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REVIEW

Endogenous Opiates: 1993

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OLSON, G. A., R. D. OLSON AND A. J. KASTIN. *Endogenous opiates: 1993.* PEPTIDES **15**(8) 1513–1556, 1994.—This paper is the sixteenth installment of our annual review of research concerning the opiate system. It is restricted to papers published during 1993 that concern the behavioral effects of the endogenous opiate peptides, and does not include papers dealing only with their analgesic properties. The specific topics this year include stress; tolerance and dependence; eating; drinking; gastrointestinal, renal, and hepatic function; mental illness and mood; learning, memory, and reward; cardiovascular responses; respiration and thermoregulation; seizures and other neurological disorders; electrical-related activity; general activity and locomotion; development; immunological responses; and other behaviors.

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

ALMOST 20 years since the discovery of the endogenous opiate peptides, much remains to be learned about their effects on behavior and the mechanisms involved in those actions. Interest in them continues to be great, although the term opioid is no longer used to denote peptides with opiate activity. In 1993, as in previous years, much research about opiate peptides concerned their ability to modulate behavior pharmacologically, although there has been increasing emphasis on their physiological role, especially through their manipulation by the use of opiate antagonists, both endogenous and exogenous. It has become obvious that the opiate system does not work in isolation, but instead is highly interrelated with other systems, including neurotransmitters and hormones, so that the functions of the opiate system are complex and difficult to discover. This paper reviews work published in 1993 that investigated the behavioral and nonanalgesic, except stress-induced analgesic, activity of the endogenous opiate system. It is the sixteenth installment in our series of reviews summarizing the annual developments in the field.

There was still much concern over stress-induced behaviors, not only analgesia, but also changes in activity, self-administration of opiates, and vocalizations. There continued to be focus on the variables that affect the opiate or nonopiate nature of the stress-related behavior, as well as attempts to specify which receptor subtypes are responsible for the different reactions. Interest continued to grow in the mechanisms and functions affecting opiate tolerance and dependence, with special attempts to link them with other agents and systems, including dopamine, serotonin, norepinephrine, and nitric oxide. Limited success was achieved in attempts to use antagonists in treatment of addiction.

Research continued on the opiate mediation of feeding, attempting to delineate variables that affect agonist stimulation and antagonist inhibition of it. Success in linking the opiate system to eating disorders still remained somewhat elusive. There was, however, a growing line of evidence to indicate that the opiate system might be involved in the consumption of alcohol, although its usefulness in treatment of alcoholism has yet to be demonstrated. The role of the opiate system in the regulation of intake of liquids, in general, is less clear, and its effect with ethanol may reflect alteration of reward value rather than of fluid homeostasis. Interest in opiate modulation of gastrointestinal function decreased, with sparse support for previous findings of opiate inhibition of motility. There was, however, an increase in research concerning the role of the opiate system in renal function. Receptor specificity and other variables were crucial in this area, so that no new generalizations were able to be drawn.

Interest in opiate mediation of mental illnesses continued its recent trend of decline, although there was evidence that depression is associated with a disturbance in the hypothalamus–pituitary–adrenal axis that may involve the opiate peptides. Some symptoms of autism also seem to be modulated by them. The area of opiate mediation of learning and memory drew increased interest this past year, as it had in recent years. The role of the opiates as conditioned stimuli in classical conditioning, especially in conditioned place preference, received much attention, as did their ability to act as discriminative stimuli in operant tasks. The amnestic properties of the agonists and the facilitation of memory by the antagonists also were studied, as was the mechanism that might be involved in opiate reward. Research on the regulation of cardiovascular activity by the opiates decreased

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somewhat in 1993. As in previous years, there were no generalizations that could be drawn about their effects on heart rate or blood pressure, due to conflicting findings. Interest in the involvement of the opiate system in cardiovascular shock also was less that in previous years, and results were still confusing.

Attention to the opiate mediation of respiration was not great in 1993. The μ and κ agonists tended to depress ventilatory responses and the antagonists stimulated them. There was a possible relationship between respiratory disorders and endogenous opiates found. Similarly, the μ and κ agonists produced hypothermia is most cases, and the antagonists did the opposite. Interactions between the opiate system and other variables received some focus. There was less interest in opiate modulation of seizures, with research indicating possible proconvulsant action by the μ agonists and anticonvulsant effects of the κ agonists, although there were exceptions. The role of the opiates in brain injury became more confusing, with conflicting results. There appear to be changes in the opiate system with Alzheimer's disease, but it is still too early to explain much about their relationship to the symptoms.

Interest in electrical-related activity remained high, although there were no overriding generalizations that could be drawn from the studies because the effects of the opiates depended so crucially on the areas of the nervous system being monitored. Many effects were also receptor specific, whereas others seemed to be modified by almost any agonist. Similarly, although there continued to be large amounts of work done on the opiate mediation of general activity and locomotion, no definitive conclusions were reached, perhaps because of the many ways in which these behaviors are measured and the multiple variables that affect them. There was more promising work on the possible role of the opiates in exercise, however. Little attention was paid to the opiate modulation of sexual behavior, but more was directed to the involvement of the endogenous opiate system in development, prenatally through senescence. There are clear changes that occur both at the behavioral and receptor levels, although the relationship between the two is not always as easily determined.

Although there remained strong interest in the interaction between the opiate system and immune function, little was able to be determined about it. Conflicting results occurred at nearly every aspect studied, indicating an extremely complex relationship that probably involves other systems as well. Much remains to be learned about it. Scant attention was paid to the role of the opiate system in social behavior, coughing, and hibernation, although there still continued to be some studies of it. Finally, there was interest in the new opiate modulating Tyr-W-MIF-1 peptide.

STRESS

It has long been known that many, but not all, kinds of stressors can activate the endogenous opiate system and, thus, produce opiate-mediated behaviors, including analgesia. Often the opiate or nonopiate nature of the stressors depends on small differences in them (i.e., intermittent vs. continuous foot shock or cold water vs. warm water swims), as well as the behavior being measured (i.e., analgesia or activity). Typically, the opiate nature is determined by the ability of antagonists to block or reverse the effects of the stressor. In 1993 the variables that contribute to this determination continued to be studied, with particular emphasis on interactions between the opiate system and other physiological systems.

Over the years, one stressor receiving much attention is foot shock, which is one that produces both opiate and nonopiate effects. Inescapable intermittent shock resulted in analgesia that was reversed by naloxone (55,339) if the antagonist was administered subcutaneously (SC) or intrathecally (IT), but not intraventricularly (ICV), suggesting that the opiate effect was probably at the spinal cord level (339). Because naloxone influenced morphine analgesia somewhat differently than it did shock-induced analgesia, requiring lower doses SC and IT and being effective ICV in reversing morphine analgesia, the action was probably not primarily mediated by the μ receptors (339). The selective δ receptor antagonist naltrindole had no effect on the analgesia, but the selective κ antagonist nor-binaltorphimine either intraperitoneally (IP) or IT blocked it, strongly suggesting that spinal κ receptors are responsible for this analgesia (339). Prolonged shock (240 shocks for a total of 20 min) resulted in no analgesia, but the mechanism involved was not clear. The prolonged shock potentiated morphine analgesia, indicating that there was no desensitization of μ receptors, and although glucocorticoids increased during the shocks, corticosteroid inhibitors did not cause the otherwise ineffective shocks to produce analgesia, indicating that this was not the mechanism for the lack of analgesia (340). Corticotropin-releasing hormone (CRH), however, may interact with the opiate system in shock-induced analgesia, since an antagonist of CRH blocked the analgesia from intermittent shock but had no effect on the analgesia of continuous shock (55).

Shock also affected other behaviors, including a reduction of daily running in a wheel in rats by both escapable and inescapable shock. This finding is opposite that for shock-induced analgesia, which occurs only after inescapable shock, perhaps because the daily running is not a part of the fear response, but analgesia is. Regardless, naltrexone did not alter the suppression of running by shock, indicating that it is probably an opiate effect (550). Another response to shock is an increase in self-administration of opiates in rats. Lever pressing for access to a fentanyl solution sped up after shock, and when water or quinine (which has a similar taste to fentanyl) was substituted for the agonist, extinction occurred (463), indicating that opiate actions were involved in the change, with stress-released endogenous opiates potentiating the exogenous one.

Repeated daily shocks produced an increase in the rate of biosynthesis of proopiomelanocortin (POMC) and POMC mRNA and in the rate of conversion of POMC to its end products. There was a shift in the β-lipotropin/β-endorphin ratio, with a decrease in the proportion of the endorphin released from the anterior pituitary, suggesting that peptidergic endocrine cells may deliver somewhat different messages to their targets, depending upon what regulatory adaptations need to occur with repeated demands (558). Intermittent, but not chronic, shock increased the concentration of β-endorphin immunoreactivity in splenocytes, lymph node cells, and peripheral blood mononuclear cells, and the rise was blocked by a CRH antagonist, suggesting an interaction between the opiate peptide and CRH in mediating the effects of stress on the immune system. Infusion of β-endorphin ICV inhibited the release of cortisol into plasma in shocked sheep but increased it in nonstressed ones. Furthermore, β-endorphin induced release of prolactin in stressed animals, and β-endorphin antiserum during stress increased the cortisol and aggravated some of the stress symptoms, indicating a role for the endogenous opiate in the mediation of stress (117).

As with foot shock, forced swimming has been shown to induce both opiate and nonopiate analgesia. Cold-water swims (193,269,387,425) and swims in water of intermediate (15°C) or warm (20°C) temperature (354,365,366) produced analgesia under a variety of conditions. Although continuous cold-water swims (CCWS) typically produce nonopiate analgesia, activation of the opiate system by pretreatment with either morphine or

naltrexone altered the analgesia, demonstrating that there can be an interaction between opiate and nonopiate systems in nociception (193). Similarly, although cold-water swims of 30-s duration did not result in analgesia in mice, they did shift the dose–response curve for morphine analgesia to the left (532), thus supporting the lack of independence of the two kinds of analgesia. Intermittent cold-water swims (ICWS) usually produce opiate-mediated analgesia, and this was confirmed by the finding that pretreatment with naltrexone reduced the analgesia (269). Chronic presentation of CCWSs or ICWS each developed tolerance, and they were tolerant to each other (387), providing additional evidence of interactions between opiate and nonopiate analgesia mechanisms. Analgesia from swims in 15°C water was nonopiate, but in 20°C water was at least partially opiate (354,365,366), so that the temperature of the water was critical for the underlying mechanism. Short swims resulted in nonopiate analgesia, but longer ones produced opiate antinociception (166), demonstrating that length of swim was another crucial variable.

In an attempt to determine what receptor subtypes modulate the CWS analgesia, specific antagonists were coadministered with morphine after the CWS. The δ antagonist ICI 174,864 and the δ_2 antagonist 5′-isothiocynate had no effect on morphine analgesia but inhibited the leftward shift of the morphine dose–response curve after the swims. The $\delta 1$ antagonist [D-Ala^2,Leu,Cys^6]enkephalin had no effect on either measure, suggesting involvement of the δ_2 receptors in the swim analgesia. The μ antagonist β-funaltrexamine (β-FNA) inhibited morphine analgesia, and the swims did not affect it, so that μ receptors were probably not involved in the swim analgesia. Neither Leu- nor Met-enkephalin altered morphine analgesia, and antibodies to Met-enkephalin had no effect on the swim analgesia, but antibodies to Leu-enkephalin inhibited it. These findings indicate that the μ receptors may modulate the primary action mediated by the δ_2 receptors (532). In rats, however, repeated CWSs for 5 days produced analgesia that was increased by naltrexone and reduced by morphine (193), with the difference possibly being due to species differences or repeated measures, resulting in collateral inhibition of the actions.

Sex differences were found in the ability of naloxone to reverse analgesia of 20°C water swims. Although it was naloxone reversible in males, it was not affected by the antagonist in females, whether intact or gonadectomized, and the addition of estrogen did not alter the finding. The mechanism responsible for the sex difference was not clear, but it did highlight the need to consider gender a factor in both research and clinical practice with regard to pain (354). Similarly, breeding males experienced greater swim analgesia than breeding females, but there were no sex differences in nonbreeding mice, so that reproductive status must also be taken into account (166). Genetic factors are also important, because strains of mice have been selectively bred for high swim analgesia and low swim analgesia (353). There is also an interaction between the opiate system and thyrotropin-releasing hormone (TRH) for CCWS analgesia, because injection of TRH into the posterior periaqueductal gray facilitated the analgesia but into the anterior area reduced it (425).

Age, too, is a critical variable, although seemingly conflicting studies of it may not be incompatible as first appears. One study reported that swim stress analgesia with warm water was absent up to day 10 in rats, after which time it occurred at a low level and was naloxone reversible. The adult profile was fully developed by day 25 (365). Another report found weaning status affected the swim analgesia, with naloxone partially reversing the analgesia in 25-day-old rats whether they were weaned or not, but naltrindole reversing it only in weaned animals. At 30 days, naltrindole blocked the analgesia completely, leading to the conclusion that there is a transition from μ to δ receptor control of the response that is affected by weaning (366). The apparently contradictory finding that swim analgesia in preweanling (20-day-old) rats was weak and not naloxone reversible but showed the normal adult naloxone-reversible level in weaned (25-day-old) rats (405) can be reconciled with the other studies in that the former used higher doses of naloxone, which would make it more likely that it would antagonize the opiate effect, and used a different measure of analgesia. They (365,366) used the tail water immersion test, which is essentially a spinal reflex, but the conflicting study (405) used the tail electrical stimulation test, measuring vocalization afterdischarge threshold, tail withdrawal, and vocalization, which additionally assesses emotional/affective reactions to pain. Thus, there may be differential nociceptive responses at different levels of neural integration.

Another change that occurred as a result of swim stress, as well as stress associated with handling and constant sound in a novel environment, was stimulation of the release of corticosterone. This increase was attenuated by administration of α-interferon, suggesting a possible mechanism for the effect of stress on physical health. The action of α-interferon was blocked by naloxone (mainly a μ antagonist) and naloxonazine (a μ_1 antagonist) but not by naltrindole (a δ antagonist) or nor-binaltorphimine (a κ antagonist) (448), indicating an interaction between the immune and opiate systems in response to stress.

A different line of support for the idea that the endogenous opiate system plays a role in swim stress came from the findings that swims increased β-endorphin immunoreactivity (9,56,557). Both a single acute swim or chronic swims raised plasma β-endorphin, but although the increase from the acute swim was blocked by apomorphine, that produced by chronic swims was not, questioning the role of dopamine in this response. Furthermore, if the dopamine antagonist haloperidol was presented with the chronic swims, there was an increase in POMC mRNA, supporting the nondopaminergic aspect of the reaction (557). Chronic ICWSs raised β-endorphin in both plasma and anterior pituitary until the 10th day, at which time there was a decrease in pituitary concentrations, perhaps because of habituation or tolerance. Similarly, the increase in neurointermediate pituitary β-endorphin in response to a combination of ICWSs and ether disappeared over 10 days of exposure. Administration of acetyl-*l*-carnitine, a neurotropic drug acting on cholinergic, serotonergic, and GABAergic pathways, blocked the effects of the swims on β-endorphin (56), indicating a complex interaction. Further evidence for that idea comes from the report that rats subjected to swims and corticosterone exhibited a transitory increase in β-endorphin, but those with swims and saline had a sustained rise in the peptide (9). There appears to be little doubt that the stress produces a dysfunction of the hypothalamo–pituitary–adrenal (HPA) axis.

Restraint is another frequently used stressor to study opiate effects. It potentiated morphine analgesia (306,552), and naltrexone blocked the action of morphine (552), indicating its opiate nature. Chronic naloxone, however, appeared to produce an upregulation of the opiate receptors, because the antagonist potentiated morphine analgesia when given with restraint, resulting in an even greater potentiation than with either alone. The upregulation was only transitory, because a few days after its removal the naloxone no longer potentiated morphine analgesia (306).

Restraint also induced a biphasic reaction for heart rate, with a transitory increase followed by a reduction. The additional stress of a noxious tail clip potentiated the effect, which was nonopiate, because naloxone did not alter it (218). The reverse

was true for body temperature, with restraint producing hypothermia that was accentuated by naloxone but unaffected by tail clip (218). Because naloxone did not block the effect of restraint, there is some doubt that these responses are mediated by opiate receptors.

Immobilization stress each day before a period of opiate self-administration increased both amount of drug self-administered and the harshness of subsequent naloxone-precipitated withdrawal, suggesting that the stress helped in the development of tolerance to opiates. The finding that exposure to the restraint after the self-administration procedure did not affect either measure indicates that there was probably a learned association between the stress and drug availability that mediated the tolerance (461).

Support for the idea that at least some of the effects of restraint stress are opiate modulated comes from the report that immobilization resulted in a decrease in β-endorphin-like immunoreactivity in the periaqueductal gray but not in the pituitary a day later, suggesting it was a central opiate effect (144). Restraint of a pregnant rat for 5 days during early gestation raised concentrations of β-endorphin in the hypothalamus of her offspring when tested at postnatal day 10, but longer restraint (15 days) had no effect, indicating that stress during the embryonic period can affect development of the endogenous opiate system, with the amount of change depending on the length of exposure to stress (446).

Restraint in young pigs increased plasma adrenocorticotropic hormone (ACTH), cortisol, prolactin, and growth hormone, and initially naloxone potentiated all but growth hormone. After chronic exposure to immobilization for a short period each day, naloxone inhibited the production of growth hormone, indicating an interactive role for the endogenous opiate system and pituitary–adrenocortical responses (441).

The endogenous opiate system may be involved in stresses associated with fighting or defense. Although defeat has typically been shown to produce nonopiate analgesia, rats exposed to defeat repeatedly exhibited analgesia that was enhanced by naltrexone and that attenuated morphine analgesia (193), indicating a possibly interaction between the opiate and nonopiate mechanisms of analgesia. The effects of aversive encounters was long lasting, because a week after brief exposure to attacks, rats still had reduced sensitivity to morphine analgesia (203). Brief exposure of meadow voles (*Microthus pennsylvanicus*) to a natural predator, a garter snake, produced nonopiate analgesia that was inhibited by a serotonin agonist, but longer exposure resulted in naloxone-reversible analgesia. The analgesia decreased with age, so the threat presented by the snake decreased (444).

Rats placed in the cage of another resident readily emitted ultrasonic vocalizations indicative of stress that were suppressed by morphine. Because naltrexone reversed the action of morphine, the affective response appeared to be opiate mediated (536). Even threat of the encounters was sufficient to produce the vocalizations (536), suggesting that emotional factors, as well as physical ones, were involved in the response. Similarly, threat of capture for cynomolgus monkeys (*Macaca fascicularis*) produced the reaction of increased heart rate. Because this change did not occur in monkeys pretreated with naloxone, it was assumed that the response was opiate mediated. Concentrations of β-endorphin immunoreactivity increased, supporting the idea that the peptide might be involved in the response (332).

When tested with a nonaggressive partner in a neutral cage, morphine-tolerant rats given naloxone to precipitate withdrawal demonstrated confrontational defensive responses like backward movements and upright postures. Naloxone methylbromide given directly into the periaqueductal gray produced the same responses and, additionally, ultrasonic vocalizations (108). These findings suggest involvement of the endogenous opiate system in specific defense strategies involving the periaqueductal gray in rats.

Not only do some kinds of social behavior create opiate-mediated stress behaviors, but lack of social behavior also does. Isolation of rat pups induced ultrasonic vocalizations that were attenuated by morphine, [D-Ala^2,*N*-MePhe^4,Gly^5-ol]enkephalin (DAMGO), or [D-Pen^{2,5}]enkephalin (DPDPE), but did not induce analgesia (184). Hypertension that occurred in rat pups subjected to isolation was probably mediated by the endogenous opiate system, because chronic treatment with morphine inhibited it, and withdrawal of the morphine resulted in a return to high arterial pressure (254). Even undisturbed in the home cage in the presence of their littermates, a situation that rarely produces ultrasonic vocalizations, injection of U50,488 [(±)-*trans*-3,4-dichloro-*N*-methyl-*N*-(2-(1-pyrrolidinyl)cyclohexyl) benzeneacetamide], a highly selective κ agonist, elicited ultrasonic vocalizations and other signs of stress. Naltrexone had no effect (73), however, calling into question the role of the endogenous opiate system in the reaction.

Handling early in life appears to be stressful, because when the rats were tested several weeks after handling, they had analgesia relative to nonhandled controls. When tested a second time several weeks after the first test, there was no difference between them, but there was an attenuated response to β-endorphin analgesia in the handled rats (103). This might indicate that the early handling stress produced an upregulation of the opiate system that remained functional, although weakened, for a considerable time. There were sex differences in susceptibility to this stressor, because males were unaffected by neonatal handling alone and females were analgesic. The opiate nature of the analgesia was indicated by its potentiation by morphine in most cases. When combined with prenatal stress, however, handling produced hyperalgesia in both sexes, suggesting that it may have offset the effects of prenatal stress (478).

Novelty can be a stressor that results in opiate-mediated analgesia because naloxone attenuated it. Pretreatment with the α_1-noradrenergic receptor antagonist prazosin or the nonselective α antagonist phentolamine had no effect on the action of naloxone, but yohimbine, an α_2 antagonist, potentiated it, and clonidine, an α_2 agonist, reversed the action of yohimbine, indicating that the response involves the α_2 receptors (431,432). The novelty-induced analgesia was not affected by tolerance to morphine analgesia, further suggesting it was a nonopiate effect. Chronic naloxone produced analgesia by attenuating the habituation of novelty-induced hypoalgesia, so that there might have been an opiate effect involving habituation that modified the nonopiate antinociceptive effect (431).

Another stressor that seems to have an opiate substrate interacting with other systems is restriction of food. It prolonged morphine-induced locomotion in intact but not in adrenalectomized rats. Endogenous corticosterone was necessary for the response because replacement with the exogenous hormone was ineffective, indicating that secretion of the hormone was one of the mechanisms by which the stressor worked (109). Chickens that had had food restriction had increased concentrations of dynorphin in the brain, but normal β-endorphin- or Leu-enkephalin-like immunoreactivity in the brain, possibly indicating a role for the κ receptors in the response (450).

Exposure to extreme temperatures has also been used as a stressful stimulus. Although confinement to a cold room with little clothing for a short time (30 min) did not affect plasma β-endorphin in men (535), submersion in cold to cool water for

a longer period (120 min) produced an increase in the peptide. There was no relationship in its rise and the time of immersion or to any other variables, so that it is difficult to interpret the finding. Perhaps it was the immersion itself, not the temperature, that was stressful (183). The cold pressor test caused a release of epinephrine and norepinephrine that was blocked by the highly selective δ agonist deltorphin, suggesting δ opiate receptor mediation of the effect (519).

A number of other stressors have been shown to elicit opiate system responses. Administration of ether increased pituitary β-endorphin immunoreactivity (56), and chronic seizures stimulated the biosynthesis of POMC and POMC mRNA in the pituitary (558). Injection of hypertonic saline raised proenkephalin A mRNA in the paraventricular nucleus of the rat (205). Chronic exposure to weak magnetic fields or to naloxone produced hypoalgesia in snails (*Cepaea nemoralis*), consistent with either a facilitation of aversive conditioning and/or antagonism of the excitatory, hyperalgesic effects of low amounts of endogenous opiates (276). In humans, the stress of a difficult task or perceived failure increased rather than decreased reports of pain to cold, although it was not clear whether the effect was due to a change in reporting or in sensitivity to the aversive stimuli (308). The involvement of the endogenous opiate system was also not delineated.

TOLERANCE AND DEPENDENCE

Since the discovery of the endogenous opiate peptides, interest in how they relate to opiate tolerance and dependence has been extremely high, perhaps more than in any other behavior associated with the opiates, and research has investigated the mechanisms and variables that affect them. It has become clear that there is much receptor specificity in tolerance and dependence, although some cross-tolerance also exists. Particular interest as focused on withdrawal from opiates, and the increasingly recognized complexity of this area.

