgesia undergo developmental changes as the δ receptor antagonist, naltrindole, completely antagonized analgesia in 25-day-old rat pups, but only partially antagonized analgesia in 20-day-old pups and had no effect in adult rats [9]. In addition, chronic treatment during the first 19 postnatal days with naltrindole decreased the analgesic effects of swim stress in 25-day-old pups, which was antagonized by naloxone but not naltrindole, suggesting that the normal δ mediation of stress analgesia at this age was compromised [9]. Increased pain threshold observed during pregnancy is mediated by spinal κ- and δ-opiate receptors because intrathecal (IT) nor-BNI, BNTX, and NTB abolished analgesia during gestational Day 20 or Day 19 of hormone-stimulated pregnancy [92]. However, combinations of the antagonists in suboptimal doses did not produce a greater magnitude of blockade than was obtained by administration of suboptimal doses of the antagonists alone, suggesting that analgesia during pregnancy requires activation of both κ- and δ-opiate analgesic systems [92].

Conditioned stress-induced analgesia, in which an auditory signal that was previously paired with foot-shock elicits analgesia, is mediated by μ-opiate receptors within the ventrolateral periaqueductal gray (PAG) because injection of the μ-opiate antagonist CTAP, but not by the κ-opiate antagonist nor-BNI, into that brain region blocked the analgesia [32]. In contrast, injection of CTAP into the dorsolateral PAG had no effect, suggesting a differential role of these subdivisions in defensive responses [32]. The ventral and dorsal aspects of the lateral PAG may be involved in the integration of defensive freezing and flight reactions, because morphine injection into the dorsolateral PAG produced analgesia that was associated with increased locomotor activity, whereas ventrolateral PAG morphine injections produced immobilization [270]. Social conflict also activated opiate mechanisms, as defeated rats showed enhanced analgesic responses to morphine, DAMGO, and DPDPE, as compared with socially inexperienced rats [410].

Besides analgesia, stress also affects locomotor activity. Forced swimming suppressed locomotor activity in male mice for 10 min post-stress, which recovered after 20 min [183]. This effect is opiate-mediated because naloxone suppressed the recovery of locomotor activity after swimming [183]. Because the behavioral suppression after swimming is likely related to fatigue it may provide a model for recovery from fatigue after exercise, and suggests that opiate systems contribute to this recovery [183]. Sex differences were found in the opiate modulation of freezing behavior observed after uncontrollable foot-shocks as naloxone potentiated freezing behavior in male rats, but not in females [199].

Chronic restraint attenuated hypoactivity induced by the α_2-adrenoreceptor agonist, clonidine, which is opiate-mediated because naloxone prevents it [186]. In contrast, chronic restraint does not modify clonidine-induced hypoactivity in rats that had been malnourished at a perinatal age [186]. It is likely that malnourishment impairs activation of endogenous opiate mechanisms as pretreatment with morphine or β-endorphin before restraint sessions in malnourished rats reinstated the effect of stress on clonidine-induced hypoactivity [186]. Chronic restraint also reduced testicular steroidogenis that is mediated by peripheral opiate receptors, because the effects are prevented by intratesticular injection of naltrexone-methobromide, an opiate antagonist that does not cross the blood-brain barrier [204].

In fish, exposure to confinement and crowding for one month produced increases in both plasma cortisol and acetyl salmon endorphin, whereas no increases in acetyl salmon endorphin were found after exposure to confinement alone [271]. Furthermore, in fish exposed to short-term (60-min) confinement, crowding, and manipulation (captured in nets and hand sorted), plasma cortisol was elevated at 30 min but not 60 min, pituitary acetyl salmon endorphin was elevated at 30 and 60 min, and plasma acetyl salmon endorphin only at 60 min [271]. These effects are opiate-mediated because injection of naltrexone further increased levels of acetyl salmon endorphin and antagonized the stress-induced increases in cortisol [271]. Plasma β-endorphin levels were higher in horses when they were allowed to crib-bite than when crib-biting was prevented [252]. However, because no differences were found in cortisol levels between groups, it does not support the hypothesis that crib-biting functions to reduce stress [252].

Stress has been shown to affect reward systems that are opiate-mediated, as foot-shock reduced self-stimulation derived from the dorsal aspect of the ventral tegmental area (VTA) that was attenuated by intraventricular administration of the μ-and δ-agonist DALA, the μ-agonist DAMGO, and the δ-agonist DPDPE [442]. Foot-shock also reinstated drug seeking behavior after a period of extinction in rats trained to self-administer heroin, suggesting that stress may be a factor leading to relapse in opiate addicts [368]. In addition to opiate reward, stress also is important in the development of ethanol reward, as ethanol-induced conditioned place preference developed only under conditions in which animals also were exposed to foot-shock stress [248]. It is likely that μ- and δ-opiate receptors are involved because the development of ethanol reward in stressed animals was attenuated by the μ-antagonist β-FNA and the δ antagonist naltrindole, but not by the κ-antagonist nor-BNI [248]. However, previous exposure to ethanol did not modify opiate-mediated swim stress analgesia, a finding that does not support an ethanol-opiate interaction [30].

As in 1997, there was continued interest in the cellular and molecular changes produced by stress. Forced swim increased c-Fos immunoreactivity in the ventrolateral PAG neurons that had projections to the ventromedial medulla [31], which is consistent with the role of these cells in mediating stress–induced analgesia [31,32,270]. Injection

of dilute formalin into the hindpaw of rats was shown to affect opiate gene expression, as preprodynorphin mRNA was increased in the spinal cord after formalin, indicating that peripheral tissue injury can alter neuronal excitability [387]. Both acute and repeated exposures to electroconvulsive shock increased proenkephalin gene expression in the nucleus accumbens and ventromedial nucleus of the hypothalamus, but not in the paraventricular nucleus or striatum [120]. Because the ventromedial nucleus of the hypothalamus is involved in many diverse functions, the increased opiate gene expression in this area may be related to post-electroconvulsive shock side effects, including changes in energy, sexual behavior and hormonal secretion [120]. In contrast, a stressful injection of hypertonic saline was found to increase proenkephalin mRNA in the paraventricular nucleus [119].

The effect of stress on proenkephalin gene expression is likely mediated by endogenous glucocorticoid activity as increases in proenkephalin mRNA in the paraventricular nucleus produced by the injection of hypertonic saline were completely blocked by the type II glucocorticoid antagonist RU 486 [119]. The effects of stress on proenkephalin gene expression was not influenced by age, however, as increases in adrenal preproenkephalin mRNA observed after 2 h restraint were the same in 7-, 16-, and 23-month-old Fischer rats [359]. Expression of enkephalin hnRNA also was increased after immobilization stress in the paraventricular nucleus in both borderline hypertensive rats and normotensive controls [240]. Because enkephalin neurons may modulate sympathetic activity, the alterations in enkephalin activity in the borderline hypertensive rats may contribute to their increased sympathetic activity [240]. Stress also affects enkephalin content in newborn rabbits as asphyxia caused by enclosure in an airtight box for 60 min increased enkephalin-like immunoreactivity in the paraaortic body and adrenal glands [424]. On the other hand, insulin-induced hypoglycemia decreased enkephalin-like immunoreactivity in the adrenal glands [424].

The effects of stress in humans also was examined. Endogenous opiates were found to inhibit blood pressure responses during naturally occurring emotional stress because naltrexone increased blood pressure in subjects during periods of high stress, but had no effect on blood pressure during periods of low stress [251]. Patients with acute congestive heart failure showed increases in blood pressure, heart rate, plasma levels of Met-enkephalin, dynorphin-B, β-endorphin, norepinephrine, atrial naturetic factor, and endothelin-1 after undergoing a mental arithmetic test [107]. Because the increases in norepinephrine and hemodynamics were higher in subjects given naloxone during the stressor, it is possible that increased opiate activity during stress attenuates the hemodynamic response by reducing norepinephrine activity [107]. However, opiates do not modify labor stress, as the opiate analgesic pethidine hydrochloride did not modify hypothalamic-pituitary-adrenal (HPA) axis activity during childbirth [34].

Strenuous physical exercise has been shown to interact with endogenous opiates, as plasma β-endorphin levels increased in untrained women 5 min after running a treadmill to exhaustion, which returned to basal levels 30 min later [147]. However, although no changes were observed in basal levels of β-endorphin after the women received endurance training, the increases in β-endorphin to exhaustive exercise were less dramatic after training, suggesting that adaption occurs to this response [147]. In contrast, women with a history of endurance training had higher levels of basal β-endorphin as compared with women with no history of endurance training, and this was not modified by exposure to a cold air stressor [13].

3. Tolerance and dependence

As in 1997, much of the research on opiates focused on the induction of tolerance and dependence after chronic administration. The biologic bases of tolerance and dependence were elucidated, including the long-lasting cellular and molecular changes that accompany chronic morphine, and the interactions between opiate and nonopiate systems [5,42,142,206,374]. Clearly, a better understanding of the mechanisms that underlie opiate tolerance and dependence will aid in the application of pharmacological treatments to prevent their occurrence.

Chronic administration of opiate agonists is associated with changes in endogenous opiate systems, as chronic treatment with μ-opiate agonists, morphine, fentanyl, or DAMGO down-regulated μ-opiate receptor density in μ-opiate receptor-expressing Chinese hamster ovary cells [182]. Similarly, chronically administered morphine by implantation of a 75-mg morphine pellet in mice followed by injections of 20 mg/kg morphine every 12 h for 4 days decreased in μ-opiate receptor protein quantity by 50% [36]. An acute injection of morphine, however, had no effect [36]. Chronic morphine produces a down-regulation of proopiomelanocortin (POMC) mRNA in hypothalamic neurons, suggesting that the synthesis of β-endorphin is under negative feedback control by μ receptors [105]. In contrast to the down-regulation of μ receptors, chronic morphine produced an up-regulation in σ receptor sites as demonstrated by enhanced binding of [^{3}H]DTG [207]. However, the σ receptor subtype that is up-regulated after chronic morphine remains unclear because [^{3}H](+)-pentazocine labeling of the σ_1 receptor subtype was unaffected by chronic morphine, and labeled [^{3}H]DTG, which has equal affinity for both σ_1 and σ_2 subtypes, was unchanged when measured in the presence of (+)-pentazocine [207].

Chronic morphine produces long-lasting molecular and cellular adaptions including changes in cAMP pathways [140,142]. Prolonged in vivo exposure of the guinea pig longitudinal muscle myenteric plexus tissue to morphine increased levels of adenylyl cyclase type IV mRNA, but not adenylyl cyclase type I mRNA [325]. Because adenylyl

cyclase type I is inhibited by $G_{\beta\gamma}$ and $G_{\alpha i}$-proteins, whereas type IV is stimulated by $G_{\beta\gamma}$ and unaffected by $G_{\alpha i}$, the increase may represent a change from inhibitory to stimulatory opiate receptor G-protein signaling [325]. An increase in protein kinase C-mediated phosphorylation of adenylyl cyclase was also observed after chronic morphine that may be related to the increase in stimulatory responsiveness to G-proteins [64]. Increases in protein kinase C may mediate desensitization to δ-opiate-mediated increases in Ca^{2+} in neuroblastoma cells because the desensitization observed after prolonged exposure to DADLE was reduced by treatment with protein kinase C inhibitors staurosporin and GF-109203X [438]. In contrast, chronic morphine also has been shown to decrease protein kinase A-induced receptor phosphorylation, suggesting that the μ receptor may be structurally altered after chronic morphine [36]. However, opiate-induced down-regulation of μ receptors and changes in cAMP pathways may be mediated by distinct mechanisms because pertussis toxin inhibited increases in cAMP after chronic DAMGO, but not μ receptor down-regulation [182].

Long-lasting changes in cellular activity after chronic morphine also were demonstrated by greater morphine-induced c-Fos expression in various brain areas in rats given repeated injections of morphine [103]. However, the expression of morphine-induced c-Fos is likely modulated by nonopiate mechanisms, because the serotonin-3 receptor agonist MD72222 dose-dependently potentiated c-Fos expression in the dorsomedial caudate putamen [110]. Opiate gene expression seems to be related to individual propensity to self-administer opiates as rats that show high locomotor responses to novelty, which is a predictor of opiate self-administration, have higher levels of preproenkephalin and preprodynorphin mRNA in the nucleus accumbens [231]. Chronic morphine also can lead to changes in neural transmission within primary visual areas of the brain as methadone-maintained opiate addicts exhibited delays in the N75 and P100 component of the pattern shift visual evoked potential, which was correlated with length of heroin abuse [25].

Chronic treatment with the opiate antagonists generally produces an up-regulation of opiate receptors, as naloxone induced a slight increase in μ-opiate receptor density in μ-opiate receptor-expressing Chinese hamster ovary cells [182], and naltrexone produced an up-regulation of δ receptor binding, which was greater for δ_2 than δ_1 [190]. The up-regulation of opiate systems produced by naltrexone may provide a possible explanation for the increased tolerance to pain observed in opiate addicts receiving naltrexone treatment [73]. Prenatal exposure to the mixed opiate agonist-antagonist buprenorphine, which is being used in clinical trials for opiate-dependency (see below for more on this topic), produced an up-regulation of κ_1 receptor density but a down-regulation of μ-opiate receptors in 1-day-old pups [29]. However, there are sex-dependent differences in the effects of prenatal exposure to opiates because μ-opiate receptor down-regulation was greater in males than females [29].

Antiopiate peptides affect opiate receptor binding that may be involved in the induction of compensatory responses after chronic morphine [142]. The endogenous antiopiate peptide Tyr-W-MIF-1 counteracts the effects of chronic morphine as morphine-induced down-regulation of μ and δ receptors was blocked by Tyr-W-MIF-1, suggesting that antiopiate peptides may modulate morphine tolerance by inhibiting receptor down-regulation [143]. Moreover, although Tyr-W-MIF-1 prevented down-regulation of μ receptors induced by the μ-selective agonist PL017, it did not affect δ receptor down-regulation produced by the δ-agonist DPDPE, suggesting a differential response of cells to μ- and δ-agonists [143]. Continuous intracerebroventricular (ICV) infusion of anti-dynorphin$_{1-8}$ IgG or anti-NPFF IgG increased μ labeling in the caudate-putamen, nucleus accumbens, and cingulate cortex [136], whereas anti-α-MSH IgG decreased μ labeling in the thalamus [136]. These results suggest that antiopiate peptides may tonically regulate opiate receptor density and thus modulate the effects of opiates [136]. Such a modulatory role of antiopiate peptides is supported by the finding that the NPFF agonist, [D-Tyr^1,(NMe)Phe^3] NPFF, increased the intensity of morphine tolerance, and treatment with the antisense oligodeoxynucleotide to NPFF mRNA attenuated the development of morphine tolerance [124]. Further, the antiopiate efficiency of NPFF is increased after chronic morphine, as NPFF blocks morphine analgesia at doses 60-fold lower in morphine tolerant mice than nontolerant mice [125].

Behaviorally, chronic administration of opiates generally produce tolerance [11,37,78,121,124,125,138,171,202,224,226,255,266,279,332,392,393,427,434]. The development of tolerance depended on both the dose and duration of morphine treatment, as tolerance to the suppressive effects of morphine on carrageenin-induced c-Fos activity in nociceptive spinal cord neurons was observed after 4 days but only at high doses (≥10 mg/kg), and was only observed by the 4th day of treatment to a fixed dose of morphine (10 mg/kg) [226]. Stress influenced tolerance because concurrent exposure to foot-shock suppressed the development of tolerance to morphine analgesia [381]. Interestingly, although the mechanisms are not understood, the suppressive effects of stress were inhibited by the herbal drug, ginseng [381]. Tolerance to morphine analgesia did not depend on the pain test used as tolerance developed to the analgesic effects of spinally administered morphine independent of whether the pain induced was visceral or cutaneous [279]. However, the development of tolerance to spinally administered morphine does not seem to limit the clinical use of opiates to achieve effective pain control, as cancer patients showed only a moderate dose escalation after 95 days [332].

Typically, cross-tolerance occurs between opiate agonists with the affinity for the same receptor. Cross-tolerance was shown between fentanyl and morphine, as infant rats exposed to chronic fentanyl showed reduced morphine an-

algesia as juveniles and adults, suggesting that early exposure to opiates may have long-lasting effects opiate pain modulation [392]. However, although tolerance developed in pigeons to the rate-decreasing effects of morphine that was cross-tolerant with fentanyl and its derivative OHM3463, cross-tolerance did not develop between morphine and the fentanyl derivatives mirfentanil or OHM 3925 [121]. The lack of cross-tolerance between morphine and mirfentanil, and morphine and OHM 3925 is likely explained by nonopiate effects of these drugs because the rate-decreasing effects of mirfentanil or OHM 3925 were unaffected by naloxone [121]. The development of tolerance and cross-tolerance to the rate-decreasing effects of butorphanol depended on the dose, as rats maintained on a low maintenance dose of butorphanol developed tolerance to the effects of butorphanol, buprenorphine, and morphine, but not to fentanyl, sufentanil, and U50488H [364]. In contrast, when a high maintenance dose of butorphanol was used, cross-tolerance developed to the effects of butorphanol, buprenorphine, morphine, fentanyl, and sufentanil, but not U50488H [364]. Cross-tolerance occurs between the μ-agonists LAAM and hydromorphone, as opiate addicts maintained on LAAM showed decreased physiological and behavioral effects to a subsequent challenge with hydromorphone [159]. However, cross-tolerance was not demonstrated between morphine and methadone because analgesia was restored by methadone in pediatric burn patients that were tolerant to morphine, suggesting that the analgesic actions of methadone and morphine may be different [427]. The analgesic effects of tramadol were unaffected by chronic treatment with morphine or tramadol, indicating that the analgesic actions of tramadol cannot be solely explained by its limited activity at opiate receptors [266]. An interaction between μ and δ receptors was demonstrated as chronic neonatal treatment with the δ-antagonist naltrindole blocked subsequent analgesia to the μ-agonist alfentanil, but not the κ-agonist CL-977 [106]. There also is evidence of μ-κ interaction, as many of the effects of μ-agonists, including tolerance, are opposed by activation of κ receptors [131, 292].

Besides analgesia, tolerance develops to other effects of morphine, including morphine-induced suppression of single unit activity in the nucleus paragigantocellularis [138], and inhibition of guinea pig ileum contractions [171]. Tolerance develops to the EEG effects of the μ- opiate agonist, alfentanil, after repeated injections, suggesting that reliable estimates of in vivo concentration-EEG effects cannot be obtained after chronic morphine [78]. However, tolerance did not develop to all of morphine's effects because tolerance does not occur to morphine-induced locomotor activity, but showed sensitization after chronic morphine [368]. Tolerance does not develop to the gastrointestinal effects of opiates, as 58% methadone-maintenance of patients experienced constipation, and delayed gastrointestinal transit that corresponded to constipation and laxative use [439]. Further, the degree to which decreases in morphine analgesia in cancer patients is explained solely by tolerance is not entirely clear, as opiates interact directly with tumors, thus possibly diverting opiates from interacting with analgesic systems [10]. This raises the possibility that the tumor itself may contribute to a decrease in analgesia, which could improperly be labeled as opiate tolerance in these patients [101]. In addition, although tolerance developed to the central analgesic actions of morphine it did not develop to peripheral morphine analgesia, suggesting that tolerance cannot be explained by receptor desensitization [393].

As in 1997, there was continued interest in the role of the glutamate receptor in the development of tolerance. Systemic administration of the noncompetitive *N*-methyl-D-aspartate (NMDA) antagonist, MK-801, reversed the development of tolerance to morphine analgesia in rats presented with a saccharin solution paired with morphine [255]. It is likely that the reversal of tolerance is mediated by spinal mechanisms as the competitive NMDA antagonist AP5 reversed morphine tolerance when administered IT but not ICV [255]. Acute opiate tolerance also is NMDA-mediated, as MK-801 reversed tolerance after a single injection of heroin [224]. It is possible that acute opiate tolerance is related to an activation of NMDA-mediated pain facilitory systems because MK-801 also reversed naloxone-induced hyperalgesia after heroin injection [224]. However, because both ICV and IT AP5 reversed morphine-induced hyperalgesia but only IT AP5 reversed morphine tolerance, it suggests that tolerance to opiate analgesia can be dissociated from co-occurring hyperalgesia [255].

The strain of mouse used to study tolerance is important as tolerance developed to chronic morphine administered systemically, via pellet implant, or given ICV in CD-1 mice, but not in129/SvEv mice [202]. Similarly, tolerance developed to the δ-agonist DPDPE in CD-1 mice but not in129/SvEv mice [202]. In contrast, tolerance to the κ_1-agonist U50488H and κ_3-agonist naloxone benzoylhdrazone developed in both strains, suggesting that the mechanisms that mediate κ and δ tolerance are different [202]. Consistent with the blockade of tolerance to morphine analgesia with NMDA antagonists, co-administration of NMDA accelerated tolerance to morphine analgesia and attenuated analgesia in CD-1 mice [202]. However, because NMDA did not affect morphine analgesia or tolerance in 129/SvEv mice, the lack of tolerance to morphine analgesia in this strain is likely related to a defect in the NMDA receptor [202]. An interaction between opiate-induced sensitization and NMDA activity was shown as acamprosate, a compound used for alcohol abuse that interacts with NMDA systems, was shown to suppress morphine-induced sensitization of locomotor activity [368]. In addition, DAMGO potentiated amygdala evoked glutaminergic activity, also suggesting an interaction between central opiate and glutaminergic systems [268].

Activation of NMDA receptors can lead to production of the second messenger nitric oxide (NO). NO is involved in morphine tolerance as administration of the nitric oxide

synthase (NOS) inhibitors L-NAME, 3-bromo-7-nitroindazole, 7-nitroindazole, and N^G-monomethyly L-arginine attenuated the development of acute tolerance after a single ICV injection of morphine in mice [434]. Because the guanylyl cyclase inhibitor LY-83,583 also blocked tolerance, it is likely that NO acts through the cyclic GMP pathway to mediate tolerance to morphine analgesia [434]. NO also can modulate opiate gene expression as the NO donor L-arginine inhibited kainic acid-induced proenkephalin and prodynorphin mRNA in the hippocampus [429]. However, the lack of tolerance to morphine analgesia observed in the 129/SvEv strain of mice is likely not related to a deficit in the NO pathway, as sodium nitroprusside and L-arginine, which increase levels of NO, block morphine analgesia in both CD-1 and 129/SvEv mice [202]. Although chronic administration of μ- and κ-agonists are associated with increases in NOS activity, tolerance to the δ-agonist DPDPE is associated with a decrease in NOS activity in the cerebellum and spinal cord, that may explain the inability of NOS inhibitors to attenuate tolerance to DPDPE [37].

