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The Effects of Opioids and Opioid Analogs on Animal and Human Endocrine Systems

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Opioid abuse has increased in the last decade, primarily as a result of increased access to prescription opioids. Physicians are also increasingly administering opioid analgesics for noncancer chronic pain. Thus, knowledge of the long-term consequences of opioid use/abuse has important implications for fully evaluating the clinical usefulness of opioid medications. Many studies have examined the effect of opioids on the endocrine system; however, a systematic review of the endocrine actions of opioids in both humans and animals has, to our knowledge, not been published since 1984. Thus, we reviewed the literature on the effect of opioids on the endocrine system. We included both acute and chronic effects of opioids, with the majority of the studies done on the acute effects although chronic effects are more physiologically relevant. In humans and laboratory animals, opioids generally increase GH and prolactin and decrease LH, testosterone, estradiol, and oxytocin. In humans, opioids increase TSH, whereas in rodents, TSH is decreased. In both rodents and humans, the reports of effects of opioids on arginine vasopressin and ACTH are conflicting. Opioids act preferentially at different receptor sites leading to stimulatory or inhibitory effects on hormone release. Increasing opioid abuse primarily leads to hypogonadism but may also affect the secretion of other pituitary hormones. The potential consequences of hypogonadism include decreased libido and erectile dysfunction in men, oligomenorrhea or amenorrhea in women, and bone loss or infertility in both sexes. Opioids may increase or decrease food intake, depending on the type of opioid and the duration of action. Additionally, opioids may act through the sympathetic nervous system to cause hyperglycemia and impaired insulin secretion. In this review, recent information regarding endocrine disorders among opioid abusers is presented. **(*Endocrine Reviews* 31: 98–132, 2010)**

I. Introduction/Epidemiology

The National Institute on Drug Abuse (NIDA) "Research Report Series-Prescription Drugs: Abuse and Addiction" (1) defines prescription drug misuse as "taking

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Abbreviations: AVP, Arginine vasopressin; CNS, central nervous system; CS, corticosterone; DALA, D-ala2-met-enkephalinamide; DAMME, D-Ala2,MePhe4,met-(O)enkephalin-ol; ED, emergency department; HPA, hypothalamic-pituitary-adrenal; HPG, hypothalamic-pituitary-gonadal; i.c.v., intracerebroventricular; OT, oxytocin; PC, prohormone convertase; PCOS, polycystic ovary syndrome; POMC, pro-opiomelanocortin; PRL, prolactin.

a medication in a manner other than that prescribed or for a different condition than that for which the medication is prescribed" and prescription drug abuse as "the intentional misuse of a medication outside of the normally accepted standards of its use." Because prescription analgesics have been increasingly used to treat chronic pain, opioid use/abuse has been on the rise in recent years. Physicians are increasingly prescribing opioid analgesics, such as vicodin (hydrocodone/acetaminophen), darvocet-N (propoxyphen/acetaminophen), fentanyl and methadone because they are very effective in reducing pain and are inexpensive and long-lasting, despite the potential risk for addiction to these drugs (2). These medications are frequently used for osteoarthritis, back pain, sports injuries, and other muscular-skeletal conditions, rheumatological conditions, and headaches. Currently, little information is available on the long-term consequences of chronic opioid use, making it difficult for physicians and their patients to weigh the risks and benefits of prescription opioids before the initiation of therapy. Thus, the goal of this article is to comprehensively review the endocrine effects of opioids to inform clinicians of the endocrine (side) effects that may occur and identify knowledge gaps that need further research.

In the 1990s, there was an increase in the use of opioids, which is illustrated by the almost 10-fold increase in methadone prescriptions from 1997 to 2005 (3). After the increase in the 1990s, the epidemiological data over the mid-late 2000s shows a steady, high prevalence of prescription opioid misuse in the United States (4, 5). International prevalence data show similar trends concerning levels of misuse (6). Many factors probably contribute to the increased prevalence of prescription opioid misuse, including changes in medication formulations, pharmaceutical industry marketing, and the aging population (7). However, the situation that has been most associated with prescription opioid misuse is the increased treatment of chronic noncancer pain (8, 9). The following surveys give some epidemiological description of opioid use and misuse.

The 2006 National Survey on Drug Use and Health (NSDUH) (10) ascertained drug use patterns of a nationally representative sample of more than 67,000 noninstitutionalized individuals, age 12 and older. According to the NSDUH, an estimated 2.1% of the individuals of that age group were current nonmedical users of prescription pain relievers in 2006. Thus, the number of Americans estimated to use opioid pain relievers was 5.2 million, compared with 1.2 million using stimulants and 2.1 million using sedatives and tranquilizers. Of particular concern is that more persons age 12 and over initiated misuse of pain relievers (2.2 million) than any other illicit substance. By comparison, 2.1 million started using marijuana (10).

Perhaps the most interesting new fact from the recent NSDUH survey relates to the source of pain relievers that were used. According to the 2006 NSDUH (10), 55.7% of those who misused pain relievers said they received their medication from friends and family, and 80.7% of these individuals reported the friend or relative had obtained the drugs from just one doctor. Only 3.9% reported obtaining the drug from a drug dealer or stranger, and only 0.1% reported buying the drug from the Internet, although this may have increased in the last few years.

Monitoring the Future (5) is a series of large, annual surveys of nationally representative samples of public and private secondary school students throughout the United States. Among the 12th-graders, annual prevalence rates for opioids increased substantially between 1990 and 2002, but rates have leveled off since 2003, currently standing at about 9.0% (5).

The Drug Abuse Warning Network (DAWN) is a public health surveillance system that monitors drug-related hospital emergency department (ED) visits and drug-related deaths in select metropolitan areas from 1995 to 2002. DAWN data show that "drug-related" ED visits involving prescription opioids increased yearly in this period from 42,857 to 108,320, representing a 153% increase (11). In 2002, prescription opioids represented 16% of total drug-related ED visits, with hydrocodone and oxycodone the most frequently mentioned opioids. In 2002 and 2003, the past year use of OxyContin (oxycodone hydrochloride) and Vicodin by 12th-graders was reported at about 4 and 10%, respectively. This raises serious concern about prescription opioid abuse among youth. In general, opioids are the most common cause of drug poisoning, pointing out the potential danger of prescription opioids (12).

In addition, evidence points toward an increase in substance abuse among adults aged 60 yr and older (13). A similar increase in substance abuse has been found among aging baby boomers (14). Alcohol and prescription drug misuse may affect as many as 17% of older adults (13, 15). An interesting difference between prescription opioid misuse and illicit drug abuse is the greater nonmedical use of opioids by adolescent females (16). This study also showed that the motive for use of prescription opioids was more consistent with a therapeutic indication (79%) than that for other prescription medication misuse. In an adult population, regular opioid use increased with age, decreased with education level, and was more common in females and in non-Hispanic whites (17). African-Americans had slightly lower rates of opioid use than non-Hispanic whites, with Hispanics having the lowest rate (17).

Opioids, primarily Vicodin and heroin, are present and highly sought after within illicit drug markets. The Internet has also been a portal for sales and access to prescription opioids (18), although as stated above, the percentage as reported in surveys is probably low. An Internet search for Vicodin using the search engine "Google" resulted in more than 15 million hits, and several of these are advertisements for this drug that guarantee next day delivery. Thus, there appears to be relatively easy access to opioid drugs, despite governmental attempts to curb illicit drug sales.

In summary, the greatest factor associated with increasing prevalence of prescription opioid misuse appears to be the increased willingness of physicians to prescribe these drugs (19). This appears to be in large part due to the increased number of prescriptions for treatment of chronic noncancer pain. Importantly, the growing use of opioid drugs occurs in the absence of sufficient understanding of the health implications of long-term opioid use. For example, the effects of long-term opioid use/abuse on the endocrine system have not been well studied because most studies on the effects of opioids on the endocrine system focus on acute effects. It is important to realize that chronic effects of opioids on the endocrine system cannot simply be presumed to be a prolongation of acute effects because acute and chronic treatment regimens may produce entirely different profiles with respect to both the magnitude and the direction of the effects.

A. Clinical importance of opioids on the endocrine system

Most clinical studies have focused on hypogonadism in relation to opioid abuse, particularly in men. Currently, the limited clinical awareness of the endocrine effects of opioids, together with the lack of information on their long-term effects, may result in insufficient discussion with patients when initiation of long-term opioid therapy is being considered.

This review includes both clinical and laboratory studies on the effects of opioids and their analogs on the endocrine system as a way to understand the underlying mechanisms and the complications of long-term opioid use/abuse. We analyze and summarize in detail, for both animals and humans, the effects of opioids on the hormones of the anterior pituitary [GH, prolactin (PRL), TSH, ACTH, LH, and FSH] and the posterior pituitary [arginine vasopressin (AVP) and oxytocin (OT)]. An exploration of the differences in the effects of opioids between humans and animals is included, as well as differences between sexes. An understanding of the intricacies of the opioid interaction with the endocrine system and of the resulting medical consequences of use/abuse will increase awareness of the detrimental effects of opioids and hopefully spur more research on their long-term health effects.

II. Pharmacology and Physiology of Opioids and Their Derivatives

A. Opioids and their derivatives

Opiates are derived from opium, which is extracted from the sap of the opium poppy. The term "opiate" is used for the alkaloids of opium, such as morphine, as well as for the synthetic drugs derived from opium alkaloids, such as codeine and heroin. The term opioid includes all opioid analgesics regardless of their source. The endogenous opioid system consists of the endogenous opioid peptides and their corresponding binding sites with which these peptides interact to produce their effects. Figure 1A depicts the structure of common opioids, and Fig. 1B depicts the structure of the main endogenous opioids. Early classical pharmacological studies identified several classes of opioid receptors. At least three classes of opioid receptors, named mu (μ), delta (δ) and kappa (κ), have been cloned (20, 21). These classical opioid receptors belong to the family of the guanine regulatory binding (G) protein-coupled receptor and are coupled to the second messenger systems via inhibitory G proteins (Gi/Go). Opioid receptors mediate the actions of endogenous and exogenous opioids and are present in the brain and throughout the body, including the endocrine organs, such as the adrenal cortex and the gonads (22).

B. Classes of opioids

Three major classes of endogenous opioid peptides (endorphins, enkephalins, and dynorphins) have been identified (Table 1). These peptides are derived from three distinct precursor proteins: pro-opiomelanocortin (POMC), preproenkephalin A, and preproenkephalin B, respectively (23). The discovery of endomorphin-1 and endomorphin-2 has extended the endogenous opioid peptide family (24). It is generally thought that β-endorphin, enkephalins, and dynorphins are selective agonists for the μ-, δ-, and κ-opioid receptors, respectively (Table 1). Endomorphin-1 and endomorphin-2 have μ-receptor affinity and play a biological role in pain perception, stress responses, and homeostasis (25). However, the endogenous opioid peptides (as well as exogenous opioids) can bind to more than one type of opioid receptor to produce their actions (Table 2). The endogenous opioid peptides exert diverse physiological and pharmacological effects in mammals and humans, including modulation of motor activity (26), seizure threshold (27–29), immune responses (30, 31), water and food intake (32), and regulation of gastrointestinal (28, 33, 34), cardiovascular (35–37), neuroendocrine (38–41), and cognitive (28, 42) functions. However, their most widely recognized clinical effect is analgesia or pain relief (antinociception in ro-