As found in past years, chronic treatment with exogenous opiate agonists or antagonists altered the endogenous opiate system, both in concentrations of the peptides present in the brain and in receptor activity. Most of the findings are contingent upon the specific peptide being measured and the area in which it is assessed. Tolerance to morphine increased β-endorphin immunoreactivity in the thoracic and cervical regions of the spinal cord but not in the medulla, indicating a dissociation in the regulation of the peptide between the spinal cord and other parts of the central nervous system (CNS) (67). In the spinal cord, chronic morphine produced increased binding sites for the δ agonist [D-Ala^2]deltorphin-I but not for the μ ligand FK33,824, so that the δ receptors may be of special relevance with regard to the development of tolerance in the spinal cord (189). Although chronic morphine produced no change in dynorphin(1–17) immunoreactivity in the brain, removal of the morphine rats reduced dynorphin(1–17) in the nucleus accumbens, suggesting a possible suppressive role of the dynorphinergic neurons in the limbic system during dependence (560), although its nature was unclear.

Dynorphin(1–13) increased in the hypothalamus, hippocampus, and pons/medulla with dependence on U50,488, and abstinence from it produced an increase in dynorphin in the midbrain. Concentrations of the peptide also increased in the heart in both tolerant and abstinent animals, but only withdrawal resulted in changes in dynorphin in body tissues. Because these findings were different from those found with morphine dependence, it was suggested that chronic stimulation of μ receptors produces a different effect than that for the κ receptors (49). Nevertheless, tolerance to U50,488 increased μ binding in the brain and decreased it in the spinal cord, suggesting that chronic stimulation with the κ agonist can alter μ receptors (510). There is some interaction among the receptor subtypes, apparently, although it is probably limited, as will be seen in the discussion of cross-tolerance.

Support for the role of κ receptors in dependence came from the finding that butorphanol, which has been shown to act on μ, δ, and κ receptors, decreased the density and affinity of receptors for [^{3}H]U69,593 in the brain (252). It seems, though, that the changes in opiate binding or concentrations with repeated administration of opiate agonists are correlated with the potency of the given opiate in producing its acute effect (78), so that comparisons across peptides are difficult to make.

Chronic administration of opiate antagonists also altered the endogenous opiate system. Chronic naltrexone increased binding for [^{3}H]DAMGO in brain and spinal cord (52,113), supporting the idea that upregulation of the μ receptors can occur in this situation. Similarly, continuous infusion with naloxone increased the number of μ or δ binding sites in the spinal cord, as measured by [^{3}H]FK33,824 or [^{3}H][D-Ala^2]deltorphin, respectively (189). However, chronic naloxone did not affect concentrations of β-endorphin in the spinal cord or medulla (67), suggesting that the action is receptor specific. Chronic nor-binaltorphimine blocked the changes in receptor binding that occurred with chronic butorphine, which were thought to be mediated by κ receptors (252), supporting the notion of receptor specificity.

It has been demonstrated many times that chronic administration of morphine produces behavioral tolerance in a wide variety of measures, with analgesia being the most common. Other agonists also were shown in 1993 to produce tolerance or dependence when given repeatedly or continuously, including DAMGO (132,195), the μ_2 agonist TRIMU-S, which is an enkephalin analogue (132), Tyr-D-Arg^2-Phe-(NME)Gly^4 (TAPS) (195), U50,488 (49,508,534), U69,593 (231), butorphanol (250–252), and bremazocine (231). TAPS produced more analgesia than DAMGO or morphine, and it developed less dependence, suggesting that TAPS might have clinical significance (195). In the first demonstration of tolerance in a nonmammalian vertebrate species, tolerance to chronic morphine was exhibited in the Northern grass frog (*Rana pipiens*) after only 3 days (485). It had previously been shown in invertebrates, however.

In general, there tends to be cross-tolerance among agonists of the same receptor subtype, but little among agonists with affinity for different subtypes. The exceptions to this rule noted in 1993 were likely the result of the technique used for measuring tolerance or, perhaps, species, because mice tended to show more cross-tolerance than rats. Cross-tolerance was found between the μ ligands morphine and DAMGO (221), but not between the κ agonists U69,593 and bremazocine, suggesting that they might have affinity for different subtypes of κ receptors (231). Despite the report of no cross-tolerance between morphine and the delta agonist Tyr-D-Ser(otbu)-Gly-Phe-Leu-Thr (DSTBULET), as measured by amount of change in the responses of neurons from the spinal cord in rats to acute challenge (262), there was cross-tolerance between morphine and the δ ligand DPDPE, as measured by its attenuation of analgesia in morphine-dependent mice (516). Morphine was not cross-tolerant with β-endorphin in this test, however (516). There were also conflicting reports of cross-tolerance between morphine and U50,488, with none being found when measuring change in electrical discharge activity of oxytocin-secreting neurons in the rat supraoptic nucleus (407,442), but there was cross-tolerance reported with measures of analgesia in mice (510).

Cross-tolerance developed between morphine and serotonin, because analgesia produced by serotonin was attenuated in mice implanted with morphine pellets (516). Similarly, there was cross-tolerance between morphine and the α_2-adrenergic agonist dexmedetomidime, although the δ agonist DSTBULET was not cross-tolerant to it, as measured either behaviorally by analgesia or electrophysiologically by response characteristics of neurons from the spinal cord (262). Thus, the research of cross-tolerance, as with other kinds of studies, demonstrated interactions between the opiate system and other systems.

The role of serotonin in opiate-mediated behavior was also demonstrated by the finding that agents that increase serotonergic neurotransmission also attenuate the hyperactivity of the locus coeruleus neurons induced by withdrawal from morphine, perhaps due to a decrease in augmented excitatory amino acid input to those neurons by the agents (8). The calcium channel agonist BAY K 8644 and antagonists nimodipine and diltiazem reduced the symptoms of naloxone-precipitated withdrawal from morphine, but they did not affect metabolism of serotonin during withdrawal, so that those symptoms, at least, were independent of serotonin (89). Thus, the role of serotonin in withdrawal is confusing.

The interaction between dopamine and the opiate system has also received attention. Chronic morphine increased dopamine concentrations in the nucleus accumbens (258) and in the medulla (499), and in dependent rats, acute morphine produced a greater increase in dopamine in the nucleus accumbens (258) and a decrease in it in the hypothalamus (345). Dopamine depletion by α-methyl-*p*-tyrosine was retarded in the striatum, rest of forebrain, and midbrain in mice removed from repeated morphine treatment (134), further supporting a role for dopamine in opiate dependence. Withdrawal also caused a decrease in electrically evoked dopamine in the striatum, and this change was long lasting, indicating that it may play a part in the maintenance of dependence (454). It appears that the D_2 receptor is important in dependence, because both the nonselective dopamine agonist apomorphine and the selective D_2 agonist propylnorapomorphine reduced withdrawal signs, but the D_1 agonist SKF-38393 produced no effect on withdrawal (207). The D_1 receptor-stimulated release of cAMP in striatal slices was enhanced in rats treated chronically with morphine and was reduced in those with chronic naltrexone (113), so that the D_1 receptor might have an indirect effect on morphine dependence. After chronic U50,488, there was no supersensitization of the D_2 receptors, as there was with morphine (534), so that they might not have a role in κ receptor dependence.

The β-adrenergic system seems to play a role in opiate tolerance and withdrawal. Acute DAMGO or chronic morphine released [^{3}H]norepinephrine in cortical slices, although there was no additive effect when they were combined (113). Acute morphine produced a depletion of norepinephrine from the hypothalamus (345), forebrain, striatum, or midbrain (134), but that effect developed tolerance with chronic administration. Furthermore, both tolerance to morphine and withdrawal from it produced changes in the β-adrenergic system, especially in the pyramidal neurons (3). In addition, the symptoms of naloxone-precipitated withdrawal in morphine-dependent mice were attenuated by administration of the β-adrenergic antagonists propranolol or atenolol, suggesting they might be effective in the treatment of opiate addiction (208). Clearly, therefore, there is an interaction between the adrenergic and opiate systems.

The excitatory amino acid *N*-methyl-D-aspartate (NMDA) may be involved in opiate dependence, because its antagonist MK-801 blocks the development of tolerance to morphine (48,50,200,512). Tolerance was also attenuated by another NMDA antagonist, LY 274614 (512). Some, but not all, withdrawal symptoms precipitated by naloxone in morphine-dependent rats were inhibited by MK-801 (329,515), suggesting that the effect on withdrawal was not direct and that MK-801 blocked the development rather than the expression of dependence (515). The NMDA antagonist itself reduced distress vocalizations and social play in young rats, so that it is not clear whether its inhibition of tolerance is an artifact of its own behavioral effects or a real blockade of the effects of morphine (48). Pretreatment with MK-801 inhibited the development of tolerance to chronic U50,488 also (508), so that it was not limited to interacting with μ receptors.

Similarly, nitric oxide seems to play a role in the development of tolerance, because its inhibitor N^G-monomethyl-L-arginine or its analogues attenuated the effects of chronic opiate agonists (51,72,221,285,329,509). The inhibitors of nitric oxide synthase reduced the tolerance for DAMGO challenge in morphine-tolerant rats (221) and the loss of analgesia (51,509) and hypothermia (509) in U50,488-dependent mice. The inhibitors also reduced the withdrawal symptoms of weight loss and wet-dog shakes (285) and of jumping (72,329), suggesting that nitric oxide might play a role in the hyperactivity responses of withdrawal. Nitric oxide, thus, may be involved in tolerance to both μ and κ agonists.

The benzodiazepine receptors also can be important in response to chronic opiate stimulation, because chronic morphine increased benzodiazepine binding in the brain (430). Furthermore, the benzodiazepine agonists midazolam (501) or diazepam (482) partially blocked the development of tolerance or dependence with continuous morphine infusion and attenuated naloxone-precipitated withdrawal in morphine-dependent rats. These effects may be mediated by changes in the concentration of Met-enkephalin in brain and spinal cord, with morphine reducing it and diazepam inhibiting that reduction (482). Muscarinic receptors, likewise, influence morphine dependence, because two muscarinic antagonists, pirenzepine and 4-DAMP (4-diphenylacetoxy-*N*-methylpiperidine methiodide) attenuated withdrawal symptoms, perhaps through an inhibition of spinal and supraspinal cholinergic neurons (227). Tolerance to morphine reduced spontaneous electrical activity of oxytocin-secreting neurons in the supraoptic nucleus, thereby reducing plasma oxytocin, but chronic U50,488 increased to, so that μ but not κ receptors seemed to be involved (407). There seems to be, therefore, a large number of physiological agents contributing to opiate tolerance and dependence.

Because acute morphine increases plasma corticosterone and chronic morphine eliminates that response due to tolerance (345), corticosterone may play a role in opiate dependence. A rise in this steroid, however, also is a symptom of withdrawal (289), so that the hormone may be indirectly involved through the mechanism of stress. Opiate tolerance and dependence could be due to a functional decoupling of opiate receptors from G-proteins and a subsequent decrease in the endogenous opiate peptides, and the NMDA receptors could mediate the response by an increase in intracellular calcium (153). Because signs of naloxone-precipitated withdrawal in morphine-dependent rats were attenuated by pertussis toxin, it has been suggested that G-proteins sensitive to the toxin may play a role in dependence (162). Questioning the involvement of G-proteins, however, came from the finding that their concentrations did not change with chronic morphine in most rats, although there were strain differences so that only Sprague–Dawley rats exhibited any alteration, and it depended on the area of the brain and specific G-protein measured (196).

Activity in the locus coeruleus was influenced by chronic opiate stimulation, with morphine increasing cAMP-dependent protein kinase and adenylate cyclase (196) and adenylate cyclase mRNA transcript (328) in that area. Morphine also reduced catechol oxidation current (CA · OC) in the locus coeruleus, and naloxone-precipitated withdrawal increased the CA · OC signal, and the response was attenuated by excitatory amino acid antagonists, suggesting that it was mediated in part by excitatory amino acid pathways (230). The hyperactivity of the locus coeruleus due to naloxone-precipitated withdrawal was also reduced by administration of agents that increased serotonergic neurotransmission, perhaps by decreasing the augmented excitatory amino acid input to the locus coeruleus (8). Lesions of the locus coeruleus attenuated symptoms of withdrawal (319), further supporting that idea. In addition, there was a release of glutamate in that area after withdrawal, perhaps contributing to its activation of locus coeruleus neurons (5).

Prolonged opiate treatment, including U50,488, ethylketocyclazocine, dynorphin, and DADLE ([D-Ala^2-D-Leu^5]enkephalin), increased concentrations of synapsin I immunoreactivity in spinal cord cultures, suggesting that synapsin I could contribute to the development of tolerance (368). The autonomic areas of the rat brain exhibited increased fos-like immunoreactivity during withdrawal in rats, especially the medullary nuclei, paraventricular nucleus, and amygdala, so that autonomic areas are activated during withdrawal and may contribute to the autonomic symptoms (490). Other areas, including the hypothalamus, striatum, and cerebellum, also showed dramatic changes in c-fos mRNA with withdrawal, but fosB, junB, and zif-268 mRNA had little or no change, indicating that there is an alteration in gene expression in withdrawal (98). Repeated administration of morphine increased CCK immunoreactivity and CCK mRNA in the hypothalamus, brain stem, and spinal cord, so chronic morphine stimulation stimulated endogenous CCK biosynthesis, indicating an interaction (116). Neither chronic morphine nor naloxone-precipitated withdrawal, however, produced a change in the expression of mRNA encoding galatin, neuropeptide Y, CRH, or somatostatin (228), so that they may not play a role in opiate dependence, at least in the areas of the brain studied.

Learning has been demonstrated to influence tolerance and dependence, because those states can become linked to events that occurred when they were being established. Classical conditioning is involved, with the environment being the conditioned stimulus, and the effect of the drug being the unconditioned stimulus, so that the environment comes to elicit the drug effect (487). Morphine-dependent rats given naloxone in the presence of a distinct tone and smell were later tested with those same stimuli. Their lever pressing was suppressed relative to those having undergone withdrawal not paired with the stimuli, so that behavior was disrupted in the absence of receptor occupancy (33). State-dependent behavior involving opiate withdrawal was also demonstrated. Rats were given morphine and put in a box that had previously been paired with shock or not. Then they were subjected to naloxone-precipitated withdrawal. The group that demonstrated the most withdrawal symptoms had received both morphine and the naloxone in the box associated with shock, indicating that learned contextual fear can exacerbate acute withdrawal (1).

Tolerance can be divided into two classes: dispositional or nonassociative and conditioned or associative. These can be differentiated by testing for analgesia in a place previously associated (or not associated) with morphine. Only dispositional tolerance was found with SC administration, but both forms were exhibited with IV administration. The explanation for the result, however, was not given (194).

Interestingly, it was reported that the experience of pain antagonized the development of morphine dependence. Tolerance to morphine administered daily developed in 3 days in animals tested daily for analgesia, but in those tested only on the 8th day, some analgesia still remained (485). Similarly, rats were given morphine daily, and half were tested for analgesia whereas the other half were not. When given naloxone-precipitated withdrawal, the symptoms were much greater in animals that had not been tested for pain each day, which is consistent with clinical studies showing that patients who take morphine for pain do not develop much dependence (526). When there is a need for increased pain medication in cancer patients, it is due to the progression of the disease, producing more pain, rather than to tolerance to the morphine, because there were no demands for increased doses in those in whom the disease was stable or in remission (90).

The most frequent test for dependence on opiates is the appearance of withdrawal symptoms, either after removal of the agonist or after administration of an opiate antagonist, with the latter method most typically being used. Not surprisingly, however, withdrawal signs do not differ between the two techniques. Some of the most common symptoms found are teeth chattering (41,89,228,249–251,319,322), wet-dog shakes (41,89,132, 228,249–251,285,289,319), diarrhea (41,89,228,250,349,351), jumping (162,319,329,348–352), ptosis (249,250,319,322,515), weight loss (250,285,289,329), change in activity level (64,261,319,457), rearing (162,319), tremors (249–251,322,515), yawns (249–251,322), ejaculation (249,251), changes in temperature (250,329), salivation (249), mouthing responses (289,319,515), urination (250,251), and defecation (329). Other signs noted also included changes in activity, such as grooming (89), writhes and gasps (322), eye twitch (319), and piloerection (319); changes in heart rate and blood pressure (100); social behaviors, such as defense responses in the presence of other rats (108); changes in operant behavior, such as escape (250), disruption of responding for reward (136,457), increased self-administration of heroin (457), and increase in ICSS threshold (457); and changes in hormones or neurotransmitters, such as increased plasma corticosterone (132) and increased release of norepinephrine, acetylcholine, and dopamine (454).

There appeared to be different mechanisms in morphine-dependent mice for the naloxone-precipitated withdrawal signs of jumping and diarrhea, because there was differential reactivity of the two depending on route of administration, thus indicating differential importance of spinal and supraspinal sites for each response (351,352). Age was another factor influencing the appearance of the withdrawal symptoms, because in week-old rats, there were head movements, rolls, stretches, walking, wall climbing, and a decrease in time spent with littermates (261), one of which is a common response of withdrawal in adult rats.

The induction of withdrawal was contingent on the agonist used to develop dependence and the antagonist used to precipitate withdrawal. In morphine-dependent animals, naltrexone produced withdrawal (329), and β-funaltrexamine suppressed naloxone-precipitated withdrawal symptoms, supporting the role of the μ receptors in morphine dependence (351). Administration of methylnaloxonium into the locus coeruleus of morphine-dependent rats induced behavior characteristic of withdrawal, indicating that structure might be the primary site of withdrawal (284). However, naloxone given ICV did not precipitate withdrawal in dependent mice, although SC and IT injections did produce it, suggesting that there may be a methodological confounding effect in studies using ICV naloxone to produce withdrawal (350). The IT route was most effective in producing rapid withdrawal, as measured by jumping (350,352).

In morphine-dependent rats, the endogenous antiopiate Tyr-MIF-1 protected by the enzyme inhibitor bestatin precipitated withdrawal (322), as did FMRFamide or two of its conformationally constrained peptidomimetics (321) or dansyl-Pro-Gly Arg-Phe amide, an analogue of the mammalian form of it, neuropeptide FF (298). Neuropeptide FF itself, however, did not alter the development of tolerance to chronic morphine, despite the fact that it acted like an antiopiate in other tests (435). Naltriben, a δ antagonist, or its analogue naltrindole 5′-isothiocyanate (5′NTII) produced withdrawal in morphine-dependent mice (349), and chronic pretreatment before morphine slowed the development of dependence, as measured by severity of naloxone-precipitated withdrawal (348,349). Chronic naltriben after, rather than before, implantation of the morphine pellet had no effect (349), and the antagonist had no effect in morphine-naive animals (348), indicating a role for the δ receptors in dependence on morphine.

In rats made dependent on butorphanol, the κ antagonist nor-binaltorphimine (249), the δ antagonist naltrindole (251), and the μ antagonist naloxone (249,250,252) precipitated withdrawal, but the μ antagonist β-funaltrexamine did not (251). Pretreatment and concurrent treatment with butorphanol of naltrindole (250) or nor-binaltorphimine (252) markedly blocked most of the signs of naloxone-precipitated withdrawal, suggesting that either antagonist greatly attenuated the development of tolerance. These studies together indicate that butorphanol dependence involves all three main receptor subtypes.

Even in the absence of cross-tolerance, one opiate agonist can affect withdrawal symptoms differently from another agonist. Dynorphin(1–17) and the nonopiate dynorphin analogue [des-Tyr^1]dynorphin(2–17) blocked tolerance and withdrawal in animals after chronic morphine, but dynorphin B and α-neoendorphin had no effect on it (497). Although U50,488 alone did not alter morphine withdrawal, pretreatment with nor-binaltorphimine before U50,488 inhibited most withdrawal symptoms. Naloxone before U50,488 potentiated the hyperactivity of withdrawal. In the guinea pig ileum, nor-binaltorphimine produced withdrawal contractions, so that κ receptors can develop acute dependence on U50,488, which is nonmorphine-like in the CNS but morphine-like in the enteric nervous system (64). Morphine tolerance did not affect the analgesia produced by the δ agonist BUBU [Tyr-D-Ser(*O*-t-butyl)-Gly-Phe-Leu-Thr(*O*-t-butyl], but the selective δ antagonist naltrindole blocked it, demonstrating receptor specificity (111).

Chronic stimulation of opiate receptors also produced effects other than those typically used to measure tolerance and dependence. Chronic morphine slightly increased the threshold for intracranial self-stimulation (ICSS), and naloxone-precipitated withdrawal greatly increased it (41), thus reducing the pleasure that the rats received from it. Naloxone-precipitated withdrawal in morphine-dependent rats suppressed responding for food and inhibited conditioned suppression established by pairing a novel stimulus with the injection of naloxone (136), thus indicating a disruption of operant behavior due to withdrawal. In the isolated guinea pig ileum, dependency, as measured by the magnitude of withdrawal, developed in as little as 7.5 min (99), indicating that prolonged exposure is not necessary.

Just as chronic opiate agonists produce tolerance and dependence, chronic antagonists produce effects. Implantation of naltrexone pellets in rats increased binding sites for [^{3}Hot in the affinity (52), so that the chronic naltrexone produced an upregulation of the μ receptors. Continuous infusion of naloxone increased binding sites for [^{3}H][D-Ala^2]deltorphin-I and for [^{3}H]FK33,824 in the spinal cord (189), indicating that both δ and μ receptors underwent upregulation with the chronic antagonist. Two days of treatment with naloxone, but not 50 days of it, increased benzodiazepine receptor binding in the cortex (430), so that there appeared to be an interaction between the GABAergic and opiate systems in the early stages of dependence. Chronic blockade of the μ receptors with naloxone produced a supersensitivity to μ, but not to κ agonists, because the response to morphine, but not to U50,488, was attenuated by continuous infusion of naloxone (15). Behaviorally, daily injections of naloxone or Tyr-MIF-1 produced hypoalgesia in deer mice, but only if the animals were also tested for pain daily, indicating involvement of aversive conditioning in the effect (275).

There is, of course, much interest in the applicability of all these findings to the clinical treatment of addiction. Limited success has been achieved, although hope remains that breakthroughs will occur. Buprenorphine was compared with methadone for its usefulness in maintenance of opiate dependency. Buprenorphine reduced illicit opiate use (295,455), but it was not as effective as methadone, the retention rate for it being less than for methadone, and withdrawal symptoms associated with it were greater than for methadone (295), so that it is unlikely to become a drug for treatment. Similarly, naltrexone fell short of expectations, because it had abuse potential, and the patients who abused it left the program and three of four committed suicide (304). A new drug, levomethadyl acetate (LAAM) was longer lasting than methadone, which was an advantage because it needed to be taken only every other day, but there was risk of accidental overdose because it had a slow onset of action (376), so it is unclear if it will be useful in treatment. Addicts maintained on methadone stayed in the treatment program better than those on vehicle, and a large dose reduced the rate of illicit opiate use, so its continued use in treatment was still recommended (491).

Some of the findings reported in 1993 suggest a possible benefit for treatment of abuse, but they have not yet been tested in a clinical setting. The NMDA inhibitor MK-801, for example, blocked the development of tolerance (48,50,200,512), but it also exhibited toxicity, which limits its value (50). Nitric oxide inhibitors also have potential for treatment, because they also blocked the development of dependence (51,221,285,509). Withdrawal symptoms were reduced by β-adrenergic antagonists (207,208), suggesting they might be effective in the treatment of addiction. Serotonin releasers or uptake blockers also attenuated signs of withdrawal (8), indicating that it could become a component of treatment. Gamma hydroxybutyric acid (GHB) suppressed most of the withdrawal symptoms in heroin addicts or methadone-maintained subjects, and after 8 days GHB was stopped, and the patients were maintained on naloxone with no adverse effects (169), so that GHB may be useful at least in the short term.

The report that withdrawal intensity is inversely related to the pretreatment spacing of morphine was pertinent to the transition from acute to chronic physical dependence. With widely spaced intervals, there was no greater danger of dependence than with a single exposure (287). Another beneficial methodological finding was a newly developed enzyme immunoassay, enzyme-linked immunoassay (ELISA), to detect the specific antibodies to morphine in chronic opiate users. It is superior to other tests, and offers the theoretical notion of the presence of circulating antibodies specific to morphine (170).

Finally, there was an interesting study of an obese woman who experienced withdrawal symptoms after treatment with naltrexone to suppress eating. She had no addiction to exogenous opiates, but it was speculated that she had hyperactivity of the

endogenous opiate system that was required because she had tolerance to the normal levels. Caution concerning use of opiate antagonists to treat obesity was suggested (237).