Interactions between opiates and other systems also have been noted after chronic morphine. An interaction between opiates and nucleus accumbens dopamine receptors was demonstrated as chronic morphine sensitized morphine-induced dopamine release from the nucleus accumbens [368]. The NMDA receptor probably is involved in morphine-induced sensitization of dopamine release because acamprosate suppressed morphine-induced dopamine release in rats previously exposed to morphine but not after an acute injection of morphine [368]. On the other hand, the effect of acute opiates on accumbens and striatal dopamine release are likely opiate-mediated because they are blocked by both naltrexone and naloxone [102,380]. Serotonergic systems also are involved in tolerance to morphine analgesia as fenfluramine, which increases synaptic availability of serotonin by stimulating serotonin release and inhibiting reuptake, attenuated tolerance in rats continuously infused with 22 mg/kg of morphine daily over 8 days [11]. An up-regulation of cholecystokinin (CCK) receptors may offset the inhibitory actions of morphine and thus contribute to tolerance, as ICV infusion of morphine over 5 days increased CCK8S binding sites in the supraoptic nuclei [272]. Tolerance to morphine analgesia is inhibited by the benzodiazepines as diazepam attenuated tolerance to morphine analgesia [390]. The mechanism of action of diazepam seems to be related to morphine-induced μ-opiate receptor up-regulation because diazepam also inhibited up-regulation of μ receptors in morphine-tolerant rats [390].

Chronic administration of opiates usually results in dependence as measured in terms of the appearance of withdrawal symptoms after cessation of the drug, or when an opiate antagonist is administered. In animals, withdrawal symptoms include abnormal posture [195,305,388], aggression [180], coughing [48], contraction of the guinea pig ileum [58], c-Fos expression [31,322], diarrhea [178,180,183,185,266,305,321,336,360,367,370,388,392], digging [100,321,430,431], ejaculation [305], escape [394], eye twitching [305], grooming [195,321,388,430,431], HPA activity [264], hypothermia [100,180,392], jumping [100,124,178,180,183,191,195,266,309,336,360,390,392], lacrimation [180,305,367,388], lying on the side [48], mastication [180,195], masturbation [48], changes in blood pressure [445], naltrexone-lever pressing [48], naloxone-induced conditioned place aversion [215,295,345], naloxone-conditioned suppression of operant responding [345], excitation of oxytocin neurons [52], time spent in an elevated plus maze [344], paw tremor [322,367,430,431], penile erection [180,305,388], penis licking [195,394,430,431], piloerection [180,185,266,305,367], ptosis [180,183,185,305,336,360,367,388,392,394,430], rearing [195,388,394,430,431], retching [48], changes in regional cerebral blood flow [89], rhinorrhea [180,305,367,388,392], seizures [266], sniffing [360], spontaneous activity/locomotion [180,375,392,394,430,431], salivation [394], scratching [394], changes in sleep patterns [375], stretching [392,394,430,431], tachypnea [266], teeth chattering [178,180,185,195,321,336,360,367,369,388,394,430,431], tremors [178,180,183,360,392], urination [266], vocalization [48,180,367,430,431], vomiting [48], weight loss [100,178,180,321,367,388,394], wet-dog shakes [48,100,180,195,266,321,336,360,367,369,388,392,394,430,431], writhing [185,367], and yawning [48].

In humans, withdrawal symptoms include changes in skin temperature [159,328], irritability [8], aches and pain [338], abdominal cramping [8,83,114,338], sweating [114], nausea [114], changes in respiration [159], lacrimation [369], changes in pupil size [329], changes in heart-rate and blood pressure [114,159,328,338,395], painful joints and muscles [8,114,159,395], muscle spasms [338], insomnia [8,338,395], yawning [8,93,114,159,338,369,395], piloerection [83,369], restlessness [114,369], tremors [144], poor appetite [8], feeling sick [8,338,395], anxiety [83], sweating [83], sneezing [8,83], runny nose [159,369], runny eyes [8,83,159,338,395], chills/coldness [114,159,338,395], hot/cold flashes [8,83,114,159], and depression [8,159].

Chronic morphine produces dependence as shown by precipitated withdrawal by naloxone [31,52,58,100,114,124,137,138,178,179,180,183,185,191,215,264,266,290,295,305,309,328,336,338,345,346,349,351,360,367,388,390,392,394,418,430,431,445], naltrexone [48,83,321,322,338,370], methylnaloxonium [195], and abstinence [48,89,345,367,375,445]. Although opiate dependence was typically studied in adults, neonatal opiate dependence also was demonstrated as naloxone precipitated withdrawal in14-day-old rats given fentanyl for 3 days via an osmotic minipump [392], and in 7-day-old rats exposed to methadone prenatally and postnatally via the dam's milk [24].

Chronic administration of morphine is not necessary for dependence to develop as naloxone-precipitated withdrawal in mice was demonstrated after a single injection of morphine [191]. However, one day of morphine treatment produced less naloxone-precipitated withdrawal than 3 days of

treatment, although no differences were found between 3 and 6 days of morphine treatment [309]. The dose of naloxone did not influence the severity of withdrawal because 8 mg/kg of naloxone did not produce more withdrawal symptoms than 1 mg/kg in mice chronically treated with 30 mg/kg morphine for 3 days [309]. The development of dependence was influenced by pain during morphine administration as naloxone-precipitated withdrawal was higher in neuropathic rats treated with chronic morphine as compared with normal rats [185]. However, morphine dependence was not related to genetic differences in stress-induced analgesia, because naloxone-precipitated withdrawal in mice selectively bred to display high levels of stress analgesia did not differ from mice bred for low levels of stress analgesia [191]. In contrast, mice selectively bred for low levels of levorphanol analgesia showed greater morphine dependence than mice bred for high levorphanol analgesia, suggesting that selection for endogenous (stress) and exogenous analgesia (levorphanol) differentially affects morphine dependence [191]. Further, because mice bred for high stress and levorphanol analgesia also show greater sensitivity to morphine analgesia, it suggests that sensitivity to morphine analgesia cannot predict sensitivity to morphine dependence [191].

Antagonist-precipitated withdrawal is greater than abstinence withdrawal, as naloxone produced a greater number and magnitude of withdrawal symptoms, including naltrexone-lever pressing in rhesus monkeys treated with the long-acting μ-opiate agonist LAAM, as compared with monkeys in which LAAM treatment was discontinued [48]. In addition, the μ-antagonists quadazocine and naloxone, but not μ-agonists nalbuphine or morphine, were able to substitute for naltrexone [48]. Both abstinence and naloxone precipitated anxiogenic-like withdrawal symptoms in morphine-dependent rats, as measured by time spent in an elevated plus maze [345]. Abstinence withdrawal symptoms in rats given chronic morphine were shown to have different acute and long-term consequences, however, as dependent rats showed increased locomotor activity and waking, and a reduction in REM and non-REM sleep 3 to 4 days after morphine [375]. In contrast, although normal REM, non-REM, and waking patterns resumed after 4 days, some of the locomotor effects continued [375].

Long-term opiate treatment is associated with abnormal regional cerebral blood flow (CBF) in the temporal, frontal and parietal lobes during withdrawal [89,128]. However, because this was not correlated with the length or dose of heroin consumption, or the self-ratings of withdrawal, it is likely that these changes are related to long-term heroin use and not withdrawal [89]. In addition, abnormal regional CBF in addicts was correlated with comorbid depression and antisocial tendencies, suggesting that the differences in regional CBF may be related to differences in mood and behavioral traits rather than abuse [128]. Similarities in the neurobiology of depression and drug dependence indicates a possible relationship between these 2 disorders, explaining their often observed comorbidity [242]. The effects of opiates on the pattern of CBF depended on the opiate receptor subtype activated as butorphanol increased CBF in the temporal lobe, whereas hydromorphone increased CBF in the anterior cingulate, thalamus, and amygdala [340]. Furthermore, because butorphanol was subjectively rated as producing 'bad effects' and hydromorphone as producing 'good effects', the patterns of CBF produced by different opiates may provide a useful tool for measuring abuse liability [340].

As opposed to morphine, chronic treatment with the analgesic tramadol does not produce dependence as measured by naloxone-precipitated withdrawal, suggesting that tramadol interacts with both opiate and nonopiate mechanisms and has low abuse potential [266]. CH-13854, which has antitussive properties similar to morphine and codeine, does not produce dependence as measured by naloxone-precipitated withdrawal [180]. However, although the antitussive effects of CH-13854 are blocked by naloxone, nor-BNI, and β-FNA, CH-13854 does not bind to μ, κ, or δ receptors in vivo, suggesting that its mechanisms of action are different than morphine [180]. The analgesic pentazocine, which has mixed κ-agonist and partial μ-agonist/antagonist properties, may have abuse liability because it produces dose-dependent subjective, psychomotor, and physiological effects in humans, including a greater amount of dysphoria and psychomotor impairment than morphine [443]. Levamisole, which produces an elevation of endogenous opiate alkaloids and monoamines, attenuated naltrexone-precipitated withdrawal in rats chronically treated with morphine, suggesting that levamisole may be useful in treating opiate dependence [370]. The calcium channel blocker nifedipine also may offer a new treatment for opiate dependence, as it suppressed the subjective effects of opiates in heroin-dependent subjects, that may be mediated by modification of dopaminergic or opiate transmission [365].

The opiate receptor subtypes that mediate dependence have been further elucidated. Withdrawal signs were precipitated in rats treated chronically with IT morphine when challenged with IT naloxone or the μ-antagonist CTOP. The δ-antagonist naltrindole, however, produced only mild withdrawal signs, and the κ-antagonist nor-BNI had no effect, suggesting that morphine dependence is predominately μ-mediated [430]. In contrast, dependence to the mixed κ-agonist/μ-antagonist butorphanol is likely κ-mediated as rats treated chronically with butorphanol showed strong withdrawal signs after nor-BNI, and mild withdrawal after naloxone and CTOP, and none after naltrindole [430]. The development of dependence after chronic butorphanol, however, may depend on the dose used, as naloxone-precipitated withdrawal signs were evident in rats given high daily doses of butorphanol (30 mg/kg) but not in those given low doses (3 mg/kg) [364]. In nondependent heroin users, naloxone precipitated withdrawal symptoms after morphine, but not after butorphanol, which is likely explained by their different actions at μ and κ receptors [137]. Con-

sistent with these behavioral studies, binding assays revealed that spinal μ and δ, but not κ receptors became supersensitive to their corresponding antagonists in morphine-dependent rats, and in butorphanol dependence μ, δ, and κ receptors are more sensitive [431]. Taken together, these results suggest that spinal μ and to a lesser extent δ receptors are involved in morphine dependence, whereas spinal κ receptors, and partially δ and μ receptors are involved in dependence to butorphanol [430,431]. In contrast, morphine-dependent κ-opiate deficient mice revealed only a slight attenuation in naloxone-precipitated body tremors, ptosis, jumping, sniffing, and diarrhea, and no difference in wet-dog shakes, teeth-chattering, and paw tremor as compared with controls, suggesting that κ receptors are involved in morphine dependence [360]. Antiopiate peptides also modulate withdrawal because treatment with the antisense oligodeoxynucleotide to NPFF mRNA attenuated the development of morphine dependence [124].

As with tolerance, interactions between opiate dependence and nonopiate systems also were noted. The role of catecholamines in dependence was shown as stimulation of the dopamine system with L-dopa potentiated naloxone-precipitated jumping, wet-dog shakes, burrowing, and body weight loss, but inhibited hypothermia [100]. In addition, low doses of the dopamine agonist apomorphine potentiated jumping, wet-dog shakes, burrowing, and hypothermia, but reduced body weight loss [100]. In contrast, the dopamine antagonists haloperidol, pimozide, and flupenthixol inhibited naloxone-precipitated jumping, wet-dog shakes, and burrowing [100]. The effects of dopamine agonists and antagonists are likely mediated in part by noradrenergic pathways since neonatal treatment with 6-OHDA, which destroys noradrenergic nerve terminals, potentiated naloxone-precipitated withdrawal, and tended to reverse the effects of dopamine agonists and antagonists [100]. Dependence induced by chronic administration of the μ-opiate agonist, etonitazene, increased dopamine binding density in the nucleus accumbens after acute withdrawal, but down-regulated dopamine receptor binding after long-term abstinence, suggesting that chronic opiates can produce long-lasting neuroadaptive changes within dopaminergic systems [249]. Chronic morphine also up-regulated tyrosine hydroxylase, an enzyme involved in the synthesis of catecholamines, in both the locus coeruleus and VTA, but by different mechanisms [44]. Opiate dependence can lead to deficits in dopaminergic function because during morphine withdrawal dopamine turnover and release are decreased in the nucleus accumbens and lateral striatum, and dopamine uptake is diminished in the striatum [130]. Dependence to κ-selective opiates also produced changes in dopaminergic systems during withdrawal as repeated administration of the κ-agonist U-69593 produced a depletion in dopamine D_2, but not D_1 receptors, in the caudate and nucleus accumbens 2 to 10 days after cessation of U-69593 treatment [168]. Conversely, cocaine and amphetamine increased prodynorphin mRNA and α-neoendorphin levels in the nucleus accumbens and striatum, which was followed by a long-lasting decrease in κ receptor density [399].

The enhanced neuroendocrine responses during withdrawal may be mediated by noradrenergic pathways because naloxone-induced hypothalamic noradrenergic hypersecretion was correlated with increases in plasma corticosterone and decreased CRF content in the paraventricular and arcuate nuclei in morphine-dependent rats [264]. In contrast, noradrenergic systems are not involved in excitation of oxytocin neurons during withdrawal because treatment with ICV 6-OHDA before chronic morphine did not affect naloxone-induced oxytocin release from the supraoptic nucleus [52]. A review of the literature suggested that the locus coeruleus, a major source of noradrenergic innervation in the brain, plays an important role in withdrawal from opiates [402]. A role of the locus coeruleus in opiate withdrawal is supported by the finding that injections of methylnaloxonium into the locus coeruleus precipitated withdrawal symptoms in morphine-treated rats, and increased cerebral glucose metabolism in brain areas that receive noradrenergic input from the locus coeruleus [195]. In addition, destruction of noradrenergic neurons of the locus coeruleus with the toxin anti-dopamine-β-hydroxylase-saporin increased naltrexone-precipitated withdrawal behavior in morphine-dependent rats, suggesting that activation of locus coeruleus neurons during withdrawal dampens the withdrawal syndrome [322].

The nucleus paragigantocellularis, which has a strong input to the locus coeruleus, also shows enhancement of neural activity after naloxone in morphine-treated rats and thus is likely involved in opiate withdrawal [138]. However, although the α_2-adrenergic agonists, clonidine or ST-91, injected into the locus coeruleus reduced naloxone-precipitated withdrawal, injections into the amygdala produced only mild decreases in withdrawal, suggesting that the amygdala is not a primary noradrenergic site for the induction of withdrawal [388]. Interestingly, clonidine blocks the acquisition, but not the expression of conditioned opiate withdrawal, as naloxone-conditioned place aversion and suppression of operant food responding in opiate-dependent rats was blocked by administration of clonidine before conditioning trials, but not when administered before the test session [345]. Therefore, it is important to recognize that learning may also underlie some aspects of opiate withdrawal [283,295,345], and may involve a separate neural substrate than those underlying unconditioned opiate withdrawal [345].

Interactions between opiate dependence and other transmitter systems were noted. Cholinergic systems may play an important role in mediating the sympathetic component of withdrawal because the acetylcholinesterase inhibitor DPF given during chronic morphine inhibited postwithdrawal increases in mean arterial pressure [445]. The reduction in mean arterial pressure was correlated with an interference with morphine-induced M2 muscarinic receptor adaption, because DPF also inhibited postwithdrawal in-

creases in the expression of M2 muscarinic receptors and mRNA [445]. Naloxone also precipitated withdrawal symptoms in nicotine-dependent rats, suggesting an interaction between opiate and nicotinic receptors [2].

Morphine dependence was inhibited by benzodiazepines as administration of diazepam during chronic morphine attenuated naloxone-precipitated jumping [390]. The effect of diazepam on morphine dependence may be related to μ-opiate receptor up-regulation, because diazepam also inhibited the up-regulation of μ receptors in morphine-treated rats [390]. In addition, diazepam binding inhibitor mRNA, an endogenous peptide with properties as an inverse benzodiazepine agonist, increased after chronic morphine and accelerated after naloxone-precipitated withdrawal [183]. This increase is opiate-mediated because it was prevented by concomitant treatment with naloxone, and suggests that increases diazepam binding inhibitor expression induced by chronic activation of opiate receptors by morphine is involved in the formation of dependence and the appearance of withdrawal symptoms [183].

A role for CCK in dependence has been shown, as the CCK_B antagonist L-365,260 decreased the expression of naloxone-precipitated withdrawal in both normal and neuropathic rats treated with chronic morphine [185]. Interactions between opiate withdrawal and GABAergic systems were also demonstrated as γ-vinyl-GABA, an antiepileptic drug that increases extracellular GABA concentration in the brain, potentiated the severity of naloxone-precipitated withdrawal [336]. However, GABAergic function was impaired only in detoxified heroin addicts with comorbid anxiety disorders, suggesting that the GABAergic system is not directly involved in abuse [129]. ICV administration of neuropeptide Y dose-dependently attenuated naloxone-precipitated withdrawal, particularly motor signs of withdrawal, suggesting the potential therapeutic role for neuropeptide Y in treating dependence [428]. An interaction between endogenous brain cannabinoid systems and opiates was suggested, as the cannabinoid receptor antagonist, SR 141716A induced withdrawal symptoms in morphine-dependent rats [275]. The synthetic congener of ibogaine, 18-methoxycoronardine, attenuated signs of naltrexone-precipitated withdrawal in morphine-dependent rats [321]. Although the mechanism of action of 18-methoxycoronardine is not known, it does not have the adverse side-effects of ibogaine and may have therapeutic value [321].

Chronic morphine produces long-lasting molecular and cellular adaptions that may contribute to dependence, including alterations in cAMP pathways and signaling proteins [36,64,178,179,182,325]. Both long-term exposure to morphine and naloxone-precipitated withdrawal were shown to increase G-protein mediated adenylyl cyclase activity in the striatum but decrease it in the cortex [179]. The increase in striatal G-protein mediated adenylyl cyclase activity is suggested to represent an adaptive compensatory response to inhibition of adenylyl cyclase activity produced by chronic μ receptor activation, that would go unopposed by sudden discontinuation of opiate treatment with naloxone and thus produce withdrawal symptoms [179]. Chronic morphine increased the efficiency of μ-opiate agonists on GABAergic nerve terminals in the PAG, and withdrawal enhanced GABA-mediated electrically evoked inhibitory synaptic currents and increased the frequency of spontaneous miniature GABAergic synaptic currents [164]. It is likely that enhanced cAMP and protein kinase A are involved because it is blocked by protein kinase A inhibitors and metabolically stable cAMP analogs [164].

Chronic treatment with morphine, however, did not alter G-protein-coupled kinase 2 immunoreactivity in rat brains and chronic methadone produced only a modest increase [290]. Similarly, human opiate addicts who died of opiate overdose did not differ in total brain G-protein-coupled kinase 2 immunoreactivity, as compared with controls [290]. However, spontaneous or naloxone-precipitated withdrawal from morphine or methadone in rats led to an up-regulation of G-protein-coupled kinase 2 in the frontal cortex of rats, suggesting that withdrawal-induced up-regulation may be related to removal of a μ-mediated suppression of G-protein-coupled kinase 2 expression [290]. Similar adaptions also were observed in mitogen-activated protein kinase because chronic morphine did not change levels mitogen-activated protein kinase phosphorylation, whereas increased levels were observed in the locus coeruleus, solitary tract and hypothalamus after naloxone-precipitated withdrawal [349]. Treatment with adenosine kinase inhibitors attenuated naloxone-precipitated withdrawal, suggesting that adenosine is involved in withdrawal [178]. The effects of adenosine kinase inhibitors is explained by activation of adenosine receptors because the effects are reversed by the adenosine receptor antagonist caffeine, but not by the selective phosphodieterase inhibitor Ro 20-1724 [178].

Excitatory amino acids are involved in opiate dependence as the noncompetitive NMDA antagonist MRZ 2/579 and the glycine site antagonists MRZ 2/570 and L-701,324 blocked the expression of naloxone-precipitated withdrawal [309]. Similarly, residual naloxone-precipitated withdrawal symptoms observed 3 days after morphine treatment also were reduced by all three NMDA antagonists [309]. Naloxone increased glutamate and aspartate release in the nucleus accumbens in morphine-dependent rats [351], and glutamate from the locus coeruleus in rats chronically treated with morphine or butorphanol [394]. Behaviorally, direct injection of glutamate or naloxone into the locus coeruleus precipitated withdrawal symptoms in morphine- and butorphanol-dependent rats [394]. Because the protein kinase inhibitor H-7 prevented naloxone-induced glutamate release in the locus coeruleus, as well as the withdrawal precipitated by locus coeruleus injections of naloxone and glutamate, the action of glutamate release probably is dependent upon cAMP-dependent protein kinase and/or protein kinase C activity [394]. Acamprosate, an anticraving drug with NMDA antagonist properties that is used for treatment of alcoholism, also may have therapeutic potential

for opiate abuse, as it inhibited naloxone-induced conditioned place aversion in morphine-dependent rats [215]. In contrast, lomotrigine, a glutamate release antagonist, did not attenuate naloxone-precipitated withdrawal in heroin-dependent subjects [328]. Non-NMDA excitatory amino acids also are involved in withdrawal because the non-NMDA antagonist CNQX injected into the locus coeruleus or amygdala attenuated naloxone-precipitated withdrawal [388].

NOS is involved in dependence as systemic injection of NOS inhibitors attenuated some signs of naloxone-precipitated withdrawal and hyperactivity of the locus coeruleus [305]. However, it is not clear why injections of NOS inhibitors directly into the locus coeruleus produced less of a reduction of withdrawal-induced locus coeruleus hyperactivity than systemic injection [305]. In vitro exposure of the guinea pig ileum to morphine, DAMGO, or the κ-agonist U50488H for 4 min produces naloxone-induced contractures that are dose-dependently inhibited by pretreatment with the NOS inhibitor, L-NAME [58]. These effects of both μ- and κ-agonists were dose-dependently reversed by the NOS precursor L-arginine, suggesting the role of NOS in both μ- and κ-opiate withdrawal [58]. Prostaglandins also are likely to be involved in the effects of NOS on opiate dependence because glyceryl trinitrate, which enhances the production of prostaglandins, increased naloxone-induced contractures after exposure to μ- and κ-agonists and reversed the inhibition caused by L-NAME [58]. Withdrawal from morphine produced neuronal hyperactivity in the spinal cord as injection of naltrexone in morphine-dependent rats increased total c-Fos immunoreactivity in the spinal cord [322]. Because both destruction of noradrenergic neurons of the locus coeruleus and spinal transection result in further increases in the magnitude of c-Fos expression after naltrexone, it is likely that the effects of spinal transection are related to a loss of noradrenergic inhibitory control [322]. However, although naloxone-precipitated withdrawal also increased c-Fos immunoreactivity in several subdivisions of the PAG, it did not activate PAG neurons that had projections to the ventromedial medulla [31].