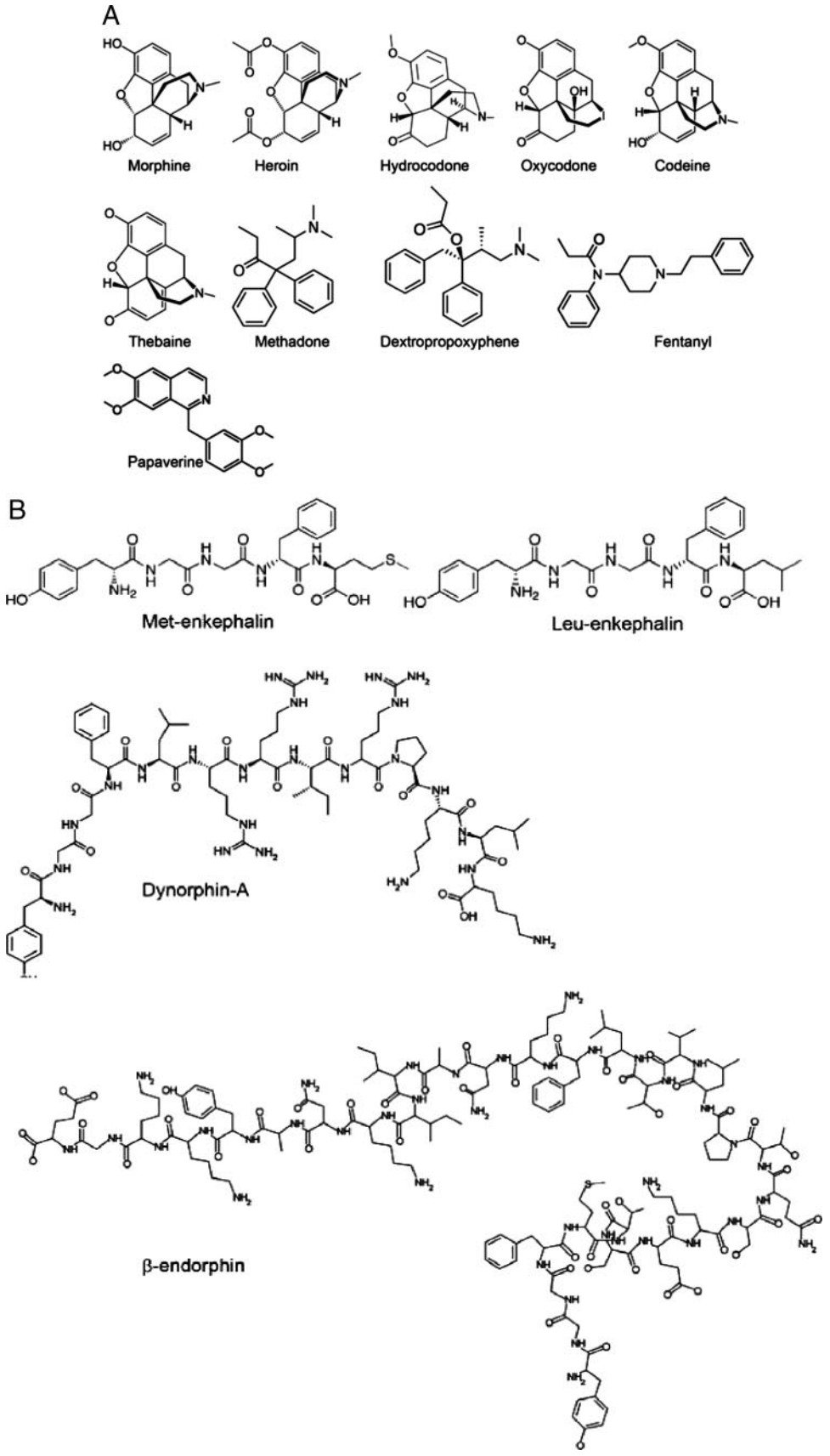

FIG. 1. Structure of common exogenous (A) and endogenous (B) opioids.

TABLE 1. Overview of endogenous opioids, their precursors, and main receptors

Endogenous peptide	Precursor	Main opioid receptor
β-Endorphin	POMC	μ
Enkephalins	Preproenkephalin A	δ
Dynorphins	Preproenkephalin B	κ

dents) (43, 44). Brain regions containing opioid receptors are given in Table 3.

C. Analgesic effects of opioids

The analgesic effects of opioids are thought to be mediated at both central and peripheral synapses (43). It is generally accepted that opioids suppress pain transmission at the spinal cord via both pre- and postsynaptic mechanisms involving inhibition of calcium channels and activation of potassium channels, respectively (44). Opioids can also facilitate the function of the descending pain inhibitory systems by inhibiting the activity of γ-aminobutyric acid-ergic interneurons (44, 45). In addition, opioids suppress pain perception at the somatosensory cortex and alter the affective component of pain via an action at the level of the limbic structures (46). However, in patients, chronic administration of opioid analgesics, such as morphine, at least under some conditions, produces a state of higher pain sensitivity or hyperalgesia (47). This may lead to higher doses of opioids used with potential complications. Endogenous opioid peptides, particularly enkephalins, are released at numerous central nervous system (CNS) structures that play a critical role in pain modulation (48, 49). For example, laminae I, II, and V of the spinal cord are rich in enkephalinergic neurons. Enkephalins are also released in the periaqueductal gray and rostral ventromedial medulla, both of which play an integral role in opioid-induced analgesia (44). Endogenous morphine has been found in low concentrations in the brain (50).

Some natural derivatives of opium such as morphine, thebaine, and papaverine have long been used for their analgesic effects (51). Morphine and other opioids with high abuse potential bind preferentially to the μ-opioid receptors; however, the ability of these drugs to activate opioid receptors and alter signaling varies from partial to full agonists. In addition, morphine binds, albeit with lower affinity, to the δ- and κ-opioid receptors (52). However, the antinociceptive effect of morphine and its rewarding and addictive effects are mediated primarily

TABLE 2. Endogenous and exogenous opioid ligands and their relative receptor selectivity

Ligand	Opioid receptors		
	μ	δ	κ
β-Endorphin	++++	++	++
Leu-enkephalin	++	+++	0
Met-enkephalin	++	+++	0
Dynorphin A (1-17)	++	0	+++
Endomorphin-1	+++++	0	0
Endomorphin-2	+++++	0	0
Morphine	+++	0	+
Heroin	+++	+	0
Fentanyl	+++	0	0
Sufentanil	+++	0	0
Methadone	+++	0	0
DALA (FK 33-824)	++	+++	0
DAMME	++	++	0
U50,488H	0	0	++++
Nalorphine	−	0	+++
Naloxone	−	−	−
Naltrexone	−	−	−
CTOP	−	0	0
Buprenorphine	+/−	− (?)	−
Pentazocin	−	0	+++

+, Agonist; −, antagonist; 0, no significant affinity; +/−, partial agonist; (?), unclear; CTOP, D-Pen-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2. [Taken from Refs. 24 and 404–408.]

TABLE 3. Localization of opioid receptors in related brain regions and peripheral tissues

Brain region	Opioid receptors		
	μ	δ	κ
Cortex			
Cingulate cortex	+/++++	+/++++	+/++
Frontal parietal cortex	++/+++	++/+++	−/++
Temporal cortex	++/+++	+/+++	−/+
Hippocampus			
Pyramidal cell layers	+++	++	+
Dentate gyrus (dorsal)	−	−	−
Dentate gyrus (ventral)	+++/++++	+	+
Caudate putamen	++++	++++	+++
Nucleus accumbens	++++	++++	+++
Amygdala			
Medial nucleus	+++	++	++
Central nucleus	−	−	++
Lateral	++++	+++	+++
Basolateral	++++	+++	+++
Thalamus			
Laterodorsal nucleus	++	−	−
Central medial nucleus	++++	+	++
Medial geniculate nucleus	++++	−	+
Zona incerta	−	−	++
Hypothalamus			
Lateral	+	−	++
Paraventricular nucleus	−	−	++
Supraoptic nucleus	−	−	++
Median eminence	−	−	+++
Arcuate nucleus	−	−	++
Ventral tegmental area	++	−	
Raphe nucleus	+++	−	++
Pituitary (rat)	+/−	+/−	++
Pituitary (human)	+++	+/−	++

+, ++, or +++ shows the expression level of the receptor; −, no detectable density; +/− or +/++, shows the density in different layers or nuclei. [Taken from Refs. 409–412].

through the μ-opioid receptors. For example, mice lacking the μ-opioid receptors do not exhibit morphine-induced antinociception, reward, or naloxone-precipitated withdrawal symptoms (53, 54).

D. Synthetic and semisynthetic opioids

Synthetic opioids have been used to mimic the effects of endogenous opioids in the body because these drugs and endogenous opioids bind to the same opioid receptors. Heroin, or diacetylmorphine, a semisynthetic opiate derived from morphine, can be used for pain suppression and is used as a recreational street drug. This μ-receptor agonist is highly addictive (55). Other examples of semisynthetic opioids are hydrocodone and oxycodone. Fully synthetic opioids are used as very powerful analgesics; fentanyl is about 75 times more potent than morphine (56). Methadone, another synthetic opioid, is commonly used to prevent relapse in opioid addicts because of its longer-lasting effects that prevent withdrawal syndrome (50). D-Ala2-met-enkephalinamide (DALA), also known as FK 33-824, and D-Ala2,MePhe4,met-(O)enkephalin-ol (DAMME) are synthetic met-enkephalin analogs.

E. Opioid antagonists

Opioid receptor antagonists are commonly used in preclinical studies to determine whether a response is specifically mediated by the endogenous opioid system. These drugs are also used clinically to decrease opioid intake and to reverse the effects of opioid overdose. The most commonly used antagonist is naloxone, which binds to μ-opioid receptors in a competitive manner (57). Naloxone is synthesized from thebaine, a natural derivative of opium. Naltrexone is another opioid receptor antagonist, used similarly to naloxone to block opioids from binding to their receptors. Naltrexone has a slower onset but longer duration of action than naloxone. These antagonists have preference for μ-opioid receptors, but at higher doses they antagonize both δ- and κ-opioid receptors. Accordingly, these drugs are considered nonselective opioid receptor antagonists (Table 2).

F. Opioids and the stress response

The endogenous opioid system is implicated in the response to stress (58–60). Opioid-containing neurons have been shown to innervate the median eminence and paraventricular nucleus of the hypothalamus, thereby regulating inputs to ACTH-controlling neurons in the anterior pituitary (61, 62). In addition, dynorphin-like peptides have been found to colocalize with CRH and may be cosecreted with CRH in the hypophyseal portal circulation to modulate ACTH release (63). Thus, the hypothalamic-pituitary-adrenal (HPA) axis represents a modulatory target for the action of exogenous and endogenous opioid ligands. Indeed, a growing body of evidence suggests that opioids regulate mechanisms activated during the stress response (58, 60). Conversely, the endogenous opioid system is activated by stressful situations (64), raising the possibility that activation of the endogenous opioid system may play a role in stress-mediated events.

Although stress is often linked to unpleasant events, the stress response can be beneficial. For example, exposure to mild stressors has been shown to activate the HPA axis, which is thought to play an important role in mediating cognitive adaptive changes that promote survival (65). The HPA axis is essential in mediating the stress response (66). Activation of the HPA axis is initiated by secretion of CRH from the paraventricular nucleus of the hypothalamus to the portal system of the median eminence. Subsequently, CRH binds to its receptor in the anterior pituitary that leads to the synthesis of POMC, a large precursor molecule that is cleaved into several smaller functional peptides, such as ACTH and β-endorphin (67). ACTH is then secreted and circulates to the adrenal gland, where it causes the release of glucocorticoids, cortisol (in humans), or corticosterone (CS) (in animals). Circulating glucocorticoids mediate the stress response and are essential for survival. Cortisol/CS also modulates CRH and ACTH release through a negative feedback mechanism. The inhibitory action of cortisol/CS, however, can be overcome by further release of CRH under severe or chronic stress situations (65, 68). Thus, severe stressors may lead to a greater stress response (69) and possibly to unpredictable and uncontrollable adaptive changes.

III. The Effects of Opioids on Endocrine Systems in Animals and Humans (Fig. 2 and Table 4)

A. GH/IGF-I axis

1. Animal studies

Opioids and their analogs have been well recognized as stimulants of GH release in animals. Several studies in rats have examined the acute effects of opioids on GH release and the pathways involved. For example, morphine sulfate produced a 3-fold increase in plasma GH concentrations 2 h after intracerebroventricular (i.c.v.) injection and transiently increased the plasma concentration and liver content of IGF-I and IGF binding protein-1 (70). However, morphine-6-glucuronide did not produce any significant alterations in plasma GH and IGF-I levels, suggesting that differential affinities and/or selectivity of morphine and morphine-6-glucuronide to different opioid receptor/subtypes might be responsible for their distinct effects on the GH/IGF-I system (70). β-Endorphin, administered iv or directly into the rat hypothalamus, increased GH levels

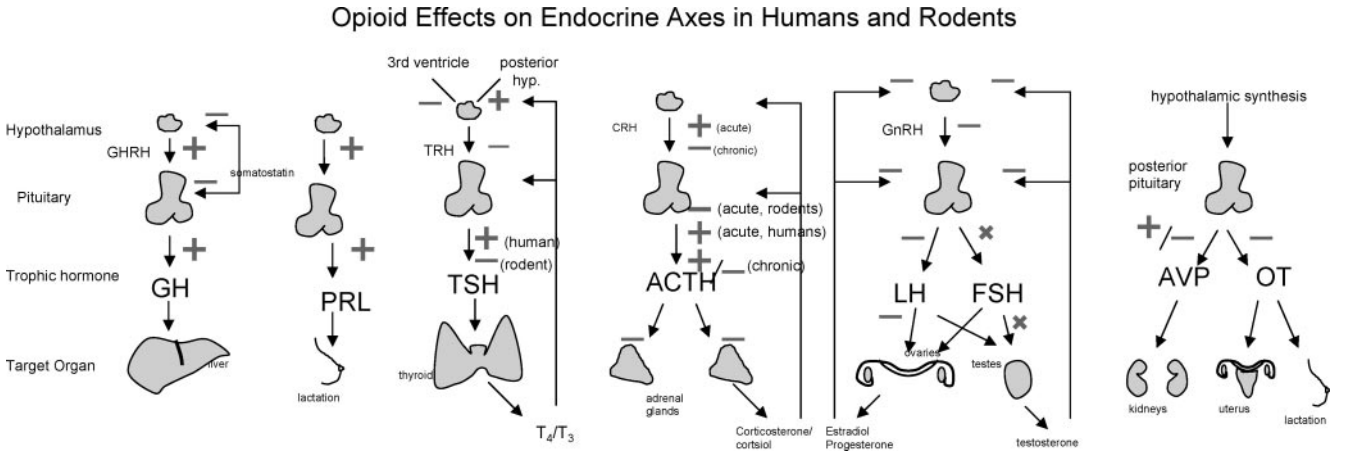

FIG. 2. Summary of the effects of opioids and opioid analogs on endocrine axes in humans and rodents. X indicates no effect.

