Annu. Rev. Pharmacol. Toxicol. 1993. 32:353–82

EFFECTS OF OPIOIDS ON THE HYPOTHALAMO-PITUITARY-ADRENAL AXIS

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KEY WORDS: ACTH, CRF, glucocorticoids, PCP/NMDA receptor, sigma receptor

INTRODUCTION

Opiates and opioid peptides affect many different physiological systems. As well as having well-known analgesic and behavioral properties, opioids can affect neuroendocrine function and, depending on the specific hormonal axis, stimulate or inhibit the release of hypothalamic releasing factors and pituitary and target gland hormones. Opiates have important uses in clinical medicine, and altering the hormonal milieu can have pathophysiological consequences by affecting reproductive and immune function, growth, and development, as well as disrupting circadian rhythms and the responses to stressors. For example, opiates used during surgery as part of balanced anesthesia may alter the stress response to surgery, and the response to other stressors may be altered in individuals taking opiates for the treatment of pain, individuals abusing opiates, or those on methadone maintenance for the treatment of opiate dependence. In addition, because opiates are subject to abuse, their effects on neuroendocrine systems can contribute to the adverse sequelae of drug exposure.

Aside from the clinical implications of opiate-induced changes in neuroendocrine function, these responses can be used as a functional response to study the underlying mechanisms of drug action. Although researchers have been studying the effects of opiate alkaloids on neuroendocrine function for several decades, these studies took on added meaning upon the discovery of the

0362-1642/92/0415-0353$02.00

endogenous opioid peptides. Thus, the finding that opiate alkaloids could affect neuroendocrine function suggested that the endogenous opioid peptides might play an important role in the physiological regulation of neuroendocrine function.

The hypothalamo-pituitary-adrenal (HPA) axis is central to the maintenance of homeostasis and is a model neuroendocrine system, linking changes in central neuronal activity to alterations in target gland function. The signal is propagated first by the release of corticotropin-releasing factor (CRF) from the hypothalamus, which stimulates the synthesis and release of the anterior pituitary hormone adrenocorticotropin (ACTH), finally leading to increases in the synthesis and release of adrenal cortical hormones, corticosterone and/or cortisol. This hierarchy can be viewed as a signal transduction system at the marcroscopic level, with properties in common with those of other signal transduction systems, such as signal amplification as the signal moves down the pathway and multiple feedback control points.

Initial experiments suggesting that the adrenal gland might play a role in the modulation of the acute and chronic effects of morphine (1) stimulated research on the effects of morphine on the adrenal. One of the earliest pieces of evidence that opiates can affect the function of the HPA axis came from the finding that the chronic administration of morphine causes hypertrophy of the adrenal primarily as a result of an increase in the volume of the adrenal cortex (1). Selye later studied morphine during the formation of his concept of the alarm reaction and found that morphine administration increased the weight of the adrenals in rats (2). Later, using adrenal ascorbic acid depletion as an indirect measure of glucocorticoid release, it was shown that the effects of *d*- and *l*-methadone showed stereoselectivity and that nalorphine inhibited the adrenal ascorbic acid-depleting effects of morphine (3), suggesting that the effects of opiates on the adrenal are receptor mediated. These initial experiments led to subsequent studies characterizing the effects of the acute and chronic administration of numerous opiates and, more recently, opioid peptides on the HPA axis in different species. The object of this review is to summarize these data, including the more recent work on the possible involvement of endogenous opioid systems in the control of the HPA axis, first focusing on the effects of opioids in rodents and later discussing their effects in humans.

METHODOLOGICAL ISSUES

The literature on the effects of opioids on the HPA axis is filled with many apparent contradictions, and seemingly similar experimental protocols have yielded disparate results. It is obvious that differences in the species used, the specific opioid tested, the doses of the drug tested with regard to the

dose-response characteristics of the compound, the route of administration, and the time of plasma hormone sampling in terms of the overall time course of drug response could lead to different results. Thus, the lack of a response could be due to the administration of too low a dose of drug or to sampling plasma hormone levels either too early or too late after drug administration. However, other less apparent experimental variables can have profound effects and make it difficult to compare results across different studies.

Some of these factors are unique to opioids. Because opioids can produce tolerance and physical dependence, the time point within the dependence–withdrawal cycle when the subjects are tested is important. For example, measurement of hormone levels in plasma in chronically opioid-treated animals can reflect basal levels, the acute response to drug, or withdrawal-induced changes depending on how much time has elapsed since the drug was last administered. Moreover, because certain acute and chronic conditions such as stress (see below) may activate endogenous opioid systems, exogenously administered opioids could interact with endogenous opioid systems and confound the interpretation of the data.

Other design factors that can affect the interpretation of the results are unique to approaches that use changes in neuroendocrine function as the dependent variable. The basal state of the subject is critical in studies of the effects of drugs on the HPA axis. The HPA axis is activated by many stressors; for example, handling and injecting a previously unhandled rat and placing it into a novel environment can cause activation of the HPA axis. If the experimental procedure is stressful, administering an opioid agonist or antagonist to the subject will provide information about the effects of the drugs on stress-induced responses and will not yield meaningful information about the effect of a drug on basal hormone release. There are circadian rhythms of hormone release within the HPA axis (4–9) that vary across species, and testing subjects at different times of the day or housing them under different light–dark cycles can affect the neuroendocrine response to opioids. For example, the ability of morphine to increase plasma levels of corticosterone in rats is decreased in the afternoon, whereas the effects of the kappa opioid agonist U50,488 are not changed (10). In addition, there are seasonal variations in drug response; a study found that in rabbits a rise in plasma corticosterone in response to acute morphine administration occurs only in summer and that in winter morphine decreases the corticosterone levels (11).

Factors prior to drug administration can affect the experimental outcomes. For example, behavioral testing can increase plasma corticosterone levels several days later (12). In addition, housing conditions, i.e. single or group housing, can affect basal hormone levels and conceivably the hormonal responses to drug challenge. For example, individually housed rats have been found to have higher basal corticosterone levels (13). Some studies have shown

that rats chronically cannulated with intravenous (i.v.) catheters for sampling plasma have higher basal corticosterone levels, but these higher levels may be due to the individual housing of cannulated subjects rather than to the surgical procedure. Many of these factors could account for the discrepancies in the results obtained in different studies.

MORPHINE AND OTHER NONSELECTIVE OPIATE ALKALOIDS

Effects of Acute Administration

Many of the early experiments were carried out before the development and widespread use of radioimmunoassays for ACTH and glucocorticoid hormones. The results and conclusions of these studies were based on indirect measurements of pituitary and adrenal activity, including morphological changes, various bioassays, plasma and/or urinary levels of adrenal cortical hormones and/or their metabolites, and biochemical changes such as adrenal ascorbic acid depletion, an indirect indicator of adrenal hormone release. Although it was believed to be possible that opiates stimulated the adrenal cortex directly, evidence suggested that the release of adrenocortical hormones was secondary to the opiate-induced stimulation of the release of ACTH from the pituitary. Supporting this hypothesis, it was found that hypophysectomy could abolish the effects of morphine on adrenocortical hormone release (3, 14–16). Eventually, radioimmunoassays for ACTH came into widespread use, and it was shown that the morphine-induced stimulation of the release of adrenocortical hormones is secondary to the release of ACTH from the anterior pituitary.