Pharmacotherapies for the treatment of opiate abuse and the management of withdrawal symptoms include both opiate and nonopiate treatments. Long-acting opiate agonists, such as methadone, were used for the management of opiate withdrawal [265,280,298]. The synthetic μ-opiate agonist LAAM also may have therapeutic potential for the treatment of opiate addictions that depended on the dose used, as 75 mg but not 25 mg of LAAM suppressed withdrawal in opiate addicts for up to 96 h after LAAM dosing [159]. Pupil size was correlated with withdrawal symptoms in methadone- and LAAM-maintained opiate addicts, suggesting that pupil size can provide an objective measure of withdrawal during opiate detoxification [329]. Methadone-maintenance decreased illegal heroin use and depression, and increased legal financial outcome [265,298]. Women were less likely to benefit from methadone-maintenance programs, as 38% of women, but only 16% of men, did not complete methadone-maintenance after 2 years [265]. However, this was not supported by another study that found no gender differences in retention rates [343]. The decrease in depression in methadone-maintained patients was not further improved by antidepressants, as the serotonin specific antidepressant fluoxetine did not affect depressive symptoms [298]. In contrast, the antidepressant imipramine was effective in treating depression in a population of methadone-maintained subjects with comorbid depression [281]. Because imipramine treatment also was related to decreases in self-reported substance abuse, it suggests that the improved mood may have contributed to the decrease in abuse [281]. Therapeutic monitoring of methadone concentrations in methadone-maintained patients did not predict heroin use or withdrawal symptoms, as plasma concentrations of methadone or its main metabolite EDDP were not correlated with withdrawal symptoms, and did not differ in patients who tested positive for heroin use [395]. Detoxification from methadone or clonidine treatment can be accomplished successfully during pregnancy, as 59% of women completed detoxification and did not relapse, and showed no evidence of fetal distress or premature delivery [91].

As in 1997, there was continued interest in the use of the partial μ-agonist and κ-antagonist buprenorphine for the treatment of opiate abuse. In contrast to methadone-maintenance, in which it was reported that males showed better retention rates than females [265], buprenorphine-maintained females had better retention and increased rates of abstinence than males [343]. Daily dosing of buprenorphine in opiate-dependent subjects produced slightly fewer withdrawal symptoms than an alternate-day dosing schedule [8]. However, 96% of the subjects preferred alternate dosing when given a choice, suggesting that the differences in withdrawal were not influential, and that alternate-day dosing is a viable alternative to daily buprenorphine dosing [8]. Although buprenorphine itself may have a potential for abuse, the combination of naloxone and buprenorphine has low abuse potential as it produced significant withdrawal as compared with placebo [114]. Dynorphin A_{1-13}, which is selective for κ receptors, but also binds to δ and μ receptors, produced a moderate and brief suppression of withdrawal symptoms in opiate-dependent subjects [369]. Similarly, the novel endogenous neuropeptide delta sleep-inducing peptide, which modulates opiate activity, suppressed withdrawal symptoms in opiate-dependent subjects [22].

Opiate antagonists are used for the treatment of opiate addiction and overdose. In a population of emergency room patients presented with opiate toxicity, 50% showed an initial response to naloxone, including improved respiration and mental function, and the occurrence of withdrawal [418]. However, toxicity recurred in 31% of those patients, which was not related to route of administration, but was more common for long-acting opiates [418]. Rapid opiate detoxification with high doses of opiate antagonists given under general anesthesia can be used safely, as no life

threatening complications were found in opiate addicts administered 12.4 mg naloxone over a 1 h period under methohexial or propofol anesthesia, followed by naloxone infusion and subsequent daily naltrexone treatment [338]. Further, although withdrawal symptoms persisted for 1 week after treatment, only one patient discontinued detoxification treatment and 75% of the patients were willing to be referred for further treatment [338]. In contrast, although only minor complications were found in opiate addicts given oral naltrexone after deep sedation with midazolam, including vomiting and diarrhea, 80% of the patients relapsed during a 6-month follow-up [83]. Furthermore, the benefits of rapid detoxification under general anesthesia are not supported by animal studies, as withdrawal symptoms were more intensified and prolonged when naloxone was administered over 8 h under sodium pentobarbital anesthesia, as compared with rats in which morphine was discontinued [367]. Therefore, although the use of naloxone-precipitated withdrawal under general anesthesia is sometimes used clinically to help manage opiate detoxification, the need for more controlled studies may be necessary to properly evaluate its benefits [284,326]. Genetics also may contribute to opiate addiction. The most common single nucleotide polymorphism in the coding of the μ opiate receptor gene, the A118G variant, was identified in 10% of a sample population of both former heroin addicts and controls [43]. Because the A118G variant shows a threefold increase in β-endorphin binding affinity and potency as compared with the next most common allele, it suggests that individuals with this variant gene may show differences in opiate responses, including vulnerability to opiate abuse [43]. Genetic differences in dopaminergic function may also contribute to opiate use, as opiate addicts with high sensation seeking scores were more likely than low sensation seekers to display a higher frequency of homozygosity at the dopamine D_3 receptor *Bal I* polymorphism [94]. Genetic factors also may contribute to mental illness in children of opiate addicts, as male offspring of addicts with comorbid depression showed a higher incidence of childhood psychopathologies [282].

There is evidence that drug craving is an important motivating factor in opiate dependence that may contribute to relapse after long periods of abstinence. Opiate addicts who had been drug free for at least one year and asked to describe a strong craving for opiates showed increases in blood pressure and heart rate, and subjective ratings of craving, as compared with neutral descriptions, suggesting that imagery can induce craving and may contribute to relapse [421]. The neural mechanism that mediate drug craving were elucidated, and included increased metabolic activity in the basal ganglia, which interestingly is similar to those seen in obsessive-compulsive disorder [421]. A review of the literature suggests that learning may play a role in drug dependence and craving, as stimuli associated with drug use can under certain situations elicit drug craving and withdrawal [283]. However, although there is evidence that stimuli (both external and internal imagery) associated with opiate use can elicit both physiological and subjective states of craving in abstinent drug addicts, whether that motivates drug taking and contributes to relapse is not conclusive [283,421]. An integrative model of addiction was presented which emphasized the relationship between chronic drug use, disruption of the HPA axis, and dysregulation of brain reward systems [216]. Because changes in stress and reward systems can persist for long periods, such a model may be useful in explaining not only the acquisition and maintenance of opiate addiction, but also the potential for relapse after extended abstinence [203,216]. Indeed, foot-shock reinstated drug seeking behavior after a period of extinction in rats trained to self-administer heroin, suggesting that stress may contribute to relapse in opiate addicts [368].

4. Eating and drinking

There was continued interest in the role of opiate systems in the modulation of eating and drinking. As in previous years, in 1998 the effects of opiate agonists and antagonists were examined, with special emphasis focused on the palatability of the food. In general, opiate agonists tended to increase food intake, including sucrose [149], carbohydrates [446], and fat [149,446], that occurred under a variety of different conditions [133,134,167,228,229,446]. As was typical of most μ-agonists, ICV injections of the recently isolated tetrapeptides endomorphins-1 and -2 dose-dependently increased food intake in mice for up to 4 h after injection [19]. The morphine metabolite, morphine-6β-glucuronide also increased feeding that was μ-mediated because it was dose-dependently attenuated by the μ-antagonist, β-FNA, but not by δ_1-, δ_2-, or κ_1-antagonists, or by an antisense oligodeoxynucleotide directed against δ_1,κ_1, or κ_3 receptor clones [228,229]. However, although an antisense oligodeoxynucleotide directed against either exons 2 or 3 of the MOR-1 clone blocked morphine-6β-glucuronide-induced hyperphagia, an antisense oligodeoxynucleotide directed against exons 1 or 4 did not. This is in contrast to morphine-induced hyperphagia which is reduced by an antisense oligodeoxynucleotide against exon 1 but not exon 2, suggesting that morphine-6β-glucuronide-induced hyperphagia is mediated by a receptor that is distinct from traditional μ-agonists [229]. Therefore, although morphine and its metabolite have similar effects on feeding, it is unlikely that a single opiate receptor subtype is responsible for their common effects [229]. Endogenous opiate systems are involved in the hyperphagic actions of glucoprivic agents, as hyperphagia induced by the anti-metabolic glucose analog 2-deoxy-D-glucose is reduced by an antisense oligodeoxynucleotide directed against exons 1 or 2 of the MOR-1 clone [57]. However, similar to the effects of μ-agonists, these effects are exon specific because an antisense oligodeoxynucleotide directed against exons 3 or 4 of the MOR-1 clone only had limited effects [57].

Besides μ receptors, κ and δ receptors are involved in feeding as hyperphagia was induced by the selective δ_2-agonist Delt II, κ_1-agonist U50488H, and κ_3-agonist nociceptin/orphanin FQ, which was blocked by antisense oligodeoxynucleotides directed against δ_1,κ_1, or κ_3 receptor clones, respectively [228,229]. In contrast, although 2-deoxy-D-glucose-induced hyperphagia was decreased by antisense oligodeoxynucleotide-induced knockdown of κ_1 and κ_3 receptors, it was not affected by an antisense oligodeoxynucleotide directed against the δ receptor [57]. Consistent with the role of the κ receptor in mediating eating and drinking, ICV injection of the κ receptor agonist dynorphin $A_{1\text{-}17}$ increased feeding in rats, and U50488H increased both the number of licks and duration of licking bouts for both a sucrose or a fat solution. However, although morphine also increased the number of licks and the number of bouts for both a sucrose or a fat solution, the mean duration of licking bouts decreased for the fat solution [149]. Because bout duration may be a reflection of palatability, it is possible the differential effects of κ and μ receptor agonists reflects differential effects related to palatability [149]. However, the decreased consumption of a flavored solution by the δ-antagonist naltrindole may be related to its aversive effects, because intake of a banana flavored solution in rats was decreased if it was previously paired with injections of naltrindole [113].

The neural mechanisms that mediate opiate-induced feeding have been further elucidated. Injection of DAMGO into the central nucleus of the amygdala or the paraventricular nucleus of the hypothalamus increased food intake as compared with controls [133]. It is likely that a direct opiate-mediated pathway exists from the paraventricular nucleus to the amygdala that influences feeding because injection of naltrexone into the paraventricular nucleus abolished feeding induced by DAMGO injections into the amygdala [133]. However, a similar reciprocal connection does not exist because injections of naltrexone into the amygdala did not affect feeding induced by DAMGO injections into the paraventricular nucleus [133]. In contrast, a reciprocal opiate–opiate connection exists between the central amygdala and nucleus of the solitary tract because naltrexone injected into the amygdala blocked feeding induced by DAMGO injections into the solitary tract, and vice versa [134]. Injection of DAMGO into the nucleus accumbens also increased feeding that is opiate-mediated because it is blocked by naltrexone [446]. However, the effects of DAMGO are likely related to the palatability of the food because DAMGO stimulated the intake of fat or carbohydrates diets when presented individually, but preferentially affected fat intake when the diets were presented simultaneously [446]. In contrast to the differential effects of DAMGO, food deprivation increased intake of both diets equally, and this shifted to a fat diet preference after intra-accumbens DAMGO [446]. The effects of both DAMGO and food deprivation on fat intake are opiate-mediated because in both paradigms fat intake was blocked by naltrexone [446]. Taken together these results suggests that endogenous opiates located within the nucleus accumbens are involved in the mechanisms underlying preferences for highly palatable foods, in particular foods high in fat [446]. The preferential effects of opiates on high fat food may have had evolutionary significance to ensure animals obtain high caloric foods during times of food shortages. However, in modern times where the food supply is abundant, such an overactivation of opiate systems may contribute to obesity [297,446].

The effects of opiate antagonists can be inconsistent, as they sometimes decreased feeding behaviors [39,149,380, 425,446], but in some conditions had no effect [109,217, 229,361,380]. Systemic injection of naltrexone reduced food consumption in hungry rats, that was not mediated by opiate receptors in the VTA because unilateral injection of naltrexone into that brain area was ineffective [380]. Naloxone did not affect food palatability in nondeprived rats, as naloxone decreased the number of licks and bouts for sucrose and fat solutions, but had no effects on the duration of bouts [149]. In contrast, in hungry rats injection of naltrexone into the nucleus accumbens inhibited fat intake more than carbohydrates, suggesting that effects of naltrexone on food palatability may depend on the motivational state of the animal [446]. Naltrexone decreased the intake of sweet solutions, including decreased sucrose-reinforced responding in rhesus monkeys [425], and decreased intake of both chocolate and saccharin solutions in high-alcohol preferring rats [39]. Not all opiate antagonists suppressed eating and drinking, however, as the selective μ-antagonist β-FNA did not alter the intake of water or a saccharin solution [217] and did not alter food intake at doses that effectively blocked morphine-6β-glucuronide-induced hyperphagia [229]. In addition, glycyl-L-glutamine, which is co-released with β-endorphin and antagonizes the effect of β-endorphin, did not affect food or water intake in high-alcohol-preferring rats, even though it reduced alcohol intake [361]. Similarly, neither naloxone nor the selective δ-antagonist, ICI-174864 affected water or food intake [109]. The reasons for these discrepancies are not clear, but may not be too surprising given the complex interactions between opiate systems, motivational states, and food palatability.

Eating a palatable meal high in fat and sucrose increases c-Fos immunoreactivity in neuroanatomical substrates of motivation and reward, including the lateral hypothalamus, VTA, and medial preoptic area, but decreased c-Fos in the habenulla [294]. Actual ingestion of the food is not necessary, however, as rats placed in an environment that had been previously paired with the meal showed increases c-Fos expression in the VTA and nucleus accumbens, that is probably related to the conditioned rewarding effects of the food-paired environment [294]. Because naltrexone blocked increases in c-Fos immunoreactivity in both food- and environment-paired conditions, without blocking consumption of the meal, it is likely that naltrexone blocks the rewarding effects of the food [294]. Further, the blunting of the inges-

tion reward may be related to activating effects on opponent neural activity, as naloxone alone also increases c-Fos immunoreactivity in the VTA, nucleus accumbens, central amygdala, and bed nucleus of the stria terminalis [294]. However, the pattern of c-Fos immunoreactivity seems to depend on the motivational state of the animal, as naltrexone increases in c-Fos immunoreactivity in the bed nucleus of the stria terminalis and the central amygdala in free feeding rats, whereas in food deprived rats naloxone increased c-Fos in the lateral and dorsomedial hypothalamus, and arcuate hypothalamus [60].

Endogenous opiates also may contribute to obesity, as waist to hip ratios in obese women was correlated with higher plasma β-endorphin levels [297]. Because plasma β-endorphin levels were higher in obese women with high insulin resistance, and insulin sensitivity was negatively correlated with β-endorphin levels, it is possible that the reduction in insulin sensitivity results from the additive effects of obesity, elevated β-endorphin, and changes in metabolic and endocrine activity [297]. This also raises the possibility that elevated β-endorphin in obesity may contribute to type 2 diabetes by modulating insulin sensitivity and secretion [297]. Indeed, obese-diabetic mice, which were used as an animal model of type 2 diabetes, showed an up-regulation of both β-endorphin and its receptors in the spinal cord as compared with lean mice [233]. However, obesity does not alter the pharmacokinetics of the short-acting opiate, remifentanil, suggesting that dosing of opiates should be based lean body mass, not total body weight [98].

Chronic perinatal malnourishment also impairs endogenous opiate systems, as activation of opiate systems by chronic stress attenuates clonidine-induced hypoactivity in controls but not in malnourished rats [186]. Because the effects of stress are reinstated by pretreatment with morphine or β-endorphin, it possible that the process of adaption to chronic stress in malnourishment rats leads to a deficiency in the endogenous opiate systems [186]. In contrast, however, anorexia induced by central lipopolysaccharide (LPS) or muramyl dipeptide did not affect hypothalamic POMC mRNA [123].

Interactions between opiate and nonopiate systems in eating also were noted [133,380,385]. An interaction between neuropeptide Y and opiate systems was demonstrated, because neuropeptide Y injected into the paraventricular nucleus increased feeding, that was antagonized by injection of naltrexone into the central amygdala [133], or the rostral nucleus of the solitary tract [205]. Feeding-induced dopamine release from the nucleus accumbens was opiate-mediated because systemic injection of naltrexone blocked it [380]. In contrast, unilateral injection of naltrexone into the VTA was ineffective, suggesting that opiate receptors in this brain area do not contribute to feeding-induced dopamine release [380]. However, the role of the VTA on dopamine release may be related to the palatability of the food, as bilateral injection of naloxonazine, an irreversible μ_1-antagonist, blocked accumbens dopamine release induced by the highly palatable food, Fonzies [385].

5. Alcohol

In 1998, as had been the trend in previous, interest in the modulation of alcohol intake by endogenous opiate systems continued to grow. A number of different paradigms were used to study the effects of opiate antagonists on alcohol intake, including limited alcohol access [377,378], two-bottle free choice [109,217], and ethanol-reinforced responding [135,425,426]. Although opiate antagonists generally decreased alcohol consumption in most paradigms and species used, the mechanisms by which they do so is not fully understood because opiate antagonists also decreased consumption of nonalcoholic solutions [39,377,378,425, 426]. Therefore, whether the effects are specific to alcohol, or explained by nonspecific effects on fluid consumption in general is not conclusive. However, because opiate systems interact with brain reward systems and opiate antagonists decrease ethanol reinforcement, it is likely that in addition to nonspecific effects on fluid consumption, opiates also affect alcohol consumption by modulating the reinforcing properties of alcohol [425,426].

In general, naltrexone decreases alcohol intake [46,109, 135,377,378,425]. The paradigm used was unimportant as naltrexone similarly reduced ethanol consumption in rats by using either a two-bottle free choice paradigm [109] or limited access paradigm [378], and in monkeys by using ethanol-reinforced operant responding [46,425]. However, it is not clear whether the effects of naltrexone are specific to ethanol consumption or on consumption in general, as naltrexone also reduced intake of chocolate, sucrose, and water solutions [39,425,378]. The route of ethanol intake did not seem to influence the effects of naltrexone, as ethanol-reinforced responding was decreased in rhesus monkeys independent of whether the monkeys self-administered ethanol orally or IV [46]. The effects of altering ethanol concentration were inconsistent, however, as drug-experienced rhesus monkeys showed naloxone-induced decreases at ethanol concentration above 2%, but increased responding occurred in several monkeys at concentrations below 2% [46]. In contrast, although ethanol-reinforced responding in monkeys showed an inverted-U for the ethanol-concentration curve, with most responding occurring at the 1 to 2% concentration, naltrexone decreased ethanol self-administration independent of the concentration [425].

The effects of chronic administration of naltrexone on alcohol intake have been studied but were inconclusive. In rats, naltrexone administered daily suppressed alcohol intake over both a 30- and 60-day observation period, suggesting that longer clinical use of naltrexone may be beneficial for reducing the risk relapse in alcoholics [378]. In addition, although tolerance did not develop to repeated naltrexone, based on receptor up-regulation or supersensi-

tivity, ethanol consumption during the final third of the 30- and 60-day paradigms was lower than during the initial sessions and remained suppressed after naltrexone treatment was terminated in the 60-day group [378]. This decrease may reflect the ability of naltrexone to block the reinforcing properties of ethanol, such that the animals learned that ethanol was no longer reinforcing across repeated exposures and thus reduced intake [378]. In contrast, however, the effects of naltrexone on ethanol-reinforced responding in drug-experienced rhesus monkeys was transient, as ethanol consumption was decreased by up to 52% after the first naltrexone injection, whereas chronic administration decreased consumption by only 26%, suggesting that tolerance develops to the effects of naltrexone [46]. Furthermore, because ethanol-reinforced behavior recovered after termination of naltrexone injections, it is unlikely that naltrexone produced any learned changes in behavior [46]. Daily injections of naltrexone or the hypertensive agent isadipine may be useful for the long-term treatment of alcohol abuse, because they decreased alcohol intake for up to 21 days when given alone or combined [80].

Additional confusion arises in determination of the opiate receptor subtypes that mediate alcohol consumption. Although both naltrexone and β-FNA decreased ethanol consumption in rats in a limited access paradigm naltrindole did not, suggesting that ethanol consumption is mediated by μ but not δ receptors [377]. In direct contrast, however, the selective δ-antagonists, ICI-174,864 and naltrindole, but not the selective μ_1-antagonist, naloxonazine, reduced ethanol intake in rats by using a two-bottle free choice bottle [109]. The effect of ICI-174,864 and naltrindole are likely explained by interactions with central δ receptors because systemic naloxone methiodide, a nonselective opiate antagonist that does not cross the blood–brain barrier, had no effect [109].

To add to the confusion, ethanol-reinforced responding in monkeys was unaffected by selective μ-, κ-, and δ-antagonists, which was then decreased when naltrexone was given concurrently with the antagonists [426]. This raises the interesting possibility that the effects of naltrexone on alcohol consumption are explained by its interaction with a distinct, uncharacterized opiate receptor site, or through a nonopiate mechanism [426]. Indeed, the effects of naltrexone on ethanol-reinforced responding are not characteristic of traditional opiate antagonist effects, as the effects of naltrexone are not overcome by increasing the oral concentration or IV dose of ethanol, and the doses required to affect ethanol-reinforced responding are much higher than those needed to antagonize the effects of exogenous opiate [425,426]. A nonopiate mechanism was suggested, as naltrexone suppressed self-administration of an ethanol/saccharin solution and prevented increases in dialysate dopamine levels in the nucleus accumbens [135]. Because dose-effect analyses revealed a correlation between the reduction of ethanol intake and the ability of naltrexone to attenuate the efficiency of ethanol to elevate dialysate dopamine levels, it is possible that the effect of naltrexone on alcohol intake is explained by interference with ethanol-induced dopamine release [135]. It is not likely that the addition of saccharin to the ethanol solution could account for these findings because saccharin alone does not increase dialysate dopamine levels, and increases in dialysate dopamine produced by saccharin-containing ethanol does not differ from the effects of ethanol alone [135].