(71). This increase was attenuated by naloxone (71), suggesting that opioid receptors are involved in this response. α-Adrenergic receptors are also involved in the action of opioids on the release of GH, as phenoxybenzamine, an α-adrenergic blocking agent, inhibited both spontaneous GH release and the response to FK 33-824, a synthetic enkephalin analog (72). In addition, β-endorphin or other endogenous opioid peptides may mediate the GH secretion that is induced by α-2-adrenergic stimulation because β-endorphin antiserum and naloxone reduced the stimulatory effect of the α-2-adrenergic agonist, clonidine, on GH release (73). Induction of stress resulted in a decrease of GH in male rats, whereas sc administration of morphine and methadone increased plasma GH levels (74, 75), suggesting that stress and opioids may influence GH release via separate mechanisms. In neonatal rat pups exposed to morphine, naloxone-induced opioid withdrawal suppressed GH levels in a dose-dependent manner (76).

The effect of opioids on GH is influenced by sex hormones. In male but not female rats, morphine treatment for 6–12 h resulted in a 12-fold increase of plasma GH levels that peaked after 3 h (77). The opioid-induced GH increase was significantly blunted during an estradiol/progesterone-induced LH surge (77). In female rats, naloxone treatment reduced GH levels by 64% over a similar time period (78).

Opioid analogs have been studied in animals other than the rat. In wethers, administration of FK 33-824 increased GH concentration for up to 3 h after administration, with a return to basal levels by 2–6 d after the infusion (79). Likewise, a 30-min infusion of DAMME, a μ/δ-opioid agonist, increased plasma GH in Holstein heifer calves via opioid receptors located inside the blood-brain barrier (80). In prepubertal gilts, naloxone attenuated the stress-induced increase in GH secretion (81). The effect of these opioids and their analogs is not specific to mammals because FK 33-824 and a β-adrenergic agonist were seen to affect the amplitude and increase mean plasma concentration of GH secretion in broiler chickens (82, 83). Thus, opioids and their analogs have similar stimulatory effects on GH secretion across a number of experimental conditions and animal preparations.

Several investigators have studied the mechanisms by which opioid receptor stimulation affects GH secretion. Acute iv morphine administration results in a GH pulse, suggesting that opioids reset the hypothalamic GH pulse generator (84), an effect that has been shown to be mediated by μ-, κ-, and δ-receptors (85). In neonatal rats, stimulation of μ- and κ-receptors resulted in stimulation and inhibition of GH secretion, respectively, with δ-receptors acting synergistically with the μ-receptors in producing the opioid-induced GH-stimulation (86).

GHRH and somatostatin are also affected by opioids. Treatment of rats with an antiserum against GHRH inhibited the GH stimulatory response to both β-endorphin and morphine (87). The inhibitory effect of somatostatin on GH release was antagonized by endogenous opioids, thus increasing GH pulse frequency and amplitude in hamsters (88). This suggests that opioids stimulate GH

TABLE 4. Summary of the effects of acute and chronic opioids on the endocrine systems of animals and humans

	Acute		Chronic	
Hormone	**Animals**	**Humans**	**Animals**	**Humans**
GH	↑	↑	=	?
PRL	↑	↑	↑	↑/=
TSH	↓	↑	?	?/=
ACTH	↑	↓	↓/↑	↓/=
LH	↓	↓↓	↓	↓↓
FSH	=	=	=	=
Estradiol	↓	↓↓	=	↓=
Testosterone	↓	↓↓	↓	↓↓
AVP	↑/↓	↑/↓	↑/↓	↑/↓
OT	↓	↓	↓/=	↓/=

↑, Stimulation; ↓, inhibition; ↑ ↓, conflicting; =, no change; ?, not studied.

secretion through the release of GHRH and the inhibition of somatostatin.

Other studies have focused on the effects of opioids on hormonal gene transcription. Dobado-Berrios *et al.* (89), using *in situ* hybridization in rat pituitary, found a 22% decrease in GH mRNA levels after chronic (4-d) morphine administration. Furthermore, a single morphine dose decreased the gene transcripts of both the GH receptor and GH binding protein in male rat hippocampi (90). Both studies reveal that opioids act through mechanisms involving regulation of gene expression and transcription.

Overall, these studies indicate that acute administration of opioids usually results in an increase of GH concentrations, which appears to be mediated primarily via central μ-receptors. Given the acute (several hours) time course, this may well be due to release of already stored rather than newly synthesized GH. The sparse information available suggests that chronic (several days) administration of opioids reduces GH mRNA levels. It is not known whether this reduction is dose-dependent or more profound with longer duration of administration. Furthermore, to our knowledge, the effects of opioid treatments lasting more than 1 wk on GH secretion or expression have not been examined either at baseline or after stress or other stimulatory factors.

2. Human studies

Similar to animals, acute administration of opioids and their analogs in human subjects results in increased GH secretion through mechanisms involving the opioid receptors, feedback levels, and gene transcription. In healthy subjects, the minimum morphine dose required for GH stimulation is approximately 15 mg (91). Naloxone, in a constant infusion for 120 min, attenuated the stimulatory effect of GHRH on the secretion of GH, indicating the existence of an opioid-mediated stimulatory tone on GH secretion (92). In healthy women, naloxone infusion starting 1 h before GHRH administration reduced the GHRH-induced release of GH, whereas in healthy men, naloxone did not change this response (93). This sex-related difference in the effect of naloxone on GH secretion suggests a role of sex steroids in mediating the effects of endogenous opioids on GH secretion.

In contrast to the animal studies, there is one human study on the effect of chronic opioid administration on GH. In a study in patients with severe chronic pain receiving intrathecal opioids for a mean duration of 27 months, Abs *et al.* (94) found an IGF-I below -2 SD in 12 of 73 patients and a peak GH response to hypoglycemia below 3 mg/liter in about 15% of subjects. This suggests that chronic opioid administration can result in severe GH deficiency in some, but not all subjects. Insulin levels and sensitivity, and perhaps counterregulatory hormones, may affect this response (95). The involvement of opioid receptors in the effect of opioids on GH is supported by a study in human lymphoblastoid IM-9 cells that showed that morphine significantly altered GH receptor gene expression and GH binding in a naloxone-reversible manner (96). It is not clear whether the *in vivo* effects of opioids are dose-dependent, depend on route (oral or transdermal administration), or to what extent pain and other medications or coexisting conditions may play a role. Furthermore, it is not known whether GH therapy might have any beneficial effects in patients with low GH secondary to opioids.

Other studies used opioid antagonists to examine the effects of opioids on GH. Although chronic administration of naltrexone (50 mg/d for 4 wk) resulted in a 75% decrease in the GHRH-induced GH response in healthy premenopausal women (97), it resulted in a 3-fold increase of the GHRH-induced GH response in obese women (95), even though basal levels of GH, IGF-I, and IGF binding protein-3 were not affected in either group. Opposite effects of naltrexone administration were found in women with polycystic ovary syndrome (PCOS), with an increased GH response after GHRH in lean PCOS women, whereas no effect was seen in obese PCOS women (98). Although these data indicate that opioids alter the response of GH to GHRH and that body composition, sex hormones, and insulin resistance may play a role, the direction and magnitude of the effect of these factors remains poorly understood.

Several human studies involving the effects of opioids on GH levels have been conducted in patients with various diseases. Morphine caused an elevation of GH in both acromegalics and normal subjects. However, higher doses of morphine were required to stimulate GH secretion in normal subjects than in acromegalic subjects, indicating that opioids exert a positive modulating effect on GH secretion in patients with active acromegaly (91). Alternatively, GH secretion in acromegalic patients may be more sensitive to the stimulating effects of opioids. In a retrospective study in patients receiving intrathecal opioids for intractable pain, both IGF-I levels and the GH response to insulin-induced hypoglycemia were significantly decreased compared with controls (94). Fifteen percent of these patients met the criteria for GH deficiency.

3. Summary and overall mechanisms of opioid effects on GH

Overall, whereas acute administration of opioids results in an increase of GH secretion, the effects of chronic opioid administration appear to be much more complex, with GH secretion being inhibited by intrathecal opioids in chronic pain patients and by an opioid antagonist in healthy subjects, whereas the same antagonists increased the GHRH-induced GH response in obese women. Although this response appears to be affected by sex, body

composition, and insulin resistance, much research is needed to understand the potential for opioids to induce GH deficiency.

B. Prolactin

1. Animal studies

Generally, opioids and their analogs stimulate PRL release from the anterior pituitary through an effect at the hypothalamus (99). Direct incubation of morphine or morphine analogs on isolated perfused pituitaries had no effect on PRL release (100, 101). However, across several species, a single systemic injection of morphine or an opioid agonist, such as DAMME or FK 33-824, has been shown to consistently increase serum PRL concentrations (80, 82, 102), and this effect was attenuated by naloxone in both heifers and rats (103–105). In addition to effects on PRL release, administration of morphine for 4 d increased PRL mRNA by 12%, whereas naloxone decreased PRL mRNA levels by 10% in rats (89), demonstrating that opioids affect morphine gene expression. The mechanism of the effect of opioids on PRL secretion is complex because PRL release is enhanced by serotoninergic but reduced by dopaminergic pathways that interact with the opioid system in rats (106). Additionally, the dopaminergic system develops in neonatal rats, whereas the serotoninergic system is not functional until 10 to 15 d of age and is not able to mediate the effects of opioids on PRL secretion. In contrast, in monkeys, PRL release is enhanced by serotoninergic pathways but is not affected by dopaminergic pathways (107). This study also confirmed a hypothalamic site of regulation of opioids on PRL secretion. Nicotine, morphine, and a serotonin agonist [8-hydroxy-2-(di-n-propylamino) tetralin] were found to utilize a common synaptic pathway for PRL release with serially arranged synapses in the dorsomedial arcuate nucleus of rats (108). Most importantly, this study (108) supported the findings of Bero and Kuhn (106) that inhibition of dopaminergic pathways plays an important role in the induction of PRL release by opioids. However, administration of morphine, leu-enkephalin, and DAMME showed little effect on dopamine-induced inhibition of PRL secretion (100, 101), although these experiments using isolated rat pituitaries in culture are not physiological and do not take into account the interactions between the hypothalamus and pituitary. All three opioid receptors are involved in the opioid-induced PRL stimulation (109); however, the μ-opioid receptor appeared to play a primary role in mediating the effect of opioids on PRL secretion (110). These experiments should be confirmed in opioid receptor null mice.

Acute stress resulted in an increase of PRL, an effect that is modulated by endogenous opioids, β-endorphin and dynorphin-A (111). Although one paper in pigs reported that administration of naloxone enhanced the stress-induced increase in PRL secretion (81), this response was mild and was not confirmed statistically. Most articles report that naloxone inhibits PRL release (reviewed in Refs. 112 and 113), which is the expected response.

β-Endorphinergic neurons in the arcuate nucleus participate in the acute response of PRL release after mating in female rats, suggesting that endogenous opioid peptides are involved in the neuronal transmission of genitosensory stimulation inducing PRL secretion (114). Furthermore, medial basal hypothalamus β-endorphin also regulated progesterone-induced PRL secretion in female monkeys (115).

Unlike GH, the effects of opioids on PRL secretion vary considerably and are dependent on the timing of the effects of opioids, particularly in the female cycle. Acute morphine administration increased PRL secretion in diestrous and proestrous rats, but did not produce any effects of PRL levels in lactating rats, possibly as a result of down-regulation of the μ-opioid receptor (116). In contrast, β-endorphin and a leu-enkephalin analog increased PRL during lactation in female rats (116). Additionally, opioids can have an impact on premature reproductive systems, resulting in later deficiencies in adulthood. Morphine administered to juvenile female rats led to reduced suckling-induced PRL secretion in adulthood, but other maternal behaviors were unaffected (117). Thus, opioid use during adolescence has long-lasting effects on PRL secretion.