EATING

There was, in 1993, continued interest in the role that the endogenous opiate system might play in eating. As in the past, the general finding was that the opiate agonists stimulated feeding and the opiate antagonists inhibited it, although there were a few dissonant findings. There is still the persisting need to delineate the variables that affect these actions and the lingering hope that this knowledge will be useful in eating disorders, such as anorexia nervosa or obesity, although there has been limited reinforcement for this idea.

Administration of morphine consistently promoted eating (32,70,124,186,379) except when given repeatedly, and then total caloric intake was down (185). Withdrawal from chronic morphine reduced intake (185), as might be expected when available opiates decline. Another μ agonist, DAMGO, increased eating (31,363), as did the δ agonist DPEN ([D-Pen^{2,5}]enkephalin) (31). The κ agonist U50,488, however, did not fit the typical pattern, having no effect on eating in some situations (31,379), although stimulating in another (27). Dynorphin, too, failed to promote feeding, but rather inhibited it (363). The mixed agonist/antagonist butorphanol did increase eating (437), indicating an agonist action for it in this case.

It appears that opiate mediation of eating is involved in the maintenance, rather than the initiation of eating (76), because morphine increased the speed of eating but not the latency to eat in food-deprived rats (379). Because U50,488 affected neither response, it was concluded that the μ, not κ, receptors were involved in the regulation of feeding in deprivation tests (379). The κ receptors may be triggered by the taste of food, and may sustain feeding by facilitating incentive rewards (76) or by delaying the development of satiation (27).

Several areas of the brain have been identified as being important in opiate mediation of eating. DAMGO or DPEN injected into the ventral striatum, nucleus accumbens (31,32), or anteroventromedial striatum stimulated eating in nondeprived animals, although the amount of change varied with the specific area of those structures that was injected (32). Because these regions are also involved in impulse control, they may be the opiate mechanism for overeating (32). The lateral hypothalamus, previously shown to mediate taste preferences, increased consumption of saccharin when injected with DAMGO (363), so that it may also play a role in opiate regulation of eating.

Modification of the effects of morphine occurred with several different agents. Nitric oxide can be influential, as indicated by the finding that an inhibitor of it suppressed morphine-induced eating in food-deprived mice (70). Because L-arginine, but not D-arginine, potentiated morphine's promotion of eating, the role of dopamine in the response is also suggested (70). Chronic amphetamine increased the prophagic effect of U50,488 in rats, although the mechanism involved was not clear (27). Strain differences also occurred in the feeding response to morphine, with Lewis rats being stimulated more than Fischer 344 rats. There was differential consumption of specific macronutrients, as well, but the explanation for the effects was not clear, because there were only small differences in tissue concentrations of morphine in them (186).

There were some changes in the endogenous opiate system that occurred with food deprivation, suggesting a possible mechanism for opiate regulation of eating. Deprivation increased β-endorphin in the hypothalamus of rats, as early as the first day of deprivation (347). The deprivation also increased serum corticosterone and decreased dexamethasone suppression of adrenal glucocorticoid secretion, indicating that there was impairment of the HPA axis, not just the opiate system (347). Dynorphin expression in the hypothalamus showed a complex pattern after deprivation, with increases in the supraoptic nucleus retrochiasmatic, but no changes in the supraoptic nucleus or arcuate nucleus, and a decrease in the ventromedial nucleus, dorsomedial nucleus, and paraventricular nucleus, thus not permitting a simple interpretation of the role of dynorphin in eating (546).

Most of the work in this field focused on the effect of opiate antagonists on eating, and it was typically a suppression of intake under a wide variety of conditions. Antagonists decreased feeding in satiated animals (235,241,337,346,464,554), deprived animals (13,57,178,240,253,293,307,451), in palatability-induced eating (57,307), in 2-deoxy-D-glucose (2-DG) hyperphagia (293,451), tail pinch-induced eating (292), high-fat-induced feeding (240), and electrically stimulated eating (76). A number of different antagonists produced that inhibition, including naloxone (13,57,178,201,240,296,307,554), the μ antagonist naltrexone (241,253,293,451,464), the κ antagonist nor-binaltorphimine (76,296), the irreversible μ antagonist β-funaltrexamine (292,296), the μ_1 antagonist naloxonazine (292), the δ antagonist naltrindole (253), methyl naloxonium bromide given into the nucleus accumbens (57), phenylpiperidine-based opiate antagonists like 11,LY255582 (346,464), the μ antagonists CTOP (D-Phe-Cys-Try-D-Trp-Orn-Thr-Pen-Thr-NH_2) (235,292) and CTAP (D-Phe-Cys-Tyr-D-Trp-Arg-Thr-Pen-Thr-NH_2) (253), and the mixed agonist/antagonists nalbuphine and butorphanol (337). Naltrindole, however, failed to block either tail pinch-induced feeding (292) or neuropeptide Y-induced eating (296), and naltrexone (292), nor-binaltorphimine (292), and DALCE ([D-Ala^2-Leu^5-Cys^6]enkephalin) (292) also did not suppress tail pinch-induced hyperphagia. Naloxonazine (293) had no effect on 2-DG feeding.

A number of variables affected opiate mediation of deprivation-induced eating, including dose of antagonist, age, gender, and gonadectomy, producing complex interactions. Age, gender, and gonadectomy did not influence the action of a low dose of naloxone, but with a high dose sham-operated males had greater age-related and gender-related inhibition of eating. Gonadectomy at a young age also increased the effect of a high dose of naloxone. With high-fat-induced eating, the potency of naloxone increased in sham-operated females as a function of age but decreased in sham-operated males and in ovariectomized females as a function of age (240). It is clear that there is a dissociation based on motivation for consumption and that these variables are crucial to an understanding of this phenomenon, but their significance has not yet been delineated. Similarly, receptor specificity, route of administration, and the macronutrients eaten interacted (293), but the meaning of these findings has not been totally sorted out.

Pretreatment with milk, either whole or skim, potentiated the suppression of eating of naloxone, probably due to the consequence of caloric intake, not upregulation of the endogenous opiate system, because whole milk had a stronger effect than skim milk, despite the fact that equal volumes of it were consumed (554). Repeated presentation of LY255582 for 30 days did not produce tolerance, with the antagonist maintaining its ability to inhibit intake, but naltrexone lost its effectiveness after no more than 12 days (464), so that different antagonists can have differential amounts of upregulation of the opiate system.

Serotonin has been shown to alter the opiate mediation of eating somewhat, as measured with opiate antagonists. Although the general serotonin antagonist methysergide and the 5-HT_3

antagonist ICS-205930 had minimal effect on naltrexone inhibition of eating, ritanserin, which binds to the 5-$HT_2$1C receptors, blocked naltrexone's effect, suggesting a receptor-specific interaction with the opiate system (241). The serotonin reuptake inhibitor fluoxetine, however, did not affect symptoms of anorexic patients, even though there was an increase in dynorphin in them, suggesting no interaction between the systems in this disorder (22). In bulimics, though, both serotonin and dopamine metabolites correlated with changes in β-endorphin in cerebrospinal fluid (CSF) (107), indicating a complex relationship among the systems. Dopamine also was shown to affect opiate-mediated eating in rats, although the action was situation dependent, with the D_2 antagonist haloperidol enhancing naltrexone inhibition of 2-DG-induced feeding, but the D_2 agonist quinpirole enhancing it in deprivation-induced eating (451). Clearly, further delineation of the interactions between these neuropeptides is needed.

In recent years, some interest has shifted from opiate modulation of gross changes in amount of food consumed to focus on differential effects on specific macronutrients. Continuous infusion of morphine in rats produced a biphasic effect, reducing carbohydrate intake and increasing fat intake for the first few days, but after that the reverse occurred. The termination of morphine produced a decrease in the relative preference for fat, but eating returned to baseline within 4–5 days (185). There was a strain difference in response to acute morphine, with consumption of carbohydrates increasing more for Lewis rats than for Fischer 344 rats, although morphine increased fat intake equally between them (186), indicating that there may be genetic differences in preference for macronutrients and responsiveness to opiate manipulation. The effect is not specific to eating, because rats preferring a high-fat diet exhibited more analgesia to morphine, but not baseline antinociception, than those preferring a high-carbohydrate diet (187).

Modulation of the opiate system with antagonists also demonstrated a role for the opiate peptides in intake of macronutrients, although it was specific to manipulation of several variables. Systemic naltrexone inhibited consumption of all macronutrients in 2-DG hyperphagia but only that of carbohydrates and fats after food deprivation; when it was centrally administered, the antagonist attenuated only intake of fat under both conditions of motivation. Central β-funaltrexamine inhibited eating of both carbohydrates and fats in both situations, but naloxonazine suppressed it only with deprivation. None of the δ or κ antagonists had a differential effect on the macronutrients, indicating that opiate mediation of it is probably through the μ receptors (293). Naltrexone reduced intake of both simple (maltose dextrin) and complex (sucrose) carbohydrates (241), so that all kinds of carbohydrates might be affected by the opiate system.

The opiates have also been shown to modulate taste preferences, which is not surprising, because they have some hedonic or aversive properties. Morphine enhanced palatability of pleasing tastes, as seen by the finding that rats increased eating of sucrose but did not alter amount of quinine-flavored food consumed (124). DAMGO, too, increased ingestion of saccharin, but dynorphin reduced it, suggesting a receptor-specific reaction (363). Naloxone reduced deprivation-induced intake of chocolate chip cookies, which were preferred, more than that of normal rat chow, when presented on separate occasions. When given concurrently, however, the difference disappeared, and when offered an aversive taste of high-fiber chow, naloxone decreased intake only at high doses, indicating that the effect of the antagonist depended on the palatability of the food (178). Further support for opiate mediation of tastes came from the finding of Met-enkephalin-Arg^6-Gly^7-Leu^8 immunoreactivity in the taste buds of rats, mice, and guinea pigs (556).

Because the endogenous opiate system modulates consumption of food, it is not surprising that it also affects body weight. Chronic morphine (501) or U50,488 (51) produced weight gain in rats, and abstention reduced the amount of expected weight gain (185). The gain associated with morphine was attenuated by midazolam (501), but that from U50,488 was unaltered by a nitric oxide synthesis inhibitor (51), indicating that the opiates can interact with benzodiazepines but not nitric oxide in this situation. Further support the role of the opiate system in the regulation of weight came from the report that the opiate antagonists naloxone (14) and LY255582 (464), but not CTOP (235), reduced weight gain in rats.

Because the opiates are involved in control of weight, it is natural to look to the opiate system in the etiology and treatment of eating disorders. So far, evidence has not been very encouraging, although some effects have been seen. Some studies found that concentrations of β-endorphin in CSF (107,327) and in plasma (327) were reduced in patients with anorexia nervosa, and there was a correlation between body mass and β-endorphin in CSF (327). However, treatment with megestrol acetate reversed the decrease in β-endorphin but did not affect body weight or body mass (327). Another study found no difference between anorexics and normal individuals in basal plasma β-endorphin, and there was no correlation between it and body mass, but the response of the peptide to CRH was blunted in anorexics relative to normals (62), so that β-endorphin may play an as yet undelineated role in the disorder. Similarly, dynorphin in the suprachiasmatic hypothalamic nucleus was greater in anorexics given treatment consisting of exercise than in normals who were weight matched with anorexics (thus deprived) but not exercised, but was not different from that in those not deprived, with or without exercise (22), so opiate involvement is complex and confusing. Apparently, the opiate system does not mediate bulimia, because CSF β-endorphin did not differ in them relative to normals (107).

The findings with obesity were similar to those for anorexia. Although there was no difference in basal plasma β-endorphin in obese (either abdominal or peripheral) and control women, there was a differential response to injection of CRF, with abdominally obese showing a greater response than the other two groups, which did not differ from each other (386). Thus, abdominal obesity may have increased opiate activation. In dietary obesity induced in sheep, there was no increase in plasma β-endorphin relative to lean animals, but there was a potentiation of the inhibitory effect of naloxone on eating in overweight sheep (13), so that there did appear to be an alteration of the opiate system with obesity. In rats with obesity induced by high-fat diets, the latency for the tail flick response was higher than for controls, indicating a reduction in sensitivity to pain, which is consistent with an increase in the activity of the endogenous opiate system in obesity (412). Support for that notion came from the report that injection of naltrexone in an obese woman, to help control her eating, produced opiate withdrawal symptoms (237), so that her possibly hyperactive opiate system might have contributed to her obesity.

Other responses have been used as indices of the opiate modulation of eating. Morphine increased blood glucose and glucagon in fed, but not fasted, rats, and the effect was naloxone reversible, indicating opiate control. Morphine increased insulin in both fed and fasted rats, but the action was blocked by naloxone only in fed ones (256), so that the physiological reactions to feeding seemed to be opiate modified. Consumption of food altered nociception, both basal and morphine induced. Basal analgesia was potentiated by corn oil (160), and morphine an-

algesia increased after a high-fat diet (187) or a corn oil diet (160). The effect of a sweet taste, however, produced contradictory results, with a chronic sucrose diet facilitating morphine analgesia (160), but chronic saccharin attenuating it (147). It is possible that the differential nutritional benefits of the two sweeteners might be responsible for the difference, because neither had an immediate effect.

Chronic naloxone not only affected body weight, but also inhibited the stimulation of corticosterone by U50,488, suggesting an interaction between the hormone and the κ receptors might be responsible for the weight loss (14). Hypothermia induced by morphine was enhanced by saccharin, supporting the view that sweet substance activate the endogenous opiate system (60). In individuals reporting a greater than normal number of illness, there were also reports of more limitation of foods that mobilize the opiate system (sweets, fats, and bread), as well as more illness from opiate drugs and alcohol, indicating a correlation between the opiate system and these illnesses (45).

A mechanism for opiate mediation of food intake was postulated. It starts with a feeding initiating signal, which produces activation of the κ receptors, thereby inducing eating. Eating produces a circular reaction starting with hedonic input from the eating, which activates the μ receptors, which regulates K^+_{ATP}, opening and closing it. This, in turn, produces reward, which causes further eating, completing the circle (423). Thus, both the κ and μ receptors are involved, but at different places in the eating process.

DRINKING

In 1993, interest in the possible regulation of drinking fluids continued its decline of recent years. Much of the work done that year involved the hypothesized relationship between the endogenous opiate system and the consumption of alcohol. The opiates do influence intake of alcohol, and drinking it alters the opiate system, although the exact nature of the connection between them still is unclear. The overall picture of opiate mediation of drinking is not as simple as it was with eating, because there are conflicting findings with both the opiate agonists and antagonists.

Morphine was reported to increase drinking (186,233), which would be consistent with its effect on eating, or to suppress drinking (233), or have no effect on it (32), depending on the specific conditions. Dose, understandably, was a factor, because low doses facilitated, but high doses inhibited intake of fluids, specifically a sodium solution in sodium-deficient rats (186,233). Strain differences were also crucial, with Lewis rats exhibiting greater responses to morphine than Fischer 344 rats (186). Although those effects were seen with systemic injection, microinjection of morphine into striatal regions produced no effect on drinking (32).

The μ agonist DAMGO stimulated eating in intact, satiated rats (188,363) but suppressed it in those with lesions of the lateral hypothalamus (363), indicating that μ receptors in that area were important for opiate regulation of drinking. The striatum, however, apparently was not involved, because neither DAMGO nor the δ agonist DPEN or the κ agonist U50,488 affected drinking when they were injected directly into that structure (31). DTLET ([D-Thr^2-leucine enkephalin-Thr) (188) did increase responding for a saccharin solution, suggesting a role for δ receptors in other areas.

Involvement of the κ receptors received mixed reports, because a large dose of dynorphin was required to have an effect on ingestion of saccharin (inhibitory) in intact animals, and those with lateral hypothalamic lesions drank less water but not saccharin solution (363). An analogue of dynorphin, DAKLI, had no effect on the response for saccharin (188), and U50,488 microinjected into the striatum did not alter drinking, leading to further questions concerning the involvement of κ receptors in this response. However, intake of high concentrations of sucrose was facilitated but that for low concentrations was inhibited by U50,488 in sham-feeding rats (486), so that the hedonic properties of the solution consumed were important. In normal rats, IP U50,488 suppressed drinking in the first hour, and this action was not affected by chronic treatment with amphetamine (27), indicating that there was no interaction between the opiate system and amphetamine in this situation.

The findings for naloxone and naltrexone were more consistent, with the antagonists inhibiting drinking (6,44,233,394,438), except at a low dose of naloxone (6). They were effective in decreasing intake of saccharin (44), maltose dextrin (44), sodium in sodium-deficient rats (233), and sucrose (394), thus exhibiting much generality. The ontogeny of the effect, however, did depend on the means of ingestion, because naloxone was effective at 11 days of age in rat pups when they drank from a beaker on the floor but did not suppress drinking until 14 days of age in those with continuous intraoral infusion through an anterior, sublingual catheter (394). Route of administration was crucial for naltrexone, because with systemic injection it inhibited drinking induced by angiotensin II or hypertonic saline, but central naltrexone reduced only angiotensin II-induced intake (438).

Other antagonists produced somewhat more situation-specific results, depending on the source of motivation for drinking. The μ antagonist β-funaltrexamine had no effect on consumption of a palatable saccharin solution, although it inhibited that for maltose dextrin (44) or that induced by angiotensin II or hypertonic saline (438), indicating a strong role for μ receptors. Because the μ_1 antagonist naloxonazine did not alter drinking under any condition (44,438), the suppressive effects of β-funaltrexamine probably were mediated by μ_2 receptors. The δ_1 and δ_2 receptors mediated slightly different effects, with only the δ_1 antagonist DALCE decreasing angiotensin II-induced drinking (438), but with both DALCE and the δ_2 ligand naltrindole slowing drinking of saccharin (44) and having no effect on maltose dextrin (44) or in response to hypertonic saline (438). The κ antagonist nor-binaltorphimine did not affect intake of the palatable substances saccharin or maltose dextrin (44) but did reduce that induced by hypertonic saline or angiotensin II (438), suggesting that the κ receptors mediated maintenance of physiological homeostasis and not taste.

Drinking of milk appeared to produce indirect activation of κ receptors, through dopamine mediation, because the decrease by milk in rat fetal facial wiping to a tactile probe was inhibited by nor-binaltorphimine or the D_1 antagonist SCH-23390. Either U50,488 or the D_1 agonist SKF-38393 mimicked milk's effect of reduced wiping responses, and these actions were blocked by the appropriate antagonist (428). Intake of sucrose lowered concentrations of β-endorphin in the dorsal, but not ventral, hypothalamus in spontaneously hypertensive rats, but not in normal rats (565), so that the endogenous opiate system was activated by the sucrose in a specialized population.

Much of the research in drinking in 1993 centered around the role of the opiate system in consumption of alcohol. There appears to be an upregulation of the opiate system after ingestion of ethanol, including an increase in δ receptor expression in vitro after long-term treatment with ethanol (82) and in prodynorphin mRNA in brains of ethanol-fed mice (197). Administration of alcohol to rats raised concentrations of β-endorphin in the hypothalamus (114,280) and hippocampus (280), but not the cortex, and concurrent injection of ethanol and RO 15-4513,

a benzodiazepine inverse agonist, blocked that rise in the hypothalamus and of ethanol and flumazenil, a benzodiazepine antagonist, attenuated it in the hippocampus, but ethanol and the benzodiazepine agonist diazepam did not alter it, suggesting that the effect was mediated through γ-aminobutyric acid/benzodiazepine receptors (280).

The stimulated release of β-endorphin in the hypothalamus was only transitory, spiking rapidly and then returning to baseline within 10 min. If a second injection of ethanol was given within 30 min of the first one, no increase in β-endorphin was seen (114), suggesting temporary tolerance to ethanol. This effect occurred in both in mice bred to prefer ethanol and to find it aversive, with the former reacting more strongly, indicating genetic differences in susceptibility to alcohol (114). Support for this idea came from the finding that there were also strain differences in opiate activity in mice selectively bred for resistance to or sensitivity to ethanol-induced hypothermia, with μ binding increased in the frontal cortex for those resistant to the effect (492).

Manipulation of the opiate system by administration of opiate agonists or antagonists had an effect on intake of alcohol, providing further evidence for a role of the opiate system in this response. Morphine increased both drinking of ethanol and blood alcohol levels in rats (232), and antagonists generally suppressed the consumption (173,235,236,300). The receptors involved are not clear, because naloxone (173,236) and CTOP (235) inhibited drinking of ethanol, but β-funaltrexamine did not (300), questioning whether the μ receptors mediated the response. Similarly, the role of the δ receptors was undecided, because naltrexone (173,300) and naltrindole (300) reduced intake of alcohol, but ICI 174,864 did not, at least in males. In females drinking could not be measured because the antagonist produced confounding motor dysfunction (235). Perhaps receptor subtypes will need to be investigated to delineate the specificity of the action.

It is likely that there is not a simple, direct modulation of the effect by the opiate system, but rather an interaction with other systems. Support for this idea came from the finding that naltrindole infused into the nucleus accumbens of rats blocked the increase in extracellular dopamine elicited by ethanol or [D-Ala^2]deltorphin II (4). Similarly, locally applied ethanol increased dopamine release, but not that of serotonin, in the nucleus accumbens, and that effect was reversed by naltrexone, suggesting the opiate system as a mediator of the reward of ethanol (46). Naloxone also inhibited the suppression of amplitude of excitatory postsynaptic potentials evoked by ethanol in the nucleus accumbens, indicating that ethanol might be acting by an opiate mechanism (375). Although there appears to be more evidence for that idea, there are still few clinical findings to indicate that it may be a useful tool in treatment of alcoholism.

GASTROINTESTINAL, RENAL, AND HEPATIC FUNCTIONS

In 1993, as in other recent years, interest in opiate modulation of gastrointestinal (GI) function has dwindled considerably. As reported in previous years, opiate agonists, including morphine, Met-enkephalin, DAMGO, and DPDPE, slowed gastric motility, and there was a correlation between the duration of the inhibition and affinity of the agonist for μ receptors (255). Acupuncture-like stimulation of the abdomen in anesthetized rats suppressed gastric motility, but probably through a nonopiate mechanism, because naloxone had no effect on it (449). The μ agonist loperamide and the enkephalinase inhibitor acetorphan rapidly and similarly reduced diarrhea of presumed infectious origin in humans, a well-known action of opiates, with acetorphan reducing abdominal distension more rapidly and producing less reactive constipation (433), suggesting possible clinical benefit. GI transit of a liquid meal in humans, however, was unaltered by naloxone, either under normal conditions or with mild exercise, which accelerated transit time (206), indicating a lack of mediation by the opiate system in the response.

The opiate agonists, contradictorily, also produced intestinal hyperactivity in chicks, again related to μ affinity, so that the δ ligand produced duodenal hyperactivity that was not propagated (255). Naloxone lengthened the duration of the migrating motor complexes (255), further indicating involvement of opiate system in this response. Jejunal excitatory motor responses in anesthetized cats were also produced by morphine and vagal nerve stimulation, with approximately equal efficacy. They were contractile responses, consisting of increased tone and phasic activity (198). The excitatory and inhibitory potentials of isolated muscle strips of pyloric sphincter were inhibited by both Met-enkephalin and DADLE, but both had no effect on resting potential or slow-wave activity, suggesting an effect on junction potentials, not a direct effect on smooth muscle cells.

The guinea pig ileum has been a frequently used preparation to study the effect of opiates on GI tissues, with the agonists typically inhibiting electrically stimulated contractions. In 1993, that observation was again reported, the effect developing tolerance as a function of the concentration of the morphine and the exposure time to the morphine (99). As expected, after chronic opiate application, naloxone (357,528) or nor-binaltorphimine (357) stimulated the contractions, but the action was receptor specific, with nor-binaltorphimine working only after U50,488 and not after morphine. Naloxone produced contractions only after low doses of U50,488 or after the agonist had been washed out of the preparation (357).

When opiate agonists or antagonists were superfused on the longitudinal or circular muscle strips from human sigmoid colon, neither dynorphin(1–13) nor U50,488 altered spontaneous contractions, but both dramatically reduced the amplitude of contractions elicited by electrical stimulation. The effects of both κ ligands were blocked by the κ antagonist nor-binaltorphimine but not by the δ antagonist ICI 174,864, indicating involvement of the κ receptors in this action (80). In the conscious rat, the enkephalinase inhibitor acetorphan increased the percentage of long spike bursts going to the distal colon, as occurs typically after feeding, and it reinforced the increase induced by feeding. This indicated a role for the opiate system in electromyographic activity of the colon, and this idea was supported by the naloxone reversibility of the action (47).