Alcohol intake is associated with changes in endogenous opiate systems that depend on the brain site studied, as a single injection of ethanol increased levels of β-endorphin-like peptides in the hypothalamus, but decreased levels in the hindbrain [310]. However, the increase in hypothalamic β-endorphin levels is not explained by increases in synthesis as ethanol did not alter hypothalamic POMC mRNA [310]. However, the effects of ethanol on β-endorphin levels and POMC mRNA may depend on the amount of ethanol, as moderate plasma levels of ethanol increased β-endorphin immunoreactivity in the VTA, whereas higher concentrations increased levels in the VTA and nucleus accumbens, and increased hypothalamic POMC mRNA [318]. Behaviorally, a relationship between alcohol intake and β-endorphin activity was demonstrated as glycyl-L-glutamine, which is co-released with β-endorphin and antagonizes the effect of β-endorphin, reduced alcohol intake in high-alcohol-preferring rats, without affecting food or water intake in high-alcohol-preferring rats [361]. In contrast to acute alcohol effects, chronic administration of ethanol (160 mg/kg/day for 7 days) had no effect of predynorphin and preproenkephalin mRNA in the striatum [247]. The activity of neutral endopeptidase, an enzyme that inactivates a number of peptides including enkephalins, was correlated with alcohol consumption in coal miners, suggesting a possible role of this enzyme in mediating alcohol intake [112]. However, the relationship between serum neutral endopeptidase activity, endogenous opiates, and alcohol consumption is not known, and is probably not causally related as neutral endopeptidase does not cross the blood–brain barrier [112].

The contribution of genetics in mediating alcohol intake were studied in rodent lines bred for high and low alcohol intake. Repeated injections of alcohol produced a greater increase in POMC mRNA in the anterior and neurointermediate lobes of the pituitary in alcohol-preferring rats, as compared with alcohol-nonpreferring lines, suggesting that high alcohol intake may be associated with increased responsiveness of endogenous opiates to alcohol [217]. Similarly, although high and low alcohol-preferring rats did not differ in basal preproenkephalin mRNA content, acute alcohol challenge produced increases in preproenkephalin mRNA in the nucleus accumbens in alcohol-preferring rats but not nonpreferring rats [230]. Furthermore, even without ever being exposed to alcohol, μ-opiate receptor binding in alcohol-preferring lines, was higher in limbic areas, including the olfactory tubercule, nucleus accumbens, basolateral/lateral amygdala, lateral septum caudate-putamen [250],

and substantia nigra [363], but lower in the areas of the hippocampus [250,363], and posterior medial cortical amygdala [250]. Because these limbic areas also are critical to mediating reward, these results suggest that innate differences in brain reward systems may contribute to higher alcohol intake by modifying the reinforcing properties of alcohol [230,250,363]. Behaviorally, because β-FNA dose-dependently decreased alcohol intake with or without saccharin, but did not decrease the intake of water or a saccharin solution alone, it suggests that alcohol intake in this line of rats is μ-mediated [217].

Besides differences in μ receptor activity, differences in δ receptors activity also may contribute to genetic differences in alcohol intake, as δ-opiate receptor binding also was different between high and low alcohol-preferring lines [363]. Differences also were noted in lines of mice that differed in alcohol withdrawal-induced seizure activity, as withdrawal seizure-prone mice had higher concentrations of Met-enkephalin than seizure-resistant mice [307]. These differences were not explained by differences in synthesis or rate of transport out of the brain, because no differences were found in preproenkephalin mRNA or peptide transport system-1 activity [307]. Because withdrawal seizure-resistant mice drink more ethanol than withdrawal seizure-prone mice, ethanol withdrawal seizure activity and consumption are inversely related, but both are probably mediated by Met-enkephalin [307].

In humans, there is evidence that genetics are involved in alcoholism that is related to differences in endogenous opiate activity, as nonalcoholic offspring of families with a high incidence of alcoholism showed a greater cortisol response to a naloxone challenge as compared with offspring of nonalcoholic parents [415]. Therefore, diminished hypothalamic opiate activity may provide a marker for identifying individuals at risk for alcohol dependence [415]. However, whether alcohol-seeking behavior is a means of compensating for diminished hypothalamic opiate activity cannot be concluded, as other factors could contribute altered opiate activity in these individuals, including chronic stress associated with dysfunctional families [415]. Genetic differences in μ-opiate receptor activity and alcohol dependence in humans is not conclusive, as there was an association between OPRM-1 alleles (the gene coding for the μ-opiate receptor) and alcoholism, but only for Caucasians and when subjects with alcohol or drug dependence were combined [213].

Besides alcohol consumption, the role of endogenous opiates in modulating the motivational effects of alcohol also were studied. The conditioned place preference paradigm was used to measure the motivational effects of alcohol, in which alcohol (unconditioned stimulus) was paired with a neutral environment (conditioned stimulus), and the ability of the environment to then produce a conditioned approach (preference) or avoidance (aversion) response in the absence of alcohol was measured. Stress may be important in modulating the rewarding effects of alcohol because ethanol induced a conditioned place preference when paired with foot-shock stress, but not in the absence of foot-shock [248]. It is likely that the rewarding effects of ethanol under stressful conditions are mediated by μ and δ receptors, but not κ receptors, because they are blocked by naloxone, β-FNA, and naltrindole, but not by nor-BNI [248]. In support of this, ethanol without foot-shock produced a conditioned place preference when combined with nonreinforcing doses of morphine or the selective δ-agonist TAN-67, but not with the κ-agonist U50488H [248]. The development of conditioned place preference depended on the whether the alcohol was give before or after the conditioned stimulus, as ethanol injected before presentation of the neutral stimulus produced a conditioned place preference, whereas ethanol given after produced a conditioned place aversion [84].

It is likely that the rewarding effects ethanol may be maintained by the release of endogenous opiates, because naloxone facilitated the extinction of the place preference, but enhanced the place aversion and thus increased resistance to extinction [84]. Moreover, because naloxone weakened ethanol-induced approach behavior (preference), whereas enhancing avoidance behaviors (aversion), it supports the use of opiate antagonists for the treatment of alcohol dependence [84]. Alcohol also produced a conditioned taste aversion as consumption of a banana–flavored solution was decreased when paired with injections of naloxone [113]. Alcohol aversive may be mediated by the δ receptor because doses of ethanol or naltrindole that did not produce a conditioned taste aversion became aversive when given in combination [113].

Alcohol affects other behaviors as well, some of which are opiate-mediated and some are not. The role of opiates in mediating attentional processes was examined by assessing the effects of alcohol on auditory event-related potentials in healthy social drinkers asked to detect deviant tones presented to one ear while ignoring tones to the other [169]. When presented with this task, ethanol administration produced changes in event-related potentials that reflected impairments in selective attention and involuntary attention switching [169]. However, although naloxone blocked some of the effects of alcohol on attention, it augmented the effects of ethanol on attentive processing of stimulus change, which may have relevance for alcoholics who relapse during naltrexone treatment [169]. Repeated ethanol injections also decrease spontaneous locomotor activity that is opiate-mediated because it is antagonized by naloxone [7]. However, the effects of chronic ethanol on open field activity and avoidance behavior in a shuttle box are not antagonized by naloxone and are thus nonopiate [7]. Alcohol also interacts with endogenous analgesic systems depending on the route of administration, as ethanol injections but not ethanol drinking decreased the subsequent expression of stress-induced analgesia [30]. However, it is likely that alcohol does not interact with opiate analgesic systems, because pretreatment with alcohol injections reduced nonopiate stress-induced analgesia, but not opiate-mediated

stress-induced analgesia [30]. The κ-opiate receptor mediates ethanol induced motor incoordination, as cerebral infusion of κ-agonists accentuate the effect of alcohol, whereas as κ-antagonists prevent it [90]. Alcohol also may negatively affect the male reproductive system, as ethanol suppressed testosterone in 45- and 55-day-old rats, an affect that was opiate-mediated because it was prevented by naltrexone [101].

Because naltrexone typically suppresses intake of alcohol, it has been used in the treatment of alcoholism with the hopes of both reducing alcohol use in subjects prophylactically taking naltrexone and causing extinction of drinking [362]. Alcoholic subjects given an injection of sustained-release naltrexone to deliver the medication over a 4-week period combined with psychotherapy showed a reduced frequency of heavy drinking as compared with placebo controls given psychotherapy, both during the injection period and in a 4-week postinjection follow-up [214]. Naltrexone treatment in depressed alcoholics may have beneficial effects as it decreased the number of drinks and cravings for alcohol, and there was a trend toward improvement of depression as well [333]. However, replication of these finding with a double-blind placebo-controlled study is needed to confirm its clinically efficiency in this population. Alcoholics with comorbid cocaine use may not benefit from naltrexone treatment, as comorbid users given naltrexone daily for 8-weeks did not differ from placebo controls with respect to consumption, although both groups showed a reduction [148].

6. Gastrointestinal, renal, and hepatic functions

As in 1997, interest in the role of endogenous opiate systems in gastrointestinal (GI), renal, and hepatic function continued. As reported in previous years morphine inhibited GI function, including transit and gastric emptying [16,17, 315,386,440], and this was reversed by naloxone [16,17, 386]. In contrast, although the mechanisms are not known, a paradoxical effect of naloxone was reported as naloxone inhibited gastric emptying of saline and milk in rats [18]. However, because naloxone did not affect GI transit, it is likely that the mechanisms that mediate gastric emptying and transit are different [18]. The effect of morphine on delaying gastric emptying should be of concern at low doses as well, as a single dose of 0.05 mg/kg morphine given to healthy volunteers decreased the rate of gastric emptying, as measured by acetaminophen absorption [440]. Such effects of low doses of morphine on gastric emptying are of clinical importance because patient controlled analgesia protocols use repeated low doses of morphine for pain control [440]. Gut motility and transit changes also are a concern for opiate addicts receiving long-term methadone-maintenance, as 58% of patients experienced constipation, which was a serious problem in 2 of the 19 patients studied [439]. The increased reports of constipation and laxative use in opiate addicts also corresponded with delayed GI transit as measured by the lactulose hydrogen breath test, suggesting that tolerance does not occur to the unwanted GI side effects of opiates [439].

Morphine and the mixed agonists-antagonists nalbuphine and pentazocine inhibit gastric emptying of indigestible solids (steel balls), and effect that is opiate-mediated because it was antagonized by naloxone [16]. However, although the inhibitory effects of nalbuphine were antagonized by naloxone at doses that antagonized the effects of morphine, higher doses were required to antagonize the effects of pentazocine, suggesting that the effects of pentazocine are explained by interactions with different opiate receptors than morphine and nalbuphine [16]. Morphine, nalbuphine and pentazocine also delayed both gastric emptying of saline and GI transit [17]. It is likely that nalbuphine acted as a partial μ-agonist, whereas pentazocine acted as a full μ- or non-μ-agonist, because nalbuphine antagonized the effects of morphine on gastric emptying and GI transit, but pentazocine did not [17]. However, the effects of pentazocine are probably not explained by its action at the κ receptor, as U50488H did not affect gastric emptying and GI transit [17]. Furthermore, although nalbuphine and pentazocine delayed gastric emptying of both liquids (saline) and indigestible substances (steel balls), the mechanisms by which they did so are likely different because nalbuphine was more potent than pentazocine on the gastric emptying of steel balls [16], whereas pentazocine was more potent than nalbuphine for the emptying of saline [17].

Selective μ-, δ-, and κ-agonists dose-dependently decrease the velocity of colonic propulsion in isolated segments of the guinea pig colon, whereas selective μ-, δ-, and κ-antagonists dose-dependently increase colonic propulsion [108]. It is likely that the δ receptor is preferentially involved in this response because naltrindole was more potent than nor-BNI and CTOP [108]. Furthermore, interactions between opiate and serotonergic systems were noted as combinations of naltrindole and 5HT agonists acted synergistically to facilitate colonic propulsion [108]. The novel δ receptor agonist SNC 80 also decreased GI transit and colonic propulsion, and this was antagonized by naloxone, naltrindole and the μ_1-antagonist naloxonazine [49]. It is likely that SNC 80 inhibits GI transit and colonic propulsion via a central mechanism because its effects are not antagonized by peripherally injected naloxone methiodide, an opiate antagonist that does not cross the blood–brain barrier [49]. However, because SNC 80 inhibits GI propulsion at much lower doses than required to achieve analgesia, its use as an analgesic may be limited [49]. Nociceptin/OFQ also is involved in GI function because it stimulated contractions in the isolated colon, and accelerated the rate of colonic transit in anesthetized rats [386]. However, the effects of nociceptin on colonic contractions and transit are probably nonopiate-mediated because they were unaffected by naloxone, naltrindole, and nor-BNI [386].

Chronic intestinal inflammation induced by croton oil increases GI transit and enhances the antitransit effects of morphine, fentanyl, DPDPE, loperamide, but not U50488H, which were reversed by their specific antagonists [315]. Furthermore, because the dose of β-FNA needed to antagonize the antitransit effects of 1 mg/kg of morphine were higher after chronic croton oil than in controls, it suggests that the active concentration of μ-opiate receptors is increased during chronic inflammation [315]. The κ-opiate receptors agonists, U50488H, nalBzoH, and bremazocine, but not μ- or δ-opiate agonists attenuated high-voltage activated calcium currents in colonic sensory nerves, and this was attenuated by naloxone and nor-BNI [379]. This inhibition of calcium currents in the rat colon sensory nerves by κ-agonists may contribute to their selective analgesic effects in visceral-mediated pain [379].

Stimulation of the vagus nerve causes the release of acetylcholine from the isolated rat stomach, which is μ-opiate-mediated as it is inhibited by β-endorphin, but not by Leu-enkephalin or U50488H, with the effects of β-endorphin blocked by naloxone [437]. Similarly, the recently identified endogenous μ-opiate agonists, endomorphins 1 and 2, also inhibited acetylcholine release [437]. External anal sphincter control is opiate-mediated as ICV and IT injection of morphine and Leu-enkephalin decreased reflexive sphincter responses after stimulation of the pudendal nerve, and affect that was blocked by naloxone [1]. Because spinalization at the cervical and lumbar levels also blocked the effects of morphine and Leu-enkephalin, it is likely that supraspinal opiate neurons control motility of the external anal sphincter [1]. However, the inhibitory effects of opiates disappeared in animals treated with nicergoline, an α_1-adrenoreceptor antagonist, suggesting an interaction with noradrenergic neurons [1].

The classic guinea pig ileum preparation has been used to determine opiate modulation of contractions of the ileum. Morphine inhibited electrically induced contractions of the guinea pig ileum [171,382] that showed signs of tolerance after chronic incubation [171]. The inhibitory effects of morphine on electrically induced contractions in guinea pig ileum is μ_2-mediated because it was prevented with pretreatment with β-FNA [382]. However, when the dose of β-FNA was increased, no further inhibitory effect was observed, suggesting that the existence of β-FNA-sensitive and -resistant μ_2 receptors [382]. This was complimented by the competitive inhibition curve for binding of [^{3}H]naloxone by morphine that showed the presence of low- and high-affinity μ receptor sites [382]. Although the κ-agonist fedotozine causes a concentration-dependent contraction of intestinal cells, it is not explained by interaction with κ receptors, as it is not modified by naloxone, and the κ-agonist U50488H is without effect [76]. In preparations incubated with morphine, DAMGO, or U50488H, naloxone-induced contractions indicating opiate withdrawal were enhanced by increasing the production of prostaglandin [58].

Opiate receptors are involved in renal excretory function. As compared with saline-controls, morphine, fentanyl, nalbuphine, and buprenorphine delayed full bladder sensations, increased bladder capacity, and increased the volume at which patients desired to void [236]. With the exception of morphine, these opiates also increased residual volume after voiding [236]. Bladder contractions decreased after fentanyl and buprenorphine but not after morphine and nalbuphine, and micturition was inhibited in some patients after morphine, fentanyl, and buprenorphine [236]. IV infusion of the δ-agonist BW373U86 at a rate of 50 μg/kg/min, or peripheral injection of SNC80, increased urine flow rate and sodium excretion, that were prevented by pretreatment with naltrindole [354]. In contrast, infusion of 30 μg/kg/min produced diuresis without affecting urinary sodium secretion, and 10 μg/kg/min had no effect [354]. However, it is unlikely that δ-opiate systems exert a tonic influence on renal responses, as naltrindole alone had no effect [354]. The κ receptor is also involved in renal function that is sex-dependent, as the κ-agonist U69,593 produced significantly less urine output in females as compared with males [79]. Because no sex differences were found in the analgesic effects of U69,593 or the brain/blood ratio of [^{3}H]U69,593, it is unlikely that this difference is due to differences in pharmacokinetics [79].

Endogenous opiate systems are involved in liver disease, in particular δ ligands, as patients with hepatic encephalopathy had higher plasma Met-enkephalin levels as compared with healthy volunteers and patients with lumbar back pain, whereas levels of β-endorphin and Leu-enkephalin were not significantly elevated [441]. These increased levels of Met-enkephalin suggest a possible pathophysiological role for δ-opiate ligands in hepatic encephalopathy and provide a rationale for treatment of this disease with opiate antagonists [441]. Endogenous opiates may also be involved in pruritus in liver disease, as naloxone reduced itching in patients with cholestatic liver disease [35,391].

7. Mental illness and mood

As in previous years, interest in the possible role of opiate systems in the modulation of mental illness and mood continued to decline. A likely contributing factor to this decline was the continued failure to demonstrate any clear global therapeutic benefit from treatment with opiate antagonists, thus obscuring the role of endogenous opiate systems in mediating mental illness. However, it is clear that endogenous opiate systems interact with many neurotransmitter systems involved in different mental illnesses, thus providing a rationale for the use of opiate antagonists in combination with other medications or behavioral therapies to target specific behaviors rather than the diseases themselves [320].

Naltrexone treatment has no clinical benefits for the treatment of schizophrenia, as patients given naltrexone

during neuroleptic treatment showed no differences in the positive or negative symptoms of schizophrenia as compared with placebo controls [352]. In fact, when patients who initially received placebo were given naltrexone treatment, a transient worsening of negative symptoms was found [352]. An animal model of schizophrenia was used that mimicked the positive and negative systems of phencyclidine (PCP)-induced psychosis, including stereotyped behaviors and social isolation [334]. Methadone potentiated both PCP-induced stereotypy and ataxia, but did not affect social isolation [334]. However, because the effects of methadone were not dose-dependent, and its effects were observed only at near toxic levels, it is unlikely that the effects were explained by a specific interaction with PCP [334]. The effects of naloxone on PCP-induced psychosis also were probably nonspecific, because naloxone inhibited locomotor activity in both control animals and PCP treated rats [334]. Acute injection of PCP also causes a selective loss of enkephalin-positive striatal cells, similar to the loss observed in the early stages of Huntington's disease [267]. It is possible, therefore, that a loss of enkephalin-positive striatal neurons may underlie psychosis associated with both acute PCP and the early stages of Huntington's disease [267].

Although opiate antagonists have no effect on various measures of anxiety when given alone [3,33,212,323], they modulate the anxiolytic effects of other drugs. The anxiolytic effects of benzodiazepines in the elevated plus maze are likely mediated by μ and κ receptors, but not δ receptors, because the anxiolytic effects of chlordiazepoxide, as measured by increased open arm entries, were blocked by β-FNA and nor-BNI, but not by naltrindole [3]. In contrast, naloxone potentiated the anxiolytic effects of subeffective doses of chlordiazepoxide in the elevated plus maze in C57BL/6 mice [33]. It is unlikely that the effects were explained by nonspecific locomotor effects, as entries to closed arms, which measures general locomotion, were unaffected [3]. Interactions between endogenous opiates and neurokinin receptors also were shown, as naloxone potentiated both the anxiolytic actions of neurokinin agonists, and the anxiogenic actions of neurokinin antagonists in the elevated plus maze [323]. Endogenous opiates also may regulate CCK-induced anxiety, as naloxone potentiated the anxiogenic actions of CCK agonists, caerulein and BOC-CCK-4 [212]. The μ receptor also contributes to the regulation of anxiety because endomorphin-1 increased the total time spent in the open arms of an elevated plus maze [19]. Conversely, naloxone had anxiogenic effects in morphine tolerant rats, as it decreased the time spent in the open arms in morphine pellet implanted rats [346]. Therefore, because opiate agonists decrease anxiety [19] and withdrawal increases it [346], anxiety associated with opiate withdrawal may provide a strong motivating factor for the maintenance of addiction [346]. Post-traumatic stress disorder (PTSD) may be related to opiate use, as women with primary PTSD were more likely to abuse opiates after the onset of PTSD, as compared with women in whom PTSD was secondary to cocaine dependency [47].

The mixed enkephalin catabolism inhibitor RB 101 shows promise for treatment of depression as it produces anti-depressant-like effects in the learned helplessness model of depression, in which animals are exposed to inescapable shocks [389]. It is likely that the δ receptor is involved in the effects of enkephalin, because the δ-agonist BUBU produced similar effects and the effects of RB 101 were antagonized by naltrindole [389]. However, the role of endogenous opiates in depression in alcoholics was not convincing, as naltrexone produced a slight trend toward improvement in depressed alcoholics, which was not statistically significant [33]. Similarities in the neurobiology of depression and drug dependence indicate a possible relationship between these two disorders that includes alterations in the same neurotransmitter systems within limbic-related structures [93,242] and may explain their often observed comorbidity [234,242]. Furthermore, children of opiate addicts, in particular male offspring of addicts with comorbid depression, may be at a higher risk of developing mental illness in childhood, thus allowing early detection [282].

Exogenous opiates, such as morphine, pentazocine, and codeine, produced subjective effects such as coasting, sluggishness, feeling sleepy, and liking the effects [414,443]. However, although both oral morphine and codeine increased ratings of mood, the effects were only modest and probably should not limit the use of these drugs for outpatient pain control [414]. The effects of opiate agonists on mood depended on the type of opiate used, as positive mood states increased in patients receiving epidural morphine delivered by patient controlled pumps, but decreased in those receiving fentanyl [398]. Opiates may interact with glucocorticoids to modulate some aspects of mood, as subjects treated with dexamethasone, a potent glucocorticoid, had higher levels of bewilderment, but no changes in depression, or irritability [246]. Acupuncture also may improve mood and mental functions, that may be mediated by endogenous opiate systems [356]. However, naloxone did not affect mood in cigarette smokers, but did decrease the self-reported satisfaction of smoking [423].

8. Learning, memory, and reward

As in previous years, there was continued interest in the involvement of endogenous opiates in learning, memory, and reward. The modulation of different learning and memory tasks by the opiate system was elucidated, including operant and classic conditioning, as well as various cognitive tasks. In addition, examination of the reinforcing and discriminative properties of opiates provided a means of assessing their motivational and subjective effects. Because most drugs that act as reinforcers also have abuse potential [111,358], evaluation of the reinforcing and discriminative

properties of opiates has clinical relevance, and may provide new insights into the treatment of opiate abuse. Also, because there is an overlap between neural substrates that mediate opiate analgesia and opiate reward, elucidation of the mechanisms that mediate opiate reward will provide valuable insights into the mechanisms that underlie narcotic analgesics, and their relationship to opiate abuse [111]. Obviously, this is not a simple task because, like other behaviors, both the primary and conditioned reinforcing effects of opiates also involve interactions with nonopiate systems [5,358].