It is now known that the acute administration of morphine stimulates the release of both ACTH from the pituitary and glucocorticoid hormones from the adrenal cortex in many species, including the rat (3, 14, 17–19), mouse (20), guinea pig (21), and cat (22–24). However, it is important to note that morphine and other opioid agonists inhibit the HPA axis in humans (see below). It is interesting that although the behavioral effects of morphine can be different across species (e.g. sedation versus arousal in rats and cats, respectively), the effects on the HPA axis may be similar.

The systemic administration of morphine causes a rapid rise in plasma levels of ACTH and corticosterone in the rat (18, 25–26); however, the initial corticosterone rise can be followed by a fall relative to the level in saline-injected controls several hours later, probably owing to an effect of morphine on the normal diurnal variation of serum corticosterone levels (4). Morphine stimulates the HPA axis only after administration at relatively high doses ($\geq$20.0 mg/kg) (17, 19, 25, 27, 28), and these doses are much higher than

those required to produce analgesia or affect the function of other neuroendocrine axes (29). The stimulation of the HPA axis by such high doses of morphine could be due to a stress effect, for example secondary to morphine-induced respiratory depression. However, some studies have found stimulation of the HPA axis after lower systemic doses of morphine (26, 30). Morphine-induced activation of the HPA axis occurs early in development, since rats as young as 5 days old show increases in plasma corticosterone levels in response to morphine (31, 32).

Other nonselective opiate alkaloids also cause stimulation of the HPA axis. The activation is receptor mediated, since the enantiomeric pairs *d*- and *l*-methadone (3) and levorphanol and dextrorphan (33) show stereoselectivity. Other nonselective opiate alkaloids that can stimulate the HPA axis include methadone (25, 27, 34), levorphanol, (33), normorphine (20), and codeine (25). However, buprenorphine, which is a partial agonist at mu receptors but may have antagonist activity at kappa receptors, does not affect the release of corticosterone in rats (35).

The ability of opiate alkaloids to stimulate the HPA axis is blocked by opioid antagonists. Early on, it was found that nalorphine can inhibit the adrenal ascorbic acid–depleting effects of morphine (3). Later, it was found that opioid antagonists such as naloxone (36, 37), as well as the mu receptor antagonist β-funaltrexamine (-FNA) (26) and the kappa receptor antagonist WIN 44,441-3 (36, 37), can antagonize the effects of morphine on the HPA axis in the rat.

Effects of Chronic Administration

Tolerance to the stimulatory effects of morphine on the HPA axis develops in rats (25, 27, 38) and cats (22–24). Tolerance to the effects of methadone on corticosterone release also develops in rats (27). The tolerance is long lasting, because the response to methadone is decreased even 3 weeks after chronic treatment (34). It is intriguing that although tolerance to the effects of opioids on the HPA axis develops, chronic drug administration causes adrenal hypertrophy (1, 39), indicating continued and excessive adrenal stimulation.

Although tolerance to the effects of opioids on the HPA axis could be mediated directly at the level of the opioid receptor, it also could involve a decrease in the response in any or all of the individual components of the axis. Chronic exposure to opioids could reduce the ability of the hypothalamus to release CRF, and the release of CRF from hypothalami of chronically morphine-treated rats in response to morphine, met-enkephalin, acetylcholine or serotonin has been found to be decreased (38). Thus, chronic morphine exposure does attenuate hypothalamic CRF release, but the reduction is not unique to the opioid-mediated stimulation of CRF release.

Tolerance also could occur at the level of the pituitary by several mecha-

nisms. It could be due to depletion of pituitary ACTH as a result of chronic stimulation. Nikodijevic & Maickel (40) found that whereas single doses of morphine had no effect on the pituitary ACTH content, three repeated doses over 24 h caused a decrease in pituitary ACTH levels and reduced the adrenocortical stress response to cold exposure. However, others (41) have not found that chronic morphine affects ACTH levels in the anterior pituitary. Tolerance at the level of the pituitary could be due to a decrease in sensitivity to CRF. Although the response to hypothalamic extracts of pituitaries from chronically morphine-treated rats is reduced in vitro (38), the response to CRF is not impaired in vivo (42). The reduction in the adrenocortical response to morphine in chronically morphine-treated rats is not due to a direct suppressive effect of morphine on the adrenal, because the ACTH-induced release of adrenocortical hormones is not impaired (27, 42). Thus, the role of changes in response of the various units of the HPA axis in the phenomenon of tolerance after chronic drug administration is not clear.

Effects of Withdrawal

Withdrawal can be produced by discontinuing the chronic administration of an opioid agonist, or it can be precipitated in a chronically treated subject by using an opioid antagonist. Either method causes stimulation of the HPA axis and increases in adrenal weight (43), indicative of activation of the HPA axis. Thus, the pattern of the response of the HPA axis during withdrawal is the same as the acute response to opioids.

Early on, it was found that spontaneous withdrawal from morphine in chronically morphine-treated rats caused a large increase in the urinary levels of hydroxysteroids (44). Corticosterone levels are elevated 12 h after day 5 of chronic morphine treatment (42) and 24 h after the previous injection in morphine-dependent rats (43). Withdrawal from morphine also causes an increase in plasma cortisol levels in cats (23). However, it is important to point out that elevated corticosterone levels at some time points between morphine injections in morphine-tolerant subjects could be due to alterations in the normal circadian rhythms of hormone release as well as drug withdrawal. Rather than increasing corticosterone levels, the administration of morphine to chronically morphine-treated rats which are undergoing abstinence can decrease elevated corticosterone levels by suppressing abstinence (42). Corticosterone levels also have been found to be elevated during withdrawal from methadone in rats (34).

The administration of an opioid antagonist to chronically opioid-treated subjects also causes activation of the HPA axis. Initially, administration of nalorphine to chronically morphine-treated rats was found to cause a large rise in the urinary levels of hydroxysteroids (44). Nalorphine and naloxone cause an increase in plasma corticosterone levels in chronically morphine-

treated (22, 23, 25, 42) and methadone-treated (34) rats and a rise in plasma cortisol levels in chronically morphine-treated cats (23, 24). The stimulatory effects of naloxone on the HPA axis in morphine-dependent animals are centrally mediated, since injection of naloxone into various intracerebral sites causes increases in plasma cortisol levels in morphine-dependent cats (45) and plasma corticosterone levels in morphine-dependent rats (46).