As with other responses, there appear to be interactions between the opiate and other systems in GI functions. Nonadrenergic, noncholinergic mechanisms were suggested for the modulation of opiate activation of circular muscle of the small intestine, because the potency of the effect of morphine was equivalent to that of vagal nerve stimulation (198). In the GI system of goldfish, Met-enkephalin counteracted the effect of serotonin (283), indicating involvement of both systems in its responses. There was probably opiate mediation of nitric acid-dependent neurotransmission, because either Met-enkephalin or DADLE suppressed a portion of the inhibitory junction potential that was sensitive to arginine analogues (29).

The opiate system seems to play a role not only in muscular and electrical activity of the GI tract, but also in its secretions. Dermorphin increased basal gastric acid secretion, although neither DADLE nor dynorphin(1–13) altered it. Opiate modulation of gastric acid secretion elicited by 2-DG depended upon the preparation studied, because in dogs with a gastric fistula, only DADLE had an effect, and it was inhibitory, but in those with a Heidenhain pouch, dermorphin was the only active agonist,

and it stimulated the secretion. Pentagastrin-stimulated acid secretion was increased by dermorphin and blocked by DADLE in dogs with the fistula and in dogs with the pouch it was increased by both dermorphin and DADLE. It was concluded that peripheral μ receptors mediate excitatory effects, δ receptors produce mainly inhibitory ones, and κ receptors do not seem to be involved (239).

The opiate system might also be affected by GI activity. Enkephalin was released from longitudinal myenteric tissues by electrical stimulation, and in vivo, when peristalsis occurs, enkephalins may be released to suppress movement of the small intestine (555). Thoracic splanchnic nerve ligation decreased enkephalin-like immunoreactivity in the gastro-duodenal region, suggesting that the peptide may be involved in intestinal motility, although there was no change in its concentration in the ileocolonic region (28).

Some species previously not studied were found in 1993 to have opiate activity in the gut. In a wide variety of insects, all had reactions to antisera to β-endorphin, Met-enkephalin, and Leu-enkephalin in gut innervation and endocrine cells of the midgut, suggesting some possible opiate control of their functions (566). Enkephalin-like immunoreactivity was found in the teleost species of tilapia (*Oreochromi s. mosambicus*) and goldfish (*Carassius auratas*) in mucosa endocrine cells, circular layer fibers, myenteric plexus fibers, and longitudinal muscle layer fibers (283). It is likely that the physiological effects are similar to those in other species studied.

In past years, there had been research on the protective effect of opiates on ulcers. In 1993, there were few studies about it. Both DAMGO and DPDPE were shown to reduce gastric lesions in rats subjected to cold-restraint stress. Naloxone blocked the effect of both agonists, but naltrindole reversed the action of only DPDPE. Nevertheless both μ and δ receptors seem to be involved in the response (459). In patients with chronic ulcer disease, the addition of β-endorphin strongly enhanced the immune response to phytohemagglutinin. The significance of this finding was not clear, because it did not relate to treatment of the ulcers, but it did suggest that the opiate system might mediate the effect stress-induced disorders have on the immune system (377). Morphine has been known to produce nausea and vomiting, which is a problem for its clinical use. Injection of methylnaltrexone blocked morphine-induced emesis, but did not alter its analgesic potency, indicating the elimination of the unwanted side effect without reducing its primary function (156).

There was little work done on opiate mediation of hepatic function in 1993. There is an increase in Met-enkephalin in rats with acute cholestatic hepatitis, and the source of this rise was identified as the sympathetic nervous system rather than the adrenal gland (495). Repeated administration of naltrexone was not found to alter the liver enzyme tests SGOT and SGPT, clearing the antagonist of unwanted side effects on the liver when used in treatment of other disorders, such as autism (25).

There was, however, increased interest in the possible opiate involvement of renal function. Administration of opiate agonists produced conflicting results, although much of the inconsistency could be accounted for by the kind of receptor being stimulated. The μ agonists morphine (30,238) or a metabolite of it, morphine-6-glucuronide (M6G) (238), reduced urine output, although morphine-3-glucuronide (M3G) increased it (238). Naloxone reversed the effect of all three, but it was thought that the action of M3G was not through opiate receptors because it is not found to bind to any receptors (238). Dermorphin, another μ agonist, given ICV but not IV, produced the opposite effect, increasing urine flow, and the μ antagonist β-funaltrexamine blocked the effect. Dermorphin, however, had no effect on effective renal plasma flow or glomerular-filtration rats and increased efferent renal sympathetic nerve activity, so that the action was not mediated by central changes in renal outflow to the kidneys or hemodynamics (272). Activation of different μ subtypes might be responsible for the differences.

For κ receptors, it appeared that the effect was determined by the site of administration. Microinjection of dynorphin, U50,488, or DAKLI (Tyr-Gly-Gly-Phe-Leu-Arg-Arg-Ile-Arg-Pro-Arg-Leu-Arg-Gly 5-aminopentylamide) into the paraventricular nucleus produced an antidiuretic effect, as did dynorphin into the supraoptic nucleus (518). Because the action of dynorphin was reversed by atropine and timolol at both sites and by naloxone only in the paraventricular nucleus, it was concluded that its action in the supraoptic nucleus was not opiate mediated and that both sites involved adrenergic and cholinergic mechanisms (518). It is possible that U50,488 and DAKLI in the paraventricular nucleus also produced nonopiate effects, because DAKLI was not inhibited by naloxone and U50,488 might have responded only to the doses used.

Systemic (68,174) or ICV (271) κ agonists had a diuretic effect. In rat, U50,488 produced a nor-binaltorphimine-reversible increase in urine output (174,271) and renal sympathetic nerve activity (271). Although U50,488 (271) and dermorphin (272) stimulated urine output, it reduced sodium excretion, at least when centrally administered, indicating both κ and μ mediation of the antinatriuretic response. Cyclazocine (a mixed κ and δ agonist) (174), and three κ agonists, BRL 53114, BRL 52656, and BRL 52974 (68), also stimulated diuresis, depending on their ability to cross the blood–brain barrier. Because the serotonin antagonist metergoline suppressed the increased urine due to cyclazocine or U50,488 (174), it was suggested that serotonin might be involved in the complex mechanism of κ agonist-induced diuresis (174). The effect of microinjection of DADLE into the paraventricular nucleus or supraoptic nucleus was similar to that for dynorphin, with only the former producing an opiate-mediated effect and with an interaction between opiate, adrenergic, and cholinergic mechanisms at both sites (517). Naloxone alone (238) and naltrindole during naloxone-precipitated withdrawal from butorphanol (250) had no effect on urine output, leading to questions concerning the involvement of the opiate system in its normal regulation.

Opiate-mediated renal function might be related to cardiovascular activities as well. Rats bred to be possess renal hypertension appear to have increased sensitivity to opiates, and this response might occur through an interaction with angiotensin II in the brain (547). In addition, kidney damage due to reperfusion after hemorrhage was inhibited by naloxone (11), suggesting that the endogenous opiates might be responsible for the tissue damage in that situation.

MENTAL ILLNESS AND MOOD

Research in opiate modulation of mental illness and mood continued to decline in 1993, as in recent years, perhaps due to the lack of promising findings. There was still some interest in opiate involvement in depression and in autism, but other areas were overlooked for the most part. In depressed patients, baseline plasma β-endorphin was lower than in normal controls (356), but that may be due in part to a confounding with age, because advancing age produces lower baseline β-endorphin, particularly in women, and depression is found more frequently in older populations (10). There appears to be abnormal functioning of the HPA axis in depressed patients, as indicated by nonsuppression of β-endorphin in several tests. Infusion of cortisol produced less release of the opiate peptide in depressed individuals than

in normal controls (9,179), and the suppression of β-endorphin by dexamethasone was found in some patients (10) but not in others (179). Increasing age potentiated the likelihood that dexamethasone would suppress β-endorphin (10), supporting the ideas that age is a confounding factor. Inhibition of cortisol synthesis with metyrapone increased plasma β-endorphin (9), but after the test, concentrations of the endorphin were again below that of controls (356), further supporting the notion of impairment of HPA responsiveness in the disorder. Within the patient population, however, there was no difference between melancholic individuals and those with minor depression either in baseline plasma β-endorphin or in response to ACTH (316).

With both positron emission tomography (PET) and single photon emission tomography (SPECT), it was found that there is an increase in μ receptors in depressed patients in the frontal and cortex and temporal cortex. In those with symptoms severe enough that they had committed suicide, retroactive findings after death indicated that the increases were of a magnitude several fold above normal. Because δ and κ ligands for PET imaging were not available, no determination could be made about any change in them with depression (159).

An animal model of depression is learned helplessness, and it was modified through manipulation of the opiate system. Two inhibitors of enkephalin catabolism, RB 38A and RB 38B, produced imipramine-like antidepressant effects, as measured by a decrease in escape failures. Naloxone increased the helplessness and antagonized the effects of R 38A and R 38B, indicating the opiate nature of the effect (500). The findings might have clinical significance in therapy for depression.

Similarly, autism might be meditated, at least in part, by the endogenous opiate system, so that manipulation of it might be used in its treatment. Baseline concentrations of β-endorphin were lower in autistic children than in normals, and there was a strong correlation between the peptide levels and severity of stereotypies (133). Although naltrexone did not affect measures of β-endorphin (133), short-term administration of haloperidol in therapy did increase them. Long-term use of the drug, however, lowered concentrations of the peptide, and its removal produced an increase in the endorphin, indicating a disturbance of the opiate system (133). Similarly, naltrexone reduced the number and intensity of symptoms of autism when given acutely but not chronically (58,219). Some symptoms responded better than others, with hyperactivity (219) and nonmeaningful vocalization (58) decreasing, but talking in the presence of others not changing (58). Indirect support for the disturbance of normal opiate functioning in autistics came from the finding that a subgroup of patients that was normally insensitive to pain had significant hyperalgesic responses to acute naltrexone (313).

The opiate system may also play a role in posttraumatic stress disorder (PTSD). About half of the PTSD patients had an increased hormone response to naloxone, but the endocrine changes did not correlate with the severity of PTSD symptoms or with other standard psychiatric illness or other measures of psychological testing. In this subgroup, it is possible that there was an opiate-mediated hypersensitivity of the HPA axis (224). In vitro studies of blood cells from patients with PTSD revealed an alteration of immune functioning in response to opiates, with Met-enkephalin increasing natural killer cell activity in patients with symptoms but not in normals (358).

Other disorders have tenuously been linked to the opiate system. Self-injurious behavior was reduced by naloxone or naltrexone in some patients, but the characteristics that distinguished responders from nonresponders were not determined. Possible mechanisms to explain the decreases when they occurred included the suggestion that the self-injurious behavior might cause a release of endogenous opiates, which would be rewarding or would dull the pain, making the behavior less aversive (43). In schizophrenic patients, nalmefene, a long-lasting antagonist active at δ, κ, and μ receptors, potentiated the benefit of neuroleptic (415), suggesting manipulation of the opiate system might have clinical value. There was a negative correlation between concentrations of β-endorphin in CSF and dissociative symptoms in bulimic patients (107), indicating a disturbance in opiate peptides might mediate the experiences in a subpopulation of individuals. There may also be a relationship between endogenous opiates and hypochondria, because people who self-reported more illness also consumed fewer foods that mobilize the opiate system, thus possibly causing it to be underactive (45).

Moods, too, can be modulated by the endogenous opiates. Anxiety, as measured by burying of novel objects by rats, was correlated with a decrease in β-endorphin in plasma (395). In accordance with that finding, administration of U50,488 reduced anxiety on the elevated plus maze, although it did not affect anxiety in an open field maze (403). Both the μ agonist hydromorphone and the mixed agonist/antagonist pentazocine produced euphoria and other μ-mediated subjective effects that were reversed by naltrexone (402), indicating their opiate nature. Withdrawal from methadone maintenance produced an increase in symptoms of dysphoria, insomnia, and somatic complaints, leading to the conclusion that the development of organic mood syndrome is a common occurrence in patients undergoing slow detoxication from methadone and is related to changes occurring in the endogenous opiate system (270).

LEARNING, MEMORY, AND REWARD

In recent years, there has been increasing interest in the role of the opiate system in the mediation of learning and memory, as well as in the reinforcing properties of the opiates, and 1993 was no exception. Different kinds of learning respond differentially to opiate modulation, and many methodological variables alter the actions within a paradigm, so that few generalizations about their effects can be made, and the learning tasks must be reviewed separately. However, many studies have reported that the agonists inhibit learning and the antagonists facilitate it.

The involvement of the opiate system in behaviors established by classical or Pavlovian conditioning received increasing attention in 1993, especially conditioned place preference or aversion. They are acquired by the pairing of a distinctive environment with a drug, so that the environment develops pleasurable or negative properties, depending on whether the drug has rewarding or aversive effects. A variety of opiate agonists were used in this context, including morphine (42,161,353,378,493,494), one of its metabolites, M6G (42), DAMGO (34,42), U50,488 (34,42,161), a stable dynorphin derivative E-2078 (34,161), DPDPE (42), buprenorphine (436), and an inhibitor of enkephalin-degrading enzymes, which can act like an antagonist (378). In most situations the agonists apparently had rewarding properties, because preferences developed for the areas associated with them (34,42,161,353,378,436,493,494), although there were some exceptions, based on specific manipulations made.

Site of administration was one crucial variable. DAMGO produced place preferences when microinjected into the ventral tegmental area but not when administered to the lateral hypothalamus, nucleus accumbens, medial prefrontal cortex (34), or substantia nigra (42). The κ agonists U50,488 and E-2078, however, induced place aversions when introduced into any of those areas (34), except for the substantia nigra, in which they, like

the μ agonist DAMGO and the δ agonist DPDPE (42), had no effect (34). Similarly, neither κ nor μ ligands altered preferences when injected into the nucleus caudatus-putamen (34). With systemic administration, morphine produced place preferences (161,353,378,493,494), but U50,488 (161,493) and E-2078 (161) induced place aversions. Thus, when they had an effect, the κ agonists were aversive and the μ agonists were pleasurable.

Pretreatment with U50,488 or E-2078 blocked morphine-induced place preferences, an action blocked by nor-binaltorphimine (161), supporting the aversive nature of the κ agonists. Place preference with morphine was also suppressed by the μ antagonist β-funaltrexamine but not the μ_1 antagonist naloxonazine, suggesting the effect might be mediated by the μ_2 receptors (493). There might be an interaction between the μ_2 and D_1 receptors, because the D_1 antagonist inhibited morphine place preference, thus implicating the dopaminergic system as well as the opiate system (493). The immunosuppressant cyclosporine A also blocked preferences for morphine-associated places (494), although the involvement of the immune system in morphine reward is not clear. The enkephalinase inhibitor RB 101 did not produce place preference, indicating no reinforcing properties to it, but because it did have antinociceptive potency, the clinical potential of the nonaddictive analgesic was suggested (378).

Opiate antagonists alone, including naloxone (6,381) and naltrexone (143), developed place aversions. In morphine-dependent rats, withdrawal produced place aversion for the chamber associated with it, and the β-adrenergic antagonists propranolol and atenolol attenuated the aversion, suggesting that those agents might be effective in the treatment of opiate addiction (208). Aversiveness of withdrawal in morphine-dependent rats was also associated with a complex conditioned stimulus when naloxone was paired with the presentation of a combination of a distinctive odor and tone (33) or a tone and light (136), but not when the antagonist and the complex stimulus were presented independently, at different times, indicating contiguity of the stimuli was necessary for learning (33).

Conditioned taste preference or aversion is similar to place preference or aversion, in that a distinctive taste associated with a drug might take on the affective properties of that drug. Morphine, when paired with a particular taste, produced taste aversion at a wide range of doses (529). Delay of morphine for 6 h after the taste eliminated the effect (529), despite the typical finding that postponing the aversive stimulus for that period of time does not affect conditioning. Antagonists, including naloxone, the κ antagonist MR 2266, and the mixed μ/κ antagonists nalorphine and buprenorphine failed to produce conditioned taste aversion, even with high doses and multiple trials (146). Usually, a single trial is all that is necessary for taste aversion to develop.

A somewhat more complex form of conditioned taste aversion has also been used, in which the animal is pretreated with an opiate and is then given an opportunity to consume a distinctive taste, followed by the nausea-inducing injection of lithium chloride. Later intake of the solution is measured after injection of morphine, relative to controls that were given neither morphine nor the aversive nausea. Consumption of the solution decreased after morphine (246,400), indicating that the opiate had developed negative qualities as a result of the training. In a generalization test, buprenorphine substituted for morphine, but the reverse was only partially true. Buprenorphine did not generalize to MR 2266 or diprenorphine, but the latter did substitute for morphine, so that the action of buprenorphine in this situation was probably at the μ receptors (400). Naltrexone reduced the strain differences found between obese and lean mice in taste aversion with the frequently used saccharin and lithium chloride pairing (506), suggesting opiate involvement.

A similar phenomenon is conditioned odor preference. When rats received one odor paired with morphine and another one paired with saline, rats spent more time in the morphine-related odor if a low dose had been used but less time in it if a high dose had (413). Pairing the high dose of morphine with the odor also produced conditioned analgesia, so that the odor reduced nociception (413). Daily injections of naloxone or Tyr-MIF-1 and a hot plate test for pain produced hypoalgesia that was not found after chronic administration of the antagonists alone, indicating that the analgesia involved aversive conditioning (275), perhaps associated with the apparatus. Conditioned analgesia to a heat stressor was attenuated by morphine and enhanced by naloxone if injected ICV but not IV, so that the opiate mediation appeared to the supraspinal (155).

The opiate system seemed to be involved in a conditioned emotional response paradigm, in which the aversiveness acquired by a stimulus is measured by its ability to suppress responding in another situation. Morphine was paired with shock to produce conditioned suppression of drinking when morphine was later injected relative to drinking in animals that had not received the pairing, indicating that morphine can act as a conditioned stimulus (59). When naloxone-precipitated withdrawal in morphine-dependent rats is paired with a distinctive conditioned stimulus and later the stimulus is presented while the animal is responding in an operant chamber, the responding is disrupted, indicating that the stimulus has acquired aversive properties (33,136). Rats with lesions of the amygdala had less disruption, suggesting that the lesions interfered with learning (136).

Opiates have been used not only as unconditioned or conditioned stimuli in classical conditioning, but also as agents to modify the conditioning. When rats were given appetitive classical conditioning while under the influence of morphine, the agonist increased the magnitude of the conditioning in a dose-dependent way (527), contrary to many findings of opiate interference with learning. Antagonists had conflicting effects, depending on the task and other variables being used. Naloxone enhanced conditioning of fear for a chamber in which rats were shocked (142) and of fear of a tone paired with a shock (220), as did quaternary naloxone and CTOP (220). Naloxone, but not its quaternary form or CTOP, also delayed extinction (220). However, naloxone, CTOP, or β-funaltrexamine, but not nor-binaltorphimine, interfered with the retention of conditioned reduction of facial wiping to sucrose, after a pairing of sucrose with milk, which normally produces the response in fetal rats (24,426). This suggests that the μ receptors, but not the κ ones, were involved and that the tasks studied were crucial.

Opiate mediation in paradigms of operant conditioning has been studied, with much attention paid to inhibitory avoidance. This task typically involves presentation of a noxious stimulus as a consequence of a specific response in a distinctive environment and after a delay period often of a day, return to that environment to determine the latency of making that response again. It is a test of retention of the aversive event, and if memory is good, the response is not made. The opiate agonists usually impair retention, so that the response is made soon after reintroduction to the apparatus, and antagonists facilitate memory. In 1993 that was found to be the cause for morphine (79), Met-enkephalin (91), Leu-enkephalin (548), dynorphin(1–13) (92), and a novel dermorphin, TAPA (Tyr-D-Arg-Phe-β-Ala-NH_2) (522). There were, however, some exceptions to the general rule, with DAMGO (301) and Met-enkephalin (91) having no effect in some cases and with dynorphin(1–13) (244,521) and U50,488

(245) actually improving retention in another. Naloxone did facilitate memory (470), as expected.

As with other paradigms, the specific manipulations made were important in determining the outcomes. When Met-enkephalin was injected into the medial hyperstriatum, it produced amnesia, but when administered to the lobus parolfactorius, it had no effect on chicks trained on a peck-avoidance task (91). In the same situation, microinjection of DAMGO into the medial hyperstriatum also failed to alter retention (301), but injection of dynorphin(1–13) into that area did impair memory (92), suggesting that in this structure of the brain, the effect was receptor specific. In these studies, the opiates were given before training, which could have affected the results, as found in a comparison of pre- and posttraining injections of TAPA. Although injections at both times inhibited retention, those given after training produced stronger effects (522).

The age of the animal may also be important, because morphine, the endogenous antiopiate Tyr-MIF-1, or a combination of them had no effect in rat pups in the first week of life (92), whereas morphine did reduce retention in older animals (79). In chicks lower doses of dynorphin(1–13) were more effective in 2-day old chicks than in 4-day old chicks, indicating a loss of sensitivity, at least in area of the brain in which injections were made, the intermediate medial hyperstriatum. Higher doses were effect at both ages (92). An inverse relationship exists between the endogenous opiate system and the dopamine system, because the impairment of memory produced by morphine was potentiated by D_1 and D_2 antagonists and antagonized by D_1 and D_2 agonists (79). Vagotomy eliminated the disruptive effect of Leu-enkephalin (548), although the mechanism involved was not clear. The opiates have been demonstrated to modify the amnestic effects of several manipulations, including lesions of the basal forebrain using the cholinergic neurotoxin ibotenic acid before training. Dynorphin(1–13) increased retention, thus reversing some of the impairment (521). Transient cerebral ischemia produced marked memory dysfunction, and both dynorphin(1–13) (244) and U50,488 (245) prevented the disruption. The effect of both peptides was reversed by nor-binaltorphimine (244,245), suggesting mediation by the κ receptors in these beneficial reactions. The facilitation of memory by posttraining injection of substance P was modified by naloxone, but only in a state-dependent fashion. When naloxone was given both before and after training, naloxone potentiated the improvement by substance P, but if given only before or after training, the antagonist inhibited the effect (470). The differential mechanisms of this state-dependent action were not clear.

Active avoidance, like inhibitory avoidance, is modified by the opiates. Lever pressing to postpone shock was reduced by the μ agonists morphine, fentanyl, and methadone, but Sidman avoidance, which is based on the passage of time since the last shock, was unaffected by them (167), suggesting task-specific effects. The κ agonist U50,488 produced only variable effects at low doses and a nonselective decrease in responding in general at high doses (167), indicating that the μ, but not the κ receptors, play a role in time-out lever pressing. As is typical of antagonists, naloxone increased retention of foot shock avoidance in a T-maze (151), but the facilitation disappeared in senescence, indicating a change in the endogenous opiate system with age (151).

Spontaneous alternation is a task measuring working memory, because the animal must remember the last response and go in a different direction on the next response. DAMGO interfered with performance on this task, and the effect was reversed by β-funaltrexamine. Dynorphin(1–13) also reversed the action of DAMGO, an action blocked by nor-binaltorphimine, indicating that the μ and κ receptors have opposite effects on working memory (520). Support for the facilitation of κ agonists on this task came from the reports that dynorphin(1–13) (244) or U50,488 (245) reduced the amnesia of transient cerebral ischemia (244,245) and that dynorphin(1–13) reversed impairment induced by scopolamine (242). Likewise, performance on the elevated plus maze was improved after injection with dynorphin(1–13) (244) or U50,488 (245), and DAMGO interfered with it (520), providing further evidence for the enhancement of memory by κ agonists and interference with it by μ agonists.

The μ agonists morphine (334) and sufentanil (547) also disrupted performance in the Morris water maze. The effect of morphine depended on the timing of the injection, however, because only pretraining, not posttraining, injections were effective (334). In an atypical finding, dynorphin(1–13) inhibited learning in the maze (334), perhaps because of the site of injection into the hippocampus. Naloxone facilitated learning of this task, but, like morphine, was effective only if given before training (334). Pretraining administration of the endogenous antiopiate neuropeptide FF also produced a marginal improvement of learning and its antiserum inhibited it (274), further suggesting involvement of the opiate system in this spatial acquisition.