Opiates are involved in classic conditioning, as administration of morphine during the acquisition of a conditioned avoidance task, in which a white light (conditioned stimulus or CS) has been previously paired with a foot-shock (unconditioned stimulus or US) produces an increase in the avoidance response (conditioned response or CR) and a decrease in escape responses [4]. However, although these results might suggest that morphine facilitated conditioned avoidance, the effects may be nonspecific as morphine also increased locomotor activity [4]. Indeed, when animals were subsequently shifted from morphine to saline, locomotor activity returned to normal and avoidance responses decreased [4]. In fact, when motor behavior was taken into account, morphine-treated animals showed no learning curves but controls did, suggesting that morphine actually impaired conditioned avoidance that was masked by the locomotor effects [4]. Analgesic responses to stress also can be classically conditioned, as an auditory signal (CS) that was previously paired with foot-shock (US) elicited analgesia [32]. This classically conditioned response is likely μ-mediated, because it is blocked by injection of the μ-opiate antagonist CTAP, but not by the κ-opiate antagonist nor-BNI, into the ventrolateral PAG [32]. Conditioned taste aversion (CTA) is another paradigm of classic conditioning that was used to measure the aversive properties of opiates, as a novel and detectable flavor paired with an unpleasant stimulus is avoided. When morphine was used as an aversive stimulus it suppressed the intake of a saccharin when paired with it [116]. The δ-antagonist naltrindole also is aversive because both a high dose (20 mg/kg) produced CTA when paired with a banana–flavored solution, and lower doses made nonaversive amounts of alcohol aversive [113].

The use of conditioned place preference (CPP) and conditioned place aversion (CPA) paradigms has grown over the years, as demonstrated by steady increases in the number of publications since 1957 [337,400], that included 312 articles, abstracts, book chapters, and reviews published between 1992 through 1996 [337]. The CPP paradigm was used to evaluate the reinforcing properties of morphine by pairing morphine with a distinctive environment, and a neutral stimulus with another environment. When tested in a drug-free state the animals chose the side paired with morphine [116,309,339]. Although many of the effects of μ-agonists are opposed by activation of κ receptors [292], κ-opiate receptor deficient mice showed similar morphine-induced CPP as compared with controls, suggesting that the absence of κ receptor sites does not influence morphine reward [360].

Once established, morphine CPP can persist for long periods of time without any further conditioning trials, as CPP was observed for 14 days after conditioning ended [309].The reinforcing properties of morphine are mediated in part by the NMDA receptor, as NMDA antagonists inhibited both the acquisition and expression of morphine-induced CPP [309]. However, NMDA antagonists do not contribute to the extinction of morphine CPP, as NMDA antagonists given for 3 days after the end of conditioning did not influence extinction [309]. Interactions between opiate and dopaminergic systems also were noted, as morphine produced a dose-related CPP that was potentiated by co-administration of *d*-amphetamine [116]. This is consistent with the clinical literature suggesting that amphetamines are sometimes used by opiate abusers to increase the effects of methadone or poor quality heroin [116]. However, the neural substrates that mediate morphine- and amphetamine-induced CPP can be dissociated, because amphetamine but not morphine produced CPP when injected into the nucleus accumbens [339].

Endogenous opiate systems also modulate CPP produced by other drugs, including alcohol [84,248] and cocaine [81]. It is likely that μ- and δ-opiate receptors are involved in the development of ethanol CPP in stressed animals, as it was attenuated by naloxone, the μ-antagonist β-FNA, and the δ-antagonist naltrindole, but not by the k-antagonist nor-BNI [248]. Similarly, although ethanol did not produce a CPP in nonstressed animals, it did so when combined with nonreinforcing doses of morphine or the selective δ-agonist TAN-67, but not with the κ-agonist U50488H [248]. It is possible that the rewarding effects of ethanol may be maintained by the release of endogenous opiates, because naloxone facilitated the extinction of the ethanol CPP [84]. CPP induced by cocaine also is opiate-mediated, as it was blocked by naltrexone when given in combination with the calcium channel blocker isradipine [81].

Classic conditioning may underlie some aspects of opiate withdrawal, as naloxone produced greater CPA in morphine-dependent subjects as compared with morphine-naive [215,295,345]. In this context, removal of opiates by naloxone acts as the US and the distinct environment as the CS producing a conditioned aversive response. Because the conditioned aspect of opiate withdrawal should be sensitive to manipulation of neural substrates that subserve learning, impairing the formation of a CS-US relationship would provide a valuable means of reducing conditioned opiate withdrawal. Interestingly, clonidine, which is used for the treatment of opiate dependence, blocked the acquisition but not the expression of conditioned opiate withdrawal [345]. Therefore, clonidine may lessen the salience of the US (naloxone) thus impairing the formation of the CS-US pathway and lessening withdrawal. However, this aspect of

withdrawal is resistant to the same manipulation given after establishment of the CS-US pathway [345].

Besides classic conditioning, the rewarding properties of opiates were examined with operant conditioning paradigms, including the self-administration of opiates, most notably heroin [68,72,244,245,259,285]. Self-administration of heroin in rats produced an inverted U-shaped dose-response curve [244,245], that was μ-mediated because ICV injection of β-FNA increased the ED50 of both the ascending and descending limbs in a dose-dependent fashion [244]. The effects of β-FNA, however, were overcome by increasing the dose of heroin, suggesting that there are spare μ-opiate receptors for the production of it's reinforcing effects [244]. Furthermore, because [^{3}H]DAMGO binding decreased after β-FNA for periods that outlasted the effects of β-FNA on self-administration, it suggests that a full compliment of opiate receptors are not necessary for heroin to exert its reinforcing effects [244]. Heroin self-administration in rats was influenced by the training dose, as doses of heroin lower than 5.4 μg per infusion maintained higher rates of responding in rats trained with 5.4 μg per infusion as compared with those trained with 18 μg [245]. Doses higher than 5.4 μg, however, were not influenced by the training dose [245]. In addition, as the time within each session progressed the dose-intake curves shifted down and to the right to a greater extent in animals trained with 5.4 μg per infusion [245].

Both μ and δ receptors are involved in heroin self-administration because naloxone and naltrindole altered responding [245]. However, although the effects of naloxone were consistent with its pharmacokinetics, as its potency decreased over the session time, the effects of naltrindole outlasted its expected duration, suggesting that its effects occurred during the first part of the session [245]. Consistent with the use of the partial μ-agonist/κ-antagonist buprenorphine for treatment of drug abuse, buprenorphine decreased self-administration of both heroin and 'speedball' combinations of heroin and cocaine in monkeys [259]. The effects of buprenorphine cannot be explained by a nonspecific suppression of operant responding, because buprenorphine had minimal effects on food self-administration [259]. When allowed to self-administer heroin under a progressive-ratio schedule, heroin addicts worked harder for higher doses, as the heroin break point value increased as a function of dose [72]. However, when given a alternative choice of $20, the heroin breakpoint occurred earlier, suggesting that alternative reinforcers are effective in reducing heroin self-administration [72].

Lesions of the pedunculopontine nucleus have varying effects as they disrupt the acquisition of fixed ratio responding for IV heroin in some animals, whereas others increased their heroin intake over session but never reach the levels of control animals [285]. However, when tested on a progressive-ratio schedule the breakpoint was reduced by pedunculopontine lesions, suggesting that the pedunculopontine nucleus mediates some of the rewarding effects of opiates [285]. Interestingly, the ability of pedunculopontine lesions to block the rewarding effects of opiates may depend on the drug experience of the animal, as the lesions were not effective in either paradigm when given after the rats were trained to self-administer heroin [285]. Mesocorticolimbic neurons also are involved in opiate reward, as a subpopulation of neurons in the nucleus accumbens and medial prefrontal cortex become active during heroin self-administration [68]. The septal region also is involved in opiate reward because mice were able to discriminate between the arms of a Y-maze to self administer 5 ng of morphine into the lateral or medial septum, although both the acquisition and extinction were more rapid in the lateral septum group [63]. In contrast, when the dose of morphine was increased to 50 ng the medial septum group learned to avoid the reinforced arm, suggesting that this dose of morphine in the medial septum is aversive [63]. However, this aversive effect of a higher dose was not confirmed when mice were given access to only the reinforced arm, as both lateral and medial septal groups showed decreased self-administration latencies, regardless of the dose [63].

Endogenous opiates can mediate operant responding to other forms of reinforcement as well, including ethanol [46,425,426], cocaine [258,259,276], sucrose [425], and food [258,345]. Naltrexone reduced operant responding for both ethanol [46,425] and sucrose [425] in monkeys trained under a fixed ratio schedule, and naloxone suppressed operant responding for food in morphine-dependent rats [345]. However, it is not clear which opiate subtype mediates operant responding to ethanol, as selective μ-, κ-, and δ-antagonists did not modify responding [426]. In contrast to ethanol, food-maintained responding under a fixed-ratio 30 schedule is κ-mediated because it is decreased by administration of 6 different κ-agonists [258]. However, chronic administration of κ-agonists affected cocaine- and food-maintained responding that depended on the type of agonist used, as endoline, bremazocine, and Mr2033 reduced self-administration, whereas cyclazocine, spiradoline, and PD117302 did not [258]. In contrast, κ-opiate agonists administered alone also are rewarding, because rats will self-administer both RU 51599, a selective κ-agonist, and heroin when a low ratio requirement is used [241]. The strength of reinforcement produced by κ-agonist is weak in comparison, as responding to RU 51599 but not heroin is extinguished when the number of responses required to receive the drug are increased [241].

The reinforcing properties of intracranial self-stimulation (ICSS) can be modified by opiates because systemic morphine increased the threshold for self-stimulation maintained from the ventral pallidum, suggesting a reduction in reward value [293]. In contrast to systemic injections, however, injections of morphine directly into the VTA, but not the nucleus accumbens, increased the rewarding effects of ICSS, as it reduced the threshold for responding to ventral pallidum self-stimulation. These differential effects of systemic and central morphine on ICSS are likely related to the

number of different neural sites that systemic injections affect, that may produce synergistic or antagonists effects [293]. The influence of opiates on ICSS derived from the VTA involves a complex interaction between the site of stimulation and exposure to stress [442]. Foot-shock reduces self-stimulation from the dorsal aspects of the VTA, and this is opiate-mediated because ICV injection of the partial μ- and δ-agonist DALA, the μ-agonist DAMGO, and the δ-agonist DPDPE attenuated the effects of stress [442]. In contrast, self-stimulation derived from ventral VTA was slightly increased after stress, and suppressed in stressed animals that received DALA, but not DAMGO or DPDPE [442]. The effects of naltrexone on ICSS can be enhanced by inhibition of calcium channels because a low dose of naltrexone does not block cocaine-induced enhancement of ICSS in the lateral hypothalamus, but does when combined isradipine, a calcium channel blocker [291].

As in previous years, opiate agonists and antagonists have been used as stimuli in drug discrimination tasks, where animals are trained to respond differentially for drugs or vehicle. The ability of opiates to produce discriminative effects was used to assess the subjective effects of opiates, thus providing an indication of abuse liability. In studies that used ICV or subcutaneous (SC) morphine as the discriminative stimulus (S^D) against saline, the S^D effects of morphine generalized to its metabolite M6G regardless of the route of administration, although it was less potent when given systemically [97]. Both the analgesic and discriminative effects of MG6 are opiate-mediated because they are blocked by naltrexone [97]. In contrast, the morphine metabolite MG3 did not have morphine-like effects, as it did not substitute for morphine and did not produce analgesia [97]. These results suggest that the conversion of morphine to MG6 but not MG3 may contribute to the subjective effects of morphine and may underlie its abuse liability [97].

In pigeons trained to discriminate morphine from distilled water, fentanyl, *l*-methadone, buprenorphine, butorphanol, nalorphine, nalbuphine, and levallorphan generalize to it, indicating that these drugs share μ-opiate-like stimulus effects [269]). However, although the stimulus effects of nalorphine, nalbuphine, and levallorphan were antagonized by 5 mg/kg of β-FNA, higher doses were required to antagonize the effects of morphine, butorphanol, and buprenorphine, and the effects of fentanyl and *l*-methadone were unaffected by β-FNA [269]. This differential sensitivity to β-FNA indicates that these opiates have different intrinsic activity at the μ receptor in the order of fentanyl = *l*-methadone $\geq$buprenorphine $\geq$morphine $\geq$butorphanol $\geq$nalorphine = nalbuphine = levallorphan [269].

The S^D effects of butorphanol [75] and heroin [223] are opiate-mediated because opiate antagonists blocked their stimulus effects, and both morphine and nalbuphine generalized to the effects of butorphanol [75]. When the mixed opiate agonist/antagonist pentazocine was used as the S^D, morphine and DAMGO generalized to it, whereas the δ-agonist DPDPE only partially generalized and the κ-agonist dynorphin did not, suggesting that μ receptors and to a lesser extent δ receptors mediate the S^D effects of pentazocine that may be related to it's high abuse liability [401]. This is further supported by the ability of β-FNA to antagonize the pentazocine-like discriminative effects of both morphine and DAMGO [401].

There is evidence that μ-agonists can produce δ-opiate-like effects because when the δ-agonist BW373U86 was used as the S^D in pigeons against saline, its discriminative effects were partially substituted for by various μ-agonists, including levallorphan, [−]-cyclazocine, [−]-n-allylnormetazocine, morphine, butorphanol, nalbuphine, [+]-propoxyphene, etorphine, and fentanyl [302]. However, because naloxone was more effective than naltrindole in antagonizing these substitution patterns, it is likely that the δ-like discriminative effects of μ-opiates are μ-mediated [302]. When morphine was used as the S^D against saline, BW373U86 generalized to it, but this is not μ-mediated because it was not antagonized by β-FNA and the pkB value of naloxone was lower than that observed for morphine and fentanyl [269]. The stimulus effects of BW373U86, however, are likely δ-mediated because naltrindole was more effective than naloxone in antagonizing the stimulus effects of BW373U86 [302].

The stimulus properties of morphine are not shared by κ-agonists, as fentanyl but not the κ-agonists U50488H, fedotozine, and CI-977 substituted for morphine in rats trained to discriminate between morphine and saline [50]. Conversely, the discriminative effects of U50488H generalized to CI-977, but not to morphine [50]. However, the discriminative effects of U50488H were not shared by fedotozine, suggesting that fedotozine is devoid of subjective effects associated with both κ- and μ-agonists, thus providing a potential alternative as an analgesic for treatment of gastrointestinal disorders [50].

Although typically studied in animals, opiate agonists also produce discriminative effects in humans, as male subjects with a history of opiate abuse were able to discriminate hydromorphone from placebo when presented with a financial reinforcement for correct responses [313]. Furthermore, although the lowest training dose of hydromorphone produced no physiological effects and only a few subjective effects, discrimination remained high (75%), suggesting that discrimination procedures in humans may be more sensitive than subjective effects for differentiating among drug conditions [313].

Because stimulants and opiates are often abused together (i.e., speedballs), there is growing interest in the interactions between the discriminative stimulus effects of dopaminergic compounds and opiates. The ability of dopaminergic agonists to produce μ-like stimulus effects depends on the dose of opiates, as the S^D properties of a low dose of butorphanol but not a high dose generalized to various direct and indirect dopamine agonists, including cocaine, mazindole, nomifensine, SKF 38393, quinpirole, and (±)-7-OH-DPAT [75]. Because dopamine D_1 and D_2 antagonists did not alter the

stimulus effects of either dose of butorphanol, the effects of butorphanol are not explained by interactions with these dopamine receptors [75]. However, the S^D effects of a high training dose of butorphanol, as well as the butorphanol-like stimulus effects of morphine and nalbuphine, may interact with dopamine D_3 receptors, because their effects were attenuated by the D_3 agonist (±)-7-OH-DPAT [75]. Cross-substitution between heroin and cocaine is not clear, however, as cocaine did not generalize in rats trained to discriminate heroin, but heroin did sometimes substitute for cocaine in rats trained to discriminate cocaine, suggesting that discriminative effects of cocaine and heroin are usually distinct, but there may be a small degree of overlap [223]. Furthermore, the overlap may be explained by an activation of a common dopaminergic systems because the S^D effects of heroin and cocaine are both antagonized by the dopamine antagonist flupenthixol [223].

When administered as pretreatment to morphine, *d*-amphetamine increases the S^D properties of morphine, which is consistent with the clinical reports that amphetamines are at times taken to enhance the effects of opiates [115]. Opiate enhancement of the stimulus effects of cocaine are mediated by both μ and δ receptors, as the stimulus effects of cocaine are enhanced in squirrel monkeys by both fentanyl [331] and the δ-agonist SNC 80 [277,331]. In support of this, naltrexone blocked the cocaine-enhancing effects of fentanyl but not SNC 80 [331], and naltrindole blocked the effects of SNC 80 [277,331] but not fentanyl [331]. However, although SNC 80 completely substituted for cocaine, it may have relatively low abuse potential as it did not maintain responding in monkeys trained to self-administer cocaine [277].

The ability of opiates to modify the stimulus effects of cocaine may be related to individual differences, as morphine and fentanyl increased responding to cocaine and amphetamine in some monkeys but not in others, raising the possibility that combinations of opiates and stimulants also may have differential effects among humans [277]. The direction of morphine's effects on the stimulus properties of amphetamine also depends on the individual differences in sensitivity, as amphetamine doses equal to the lowest generalized dose are attenuated by morphine, whereas morphine increased responding for half of the lowest generalized dose of amphetamine [115]. However, contrary to the notion that stimulant-opiate combinations are used to enhance their effects, cocaine or mazindol did not increase the stimulus effects of butorphanol or morphine, which surprisingly was less than additive in some circumstances [75]. Similarly, cocaine did not alter the discriminative effects of heroin, nor did heroin alter those of cocaine [223].

Spatial working memory involves an interaction between opiates and cholinergic systems, as naloxone antagonizes the inhibition of substance P on scopolamine-induced deficits in spontaneous alteration in a Y-maze [173]. However, these effects are likely not related to a single opiate receptor, because they are not blocked by any one antagonist specific for μ, δ, or κ receptors [173]. Interactions between opiate and cholinergic systems also were demonstrated in the passive avoidance paradigm, as deficits in avoidance learning and memory induced by cholinergic antagonists were reversed by administration of the κ-agonist U50488H [153]. Similarly, dynorphin A reverses the impairments produced by low doses of the muscarinic agonist charbacol [152]. As would be expected, the effects of both U50488H and dynorphin A are prevented by the κ-antagonist, nor-BNI [152, 153]. Therefore, κ-agonists may have beneficial effects on various cognitive deficits related to decreased cholinergic function, including Alzheimer's disease [151,152,153].

Although κ-agonists may have beneficial effects in subjects with memory impairments explained by cholinergic dysfunction [152,153], opposite effects were found for spatial tasks in the absence of brain dysfunction, as hippocampal injections of dynorphin B impaired learning in rats trained to locate a submerged platform in the Morris Water Maze, an effect that was blocked by nor-BNI [335]. The nociceptin/OFQ receptor also is involved in spatial learning as nociceptin receptor-knockout mice showed better retention than controls in a task that involved recalling the location of a drinking tube in an open field [237]. However, because dopamine content also was lower in the frontal cortex in knockout mice than controls, it is possible that the nociceptin receptor plays a role in spatial memory by modulating dopaminergic systems [237]. Opiates may have adverse effects in human memory, as cancer patients receiving intraventricular morphine showed disturbances of numeric, verbal, and visuospatial recent memory on the Wechsler Memory Scale [306]. The loss in memory was not uniform, however, as autobiographical and long-term memory remained intact [306].

9. Cardiovascular responses

The endogenous opiate system plays a role in mediating cardiovascular responses. In 1998, much of the research examined the effects of opiate agonists on blood pressure and heart rate, but the results were inconsistent. Endomorphin-1 and -2, endogenous opiate peptides with high specificity and selectivity for the μ receptor, decreased blood pressure and lowered heart rate in both rats [65,85,222] and mice [67], indicating that these peptides are active in cardiovascular function. Similarly, the μ-agonists DAMGO and PL107 also decreased blood pressure and heart rate [65,66]. Because naloxone antagonized the decreases in heart rate and blood pressure produced by endomorphin-1 and -2 their effects are likely opiate-mediated, presumably μ [67,85,222]. Furthermore, vagotomy abolished the effects of endomorphin-1 on heart rate and attenuated it's effects of blood pressure, suggesting that the effects of these peptides are related to activation of vagal afferents, although it's hypotensive effects may be secondary to bradycardia [222]. In contrast, endomorphin-1 and -2 produced dose-depen-

dent biphasic changes in systemic arterial pressure in cats, characterized by an initial increase followed by a decrease, with both effects blocked by naloxone [66].

Injection of the enkephalin analog DAME also decreases blood pressure, an effect exaggerated in anesthetized rats placed in a diabetic state by an injection of streptozocin [353]. Because the effects of DAME were reversed by naloxone, and insulin replacement reversed the exaggerated response in diabetic rats, it suggests that diabetics may have altered μ-opiate-mediated hemodynamic responses that should be of clinical concern [353]. In contrast, injection of the μ-agonist DALDA produced mild hypertension and loss of heart rate in pregnant ewes, whereas the δ-agonist DP-DPE produced maternal hypertension, respiratory depression, and a fall in heart rate of both mother and fetus [70]. Because the effects of DALDA but not DPDPE were reversed by naloxone, DPDPE has multiple nonopiate effects that would limit is clinical use [70]. Neither morphine or codeine affected blood pressure, and produced only mild decreases in heart rate [414].

Heroin and the κ-agonist U69593 dose-dependently decreases heart rate in rhesus monkeys, an opiate-mediated effect because quadazocine blocked it [409]. However, differential involvement of μ- and κ-agonists were noted in cardiovascular responses, as IV administration of DAMGO and U50488H produced an immediate increase in blood pressure in awake sheep that was opiate-mediated because it was blocked by naloxone [287]. In contrast, although the pressor response to U50488H was accompanied by a naloxone-reversible increase in heart rate, DAMGO did not produce any changes in heart rate [287]). The tachycardia elicited by U50488H are probably related to sympathetic activation of the heart rate, as pretreatment with the β-adrenergic agonist propranolol blocked its effects on heart rate. On the other hand, the lack of effects of DAMGO on heart rate despite an increase in blood pressure is likely explained by an attenuation of baroflex-mediated bradycardia, because reflex-bradycardia induced by norepinephrine was attenuated by both DAMGO and the μ-agonist DALDA [192], but not U50488H [287].

The effects of μ-agonists on baroflex mediated bradycardia are peripherally mediated because reflex-bradycardia induced by norepinephrine was unaffected by DALDA when administered in the presence of the peripheral opiate antagonist naloxone methiodide [192]. However, μ-agonists are not involved in the tachycardic response to hypotensive stimuli, as baroflex-mediated tachycardia induced by sodium nitroprusside was unaffected by DALDA [287]. In contrast, injection of the κ-agonists, bremazocine, spiradoline, and U50488H into the dorsal hippocampus dose-dependently lowered blood pressure in both hypertensive rats and normotensive rats, with a slightly greater effect in hypertensive rats [444]. Furthermore, these decreases in blood pressure were accompanied by mild increases in heart rate, that were only significant at the highest dose of bremazocine [444]. However, although the hypotensive effects of all agonists tested were blocked by intrahippocampal injections of nor-BNI, differences between κ-agonists were observed in potency and duration, with bremazocine producing the larger hypotensive effects. This difference may be related to the differential selectivity of these drugs for different κ receptor subtypes, as bremazocine is more selective for κ_2 receptors, whereas spiradoline, and U50488H are predominately κ_1 selective [444]. The increased sympathetic activity observed in borderline hypertensive rats also may be related to altered endogenous opiate activity, as basal levels of paraventricular enkephalin hnRNA are lower in these rats as compared with normotensive controls, and are increased after stress [240].