ACUTE DEPENDENCE An acute dependence phenomenon has been described with respect to the effects of opioids on the HPA axis. For example, corticosterone levels are elevated 12 h after a single injection of morphine (42). In addition, naloxone can produce a rise in plasma corticosterone levels when administered 3 h after the acute administration of the opioid agonist levorphanol, showing the development of physical dependence after a single exposure to an opiate agonist. However, administration of naloxone at the same time as the initial injection of levorphanol prevented the rise in response to the naloxone given later (33). Acute dependence also occurs after the administration of a single dose of morphine, and the magnitude of the corticosterone elevation is a function of the priming dose of morphine and the dose of naloxone used to precipitate the response (47). The naloxone-induced rise in the corticosterone level was still present when it was given up to 25 h after morphine administration (47). Naloxone can precipitate an acute withdrawal-type response 3 h after the intracerebroventricular (i.c.v.) administration of morphine (48).

NONSELECTIVE OPIOID PEPTIDES

Opioid peptides, as well as opiate alkaloids, cause activation of the HPA axis. β-Endorphin injected intracisternally (49) or i.c.v. (50) increases plasma ACTH and corticosterone levels in rats, and tolerance to this effect develops (49, 51). The i.v. administration of (D-Ala2, Met5)-enkephalinamide increases plasma levels of both ACTH and corticosterone in rats and these effects are blocked by naloxone (52) or naltrexone (49). The rise in the corticosterone level produced by (D-Ala2, Met5)-enkephalinamide is mediated by the release of ACTH from the pituitary, since hypophysectomy or dexamethasone pretreatment blocks the response (49). Interestingly, it has been reported that the administration of (D-Ala2, Met5)-enkephalinamide directly into the third ventricle of rats does not elevate plasma ACTH or corticosterone levels (53).

SELECTIVE OPIATE ALKALOIDS AND PEPTIDES

It is known that there are multiple subtypes of opioid receptors. Investigators have used receptor-selective agonists and antagonists to determine the

differential role of the various subtypes of opioid receptors in the stimulatory effects of opioids on the HPA axis. Although some of the compounds that have been used as probes differ in their degree of selectivity, receptor selectivity is a function of dose, and at high doses interactions with other receptor subtypes can occur.

Mu Receptor-Selective Compounds

Mu-selective agonists can stimulate the HPA axis in the rat. For example, the mu-selective opioid agonist fentanyl increases plasma corticosterone levels in rats, and this effect is antagonized by pretreatment with either the nonselective opioid antagonist naloxone or the mu receptor antagonist β-FNA (30). Morphiceptin increases serum corticosterone levels in neonatal rats (54), and the i.c.v. administration of the mu-selective peptide (D-Ala2–*N*-Me-Phe4, Gly-ol)-enkephalin (DAMGO) causes an increase in plasma levels of ACTH in adult rats (26). Mu-selective peptides also can cause the release of CRF from hypothalami in vitro, and these effects are antagonized by naloxone and the mu antagonist β-FNA, but not by the delta receptor antagonist ICI 154129 (55).

Kappa Receptor–Selective Compounds

The greatest amount of work on defining the receptor subtypes that mediate the effects of opioids on the HPA axis has involved the kappa receptor. Compounds with activity at kappa receptors also stimulate the HPA axis in rats. For example, the kappa opioid agonist U50,488 stimulates the HPA axis in rats, increasing plasma levels of corticosterone (30, 37, 54, 56–59), and it is more potent than morphine even though it is less potent as an analgesic (37, 57, 58). U50,488 can induce activation of the HPA axis as early as postnatal day 2. However, morphine does not produce significant activation until postnatal day 5; this suggests that kappa receptor–mediated control is functional before mu-mediated control of the HPA axis (32).

The stimulatory effects of U50,488 can be blocked by pretreatment with naloxone (30, 37, 56, 58) but not by pretreatment with the mu receptor antagonist β-FNA (30) or the kappa-selective antagonist WIN 44,441-3 (37, 58). U50,488 also stimulates CRF release from rat hypothalami in vitro (55), and this effect is antagonized by high doses of naloxone but not by pretreatment with either the mu receptor antagonist β-FNA or the delta receptor antagonist ICI-154129.

Rats given repeated injections of U50,488 develop tolerance to the stimulatory effects on corticosterone release (58), and U50,488-tolerant rats are not cross-tolerant to morphine (42, 58). Although morphine can suppress elevated corticosterone levels in chronically morphine-treated rats undergoing abstinence, U50,488 does not reduce corticosterone levels in these subjects

(42). Corticosterone levels are elevated 12 h after day 5 of chronic morphine treatment, but rats chronically treated with U50,488 do not show similar withdrawal-induced secretion (42). The kappa antagonist MR2266 does not precipitate an increase in corticosterone levels in rats chronically treated with U50,488. In addition, acute dependence is not observed after acute administration of U50,488 (42). These data suggest that withdrawal after treatment with kappa agonists is not associated with activation of the HPA axis.

Ethylketocyclazocine, although not as selective as U50,488, also causes activation of the HPA axis in rats after systemic or i.c.v. administration (19, 36, 37, 48, 58, 60). The effects of ethylketocyclazocine can be blocked by naloxone (37, 48, 58) and WIN 44,441-3 (37, 58); however, others have not found blockade by either naloxone or WIN 44,441-3 (36), possibly owing to differences in the doses of the antagonists used and/or the timing of drug administration. It has been reported that the effects of i.c.v. ethylketocyclazocine are not attenuated by pretreatment with the mu antagonist β-FNA (48), indicating that its effects are not mediated by mu receptors. Naloxone does not precipitate an acute withdrawal response after i.c.v. administration of ethylketocyclazocine, indicating that acute dependence does not develop (48). Other opiate alkaloids that have activity at kappa receptors and have been found to stimulate the HPA axis include cyclazocine and pentazocine (56), bremazocine (61), tifluadom (30, 37, 58), and MR-2034 (26, 37, 58). Naloxone blocks the stimulatory effects of bremazocine (61), tifluadom (37, 58), and MR-2034 (26, 37, 58) on the HPA axis, and whereas WIN 44,441-3 blocked the effects of tifluadom (37, 58), it did not reverse the effects of MR-2034 (37, 58). Dynorphin$_{1-13}$ (51, 62) and the kappa-selective peptide met-enkephalin-Arg-Phe (62) administered i.c.v. increase plasma levels of corticosterone. The effects of dynorphin$_{1-13}$ and met-enkephalin-Arg-Phe were reduced in chronically U50,488-treated rats but not in chronically morphine-treated rats (51); this shows that cross-tolerance with morphine is absent.