In an appetitive discrimination learning task, dynorphin(1–13) had the same disruptive effect that it had on peck avoidance in young chicks, with a dose-dependent action (92). Morphine reduced performance in a visual discrimination task involving dimensions of both wavelength and luminance in pigeons. The opiate decreased sensitivity to both dimensions and lowered control by luminance, so that it affected not only learning, but also sensory processes. The interference was reversed by naloxone, suggesting opiate modulation of it (61).

Physiological evidence for the role of the opiate system in operant or instrumental conditioning came from the finding that training on an inhibitory avoidance task increased concentrations of Met-enkephalin in the some areas of the forebrains of chicks but not in other areas (91). Similarly, dynorphin(1–13) is elevated in aged rats with a deficit in place learning, but is normal in those without the deficit (334), providing indirect support for the idea. After training on passive avoidance in chicks, there was increased δ binding in some areas of the forebrain and decreased δ binding in other areas, but no changes were found for μ or κ_1 binding, suggesting the δ receptors might mediate that kind of learning (101).

Not only does the opiate system modulate learning, but opiate agonists and antagonists can themselves be used as discriminative stimuli (SDs), with their subjective properties indicating what kind of response is appropriate. Typically in this form of learning, the drug becomes associated with one response and its absence with another. Then other drugs are tested for their ability to substitute for the original one and produce the same response. In 1993 a number of opiate agonists were used as SDs, including morphine (94,125,257,268,533), U50,488 (66,157), bremazocine (94), BW373U86 (94), fentanyl (396), buprenorphine (401), and nalbuphine (538). Among the antagonists successfully becoming SDs were naloxone (268), naltrexone (157), and nalorphine (477). A three-choice discrimination was also learned between morphine, naloxone, and placebo (268), and another between U50,488, naltrexone, and saline was established in pigeons given chronic U50,488 (157). Naloxone was able to block the SD effects of morphine (257), naltrexone antagonized those of nalbuphine (538), and naltrindole reversed those of BW373U86 (94), confirming their opiate nature.

Of the substances tested, only high doses of nalbuphine (533) were able to substitute for morphine, with bremazocine, BW373U96 (94), low doses of nalbuphine (533), and naloxone (268) failing to do so. Bremazocine also did not substitute for

BW373U86 (94). However, morphine was able to produce amphetamine-appropriate responding (125), indicating similar properties for the two. Acute tolerance to morphine reduced the ability of nalbuphine to induce morphine-appropriate responding (533). None of three 5-HT_3 antagonists affected the SD potency of morphine, so that serotonin was not involved in the subjective properties of morphine (257).

Morphine substituted for nalorphine, but U50,488, naloxone, and naltrexone did not (477), suggesting that nalorphine has μ-mediated agonistic properties. Similarly, in buprenorphine-dependent animals, buprenorphine generalized to morphine but not to the κ antagonist, MR 2266 (401), indicating the drug acted like a μ agonist in this situation. Likewise, μ agonists, including morphine, etorphine, fentanyl, nalorphine, and buprenorphine, substituted for nalbuphine, but the κ agonists U50,488 and ethylketocyclazocine did not. The nonopiates *d*-pentazocine, *d*-amphetamine, and ketamine also failed to generalize to nalbuphine, and naltrexone produced saline-appropriate responding, providing further evidence of its μ activity (538). The differential efficacy of drugs at the μ receptor was also demonstrated in tests of generalization of discrimination learned with high doses of fentanyl, with morphine substituting completely, a number of agents substituting considerably but not completely [(butorphanol, buprenorphine, ethylketocyclazocine, ketocyclazocine, proxorphan, (−)-pentazocine, and (−)-metazocine], and others substituting little [nalbuphine, nalorphine, (−)-cyclorphan, (−)-cyclazocine, (−)-*n*-ally normetazocine, and levallorphan]. At low doses they all substituted completely (396).

In generalization tests to U50,488, spiradoline (66), and bremazocine (157) substituted easily, but levallorphan, nalbuphine, nalorphine, and quacazocine produced naltrexone-appropriate responding in a three-way discrimination between U50,488, naltrexone, and saline in pigeons getting chronic U50,488 (157). Morphine did not substitute for either U50,488 or naltrexone (157). When chronic U50,488 was stopped, saline produced responding on the saline key, not the naltrexone key, indicating no dependence on U50,488 (157). There was no generalization to the nonopiate phencyclidine or to serotonergic compounds, although some of them attenuated the effects of U50,488 or spiradoline, suggesting that serotonin release is an important component of the SD effects of κ agonists, but is not sufficient alone to mimic them (66).

The δ-selective agonist DPLPE ([D-Pen^2,L-Pen^5]enkephalin) fully generalized to the cocaine cue in rats, and this effect was almost completely blocked by the δ antagonist naltrindole. Because the μ agonist DAMGO did not substitute for cocaine, it was suggested that cocaine is mediated by the δ receptors (523). Morphine blocked the discriminative properties of cholecystokinin, and naloxone potentiated them (338), suggesting that the opiate system might mediate those effects.

The subjective properties of the opiates have been used not only as discriminative stimuli, but also for their reward or aversive value. This is typically tested in terms of their modulation of responding for other reinforcers, such as intracranial self-stimulation (ICSS). Acute injections of morphine potentiated the reward effects of ICSS in rats (40,41), but there was either no change (40) or only a slight tolerance (41) to the effect with chronic morphine. Naloxone-precipitated withdrawal, however, greatly increased the threshold for ICSS (41), indicating that dependence had developed. Morphine potentiated the ability of nicotine to increase the reinforcement value of ICSS in rats, suggesting that the substrate that supports and reinforces morphine reward also supports that of nicotine (234).

The changes in ICSS produced by DAMGO varied with the placement of the injection of the peptide, with injection into the rostral ventral pallidum reducing its reward value but into the caudal ventral pallidum enhancing it (259). It appears that the δ receptors, as well as the μ ones, mediate reinforcement, because intra-accumbens injection of DPDPE lowered the threshold for ICSS, thus potentiating it (127). In the medial forebrain bundle, however, the δ antagonist naltrindole had no effect on responding for ICSS (416), suggesting that the area of the brain being affected is crucial for the effect. In the lateral hypothalamus, naloxone reversed the enhancement of ICSS produced by restriction of food with perifornical placement but did not affect it with any other placement, so that hunger interacts with the reward of electrical stimulation of the brain (77). Electrical stimulation of the lateral hypothalamus can also induce eating, and microinjection of the κ antagonist nor-binaltorphimine into that region blocked the effect. The antagonist had no effect for self-stimulation in the absence of food (i.e., ICSS), however (76). Opiate mediation of these effects seems complex and confounded, so that the mechanisms involved have not yet been understood.

The opiates mediate other kinds of reward besides that associated with ICSS. Responding for food was increased by the mixed agonist/antagonist butorphanol, shortening the latency to start responding, although the time to complete the fixed ratio for reward was not affected (437). This finding was in contrast to those with other opiates, with alfentanil, fentanyl, ethylketocyclazocine, U69,593, and BW373U86 all reducing the responding rate for food (371). Perhaps the difference in results was associated with the mixed nature of butorphanol. Responding for saccharin in nondeprived rats was increased by DAMGO or DTLET but not the dynorphin A analogue DAKLI (188), so that the differential reward of satisfaction of hunger as opposed to obtaining a palatable taste might explain these findings. Heroin, itself, was used as a reinforcer for traversing an alley, and rats reduced latency to start running and to reach the goal, suggesting that the heroin was rewarding (135). Because there was only one trial per day, the rats did not ever run under the influence of the drug, which would have confounded the experiment because both morphine and alfentanil were shown to impair ability to process information in humans (88).

Self-administration of the opiate agonists has been studied as another way to assess their reward properties. Animals quickly learn to respond to receive injections of opiates, including morphine (192) and, especially, heroin (282,372,424). The self-administration rates of morphine were positively correlated with previous exposure to morphine (192), suggesting the development of tolerance. With a progressive ratio schedule of self-administration of heroin, designed to restrict intake and minimize dependence, final rates of responding were stable and did not increase with chronic reinforcement, so that such a schedule was effective in preventing dependence. Naltrexone reduced the final rate of responding, suggesting that the antagonist attenuated the reinforcement received from heroin (424). Responding, however, was increased with β-funaltrexamine, naloxonazine, and naltrindole, but not with nor-binaltorphimine in more typical methods of self-administration (372), indicating that the schedule of reinforcement was crucial to the results. In addition, the study demonstrated that the μ receptors are most involved in self-administration, then the μ_1 subtype and δ receptors, and that the κ receptors are not involved (372). Lesions of the pedunculopontine nucleus, which is thought to mediate opiate reward, reduced self-administration of heroin, indicating that heroin must not be rewarding after the lesions and providing support for the importance of the nucleus in the reinforcing properties of opiates (282).

The opiates mediate one of the simplest forms of learning, habituation, although the findings are conflicting. Two species

of crabs responded differentially to opiate modulation, with one species having habituation inhibited by morphine and facilitated by naloxone and the other species being unresponsive to either (513). Antagonists including naloxone, CTOP, nor-binaltorphimine, and a combination of CTOP and nor-binaltorphimine all failed to alter habituation, but naloxone and nor-binaltorphimine increased dishabituation produced by presentation of a novel stimulus after habituation to the original one (475), indicating a slight role for the endogenous opiates in the response, although its nature was unclear. The response to a novel stimulus changed expression of dynorphin B in the hippocampus, with the direction of the change depending on the strain of rat. Apomorphine-susceptible animals had a decrease in the peptide, but unsusceptible ones had an increase (95). The response of dynorphin B to two-way avoidance was greater in the unsusceptible ones (95), thus providing additional evidence for an interaction between the opiate system and dopamine in learning tasks.

CARDIOVASCULAR RESPONSES

Interest in the possible role of the opiate system in cardiovascular functioning has been high, but in 1993 it decreased somewhat. This may be, in part, due to the lack of consistency in previous work, thus allowing few generalizations to be drawn. The cardiovascular responses to opiate mediation are highly susceptible to influence from experimental manipulations, as well as the response being measured, contributing to the conflicting results. In early studies, it appeared that whether the animal was conscious or anesthetized was crucial, but that variable cannot account for all the discrepancies currently being observed. Mean arterial pressure was raised by Met-enkephalin, but when acute hypotension was induced by isoproterenol or sodium nitroprusside, the enkephalin produced a depressor effect, indicating that hemodynamic responses to the peptide can be altered by acute manipulation of blood pressure (181). To some extent, the receptor type that was activated was important. The μ agonists tended to reduce blood pressure, although not without exception. Morphine (36,100,119,414), DAMGO (119,414), PLO17 (336), alfentanil (226), and remifentanil (226) lowered it in some situations, but hydromorphone (402) and morphine (100) raised it, and dermorphin had no effect (272). The single pressor effect by morphine was in spinal rats and was only transient (100), so that specialized conditions were required. Increased blood pressure by hydromorphone was observed in humans who were substance abusers (402), also an atypical population for this kind of study.

Inconsistent cardiovascular responses also were found after administration of κ agonists, with about half of the studies reporting hypotension and the other half finding no effect. Among those producing a depressor effect were dynorphin(1–17) (141,541), dynorphin(1–8) (541), dynorphin(1–13) (541), U50,488 (414,541), 66A-078 (336), PD 129290 (404), and ICI 196967 (540). In other situations, some of those same agents, including U50,488 (119,271), dynorphin(1–13) (139), and dynorphin(1–17) (139), as well as others, such as dynorphin(2–17) (139) and dynorphin B (541), had no effect. The site of injection affected the results, with ICV administration of U50,488 not altering blood pressure (119,271), but IV injection (414) or microinjection into the hippocampus (541) reducing it. Likewise, ICV administration of dynorphin(1–13) or −(1–17) reduced blood pressure (141), but microinjection of them into the nucleus of the solitary tract had no effect (139).

Similarly, the effects of the δ agonists were highly variable, producing hypotension (23) or not changing after DADLE (517) and producing hypertension after DPDPE (414). DADLE raised systolic pressure when administered to epicardial ganglia (23) but had no effect when microinjected into the supraoptic nucleus or paraventricular nucleus (517), so that the site of injection was crucial for these agonists, too. The mixed agonist/antagonist pentazocine also had a pressor effect (402). Vagotomy did not affect the rise in blood pressure due to DPDPE or decreased pressure due to U50,488, but it did attenuate the hypotension caused by morphine or DAMGO (414), suggesting that the vagus interacted with μ agonists. However, vagotomy did not block the ability of naloxone to reverse all cardiovascular effects of acute morphine, and even produce an overshoot, suggesting withdrawal (36). The reduction in mean arterial pressure by the μ agonist PLO17 or the κ agonist 66A-078 was suppressed by cholecystokinin-8, and its antagonist reversed the effect (541), indicating an interaction of the opiate system with cholecystokinin-8.

There were inconsistent changes in blood pressure after administration of opiate antagonists as well, with specific manipulations probably being responsible. Naloxone produced hypertension in some situations (36,100,247) or had no effect in others (247). Naloxone and naloxone methobromide raised it when injected IV, suggesting that their action occurred at peripheral sites, because naloxone methobromide crosses the blood–brain barrier little, if at all (247), but close-arterial injection of either into the hindquarter vasculature did not affect blood pressure, calling that conclusion into question (247). Although naloxone alone produced a small rise in mean arterial pressure, naloxone-precipitated withdrawal from morphine induced a large one (100), so that the cardiovascular system is highly sensitive to opiate manipulation. The results were the same for nor-binaltorphimine, increasing blood pressure when given to unanesthetized piglets (360) and not when injected into the hippocampal formation of rats (541). At doses used in treatment of autistics, naltrexone had no effect on blood pressure, indicating that it has no cardiovascular side effects to worry about (25).

Similar results were reported for opiate modulation of heart rate, although changes in blood pressure are not always correlated with those in heart rate. Opposite effects were found for Met-enkephalin, depending on cardiovascular state, with the peptide increasing heart rate under normal conditions but reducing it when the animal is experiencing induced hypotension (181). Morphine produced bradycardia in most cases (100,119,414), as did DAMGO (119,414), but the direction of the response varied with morphine depending on dose, because tachycardia occurred at some doses (119). An increase in heart rate was also seen after hydromorphone (402), but dermorphin did not affect the action, except on the fourth day of chronic administration, when it speeded up (272). Remifentanil and alfentanil decreased the pulse rate (226).

Various κ agonists had differential effects on heart rate as well. U50,488 reduced it when given IV (414) or into the hippocampal formation (541) but had no effect after ICV administration (119,271). Bradycardia occurred after ICV injection of dynorphin(1–8), -(1–13), or -(1–17) (541) under normal conditions, but the latter did not alter heart rate when given centrally during hemorrhage-induced hypotension (139,141). During hemorrhage, dynorphin(1–13) also was inactive (141), but after hemorrhage it increased heart rate (139), as did dynorphin(2–17) (139). Dynorphin B, however, did not affect it (541), so that dynorphins may play a complex role in the regulation of cardiovascular temporal homeostasis. The κ agonist PD 129289 slowed heart rate (404), but ICI 196967 had no effect (540), so that no logical generalizations could be drawn concerning the action of the κ agonists on this response.

Similar findings occurred with δ agonists. Microinjection of DADLE into the supraoptic nucleus or paraventricular nucleus had no effect on heart rate (517), but DPDPE reduced it (414). The effects of DPDPE and of U50,488 were not altered by vagotomy, but the lesion attenuated the bradycardia produced by morphine or DAMGO (414), suggesting that the vagus nerve played a role in the effect of the μ agonists. The mixed agonist/antagonist pentazocine increased heart rate, and the effect was partially reversed by naltrexone, so that the effect was probably opiate in nature (402).

Naloxone had no effect on heart rate by itself (25), but in morphine-dependent rats, it precipitated withdrawal, which produced a biphasic response of heart rate, first reducing it, then speeding it up (100). Naltrexone alone had no effect on heart rate after microinjection into the hippocampus of rats, but it blocked the bradycardia of U50,488 (541). The antagonist produced tachycardia in piglets (361), however, perhaps due to species differences.

The opiate system may mediate rhythmicity as well as pacing of heart beat; the κ agonist PD 129290 induced arrhythmia in both the isolated rat heart and in intact rats (404). Electrical stimulation of the vagus produced arrhythmia that was reduced or completely alleviated by injection of Met-enkephalin (383). Epinephrine-stimulated arrhythmia was facilitated by the κ agonist ethylketocyclazocine (411) and was inhibited by the μ agonists morphine and morphiceptin (410), indicating both kinds of receptors can be involved in it.

Another cardiovascular response that appears to have opiate mediation is blood flow. Morphine reduced neurohypophyseal blood flow at doses not affecting blood pressure (225), so that the two measures are not completely correlated. Both remifentanil and alfentanil also decreased blood flow to the cortex, hippocampus, and caudate, but this occurred at doses that also reduced blood pressure and heart rate (226). Naloxone, however, did not alter cerebral blood flow in patients with complex partial seizures, as measured with PET (502), so that the role of the endogenous opiate system here is not clear. Because naloxone did increase blood flow to the stomach, small intestines, colon, and spleen, as well as renal and coronary blood flow during endotoxin shock (129), it may be that the opiate system might mediate blood flow only under stress. These effects were attenuated by the β-adrenergic blocker propranolol (129), thus indicating an interaction between β-adrenergic and opiate actions. However, renal blood flow was not affected by dermorphin (272), suggesting that the μ receptors were not involved in that response.

During hypotension induced by acute hemorrhage, the opiate system might play a role, because concentrations of preproenkephalin in the CNS changed during it (140). Dynorphin(1–17) administered ICV during hemorrhage exacerbated the decrease in blood pressure and slowed recovery of cardiovascular functions (141), but dynorphin(1–13) attenuated recovery only of stroke volume, not affecting heart rate or cardiac output (141). When given before hemorrhage into the nucleus ambiguus, dynorphin(1–17) and -(2–17) produced a transient further suppression of blood pressure, but U50,488 did not alter it at all (445). After hemorrhage, injection of dynorphin(1–13) or -(1–17) into the nucleus of the solitary tract had no effect on cardiovascular measures, except for an increase in heart rate dynorphin(1–13) (139). It appears that a form of dynorphin is involved in responses to hemorrhage, but the differential effects of the fragments tested leave an unclear picture. Naloxone produced a pressor effect (247) during hemorrhage and reduced tissue damage resulting from reperfusion after hemorrhage (11), suggesting that the endogenous opiate system might play a deleterious role in the effects of acute bleeding.

Changes in the opiate system have been reported to correlate with cardiovascular activity. Diurnal increases in plasma β-endorphin immunoreactivity peaked at the same time as the highest heart rate occurred in horses (202), suggesting that the peptide might mediate the response. There was, however, no change in plasma dynorphin in hypertensive patients given clonidine, even though both heart rate and blood pressure declined (211). In patients undergoing hemodialysis, there was an increase in plasma β-endorphin during the first stage of isolated ultrafiltration and then a subsequent decrease in it in the second stage of isovolemic bicarbonate hemodialysis (212). It was suggested that the rise was analogous to that in animals with hypovolemic shock and that the drop in it might have been due to a negative feedback effect of the endorphin on its own release (212). During hemorrhage in rats there was an increase in preproenkephalin in the midbrain and spinal cord, but that in the brain stem was decreased (140), providing additional evidence that the opiate system might be involved in cardiovascular activity. Binding of DPDPE in the amygdala was greater in spontaneously hypertensive rats than in normals, but in other areas, such as the hippocampus, hypothalamus, corpus striatum, midbrain, cortex, pons, medulla, and spinal cord, there was no difference. It was not clear if the binding in the amygdala was related to the increased blood pressure in the genetically disposed rats, however, because the number of sites but not their affinity was greater (53).

RESPIRATION AND THERMOREGULATION

There has not been much interest in the possible role of the opiate system in the modulation of respiration and thermoregulation in recent years, and that was true in 1993, as well. The well-known clinical finding that opiate agonists depress respiration was confirmed by the findings that morphine (30,36,119,374), DAMGO (119), other μ ligands, including dermorphin (384), hydromorphone (402), and sufentanil (439), Met-enkephalin (355), and the κ agonist ICI 196967 (540) suppressed ventilatory function, although ICI 196967 did so only at high doses (540). In addition, because U50,488 did not alter respiration when administered alone, but did reverse the depression of DAMGO and morphine (119), it has been assumed that the κ receptors do not have primary effects on the response, but the μ receptors do. Microinjection of the δ agonist into either the supraoptic nucleus or the paraventricular nucleus failed to alter ventilation (517), so that either those sites or the δ receptors, or both, are not involved in regulation of respiration.

Opiate agonists depress the ventilatory response to CO_2 (152), with morphine producing a long-lasting suppression of it that does not change with age in children (374), even when it is given IT (30,374), a route previously reporting to have no effect. The opiate system appears to interact with other agents in its action on respiration, because the depression by dermorphin was antagonized not only by naloxone, but also by the benzodiazepine antagonist flumazenil. The effect of the benzodiazepine agonist alprazolam depended on dose, with a small dose potentiating the suppression of dermorphin, but a larger dose reversing it. The benzodiazepine/GABA receptor complex, therefore, modulated the respiratory depression of μ agonists (384). Pretreatment with nimodipine, a Ca^{2+} antagonist, potentiated the effect of sufentanil (439), and Met-enkephalin inhibited the serotonin-induced respiratory rhythm in a mollusc (*Lymnaea stagnalis*) (355), indicating opiate interaction with those actions in ventilation.

In general, the opiate antagonists produced opposite results to those of the agonists, especially the μ antagonists. Naloxone

(12,36,152,440,514,543) and naltrexone (145,361) facilitated respiration in a variety of situations. Antagonists of other receptor types did not affect respiration, because the δ antagonist naltrindole (361) and the κ antagonist nor-binaltorphimine (360) did not after respiratory frequency in piglets.

Naloxone increased the ventilatory responses to hypoxic progressive hypercapnia in normal individuals (12,152,543), but was ineffective in diabetics, with or without accompanying autonomic neuropathy. It appeared, therefore, that the ventilatory response itself was impaired in diabetics (543). Naltrexone reduced hypoxic events and improved blood gas patterns in patients with obstructive sleep apnea syndrome, and its effects were correlated with sleep patterns, indicating a role for the endogenous opiate system in this disorder (145). Age appeared to be a crucial factor, because naloxone consistently improved the ventilatory response to CO_2 in infants, but produced conflicting results in adults, sometimes stimulating and at other times not affecting breathing (152). Similarly, in animals, the effectiveness of naltrexone decreased with age (361).

Naloxone potentiated responsiveness to acetylcholine or physostigmine, either of which increased the activity of CO_2-sensitive neurons in the ventral medullary surface (514). The antagonist also increased responsiveness to H^+ ion superfusion, suggesting that the opiate system might be involved in the central regulation of respiration by interaction with CO_2-sensitive cholinergic structures in that area of the brain (514). Activation of Ca^{2+} channels may elicit release of endogenous opiate peptides in medullary respiration-related structures, because naloxone reversed the ventilatory depression produced by the Ca^{2+} agonist Bay K8644 and its enantiomer Bay R5417 (440). In naloxone-precipitated withdrawal from acute morphine, the antagonist reduced the inspiratory phase (36), thus demonstrating facilitation of respiration.

The opposite of the typical findings was reported in fetal lambs, with both morphine (84) and the δ agonist [D-Ala^2]deltorphin (83,84) stimulating fetal breathing. Naloxonazine, a highly specific μ_1 antagonist, or naltrindole, a δ antagonist, alone suppressed it, and they inhibited the increases of morphine (84) or [D-Ala^2]deltorphin (83,84), respectively. At high doses, naloxonazine also blocked the effect of[D-Ala^2]deltorphin, so that it loses receptor specificity at higher doses (83). Thus, the endogenous opiate system appears to play a tonic role at both the μ_1 and δ receptors in the control of breathing, at least in the fetus.