Opiate antagonists affect cardiovascular function that is influenced by chronic treatment with morphine, as application of naloxone to the isolated heart of morphine-tolerant rats increased atrial rate, but decreased it in preparations form morphine-naive rats [316]. Because administration of naloxone in morphine-tolerant rats also decreased atrial content of norepinephrine, epinephrine, and dopamine, it indicates that the naloxone-induced increase in atrial rate in morphine-dependent rats is mediated by catecholamines [316]. Chronic treatment with morphine in dogs for 2 weeks, which is sufficient to induce dependence, produced a progressive decrease in resting heart rate that was evident within the first 3 h and persisted for 2 days, but recovered by 10 days [274]. In addition, although atropine increased heart rate in control animals that did not change across days, chronic morphine increased postatropine heart rate above baseline by Day 10 [274]. Because the difference between resting and postatropine heart rates, which represents vagal activity, was greater on Days 2 and 10 after morphine as compared with baseline, it suggests that a compensatory sympathetic response occurred in morphine treated animals [274]. This may be of clinical concern, as withdrawal from such morphine-induced increases in sympathetic activity may have significant cardiovascular effects [274]. Indeed, opiate antagonists affected cardiovascular activity in opiate addicts, as naloxone detoxification under general anesthesia produced increases in heart rate and stroke volume, which was accompanied by decreases in systemic vascular resistance and decreases in systolic arterial pressure [194,338]. Similarly, naloxone increased heart rate and blood pressure in opiate addicts detoxified without general anesthesia [328]. Therefore, long-term opiate use may alter cardiovascular function that is unmasked by opiate receptor blockade, and should be considered when using opiate detoxification techniques [194]. However, withdrawal from opiates did not affect fetal heart rate, as no changes in heart rate were observed in the fetuses of mothers detoxified from methadone [91].

The effects of opiate antagonists on blood pressure also are affected by stress, as naltrexone increased blood pressure in subjects during periods of high stress, but had no effect on blood pressure during periods of low stress [251]. Similarly, patients with acute congestive heart failure

showed increases in blood pressure during a mental arithmetic test, which was further increased after naloxone [107]. Taken together, these results suggest that endogenous opiates may attenuate cardiovascular responses during stress, effects that are unmasked by treatment with opiate antagonists [107,251].

Interactions between opiates and other drugs were examined. Benzodiazepines did not interact with opiates as midazolam given alone or in combination with fentanyl did not decrease heart rate or blood pressure [232]. Although both high doses of fentanyl and the general anesthetic propofol decreased heart rate and blood pressure in rabbits, the two drugs in combination did not produce synergistic effects [232]. Opiates did not interact with cannabinoid receptors because quadazocine but not the cannabinoid receptor antagonist SR 141716A reversed the suppressive effects of heroin on heart rate, and SR 141716A but not quadazocine reversed the suppressive effects of the cannabinoid receptor agonist, Δ-9-THC [409].

The endogenous opiate system is likely involved in hypotension resulting from hemorrhage. Recovery from hypotension during sustained hypovolemia induced by a caval cuff in rabbits is mediated by central opiate receptors because naloxone accelerated recovery whether injected IV or ICV, presumably by restoring systemic vasoconstriction [403]. Although the site of action is not yet known, a possible candidate is the rostral ventrolateral medulla, which has been implicated in opiate control of cardiovascular responses [6,403]. Fentanyl infusion in cats that received a traumatic brain injury produced a decrease in blood pressure as compared with controls [27]. However, although hypotension resulting from hemorrhage is usually accompanied by reductions in CBF, no changes in CBF were associated with fentanyl-induced hypotension, suggesting that different mechanism mediate hemorrhage- and fentanyl-induced hypotension after brain injury [27]. Fainting as a result of reduced CBF may be opiate-mediated, because rises in plasma β-endorphin levels were found at the time of syncope, although naloxone did not prevent the onset of syncope [301].

Arrhythmia seems to have opiate involvement, as ischemia-induced ventricular tachyarrhythmia was reversed by naloxone [161]. Because doses of naloxone that produced antiarrhythmic effects also inhibited Na^+ and K^+ currents, the antiarrhythmic effects of naloxone are likely mediated by inhibition of Na^+ and K^+, rather than blockade of opiate receptors [161]. U50488H dose-dependently induced arrhythmia in the isolated rat heart that was blocked by both the $G_{i/o}$-protein inhibitor pertussis toxin, and inhibitors of phospholipase C [38]. Opiates also affect cardiac contractions, as fentanyl and morphine depressed myocardial contractility [177]. However, the mechanisms by which they do so are different, as the cardiodepressant effect of fentanyl but not morphine was accompanied by a decreased intracellular Ca^{2+} concentration [177]. Both U50488H and dynorphin $A_{1\text{-}8}$, but not DADLE, decreased contractile responses in isolated ventricular cardiomyocytes, which was κ-mediated because their actions were reversed by nor-BNI and naloxone [422]. Both peptides also were blocked by pertussis toxin, suggesting that G-proteins are involved [422].

In patients with coronary heart disease, as indicated by angioplasty, plasma levels of β-endorphin in silent ischemia induced by balloon inflation are higher than exercise-induced silent ischemia, suggesting that the greater amount of myocardium at risk during coronary angioplasty than exercise is associated with increased levels of plasma β-endorphin [150]. Furthermore, because levels of β-endorphin during exercise-induced silent ischemia were similar to those during angioplasty-induced symptomatic ischemia, the presence of anginal symptoms during ischemia may depend on whether levels of β-endorphin are high enough to suppress anginal symptoms [150]. Levels of β-endorphin in peripheral blood mononuclear cells were reduced in patients with acute myocardial infarct; however it's significance is not clear but may play a role in pain and inflammation [56].

Ischemic preconditioning involving several short periods of occlusion of the coronary artery before a sustained 30 min ischemia produces a decrease in infarct size that is opiate-mediated because the effects of preconditioning are blocked by naloxone [263,397]. However, there may be a time window for opiate-mediated protection of preconditioning, as the inhibitory effect of naloxone on ischemic preconditioning was not observed after 20 or 40 min of ischemia [397]. The opiate receptor subtypes that mediate the protective effects of ischemic preconditioning also were examined. It is likely that the protective effects of ischemic preconditioning are mediated specifically by δ_1-opiate receptors because the effects of preconditioning were attenuated by the δ-antagonist naltrindole [397] and the δ_1-antagonist BNTX [347], but not by nor-BNI [347,397], β-FNA, or the δ_2-antagonist naltriben [347]. Consistent with these findings, the δ_1-agonist TAN-67 reduced infarct size in rats exposed to a 30-min coronary artery occlusion, which was blocked by BNTX [348]. Similarly, morphine-induced preconditioning decreased infarct sized and reduced neutrophil activation produced by a 30-min coronary artery occlusion, which was prevented by naloxone [263,417]. However, the effects of morphine are probably not explained by its action at the μ receptor because DAMGO did not have an effect on the infarct after ischemia [347]. The cardioprotective effects of opiates are probably mediated by changes in cAMP pathways, as the effects of TAN-67 were prevented by the $G_{i/o}$-protein inhibitor pertussis toxin, and the K_{ATP} channel antagonist glibenclamide [348], and the effects of morphine were prevented by the protein kinase C inhibitor chelerythrine [263].

Endogenous opiates are localized in the heart and may play a role in cardiac development by modulating Met-enkephalin-induced cell proliferation and differentiation [253,254,419,433]. Preproenkephalin mRNA is abundant in heart cells at embryonic Day 14 until after birth, which

declined on postnatal Days 5, 10, and 21, and increased in adults [253,254]. Furthermore, preproenkephalin mRNA is more abundant in the adult left ventricle than the right, raising the possibility that the left ventricle functions as an endocrine organ providing enkephalins to the body [419]. In contrast, POMC mRNA was found only in myocardial cells in adulthood, and preprodynorphin mRNA was not found in either developing or adult hearts [254]. The ontogeny of opioid growth factor or Met-enkephalin supports its role in the development of heart tissue, as it was detected in the embryonic heart [433], peaked in neonates, and regulated preproenkephalin mRNA in the neonatal heart [253].

10. Respiration and thermoregulation

Although endogenous opiates are likely involved in respiration and thermoregulation, research on this topic remained low after a decline in recent years. As expected, there were reports that respiratory depression was produced by opiate agonists, including morphine [88,127,181,384, 407,414,420], heroin [409], sufentanil [407], DAMGO [384], fentanyl [127,232], codeine [414], U50488H [384], U69593 [409], and remifentanil [175], but not DPDPE [384], suggesting the μ and κ, but not δ receptors are involved. Brainstem-spinal cord preparations were used to demonstrate age- and temperature-dependent effects of opiates on respiration, as the effects of morphine on firing frequency of medullary respiration-related structures increased from postnatal age 0–4 and were reduced at temperatures below 28.5°C [384]. However, the effects of opiates on neural measures of respiration differed, as morphine suppresses the amplitude and frequency of the high-frequency synchronized discharge of phrenic nerve bursts that is blocked by naloxone, but does not affect the temporal 'locking' of bilateral phrenic discharges, suggesting that the influence of morphine on the frequency of respiration rhythm and high frequency oscillations rates are not well correlated [181]. An individual's respiratory response to ozone was not related to differences in endogenous opiates, as plasma β-endorphin levels did not differ between subjects who showed weak or strong ozone-induced inhibition of inspiration, and naloxone did not elicit ozone responses in weak responders or reverse the effects of ozone in strong responders [296]. However, sufentanil reversed both ozone-induced chest pain and respiratory effects, suggesting that opiate sensitive pain mechanisms are involved [296]. No differences were found in [^{3}H]naloxone binding in brainstem nuclei related to respiratory or autonomic control in victims of sudden infant death syndrome (SIDS) as compared with age-adjusted controls, suggesting that SIDS is not related to opiate dysfunction in cardiorespiratory nuclei [198]. Remifentanil, a short acting μ-agonist, produced respiratory depression in females during pregancy but did not produce any adverse neonatal side-effects, suggesting a potential use of this analgesic in obstetrics [175].

The interactions between the respiratory effects of opiates and other drugs were examined, especially benzodiazepines that are often co-administered with opiates both clinically and recreationally [127,232,407]. Midazolam and propofol may interact synergistically with fentanyl because although these drugs produced dose-dependent decreases in phrenic nerve activity in anesthetized rabbits when given alone, combinations of midazolam or propofol with fentanyl produced synergistic effects [232]. In contrast, the ventilatory depressant effects of the benzodiazepines, triazolam, flunitrazepam, midazolam, alprazolam, diazepam, and lorazepam, combined with morphine and fentanyl were less than additive, suggesting that benzodiazepines and opiates can be coadministered without enhancing their ventilatory depressant effects [127]. Similarly, no synergy was found in rhesus monkeys, as chlordiazepoxide only minimally potentiated morphine and sufentanil-induced respiratory depression that was most pronounced at the lowest doses of the opiates but was without affect on higher concentrations [407]. The reasons for these discrepancies are not known, but may be related to differences in routes of administration, species, and methods used to measure respiration [127].

Interactions between opiates and other drugs also were assessed but not demonstrated. Morphine decreased resting ventilation, and hypoxic and hypercarbic ventilatory responses in healthy males that were unaffected by HP 228, an analog of α-MSH that is analgesic as it attenuates the synthesis and release of inflammatory cytokinines [420]. Thus, HP 288 may be potentially safe as an analgesic when given alone or in combination with morphine [420]. Opiates did not interact with cannabinoid receptors because the respiratory depressant effects of heroin and the κ-agonist U69593 were blocked by the opiate antagonist quadazocine, but not by the cannabinoid receptor antagonist SR 141716A [409].

Hypoxia produces an initial increase in respiration followed by a steady decrease that are both opiate-mediated because alfentanil decreased both [61]. However, the opiate modulation of respiration during hypoxia and hypercapnia is sex-dependent, as morphine suppressed the ventilatory response to carbon dioxide (hypercapnia) and hypoxic sensitivity in women but not men, and increased apneic thresholds in men but not women [88]. Hypoxia affects endogenous opiates in newborns, as newborn rabbits asphyxiated by enclosure in an airtight box for 60 min increased enkephalin-like immunoreactivity in the paraaortic body and adrenal glands [424]. However, the role of opiates during hypoxia depended on the duration of hypoxic exposure, because a 5-min exposure to moderate and severe hypoxia in newborn pigs had no effects on CSF Met-enkephalin and dynorphin levels, whereas both are increased after 10-min of exposure, and during 20- and 40-min exposures dynorphin continued to increase but Met-enkephalin decreased [12,406]. Hypoxic pial artery dilation during hypoxia was unaffected by β-FNA during the 5-min and 40-min exposures, but decreased pial artery dilation during the 10- and

20-min exposures [12]. In contrast, nor-BNI potentiated the hypoxic dilations during the 10-, 20-, and 40-min exposures [12]. Therefore, opiates modulate hypoxic pial dilation occurred during long-exposures, but not short exposures, and are mediated by a decrease in Met-enkephalin and an increase in dynorphin [12]. Furthermore, vasopressin contributes to the reversal of the effects of dynorphin from a dilatation to vasoconstriction after prolonged hypoxic exposure, as the vasopressin antagonists MEAVP attenuated dynorphin-induced vasoconstriction [406].

Although opiate antagonists do not typically affect respiration when given alone [127,181,232,296,409], 5 mg/kg naloxone injected SC in rats produces a decreases in ventilation, ventilatory equivalent, ventilatory response to hypercapnia, and tidal volume in response to hypoxia and hypercapnia [341]. Furthermore, aspartic acid injected into the arcuate nucleus attenuated the effects of naloxone on ventilation, ventilatory equivalent, and tidal volume in response to hypoxia and hypercapnia, but not the ventilatory response to hypercapnia, suggesting that some but not all of the respiratory effects of naloxone are NMDA-mediated [341]. In guinea pigs, naloxone decreased basal oxygen consumption in both newborns and adults, and in newborns during hypoxia [82].

Interest in the role of endogenous opiates in thermoregulation was low. Hyperthermia in rats induced by a 20-min exposure to a 600-MHZ microwave produced disruptions in an object discrimination task that was opiate-mediated because naloxone antagonized it [262]. Hypoxia produced decreases in core temperature in both adult and newborn guinea pigs that was not opiate-mediated because naloxone did not alter core temperature after hypoxia, nor did it alter basal core temperature [82]. However, although selected ambient temperature decreased in newborns during hypoxemia, it did not after naloxone, suggesting that opiates modulate thermoregulatory effector mechanisms during hypoxia [82]. In contrast, naloxone decreased skin temperature [328] and produced hypothermia [180,392] in opiate-dependent subjects that was used as a measure of withdrawal. Similarly, skin temperature decreased in opiate addicts withdrawn from LAAM-maintenance, that was increased after a challenge dose of hydromorphone [159].

A neuronal model of hypothalamic control of body temperature has been used to examine the activity of warm-sensitive neurons after administration of opiate agonists [435]. The effects of dynorphin $A_{1\text{-}17}$ were concentration-dependent, as low concentrations increased activity and temperature sensitivity in warm-sensitive neurons, whereas higher concentrations decreased firing rate and temperature sensitivity [435]. The effects of dynorphin $A_{1\text{-}17}$ were κ-mediated because they were blocked by nor-BNI, although μ receptors also may contribute to the inhibitory effect of dynorphin $A_{1\text{-}17}$, because most of the κ-sensitive neurons were co-localized with μ receptors [435]. In contrast, fewer neurons responded to the δ-agonist DPDPE, that showed mainly a decrease in firing rate and an increase in temperature in warm-sensitive neurons, that occurred predominately at low doses and was blocked by naltrindole [435]. Fentanyl produced changes in body temperature that depended on the dose used because low doses (0.2–0.5 mg/kg) produced hyperthermia, a high dose (1.5 mg/kg) produced hypothermia, and an intermediate dose (0.7 mg/kg) produced hypothermia in some animals but hyperthermia in others [412]. Subacute exposure of rats to a high environmental temperature potentiated the hyperthermic effects and attenuated the hypothermic effects of fentanyl, although the mechanism is not understood [412].

11. Seizures and other neurological disorders

In 1998, there was continued interest in the involvement of the endogenous opiate system in seizure activity, including the changes that occur after seizures, as well as the effects of opiate agonists and antagonists on seizure activity. Opiate agonists had proconvulsive effects that depended on the route of administration because a bolus injection of morphine, either IT or ICV, produced epileptic seizures in patients with malignant tumors, whereas no seizures were observed when morphine was administered by continuous infusion, even at high doses [218]. The opiate pethidine administered via a patient-controlled pump was associated with a brief self-limited seizure in a healthy male, probably due to the rapid accumulation of pethidine produced by frequent self-dosing [221]. Prenatal exposure to opiates also was associated with increased seizure susceptibility that was age-related, as exposure to morphine on Days 11 through 18 of gestation decreased the threshold to clonic seizures at postnatal Day 25, and increased the threshold by Day 38 that persisted into adulthood [404]. However, the analgesic tramadol does not seem to be associated with an increased risk of seizures, as no seizures were observed in patients exposed to tramadol alone, although seizures were observed in patients that had taken both tramadol and opiates, or opiates alone [170]. In fact, tramadol may have anticonvulsive actions, as it attenuated maximal electroshock seizures in mice that was κ-mediated because the anticonvulsive effects of tramadol were antagonized by MR 2266 and high doses of naloxone [239]. The δ-agonist pentazocine also is anticonvulsive because it too prevented maximal electroshock seizures in mice, but morphine did not [193].

Alterations in β-endorphin content have been observed in strains of rats prone to seizures that depend on the brain region studied [59]. Concentrations of β-endorphin in the anterior lobe of the pituitary were 53% and 57% higher in moderate epilepsy-prone rats (GEPR-3 strain), as compared with controls and severe-seizure rats (GEPR-9 strain) respectively, suggesting that anterior lobe secretion of β-endorphin is reduced in GEPR-9 rats [59]. In contrast, hypothalamic, central gray, and central amygdala content of β-endorphin were higher in GEPR-9 than GEPR-3 rats [59]. Because the central amygdala and central gray are activated

during audiogenic seizures in GEPR-9 rats, it is possible that elevated levels of β-endorphin in these brain areas contribute the seizure severity observed in this strain [59]. It is not clear, however, why β-endorphin content in the central gray was lower in GEPR-3 rats as compared with controls, but may be related to differences in endogenous analgesic systems as indicated by possible hyperalgesic responses in this strain [59]. The density of μ-opiate receptors in epileptic WAG/Rij rats also depended on the brain area studied, as WAG/Rij rats had higher levels of [^{3}H]DAMGO binding in the thalamus, cortex, and striatum, but lower levels in the frontal cortex as compared with controls [314]. Because injection of DAMGO into the thalamus, cortex and striatum also produced dramatic increases in spike wave discharges, it is likely that opiate systems are important for triggering and spreading spike wave discharge, thus contributing to the enhanced epileptic activity in WAG/Rij rats [314].

In the rat pilocarpine model of temporal lobe epilepsy, U50488H administered before pilocarpine increases seizure latency and decreases seizure duration, actions that were blocked by nor-BNI, suggesting that κ-agonists have anticonvulsive properties [26]. However, although pilocarpine also produced increases in mossy fiber sprouting and hilar neuron loss that were decreased by U50488H, nor-BNI did not block these the effects of U50488H, suggesting that the effects of U50488H on pilocarpine-induced histologic changes are probably secondary to the decreased incidence of seizures produced by U50488H [26]. In contrast, nor-BNI alone increased both the behavioral and histologic changes induced by pilocarpine, suggesting that κ-opiate receptors might mediate endogenous anticonvulsive and protective mechanisms [26]. Similarly, the susceptibility to seizures in EL mice may be related to deficits in endogenous opiate activity, in particular dynorphins, because these mice show κ-opiate up-regulation in various brain areas that increased as a function of age [172].

Kindling induced by daily injections of the convulsive agent pentylenetetrazol produces a progressive increase in seizure activity and has been used as a model of epilepsy [14]. Endogenous opiates released after the ictal phase may serve a protective function against seizure activity in this model, as increases in Met-enkephalin release were found in the amygdala and striatum that lasted for at least 15 days after the last seizure [14]. In contrast, Leu-enkephalin content was enhanced for only 1 day after the last seizure in the amygdala, and no increases were found in the striatum, indicating that opiate peptides are differentially enhanced after kindling [14]. However, although release of Met- and Leu-enkephalin in the amygdala were enhanced 24 h after kindling, in both control and kindled rats, Met-enkephalin levels were maximal before the onset of darkness, and Leu-enkephalin levels were maximal during the dark phase, suggesting that diurnal variations exist in the release of endogenous opiates [15].

Kindling also induces c-Fos expression in different brain areas that depends on the magnitude of seizure activity, as c-Fos was expressed in cortex in rats showing stage 4 seizures, whereas the induction of c-Fos in the hippocampus required stage 5 kindled seizures [104]. Endogenous opiates probably mediate the induction of hippocampal c-Fos because it was prevented by naloxone when given before pentylenetetrazol injections [104]. However, although naloxone blocked the expression of pentylenetetrazol-induced hippocampal c-Fos [104], it did not block seizure activity [104,344], suggesting that the increased neuronal excitability is not directly related to seizure activity, but may be related to the memory impairments often observed after epileptic seizures [104]. In contrast, naltrindole inhibited seizure activity and down-regulated enhanced glutamate binding in the hippocampus after kindling, suggesting an interaction between hippocampal glutaminergic and δ-opiate receptors in the development of seizure activity [344].

Endogenous opiate systems are involved in seizures and neurodegeneration induced by kainic acid, as receptor affinity for [^{3}H]DAMGO was increased in the cortex, hippocampus, medulla, pons, midbrain, hypothalamus, and striatum, and receptor numbers were increased in the cortex, medulla, pons, and striatum 4 h after an acute injection of a convulsive dose of kainic acid [324]. Quantitative autoradiography also showed increased [^{3}H]DAMGO labeling after kainic acid in the olfactory bulb, habenulla, dentate gyrus, interpeduncular nucleus, and throughout the cortex [324]. Seizures induced by kainic acid also raised levels of proenkephalin mRNA and prodynorphin mRNA in the dentate gyrus, which is regulated by c-Fos because levels of proenkephalin mRNA and prodynorphin mRNA were reduced with pretreatment with c-Fos antisense oligonucleotide [450]. However, it is not clear why μ-opiate receptors were not up-regulated in the hippocampus 4 h after injection kainic acid [324], despite increases in proenkephalin mRNA and prodynorphin mRNA after 3 h [450].