2. Human studies

Acute morphine administration increased serum PRL concentrations in men (118) as well as euthyroid and hypothyroid volunteers (119). Acute morphine administration also increased PRL levels in postmenopausal women (120). In postmenopausal women, a single dose of iv morphine increased PRL and decreased LH (121), demonstrating that morphine may affect a common receptor or neurotransmitter that controls both PRL and LH secretion from the anterior pituitary. After administration of a submaximal dose of metoclopramide, a dopamine agonist, morphine still increased PRL, whereas after a maximal metoclopramide dose morphine was no longer able to increase PRL. This suggests that in humans, as in animals, the effects of opioids on PRL release are mediated through dopaminergic mechanisms (118).

The effect of chronic opioid administration on PRL is less clear. PRL levels were normal in both male and female chronic pain patients that received opioids either intrathecally (94) or orally (122). In contrast, baseline PRL levels were increased in male opioid addicts on a methadone maintenance program, and decreased after treatment with bromocriptine, a dopamine agonist, for 30 d

(123). Eighty-seven percent of opium smokers in Iran had elevated PRL levels (124). The difference between the methadone study and the other studies showing high PRL after opioids may be due to some underlying difference between heroin addicts and patients on pain medicines or specifically due to the effects of methadone on PRL secretion.

The effect of naloxone, the opioid receptor antagonist, on PRL is also ambiguous. In normal men, naloxone did not change basal PRL levels or its release after stimulation with TRH (125). However, in a similar group of men, naloxone was able to reduce the increase of PRL after injection of buprenorphine (126). Two studies which found that naloxone did not affect PRL levels studied both men and women together and used small numbers of subjects (127, 128).

In women, sex steroid hormones may also modulate the effects of opioids on PRL. Naloxone did not have any effect on basal PRL secretion in menopausal women, hypogonadal women, or normal women in the early follicular or late luteal phase of their menstrual cycle (120, 129–131). However, naloxone did induce PRL release when administered for 7 d in the luteal phase of the menstrual cycle of healthy women, as reflected by an increase in LH and PRL pulse frequencies (132). Postmenopausal estrogen-treated women injected with naloxone showed lower plasma PRL concentrations than the untreated reproductive-age control group (131). These articles point to an interaction between LH and PRL that is mediated by opioids and suggest that estrogen levels (as evident by the phase of cycle or by exogenous estrogens) modulate the effects of opioids on PRL levels in women.

3. Summary and overall mechanisms of opioid effects on PRL

In both rodents and humans, acute administration of opioids increased PRL levels, an effect that appears to be mediated by hypothalamic factors rather than via direct action on the pituitary. The opioid-induced PRL release is enhanced by serotoninergic pathways but reduced by dopaminergic pathways, and circulating sex steroids modulate the response. The effects of naloxone on PRL levels and the effect of chronic administration of opioids are both variable. In some studies, naloxone decreased PRL levels, an effect that may be dependent on circulating sex steroids. Chronic administration of opioids occasionally increased PRL levels, an effect that may be due to the type of opioid. More studies need to be performed on the clinical implications of chronic opioids on PRL levels.

C. Thyrotropin

1. Animal studies

In rats, the site of opioid administration determines the effect of opioids on levels of serum TSH. Generally, acute peripheral injection of morphine decreased serum TSH levels without affecting plasma T_3 and T_4 levels, but this effect was not blocked by naloxone (133). In contrast, Männistö *et al.* (134) infused a single dose of morphine into different hypothalamic locations and found that the cold-stimulated serum TSH response was inhibited when morphine was infused into the third ventricle and stimulated when the drug was infused in the posterior hypothalamus, with both effects inhibited by naloxone. The effect of morphine on this cold-induced alteration in TSH was also found to be dose-dependent because rat serum TSH levels were stimulated by lower doses of morphine and inhibited by higher amounts of morphine (135).

In the rat hypothalamus, repeated injections (twice daily for 10 d) of morphine, but not a single injection, increased TRH levels in the striatum and hippocampus and increased TRH receptor binding in the striatum, nucleus accumbens, and hippocampus when examined 72 h after the last injection (136). Because most of the changes occurred at 72 h after the last administration of morphine, the findings are more likely related to withdrawal than morphine exposure. Morphine pellet administration for 7 d led to increased TRH biosynthesis as evidenced by increased TRH/5.4 kDa C-terminal proTRH-derived-peptide ratios in the median eminence (137). Although morphine increased TRH levels, opioid peptides exerted a modulatory effect on TRH levels. β-Endorphin decreased TRH secretion in a dose-dependent manner, and leu-enkephalin and met-enkephalin decreased TRH release (138). The effects of these peptides were blocked by naloxone (138). Neither leu-enkephalin nor met-enkephalin affected basal or TRH-stimulated TSH levels in rats (139). Systemic treatment with β-endorphin and met-enkephalin antisera increased both hypothalamic TRH and TSH concentrations (140). These results suggest a hypothalamic mechanism for the regulatory actions of endogenous opioid peptides on the hypothalamic-pituitary-thyroid axis and that exogenous morphine may have different effects than endogenous opioids.

Studies on the effect of antagonists (naloxone or naltrexone) on TSH release show conflicting results. In contrast to earlier reports that naloxone had no effect on basal (141) or cold-stimulated TSH secretion (142), more recent reports have shown an attenuating effect of opioid antagonists. Subcutaneous injection of naltrexone blocked the acute stress-induced decrease in plasma TSH and stopped the decline in TSH after chronic stressors, even slightly elevating TSH levels (143). Naloxone infused into rat pituitary cells increased basal TSH secretion, yet did not augment TRH-stimulated TSH secretion and was not blocked by β-endorphin (144). These experiments were done on isolated pituitary cells, which, as discussed above

in the PRL section, lack the hypothalamic factors that may regulate opioid action. Thus, it is possible that a different opioid receptor besides the μ-receptor is involved in the opioid regulation of TSH secretion.

The mechanisms of opioid effects on TSH secretion involve regulation of opioid receptors, feedback mechanisms, and interactions with the thyroid hormones, T_3 and T_4. In mice, hyperthyroidism increased the binding of opioids to the opioid receptor and thus increased the serum TSH response to morphine and other opioids (145). The increased thyroid hormone levels in hyperthyroidism may facilitate opioid action, although there are no clinical reports suggesting that hyperthyroid patients have an altered pain sensitivity. The locomotor stimulatory action of TRH is mediated by opioid receptors, along with adrenergic and dopaminergic receptors in the ventromedial hypothalamus of rats (146). The κ-agonist MR 2034 acted similarly as morphine, inhibiting the cold-stimulated TSH response when infused into the third ventricle and increasing the TSH response when infused in the posterior hypothalamus (147). Naloxone blocked only the stimulatory, but not the inhibitory effect of MR 2034. DAMME, a μ/δ-receptor agonist, did not affect TSH secretion (147). Thus, κ-receptors appear to be the primary receptors involved in mediating the action of opioids on TSH release.

The hormones secreted by the thyroid gland, T_3 and T_4, also affect the suppression of TSH by opioids. In rats, the normal TSH decrease after opioid administration was no longer present after thyroidectomy, indicating that circulating thyroid hormones are required for morphine to have its suppressive effects on TSH levels (148). Moreover, replacement with T_4 led to a more pronounced suppression of TSH in morphine-treated animals. Thus, morphine may exert its inhibitory effect on TSH secretion by increasing the negative feedback sensitivity to thyroid hormones.

2. Human studies

In contrast to the decrease of TSH secretion by opioids in animals, an increase in TSH is seen in humans. Morphine administration produced a rapid increase in TSH in both normal and hypothyroid subjects, and naloxone attenuated this effect (119). Four other articles report a stimulatory effect of morphine or opioid analogs on TSH levels (149–152). Opium smokers in Iran had lower TSH levels than cigarette smokers and healthy volunteers (124). One case report found that morphine inhibited TSH secretion during stress (153). This article suggested that the decrease in TSH in rodents that receive opioids is due to the stress on the experimental animals, a condition absent in the human volunteers.

In humans, met-enkephalin has been shown to localize only in TSH immunoreactive cells, suggesting a role in human thyroid function (154). In contrast, nonhumans have little or no met-enkephalin in the anterior lobe of the pituitary (155). The localization of met-enkephalin may provide a possible explanation for the difference in the effects of opioid on TSH secretion between animals and humans.

Particularly in humans, the effects of the opioids and endogenous opioid peptides are more significant during the physiological nocturnal TSH surge. Naloxone decreased TSH levels by suppressing the nocturnal surge in the TSH pulse amplitude, but did not affect daytime TSH levels or pulse frequency (156), supporting the finding that endogenous opioids stimulate TSH levels and affect the circadian rhythm of TSH (157).

The effect of opioids on the hypothalamus-pituitary-thyroid axis can be modulated by thyroid disorders. In hypothyroid patients, an infusion of naloxone did not change serum TSH levels (158), suggesting that endogenous opioids do not modulate TSH in this population. Abs *et al.* (94) did not find any effect of intrathecal opiate administration on baseline and TRH-stimulated TSH levels and found only slightly higher free T_3 levels in patients receiving opiates compared with controls.

3. Summary and overall mechanisms of opioid effects on TSH

Opioids suppress TSH in rodents and stimulate TSH in humans, with the difference possibly due to differences in the localization of endogenous enkephalins in the pituitary of animals compared with humans. The site of opioids on the hypothalamic-pituitary-thyroid axis appears to be at the hypothalamus, with little direct effect at the pituitary. κ-receptors appear to be the primary receptors involved in mediating the action of opioids on TSH.

D. ACTH

1. Animal studies

In rodents, the effect of morphine on ACTH secretion depends on the dose and the time course of its administration. Acute administration of morphine led to a robust increase in ACTH and CS levels (159). In a later study, acute morphine led to an exaggerated response of the HPA axis to stress (160). Another study found that an acute injection of morphine caused a rise in plasma and adenohypophysis ACTH and in hypothalamic CRH content at 5 and 25 min, followed by a fall in these hormones at 90 and 120 min (161). Thus, acute opioid administration results in an increase in ACTH levels.

The effect of chronic opioid administration on ACTH and glucocorticoids is more heterogenous. In rats, chronic ip morphine administration (2 mg/kg daily for 7 d) led to reduced plasma and pituitary ACTH levels and hypotha-

lamic CRH content, whereas no effect was found at a lower dose (0.5 mg/d) (161). In another study also in rats, chronic morphine treatment given sc twice a day for 16 d resulted in a marked elevation of basal CS concentrations (162). It is not clear whether this increase in the HPA axis was the result of chronic morphine administration itself or a response to the stress of repeated injections. Chronic morphine treatment did abolish the ability of either a single morphine injection or stress to increase ACTH and CS levels, suggesting that chronic morphine may desensitize a shared mechanism between acute morphine and stress to stimulate the release of stress hormones (160, 163). Interestingly, pretreatment with ACTH enhanced the analgesic response and prevented the development of tolerance to morphine in rats (164). Morphine-dependent rats that had undergone 12-h withdrawal displayed a prolonged CS response to restraint stress (162). In contrast, rats that had undergone 8- and 16-d morphine withdrawal had normal basal pituitary-adrenal activity but displayed significantly reduced and shorter ACTH and CS responses to restraint stress (162). These results suggest that chronic morphine may lead to an attenuated response of the pituitary-adrenal axis to acute stress that may vary depending on duration of the opioid treatment and the length of the withdrawal from the drug.

Further review of the literature supports the notion that the effect of opioids on β-endorphin levels and the HPA axis depends on whether it is given in an acute or chronic manner. In rats, chronic morphine administration (7 d) resulted in a down-regulation of POMC gene (the precursor of β-endorphin and ACTH) mRNA in hypothalamus (165) as well as a decrease of brain and hypophyseal β-endorphin content (166, 167). Chronic (8 d) naltrexone administration increased POMC mRNA levels to 140% of control value (168). Gianoulakis *et al.* (169) found that chronic morphine administration slightly inhibited neurointermediate lobe POMC protein levels as well as the processing of POMC to β-lipotrophin and β-endorphin, an effect that was more pronounced at 3 d than 15 d. Consistent with the later finding, Hollt, *et al.* (170, 171) found a more pronounced decrease in neurointermediate pituitary POMC mRNA, tissue concentrations of β-endorphin and in the *in vitro* release of β-endorphin from the neurointermediate pituitary; however, there were no alterations in the processing of POMC.