Delta Receptor–Selective Compounds

Less is known about the involvement of delta receptors in the stimulatory effects of opioids on the HPA axis. Some experiments have used (D-Ala2, D-Leu5)-enkephalin (DADLE) as a probe for delta receptor–mediated effects; however, this peptide has limited selectivity for delta receptors. DADLE injected i.c.v. causes increases in plasma corticosterone (51), and this effect could be blocked by pretreatment with naloxone but not with the kappa antagonist WIN 44,441-3 (37). The effects of DADLE were not reduced in chronically morphine- or U50,488-treated rats (51), demonstrating the absence of cross-tolerance. In contrast to the effects of DADLE, the highly selective delta agonist (D-Pen2, D-Pen5)-enkephalin does not increase serum levels of

corticosterone in neonatal rats (54) or stimulate the release of CRF from hypothalami in vitro (55). Thus, it is unclear whether the stimulatory effects of DADLE are specifically mediated by delta receptors or through some other opioid receptor.

Sigma and PCP/NMDA Receptor–Selective Compounds

The sigma "opiate" receptor, first described by Martin et al (63), has become a highly controversial and confusing subject. This receptor, which has been hypothesized to mediate the psychotomimetic effects that are produced by some opiates (63), was characterized from in vivo experiments in humans and spinal dogs. It was classified as an opiate receptor because the psychotomimetic effects could be antagonized in vivo by opiate antagonists such as naltrexone (63). However, the characterization of the sigma receptor, as the term is currently used, is based in large part on results of in vitro binding experiments (64). In these binding studies, opiate antagonists have very low affinity for the sigma receptor; therefore, opiate antagonists should have little or no effect on interactions involving this receptor. In fact, the term "opiate" has been removed from the sigma receptor, and the sigma receptor as originally defined by Martin et al (63) and the sigma receptor as currently defined (64) probably represent two different entities.

Some opiates and the psychotomimetic drug phencyclidine (PCP) may interact at another common site, the *N*-methyl-D-asparate (NMDA) subtype of the glutamate receptor. PCP and some opiates such as cyclazocine and *N*-allylnormetazocine (SKF 10,047) bind to a specific site on the NMDA receptor and act as noncompetitive antagonists; this site is known as the PCP/NMDA receptor (65). It is important to stress that although neither the sigma receptor nor the PCP/NMDA receptor is an opiate receptor, opiates can interact with these sites, leading to the production of nonopioid receptor–mediated side effects. Thus, the stimulation of the HPA axis produced by some opiates might involve interactions with either the sigma or the PCP/NMDA receptor.

PCP, which can bind to both sigma and PCP/NMDA receptors, stimulates the HPA axis, causing the release of both ACTH and corticosterone in rats (66–69) and corticosterone in mice (70). Some tolerance to the effects of PCP on the HPA axis develops after repeated administration (70), and, like morphine, chronic treatment with PCP causes adrenal hypertrophy in rats (71). The effects of PCP on the HPA axis are not inhibited by pretreatment with naloxone (68); this demonstrates that this effect is not mediated by opioid receptors. The loci of action of PCP are within the central nervous system, since PCP causes the release of ACTH after i.c.v. administration but affects neither the basal nor the CRF-stimulated release of ACTH from the pituitary in vitro (69). In addition, PCP also does not enhance the basal or the

ACTH-stimulated release of corticosterone from the adrenal in vitro (69). Although it is not known whether the sigma or the PCP/NMDA receptor mediates the effects of PCP on the HPA axis, the nonopioid MK-801, which is highly selective for the PCP/NMDA receptor, also stimulates the HPA axis in rats (72).

Opiates that can interact with sigma and PCP/NMDA receptors also stimulate the HPA axis in the rat. For example, (±)-SKF 10,047 causes a rise in plasma corticosterone levels after subcutaneous (s.c.) (19, 36, 48) or i.c.v. (48, 60) administration. The effects of systemically administered (±)-SKF 10,047 are not blocked by naloxone (36, 48) or WIN 44,441-3 (36), and the effects of i.c.v. (±)-SKF 10,047 are not attenuated by pretreatment with β-FNA (48), indicating that the stimulation of the HPA axis is not due to interactions with opioid receptors. In addition, naloxone did not precitate acute withdrawal in rats 3 h after i.c.v. (±)-SKF 10,047 administration (48), showing that acute opioid-type dependence does not occur. Other opiates, such as dextrormethorphan (R. N. Pechnick & R. E. Poland, unpublished data), (+)-SKF 10,047 (Pechnick and Poland, unpublished data; 73), (–)-SKF 10,047 (Pechnick & Poland, unpublished data), (+)-pentazocine (Pechnick & Poland, unpublished data; 73), and (–)-pentazocine (Pechnick & Poland, unpublished data) all interact with sigma and PCP/NMDA receptors with various degrees of selectivity, and all cause the activation of the HPA axis.

LOCI OF ACTION

Central Nervous System

Many studies have demonstrated that most, if not all, of the stimulatory effects of opioids on the HPA axis are centrally mediated. Early on, it was found that lesions of the median eminence blocked adrenal ascorbic acid depletion after the systemic administration of morphine (74, 75). Later, opioids were shown to stimulate the HPA axis after direct administration into the brain. For example, morphine injected directly into the lateral (48, 60) or third (76) ventricles stimulates the HPA axis. However, *N*-methylmorphine, a quaternary analog of morphine that does not cross the blood-brain barrier, does not produce increases in the serum levels of corticosterone when administered systemically (77). Other opioids that have been shown to stimulate the HPA axis in the rat when injected i.c.v. include β-endorphin (50, 51), DADLE (37, 51), opioids with selectivity for mu receptors such as DAMGO (26), and opioids with selectivity for kappa receptors such as ethylketocyclazocine (48, 60), MR-2034 (26), dynorphin$_{1-13}$ and met-enkephalin-Arg-Phe (51, 62). These data suggest that at least some component of the stimulatory effects of opioids are centrally mediated.

HYPOTHALAMUS A key central site for the mediation of the effects of opioids on the HPA axis appears to be the hypothalamus. The hypothalamus acts as the final common path for the integration of signals from other brain regions and the periphery, and at some point it would be involved in the opioid-mediated stimulation of ACTH release through enhancing the release of CRF. This is supported by the finding that lesions of the median eminence block adrenal ascorbic acid depletion after the systemic administration of morphine (74). The hypothalamus receives input from many brain regions, and some of the effects of opioids on the hypothalamus could be mediated by interactions at these other sites. For example, morphine injected into the mammillary body and septum causes increases in cortisol levels in the cat (45). However, there is evidence that opioids can have a direct effect on the hypothalamus.

The hypothalamus contains mu, kappa, and delta opioid receptors (78, 79), and injection of opioids directly into the hypothalamus can stimulate the HPA axis. For example, morphine microinjected into the "middle" part of the hypothalamus (the anterior, paraventricular, ventromedial, and dorsomedial hypothalamic nuclei) increases plasma levels of corticosterone, but injections into more rostral and caudal regions have no effect (80). This finding was replicated by Van Ree et al (81), who found that microinjections of morphine into the medial and ventral parts of the mid-hypothalamus elicited a greater stimulation of corticosterone release than did injections into the lateral or dorsal part. In further support for a direct role of the hypothalamus, opioids can stimuate the release of CRF from hypothalami in vitro (see below).