Opiate systems are involved in reactions to traumatic brain injury, as fentanyl administered in cats receiving fluid-percussion injury preserved CBF despite decreases in blood pressure [27]. Because hypotension-induced decreases in CBF is usually associated with poor outcome after traumatic brain injury, the restoration of CBF by fentanyl is of clinical importance [27]. Endogenous opiates also are involved after focal cerebral ischemia, as decreases in μ- δ- and κ-opiate receptor density, but not affinity, were observed in the infarct ischemic tissue [45]. However, relative to μ and δ receptors, changes in κ receptor density were delayed, supporting a possible neuroprotective action of κ-agonists in the treatment of stroke [45].

In an animal model of Parkinson's disease produced by monoamine depletion, the κ-agonists U69,593 and CI-977 increases locomotor activity, an effect that was blocked by both naloxone and nor-BNI, but had no locomotor effects in nonparkinsonian rats [160]. Furthermore, when CI-977 was co-administered with L-dopa, they produced synergistic anti-akinetic effects, suggesting a possible role of κ-agonists

as adjuncts to dopamine replacement in the treatment of Parkinson's disease [160]. In rats with 6-OHDA lesions of the striatum, apomorphine treatment differentially enhanced preproenkephalin-A and -B gene expression in the motor, associative, and limbic regions of the striatum, which may contribute to cognitive and motor deficits after long-term dopamine replacement therapy [96]. Cognitive deficits related to decreased cholinergic function, as seen in Alzheimer's disease may benefit from κ-agonists, as deficits in learning and memory induced by cholinergic antagonists were reversed by administration of U50488H [151] and dynorphin A reverses the impairments produced by low doses of the muscarinic agonists, charbacol [152]. Both of these effects are κ-mediated because they are blocked by the κ-antagonist, nor-BNI [152,153].

12. Electrical-related activity

There was continued interest in the ability of the opiate system to modulate neural activity, in particular opiate mediation of nociceptive spinal neurons. Noxious heat stimulation of the tail in rats increased neural activity in dorsal horn neurons that was reduced by microinjections of bicuculline into the ventral PAG, or by iontophoretically applied DAMGO to dorsal horn neurons [54]. Because naloxone, CTOP, and CTAP applied to these neurons antagonized the inhibitory effects of both bicuculline and DAMGO, it is likely that PAG modulation of nociceptive dorsal horn neurons is mediated by endogenous opiates acting at dorsal horn μ receptors [54]. Furthermore, although naloxone increased baseline dorsal horn neural activity, CTOP and CTAP did not, suggesting that non-μ receptors, probably δ and κ, mediate tonic inhibition of these neurons [54]. A possible candidate for the endogenous μ-opiate peptides that mediate spinal nociception are the endomorphins, as endomorphin-2 immunoreactivity was detected in the superficial laminae of the dorsal horns, supporting further the role of these peptides in spinal nociceptive mechanisms [243]. Endogenous opiates also mediate the inhibitory effects of vagal afferent stimulation on tooth pulp-induced neural activity related to the digastric electromyogram signal in the trigeminal spinal nucleus oralis, as the inhibitory effects of vagal stimulation were attenuated by naloxone [383]. Similarly, digastric electromyogram activity produced by application of mustard oil into the temporomandibular joint is suppressed by local pretreatment with morphine, that is blocked by naloxone [23]. Besides spinal nociceptive neurons, endogenous opiate peptides are similarly involved in spinal modulation of electrodermal activity because inhibition of electrodermal activity produced by stimulation of the bulbar reticular formation was attenuated by both IT and IV naloxone, as demonstrated by an increased amplitude of the responses after naloxone [396].

In slices of preoptic area/anterior hypothalamus, dynorphin $A_{1\text{-}17}$ influences firing rate in temperature-sensitive neurons that depend on the concentration used, as low concentrations increased firing rate in warm-sensitive neurons, but higher concentrations decreased firing rate [435]. Because the effects of dynorphin $A_{1\text{-}17}$ were blocked by nor-BNI, κ receptors located in the hypothalamus are probably involved in thermoregulation. [435]. However, δ receptors are also involved because DPDPE usually decreased firing rate that was blocked by naltrindole, although fewer neurons responded to the agonist [435]. In the rat supraoptic nucleus, IV nor-BNI increased the burst duration and decreased the interburst interval phasic activity displayed by vasopressin cells, whereas retrodialysis of nor-BNI directly on to the supraoptic nucleus only increased burst duration, suggesting that the effects of nor-BNI on interburst interval occurred outside the supraoptic nucleus [51].

In contrast, endogenous κ-agonists do not modulate oxytocin cell activity within the supraoptic nucleus because nor-BNI administered IV or directly onto the supraoptic nucleus did not alter the firing rate of continuously active oxytocin cells [51]. In support of this, functional down-regulation of κ receptors by continuous infusion of U50488H directly into the supraoptic nucleus for 5 days reduced spontaneous activity of vasopressin but not oxytocin cells and reduced the proportion of cells displaying spontaneous phasic activity, indicating that the expression of phasic firing of vasopressin cells depends on intact κ-opiate mechanisms [51]. However, although naloxone did not alter the firing rate of oxytocin neurons in morphine-naive animals, it increased firing rate in morphine-dependent rats, suggesting that these neurons are active during morphine withdrawal [52]. Similarly, the spontaneous firing rate of nucleus paragigantocellularis neurons was decreased by morphine and increased after naloxone in morphine-dependent rats [138]. In recordings from PAG slices, naloxone increased GABA-mediated inhibitory synaptic currents in morphine-dependent subjects but not in controls [164]. Because naloxone also increased the frequency of GABA-mediated spontaneous synaptic currents without affecting the amplitude, the effect is probably presynaptic [164].

In the centrolateral thalamus in young rats, DAMGO, but not DPDPE or U50488H causes hyperpolarization and shifted the firing pattern from tonic to bursting, an effect that was mediated by an increase in K^+ conductance [53]. The effects of DAMGO did not depend on the area of the thalamus studies, however, because a similar inhibitory action of DAMGO was observed throughout the thalamus, including relay, intralaminar and midline nuclei [53]. Because the inhibitory action of DAMGO is widespread, exogenous opiates such as morphine would be expected to hyperpolerize all thalamic nuclei, whereas endogenous opiates would inhibit only specific thalamic nuclei, depending on the origin of the presynaptic input [53].

In hippocampal slices, the κ-opiate agonist U69593 reversibly decrease excitatory postsynaptic potentials in the middle molecular layer of the dentate gyrus in the ventral but not dorsal regions of the hippocampus, which is con-

sistent with the hypothesis that endogenously released κ-agonist have anticonvulsive properties [26]. In slices from the CA1 region of the hippocampus, chronic morphine increased the amount of long-term potentiation (LTP) of orthodromic population spike amplitude [311]. It is likely that the enhanced LTP in morphine-treated subjects is mediated mainly by NMDA, and to a lesser extent by voltage-dependent calcium channels, because AP5 completely blocked LTP from both morphine-treated and morphine naive subjects, whereas the calcium channel blocker nifedipine only attenuated LTP in morphine-dependent rats [311]. In the CA3 region of the hippocampus, dynorphin $A_{1\text{-}17}$ produced a biphasic concentration-dependent effect on NMDA-mediated synaptic currents, in which the excitatory effects were blocked by ifenprodil, a polyamine site antagonist on the NMDA, thus converting dynorphin's biphasic concentration response to a monophasic inhibitory curve [62]. However, when opiate receptors were blocked with naloxone, dynorphin produced neurotoxic effects that were blocked by ifenprodil, suggesting that opiate receptors protect NMDA receptors from dynorphin-mediated neurotoxicity [62].

In the nucleus accumbens, buprenorphine facilitates single unit activity of spontaneously active neurons at low doses, but depressed activity at higher doses [273]. The inhibitory and excitatory actions of buprenorphine are mediated by distinct dopamine receptors, however, because the D_1 antagonist SCH 23390 inhibited buprenorphine-induced depression but not facilitation, whereas the D_2 antagonist eticlopride blocked facilitation but not depression [273]. The nontraditional opiate nociceptin/orphanin FQ, which has anxiolytic properties, mediates neural activity in the amygdala as 98% of neurons in the lateral amygdala showed impaired excitability after application of nociceptin, that was explained by an increase in K^+ conductance [257]. In contrast, although 32% of the cells in the central amygdala showed similar responses, 44% were not responsive, and 25% responded with only a small K^+ current [257]. The effects of nociceptin are mediated by the opiate-like orphan receptor because the responses to nociceptin were blocked by a opiate-like orphan receptor antagonist, but not by naloxone [257]. Furthermore, G-proteins are likely involved, as the effects of nociceptin also were blocked GTP-γ-S, GDP-β-S, and pertussis toxin [257]. The mesocorticolimbic system is likely involved in opiate self-administration because medial prefrontal cortex and nucleus accumbens neurons responded to both anticipation of the drug and to infusion of the drug, either by increasing or decreasing their firing rate [68].

In neuroblastoma NG108–15 or neuroblastoma SK-N-SH cells, nociceptin/orphanin FQ and DAMGO stimulate cAMP, and G-protein binding, effects blocked by NMDA, indicating that there was cross-talk between NMDA and opiate-like orphan receptors, and between NMDA and opiate signal transduction [447]. In contrast, signaling induced by the opiate agonist etorphine was sensitive to NMDA in NG108–15 but not SK-N-SH cells, suggesting a differential modulation of opiate signaling by NMDA [447]. Exposure to the δ-agonist DADLE also increased intracellular Ca^{2+} in NG108–15 that became desensitized after prolonged exposure to the agonist, which was reversible and overcome by higher concentrations of DAMGO [438]. In human SH-SY5Y neuroblastoma cells, endomorphin-1 and -2 also activated G-proteins in similar fashion to DAMGO, although the endomorphins stimulated binding to a lesser extent than DAMGO [141]. In contrast, the structurally similar peptide Tyr-W-MIF-1 produced only minimal effects on G-protein stimulation, but attenuated activation of G-proteins by DAMGO and the endomorphins [141]. In astrocytes that functionally express opiate receptors, an acute 3 h exposure to μ-, δ-, and κ-opiate agonists caused increases in Ca^{2+} and levels of oxidative products [144,373]. However, after 72 h of continuous exposure to the agonists, Ca^{2+} and carbonyl levels returned to normal, suggesting that astrocytes recover from sustained opiate exposure, and may serve a neuroprotective function [144].

Acute injection of alfentanil [77,78], sufentanil, and fentanyl [77] produce changes in EEG that correlate with the pharmacodynamic properties of these opiates in vitro, thus providing an in vivo model for the pharmacodyamics of opiates. However, tolerance develops to the EEG effects of the μ- opiate agonist, alfentanil, after repeated injections, suggesting that reliable estimates cannot be obtained after chronic morphine exposure [78]. Endogenous opiates may mediate attentional processes as measured by auditory event-related potentials in subjects asked to detect deviant tones presented to one ear whereas ignoring tones to the other [169]. In this task, naltrexone produced changes in event-related potentials that indicated impairments in selective attention [169]. However, it is not clear whether this effect was explained by interactions with opiate-mediated attentional processes or by nonspecific effects produced by naltrexone, because naltrexone also produced nausea that could have interfered with the subjects' ability to concentrate [169].

13. General activity and locomotion

As in previous years, there was continued interest in the modulation of activity by endogenous opiates, in particular locomotion. However, conclusions were difficult to reach because the effects of opiate agonist and antagonists were influenced by a number of variables, including the dose and paradigm used to measure their effects. Morphine increased locomotion under most conditions [4,196,197,270,339,368, 375], but in some conditions had no effect [413]. An acute injection of morphine increased locomotion over time, a biphasic effect displaying an immediate and delayed increase in locomotion [368]. Infusion of morphine into the nucleus accumbens produced an increase in locomotion and contraversive turning but did not affect the number of rears,

suggesting that opiate receptors in this brain area are involved in behavioral activity [339]. Morphine injected into the PAG also affected locomotor activity that depended on the time point at which the activity was measured, as injection of 0.2 μl of morphine in both the ventral and dorsal PAG tended to produce inactivity when tested 5 min after injection, but produced increased locomotor activity 20 min after injection into the dorsal PAG [270]. However, an increase in the injection volume to 0.4 μl produced more dramatic results at 20 min, producing alternations between explosive running and immobility when injected into the dorsal PAG, but suppressed activity in most animals and produced circling in others when injected into the ventral PAG [270]. Therefore, although both the ventral and dorsal PAG are involved in opiate-mediated locomotor responses, the dorsal PAG is associated with flight and the ventral PAG with immobility [270]. Morphine decreased body movement in neonatal rats treated with capsaicin that was blocked by naloxone, and may provide a useful method for quantifying analgesic compounds in this animal model of pain [219].

Repeated injections of morphine produced sensitization to increases in locomotor activity produced by an acute injection of morphine [4,368] that was blocked by acamprosate, suggesting that NMDA receptors may be involved in morphine-induced sensitization of locomotion [368]. However, dopaminergic systems also may be involved because acamprosate also blocked sensitization of morphine-induced dopamine release from the nucleus accumbens after repeated morphine [368]. In contrast, acamprosate did not affect the locomotor effects of an acute injection of morphine, suggesting that the effect of acamprosate is likely specific to the sensitization of locomotor activity [368]. In animals treated chronically with morphine, locomotor activity increased over 4 days after the last morphine injection, as compared with saline-treated rats, and may represent behavioral signs of acute withdrawal [325].

Besides morphine, the effects of other opiate agonists on locomotor activity were examined but were inconsistent. Fentanyl produced dose-dependent catalepsy that depended on the environmental temperature because the effects were more pronounced in rats exposed to a high environmental temperature (32°C) as compared with those exposed to a normal temperature of 21°C [412]. In contrast, alfentanil increased locomotion in 20-day-old rats, an opiate-mediated effect because naloxone blocked it [106]. However, pre-exposure to chronic naltrindole did not modify the effects of alfentanil on behavioral activity, suggesting that there is no interaction between μ and δ receptors [106]. Methadone alone did not alter locomotion, although at high doses it increased PCP-induced stereotypic behavior and ataxia, suggesting that methadone does not have antipsychotic actions [334]. The dextrorotory opiates, dextromethorphan and dextrophan, produced increases in circling, head swaying, and backwards walking in both female Dark Agouti and Sprague–Dawley rats, although the effects of dextrophan were more pronounced in Dark Agouti, perhaps related to their ability to metabolize dextrophan [165]. However, the effects of dextromethorphan and dextrophan are likely related to their affinity for NMDA receptors, because similar profiles were observed after administration of various NMDA antagonists [165]. The hydromorphone metabolite, hydromorphone-3-glucuronide, also produced behavioral excitation, that included chewing, rearing, myoclonus, ataxia, and convulsions [432].

DAMGO increases locomotor activity and potentiated the locomotor effects of cocaine, effects blocked by naloxone but not naltrindole [413]. However, although the differential effects of naloxone and naltrindole suggests that the effects of DAMGO are μ-mediated, it is not clear why the selective μ-antagonist β-FNA only modestly antagonized the locomotor effects of DAMGO and did not change the locomotor effects of DAMGO in combination with cocaine [413]. Furthermore, in the same paradigm morphine did not affect locomotor activity, although this may be a result of the variability observed with morphine that increased locomotion in some animals and decreased it in others, thus producing a net result of no effect [413]. The δ-agonist DPDPE increased locomotor activity that was δ-mediated because the effects were blocked by naloxone and naltrindole, but not β-FNA [413]. However, all three antagonists blocked the ability of DPDPE to potentiate cocaine-induced increases in locomotion, suggesting that the locomotor effects of DPDPE and cocaine combinations are mediated by both μ- and δ-opiate receptors [413].

Locomotor activity generally has been suppressed by κ-agonists, but there were some exceptions. In 20-day-old rats, the selective κ-agonist CI-977 decreased locomotion that was opiate-mediated because it was blocked by naloxone [106]. Although no differences were found in spontaneous locomotor activity in κ-opiate deficient mutant mice as compared with wild-type, U50488H produced strong hypolocomotor effects in wild-type mice but only had modest effects in κ-opiate deficient mice, suggesting that the κ-opiate receptor is critical for the hypolocomotor effects of U50488H [360]. In contrast, the selective κ-agonist U69,593 [413] and κ-antagonist nor-BNI [90] did not alter locomotion. However, when combined with ethanol, κ-agonists potentiated motor incoordination and κ-agonists attenuated it [90], and although not statistically significant, U69,593 had a tendency to block cocaine-induced increases in locomotion [413].

When given alone, naloxone has little effects on locomotion, as it did not induce freezing [199], nor did it alter spontaneous activity or open field ambulations [7]. However, naloxone produced a slight dose-dependent decrease in total distance traveled within a session, enhanced PCP-induced stereotypy at lowest and highest doses [334], and potentiated stress-induced freezing in male rats, but not females [199]. Naloxone also suppressed the recovery of locomotor activity after swimming, suggesting that opiate systems contribute to recovery from fatigue after exercise

[163]. In animals treated chronically with morphine, fentanyl, or butorphanol, naloxone produced increases in locomotion that was used as an index of withdrawal [392,430]. However, naloxone produced greater locomotor effects in morphine- than butorphanol-treated animals suggesting that butorphanol produces less physical dependence than morphine [430].

Other forms of activity are mediated by opiate systems, including turning behavior in rats with nigral-striatal lesions. Although morphine did not produce turning in rats with unilateral 6-OHDA lesions, it potentiated amphetamine-induced turning [197]. However, extracellular dopamine levels were not changed by morphine, suggesting that the effect of morphine was not explained by dopamine release in this area [197]. Morphine and methadone also potentiated turning induced by the dopamine reuptake blocker GBR12909 that was opiate-mediated because it was blocked by naloxone [196]. Surprisingly, naltrexone also potentiated GBR12909-induced turning that was blocked by naloxone, suggesting that naltrexone may have opiate agonist properties [196]. In contrast, naltrexone did not potentiate cocaine-induced turning, but this may be explained by the peak effect of naltrexone occurring after that of cocaine [196].

Eye movements also are mediated by the opiate system. Morphine produced myosis, as did codeine and pentazocine, although morphine had the largest effect [414,443]. Chronic morphine produced a reduction in rapid eye movements after cessation of treatment, which recovered after 4 days, thus providing an index of acute spontaneous withdrawal [375]. Although the mixed agonist-antagonist pentazocine impaired psychomotor function in normal volunteers [443], morphine and codeine had no effect [414].

There was continued research in the role of endogenous opiates during strenuous exercise. Plasma β-endorphin levels increased after strenuous physical exercise in untrained women 5 min after running a treadmill to exhaustion, which returned to basal levels 30 min later [147]. However, although no changes were observed in basal levels of β-endorphin after the women received endurance training, the increase is β-endorphin after exercise was less dramatic after training, indicating that adaption occurs [147]. In contrast, women with a history of endurance training had higher levels of basal β-endorphin as compared with women with no history of endurance training, and this was not affected by exposure to a cold air stressor [13]. Endogenous opiate systems also were activated by chronic wheel running, as rats exposed to running activity wheels for 20 days showed cross-tolerance to morphine analgesia [176].

14. Sexual activity, pregnancy, and development

As in previous years, there was continued interest in the role of endogenous opiates in sexual and reproductive function. In male rats, chronic immobilization reduced serum testosterone levels that was prevented by intratesticular injection of naltrexone-methobromide, an opiate antagonist that does not cross the blood-brain barrier, suggesting that endogenous opiates are important in the modulation of testicular steroidogenis [204]. Because immobilization stress also reduced activity of the NADPH-P45 reductase that was normalized by naltrexone-methobromide, it is probable that this enzyme mediates the inhibitory effects of endogenous opiates on testicular steroidogenis [204]. Alcohol also may negatively affect the male reproductive system that is opiate-mediated, as ethanol suppressed testosterone in 45- and 55-day-old rats, and effect that was prevented by naltrexone [101]. Although penile erections were rarely induced by injection of opiate antagonists [180], naloxone produced erections in rats that had been pre-exposed to morphine [180,305,388] or codeine [180], and was used as a measure of opiate withdrawal. Masturbation in monkeys also was observed during opiate withdrawal, and this increased for 3 days after discontinuation of treatment with the long-lasting μ-opiate LAAM [48].

Sexual behavior in females involves endogenous opiates that depend upon gonadal steroids, as levels of β-endorphin in the ventromedial and arcuate nuclei were higher in ovariectomized-adrenalectomized female rats that became sexually receptive after estradiol injections [256]. In contrast, rats that did not become sexually receptive after estradiol did not show similar increases [256]. Therefore, the enhancement of β-endorphin after estrogen is correlated with estrogen-induced stimulation of sexual behavior but not other estrogen-dependent functions [256]. Unlike adults, however, ovariectomized juvenile guinea pigs rarely show signs of steroid-induced sexual receptivity, perhaps related to a tonic inhibition produced by endogenous opiates acting on the medial preoptic area, as injections of naloxone but not saline into that brain site facilitated steroid-induced lordosis [286]. This suppressive effect is probably μ-mediated because injection of morphine into the same site prevented the facilitory effects of naloxone, although it is not clear how the suppressive effects of endogenous opiates diminish during maturation [286]. Interestingly, estrogen stimulates preproenkephalin mRNA at all stages of postnatal development in neural circuits that mediate lordosis behavior, whereas CCK mRNA is low up to postnatal Day 25, but increases during peripubertal periods [154]. Thus, CCK may be involved in the activation of neural circuits that mediate lordosis, but are not functional during early postnatal periods because of an opiate-mediated suppression [154]. Reproductive behaviors in birds also involve endogenous opiates, as ICV β-endorphin inhibited female courtship display and naloxone enhanced it [238].

Opiate systems are involved in pregnancy and reproductive function, that include both direct and indirect actions of opiates on gonadal hormones [132]. The increased pain threshold observed during pregnancy is mediated by spinal κ- and δ-opiate receptors because analgesia during gestational Day 20 or day on 19 of hormone-stimulated preg-

nancy is abolished by IT nor-BNI, BNTX, and NTB [92]. However, activation of κ- and δ-opiate receptors alone during pregnancy is not sufficient to induce analgesia and may require concomitant activation of both, because combinations of the antagonists in suboptimal doses did not produce a greater magnitude of blockade than was obtained by administration of the antagonists alone [92]. Morphine inhibited nocturnal uterine contractions in pregnant baboons that was accompanied by a suppression of oxytocin levels [211]. Because morphine-induced increases in metabolic clearance of oxytocin was small, and the myometerial responsiveness to exogenous oxytocin was not affected by morphine, it is likely that morphine inhibits uterine contractions primarily by suppressing oxytocin release [211].