Researchers have long hinted at a second site of opioid action along the HPA axis that is located outside of the hypothalamus-pituitary unit. In hypophysectomized rats, a single dose of morphine potentiated and naloxone inhibited the adrenal steroidogenesis after exogenous ACTH administration (172). The authors suggested that opioids may act via a mechanism that competes with ACTH receptors on the CS-secreting cells of the adrenal cortex (172). More recent studies focused on the specific location and mechanism of these effects. In rat zona glomerulosa and zona fasciculata cells *in vitro*, Kapas *et al.* (22) showed that opioid peptides stimulated CS secretion by the inner zona glomerulosa cells, without a specific interaction on the adrenocortical cells with ACTH. The effects were primarily mediated by μ- and, to a lesser extent, κ-receptors (22).

Other endogenous opioid peptides also modulate ACTH levels. For example, met-enkephalin, leu-enkephalin, and the analog FK 33-824 decreased plasma ACTH levels in sheep (173). One enkephalin analog in particular, DALA, has been studied extensively in relation to the adrenocortical cells and response to ACTH. In rats, DALA showed a similar pattern consisting of an increase in ACTH and CS secretion after acute administration of the analog and a decrease after chronic administration (174). DALA also produced a significant decline in the responsiveness of ACTH using dispersed adrenal cells (175). Chronic systemic DALA administration enhanced the trophic action of ACTH in the rat adrenal zona fasciculata (176). These studies suggest that DALA and other opioid peptides modify ACTH secretion and the glucocorticoid response to ACTH at the site of the adrenal cortex, suggesting a peripheral site of action of opioids. However, because DALA did not affect basal ACTH release and stimulation in rat anterior pituitary cell cultures, the authors suggest that DALA acts at the extrahypophyseal level to stimulate ACTH and CS (177). Thus, unlike morphine, the enkephalins do not exert their effects centrally; rather, they are specifically involved in the growth and steroidogenic capacity of the rat adrenal cortex.

Our laboratory has studied the effects of short-term (6 h) and chronic (7 d) morphine administration on levels of the prohormone convertases, PC1/3 and PC2 (137). These enzymes are believed to be responsible for the activation of many neurohormones, including the processing of POMC to β-endorphin and ACTH (178). The expression of these enzymes is dependent on the presence of a cAMP response element in their promoters (179). Specifically, short-term morphine exposure down-regulated, whereas long-term morphine exposure up-regulated phosphorylated cAMP response element binding protein and PC1/3 and PC2 protein levels in the rat hypothalamus (137). The regulation of the prohormone processing system by morphine may lead to alterations in the levels of multiple bioactive hormones, including POMC-derived peptides, and may be a compensatory mechanism whereby the organism tries to restore its homeostatic hormonal milieu. Thus, posttranslational regulation may be another mechanism by which opioids affect hormonal levels and may explain why long-

term opioid exposure is necessary for drug addiction to occur (137).

2. Human studies

In normal subjects, in contrast to the effect in rodents, a single dose of a slow-release oral morphine suppressed ACTH, β-endorphin, and cortisol levels both at baseline and after CRH stimulation (180). Acute naloxone administration, on the other hand, increased ACTH and β-endorphin levels (181, 182). This was also found for nalmefene, another opioid antagonist (183).

The effect of acute *vs.* chronic morphine on the HPA response in humans has not been extensively studied. In patients receiving intrathecal opioids, urinary free cortisol excretion was decreased compared with controls (94). Pain patients had elevated basal levels of cortisol and ACTH, which decreased after administration of sustained-release oral morphine for 1 to 12 wk (184).

There is concern regarding the potential development of an insufficient HPA stress response due to chronic opioid administration. In the study on the effects of intrathecal opioid administration, one patient developed adrenal insufficiency, whereas a basal cortisol level below 50 μg/liter (suggesting adrenal insufficiency) was found in 9.2% of opioid-treated patients compared with none of the control patients (94). Several case reports have documented adrenal insufficiency after oral (185) or transdermal (186) opioid administration and during methadone administration (187). Overnight dexamethasone suppression testing resulted in lower cortisol levels in patients receiving methadone-maintenance therapy than in normal volunteers, indicating that methadone affects glucocorticoid feedback and that the interpretation of dexamethasone testing may be affected by treatment with methadone (188). Schluger *et al.* (189) found that methadone-maintained former heroin addicts displayed a significantly greater increase in plasma ACTH, but not cortisol levels after high-dose but not low-dose human CRH, suggesting that the HPA axis is not completely recovered in methadone maintenance. The authors were unable to determine whether the effects on the HPA axis in methadone-maintained former heroin addicts was a consequence of heroin exposure or may have existed before the addiction. Overall, whereas these studies indicate that intrathecal opioid administration may cause adrenal insufficiency in up to 10% of patients, the risk for and clinical relevance of opioid-induced adrenal insufficiency has not been studied systematically for oral or transdermal administration.

Morphine and opioids affect the circadian rhythm of the HPA axis. Heroin addicts had constant β-endorphin, ACTH, and cortisol plasma levels throughout the day, compared with the normal circadian rhythm with high values in the morning and low values in the evening in healthy controls (190). This lack of differences across the circadian rhythm may explain why the overall long-term cortisol exposure (as measured by hair cortisol levels) was elevated in opioid-treated chronic pain patients compared with control subjects (191).

Studies on the mechanisms of ACTH inhibition by morphine and other endogenous opioid peptides have focused on the release of CRH from the hypothalamus. In healthy subjects, naloxone augmented, whereas morphine inhibited the CRH-induced increase in plasma ACTH and cortisol levels, indicating that opioid peptides inhibit the pituitary ACTH response to CRH (192, 193). The primary opioid receptor involved in the regulation of the HPA axis is most likely the κ-receptor (194, 195).

Examining the effects of opioids and their analogs in patients with disorders of the HPA axis has also helped to elucidate the effects of opioids on this axis. Patients with Cushing's disease were tested with FK 33-824, a met-enkephalin analog, and showed no change in ACTH or cortisol levels (196). Moreover, loperamide, a μ-opioid agonist, did not change ACTH and cortisol levels in patients with Cushing's syndrome, whereas it did suppress these levels in normal volunteers (197). In fact, lack of ACTH and cortisol suppression by loperamide was proposed to be an effective screening test for Cushing's syndrome (198). In patients with Addison's disease, FK 33-824 decreased plasma ACTH levels, an effect that was partially reversed by naloxone (196). Additionally, naloxone stimulated ACTH levels in patients with Addison's disease, but had no effect on ACTH levels in patients with Cushing's disease (199). This insensitivity to opioid agonists and antagonists in Cushing's disease suggests that a defect in the inhibitory opioidergic control of ACTH secretion may lead to its hypersecretion (200). On the other hand, Addison's disease patients treated with loperamide show sensitivity to opioids because the ACTH levels were decreased significantly with loperamide administration (201). Loperamide was seen to modify the effect of CRH on ACTH secretion in a nonadditive manner in Addison's patients (202), such that ACTH release was inhibited. This evidence shows that opioids primarily act at the pituitary level and also have effects on the peripheral glands, such as the adrenals. This was confirmed by a subsequent study examining the effects of naloxone in patients with primary aldosteronism suggesting that the zona fasciculata of the human adrenal gland may be a secondary site of action for opioids (203), similar to the findings in rodents (10, 177).

3. Summary and overall mechanisms of opioid effects on ACTH

Acute opioid administration results in an increase in ACTH and glucocorticoid levels in animals and either no effect or a decrease in humans. Chronic opioid adminis-

tration may be associated with a decreased glucocorticoid response to acute activation of the HPA axis, despite often chronically elevated glucocorticoid levels, a finding that may be confounded by persistent chronic stress or pain. In occasional patients, opioid administration may cause frank adrenal insufficiency, but specific information on the risk to develop adrenal insufficiency is lacking. The effects of opioids on the HPA axis appear to be primarily mediated via both the hypothalamus and pituitary. In addition, there is evidence for direct stimulatory effects of opioids on adrenal glucocorticoid secretion that are mediated via μ- and κ-receptors.

E. LH and FSH

1. Animal studies

Extensive studies have been performed in laboratory animals to examine the influence of opioids on the hypothalamic-pituitary-gonadal (HPG) axis. These studies focused on the mechanisms of action of opioids, the interaction of opioids with the steroid hormones, and the time course of action of opioids on sexual function. In ovariectomized rats, the effect of a single injection of morphine on LH was dose-dependent, with an increase of LH after a high dose (10 mg/kg), but suppression of LH after a low dose (1 mg/kg) (204). These LH responses were antagonized by naloxone (86, 133). Furthermore, naloxone increased LH concentration and pulse frequency when administered alone (105), demonstrating a tonic opioid inhibition of LH secretion.

With respect to endogenous opioid peptides, earlier studies had shown that injections of β-endorphin (at certain doses) stimulated serum LH levels (205); however, recent research points toward β-endorphin as having an inhibitory effect on LH similar to morphine. Injection of β-endorphin iv or into certain specific brain locations (including the ventromedial hypothalamic area, the anterior hypothalamic area, and the preoptic-septal area) decreased LH, suggesting that these brain areas are sites of action for β-endorphin, rather than the pituitary (206). In addition, Petraglia *et al.* (207) used β-endorphin antiserum to show that β-endorphin participates in the inhibitory action of CRH on LH secretion. Studies on the pituitary as a primary site of action for β-endorphin are conflicting because one study (208) found a direct effect of β-endorphin on LH release, whereas another (206) did not find such a direct effect. These findings suggest that endogenous β-endorphin decreases LH levels by acting on CRH-sensitive neurons and possibly by a direct effect on pituitary LH secretion.

Furthermore, β-endorphin also has modulating effects on the menstrual cycle of animals. A study of rhesus monkeys confirmed the participation of endogenous opioids during the menstrual cycle because the luteal phase of the cycle stimulated β-endorphin levels, which stimulated LH pulse frequency (209). Subsequent reports indicated that β-endorphin likely produced the latter effects via δ-receptors (210).

In contrast to their effects on LH, most opioids and their analogs appear not to affect FSH. Administration of morphine to developing male rats did not change basal FSH levels (211). Furthermore, treatment with opioid antagonists, naloxone and naltrexone, did not alter FSH concentration levels in either sex (212), suggesting that the endogenous opioids are not involved in regulation of FSH secretion. It is interesting to note that FSH levels are unchanged despite the ability of opioid treatments to stimulate hypothalamic GnRH.

The primary mechanism by which opioids affect gonadotropin secretion is through their effects on GnRH. Systemic administration of naloxone stimulated the release of GnRH, thereby stimulating LH release (213). Similarly, in ewes, naloxone treatment created a large amplitude GnRH pulse in the hypothalamus that stimulated a large LH pulse from the pituitary (214). In contrast to these effects of opioid antagonists, exogenous opioids and endogenous opioids inhibited hypothalamic GnRH secretion, leading to suppressed LH levels (215). Chronic morphine administration inhibited GnRH secretion both *in vivo* and *in vitro* (216). Li and Pelletier (217) found that opioids down-regulate GnRH mRNA levels as assessed by *in situ* hybridization, suggesting that morphine may act by decreasing the biosynthesis of GnRH.

In addition to the interaction with the hypothalamic synthesis and release of GnRH, opioids also affect, and conversely are regulated by, the end-product of the axis, the gonadal sex steroid hormones. Opioids also play a role in the feedback inhibition of LH by gonadal steroids. In castrated male and female rats, the decrease of serum LH levels by estradiol or testosterone administration could be reversed by naloxone (218). Administration of estradiol and progesterone decreased the ability of morphine to influence LH secretion (219, 220). Thus, because morphine has an effect on steroids through the inhibition of gonadotropins, the gonadal steroids, in turn, reduce the effects of opioids on LH secretion. Bhanot and Wilkinson (221) showed that after gonadectomy, there was an acute reduction in the inhibitory effects of opioids on LH and FSH release, along with a reduced ability of naloxone to stimulate LH and FSH at all stages of development. Studies by Gabriel *et al.* (222) indicate that chronic morphine has no direct effect on LH, but that it enhances the sensitivity of the hypothalamus to negative feedback by testosterone in male rats. In female rats, chronic opioid treatment increases not only estradiol-mediated negative feedback but

also the estradiol surge-induced hypersecretion of LH, indicating that morphine amplifies both negative and positive feedback on gonadotropin secretion (223).

The effect of opioids on the menstrual cycle is correlated with the rise and fall of the gonadal steroids. Exogenous opioids and endogenous opioid peptides caused a significant decrease in LH pulse frequency (224), whereas naloxone promoted an increase in the LH surge compared with saline controls (225). Tonic inhibition of LH levels by central opioid neurons occurred at all stages of the female rat cycle (219), with the luteal phase being the main phase affected. The opioid-induced decrease in the LH surge led to oligomenorrhea and amenorrhea, whereas the naloxone-stimulated increase in LH secretion stimulated the pubertal onset of menses in younger animals relative to controls (226).