Pituitary

Although it is clear that central target sites are involved in the stimulation of the HPA axis by opioids, it is possible that opioids also have direct effects on the pituitary. Opiate receptors are present in the pituitary (78), although their density in the anterior pituitary is rather low (82). *N*-Methylmorphine, a quaternary analog of morphine that does not cross the blood-brain barrier, does not stimulate the HPA axis when administered systemically (77), suggesting that morphine cannot directly stimulate the release of ACTH from the pituitary in vivo. Studies examining the effects of opioids on pituitary tissue in vitro have provided conflicting data. For example, morphine, β-endorphin, met-enkephalin, leu-enkephalin, and (D-Ala2, Met5)-enkephalinamide have been reported to affect neither the basal nor the CRF-stimulated release of ACTH from pituitary tissue in vitro (18, 38, 52, 83–85). However, in one study leu-enkephalin slightly reduced rather than enhanced the CRF-stimulated release of ACTH from cultured anterior pituitary cells, but this effect was not dose dependent (83). In addition, the enkephalin analog FK 33-824 was found to reduce the basal and lysine vasopressin-stimulated release of ACTH from rat anterior pituitaries in vitro, but this effect was not

inhibited by naloxone (86). Thus, it is clear that opioids do not have a stimulatory effect on the release of ACTH from the pituitary, but it is uncertain whether the apparent inhibitory effects in the last two studies were due to specific or opioid-mediated interactions.

Adrenal

Many of the earlier studies used the effects of opiates on adrenal cortical function and morphology as an indirect indicator of ACTH release. Experiments suggested that the stimulatory effects of opioids on the release of glucocorticoids from the adrenal are mediated via the release of ACTH from the pituitary. Supporting this conclusion, it was found that pretreatment of subjects with glucocorticoids, such as cortisol or dexamethasone, which can inhibit the release of ACTH from the pituitary, blocks the effects of morphine on adrenocortical hormone release (3, 14–16). Moreover, the effects of morphine on adrenal acid depletion are abolished in hypophysectomized rats (3). However, some studies have found that opioids can have direct effects on the adrenal.

Although in one study morphine by itself did not have a direct effect on the adrenal, it potentiates the steroidogenic response to ACTH in hypophysectomized rats, and this effect appears to be mediated by opioid receptors as it showed stereoselectivity and could be blocked by naloxone (87). Morphine also has been found to cause the release of cortisol from slices of guinea pig adrenals in vitro (88). Thus, it is possible that morphine can enhance the synthesis and/or release of glucocorticoids from the adrenal; however, other opiate alkaloids have shown inhibitory effects. For example, methadone inhibits rather than stimulates the ACTH-induced elevation of cyclic AMP (cAMP) levels (89) and production of corticosterone in adrenal cortical cells in vitro (88).

The results of studies examining the effects of opioid peptides on the release of glucocorticoids from the adrenal cortex also have been contradictory, showing both direct stimulatory and inhibitory effects. Some (87, 90, 91) have found that β-endorphin has no effect on the basal or ACTH-induced steroidogenesis in isolated adrenal cells; however, others have found that β-endorphin stimulates the synthesis (92) and release (88) of glucocorticoids in isolated rat adrenal cells. Szalay & Stark (93) found that low to moderate concentrations of β-endorphin decrease, but high concentrations increase, the basal and ACTH-stimulated production of corticosterone from adrenal zona fasciculata cells in vitro; however, the inhibition of basal production was not affected by naloxone, and this suggested that this effect is not mediated by opioid receptors. Pretreatment with met-enkephalin was found to enhance ACTH-induced corticosterone release (94); however, it also has been reported

that met- and leu-enkephalin affect neither the basal nor the ACTH-induced stimulation of cortiocosterone release from adrenal cells in vitro (91), and in another study leu- and met-enkephalin both decreased the basal and ACTH-induced stimulation of corticosterone release from adrenal cells in vitro (95). (D-Ala2-Met5)-enkephalinamide administered i.v. decreased both the basal and the ACTH-induced stimulation of corticosterone release in hypophysectomized rats (96), indicating a direct inhibitory effect on the adrenal. Thus, it is not clear whether opioid peptides have a direct effect on the adrenal cortex, and the reasons for the discrepancies are not known.

MECHANISMS OF ACTION

The exact mechanisms(s) underlying the stimulatory effects of opioids on the HPA axis is not known. Because the stimulation of the HPA occurs only after administration of high doses of opioids, it is possible that it represents a nonspecific stress effect or is related to some aversive or dysphoric properties of the drugs (56). However, this could not account for the stimulatory effects of opioids on the release of CRF in vitro (see below). It has been suggested that some of the effects of morphine on the HPA axis might be secondary to morphine-induced cardiovascular changes (97); however, others have not found a relationship between the two effects (98). Morphine can stimulate the release of vasopressin from the posterior pituitary; and vasopressin can stimulate the release of ACTH. However, very low doses of morphine release vasopressin and produce an antidiuretic effect in rats, but much greater doses are needed to cause activation of the HPA axis (75). Currently, the effects of opioids on the HPA axis are thought to be mediated by stimulating the release of CRF from the hypothalamus or by affecting neurotransmitters that can alter hypothalamic releasing factors and/or release-inhibiting factors.

Effects of Opioids on Hypothalamic CRF

Opiates might exert their effects on the HPA axis by altering the synthesis and/or release of hypothalamic releasing factors, release-inhibiting factors, and/or other secretagogues. Much work has focused on the effects of opioids on CRF, a major physiological regulator of ACTH secretion (99). Morphine, met-enkephalin, and leu-enkephalin all increase the hypothalamic CRF content and cause the release of CRF from hypothalami in vitro (18, 38). In addition, the ability of hypothalami from chronically morphine-treated rats to release CRF in response to morphine or met-enkephalin is reduced, suggesting that some component of tolerance to opioids could occur at the level of the hypothalamus (38).

Buckingham & Cooper (55) have attempted to define the specific opioid

receptor subtype involved in the stimulatory effects of opioids on the release of hypothalamic CRF. The effects of morphine are antagonized by naloxone and the mu antagonist β-FNA but not by the delta antagonist ICI-154129; this indicates that the mu-type opioid receptors mediate the response. β-Endorphin in low concentrations also increased hypothalamic contents of CRF and the release of CRF in vitro, and these effects were blocked by naloxone. However, higher concentrations of β-endorphin inhibited the spontaneous release of CRF, and this effect was blocked only by high concentrations of naloxone, suggesting that a non-mu-type opioid receptor might be involved in the latter effect. The kappa agonist U50,488 is a weak releasor of CRF, and whereas its effects can be antagonized by high doses of naloxone, they are unaffected by the mu antagonist β-FNA and the delta antagonist ICI-154129. The delta receptor agonist (D-Pen2, D-Pen5)-enkephalin does not cause the release of CRF. These data indicate that both mu and kappa opioid receptors, but not delta opioid receptors, are involved in the opioid-induced stimulation of CRF release from the hypothalamus.