Endogenous opiates modulate reproductive function in females, as naloxone stimulates the release of luteinizing hormone (LH) in nulliparous, primiparous, and multiparous female rats, suggesting that reproductive experience does not influence the inhibitory effects of endogenous opiates on LH release [156]. However, opiate regulation of LH may change as a function of reproductive experience during lactation because the magnitude of the LH response was greater after low doses of naloxone on Day 10 of lactation in multiparous females as compared with primiparous females, although this effect was modest and was not found at higher doses of naloxone or at Day 8 of lactation [156]. In contrast, LH fluctuations were not modified by chronic naltrexone, suggesting that the effects of naltrexone on LH release are transient [330]. Altered menstrual cycles and ovulation in conditioned runners are not explained by changes in opiate activity, as baseline levels of β-endorphin in runners who were anovulatory and oligomenorrheic were not different from runners who were ovulatory and eumenorrheic [261]. Endogenous opiates mediate the development of diurnal changes in tuberoinfundibular dopamine activity in females, that regulates estrogen-induced prolactin surges in the afternoon, as naloxone stimulated dopaminergic activity in the afternoon but not the morning in postpubertal but not prepubertal rats [357].

Endogenous opiates are likely involved in maternal behavior, and may contribute to infant-mother attachment [220,278]. Furthermore, because opiates are rewarding they may function to increase motivation for maternal contact [278]. Suckling in rats involves activation of endogenous opiates, as ICV injections of naloxone into caesarean-delivered pups increased latency to the first oral grasp of a surrogate milk-filled nipple, decreased time on the nipple, and eliminated injection of milk, whereas intracisternal (IC) or peripheral injections had no effect [300]. Because naloxone had no effect on a water-filled or empty nipple, it is possible that during the first suckling milk engages endogenous opiate systems that are involved in early suckling [300]. In contrast, blockade of caudal μ-opiate receptors with IC injection of CTOP in neonatal rats decreased responsiveness to an artificial nipple, reduced body weight in pups suckling from the mother, increased the latency to the first nipple attachment, and decreased total nipple attachment time, whereas blockade of rostral μ-opiate receptors with ICV injections of CTOP increased responsiveness to an artificial nipple, did not alter body weight, and decreased the latency to the first nipple attachment [299]. Thus, it seems that two distinct populations of μ-opiate receptors regulate suckling behavior but in opposite directions, a caudal population that initiates suckling early on, and a rostral population that decreases responsiveness during weaning [299]. However, δ-opiate receptors also are likely involved during weaning because δ-opiate receptor binding was increased in 25-day-old pups that had been weaned as compared with nonweaned pups when labeled with the deltorphin analogues, [^{3}H]deltorphin I, [^{3}H]S-Atc-Ile^{5,6}-deltorphin I, and [^{3}H]R-Atc-Ile^{5,6}-deltorphin II [187]. However, differences exist between δ-agonist ligand because binding of [^{3}H]Ile^{5,6}-deltorphin II and [^{3}H]naltrindole was not different between weaned and nonweaned pups, perhaps related to their sensitivity to the coupling states of the receptors [187].

Prenatal exposure to opiates can alter development. Prenatal exposure to morphine can have adverse effects on immune function, including impaired natural killer cell activity that can increase susceptibility to infection [355]. At one year of age, infants prenatally exposed to opiates and nicotine showed lower locomotor and intellectual performance, and a greater incidence of severe and mild mental retardation, as compared with infants exposed only to nicotine [55]. It is not likely that these differences were explained by environmental factors during the first year because no differences were found in fostered infants compared with infants living with their biologic mothers [55]. In contrast, there was no evidence of fetal distress, fetal death, or premature delivery in offspring of mothers detoxified from methadone or clonidine treatment during pregnancy; however 15% of the neonates were treated for opiate withdrawal [91]. The short acting μ-agonist remifentanil did not produce any adverse neonatal side-effects when given to mothers during pregnancy, suggesting a potential use of this analgesic for pain control during pregnancy and labor [175].

Prenatal exposure to nonopiate drugs also may increase susceptibility to opiate abuse in adulthood that is sex-dependent, as adult female but not male rats born to mothers exposed to Δ^9-tetrahydocannibol during gestational and lactation periods showed higher rates of acquisition of IV morphine self administration as compared with controls [405]. These differences in morphine reinforcement may be related to changes in μ-opiate receptor binding because female offspring of Δ^9-tetrahydocannibol-exposed mothers showed increased [^{3}H]DAMGO binding in the prefrontal cortex, hippocampus, posteromedial cortical nucleus of the amygdala, VTA, and PAG, and lower binding in the lateral amygdala, as compared with controls [405]. In contrast, male offspring of Δ^9-tetrahydocannibol-exposed mothers showed lower μ-opiate receptor density in the caudate-

putamen and posteromedial cortical nucleus of the amygdala [405].

Chronic administration of fentanyl with an osmotic minipump during postnatal Day 14 to 17 produces dependence and may have long-lasting effects on opiate-mediated pain modulation because morphine analgesia was reduced in these rats when tested as juveniles and adults [392]. Chronic administration of the δ receptor antagonist naltrindole during the first 19 days postnatally fully antagonized stress-induced analgesia in 25-day-old rat pups, but only partially antagonized analgesia in 20-day-old pups and had no effect in adult rats [9]. Because the decreased analgesic effects of swim stress in 25-day-old pups was antagonized by naloxone but not naltrindole, it indicates that the normal δ mediation of stress analgesia during the postnatal period was affected [9]. Chronic postnatal administration of naltrindole also blocked analgesia to the μ-agonist alfentanil, but not the κ-agonist CL-977, suggesting a functional postnatal interaction between μ and δ receptors, but not between κ and δ receptors [106]. In contrast, the locomotor effects of alfentanil and CL-977 were not modified by chronic naltrindole, indicating that the functional interaction between μ and δ receptors differs for analgesic and locomotor systems [106]. However, under normal conditions, opiate analgesia in neonates is similar to that in adults, as morphine produced analgesia in neonatal rats that was antagonized by naloxone [219].

Chronic malnourishment during perinatal periods also may affect endogenous opiate mechanisms in adulthood, as the normal inhibitory effects of chronic restraint on clonidine-induced hypoactivity were absent in rats that were malnourished for 50 days postnatally, and whose mothers were also malnourished at 14 days of pregnancy, effects normalized by administration of morphine or β-endorphin before the restraint sessions [186]. Asphyxia in neonates also modifies endogenous opiates, as asphyxiation in newborn rabbits caused by enclosure in an airtight box for 60 min increased enkephalin-like immunoreactivity in the paraaortic body and adrenal glands [424]. In contrast, insulin-induced hypoglycemia decreased enkephalin-like immunoreactivity in the adrenal glands [424]. SIDS is not related to opiate dysfunction in cardiorespiratory nuclei, as there were no differences in [^{3}H]naloxone binding in brainstem nuclei related to respiratory or autonomic control in victims of SIDS, as compared with non-SIDS controls [198].

As in previous years, there was much interest in the ontogeny of opiate systems, and the regulation of development by endogenous opiate systems. However, although no one opiate receptor subtype singly affects all cell growth and differentiation, depending on the cell type studied μ, δ, and κ receptors can modulate cell development [145]. The expression of μ-, κ-, and δ-opiate receptors occurs in different patterns and at different stages of development, as κ receptor mRNA is first detected in mice in the gut epithelium by embryonic Day 9.5, whereas μ receptor mRNA is detected on embryonic Day 10.5 in the facial-vestibulocochlear complex, and on embryonic Day 12.5 δ receptor mRNA is detected in several peripheral tissues [449]. In the brain, μ mRNA is detected in the basal ganglia by embryonic Day 11.5 in mice and extends to other brain areas during mid- and late-gestation [449]. In rats, μ mRNA can be detected in the telencephalon, striatal neuroepithelium, and cortical plate on embryonic Day 13, and in the striatum by embryonic Day 15 [126]. By embryonic Day 11.5, κ mRNA is found in the midbrain in mice; in rats it is found in the telencephalon by embryonic Day 13 and in the nucleus accumbens, striatum, substantia nigra, and VTA by embryonic Day 15 [449]. In contrast, δ receptor mRNA seems to occur later, as it remains low throughout embryonic development in mice [449] and in rats is detected in the nucleus accumbens and dorsal striatum by embryonic Day 21, and by postnatal Day 8 in the striatum [126]. In the spinal cord of mice, δ receptor mRNA occurs on embryonic Day 15.5, and μ mRNA by embryonic Day 11.5 [449]. In rats, μ- and κ-opiate binding sites are present in the spinal cord at birth, whereas δ-opiate binding sites are not detected until postnatal Day 7 [317].

The effects of aging on endogenous opiate activity also was studied. Once established, opiate receptor density in the spinal cord remains constant, as no differences in μ, κ, and δ receptor density was found between 6-, 16-, and 26-month-old rats [157]. In contrast, an age-related decreased affinity of spinal μ-opiate receptors was found, although this is probably not large enough to explain the decrease in spinal opiate analgesia that is observed with aging [157]. Enzyme degradation of plasma Leu-enkephalin increases with age, as elderly subjects (mean age of 78.3 years) showed increase activity of enkephalin-degrading enzymes and decreased activity of inhibitors of those enzymes, as compared with controls (mean age of 31.5 years) [21]. The significance of this change is not known, but may be associated with age-related impairments of immune function [21]. Dopamine-mediation of enkephalin activity in the striatum is not age-related, as haloperidol increased preproenkephalin mRNA similarly in 3-, 10-, and 23-month-old rats [225].

Morphine can inhibit cell proliferation, as it inhibited DNA expression in cerebellar extragranular layer neuroblasts that is blocked by naloxone [288]. The development of oligodendrocytes, a major macroglial cell in the central nervous system, is likely modulated by signaling through endogenous opiate systems, as μ receptors are expressed in early stages of development and before the expression of κ receptors [201]. In contrast, δ receptors are not expressed and thus probably not involved in the development of oligodendrocytes [201]. In support of the role of μ receptors in the development of oligodendrocytes, exposure of immature but not mature oligodendrocytes to the μ-agonist PL017 increased the rate of DNA synthesis that was blocked by naloxone [201]. In contrast, the κ receptor is not involved in cell proliferation, as U50488H did not affect the rate of DNA synthesis [201]. However, κ receptor receptors may

be involved in myelin production, as nor-BNI increased the size of myelin-like membrane products in normal mice, and κ-opiate receptor are deficient in mutant mice that lack myelin [201]. The nontraditional opiate nociceptin/OFQ also may be involved in neural development, as both prepronociceptin/OFQ and nociceptin/OFQ receptor mRNA are expressed in the mantle zone of the basal telencephalon, thalamus-hypothalamus border, superior colliculus, pons and medulla during embryonic development in mice, and gradually decreases postnatally [162]. In the chick, dynorphin is contained in cochlear nucleus magnocellularis that is restricted to specific developmental periods, as dynorphin immunoreactivity in primary auditory terminals of the cochlear nucleus magnocellularis first appears at embryonic Day 16 and is no longer evident by posthatch week three [71].

Endogenous opiates play a role in the growth and development of the heart probably by modulating Met-enkephalin-induced cell proliferation and differentiation [253,419, 443]. In heart cells, opioid growth factor or Met-enkephalin mRNA increased sevenfold between embryonic Day 18 and 20, and continued to increase in the neonate [253,443]. In contrast, Met-enkephalin mRNA decreased through the 2nd postnatal week, and was very low in adulthood, when it was 43-fold less than in neonates [253]. Similarly, in hearts cells at embryonic Day 14 until after birth preproenkephalin mRNA, which encodes for Met-enkephalin, is abundant in epicardial, myocardial, and endocardial heart cells, and in the walls of blood vessels, capillaries, and fibroblasts; it declines on postnatal Days 5, 10, 21, and in adulthood [254]. Therefore, the ontogeny of Met-enkephalin indicates its role in the development of heart tissue, that is regulated preproenkephalin mRNA [253,254,443]. Furthermore, preproenkephalin mRNA expression is 4-times more abundant in the adult left ventricle than the right, but not during early postnatal periods, raising the possibility that the left ventricle serves as an endocrine organ to provide enkephalins to the body [419]. In contrast, preprodynorphin mRNA was not found in developing or adult rats, and POMC mRNA was only found in the adult myocardium, making their role in heart development less clear [254].

15. Immunological responses

Interest in opiate modulation of immunologic responses continued in 1998. In general, opiates tended to suppress immune function when tested in vivo but had no effect or enhanced immune function when tested in vitro, suggesting that the endogenous and exogenous opiates may have a different mechanism of action [99]. Chronic administration of morphine was immunosuppressive, as it decreased natural killer cell activity (NKCA), produced atrophy of the lymphoid organ, and reduced the ratio of lymphocytes in the thymus of wild-type mice [122]. In contrast, chronic morphine had no immunologic effects in MOR receptor knockout mice, indicating a role of the μ-opiate receptor in mediating the immunosuppressive effects of morphine [122]. However, endogenous activation of the MOR receptor may not be important in the maintenance of immune functions, because MOR-knockouts and their wild-type controls did not differ in immune function in the absence of morphine [122]. This differential effect may reflect differences in the receptors activated by endogenous and exogenous opiates [99]. The immunosuppressive effects of morphine may be of clinical concern when used for pain relief, including orthopedic surgery that often involves insertion of foreign objects that can cause infection [158].

The immunosuppressive effects of morphine may be related to their interactions with the sympathetic nervous system, as morphine increases splenic levels of norepinephrine and decreases NKCA and lymphocyte proliferations, whereas buprenorphine, which does not induce immunosuppression, does not increase levels of norepinephrine [139]. Acute in vitro exposure of macrophages to morphine resulted in the cells rounding up and becoming nonmotile, and was opiate-mediated because it was blocked by naloxone [372]. In contrast, chronic exposure to morphine produced initial inactivity that was followed by chemokinesis, possibly preventing these cells from responding to antigenic challenge [372]. Prenatal morphine exposure also may adversely affect the immune system, as 10–12-week-old offspring of rats exposed to chronic morphine during gestational Day 12–18 had suppressed NKCA and fibral responses, and impaired regulation of LPS-induced behavioral responses, as compared with controls [355].

β-endorphin is found in immune cells and evidence for its involvement in immune function continued to grow [41, 87]. β-endorphin was correlated with immune cell activity, as administration of mistletoe lectin in patients with breast carcinoma induced an increase in plasma β-endorphin levels that was accompanied by enhanced activity of natural killer (NK) cell and T-lymphocytes [146]. In addition, patients with septic shock had higher plasma β-endorphin levels, as compared with controls, or patient with septis or septic syndrome, indicating its role in the late stage of response to infections [227]. Patients with chronic fatigue syndrome had lower levels of β-endorphin in peripheral blood mononuclear cells, which may reflect the state of chronic immune activation in these patients [74]. Exercise also may enhance immune function and β-endorphin, as 2 h of moderate physical exercise increased plasma β-endorphin levels and enhanced both NKCA and NK cell counts [118]. However, because pretreatment with naltrexone did not alter NKCA or NK cell counts, a causal link between β-endorphin and NKCA was not established [118]. In contrast, quadriplegics did not show increases in NKCA response to exercise, perhaps related to their impaired sympathoadrenal activity [200].

Met-enkephalin may play a regulatory role in immune responses, as LPS-stimulated T-cells and monocytes secrete Met-enkephalin, an effect blocked by preproenkephalin an-

tisense oligonucleotide [174]. Furthermore, blockade of Met-enkephalin production with antisense oligonucleotide resulted in an enhancement of T-cell proliferation and an inhibition of monocyte interleukin-6 (IL-6) secretion [174]. However, although addition of Met-enkephalin or deltorphin to the antisense treated cultures reversed the inhibition of IL-6 secretion, it did not modify T-cell proliferation [174]. Consistent with these finding, Met-enkephalin also stimulates IL-6 mRNA expression in vitro and enhances serum levels in vivo in mice [448]. Interestingly, in patients undergoing surgery, postoperative plasma Met-enkephalin increases precede increases in IL-6, supporting the notion that Met-enkephalin induces production of IL-6 [448]. The inhibition of spontaneous IL-6 secretion from stimulated spleen macrophages is likely opiate-mediated because β-endorphin inhibited spontaneous IL-6 secretion [376]. The relationship between opiate and cytokine actions also is demonstrated by the finding that simultaneous treatment with IL-1α and IL-1β increases μ-opiate receptor mRNA in endothelial cells, further supporting the notion that infections modulate endogenous opiate systems [408].

Injection of Met-enkephalin and its metabolites des-Met-[Met^5]enkephalin, and Tyr-Gly Gly increased NKCA and mitogen-induced proliferation of T- and B-lymphocytes that were blocked by naloxone, thus being opiate-mediated [209]. Prolonged administration also was effective, as the effects of Met-enkephalin and its metabolites on proliferation also were observed after 3 or 7 days of treatment [209]. However the effects of Met-enkephalin may depend on the dose used because 100 ng/kg injected ICV in rats stimulated NKCA, whereas 10^5 ng/kg suppressed NKCA [411]. In addition, the effects of Met-enkephalin also were time-dependent, as 100 ng/kg produced an initial suppression followed by long-lasting immunostimulation [411]. Because neuropeptide Y mimics both these concentration- and time-dependent profiles of Met-enkephalin, they may activate a common mechanism of action [411]. Met-enkephalin also influences intracellular signal transduction with T-cells, as the increase of Ca^{2+} was slow and the levels were lower in T-cells incubated with Met-enkephalin, as compared with controls [366].

The opiate receptor subtypes involved in the modulation of different aspects of immune function also have been further elucidated. U50488H alone did not have antiviral effects in HIV-1 infected brain, but it dose-dependently potentiated the antiviral effects of tumor necrosis factor (TNF)-α that was blocked by nor-BNI, suggesting the involvement of κ-opiate receptors [69]. IL-1β may mediate the potentiating effects of U50488H because antibodies to IL-1β also blocked the effects of U50488H [69]. Thus, κ-opiates may have potential benefits in the treatment of HIV-1-related brain diseases [69]. In thymocytes, U50488H inhibited the induction of ornithine decarboxylase induced by Con A, or PMA and A23187, but not by actinomycin D or H-7 [304]. However, these effects were not opiate-mediated because the effects of U50488H were not blocked by naloxone, nor-BNI, Mr 1452, or β-CNA, but were blocked by pertussis toxin, indicating the involvement of G-proteins [304]. In contrast, both DAMGO and Leu-enkephalin slightly increased ornithine decarboxylase, but morphine, naloxone, U-69593, β-endorphin, Met-enkephalin, dynorphin A, and Mr 1452 had no effect [304]. In cardiomyocytes, both Leu-enkephalin and U50488H enhanced ornithine decarboxylase activity in cardiomyocytes, effects that were opiate-mediated because they were blocked by naloxone and nor-BNI, respectively [304]. Interestingly, enzyme degradation of plasma Leu-enkephalin increases with age, and may be associated with age-related impairments of immune function [21].

The regulation of splenic NO production and lymphocyte proliferation is μ-mediated because ICV DAMGO dose-dependently increased the production of NO in splenocytes stimulated with toxic shock syndrome toxin that was blocked by ICV *N*-methylnaltrexone, and suppressed lymphocyte proliferation that was attenuated by the NOS-inhibitor L-NMMA [342]. In contrast, the κ-agonist U69,593, and the δ-agonist DPDPE had no effect [342]. In macrophages activated by interferon-γ plus LPS, Met-enkephalin, DAMGO, DPDPE, and U50488H enhanced NO production, all of which were blocked by naloxone [208]. Because none of the agonists affected NO production when given 8 h after stimulation of macrophages, it is likely that the effects of these opiates on NOS occurs at the transcriptional level [208]. DAMGO, U50488H, and DPDPE all enhanced mitogen (conA and LPS)-induced proliferation of murine T-lymphocytes, that was reversed by their respective antagonists, although 4 injections of U50488H, and DPDPE were required as compared with only one for DAMGO [210]. In contrast, the effects of these agonists on B-lymphocyte proliferation was weak [210]. The effects of opiates on the production of NO may depend on the method of cell activation because β-endorphin suppressed superoxide and nitrate production in phorbol myristate acetate-activated macrophages and enhanced production in cytokine-stimulated macrophages [40].

Enkelytin is an antibacterial peptide that is found in invertebrate proenkephalin that may function to attack bacteria and allow time for endogenous opiates to exert their immunostimulatory effects [371]. Furthermore, because enkelytin and other antibacterial peptides are colocalized with catecholamines, they may protect against infection during times of stress [260]. Indeed, natural immunity and stress responses may very well have a common evolutionary origin, including endogenous opiate which are released by the HPA axis in response to stress, and by immune cells in response to infection [289].

16. Other behaviors

There was interest in the possible opiate mediation of smoking behavior, in particular the opiate mediation of

nicotine reward and dependence [2,166,308]. Naltrexone affected smoking, as subjects receiving it daily had lower levels of plasma nicotine, reported smoking fewer cigarettes, and their self-reported satisfaction of smoking was lower, as compared with placebo controls [423]. In contrast, mood states and withdrawal symptoms did not differ between naloxone and placebo groups, nor did expired carbon monoxide [423]. Thus, endogenous opiates may mediate the rewarding aspects of nicotine [166,423], but not physical dependence [423]. However, a common mechanism of action for opiate and nicotine dependence is likely, as NOS inhibitors block both opiate [58,305] and nicotine withdrawal [2,235]. In any case, the interactions between smoking and the opiate systems is obviously a complex one, and must also consider the influence of stress and genetic factors [303,308].

Social behavior also is partly mediated by the endogenous opiate system, and may contribute to social attachment, especially the attachment of infants to their caregivers [278]. Kin interactions may activate opiate systems, as paired sibling mice showed decreases in pain responses and increases in morphine analgesia, as compared with pairs of unrelated mice [86]. Birdsong is another type of social behavior that involves endogenous opiates. In budgies, Met-enkephalin immunoreactivity was present in nuclei in the forebrain that control vocal processes [95]. However, although there was similarity between Met-enkephalin immunoreactivity between budgies and other birds, there were notable differences as well [95,319] that may be related to the flexibility of the vocal systems in budgies that allows them to acquire socially significant stimuli [95].

Itch is another response that is opiate-mediated, and opiate antagonists have been used successfully in the treatment of pruritus in patients with cholestatic liver disease [35,391]. Itch was also associated with IT administration of morphine [28,416], and fentanyl [20]. However, although both naloxone and nalbuphine reduced pruritus associated with IT morphine, nalbuphine may have greater benefits because it did not attenuate the analgesia [416]. Endomophin-1 and -2 are also involved in itching as IC administration of these peptides produced facial scratching in mice, an affect that was opiate-mediated because it was inhibited by naloxone [436]. However, endogenous opiates may also suppress itching, as the antipruritic properties of millimeter waves were antagonized by naloxone [327].

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