There are age- and development-related effects of opioid treatment on gonadal hormones, in particular between prepubertal and postpubertal animals. Specifically, FK 33-824 caused a reduction in the secretion of LH in both male- and female-gonadectomized rats, with prepubertal rats displaying a 4-fold reduced responsiveness to opioids (227). By the same mechanism, naloxone administered to immature female rats advanced the age of onset of puberty (226). However, in very young (10 to 30 d-old) male rats, naloxone failed to increase serum LH (228) and did not induce pubertal changes. These data suggest that endogenous opioids and receptors may shift the timing of sexual maturation. Thus, it is possible that opioid exposure during critical phases of development could produce profound effects on hormonal maturation and sexual development.

2. Human studies

The effect of opioids and their analogs on the HPG axis in humans is similar to that in animals. Intravenous morphine and morphine analogs such as methadone, DAMME, pentazocine, and nalorphine decreased LH levels in healthy men (149, 151). In male patients receiving opioids intrathecally (mean duration of 26 months) for nonmalignant chronic pain, LH was less than 2.0 U/liter in 20 of 29 male patients, whereas only two patients had an FSH below this level (94). In adult men, treatment with morphine resulted in a decrease of LH pulse frequency that was returned to normal by coadministration of naloxone (229), and administration of naloxone by itself increased the LH pulse frequency (230). As in animals, none of the opioids significantly altered FSH levels (151). Naloxone and other opioid antagonists increased basal and stimulated LH levels (229, 231).

In premenopausal chronic pain patients on long-term intrathecal opioids, LH level was less than 2.0 U/liter in nine of 21 women, with five patients having an FSH below 2.0 U/liter (94). During oral/transdermal opioid administration to 14 premenopausal chronic pain patients, mean LH and FSH levels were 6.9 and 6.3 U/liter, respectively (122). These findings suggest that the suppression of LH may be less profound when opioids are administered orally/transdermally compared with intrathecally. In addition to the route of administration and possibly the dose of opioids, the effect of opioids and their antagonists on the HPG axis in mature females also depends on the levels of circulating sex steroids during the menstrual cycle. A single naloxone injection resulted in a significant rise in LH during the luteal phase but not during the follicular phase (232). In contrast, long-term administration of opioid antagonists did not disrupt LH secretory patterns, temporal organization, or endocrine characteristics of the luteal phase (233). In fact, oral opioid antagonism for 7 d increased LH pulsatile secretions (132). Interestingly, naltrexone is able to induce ovulation in amenorrheic women as seen by stimulated follicular growth and an LH surge (234). A recent article demonstrated that naltrexone induced ovulation and resulted in conception for nine of 27 clomiphene citrate-resistant women with PCOS (235). Hormonal and metabolic profiles also improved with naltrexone. Thus, opioid antagonists have a potential beneficial effect on fertility in women with irregular menses.

In postmenopausal women, the administration of naloxone did not change LH levels (236). Treatment of postmenopausal women with conjugated estrogens and progestin restored the inhibitory effect of dermorphin, an opioid analog, on plasma LH levels compared with normal postmenopausal women (237). In aggregate, these findings indicate that sex steroid hormones are required for opioids to have their full effect on gonadotropin levels.

The effect of opioids on the HPG axis varies with pubertal stage. Most studies used opioid antagonists to determine the development of opioid modulation on this axis. Long-term naloxone administration failed to elevate LH secretion of boys and girls in early puberty (238). In late puberty, the opioid receptor pathway develops such that naltrexone and other opioid antagonists can increase plasma LH levels. This was demonstrated by the opposing effect of naltrexone in sexually developed boys compared with prepubertal boys: in the developed boys in late puberty naltrexone increased, whereas in the sexually immature boys naltrexone decreased LH pulse frequency and concentration (239). In a similar study, naloxone administration in both early and late pubertal boys resulted in stimulation of LH secretion in late pubertal boys, whereas no effect was found in early pubertal boys (240).

In pubertal boys, naloxone administration had no effect on the negative feedback of testosterone on LH and GnRH levels (241). Estradiol suppressed LH secretion

through an effect on hypothalamic GnRH secretion in pubertal boys, yet naloxone did not reverse these effects. Estradiol does not require the opioid receptor pathway for its negative feedback on the HPG axis during the early and middle stages of puberty (242). This and other data (240) indicate that the central opioid system affects the LH regulating system only in the presence of sex steroids. Mechanistically, Mauras *et al.* (243) found that the maturation of opioid antagonist effects during late puberty in boys occurs along the μ-opioid receptor pathway. Overall, these findings are suggestive of changes in opioid regulation along the HPG axis during puberty in both males and females.

3. Summary and overall mechanisms of opioid effects on LH and FSH

In both animals and humans, chronic opioid administration decreases LH, whereas FSH is not or is only minimally affected. The effect on LH occurs primarily by inhibiting hypothalamic GnRH secretion, although opioids also decrease the negative feedback of sex steroids on pituitary LH secretion. In turn, sex steroid hormones are required for and have major modulating effects on the sensitivity of the HPG axis to opioids and their antagonists, explaining why the effects of opioids on the HPG axis vary not only within the menstrual cycle but also with puberty and menopause.

F. Sex steroid hormones (testosterone and estradiol) and sexual behavior

1. Animal studies

As described in the previous section, the interaction of opioids with LH accounts for much of the effect of opioids on the secretion of the gonadal steroid hormones, estradiol and testosterone. As a result of a morphine-induced decrease in LH levels, testosterone and estradiol levels are also decreased (211). The effect of opioids on the steroidal hormones can be observed in the sexual behavior of male and female rats in response to opioids. Morphine, in general, inhibits the sexual receptivity of both male and female rats. In contrast, naloxone facilitated sexual behavior in both male and female rats.

In male rats, treatment with morphine inhibited sexual behavior with dose-dependent reductions in mounting, intromission, and ejaculation frequency (244). Reports from other laboratories suggested that this reduction in sexual behavior was due to failure of sexual arousal, rather than a primary erectile inability (245). Opioid antagonists facilitated sexual behavior in males. In sexually inactive male rats, naloxone was able to induce copulatory behavior (246), and it reduced the number of intromissions before ejaculation and before the time of latency (247, 248).

In female rats, morphine decreased sexual behavior in a similar manner. Specifically, morphine administered to female ovariectomized rats pretreated with estradiol benzoate and progesterone inhibited female sexual receptive behaviors (249). Naloxone reversed sexually inhibited behavior (250), induced copulatory behavior in sexually inactive female rats (246), and facilitated sexual receptivity through increased lordosis in females (251). Steroids appear to play a role in the facilitation of sexual behavior because estradiol and progesterone were necessary components for enhanced lordosis.

Mechanistically, the medial preoptic area appears to be involved in the action of opioids on sexual behavior in male rats because injection of morphine or β-endorphin in this area impaired sexual behavior; this effect was attenuated by systemic naloxone administration (252, 253). Injection of naloxone into the testes increased Sertoli cell proliferation and secretion (254), which may be linked to facilitation of sexual behavior by naloxone. Thus, peripheral opioid receptors may also play a role in mediating male rat sexual behavior.

In female rats, morphine inhibited sexual behavior via the ventromedial hypothalamus (255). The μ- and δ-receptors play a primary role in modulating sexual behavior; after i.c.v. infusion, high-affinity μ-receptor activation exerted an inhibitory effect on lordosis, whereas low-affinity μ-receptors and/or δ-receptors facilitated lordosis (256).

Morphine and opioid antagonists can also affect sexual development, both prenatally and prepubertally. Prenatal opioid exposure has been shown to have conflicting effects that appear to be sex dependent. Females administered morphine perinatally displayed disrupted ovarian cycles, inhibited lordosis, and reduced plasma estradiol levels (257), significantly reducing sexual behavior and reproductive activity. However, in males, prenatal morphine administration from d 11 to 18 of gestation did not disturb postpubertal testosterone levels, testicular weight, or masculine sexual behavior compared with controls (258, 259), but it did shorten the postejactulatory intromission latency (259). Furthermore, prenatal opioid exposure followed by castration and exposure to estrogen of male rats at 10–12 wk resulted in an increased lordosis quotient compared with placebo prenatal (260), which was interpreted as prenatal morphine giving long-lasting feminizing effects. Searching for underlying mechanisms, Vathy *et al.* (261) found that prenatal morphine exposure did not alter the density of δ-opioid receptors in adult gonadal-intact male and female rats. However, when rats were gonadectomized, the same treatment resulted in decreased levels of cortical δ-opioid receptors in male and increased receptor levels in female rat brain. These morphine-induced changes in δ-opioid receptor density were reversed

by male and female hormone replacement (261). Overall, these studies indicate that prenatal exposure to opioids may alter the way by which gonadal hormones affect central opioid levels in adult life, and that this may not be noticeable until significant changes in exposure to testosterone and/or estradiol occur. Regarding long-term effects of morphine exposure, it has also been shown that prepubertal morphine exposure inhibited sexual maturation in the male and displayed reduced testosterone and LH levels, although testicular weights were not altered (211). Thus, exposure of opioids to adolescent male rats also affected postpubertal sexual development.

2. Human studies

In humans, morphine suppresses LH secretion, resulting in lowering of the concentrations of steroid hormones of men and women that manifest with multiple effects. In premenopausal women, endogenous β-endorphin does not seem to have a direct effect on the normal cycling of gonadotropins during menstruation. The plasma levels of β-endorphin vary across the menstrual cycle, increasing during the follicular phase, falling before ovulation, and increasing during the luteal phase (262). This is intriguing in light of the previously mentioned variation of opioid effects during the rat menstrual cycle. One study hypothesized that the decline in β-endorphin levels before ovulation was correlated with symptoms of the premenstrual syndrome (263). Furthermore, naltrexone, an opioid antagonist, alleviated premenstrual syndrome symptoms in women with that syndrome (264). In women with PCOS, endogenous β-endorphin levels were decreased compared with normal controls (265). However, this decrease was less significant in obese women, signifying a relationship with insulin and body mass index (266).

Exogenous opioids have a much more drastic effect on the female menstrual cycle. After long-term intrathecal opioid administration, 14 of 21 premenopausal women developed amenorrhea, and the other seven developed irregularities in menstruation (94). Opioids led to a decline in LH, FSH, estradiol, and progesterone, thus affecting menstruation (94). Amenorrhea and irregular menses as a result of low estrogen levels are signs of hypogonadism in women; long-term opioid abuse is a major cause of this disorder. A more recent study by Daniell (267) presented similar results with oral and transdermal opioids; menstruation ceased shortly after beginning treatment with sustained-action opioids. The author noted a significant decrease in adrenal androgen production suggesting that opioids may also play a role in regulating sexual libido via androgens (267). Heroin users appear to have decreased sexual desire and performance (268), but in general, the effects of chronic opioid treatment on libido and/or fertility in women have not been documented in well-controlled studies.

Opioid antagonists have been found to help patients with amenorrhea, restoring HPG function (234, 269, 270). However, in women with hypothalamic amenorrhea, this effect is transient and is only effective after acute administration of naloxone or naltrexone (271). In hyperprolactinemic amenorrheic women, naltrexone increased LH concentrations and, accordingly, estradiol concentrations in the first day of treatment, yet these increases were not sustained with continued, chronic treatment, and normal ovulation was not restored (272). Thus, chronic administration of opioid antagonists is not useful in the treatment of central causes of oligomenorrhea/amenorrhea, although as discussed above, opioid antagonists appear to be helpful in treating oligomenorrhea associated with PCOS (235).

In men, the effects of long-term opioid use on gonadal status have been studied more extensively. Heroin addicts show significantly decreased testosterone levels (273, 274). Although one study found normal testosterone levels, this study reported abnormal semen analyses in men who used heroin or methadone (275). Using population-based reference ranges for total testosterone, hypogonadism was present in 86% of men receiving intrathecal opioids for chronic pain (94). Oral opioids, including methadone, were associated with hypogonadism in 89% of men and also resulted in decreased levels of estradiol, dihydrotestosterone, LH, and FSH (276). A similar frequency of hypogonadism was found in men receiving oral/transdermal opioids (122). Overall, these studies indicate that opioids, regardless of the administration route, are associated with a high prevalence of male hypogonadism.

SHBG was high in heroin addicts, leading to low free testosterone levels (273), an effect that was not found in men on long-term oral opioids (122). Based on this, we suggest that SHBG and/or free testosterone levels, in addition to total testosterone levels, should be measured in future studies on the prevalence of hypogonadism in men receiving opioids. This would reduce the likelihood that subjects with total testosterone levels at or just above the lower limit of normal would be classified as eugonadal while they in fact are hypogonadal.