However, other studies have found that opioids do not have a stimulatory effect on CRF release. The infusion of β-endorphin or dynorphin$_{1-13}$ decreases rather than increases portal levels of CRF, and these inhibitory effects are blocked by naltrexone (100). Although the increase in plasma ACTH caused by the kappa receptor agonist MR-2034 is blocked by pretreatment with antiseurm to CRF, the stimulatory effect of a low dose of morphine is not; this suggests that morphine may stimulate ACTH release through a non-CRF-dependent mechanism (101). Tsagarakis et al (85) found that morphine does not alter the basal release of CRF, whereas Hashimoto et al (53) reported that (D-Ala2, Met5)-enkephalin decreases the release of CRF from perifused hypothalami in vitro. Similarly, β-endorphin, dynorphin$_{1-13}$, and FK 33-824 have been reported to inhibit the release of CRF from hypothalami in vitro, and whereas the effects of β-endorphin and [D-Ala2-*N*-Me Ph4, Met(0)5-ol]-enkephalin (FK 33-824) are blocked by naloxone, the effects of dynorphin are only slightly decreased (102). The reasons underlying these discrepancies are not clear, but they could involve the different methods used to measure CRF (i.e. bioassay versus radioimmunoassay). If this is the case, it would support the contention that factors other than CRF are involved in the opioid-induced stimulation of the HPA axis.

Neurotransmitters Involved in Effects of Opioids on the HPA Axis

The effects of opioids on the HPA axis could be due to their altering the synthesis and/or release of biogenic amine neurotransmitters. Some of these

effects could be peripheral. For example, morphine can cause the release of epinephrine from the adrenal medulla, and at one time epinephrine from the adrenal was thought to modulate the release of ACTH from the pituitary. However, morphine or methadone can cause adrenal ascorbic acid depletion in rats with demedulated adrenals, showing that adrenal medullary discharge of epinephrine is not necessary (3). Moreover, morphine inhibits rather than facilitates the adrenal ascorbic acid depletion in response to epinephrine (103). Opioids could affect biogenic amine neurotransmitters centrally, and changes in the synthesis and/or release of hypothalamic releasing factors, release-inhibiting factors, and/or other secretagogues could be secondary to these effects. Many neurotransmitters, including norepinephrine, serotonin, acetylcholine, histamine, and γ-aminobutyric acid (GABA) have been suggested to play some role in the regulation of CRF secretion (104–107), but many of these data are conflicting and controversial. The lack of clear-cut knowledge of the specific involvement of various neurotransmitters in the control of the HPA axis has not aided the determination of how opioids could interact with these neurotransmitters to stimulate the axis.

Attempts have been made to relate opioid-induced changes in these neurotransmitter systems to stimulation of the HPA axis. Although diurnal variations in plasma corticosterone levels were found to be inversely correlated with striatal and cortical dopamine levels and serotonin levels in the amygdala, it was not possible to correlate the effects of the acute administration of morphine on HPA activation with changes in regional brain levels of dopamine, norepinephrine, or serotonin (5). However, others have found an inverse relationship between morphine-induced changes in ACTH release and hypothalamic norepinephrine levels (108). This has led to the hypothesis that morphine causes the release of ACTH by interfering with an inhibitory noradrenergic control mechanism, and this hypothesis is supported by the results of some in vitro experiments (98). However, it also has been hypothesized that norepinephrine can enhance rather than inhibit the release of CRF. Thus, morphine could increase the release of CRF by stimulating noradrenergic systems. Supporting this alternative hypothesis, pretreatment of rats with α-methyl-*p*-tyrosine (98) or the α_1 antagonist prazosin (97, 98) reduces the morphine-induced rise in plasma corticosterone levels. Moreover, morphine decreases the hypothalamic norepinephrine content (108, 109), possibly indicating increased turnover of norepinephrine. Acetylcholine and serotonin can stimulate the release of CRF in vitro, but, surprisingly, morphine (85) or high concentrations of β-endorphin (110) inhibit rather than increase the release of CRF caused by these substances. Thus, the neurotransmitters involved in mediating the stimulatory effects of opioids on the HPA axis are not known.

EFFECTS OF OPIOID AGONISTS ON THE RESPONSE OF THE HPA AXIS TO STRESSORS

Morphine can block the stimulation of the HPA axis in response to various stressors, such as laporotomy, ether, histamine or cold exposure, in rats (15, 40, 103, 111) and mice (20). Nalorphine antagonizes the inhibitory effect of morphine on histamine-induced stress (112), indicating that the effect is mediated by opioid receptors. The ability of morphine to reduce the pituitary-adrenal response to stressors is paradoxical because morphine itself produces adrenal hypertrophy. In chronically morphine-treated rats, insulin, pentylenetetrazole, cold exposure (27), and novelty stress (42) all increased plasma corticosterone levels, demonstrating the development of tolerance to the ability of morphine to block the activation of the HPA axis by stressors.

Although some have found that opioids inhibit the activation of the HPA axis in response to stressors, others have found the opposite effect. For example, in some studies morphine has been found to increase the release of ACTH in response to epinephrine (18), laparotomy (38), and ether (113), and the rise in corticosterone levels in response to formalin was increased in morphine-dependent rats (43). Moreover, Buckingham & Cooper (38) found that chronically morphine-treated rats showed no stress response. The reasons for these discrepancies are not known, but because morphine itself can activate the HPA axis, the experimental outcomes could be affected by such independent variables as the dose of morphine used, the timing of the administration of morphine, and the presentation of the stressor. The stimulation of the HPA axis produced by morphine could summate with the stress-induced activation; moreover, the mechanisms underlying the responses to different stressors may not be the same, and morphine may interact differentially with various stressors. Thus, generalization of the effects of morphine on the stres response across studies is difficult.

Other opioids also can affect the response to stress. Normorphine potentiates whereas pentazocine and levorphanol inhibit the ether stress-induced elevation in corticosterone in mice (20). Met-enkephalin administered into the lateral ventricles (114) and (D-Ala5, Met5)-enkephalin administered into the third ventricle (53) increase the activation of the HPA axis in response to stress. These results suggest that at least some of the effects of opioids on the response of the HPA to stress are centrally mediated, and results of other studies support this conclusion. Ether-laparotomy stress increases the hypothalamic CRF concentration, but a reduction in the concentration occurs if morphine pretreatment has been performed (109). In another study morphine pretreatment inhibited the stress-induced rise in hypothalamic CRF content; however, there was no significant difference in the plasma levels of ACTH or

corticosterone. These results suggest that the decrease in hypothalamic CRF content is not due to excess release but a decreased rate of synthesis (76). However, Buckingham (18) found that morphine increases the epinephrine stress-induced elevations in hypothalamic CRF content.

