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OPIOIDS AND OPIOID ANALOGS' IMPACT ON THE ANIMAL AND HUMAN ENDOCRINE SYSTEMS: A REVIEW

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ABSTRACT

In the past ten years, there has been an upsurge in opioid misuse, partly as a result of easier availability to prescription opioids. Opioid analgesics are also being prescribed by doctors more frequently to treat persistent non-cancer pain. Hence, understanding the long-term effects of opioid usage and misuse has significant ramifications for completely assessing the therapeutic utility of opioid drugs. Several research have looked at how opioids affect the endocrine system, but to our knowledge, no systematic assessment of the endocrine effects of opioids in both people and animals has been published since 1984. Thus, we looked at the research on how opioids affect the endocrine system. While the bulk of research have focused on the acute effects even though the chronic effects are more physiologically significant, we included both the acute and chronic effects of opioids. Opioids often raise GH and prolactin while decreasing LH, testosterone, estradiol, and oxytocin in both humans and lab animals. Opioids cause a rise in TSH in humans, but a fall in TSH in rodents. There are conflicting studies regarding how opioids affect arginine vasopressin and ACTH in rats and humans. Opioids have stimulatory or inhibiting effects on the release of hormones depending on which receptor sites they choose to act at. Although increasing opioid addiction largely causes hypogonadism, it may also have an impact on other pituitary hormones' release. Lowered libido and erectile dysfunction in males, oligomenorrhea or amenorrhea in women, and bone loss or infertility in both sexes are possible effects of hypogonadism. Depending on the type of opioid and how long it takes to take effect, opioids may cause a person to eat more or less.

Furthermore, opioids may affect insulin secretion and promote hyperglycemia by acting on the sympathetic nervous system. This review presents the most recent data on endocrine abnormalities in opiate addicts.

KEYWORDS: Negative results, Endocrinopathy, Supplemental hormones, Hypogonadism, Opioid, Drug rotation.

I. INTRODUCTION

Prescription drug abuse is defined as "the intentional misuse of a medication outside of the generally accepted standards of its use" in the National Institute on Drug Abuse's (NIDA) "Research Report Series-Prescription Drugs: Abuse and Addiction" (1). Prescription drug misuse is defined as "taking a medication in a manner other than that prescribed or for a different condition than that for which the medication is prescribed." Opioid usage and misuse have risen recently as a result of prescription analgesics being used more often to manage chronic pain. Notwithstanding the potential for addiction, doctors are increasingly prescribing opioid analgesics like vicodin (hydrocodoneiacetaminophen), darvocet-N (propoxyphen/acetaminophen), fentanyl, and methadone because they are highly effective in decreasing pain and are affordable and long-lasting. These drugs are widely prescribed for rheumatological diseases, osteoarthritis, headaches, back pain, sports injuries, and other muscular-skeletal problems. Considering the dangers and advantages of prescription opioids before starting therapy can be challenging for doctors and their patients because there is currently little research available on the long-term effects of chronic opioid usage. Consequently, the objective of this article is to provide a thorough overview of the endocrine effects of opioids so that doctors are aware of potential endocrine (side) effects and may spot any knowledge gaps that require more study.

A public health monitoring system called the Drug Abuse Warning Network (DAWN) has been tracking drug-related hospital ED visits and drug-related fatalities in a few select metro regions since 1995.

According to DAWN statistics, the number of "drug-related" emergency department visits involving prescription opioids rose annually throughout this time from 42,857 to 108,320, a 153% rise. In 2002, 16% of all drug-related ED visits involved prescription opioids, with hydrocodone and oxycodone being the most commonly reported opioids. Twelve-year-olds were found to have used around 4 and 10% of OxyContin (oxycodone hydrochloride) and

Vicodin in the previous year in 2002 and 2003, respectively. This causes grave concern about adolescents abusing prescription opioids. Opioids are often the most prevalent drug poisoning culprit, highlighting the potential risk of prescribed opioids.

II. Opioid Pharmacology and Physiology and its Derivatives

A. Opioids and their derivatives firstly0pium, which is made from the opium poppy's sap, is the source of opiates. The word "opiate" is used to describe both naturally occurring opium alkaloids like morphine and synthetic medications like codeine and heroin that are manufactured from opium alkaloids. No of where they come from, all opioid analgesics fall under the umbrella word opioid. Endogenous opioid peptides and their accompanying binding sites, with which these peptides interact to cause their effects, make up the endogenous opioid system. Several classes of opioid receptors were discovered by early classical pharmacological investigations. There are at least three kinds of opioid receptors that have been cloned: mu, delta, and kappa. The inhibitory G proteins (Gil Go) that these classical opioid receptors are related to the second messenger systems are members of the family of guanine regulatory binding (G) protein-coupled receptors. There are opioid receptors in the brain and throughout the body, including the endocrine organs like the adrenal cortex and the gonads, which modulate the effects of endogenous and exogenous opioids.

B. Groups of opiates

Endorphins, enkephalins, and dynorphins are the three main groups of endogenous opioid peptides that have been discovered. These peptides are produced from pro-opiomelanocortin (POMC), preproenkephalin A, and preproenkephalin B, three different precursor proteins. The endogenous opioid peptide family has grown with the discovery of endomorphin-1 and endomorphin-2. Enkephalins, dynorphins, and -endorphin are generally accepted to be selective agonists for the -, -, and -opioid receptors, respectively. Endomorphin-1 and endomorphin-2 are biological factors involved in the sense of pain, stress reactions, and homeostasis. They have an affinity for the -receptor. To exert their effects, endogenous opioid peptides (as well as exogenous opioids) can bind to many types of opioid receptors. The endogenous opioid peptides have a variety of physiological and pharmacological effects on mammals and people, including the modulation of motor activity, seizure threshold, immune responses, intake of food and water, and control of gastrointestinal, cardiovascular,

neuroendocrine, and cognitive processes. Nevertheless, analgesia or pain reduction is its most well-known clinical benefit (antinociception in rodents).