Chronic opioid use in males, whether for pain control or through heroin, morphine, or methadone addiction, leads to symptoms of delayed ejaculation, erectile dysfunction, and significant decreases in sexual libido (276–278). Administration of opioid antagonists such as naltrexone can improve symptoms of hypogonadism (279). Naltrexone improved erectile function over a period of 7 to 15 d, but in the majority of subjects, it did not sustain the response after cessation of treatment (279). Mecha-

nistically, the antagonist did not increase testosterone or LH levels, suggesting regulation at the central rather than the peripheral level (279). In an open-label study, treatment with exogenous testosterone improved the testosterone levels and sexual function of men exhibiting hypogonadism on prescription opioids (280). The latter finding suggests that testosterone replacement may be helpful for treatment of hypogonadism in male patients using opioids, although a double-blind placebo-controlled study needs to be performed. Alternatively, the type of opioid drug used for chronic pain may also affect the degree of hypogonadism seen. Studies on buprenorphine, a partial μ-opioid agonist used for opioid dependence, found that this drug was associated with significantly higher testosterone levels and lower frequency of sexual dysfunction than methadone (281, 282).

In men, hypogonadism may lead to decreased bone mineral density, causing osteopenia or osteoporosis. Chronic heroin users exhibit reduced bone density (283) and lower serum osteocalcin levels (284). Fifty percent of male patients receiving chronic oral/transdermal opioids had osteopenia (122). In epidemiological studies, opioid use is associated with a 1.5- to 6-fold increase of osteoporotic fractures (285). In addition to the effect of hypogonadism, opioids also affect bone directly via opioid receptors on osteoblasts; opioids inhibited osteoblast cell growth in culture, which is also likely to be the case in the whole body (286). Furthermore, hypogonadism in males as a result of opioid use also led to increased depression (280), which by itself or due to antidepressant use, may result in decreased sexual dysfunction. A limitation of these studies is that they do not control for pain or for reduced mobility that may result from pain and depression.

In males, testosterone levels decrease with age, which is also associated with change in body composition, including an increase in fat mass (287). Although the clinical relevance of this age-related decline in testosterone has not been established unequivocally (288), some studies indicate that the decline in testosterone may be associated with a decrease in cognitive performance (289). Although further studies may need to confirm this association and the potential benefit of testosterone therapy (290), it is currently unknown whether opioid-induced hypogonadism is associated with cognitive decline and other signs of hypogonadism.

Opioids are hypothesized to cause a decline in testosterone levels and sexual dysfunction via two mechanisms. de la Rosa and Hennessey (291) suggested that opioids lead to an alteration in normal gonadotropin pulse patterns or affect the response of the anterior pituitary to GnRH, both of which decreased testosterone levels. Morphine down-regulated estrogen receptor-β expression in human vascular endothelial cells, an effect partially blocked by naloxone or a selective μ-opioid receptor antagonist, D-Pen-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2, showing the involvement of the μ-opioid receptor in this action of morphine (292). A deeper understanding of the hypogonadal effects of opioids may cause users to reexamine the abuse of opioids.

Male hypogonadism can lead to symptoms of decreased sexual libido, erectile dysfunction, and osteoporosis (293). In chronic pain patients receiving intrathecal morphine, hypogonadism was found in men and in both pre- and postmenopausal women (294). However, the prevalence of hypogonadism as a consequence of oral opioids may not be similar in both genders. Fraser *et al.* (122) studied chronic noncancer pain patients receiving oral/transdermal opioids and found hypogonadism in 75% of men and 21% of women, although these groups had similar opioid dosage and pain scores. This suggests that opioid use may be associated with a higher prevalence of hypogonadism in men than in women.

3. Summary and overall mechanisms of opioid effects on sex steroids

Chronic opioid administration results in suppression of sex steroids mediated mainly by suppression of LH via effects on GnRH. In addition, there may be direct effects at the gonadal level. Opioids have significant suppressive effects on sexual behavior, which appear to be mediated primarily via activation of μ- and δ-receptors in the medial preoptic area and the ventromedial hypothalamus. Opioid antagonists can facilitate sexual behavior. In humans, the sensitivity to these opioid effects appears to be higher in men than in women.

G. Arginine vasopressin (AVP)

1. Animal studies

Opioids and their analogs not only interact with the hormones of the anterior pituitary but also have an effect on the posterior pituitary (neurohypophysis). AVP, also known as antidiuretic hormone, and OT are both individually and synergistically affected by opioids. Morphine inhibited the electrically evoked release of both OT and AVP after injection into electrically stimulated neurohypophysis cells that hypersecrete both AVP and OT (295). Naloxone reversed the suppression of OT release but was without effect against the opioid block of AVP secretion (295). Morphine injection resulted in a mean decrease in arterial pressure and urine flow in both normal and Brattleboro rats that lack AVP (296), suggesting that the antidiuretic effect of morphine may occur independently of antidiuretic hormone release. However, i.c.v. injection

of morphine also caused dose-dependent antidiuresis in rats (297), an effect blocked by naloxone, implying enhanced AVP levels after morphine. In a more detailed study, Michel *et al.* (298) found that morphine was able to increase or decrease AVP secretion, depending on the hydration state of the rats; morphine increased AVP in water-loaded rats, whereas in dehydrated Brattleboro rats, morphine induced an increased AVP response at higher doses and inhibited the AVP response at lower doses. Thus, the hydration state may regulate the response of the posterior pituitary and kidney to opioid-induced AVP secretion.

Other opioid analogs have also been shown to affect AVP levels, again with contrasting effects. β-Endorphin administration to rat neurointermediate lobe pituitaries *in vitro* inhibited AVP release in a naloxone-reversible manner (299). However, other endogenous opioid peptides preferentially stimulate secretion of AVP. The secretion, rather than inhibition, of AVP in response to opioid peptides may be the response of the animal to maintain homeostasis during dehydration and in response to an increased plasma osmolality (300, 301). Enkephalins, met-enkephalin and leu-enkephalin, did not change plasma AVP concentrations when injected by an i.c.v. or iv route in normal sheep (302, 303). However, i.c.v. leu-enkephalin inhibited baseline and angiotensin-stimulated AVP release (304), and another report found that dynorphin (1-17), β-endorphin, and leu-enkephalin inhibited the spontaneous release of AVP from the neurointermediate lobe *in vitro*. In other studies, i.c.v. and, to a lesser extent, iv leu-enkephalin increased AVP release and contributed to the antidiuretic response in rats (305, 306). We are unable to explain the discrepant reports on the effect of leu-enkephalin on AVP. Explanations for the close ties between leu-enkephalin and AVP center around the high immunoreactivity for leu-enkephalin region in the hypothalamus and posterior pituitary of rats (307), an effect that has been demonstrated particularly in AVP terminals (308), suggesting that this opioid peptide may be a significant factor in osmoregulation (308). However, met-enkephalin and leu-enkephalin do not influence spontaneous or stimulated AVP release from isolated neurointermediate lobes (309). Mechanistically, studies suggest that leu-enkephalin, along with met-enkephalin, dynorphin, and CRH are localized in the posterior pituitary in the region innervated by hypothalamic nerve terminals (310, 311). Endogenous opioids likely act directly at these neurosecretory nerve endings and not via pituicytes (312).

At the receptor level, the effects of opioids on the secretion of AVP are primarily mediated by the μ- and κ-opioid receptors (313). FK 33-824, an enkephalin analog and μ-receptor agonist, increased plasma AVP levels (302), and another μ-agonist, DAMGO, decreased urine outflow rates, also suggesting increased AVP release after μ-opioid receptor binding (314). The κ-agonist, RU 51599, inhibited AVP secretion, yet also down-regulated AVP mRNA content (315). These contrasting receptor responses to opioid agonists show that activation of μ- and κ-receptors may exert counteracting actions on AVP secretion.

The phenomenon of hormones having effects on endogenous opioids is also seen with AVP and OT. The hyperphagic response to acute morphine was reduced by both AVP and OT (316). AVP also enhanced periaqueductal gray-secreting enkephalin and β-endorphin in the rat, suggesting that central AVP is an important bioactive substance for antinociceptive regulation (317).

2. Human studies

Similar to animal studies, the information on the effect of opioids and their analogs on AVP secretion, although extensively studied, is not conclusive. Some of the difficulties in interpreting human studies of opioids on AVP are that many of these studies used indirect methods for the evaluation of AVP function or failed to consider side effects of opioids, such as hypotension or nausea, which could secondarily stimulate AVP release. The administration of morphine produced antidiuresis that was believed to be the result of increased AVP secretion (318). However, more recently, several studies using a variety of opioids including morphine (319), β-endorphin (304, 319), leu-enkephalin analogs (320), and the met-enkephalin analogs, DAMME (321–323) and metkephamid acetate (324, 325), all indicate that opioids act directly to suppress AVP secretion. However, there are other papers showing that the opioids do raise AVP levels. Intravenous or epidural morphine administered to children undergoing surgery raised AVP levels (326). Infused fentanyl, an opioid stronger than morphine that is used as an anesthetic, increased AVP release in both surgical patients (327) and healthy volunteers (328). Although in mice, κ-receptors are highly involved in AVP regulation, in humans, κ-agonists induced diuresis but did not change plasma AVP levels (329). These data confirm the role of the μ-opioid receptor in modulating AVP.

3. Summary and overall mechanisms of opioid effects on AVP

The effects of opioids on AVP are the most inconclusive of any hormone in both animals and humans. Both animal and human studies find that stimulation and suppression of AVP levels and discrepancies may be due to the fluid status of the subject as well as side effects of the administered opioid. μ- and κ-receptors appear to be involved in the regulation of AVP by opioids. Endogenous opioids likely affect AVP release by acting at neurosecretory nerve endings in the posterior pituitary.

H. Oxytocin (OT)

1. Animal studies

Despite the similar synthesis location of OT and AVP in the magnocellular neurons in the hypothalamus (330), OT is more affected by opioids and their analogs than AVP. In general, acute administration of opioids inhibits OT release (295, 301).

Opioids not only inhibit the OT release from the axon terminal in the neural lobe but also suppress the functional activity of OT neurons by opioid action on their perikarya in the hypothalamus (331–334). Opioids have been found to act directly at the neural lobe of the pituitary (335) to inhibit OT release in a variety of situations. Morphine inhibited OT levels after an isolated rat neural lobe that had been electrically stimulated (295). The hydration state of the animal did not affect the ability of μ- and κ-opioid receptor agonists to suppress OT levels (313). Opioids also inhibited OT levels in dehydrated rats during lactation (336). Hartman *et al.* (336) proposed that opioid peptides inhibit OT so that the pituitary can store and conserve OT needed for lactation. In normally hydrated rats, morphine caused a dose-dependent reduction in plasma OT levels in virgin but not lactating rats (337), and similar OT levels were found in morphine-treated and untreated lactating rats (338). This finding suggests an interaction between the lactation state and the effects of opioids on OT levels. Interestingly, during parturition, morphine administered sc or by i.c.v. to the mother during birth inhibited the levels of OT and impaired maternal behavior (339).

Chronic morphine treatment in rats affected not only the secretion of OT, but also its synthesis. In the supraoptic nucleus and nucleus accumbens of rats treated with morphine by ip injection for 7 d, decreased OT content and mRNA expression were seen by RIA and *in situ* hybridization, respectively (340). OT expression after water deprivation was reduced by the μ- or κ-receptor agonists in the neurohypophysis, in a similar manner as AVP expression (313). Stress-induced OT secretion was potentiated by μ- and κ-antagonists, with μ-antagonists potentiating the immobilization response and κ-antagonists potentiating the response to hypertonic saline (341). κ-Receptors are involved in inhibiting OT secretion in times of dehydration (342). On the other hand, μ-receptors are primarily involved in the inhibition of the OT response during pregnancy, with κ-receptors having no effect (343). Thus, the effects of endogenous opioids on OT secretion are mediated by different receptors, depending on the stimulation of OT.

2. Human studies

Women have been studied primarily for the effects of opioids on OT, particularly the effect of analgesics, during pregnancy and labor. Lindow *et al.* (344) showed that during late pregnancy, morphine and naloxone had no effect on the maternal OT levels. However, during the first stage of labor, morphine significantly inhibited plasma OT levels, whereas naloxone had no effect (345). Furthermore, fetal OT production was not affected by the administration of morphine to the mother (346). Lindow *et al.* (347) found that after delivery, morphine inhibited the rise in OT secretion in breast-feeding women, whereas naloxone again had no effect. Other opioid analgesics, such as fentanyl or sufentanil, did not suppress OT levels before labor, but suppressed OT levels during the onset of labor (348, 349).