ROLE OF ENDOGENOUS OPIOIDS IN CONTROL OF THE HPA AXIS

Opioid antagonists have been used to attempt to determine whether endogenous opioid systems are involved in the control of the activity of the HPA axis. Endogenous opioid systems could modulate basal activity, or they could play a role in the stress-induced activation of the HPA axis.

Role in Control of Basal Activity of the HPA Axis

Before the discovery of the endogenous opioid peptides, the effects of naloxone on the HPA axis were studied to determine whether naloxone was a "pure" antagonist in this system or whether it had some agonist-type effects. Later, the effects of opioid antagonists were studied to determine whether endogenous opioid systems are involved in the control of the basal activity of the HPA axis, i.e. whether opioid antagonists could block some tonic inhibitory or stimulatory "tone" produced by endogenous opioids. Naloxone, like opioid agonists, does increase plasma corticosterone levels, but only after administration of very high doses [23 and 46 mg/kg intraperitoneally (i.p.)] (25, 27). Because such high doses of naloxone were required, it is possible that the activation of the HPA axis is due to a nonspecific effect of naloxone (115). However, it is conceivable that relatively high doses of opioid antagonists are required to affect the HPA axis because the endogenous opioid systems modulating the axis involve non-mu-type opioid receptors where antagonists such as naloxone have less affinity. Some investigators have found that lower, although still high, doses of naloxone can stimulate the HPA axis. For example, naloxone at a dose equal to or greater then 6.0 mg/kg i.v. (52, 116, 117) or 10 mg/kg i.p. (50) stimulates the HPA axis in rats. However, when even lower doses were studied, the results were variable across experiments. Thus, the involvement of endogenous opioids in the control of the basal activity of the HPA axis is not clear.

It has been reported that in rats, naloxone has no effect on the release of ACTH and corticosterone (36, 68, 98, 113), stimulates the release of both ACTH and corticosterone (30, 50, 116–118), and increases the release of corticosterone in the rat, but has no effect on (16) or decreases (52) the release of ACTH and decreases the release of corticosterone (37, 58). It is possible that the effects of naloxone on the HPA axis are dependent on the time of day of testing, since Montilla et al (119) found that naloxone at (2.5 mg/kg i.p.)

had no effect on a.m or p.m. plasma levels of corticosterone, whereas 5.0 mg/kg increased p.m. levels and 10.0 mg/kg increased both a.m. and p.m. levels.

Other opioid antagonists also have been reported to affect the HPA axis. Pohorecky et al (59) found that WIN 44,441-3 causes a dose-dependent increase in plasma levels of corticosterone, but others have found that it does not affect plasma levels of corticosterone (36) or that it causes a decrease (37, 58). Another compound that has antagonist activity at kappa receptors, MR-2266, causes a slight rise in plasma ACTH levels in rats (26). Nalorphine, which has antagonist activity at mu receptors but agonist activity at other opioid receptors, causes adrenal ascorbic acid depletion in anesthetized rats (112) and increases plasma levels of corticosterone in rats (25, 27) and plasma cortisol in cats (23).

At least some of the stimulatory effects of opioid antagonists appear to be centrally mediated, since the i.c.v. administration of naloxone or naltrexone causes an increase in plasma levels of corticosterone (120). In addition, infusion of naltrexone into the third ventricle caused increases in portal levels of CRF (100), and the increases in plasma levels of ACTH produced by naloxone could be abolished by pretreatment with antiserum to CRF (101). Some data suggest that naloxone could stimulate the release of CRF through a direct effect on the hypothalamus. For example, naloxone increases plasma levels of ACTH and corticosterone in rats with hypothalamic deafferentation (118). However, naloxone affects neither the CRF content nor the release of CRF from hypothalami in vitro (18, 85, 98, 113).

Naloxone could stimulate the HPA axis by interacting at the level of the pituitary, but some studies have found that naloxone affects neither the basal nor the CRF-stimulated release of ACTH from pituitary tissue in vitro (18, 38, 52). Although Eisenberg (120) reported that systemic administration of naloxone methylbromide, a quaternary analog of naloxone that does not cross the blood-brain barrier, does not stimulate the HPA axis, others have found that it does increase plasma levels of both ACTH and corticosterone (121), suggesting that the pituitary could be a site of action.

It is not clear whether naloxone has a direct effect on the adrenal cortex or whether any effect on the adrenal is stimulatory or inhibitory. Naloxone has been reported to cause the release of cortisol from slices of guinea pig adrenals in vitro (88). The finding that naloxone increased plasma levels of corticosterone in studies in which ACTH levels were not affected (16) or were decreased (52) also supports this conclusion. However, naloxone does not increase corticosterone levels in hypophysectomized rats or in rats pretreated with dexamethasone (16, 118), and systemic administration of the quaternary analog naloxone methylbromide does not cause the release of corticosterone (120). These results suggest that there is no direct stimulatory effect on the

adrenal. Lymangrover et al (94) found that low concentrations of naloxone increased but higher concentrations decreased both the basal and ACTH-stimulated release of corticosterone from superfused rat adrenocortical tissue; however, others have found that naloxone and naltrexone reduced the steroidogenic response to ACTH (87, 122).

Role in Stress-Induced Activation of the HPA Axis

Some data suggest that endogenous opioids might play a role in the stress-induced activation of the HPA axis in rats, but the data are conflicting. It has been reported that the activation of the HPA axis in response to stress is reduced in subjects pretreated with opioid antagonists, indicating that endogenous opioid systems have a facilatory role in mediating the stress response. For example, naloxone inhibits the ether stress-induced release of ACTH and corticosterone in rats (98, 113). However, Xu & McCann (117) have found that high i.v. doses of naloxone only partially decrease the ACTH response to ether or restraint stress in rats, and others have found that naloxone does not affect corticosterone levels after stress from restraint plus exposure to cold (123). Moreover, the responses to photic or audiogenic stress are higher in naloxone-treated rats (118). Thus, the effects of naloxone might be dependent on the type of stressor. In one study, naloxone did not reduce the magnitude of the corticosterone response to restraint stress, but the fall in the corticosterone level after stress was slowed (124), suggesting that endogenous opioids might be involved in resetting the axis to basal levels. Similarly, the effects of opioid antagonists on stress-induced changes in the HPA axis in mice also are difficult to interpret. Naltrexone and naloxone were found to inhibit the ether stress-induced elevation in corticosterone in mice (20), but others have found that low doses of naloxone potentiate, whereas high doses reduce, the effects of ether stress (125).