Increases in the concentrations of opiate peptides that occurred with respiratory difficulties provide additional evidence for the involvement of the opiate system in ventilation. Activation of the endogenous opiates was reported during intense inspiratory flow-resistive loading, with opiate mediation varying with the degree of acidosis, as measured by lactic acid (393). More specifically, resistive loading increased plasma β-endorphin in normals, but not in diabetics (544). Although hypoxia itself did not raise CSF β-endorphin in children with apnea or in victims of Sudden Infant Death Syndrome, there was a higher than normal baseline concentration of β-endorphin, suggesting that the increase was of etiological significance to the disorders and not secondary to the hypoxia (489). In distressed, mechanically ventilated neonates during the first 3 days of life, plasma β-endorphin was higher than in normals, but it dropped after the start of morphine, suggesting that such infants should be given adequate analgesia without concern for respiratory effects (399). There was one conflicting report, however, that found an increase in plasma β-endorphin with a decrease in apneas when infants with apnea of prematurity were given xanthine, indicating a negative correlation between the peptide and respiratory difficulty. No change in β-endorphin occurred in those infants not responding to the xanthine treatment and, thus, continuing to have apnea (447). No explanation for the discrepancy was given.

Regulation of body temperature by the opiate system has also been studied, and much of the work from 1993 indicated that the opiate agonists reduce temperature. Both μ and κ receptors seem to be involved, because morphine (60,171) and U50,488 (50,51,54,73,508,509) lowered it. DADLE, however, had no effect (517), leading to rejection of the idea of involvement of the δ receptors in this response. Morphine was reported to have a biphasic effect, first decreasing, then increasing temperature (60). This may account for the conflicting findings of hyperthermia after morphine (50,52,314), because the measures might have occurred during the second phase. Although U50,488 did not after body temperature in one study, it did block the hypothermia induced by cerebral ischemia (245), suggesting a role for the κ receptors in thermoregulation. Dynorphin(1–13), however, had no effect in mice subjected to ischemia or sham operated (244), so that different receptor subtypes might be involved. Traumatic brain injury interfered with the ability of morphine to increase brain temperature, but the peptide did raise it in uninjured animals (314).

Numerous other variables affected the thermoregulatory effects of the opiates. The NMDA antagonist MK-801, when given daily with chronic morphine, inhibited the development of tolerance to the analgesia effects of the opiate but not to its hyperthermic effects (50), indicating a dissociation of those actions. The hypothermia and analgesia of U50,488, however, was blocked by MK-801 (508), suggesting an interaction between the κ and NMDA receptors. Nitric oxide also influenced opiate mediation of temperature, with the nitric oxide synthase inhibitor N^G-monomethyl-L-arginine attenuating the development of tolerance to the hypothermia of U50,488 in rats (509), but not in mice (51). The decrease in temperature of U50,488 was also blocked by thyrotropin-releasing hormone (54), and because the hormone did not affect binding of morphine or β-endorphin, there was probably an interaction between it and the κ receptors (54).

The physiological changes of pregnancy potentiated morphine-induced hypothermia, with the greatest drop seen at the day before parturition. During pregnancy, the animal was slower to recover from the hypothermia, but on the day after parturition, recovery occurred faster than in controls (171), providing additional evidence for opiate interactions with other systems. Saccharin enhanced the hypothermic effect of morphine and attenuated its hyperthermic phase, supporting the view that sweet substances influence the endogenous opiate system (60).

The opiate antagonists had small effects, at best, on body temperature. Naltrexone had no effect on thermoregulation in autistic children (25) or in rat pups (73), but chronic naltrexone enhanced the hyperthermic response to morphine, probably due to an upregulation of receptors in all brain regions and the spinal cord (52). The drop in temperature after administration of calcium was blocked by nor-binaltorphimine, but not by naloxone nor naltrindole (473), and the decrease after calcitonin gene-related peptide was inhibited by all three antagonists (473), suggesting an interaction between the opiate system and those substances.

There was increased μ binding in the frontal cortex during ethanol-induced hypothermia in mice selectively bred for high, but not low, sensitivity to the heat change, so that μ pathways may be involved in mediating differential hypothermic responsiveness of strains (492). In men submersed in cold water, however, there was no relationship between core temperature and plasma β-endorphin (183), indicating that the opiate system

probably does not play a role in temperature changes in this situation.

SEIZURES AND OTHER NEUROLOGICAL DISORDERS

Previous demonstrations of involvement of the endogenous opiates in seizure activity were confirmed in 1993, with the μ agonists tending to have proconvulsive and the κ agonists having anticonvulsive action. The μ agonists, including morphine (277), its metabolite M3G (164), and C-diprenorphine (39), produced seizure activity when administered, as did the δ agonist BW373U86 (93) and Met-enkephalin (498). Absence seizures precipitated by hyperventilation and C-diprenorphine were seen in patients with primary generalized epilepsy, using PET procedures (39). In patients undergoing surgery, within 3 min of the injection of morphine, epileptiform brain wave activity similar to that of benign epilepsy was seen. With increasing serum concentrations of the opiate, the number of spike discharges initially increased and then decreased (277), so that their relevance to patient welfare was not clear. In rats, a low dose of M3G injected ICV produced seizures that were attenuated by the NMDA antagonists MK-801 or CPP. It was not clear if this reflected an interaction between the opiate system and NMDA receptors, however, because naloxone did not affect the seizures, indicating that it might not be an opiate action (164).

Brief, nonlethal convulsions were produced by BW373U86 in mice, and the μ antagonist naltrexone or the δ antagonist naltrindole reduced them, indicating opiate control. A single injection diminished its capacity to produce a second seizure, even up to 2 weeks later (93), suggesting possible tolerance to its effect. Administration of Met-enkephalin into the amygdala produced kindling in rats, characterized in part by wet-dog shakes (498). Electrical kindling of the amygdala produced a similar response, as did a combination of the two, although when the enkephalin was involved the wet-dog shakes dropped out sooner than when it was absent (498). However, protease inhibitors that prevent the degradation of Met-enkephalin reduced the incidence and intensity of seizures in seizure-susceptible mice, indicating an anticonvulsant effect (294). The finding that cerebral concentrations of the enkephalin increased after the protease inhibitors suggests that it was the rise in enkephalin that was responsible for the decrease in seizures (294). This action might be different in this particular strain, as opposed to others, accounting for the convergent results.

Seizures induced by picrotoxin were potentiated by morphine (503,504), and the effect was blocked by naloxone (504), suggesting opiate receptor involvement. Naloxone alone reduced the duration of postseizure immobility after picrotoxin but did not have any effect on the development of tolerance to the proconvulsant agent (505). The endogenous antiopiate Tyr-MIF-1 inhibited morphine-induced lengthening of the duration of postseizure akinesias but potentiated morphine's increase in the number of focal seizure episodes, indicating that the opiate action may depend on the type of seizure (504). Conversely, seizure activity altered the potency of morphine analgesia, facilitating it, suggesting a change in opiate mechanisms after experience with convulsions (503).

Support for the anticonvulsant action of the κ receptors came from the finding that an analogue of U50,488, U-544944A, inhibited seizures in the maximal electroshock seizure test and with electrical stimulation of the hippocampus, although at high doses U-544944A did increase pentylenetetrazol-induced seizures (149). The type of seizure, therefore, was important with the κ agonist, as it was with morphine. Dynorphin or dynorphin(2–13) inhibited epileptiform activity produced by continuous perfusion of penicillin or bicuculline into hippocampal slices from guinea pigs (364). It was not clear whether the action was opiate or not, because it was not blocked by naloxone, and naloxone alone had a similar antiepileptic effect (364).

The pentylenetetrazol-induced seizures that did not respond to κ agonist manipulation were altered by β-endorphin, with the direction of the effect depending on the phase in the circadian rhythm. The peptide had a proconvulsant action in the day and an anticonvulsant action at night, possibly due to an interaction with dopamine (553). Plasma β-endorphin was elevated in patients with status epilepticus, but there was no difference in concentrations between those with a good prognosis and those with a bad one (69). Findings with blood β-endorphin did not always correlate with those of CSF β-endorphin (69), because CSF levels decreased at interictal and postictal times with complex partial seizures and generalized tonic–clonic seizures (112).

Concentrations of Met-enkephalin were not affected by seizures, except after generalized tonic–clonic ones, when they doubled their normal values (112). In the hippocampus, concentrations of Met-enkephalin (229), Leu-enkephalin (217), and dynorphin (217,229) decreased after seizures, whether produced by kainic acid (229), electroconvulsive shock (229), or the NMDA agonist glutamate (217). After the decline, there was a rebound above the normal level, with the amount of rebound depending on the kind of kindling (217,229). There was also an increase in preproenkephalin mRNA in the hippocampus after glutamate-induced seizures (217), as well as those produced by escalating doses of cocaine (216). The latter raised preprodynorphin mRNA, too (216), further indicating involvement of the opiate system in epileptic activity.

Additional support for that idea came from the report of increased μ binding after amygdala kindling (429) and C-diprenorphine-induced seizures (159). Enhanced binding occurred primarily in portions of the cortex, amygdala, caudate putamen, central gray, thalamus, and substantia nigra (429). Nearly a month later, however, lower than normal binding occurred in some areas (429). After seizures induced by C-diprenorphine, μ binding in the cortex increased, but because overall binding remained the same, non-μ binding, primarily κ, decreased. This might help explain the findings of anticonvulsant properties of κ agonists (159).

In 1993, as in past years, there were investigations into the role of the opiate system in brain injury. No clear-cut pattern emerged, although it appeared that the opiates do affect recovery. Both agonists and antagonists reduced deficits. Morphine before the injury provided some protection (314), but so did naloxone when given after the injury (333). In the past, typical findings indicated that κ agonists, especially dynorphin, acted in an opposite way, potentiating deficits, and in 1993 support for that idea came from the report that the κ antagonist nalmefene facilitated recovery (138). However, U50,488 given twice, both before and after spinal cord injury, also improved recovery by decreasing vascular permeability and edema (409), so that the function of the κ receptors in traumatic CNS injury is not understood at this time. Perhaps the timing of the administration is crucial.

Findings from previous years about the deleterious effect of dynorphin on motor function were confirmed with the report that IT injection of dynorphin(1–13) or -(1–17) produced reversible hindlimb paralysis in rats (408). The animal model of tardive dyskinesia, giving chronic fluphenazine, was not affected by DAMGO, DPDPE, or U50,488, suggesting none of the three major opiate receptor types mediated it (488), but naloxone potently suppressed it, so that the opiate system might play a role in it after all (488). The discrepancy may be due to the route of

administration of the drugs, with the agonists being given ICV and the antagonist SC, indicating a possible peripheral mediation of the disorder.

Although there was no change in Met-enkephalin in the striatum and its efferent system in patients with Parkinson's disease (242) and although the synthetic dynorphin spiradoline had no effect on motor performance in such patients (180), PET studies revealed decreased binding of ^{18}F-cyclofox, an analogue of naltrexone that binds to μ and κ receptors in a primate model of Parkinson's disease (120), so that there may be an alteration of the opiate system in the disease. Whether that change is a cause or result of the disease remains to be determined.

Their role in cerebral ischemia has also been studied, with equally confusing findings. The κ agonist enadoline afforded neuroprotection when given both before and after the ischemia, reducing the volume of infarction and brain swelling (210). Pretreatment with either dynorphin(1–13) (244) or U50,488 (245) prevented impairment of memory due to cerebral ischemia, as measured by spontaneous recovery, transfer, and step-through latency. The κ antagonist nalmefene, however, also protected against ischemic events, reducing glutamate release (190). Although binding of [^{3}H]naloxone (367,389) or [^{3}H]diprenorphine (389) in the hippocampus increased due to forebrain ischemia in gerbils, neither damage to pyramidal cells nor the change in binding was affected by pretreatment or subsequent injection of any of the agonists or antagonists tested, including morphine, diprenorphine, dextromethorphan, U50,488, U54,494A, naloxone, and naltrexone (389), leading to questions concerning the part the opiates play in ischemia.

There might be involvement of the opiate system in Alzheimer's disease, because some changes in opiate binding in the brain were seen in patients with the disorder. The amount of influence it has and the nature of its role in the disease, however, remain to be determined. There was a loss of δ binding sites in the hippocampus (248) and putamen (37,87) of Alzheimer's patients, as well as a decrease in κ receptors in the putamen (37,87), although κ binding increased in the amygdala of the patients (37). Binding for μ agonists was unchanged (37,87), but that for [^{3}H]Met- or [^{3}H]Leu-enkephalin decreased in almost all brain areas studied (422). No alteration in CSF β-endorphin immunoreactivity occurred in Alzheimer's disease (131), but there were increases in dynorphin and prodynorphin mRNA in the hippocampus of the aged, with the greatest changes seen in those with the greatest learning deficits (168).

There has been interest in the possible mediation of headache by the endogenous opiates. In patients with cluster headache, either in a cluster period or in remission, there was a decrease in β-endorphin in peripheral blood, and the persistence of this abnormal level even during pain-free periods suggests a primary alteration in the regulation of the peptide in patients with the disorder (302). Tension headache appears to involve an upregulation of the opiate system, because the second exteroceptive suppression period of the temporal muscle is chronically attenuated or abolished in headache patients and its inhibition is partially blocked by naloxone, so opiate receptors in this circuitry are hyperactive in tension headache (435). The response of immune cells to Met-enkephalin was not different between groups of normals and of sufferers of migraine headache, either during or not during an attack, but there were small differences within individuals during an attack or during a pain-free period (359), suggesting that the peptide may have an indirect role in the pathogenesis of migraine.

ELECTRICAL-RELATED ACTIVITY

The opiate agonists exert much control over neural activity, and interest in determining the nature of that regulation remained high in 1993. Among the concerns are the specific actions of particular agonists on brain activity, as measured by cortical electroencephalographic (EEG) techniques and their changes in the potentials of neurons or pathways. Also receiving some attention was the role of the opiate system in sleep. In general, the opiate peptides inhibited neuronal excitability, with many producing hyperpolarization of the cell membrane, although exceptions occurred, with some peptides producing facilitation in many cases.

Morphine had a biphasic effect with EEG measures, first producing high-wave, slow-wave bursts associated with behavioral stupor and then induced EEG and behavioral excitation, before producing slow-wave sleep (330,483), with the latency to slow-wave sleep being increased (330,483). In the stuporous stage, there was an increase in spectral power in the 1–10 Hz range after morphine (483). The δ agonist DPDPE inhibited the excitatory phase, and the δ antagonist DALCE attenuated the change in spectral power by morphine and the effects of DPDPE on morphine-induced changes, suggesting modulation of morphine by δ receptors (483). The alterations in spectral power were strain dependent, being greater in Lewis rats than in Fischer 344 rats (330), indicating the importance of genetic variables in these effects.

In fetal lambs, morphine increased EEG activity, and this action was reversed by naloxonazine, so that the μ_1 receptors were apparently mediating it (84). In humans, at doses of morphine that impaired cognitive abilities involving processing serially presented information, there was no change in EEG pattern, so that behavioral and electrical measures did not correlate (88). Chronic morphine in rats reduced total spectral power in rats, with those self-administering it decreasing the activity more than in yoked rats receiving the same amount of morphine. In both groups there was also a disruption of diurnal and ultradiurnal rhythms in EEG total power (192).

Morphine increased the spontaneous firing of a majority of neurons in the nucleus accumbens in rats (86,137), shortening the duration of accumbens-evoked, short-latency excitation and attenuating the magnitude of long-latency inhibition (86). It also inhibited responses to ventral pallidum projection neurons (86,137). The responses were reversed by naloxone or by the GABA agonist bicuculline, suggesting an opiate by GABA interaction in the ventral–striatopallidal pathway (86).

Inconsistent findings for the effect of morphine on neurons in were reported, with the agonist producing a decrease in normal activity in some cases (191,467) but higher spontaneous firing rates and greater morphine-induced increases to 8-bromo-cyclic AMP in another (196). In morphine-dependent animals, morphine had no effect (191) and the potentiation of the opiate response by forskolin was attenuated (467). The action of morphine in this structure, therefore, and its interaction with cAMP remain to be determined.

Morphine inhibited spontaneous electrical activity of oxytocin-secreting neurons in the rat supraoptic nucleus (406,407), reducing plasma oxytocin (407). This effect was inhibited by administration of pertussis toxin (406) or by stimulation of the anterior or ventral areas of the third ventricle (407), so that opiate mediation of oxytocin neurons may be complex. Modulation of phrenic nerve discharge amplitude also occurs after morphine, and the decrease is reversed by naloxone (36), suggesting splanchnic sympathetic regulation by the opiate.

DAMGO, like morphine, had variable results, increasing primary population spike amplitude of CA1 pyramidal cells in the rat hippocampus in a naltrexone- but not naltrindole-reversible way (545), suggesting μ mediation. Recordings from the dentate granule cells in the rat hippocampus, however, demonstrated

hyperpolarization, and the peptide reduced synaptic potentials mediated by GABA at both $GABA_A$ and GABAB receptors (397). Similarly, DAMGO inhibited most neurons in the nucleus tractus solitarius of the rat and reduced GABA-mediated evoked potentials, effects that were attenuated by naloxone (418), further indicating μ action. Likewise, the μ agonist hyperpolarized nonbursting LTS (low threshold Ca^{2+} spike) and non-LTS cells in the guinea pig paraventricular nucleus (273). In dorsal root ganglion cell bodies, there were Ca^{2+} currents that varied dramatically to DAMGO, with the variability possibly being related to differences in sensory modality among the ganglion neurons or possibly being an artifact (456).

The κ agonist U50,488 primarily had an inhibitory effect on electrical responses, producing occasional high-voltage EEG slow-wave bursts associated with an increase in spectral power in the 2.5–7.5 Hz band (559). It also suppressed spontaneous activity of the supraoptic oxytocin neurons (406) and their activation evoked by stimulation of areas around the third ventricle (407), as morphine did. Unlike morphine, the attenuation of spontaneous activity by U50,488 was not reversed by pertussis toxin (406), and the activity of some oxytocin neurons was stimulated by the κ agonist (407). Tolerance to morphine did not affect the action of U50,488 in this situation (407). The nicotinic transmission in superior cervical ganglia was depressed by the κ peptide; however, μ or δ antagonists, but not a κ antagonist, inhibited the effect (562), so that the κ receptors might not have mediated the response. In presynaptic calyciform nerve terminals of chick ciliary ganglia, U50,488 produced hyperpolarization, with an apparent increase in input resistance, but it inhibited spontaneously occurring miniature hyperpolarization in the terminals, which was considered to be due to a Ca^{2+}-dependent K^+ conductance. This effect was abolished by the κ_1 antagonist nor-binaltorphimine, so that the action at this site probably was mediated by κ receptors (150).

Dynorphin in the nucleus tractus solitarius of the rat hyperpolarized most of the neurons tested, associated with the activation of K^+ conductance, although the $\kappa 1$ agonist U69593 had no effect (418). Stimulation of the dynorphin-containing dentate granule cells in the guinea pig hippocampus released dynorphin, which activated the κ_1 receptors there, and this activation reduced excitatory transmission. In addition, released dynorphin blocked induction of long-term potentiation at granule cell–perforant path synapses, suggesting endogenous dynorphin can function as a retrograde, inhibitory transmitter (537). The role of the κ_1 receptor, clearly, remains to be determined.

The role of the δ receptors is equally confusing, as indicated by studies with DPDPE. The peptide increased EEG activity in fetal lambs, but the effect was not altered by the δ antagonist naltrindole and was reversed by the μ_1 antagonist naloxonazine (84). In rats DPDPE increased total spectral power and high-voltage bursts (483), but it also suppressed the EEG and behavioral excitation of morphine and was, itself, attenuated by the δ antagonist DPDPE (483). The agonist had differential effects on different pathways, increasing spike amplitude in CA1 pyramidal cells, where the predominant receptor subtype is δ_1. The effect was antagonized by naltrindole, supporting the involvement of δ_1 receptors (545). Increases in the concentrations of DOPAC and DOPA in the nucleus accumbens and median eminence after administration of DPDPE and its blockage by naltrindole demonstrated activation of dopaminergic neurons that was probably mediated by δ receptors (323). In dentate granule cells (397) and in superior cervical ganglia (562), however, DPDPE produced hyperpolarization, and it had no effect on neurons in the nucleus tractus solitarius (418),

Administration of DADLE to epicardial ganglia increased spontaneous neural activity, but systemic injection produced no effect (23), so that the effect was site specific. The peptide also increased primary and secondary population spike potentials in CA1 pyramidal cells. Because the action was reversed by naltrexone, the highly specific μ receptor (545), the role of the δ receptors in that situation must be questioned. Support for that view came from the finding that the δ agonist DSLET also raised the spike amplitudes, but its action was not reversed by either naltrindole or another δ antagonist ICI174,864 but was inhibited by naltrexone (545).

Deltorphin reduced the frequency of hippocampal electrical activity and the rhythmicity of electrical patterns in stress in rabbits (154), indicating an inhibitory effect for the δ peptide in this situation. Its D-Ala^2 analogue, however, had no effect on activity either in the nucleus tractus solitarius (418) or in the CA1 pyramidal cells (545), suggesting that the δ_2 receptors do not play a role in electrical activity in those areas and thus,indirectly supporting the idea that it is the δ_1 receptors that are important for it.

Leu-enkephalin did increase electrical activity in the CA1 pyramidal cells (545), but it or [D-Ala^2]Leu-enkephalin produced slow depolarization not associated with significant conductance increase in the metacerebral giant cell in the marine mollusc *Aplysia californica*, where it appeared to act by stimulating adenylate cyclase through the production of cAMP (278). When injected into the arterial supply of the superior cervical ganglia, Leu-enkephalin reduced postganglionic compound action potentials evoked by a test shock to the cervical sympathetic trunk of cats (563), indicating that the enkephalin had an inhibitory effect. The action was antagonized by naloxone, so that the receptors involved were not clear (563).

As with other peptides, the action of Met-enkephalin depended on the specific conditions being studied. The enkephalin increased input conductance in the locus coeruleus, and the effect was almost totally abolished by a combination of sodium substitution and extracellular Ba^{2+}. It was concluded that the opiate response in this area opened K^+ channels and suppressed resting Na^+-dependent inward conductance (17). Met-enkephalin also facilitated nonrectifying electrical coupling respiratory neurons in *Helix pomantia* and coupling between serotonin-containing ciliomotoneurons in *Lymnaea stagnalis*, so that the enkephalin may be involved in coordination of motor patterns (128). On isolated CNS neurons, the peptide produced a very weak hyperpolarization or depolarization in *Lymnaea stagnalis* (355) and inhibited serotonin-induced respiratory rhythms temporarily, before later slowing the oscillations of the membrane potentials (355). In the dentate granule cell, Met-enkephalin produced hyperpolarization of most cells, and the effect was potentiated by the enkephalinase inhibitor thiorphan or the animopeptidase inhibitor bestatin and was attenuated by the μ antagonist CTOP or the δ agonist ICI174,864 (397). It also reduced synaptic potentials mediated by GABA (397), thus indicating an interaction between the opiate and GABA systems for that response.

The μ agonist morphiceptin inhibited nicotinic transmission in the superior cervical ganglion of the cat, and the effect was reversed by ICI174,864 or the μ antagonists naloxone or CTAP (562), suggesting μ mediation of the response. A stimulus train to those same axons also depressed their activity, and the inhibition was blocked by naloxone (562), so that action also was probably modified by μ receptors. In the locus coeruleus, buprenorphine reduced normal electrical activity, and repeated presentations of the opiate produced tolerance (191). Alfentalil, however, did not affect EEG measures, even at doses that impaired cognitive ability (88). The κ agonist ICI196967 reduced

renal sympathetic nerve activity (540), but U69593 had no effect on neurons in the nucleus tractus solitarius (418). Heroin increased activity of the dopamine cells but decreased activity of the nondopamine cells in the ventral tegmental area, indicating a dopamine and opiate interaction (564). In support of that, in rats self-administering heroin, dopamine-related electrochemical signals increased after the first injection each day, but subsequent injections produced biphasic effects, first suppressing and then stimulating the neural activity. In rats yoked to them but not determining the administration themselves, there was a similar but weaker effect (291).