Naloxone has been shown to increase the angiotensin II-stimulated rise of OT secretion in male subjects (350). Another study showed that naloxone had no effect on baseline plasma OT levels in males (351). This highlights the need for more studies on the effects of not only naloxone but also other opioids and opioid analogs on OT levels of males and nonpregnant females.

3. Summary and overall mechanisms of opioid effects on OT

Opioids inhibit OT secretion in both animals and humans. The site of action is both directly at the level of the pituitary and at the level of the hypothalamus. Chronic morphine treatment affected both the synthesis and secretion of OT. Both κ- and μ-receptors are involved in mediating the effects of opioids on OT.

I. Obesity and diabetes

1. Animal studies

The effect of opioids on food intake is controversial and includes reports of hyperphagia (352–355) as well as anorexia (356–363), depending on the dose and dosing regimen (reviewed in Refs. 32, 364, and 365). Reviews state that the majority of studies in rodents show that opioid peptides from three families, endorphins, enkephalins, and dynorphins, when administered in the CNS, increase food intake, and opioid antagonists decrease food intake (reviewed in Refs. 32 and 365), although there are probably more studies showing that opioids cause decreased food intake. Opioids bind to multiple opioid receptor types in the CNS, with the dynorphin/α-neo-endorphin κ-opioid receptor likely being the main receptor involved in feeding modulation (365). There is limited evidence to suggest that they affect food intake when administered peripherally (32). Acutely injected heroin increased immunoreactivity of neuropeptide Y in the thalamic paraventricular nucleus and nucleus of stria terminalis (366, 367), areas known to stimulate food intake and thus lead to an increased likelihood of obesity. Continuous infusion of morphine increased food intake, and, over time, fat intake decreased whereas carbohydrate intake increased

(355). However, in contrast to these reports of hyperphagia, anorexia, characterized by decreased food intake and hyperactivity, is also noted in animals after morphine intake (359, 363). The mechanism of morphine's action on food intake is hypothesized to be a triphasic effect: morphine (15 mg/kg given by ip injection) initially suppressed food intake (1 h), enhanced intake (3 h), then suppressed intake again after 4–24 h (359, 368). The main sites of action at which opioid agonists affect feeding include the amygdala, paraventricular nucleus, perifomical area of the lateral hypothalamus, and ventromedial hypothalamus (365, 369).

Anghel *et al.* (370) conducted a study that observed the effects of short- and long-term morphine administration on rodent food intake, body weight, and hypothalamic and pituitary gene expression as determined by microarray technology. They found decreased food intake coupled with marked weight loss in the days after morphine pellet implantation. They also found that long-term morphine treatment increased hypothalamic neuropeptide Y, agouti-related protein, and cocaine and amphetamine regulated transcript expression, whereas short-term morphine decreased leptin receptors and adiponutrin expression. These studies support the anorexic effect of morphine by uncovering changes in gene expression.

Studies of genetically obese mice (*ob/ob*) showed higher levels of plasma β-endorphin in comparison to control mice. However, plasma β-endorphin levels were similar in obese Zucker rats (*fa/fa*) compared with controls (371). The increase in β-endorphin levels of obese mice was accompanied by higher δ and κ and lower μ-opioid binding sites, suggesting that altered endogenous opioid levels and receptor affinity may contribute to hyperphagia (372).

Furthermore, obesity can affect the endocrine response to opioids in rats. Obese male rats exhibited a decreased GH response to GHRH and morphine (373). However, TRH and the thyroid hormones, T_3 and T_4, did not change with obesity in these same rats (373). Studies of obese Zucker female rats concluded that endogenous opioids affect obesity and reproductive dysfunction because the opioid antagonist naltrexone increased sexual receptivity and proceptivity and also decreased food intake (374). These effects were blocked by morphine treatment, suggesting that endogenous opioids promote obesity as well as hypogonadism.

Diabetes and hyperglycemia affect and, in turn, are affected by opioids. Enkephalin agonists for the μ- and δ-receptors increased glucose and insulin levels in both lean and obese mice (375). However, other studies showed that diabetic rats exhibited increased κ binding in the medial preoptic area and decreased μ binding in the lateral habenula (376). Moreover, female mice given oral methadone for 35 d exhibited a rise in serum glucose levels and reduced glycolytic enzymatic activity, producing a metabolic state that is similar to insulin-resistant diabetes (377). Collectively, these studies demonstrate that opioid manipulations can induce diabetic-like states in animals.

The presence of diabetes can affect how opioids affect parameters related to addiction. Shook and Dewey (378) found that diabetic rats were less physically dependent on morphine than nondiabetic controls and suggested that this lower dependence was due to hyperglycemia itself (379). The antinociceptive effects of morphine were reduced in streptozocin-induced diabetic rats, which is explained not by decreasing numbers of opioid receptors or receptor affinities to morphine but by alterations in the pharmacokinetics of morphine (380). However, one study found reduced numbers of functional μ-opioid receptors in the spinal cord dorsal horn of diabetic rats, which was postulated as a mechanism for the reduced analgesic effect of morphine (381). Thus, there is also an interaction between diabetes and the analgesic effect of morphine.

2. Human studies

One of the growing problems in society today is the increasing rate of diabetes and obesity, and thus, research with opioids has come to address these issues. Treatment of obese subjects with the opioid-antagonist naloxone inhibited the insulin and C-peptide responses to glucose administration, suggesting that endogenous β-endorphins increase the responsiveness of the pancreatic β-cells and that opioid administration may contribute to the hyperinsulinemia and the hyperphagia of obesity (382). In contrast, in obese women, naltrexone decreased basal concentration of both insulin and C-peptide, but did not affect the insulin secretory response to an oral glucose tolerance test (95). Interestingly, obese women treated with naloxone showed more significant weight loss than obese men (383), which may be linked to a sex-related difference in opioid effects. Patients with anorexia and bulimia nervosa were found to have elevated levels of endogenous plasma levels of codeine and morphine; it is proposed that endogenous alkaloids are released during an initial dieting period that also reinforces the state of starvation (384). Concordantly, naltrexone administration reduced binge purging tendencies in bulimic and anorexic patients (385).

Opioids also have different effects on the endocrine system in obese persons compared with normal-weight individuals. Obese patients exhibit lowered GH and PRL responses and higher β-endorphin levels in response to raised opioid levels, an effect blocked by naloxone (386). However, Papalia *et al.* (387) suggested that opioids do not directly regulate GH and PRL levels, but rather they stimulate cortisol and insulin response to insulin-induced hypoglycemia in obese females. In studies of severely obese

patients suffering from hypogonadism, treatments with naloxone resulted in more sensitive response to LH in obese men, thus suggesting that endogenous opioids may act to suppress GnRH secretion in obesity (388).

Although naltrexone alone does not have significant weight loss properties by itself, the combination of naltrexone plus buproprion, a drug used for depression and smoking cessation (389) that is a putative stimulator of the melanocortin pathway, leads to weight loss in both an animal model and a small clinical study (390). In the clinical trial, only a small number of subjects were in each group, and there was a high rate of noncompleters. The authors hypothesized that naltrexone would antagonize the normal inhibitory feedback mechanism that limits sustained POMC activation in response to agents such as buproprion and give an additive effect on weight loss. This combination, marketed as Contrave, is in late stage clinical trials (391).

Diabetes in humans and its relationship with endogenous and exogenous opioids has been an interesting area for research. An early finding was that increased sensitivity to endogenous opioids can be associated with type 2 diabetes associated with chlorpropamide alcohol flushing (392). Naloxone administered to type 2 diabetics sharply increased insulin levels in response to glucose and confirmed the endogenous opioid involvement in impairing insulin levels (393, 394). Additionally, compared with nonaddicted diabetic patients, opioid-addicted patients with non-insulin-dependent diabetes had higher hemoglobin A1c, potassium, and iron levels, whereas their total serum protein, alanine aminotransferase, and high-density lipoprotein-cholesterol were lower. Overall, serum glucose is increased and so is the risk of metabolic disorders (395). Giugliano (396) hypothesized that opioids and opioid peptides act centrally through the sympathetic nervous system to cause hyperglycemia and impaired insulin secretion. He also suggested that heroin addicts do not respond correctly to insulin signals, implicating a higher prevalence of glucose disorders in this population (396). However, in male heroin addicts, hemoglobin A1c levels were similar to controls (397). Alternatively, opioids may also affect insulin resistance and the risk for metabolic syndrome via the induction of hypogonadism. In males, chronic hypogonadism, either spontaneous or induced by GnRH agonists, is associated with increased insulin resistance and risk for diabetes mellitus, but not frank hyperglycemia (398), and testosterone replacement may improve insulin resistance (399).

Endogenous plasma opioid levels are altered in human subjects with diabetes. For example, patients with diabetes showed a 64% elevation of plasma β-endorphin and a substantial increase in enkephalin-like immunoreactivity (400). A possible function for the increased enkephalins in the plasma is to inhibit insulin secretion because FK 33-824 administration reduced plasma glucose rises in normal and type 2 diabetics (401). In diabetic patients, the analgesic effect of morphine was also lessened in diabetic and hyperglycemic conditions, and higher doses of morphine were needed for effective analgesia during postoperative pain (402). The exact mechanisms in humans have not been extensively studied.

3. Summary and overall mechanisms of opioid effects on obesity and diabetes

Increasing data suggest that opioids play a role in regulating food intake, food choice, and perhaps the reward associated with good-tasting foods. Pharmacological studies suggest that more than one opioid receptor is involved in the regulation of feeding, with the κ-opioid receptor predominantly involved. Opioids appear to exert their effect predominantly within the central nervous system, although peripheral effects on taste and gastrointestinal motility may play a minor role. Chronic administration of opioid antagonists has not shown substantial effects on body weight. In humans, the studies so far suggest a relatively minor role for endogenous opioids in appetite modulation. The opioid antagonist, naltrexone, in combination with other drugs, holds promise for weight loss in obese patients.

In both humans and rodents, opioid administration leads to hyperglycemia and worsening diabetes. The mechanism appears to be decreased insulin secretion. Additionally, hyperglycemia decreased the antinociceptive properties of opioids. More studies are needed to explore the interactions between opioids and insulin secretion/insulin resistance.

IV. Areas of Future Research

The above studies show that opioids affect the endocrine system, but many questions remain. It is not clear whether all effects are dose-dependent or whether there is a threshold opioid dose below which effects do not occur. Many studies are cross-sectional comparisons rather than prospective studies, and results may often be confounded by the presence of other diseases or drugs. The route of administration, *e.g.*, intrathecal *vs.* oral or transdermal, may change the magnitude and/or direction of the opioid effects on hormonal secretion. The effect of partial agonists, *e.g.*, buprenorphine, on the endocrine system may be different from full opioid agonists and antagonists and remains to be determined. The mechanisms underlying the differential effects of acute *vs.* chronic opioids are not sufficiently explained. Although chronic opioid use causes

hypogonadism, the extent of gender-related differences needs to be confirmed and explained. Furthermore, there is insufficient information on the long-term effects of opioid-induced hypogonadism, including on bone density, sexual function, and fertility.

Because hypogonadism is associated with an increased risk for cardiovascular events (398) and long-term opioid use clearly leads to hypogonadism, studies on cardiovascular events and risk factors of opioid users are warranted, especially because these patients already have a high prevalence of other risk factors, including immobility and nicotine abuse (122). Overall, there is a need for prospective studies on the effect of chronic opioid therapy on the endocrine system. These studies will require adequate controls for severity and perhaps different types of pain because pain itself has multiple effects on the endocrine system (403).

V. Conclusions

The effects of exogenous opioids, opioid analogs, and endogenous opioid peptides on the endocrine system are numerous. In animals and humans, opioids generally increase GH and PRL and decrease LH, testosterone, estradiol, and OT, whereas the AVP reports are conflicting (Table 4 and Fig. 2). In animals, opioids decrease TSH, whereas in humans opioids increase TSH. The results of the effects of opioids on AVP and ACTH are less clear. Specific receptor stimulation and timing of administration play significant roles in the ability of the opioids to affect these endocrine hormones. Moreover, the mechanisms of the opioids are numerous because opioids affect receptors in the endocrine glands yet also affect endogenous opioid peptide gene expression.

In humans, the primary disorder that results from opioid abuse is hypogonadism, particularly in males. Users and abusers must be aware of not only the prevalence of this disorder on their sexual functioning, but also the effects of the opioids on the other hormones in their system, which may lead to harmful long-term effects. Opioids may cause other endocrine disorders, such as hyperprolactinemia and hyperthyroidism. More research must be done to elucidate the prevalence of these and other endocrine disorders associated with opioid use and abuse.

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