EFFECTS IN HUMANS

Effects of Opioid Agonists

The response of the HPA axis to opioids in humans is the opposite of the response in rodents; opioid agonists inhibit whereas opioid antagonists stimulate the HPA axis in humans. Some of the earlier studies with humans have been summarized by Sloan (126). In 1958 Eisenman et al (127) showed that the acute administration of morphine causes a decrease in the urinary excretion of 17-ketosteroids in males. As 17-ketosteroids are secreted by steroid-producing tissue and reflect both adrenal and gonadal steroids, this effect could be due to adrenal and/or gonadal suppression. Later, it was found that morphine decreases plasma levels of both ACTH and cortisol in both

males and females (128–131), suppressing the early-morning rise in plasma glucocorticoid levels and increasing the late morning decline (132). Although Tolis et al (133) reported that acute administration of morphine did not affect plasma cortisol levels in women, the subjects in that study were tested prior to undergoing expected surgery, and the stress of expected surgery could have confounded the interpretation of the data. Eisenman et al (134) found that the plasma levels of 17-hydroxycorticosteroids measured in the morning in individuals receiving chronic administration of morphine were lower than those in controls and that urinary excretion of 17-hydroxycorticosteroids was also decreased. Partial tolerance to the decrease in the urinary excretion of 17-ketosteroids developed in men only after administration for more than 4 months (127). Although the adrenal responsiveness to ACTH was not different between acute morphine- and placebo-treated groups (132), during chronic treatment adrenal cortical function was depressed but still capable of responding to direct stimulation by ACTH (134). Withdrawal from chronic morphine administration caused a stress-type rise in urinary 17-ketosteroid excretion (127) and increases in both plasma and urinary 17-hydroxycorticosteroids (134). Thus, as opposed to the effects of opioids in rats, the response of the HPA axis to the acute administration of opioids and the response during opioid withdrawal are opposite.

The acute administration of other opioid agonists, such as methadone (128), pentazocine (128, 130), buprenorphine (130, 135), and the mixed agonist-antagonist nalorphine (128, 130) also decreases plasma cortisol levels in humans. Serum cortisol levels in subjects undergoing chronic methadone treatment are not different from those in controls (136–138); however, ACTH levels are elevated, suggesting that chronic methadone produces a state of compensated primary hypoadrenalism wherein decreased cortisol secretion is compensated for by increased ACTH secretion (138). Supporting this conclusion, Dackis et al (137) found that cortisol release after the administration of ACTH is reduced in chronic methadone-treated subjects. In addition, most methadone-maintained individuals show a normal response to metyrapone challenge, a direct measurement of hypothalamic-pituitary reserve (139). The effects of chronic heroin use are less clear. It has been reported that there are no changes in plasma cortisol levels in men during chronic heroin use (136, 140), but there also have been reports of lower plasma ACTH levels (140) and lower plasma cortisol levels (141). Heroin users may have altered circadian rhythms of ACTH and cortisol release (9, 141).

Opioid peptides also inhibit the HPA axis. The i.v. infusion of β-endorphin into normal human subjects causes decreases in both plasma levels of ACTH and cortisol (142), but Catlin et al (143) found that β-endorphin did not affect serum cortisol levels in depressed subjects or withdrawing methadone addicts. The opioid peptide FK 33-824 decreases plasma levels of ACTH and cortisol

in normal subjects (8, 128, 144–146); however, these effects are not blocked by naloxone (128, 144, 145). The reason behind the lack of blockade by naloxone is not known, but it might indicate that a nonopioid-type mechanism mediates the effect.

In contrast to the results obtained with rodents, the data suggest that opioid agonists have a direct effect on the pituitary. Whereas the adrenal responsiveness to ACTH in acute morphine-treated (132) or FK 33-824-treated (147) subjects is not different from that in controls, the ACTH and cortisol increases produced by CRF and vasopressin are reduced by morphine or FK 33-824 (84, 131, 132, 147–150). These findings demonstrate that opioid agonists have a direct inhibitory effect at the level of the pituitary in humans.

Effects of Opioid Antagonists

Many studies indicate that opioid antagonists stimulate the HPA axis in humans, increasing plasma levels of both ACTH and cortisol in men and women (8, 151–157). This finding suggests that the HPA axis may be tonically inhibited by an endogenous opioid system; however, some others have not found such a stimulatory effect of opioid antagonists (7, 158, 159). Naloxone can enhance the stimulatory effects of CRF on ACTH and cortisol release (131, 160), as well as increase the stress-induced (152) or exercise-induced (156) rise in cortisol. However, naloxone does not enhance the rise in cortisol level in response to insulin-induced hypoglycemia (8, 158, 159). These results indicate the endogenous opioid systems may be differentially involved in the activation of the HPA axis in response to different stressors. Naloxone does not increase plasma ACTH levels in recently detoxified methadone addicts compared with opiate-naive controls (161); this suggests that endogenous opioid systems may be altered as a consequence of treatment with methadone.

CONCLUSIONS

The studies summarized above show that opioids can affect the HPA axis and suggest that endogenous opioid systems might be involved in the control of the HPA axis. Although a great deal is known about the effects of opioids on the HPA axis in many species, much remains unclear. The current lack of knowledge is due partly to the contradictory findings of different studies. In many cases disparate results appear to be the rule rather than the exception, and it is difficult to draw definitive conclusions in science on the basis of majority opinion. The discrepancies between studies may be due in part to the complexity of the systems mediating the effects. As endogenous opioid systems have been hypothesized to be involved in the control of numerous bodily functions, the effect of exogenously administered opioids on the HPA axis could be dependent on the physiological state of the organism (time of

day, level of activity, body temperature, degree of hunger and/or stress, etc) because the endogenous opioid systems may be activated differentially under these conditions. The apparent inconsistencies may be telling us something about the how the endogenous opioid systems operate and the intricacy with which the systems are controlled.

It is now thought that there are multiple subtypes of mu, kappa, and possibly delta opioid receptors; therefore, some of the discrepancies across studies might be due to the differential involvement of specific opioid receptor subtypes in the control of the HPA axis and the lack of selectivity of the compounds studied previously. Thus, many of the earlier experiments should be repeated by using highly receptor-selective opioid agonists and antagonists. This is especially true of the clinical studies, of which relatively few involved highly selective opioids. Because opioids have such profound effects on the HPA axis in humans, these experiments could yield new and important information. For example, disruption of endogenous opioid systems involved in modulating the HPA axis may lead to certain disease states. Moreover, it is possible that some receptor-selective opioids have some utility in the treatment of neuroendocrine disorders or can be used to test the functional integrity of the axis.

The study of the effects of opioids on the HPA axis began several decades before the discovery of the endogenous opioid peptides. These early studies first led to experiments characterizing the effects of the opioid peptides on the HPA axis and later to studies determining the involvement of endogenous opioid systems in the control of the HPA axis. It is noteworthy that studies of opiate alkaloids, which are subject to widespread abuse, have led to the discovery of information of fundamental importance outside of the area of drug abuse.

ACKNOWLEDGMENT

This work was supported in part by National Institute on Drug Abuse grant DA-04113.

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