More specifically, the action of the opiates on excitatory or inhibitory postsynaptic potentials (EPSPs or IPSPs) in different areas of the brain has been primarily inhibitory in nature. In the dentate granule cells of the hippocampus, dynorphin reduced excitatory transmission as shown by a decrease in EPSPs evoked by stimulation of the perforant path (537). Both DSLET and DAMGO suppressed orthodromically stimulated IPSPs in the CA1 pyramidal cells of the hippocampus (545), and both Met-enkephalin and DAMGO decreased the frequency and changed amplitude distribution of GABAergic spontaneous miniature IPSPs (417). Hyperpolarization of neuronal membranes produced by reducing extracellular K^+ or Ca^{2+} concentration had no effect on the IPSPs or on the action of the enkephalin on them, indicating that the opiate peptides had a direct action on presynaptic GABAergic terminals (417). Similarly, the μ agonist FK33-824 reduced IPSPs, but not EPSPs, in the CA3 hippocampal cells independently of K^+ or Ca^{2+} conductances, probably due to G-protein-mediated inhibition of vesicular GABA release processes (71).

Glutamate-mediated EPSPs in the nucleus tractus solitarius were attenuated by DAMGO, dynorphin, U69,593, DPDPE, or [D-Ala^2]deltorphin, with the μ agonist having a stronger effect than the δ agonists (418). In the nucleus accumbens, naloxone blocked the ethanol-produced reduction in the amplitude of EPSPs evoked by stimulation to the peritubercle region ventral to the nucleus accumbens (375), suggesting that ethanol might have been acting by an opiate mechanism. Tracer injection into arcuate nucleus was used to measure enkephalin immunoreactivity in that structure. It was determined that the arcuate nucleus is the target of enkephalinergic control originating from several regions and acting on neurons projecting to it, synapsing with the dorsal and ventral parabrachial neurons, the medial preoptic area, and the hypothalamic paraventricular nucleus (318).

Administration of the opiate antagonists, as well as the agonists, can after electrical activity. Naloxone suppressed the inhibition of activity of the superior cervical ganglia induced by a short stimulus train (562,563). After chronic morphine, injection of naloxone precipitated withdrawal, which was characterized by hyperactivity of the locus coeruleus. Agents that increased serotonergic neurotransmission attenuated the effect of the antagonist (8), indicating an interaction between the opiate and serotonin systems. Naloxonazine reduced EEG activity in fetal lambs (84), but naltrindole had no action in them (84) or in rats (483). Thus, with the antagonists, like the agonists, specificity of action appears to be the rule.

Sleep patterns, as measured by EEG activity, were influenced by the opiates, because morphine increased the latency to slow-wave sleep (330,483). Naltrexone reduced the total sleep time, amount of slow-wave sleep, and amount of REM (rapid eye movement) sleep and increased the total awake time and the number of awakenings during sleep in patients with obstructive sleep apnea (145), suggesting that the endogenous opiate system was overactive in them. In young piglets, naltrexone had no effect on the sleep–wake cycle, but naltrindole decreased the percentage of time spent in sleep and increased that in wakefulness (361). In older pigs, both antagonists produced more awake time (361). The κ antagonist did not affect the sleep–wake state at either age (360). These findings indicate that in the early neonatal period, the δ receptors modulate the rhythm of sleep and wakefulness, but later the behavior can be modified by μ receptors as well, and that the κ receptors probably do not play a role in it.

GENERAL ACTIVITY AND LOCOMOTION

In 1993, interest in the possible modulation of general activity and locomotion by the opiate system remained high, although no new insights were discovered. The effects of the opiate agonists depended greatly on dose and other experimental variables, so that few generalizations could be made. Many of the agonists showed biphasic effects over time. Typically, the opiate antagonists tended to have no effect, suggesting little tonic regulation of activity by the opiate system, or to reduce activity. There also continued to be interest in the proposed involvement of the endogenous opiates in the responses to strenuous exercise.

The reports of the action of morphine were highly variable, due in part to its biphasic effect on locomotion, producing a temporary decrease in it and then an increase in it (258). A closer analysis revealed three phases of motor reactivity to morphine, with an initial decrease due to akinesia, followed by an intermediate period characterized by akinesia interrupted by sudden bursts of hyperactivity, and then a third stage of primarily high levels of activity (317). The site of action of the opiate was also important, because morphine had no effect when injected into the anterior dorsal or posterior dorsal striatum (32), but stimulated locomotion when administered to the ventral tegmental area (125), the dorsal periaqueductal gray (362), or ventromedial or ventrolateral striatum (32). There were conflicting reports of its effect in the nucleus accumbens, with comparable doses producing either no effect (125) or greater activity (32) in rats.

Dose, of course, is crucial, and most studies in 1993 focused on doses of morphine that produced hyperactivity (70,109,163, 171,203,297,353,362,369,370,462,481,527). Some studies reported morphine-induced hypoactivity (330,536), and still others found that the opiate had no effect on motor function (88,164,203,209,474). Of the doses that stimulated activity, naloxone blocked the effect of lower one, but higher doses produced nonreversible, fearful hyperactivity (362). Strain differences in reactivity to morphine were found, with mice selectively bred for high swim-stress analgesia being less sensitive than those with low swim-stress analgesia (353), presumably due to differential endogenous opiate activity in the strains. Although upregulation of the opiate system alone, due to previous exposure to stress, did not affect morphine hyperactivity, pairing of the agonist with stress did potentiate the reaction (462), suggesting that the state of the opiate system can influence the action of exogenous opiates.

The opiate and dopamine systems may interact in the mediation of the locomotor effects of morphine, because there was a correlation between the increase in activity and an increase in dopamine in the brain (163,297). Similarly, treatment with pertussis toxin (163) or the selective κ agonist spiradoline (297) reduced dopamine turnover and also inhibited hyperactivity due to morphine. This dopaminergic action of morphine was modified by an inhibitor of nitric oxide synthase (70), so that nitric oxide could play a role in it. Endogenous corticosterone is also important for the effect, because adrenalectomy reduced the ability of morphine to stimulate activity (109).

Most findings with DAMGO reported stimulation of motor responses (16,31,163,474,520), whether the peptide was administered into the ventral striatum (31), the ventral pallidum (16), the nucleus accumbens (31), ICV (163,520), or systemically (297,474). A biphasic reaction of an initial decrease and then an increase was also seen (343,344), although the 0.01 dose produced only hyperactivity (344). Although in some cases in which DAMGO did not affect activity (524,525), it did antagonize the increase induced by methamphetamine (524), suggesting that μ receptors might mediate dopamine-related behavior. In support of that idea, DAMGO, like morphine, facilitated both dopamine metabolism and locomotion (163), and pretreatment with pertussis toxin inhibited both (163). Administration of a mixed D_1/D_2 antagonist or a D_1 antagonist, but not a D_2 antagonist, reduced the action of DAMGO, indicating that the D_1 receptors might have mediated it (16).

Conversely, the κ agonist U50,488 tended to inhibit locomotion (63,115,370,419,466), at least at low doses (115), although it had no effect in some cases (115,403,534). In guinea pigs its effect was indirect, with locomotion being difficult due to the abnormal motor responses and postures induced by the peptide (63). Naloxone and nor-binaltorphimine attenuated the effect, and sigma agonists exacerbated it, so the involvement of the κ receptors was not clear (63). U50,488 suppressed the stimulation of motor activity by morphine but not that of apomorphine, so that the κ receptors did not interact with dopamine in this situation (370). U50,488 seemed to alter the development of D_2 receptors when given prenatally, however, because in these animals there was a reduction of locomotion to the D_2 agonist quinpirole but not to the D_1 agonist SK38393 (466). There was a report of hyperactivity induced by U50,488, but naltrexone did not reverse the effect (73), suggesting that the κ receptors did not mediate the response.

Dynorphin had conflicting results, producing behavioral activation (469) in some cases and suppression in others (342). Fragments of dynorphin, including 2–17, 1–8, and 2–8, as well as the complete peptide, potentiated the dorsal immobility response in rats, so that [des-Tyr^{1}dynorphin was effective in inhibiting the response (342), indicating that it might not be opiate mediated. Dynorphin(1–13) and four of its analogues produced motor dysfunction, characterized by wild running and other forms of activity. The analogues were less potent than the whole peptide in producing the response, however (469). Dynorphin did not affect the hyperactivity of DAMGO, even though it did reverse some of the other effects of the μ agonist (520), indicating that the locomotor action of the receptor types is independent.

The δ agonist deltorphin enhanced the immobility response (154), just as dynorphin did, so that more than one type of receptor may be involved in it. Support for that idea came from the finding that Met-enkephalin and its fragments also increased the duration of the immobility (341). DPDPE produced a monophasic potentiation of locomotion, as opposed to the biphasic effect of DAMGO and the lack of action for the κ agonist DAKLI (343), indicating different profiles for the receptors. Even within a receptor type, there are differences, because DAMGO and PLO17 had biphasic effects, but DALDA suppressed locomotion consistently (344). Alfentanil did not affect simple motor function but did inhibit fine motor behavior (88), providing further evidence for that idea. DPEN stimulated locomotor behavior (32), but DPLPE did not alter the hyperactivity of methamphetamine (524), so that these δ agonists had different effects. The κ agonist U69593 reduced the motor stimulation produced by cocaine (214), indicating opiate mediation of the response.

As with the opiate agonists, the antagonists had variable actions on general activity, either not altering it or suppressing it, although there was a report of stimulation of locomotion by methyl naloxonazine bromide in food-deprived, but not satiated, rats (57). In addition, naloxone or nor-binaltorphimine attenuated the reduction in locomotion induced by U50,488 (63), thus indirectly increasing the behavior. Naloxone methobromide, however, had no effect on it (63), suggesting central mediation of the effect. Naloxone alone inhibited activity (57) but had no effect on the dorsal immobility response (342), so that the behaviors might be mediated by different receptors. Another μ antagonist, β-funaltrexamine, inhibited morphine-induced hyperactivity (370), but neither it alone nor the κ antagonist nor-binaltorphimine itself altered fetal motor activity (474), so that the role of the opiate peptides in the response was questioned.

The δ receptors appear to play a role in locomotion, because both naltrindole and a benzofuran derivative of it, naltriben, blocked morphine-induced hyperactivity (369). Naltrindole also reduced the gross motor stimulation of amphetamine but not of cocaine. Because the δ_1 antagonist DALCE had no effect and because the δ_2 antagonist naltrindole-5′-isothiocynate or a combination of it and DALCE reduced the behavior induced by amphetamine in a manner similar to that of naltrindole, it was concluded that both subtypes of δ receptors might have a role in amphetamine behavioral activation (260).

In addition to horizontal activity, indicated by locomotion, vertical behavior, measured by rearing, can be modified by the opiates. Morphine reduced rearing in animals during agonistic encounters (536), but neither it nor its metabolite M3G affected it under more normal conditions (164). DAMGO increased rearing when injected into the striatum or nucleus accumbens (31), but when administered ICV produced a biphasic effect, first inhibiting it, then stimulating it (343). The δ agonist DPEN increased it (31), and the κ agonist DAKLI did not (343), so that δ as well as μ receptors might be involved. DAMGO antagonized methamphetamine-induced rearing (524) and had no effect on apomorphine-stimulated rearing (525), but neither dynorphin (525) nor DPLPE altered them (524,525), suggesting μ mediation of the former. Although naloxone and methyl naloxonium bromide given centrally did not affect rearing in satiated rats, a high dose of the quaternary antagonist increased it in food-deprived rats (57), so that the role of the μ receptor is confusing, at best.

Circling is another behavior that may be mediated by the opiates. Injection of morphine into the ventral tegmental area of rats produced contraversive circling, even at a dose small enough that it did not develop tolerance or sensitization (40). Similarly, three novel benzomorphans [(−)-deoxypentazocine, (−)-deoxy-*N*-benzylnormetazocine, and (+)-*N*-benzylnormetazocine] induced circling behavior after microinjection into the nigra striatum. This action, however, was thought not to be opiate mediated, because the compounds had low affinity for opiate receptors and because naloxone did not affect it, suggesting that σ receptor were involved instead (539). Circling induced by methamphetamine was antagonized by DAMGO but unaffected by DPLPE, so that the μ receptors may have interacted with the dopamine-related agent (524). The D_2 agonist apomorphine-induced circling, however, was not changed by DAMGO, DPLPE, or dynorphin(1–13), suggesting that it was not mediated by any of the three major opiate receptor types (525). The role of the opiate system in this behavior is, therefore, totally unclear.

Grooming also has been shown previously to be modulated by the endogenous opiates, but the few studies of it in 1993 were mostly negative. Neither a high dose of morphine nor a low dose of its metabolite M3G, when injected either IT or ICV, altered

grooming in rats (164). In grooming induced by methamphetamine, DPLPE was ineffective in changing it, but DAMGO did attenuate it, and that reduction was reversed by β-funaltrexamine, suggesting mediation of the response by μ receptors. DAMGO alone, however, did not produce any grooming (524), so that the opiate involvement is weak, at best.

Dystonic movements in genetically predisposed hamsters were reduced by U50,488 and either induced or not affected by naloxone or naltrexone, suggesting involvement of the κ receptors in these behaviors (419). In nondystonic hamsters the only effect the peptide had was to depress locomotion (419). Conversely, in normal rats U50,488 produced ataxia, ptosis, hunching of the back, and sedation that were blocked by the σ agonist rimaczole, suggesting an interaction between the κ and σ receptors (559). Similarly, in guinea pigs abnormal motor responses and postures, with severely impaired movements, occurred after injection of U50,488 (63), supporting other findings that the κ agonists have debilitating properties. Additional support for that idea came from the finding that dynorphin(1–13) and its analogues tended to produce motor dysfunction characterized by hindlimb jerking, popcorn jumping, and barrel rolling (469). Barrel-rolling behavior also occurred after administration of Tyr-W-MIF-1, although it was unusually short-lived, suggesting that the peptide had opiate-like agonistic effects, possibly mediated by μ receptors (561). Jumping, as well as agitation, biting, and vocalization, was induced by the morphine metabolite M3G (238). Massive biting behavior was also produced by intranigral infusion of DADLE (310), although it was not clear if the δ receptors were involved. Muscular rigidity, specifically of the gastrocnemius muscle, occurred after administration of alfentanil, and the effect was attenuated by the μ_1 antagonist naloxonazine or β-funaltrexamine, suggesting that it was μ_1 mediated (373). Balance, as measured on the rotorod, was not affected by morphine, Tyr-MIF-1, or a combination of the two in rat pups in the first week of life, even though analgesia was modified by them (209), so that the opiate nature of the responses was unclear.

Opiate mediation of stereotypies was also studied. Agonists of all three receptor types, DAMGO, DPDPE, and DAKLI, produced stereotypies in rats, although they had somewhat different behavioral profiles, especially in terms of timing. DAMGO had a biphasic action, but the other two had mixed effects (343). The κ agonist U-69593 attenuated the stereotypy induced by cocaine (214), suggesting involvement of the κ receptors. Stereotyped facial wiping behavior in response to a tactile probe in the rat pup was reduced by drinking milk or injection of U50,488 or the D_1 agonist SKF-38393. The effect of milk or the D_1 agonist was blocked by the κ antagonist nor-binaltorphimine, but a D_1 antagonist did not affect the action of U50,488, suggesting that milk modulated activity at the dopamine receptors, which in turn promoted activity at the κ receptors (428). The μ agonists morphine and DAMGO also attenuated facial wiping, as did U69,593 (476), so that both κ and μ receptors appear to be involved. The κ receptors, however, probably did not play a role in stereotypy induced by the D_2 agonist bromocriptine, because U50,488 had no effect on it (534).

The involvement of the opiate system in the responses to strenuous exercise was studied in 1993, as in previous years, with some more successful results than before. Running (182,215) and exhaustive incremental graded treadmill exercise (215) increased plasma β-endorphin, with the rise being greater and the recovery slower for a marathon run (215). Less strenuous exercise did not alter plasma β-endorphin, but there was a significant difference in it between diabetic and nondiabetic patients with silent myocardial ischemia and between nondiabetic patients with and without the silent myocardial ischemia, suggesting that its assessment might be a useful diagnostic tool (222). There was no baseline difference in plasma β-endorphin between marathon runners and sedentary individuals, so that the effect of the peptide is, at best, temporary (182).

Exercise also induced an increase in hemorphins, opiates derived by enzyme degradation of hemoglobin, and there was a baseline difference in trained runners and nonexercising controls and between the sexes, perhaps due to its negative covariance with weight (182). After voluntary exercise in a running wheel, rats had higher concentrations of dynorphin-converting enzyme in CSF than their nonrunning controls, providing additional evidence that exercise affects the endogenous opiate system (390). It was proposed that the sustained beneficial effects of exercise on blood pressure might be due to an activation of the opiate system, which produces sympathoinhibition. Although this inhibition may be masked during exercise by sympathoexcitatory influences, once exercise is completed, the physiological effect of sustained activation of the opiate system may predominate and produce hypotension (279). Other exercise-induced reactions, however, including an acceleration of transit time (206), increased release of growth hormone (506), and a rise in plasma vasopressin (85), probably are not opiate mediated, because naloxone or naltrexone had no effect on them.

DEVELOPMENT

In 1993 interest in the postulated involvement of the opiate system in development, prenatally through old age, remained high and even increased, but there was little attention to the possible opiate modulation of sexual behavior, dwindling from previous years. There was a finding, however, that endogenous peptides may control testosterone biosynthesis through an interaction with the vasopressin system, because naloxone increased testosterone production by Leydig cells and reduced testicular vasopressin, but only in the injected testis (148).

Because changes in the opiate system were noted during pregnancy, it was assumed that the endogenous opiates helped regulate fetal development. During late pregnancy, concentrations of Met-enkephalin and Met-enkephalin-Arg^6-Phe^7 increased in the plasma of fetal sheep, but the total amount of Met-enkephalin-containing peptides did not change, possibly reflecting changes in the synthesis and/or secretion of enkephalin peptides within sympathetic nerves as parturition neared (471). Levels of gene expression of enkephalin precursors changed in the brain during pregnancy, with POMC mRNA in the arcuate nucleus decreasing at parturition. Preproenkephalin mRNA in the ventromedial nucleus decreased during late pregnancy and parturition, but in the paraventricular nucleus, it rose at parturition after declining at the end of pregnancy (65).

Concentrations of Met-enkephalin also increased in the lumbar region of the spinal cord in late gestation in the rat (335), possibly in association with the discomfort and preparation for labor occurring at that time. In the neural lobe of the pituitary, there was a decrease in the peptide that may be responsible in late pregnancy for the removal of inhibition of oxytocin release that occurs earlier during gestation (121,123). Opiate mediation of oxytocin was supported by the finding that the increase in the hormone that occurs just before parturition was enhanced by naloxone (123), and its release by electrical stimulation was potentiated in the final week of pregnancy but not before (121,123).

Morphine had no effect on electrically stimulated oxytocin release, and although its injection delayed the start of birth, it did not affect the progress of parturition once it had begun (442). Methadone-exposed placenta villus had no detectable opiate

binding sites, and in vitro release of acetylcholine from trophoblast tissue of the placenta was not modulated by opiates, suggesting that methadone produced a desensitization or down-regulation of opiate receptors in placenta (7).

Neural lobe dynorphin(1–8) (122,123) and supraoptic nucleus prodynorphin mRNA (123) did not change during the gestation period. In the spinal cord, however, both dynorphin(1–8) and -(1–17) increased in late pregnancy, and in parturient animals dynorphin(1–8) remained elevated, and there was an additional rise in dynorphin(1–17) (335). Supporting the role of κ receptors in parturition was the finding that U50,488, when given after the birth of the second pup of the litter, delayed the birth of the remaining pups, and preinjection of the κ antagonist nor-binaltorphimine blocked the effect (122). That this action occurred as a result of an interaction with oxytocin was indicated by the fact that injection of the hormone attenuated the delay induced by U50,488 and that the opiate peptide blocked spontaneous and oxytocin-stimulated contractions after parturition (122,442). The analgesia of pregnancy and the birth process also appears to involve the κ receptors, because administration of 17-β-estradiol and progesterone to nonpregnant rats produced analgesia that was blocked by chronic naltrexone (104).

In humans, maternal plasma β-endorphin increased in the third trimester of pregnancy, and its concentrations were correlated with those of CRH until labor. Maternal and fetal β-endorphin were correlated, as were its concentrations and fetal obstetric difficulty (81). During parturition in cows, there was a marked increase in β-endorphin that paralleled the increase in oxytocin, even to the extent that it was released in an episodic manner in conjunction with uterine and abdominal contractions, suggesting that it interacted with oxytocin (26). In pigs, however, no change in β-endorphin occurred with pregnancy (309). Alterations in β-endorphin may account for differential demonstrations of stress-induced anxiety in pregnant rats. At the end of pregnancy, when the peptide increased, anxiety as measured by burying behavior decreased (395).

After parturition, lactation affects the opiate system and opiate-mediated behavior. POMC mRNA in the arcuate nucleus and preproenkephalin mRNA in the paraventricular nucleus increased during lactation of sheep (65), so that opiate gene expression was modified even after the termination of pregnancy. Lactating rats had attenuated analgesia to morphine (551), further demonstrating changes in the opiate system at this period. They were hyperalgesia on day 6 (551), however, which coincided with a decrease in stress-induced burying behavior. These events may be related to previously reported decreases in β-endorphin between days 6–8 (395).

The opiate agonists and antagonists have been shown to alter fetal behavior. At term, U50,488 stimulated fetal motor activity (474,476), as did U69,593 (476), although morphine and DAMGO had no effect on it (474,476). Neither β-funaltrexamine nor nor-binaltorphimine alone altered it, but the κ antagonist did block the hyperactivity induced by U50,488 or by SKF-38393, indicating an interaction between the opiate and dopamine systems (474). Morphine (475,476), DAMGO (476), and U69,593 (476) attenuated facial wiping in response to cutaneous stimuli. The reduction of wiping by DAMGO was reversed by CTOP, and that by U69,593 was inhibited by nor-binaltorphimine (476), indicating that both the μ and κ receptors might mediate the response. Neither antagonist alone (476) nor naloxone alone (475), however, had any effect on facial wiping, so that there appeared to be little involvement of the endogenous opiates in this behavior.

Habituation of the wiping response to repeated presentation of the stimulus was unaffected by CTOP, nor-binaltorphimine, and naloxone, but nor-binaltorphimine and naloxone facilitated dishabituation (475), suggesting possible opiate modulation of simple learning in the fetus. Classical conditioning using the pairing of milk, which inhibits facial wiping in the fetus, and sucrose was facilitated by β-funaltrexamine or CTOP but not nor-binaltorphimine, indicating μ mediation of it. Appropriate controls that the reduction in wiping after the presentation of sucrose was due to the association between milk and sucrose rather than habituation or other confounding events (24) were used, so that the opiate effect was on the conditioning.

Late in the gestation period, but not before, administration of U50,488 promoted the stretch response to saline (19), suggesting that functional maturity of the κ receptors did not occur just a few days before birth. Presentation of an artificial nipple to the rat fetus produced appetitive responses, such as mouthing, licking, and oral grasping of the nipple, and aversive responses, such as avoidance of the nipple. DAMGO increased the appetitive behavior, but U50,488 reduced it and increased avoidance of the nipple. The μ and κ receptors, thus, mediated opposite responses to that stimulus (427), which might reflect their differential development. Infusion of milk to the near-term fetal rat reduced dopamine at D_2 receptors in septal, striatal, or hypothalamic regions, but this response was not affected by morphine, DAMGO, or U50,488 (20), so that an interaction between the dopamine and the opiate system had not yet developed in those regions at that stage.

Prenatal administration of opiates can alter postnatal behavior. Rats given U50,488 chronically through gestation had reduced locomotion to the D_2 agonist quinpirole but not to the D_1 agonist SK38393, so that the prenatal experience changed the sensitivity of the D_2 receptors (466). Chronic prenatal U50,488 also lowered birth weight of the pups, and that effect lasted through the first 10 days. Because the peptide did not alter the weight gain or food intake of the mothers or the litter size or number of dead pups (466), it appeared that the agonist was working directly on the fetuses and not indirectly through the mother. Prenatal morphine, when combined with the catecholamine synthesis inhibitor α-methylparatyrosine, apparently modified development of the norepinephrine system, because the turnover rate for norepinephrine in adulthood was greater than normal in the preoptic area and less than normal in the hypothalamus. Adult dopamine turnover, however, was not affected by prenatal morphine (130).

Similarly, some prenatal events can modify later opiate-mediated behavior. After receiving prenatal exposure to lead, rat pups were given morphine implants and then naloxone-precipitated withdrawal. High levels of lead resulted in attenuated withdrawal signs, including less weight loss, fewer wet-dog shakes, and fewer mouthing responses. However, corticosterone levels, which are used as an index of withdrawal, were increased, indicating a disruption of typical opiate functioning in those rats (289). After prenatal exposure to cocaine, the ability of morphine or DAMGO to reduce ultrasonic vocalizations in neonatal rat pups was enhanced, but sensitivity to morphine analgesia was not affected. This is consistent with an increase in [^{3}H]naloxone binding in the forebrain but not in the brain stem, which is associated with analgesia, of these rats (184).

There have also been direct demonstrations of alterations in the endogenous opiate system after prenatal experiences. Chronic administration of morphine during the middle of the gestation period produced changes in binding in the adult. Binding capacity for DAMGO increased in the preoptic area but decreased in the hypothalamus, with the latter possibly account for changes in adult male sexual behavior by prenatal morphine shown in previous years. No other areas were affected by the experience

(420). Continuous maternal administration of naltrexone, which provided a blockade of the endogenous opiate system, or of morphine restricted cortical cell proliferation and maturation measured after birth, with the effect for the exogenous opiate being more severe (460). Maternal stress, shown to induce endogenous opiate activity, altered hypothalamic β-endorphin measured on postnatal day 10, although the timing and duration of the stress was important. Immobilization from gestational days 2–6 or 7–11 increased the endorphin, but when restraint lasted from day 2–16, no effect occurred (446), although there is no easy explanation for the differences.

Not only does the opiate system change during pregnancy, it also continues to develop after birth. Basal concentrations of β-endorphin increased in the anterior pituitary (299) and the neurointermediate pituitary (542) of rats through old age. Haloperidol potentiated the rise in the peptide only at 3 months, however, indicating a change in the interaction of dopamine and the opiate system with age (299). The ontogeny of β-endorphin in the preoptic area was similar in males and females, being diffuse in the medial portion at birth and later becoming dense only in the periventricular and parastriatal nuclei (175). Receptors for β-endorphin on the soleus, extensor digitorum longus, and diaphragm muscles of rats decreased with age (472), and were denser in dystrophic mice than in normal ones (472), suggesting a role for the opiate system in the development of the genetic disorder. Because concentrations of β-endorphin rose in plasma and fell in the pituitary, hypothalamus, and medulla oblongata in response to administration of fentanyl in 10-day-old rat pups, the β-endorphin system was active at least by that age (38), if not sooner.

Age-related concentrations of Leu-enkephalin in the preoptic area varied with the sexes, although they started the same, initially being densest in the lateral portion in both sexes. In males, the distribution expanded to the medial portion, and ultimately condensed further into the lateral part of the medial portion. Females continued to exhibit diffuse medial preoptic immunoreactivity once the peptide was seen there (175). In humans ranging in age from 4 to 93 years, there were age-related decreases in Leu- and Met-enkephalin in the caduate nucleus and pallidum but no changes in the putamen or substantia nigra (421). Binding of the enkephalins in the hippocampus and caudate nucleus did not change with age (421). Through the life span of the rat, concentrations of both enkephalins increased in the neurointermediate and anterior lobes of the pituitary (542). Haloperidol reduced Met-enkephalin in the anterior lobe in younger animals but not older ones, so that age affected the opiate response to dopamine blockade in that structure (299).

The earliest detection of proenkephalin in the rat striatum occurred at day 16, although Met-enkephalin can first be seen at 10–15 days of age. The discrepancy is perhaps due to a developmental delay in the complete enzymatic processing of the proenkephalin precursor, which is likely related to dopamine innervation (480). Administering 6-OHDA to the neonatal rat increased the preproenkephalin mRNA in the adult brain, mostly in the striatum, but also in surrounding areas. This indicates that early depletion of dopamine has lasting effects on the endogenous opiate system (479). In adulthood, there were large decreases in enkephalin mRNA and enkephalin neurons in the rat striatum (452), suggesting further changes in the opiate system with age.

Although there are some exceptions, the δ receptors tend to be relatively stable from 1 month throughout life in the guinea pig (223) and rat brain (398). The number of μ receptors in the rat hypothalamus decrease in aged rats (398), but the κ receptors increase in the amygdala and thalamus in aged rats (398). The κ receptors are evident at birth, being the earliest to appear, and there are no changes in their affinity with age (290). The δ and μ receptors are highly vulnerable to perinatal lead toxicity, but the κ receptors are less sensitive, perhaps because they are fully developed at birth (288). Sexual isolation of rats from birth did not alter the number of μ receptors, but the μ antagonist β-funaltrexamine depressed them if given at day 1 but not at day 7 (105), supporting the notion that they are not mature at birth. Naloxone binding sites decreased with age in the arcuate nucleus, ventromedial nucleus, and median eminence in ovariectomized rats, and in those treated with estradiol, there was an inhibition of all the sites in young ones but not in the median eminence in middle-aged and aged ones (312), indicating a shifting interaction between the opiate system and sex hormones with age.

Perinatal administration of opiate agonists or antagonists can influence later behavior. Obstetrical medication could be a risk factor in future addicts, perhaps due to perinatal imprinting by the anesthetic during labor, because there was an uneven distribution of adult drug abusers born in hospitals with differing policies on it, independent of geographical area (380). Neonatal morphine delayed eye opening and attenuated weight gain in rat pups, as well as producing hyperalgesia. The endogenous opiate modulating peptide Tyr-MIF-1 alone had no effect but potentiated the effects of morphine, producing different effects in these young animals than are typically found with adults (209). When naloxone was administered neonatally, adult rats had hyperalgesia, so that it apparently altered the development of antinociceptive mechanisms (106).

The effects of opiate agonists and antagonists can change with age, as demonstrated by the report that the release of endogenous acetylcholine from rat striatal slices was inhibited by DPDPE at an earlier age than it was attenuated by DAMGO (388), so that the δ and μ receptors become operative with respect to this response differentially with development. Similarly, there was a change in the modulation of sleep and respiration by those receptors, with δ ones mediating sleep and μ regulating respiration in the early neonatal period, but later, both receptors were involved in both behaviors, although μ tended to predominate in respiration (361). The κ receptors did not affect those responses, but they did modulate cardiovascular activity (360), indicating differential control of these behaviors in the neonatal period. In humans, however, there was no change in the ability of IT morphine to suppress ventilatory responses to CO_2 between the ages of 4 months and 15 years (374).

There was no swim-induced analgesia in rats at 2–5 days of age, some by 10 days, and full adult-like analgesia by 25 days (365), with a corresponding transition from μ to δ receptors during that time (366). Weaning was important, because the transition was delayed by 5–10 days by a delay in weaning (366). At 20 days, the warm-water swim-induced analgesia, as measured by an increase in vocalization afterdischarge threshold, was not naloxone reversible, but it was in adults (405), indicating a further change over age. In senescence-accelerated mice and controls, naloxone facilitated learning at 4 months of age, but at 12 months, the antagonist helped only the controls at the original dose. A much larger dose was required to have the same effect in the senescence-accelerated mice (151), indicating a change in the opiate system with advancing age. This notion was supported by the report that dynorphin and prodynorphin mRNA in the hippocampus increased in aged rats, with the greatest rises occurring in those with severe spatial learning deficits (168).

The opiate system appears to be partially involved in parental behavior, because naloxone administered to new monkey mothers reduced their protective behavior toward their infants and attenuated grooming of not only their offspring but of other

adults as well. Other relationships between the mother and infant were not disturbed by the antagonist (325), however, demonstrating that some maternal behaviors are opiate mediated and others are not. Morphine decreased clinging between infant and mother, and naltrexone increased it, demonstrating the importance of the opiate system in regulating affiliation between a primate mother and her infant (465). Exposure of juvenile rats to neonatal pups typically produces full parental behavior, but administration of morphine inhibited it, and naloxone reversed the effect of the agonist. Rats allowed to develop full parental behavior before the injection of morphine still had naloxone-reversible attenuation of it, suggesting that both its onset and maintenance in juvenile rats are regulated by the opiates (286).

Administration of naltrexone from birth through weaning attenuated growth, as measured by brain or body weight in one strain of rat but not in another (392), so that prolonged early prenatal receptor blockade of opiate receptors can affect growth, although the effect is strain specific. Developmental changes were seen in naltrexone-precipitated withdrawal from morphine-dependent rat, producing different symptoms different in pups from those found in adults. In the pups, withdrawal was characterized by stretches, walking, wall climbing, head movements, and decreased time with littermates (261), as opposed to the most typical adult symptoms of teeth chattering, wet-dog shakes, diarrhea, jumping, ptosis, and change in activity level.

IMMUNOLOGICAL RESPONSES

Strong interest remained in 1993 in the interaction of the opiate system with the immune system, but confusing results and seemingly conflicting findings did not allow any generalizations about its nature. Undoubtedly it is highly complex, and it may be that specific effects rather than wide-ranging conclusions will be the outcome of research concerning it. In most cases, but not all, morphine tended to inhibit immune function. The agonist suppressed natural killer (NK) activity, when given either acutely (75,315) or chronically (74). The reduction of NK activity was suppressed by β-funaltrexamine (75) or naltrexone (315), but not by naloxonazine, naltrindole, or nor-binaltorphimine, indicating μ_2 mediation of the response (75). Both α- and β-adrenergic antagonists also blocked the effect (75), suggesting an interaction of the opiate with both pathways.

Similarly, other measures of immune function produced differential effects of morphine. In the spleen, morphine suppressed not only NK activity, but also production of interferon and interleukin-2; in blood, morphine reduced the mitogen response; but in lymph, morphine did not affect the ability of lymphocytes to proliferate or produce cytokines (315). With chronic morphine, there was less NK activity in peripheral blood mononuclear cells, probably due to the decrease in the percentage of $CD8^+CD16^+$ cells, not a direct inhibition of NK cells (74). Daily morphine also produced an increase in the percentage of $CD8^+$ lymphocytes but a decrease in that of total $CD4^+$ and $CD4^+CD45RA^+$ and a reciprocal increase in $CD4^+CD29^+$ lymphocytes, as well as greater production of polyclonal immunoglobulin (Ig) and polyclonal IgM from peripheral blood mononuclear cells. Thus, daily morphine affects immunocompetence, which could have implications in the regulation of viral pathogens in drug abusers, especially AIDS (74).

Both in vivo and in vitro, morphine reduced phagocytic activity after administration of *Candida albicans*, and the actions were blocked by naltrexone, indicating that morphine is capable of interacting directly with opiate receptors on macrophages, resulting in a decrease in phagocytic function (434). The increased activity of neutral endopeptidase of peripheral blood mononuclear cells activated by concanavalin A or cocaine was not altered by morphine or enkephalin (303), so that this response is probably not opiate mediated. Morphine can act directly by stimulation of opiate receptors of immune cells, thereby modulating macrophage production by cytokines in response to various stimuli or indirectly by triggering opiate receptors in the periaqueductal gray, which may activate the HPA axis, with subsequent glucocorticoid-mediated effects on immune cells (391). Its actions are not totally clear, however, much less their mechanisms.

The findings for enkephalins are no less confusing. Similar stimulation of cell migration was produced by [D-Ala^2]Met-enkephalinamide (DAMA) and interleukin-1, in humans and invertebrates (*Mytilus edulis*), suggesting a possible universal inhibitory mechanism (484). Human immunodeficiency virus (HIV) slowed the enhanced migration and produced a loss of direction in both species (484). An enkephalin-like molecule similar to DAMA in earthworm coelomic fluid stimulated leukocyte behavior in a naloxone-reversible way (97), indicating opiate mediation of the response. DPDPE had immunostimulatory activity, but TOPA (Tyr-D-Orn-Phe-Asp-NH_2) had the opposite effect in healthy individuals or in patients with leprosy or tuberculosis (331), indicating widely different effects of selective enkephalins. Incubation of mouse spleen cells with Leu-enkephalin suppressed their migration, and although naloxone alone also reduced the locomotion of the cells, the antagonist reversed the action of the enkephalin (165).

In cells from Vietnam veterans suffering with PTSD (358) or from patients with migraine (359), Met-enkephalin had varied effects on NK activity. There was no difference in NK activity during or outside a migraine attack or in controls when measured between groups, but when analyzed with individuals as their own controls, the enkephalin did alter immune function, increasing it in controls and outside an attack, but having no effect in more than half during an attack. When it did change it during a migraine headache, the peptide mostly suppressed immune activity (359). In cells from veterans, Met-enkephalin produced mixed results in chronic drug users and no effect in chronic alcoholics or those abusing both, but did increase NK activity in individuals healthy other than for the PTSD (358). Conversely, the immune system can also alter the activity of endogenous enkephalins. Because splenocytes, NK cells and NK cells activated by interleukin-2 were capable of hydrolyzing the *N*-terminal Tyr from Met- and Leu-enkephalin, it was proposed that NK cells may regulate enkephalin activity through their enzymatic degradation (18).

In some cases, β-endorphin facilitated immune functions, including reducing the incidence of encephalitis and paralytic-demyelinating disease induced by neurotropic murine coronavirus, an animal model for multiple sclerosis. It was accompanied by a reduction in replication of the virus in the brain (177). The endorphin also enhanced proliferation to phytohemagglutinin in lymphocytes in patients with chronic ulcer disease (377) and Ia expression on murine B cells in cultures from spleen cells, thereby most likely improving their antigen-producing capacity (530). Anti-β-endorphin suppressed antibody production to pokeweed mitogen, suggesting that β-endorphin might stimulate it (305).

A dualistic role for β-endorphin, however, was reported in that it stimulated T-cell proliferation by triggering nonopiate receptors, but the increase was blocked by an interaction with opiate receptors. This was concluded because fragments of the peptide containing the *C*-terminal but lacking the opiate-binding *N*-terminal sequence increased T-cell proliferation that was inhibited by the *N*-terminal enkephalin sequence (531). Pretreat-

ment with β-endorphin before infection with a temperature-sensitive mutant of vesicular stomatitis virus reduced immune function in a naloxone-reversible way, indicating opiate mediation of a deleterious effect of the endorphin (96). Although the response of β-endorphin to CRH was blunted in anorexics, there was no correlation between this neuroendocrine impairment and the immune response to phytohemagglutinin (62), indicating that the peptide played no role in that action. Thus, it had varying effects depending on a number of factors, including its fragmentation, the kind of immune response, and specific populations.

The opiate antagonists had no more consistent actions than the agonists. Naltrexone, but not the δ antagonist ICI74,864, blocked the enhancement of immune function by melatonin, indicating mediation by the μ receptors (172), but the δ antagonist naltrindole inhibited the lymphocyte reaction after kidney allegrafts, increasing their survival (21). This suggests that naltrindole may be a safe, useful immunosuppressant agent for organ transplants (21). However, in patients with brain tumors, administration of naltrexone in addition to radiotherapy increased tumor regression rate and survival more than radiotherapy alone, indicating involvement of the opiate system in these tumors (311).

Naloxone had differential effects in modulation of NK activity in human peripheral blood lymphocytes in vitro, with the direction of change depending on the degree of interleukin-2-induced NK activity. There was an increase with low concentrations of interleukin-2 but a decrease with high concentrations of it. The antagonist also modulated NK activity stimulated by exogenous interferon-α or endogenous Poly-I C-induced interferon, with the direction of change depending on baseline NK activity (326). Central, but not peripheral, naloxone antagonized the increase in serum of the inflammatory cytokine interleukin-6 induced by central administration of interleukin-1α or interleukin-1β (110), which might also reduce some of their deleterious behavioral effects. Interferon-α given ICV also was detrimental, producing stress-related responses and reducing NK activity, and its actions were reversed by ICV naltrexone, suggesting a possible explanation for immunosuppression associated with some kinds of opiate-mediated stress (496).

Further evidence of the relationship between the opiate and immune systems in stress is the finding that restraint produced a decrease in β-endorphin-like immunoreactivity in the periaqueductal gray and in interferon-γ production in the splenocytes (144), although the mechanisms involved were not delineated. There was a sex difference, with the change in immune function being greater in females than males (144), again with the significance of the finding being unclear. Opiate-mediated intermittent shock increased the concentration of β-endorphin in splenocytes, lymphocytes, and peripheral blood mononuclear cells, but nonopiate continuous shock did not (443), so that the opiate system was clearly involved. Food restriction increased basophil frequency and the heterophil/lymphocyte ratio and increased dynorphin but not β-endorphin or Leu-enkephalin-like immunoreactivity in the brain (450), indicating a correlation between opiate and immune responses. The effect of cold-water swims on the immune system depended on their frequency of occurrence. With three 3-min swims in 1 day, there was a reduction in interleukin-2 production, in mitogenic responses to concanavalin A or lipopolysaccharide, $CD4^+$ and $CD8^+$ percentages, and NK lymphocytes, but with 5 days of swims with one session per day, these responses all were enhanced (468), perhaps reflecting differential stressfulness of the events.

The effects of forced swimming, handling, or loud noises were reduced by α-interferon, with naloxone or naloxonazine reversing its action but naltrindole and nor-binaltorphimine not altering it, suggesting that the neuromodulatory effect of α-interferon was mediated by μ_1 receptors (448). An explanation of the involvement of the immune system in opiate dependence suggested that a well-maintained opiate dependence can be beneficial to the organism. In opiate-naive individuals, opiate exposure activates the stress axis, producing homeostatic disruption and immunological disruption. If opiate exposure continues, however, the homeostatic and immunological responses stabilize in such a way that the individual becomes dependent on opiates, so that withdrawal will produce imbalance and destabilization that is again disruptive of immune function. It may be assumed that the immune system is compromised during this procedure (118).

To support the involvement of the opiates in immune activity, there were demonstrations of changes in opiates in some tumors. In patients with gynecological malignancy, plasma β-endorphin was higher than in normal controls, suggesting that the peptide may be involved in the development of cancer through modulation of cell immunity (281). There was a strong negative correlation, however, between Met-enkephalin and the degree of malignancy in patients with brain tumors, so that the enkephalin may represent a useful malignancy marker for these tumors (199).

Similarly, other indications of immune function may involve endogenous opiates, because there was an upregulation of the opiate system, as measured by proenkephalin synthesis, after pertussis toxin (549). Atrial natriuretic factor and β-endorphin were coexpressed in a small population of macrophages, suggesting that they may comodulate some aspects of immune function (511). Lipopolysaccharides increased enkephalin mRNA and interleukin-1β, although the timing of the changes did not coincide, suggesting a feedback mechanism, rather than potentiation (458). Interleukin-1α and interleukin-1β produced a release of β-endorphin in vivo, but not from the anterior pituitary in vitro, so that the in vivo action probably occurred at a higher level, perhaps at the hypothalamus or other CNS controls of the hypothalamus (385). Thus, there is a highly complex relationship between the opiate and immune systems that remains far from being elucidated.

OTHER BEHAVIORS

Among the other behaviors that were previously shown to be mediated in part by the opiate system is social interaction, including prosocial and agonistic encounters, and it continued to be studied in 1993. Morphine reduced distress vocalizations in isolated young chicks and greatly inhibited rough-and-tumble play in juvenile rats. With repeated administration over days, weak tolerance developed, but that could be blocked by coadministration of the NMDA antagonist MK 801, indicating a possible interaction between opiate and NMDA receptors for these responses (48). Distress vocalizations, which typically do not occur in the home cage with littermates, were elicited by injection of U50,488. The meaning of this finding and its opiate mediation were not clear, because naltrexone had no effect on the κ-induced behavior (73). The preference that isolated rat pups show for the smell of soiled bedding from their own home cage as opposed to clean wood chips was not affected by naltrexone, indicating lack of opiate mediation. Instead, the response was altered by clonidine, indicating involvement of the α_2-adrenergic system (204). Ultrasonic vocalizations in adult male rats during the threat of attack in resident–intruder clashes were

attenuated by morphine in a naltrexone-reversible way, but audible vocalizations were unaffected. Thus, there were some opiate influences on affective responses to the aversive social situation (536).

The well-known antitussive action of opiate agonists was further studied in 1993, confirming previous findings. Morphine (263,265,266), DAMGO (263,267), U50,488 (265), and β-endorphin (264) reduced coughs, and although [D-Ala^2]deltorphin II alone had no effect, it enhanced the antitussive action of DAMGO (267). Naloxone antagonized the action of morphine (263,266) and DAMGO (263), but the μ_1 antagonist naloxonazine did not, indicating involvement of the μ_2 receptors. Support for that conclusion was the fact that mice deficient in μ_1 receptors showed the same response (266). The ability of β-endorphin to inhibit coughs, furthermore, was reversed by the μ antagonist β-funaltrexamine by not by the κ antagonist nor-binaltorphimine (264), again implicating the μ receptors. The effect of morphine and U50,488 was greater in diabetic than in nondiabetic rats, but the δ antagonist naltrindole wiped out the difference, suggesting involvement of δ and κ receptors also (265). Further evidence for the involvement of δ receptors came from the finding that naltrindole alone suppressed coughs in diabetic rats (265) and from the potentiation of DAMGO's antitussive action by the δ_2 agonist [D-Ala^2]deltorphin II and the blockade of this synergistic effect by a derivative of naltrindole (267).

The opiate system may also be involved with physiological rhythms, both diurnal and seasonal. Morphine, when injected at different times of the cycle, advanced the phase of circadian wheel running in some cases and delayed it in others, frequently producing bouts of intense wheel running (324). Diurnal variations in plasma concentrations of β-endorphin coincided with elevations in the pain threshold, largest pupil diameter, and increased heart rate (202), suggesting a possible regulatory function for the peptide for these responses. There were circadian rhythms in the concentration of both β-endorphin and Met-enkephalin in the neurointermediate pituitary, with peaks occurring in both day and night, but cortical concentrations of Leu-enkephalin peaked only during the day and striatum measures of it peaked only at night, thus showing an attenuated cycle (542).

A mechanism for hibernation might be seasonal increases in the endogenous opiate system, producing a downregulation of hippocampal opiate receptors. This could then induce heightened serotonergic activity. Support for this idea came from the finding that DADLE inhibited serotonin normally, but not in hibernation (282). Similarly, U50,488 enhanced release of serotonin from slices of hippocampus during nonhibernation but not during hibernation, and the potentiation was inhibited by norbinaltorphimine, implicating the κ receptors (102). DAMGO inhibited serotonin release from hippocampus slices, in a naloxone-reversible way, in both hibernating and nonhibernating ground squirrels, and in the hypothalamus, DAMGO and U50,488 produced release of serotonin in both states, indicating a complex nature of the roles of different opiates in regular hibernation (102).

Pruritus is another behavior previously shown to be mediated by the opiate system, and it was confirmed in 1993, with IT morphine producing itching in humans (30). Pupillary responses also occurred to opiates, with hydromorphone and pentazocine causing constriction of the pupils (402) and dilation being associated with increases in plasma β-endorphin (202). Because there is enkephalin-like immunoreactivity in the axons of the marginal region of the avian auditory thalamus and in perikarya of the medial margin of the inferior colliculus, it appears that there is an enkephalinergic auditory pathway in parallel with traditionally recognized auditory pathways that target regions of the avian basal forebrain (126), suggesting a role for enkephalins in auditory processes.

Dryness of the mouth caused by fractionated irradiation of the head and neck was associated with markedly enhanced Leu-enkephalin-like immunoreactivity in submandibular ganglion cells and an increase in the number of nerve fibers showing this immunoreactivity, so that the opiate system may mediate the dryness (158). The opiate system may play a role in nicotine dependence, because naloxone precipitated withdrawal in rats made dependent by 2 weeks of nicotine infusion, and morphine reduced spontaneous absence signs after termination of the nicotine (320). Nicotine also produced naloxone-reversible antinociception in mice and, at lower doses, antagonized morphine analgesia, thus having a dual action involving opiate agonist and antagonist properties (2).

It has been suggested that the analgesic nitrous oxide (gas) should be considered an opiate, because it was cross-tolerant to morphine, because its blockade by naloxone was stereospecific, because agents that inhibited its breakdown potentiated responses that were blocked by opiate antagonists, because it produced release of endogenous opiates, and because low concentrations of it competed with opiate ligands for binding sites (176). Opiate-like effects were also reported for Tyr-W-MIF-1, because it was transported out of the brain by the saturable system Peptide Transport System-1 in a way similar to, but less robustly than, Tyr-MIF-1 (35). The physiological role of the Tyr-MIF-1 family, like most of the opiate peptides, remains to be elucidated.

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