III. The Impact of Opioids on the Human and Animal Endocrine Systems

A. GH/IGF-I Axis

1. Animal research

Opioids and their analogues are widely known for stimulating the secretion of GH in animals. The acute effects of opioids on GH release and the mechanisms involved have been studied in a number of rat experiments. For instance, 2 hours after intracerebroventricular (i.c.v.) injection, morphine sulphate induced a 3-fold rise in plasma GH concentrations and momentarily elevated the plasma concentration and liver content of IGF-I and IGF binding protein-1. But morphine-6- glucuronide did not result in any appreciable changes in plasma levels of GH and IGF-I, indicating that the different selectivity and/or affinities of morphine and morphine-6-glucuronide to various opioid receptor/subtypes may be to blame for their various effects on the GH/IGF-I system. Endorphin administration by IV or direct hypothalamic injection in rats raised GH levels. Naloxone, which decreased this rise, indicates that opioid receptors are implicated in this reaction. As phenoxybenzamine, a -adrenergic blocking drug, suppressed both spontaneous GH release and the response to FK 33-824, a synthetic enkephalin analogue, -adrenergic receptors are also implicated in the effect of opioids on the release of GH. Moreover, -endorphin antiserum and naloxone decreased the stimulatory impact of the -2- adrenergic agonist, clonidine, on GH release, suggesting that -endorphin or other endogenous opioid peptides may mediate the GH secretion that is generated by -2-adrenergic activation. Male rats exposed to stress had lower plasma GH levels, but those exposed to opioids such as morphine and methadone had higher levels, indicating that stress and opioids may affect GH release through different processes. Naloxone-induced opioid withdrawal reduced GH levels in newborn rat pups exposed to morphine in a dose-dependent manner.

Sex hormones have an impact on how opioids affect growth hormone. Treatment with morphine for 6-12 hours in male but not female rats led to a 12-fold rise in plasma GH levels, which peaked at 3 hours. The estradiol/progesterone-induced LH surge considerably attenuated the opioid-induced GH rise. Naloxone therapy decreased GH levels in female rats by 64% during the same time period. Animals other than rats have been used to study opioid analogues. FK 33-824 treatment to wethers enhanced GH concentration for up to 3 hours

after administration, returning to baseline levels 2-6 days later. Similarly, a 30-min infusion of DAMME, an agonist of the /-opioid receptor, raised plasma GH in Holstein heifer calves. This was accomplished through opioid receptors inside the blood-brain barrier. Naloxone reduced the stress-related rise in GH secretion in prepubescent gilts. When FK 33-824 and a -adrenergic agonist were seen to impact the amplitude and raise mean plasma concentration of GH secretion in broiler chickens, it may be concluded that the effects of these opioids and their analogues are not limited to mammals. Therefore, under a variety of experimental setups and animal models, GH production is stimulated similarly by opioids and their analogues.

The processes by which opioid receptor activation influences GH secretion have been researched by several researchers. The fact that a GH pulse is produced after acute intravenous morphine treatment suggests that opioids reset the hypothalamus GH pulse generator, and this action has been demonstrated to be mediated through -, -, and -receptors. In newborn rats, activation of the - and -receptors caused the GH secretion to be stimulated and inhibited, respectively. The -receptors and -receptors worked together to produce the opioid-induced GH stimulation.

Opioids also interfere with GHRH and somatostatin functions. Antiserum against GHRH treatment in rats decreased the GH stimulatory response to both morphine and -endorphin. Endogenous opioids counteracted the inhibitory impact of somatostatin on GH release, increasing the frequency and amplitude of GH pulses in hamsters. This shows that opioids increase GH production by inhibiting somatostatin and releasing GHRH. Opioids' impact on the transcription of hormone genes have been the subject of several investigations. During prolonged (4-d) morphine treatment, Dobado-Berrios et al. discovered a 22% drop in GH mRNA levels utilising in situ hybridization in rat pituitary. Also, in male rat hippocampi, a single dosage of morphine reduced the gene transcripts for the GH receptor and GH binding protein. These findings demonstrate that opioids influence gene expression and transcription through several regulatory mechanisms.

Overall, these investigations show that acute opioid administration often causes a rise in GH levels, which appears to predominantly be mediated by central -receptors. This might very easily be caused by the release of previously stored GH rather than newly produced GH given the acute (several hours) time course.

The little data shows that persistent (over a few days) opioid dosing lowers GH mRNA levels. It is unknown if this decline is dose-dependent or if it becomes more severe with longer administration times.

Additionally, neither at baseline nor after stress or other stimuli have the effects of opioid therapies lasting longer than 1wk been studied on GH secretion or expression.

2. Human research

Acute opioid treatment and its analogues stimulate GH secretion in human beings through processes involving the opioid receptors, feedback levels, and gene transcription, just like in animals. The least amount of morphine needed to stimulate GH in healthy persons is around 15 mg. An opioid-mediated stimulatory tone on GH secretion was found to exist because naloxone, administered continuously for 120 minutes, reduced the stimulatory impact of GHRH on GH secretion.

Naloxone infusion beginning one hour before to the injection of GHRH decreased the GHRH-induced release of GH in healthy women, but it had no effect on this reaction in healthy males. This sex-related variation in naloxone's impact on GH secretion raises the possibility that sex hormones play a role in modulating endogenous opioids' effects on GH secretion.

There is just one human investigation on the impact of prolonged opioid administration on GH, in contrast to the animal studies. Abs et al. (94) discovered an IGF-I below 2 SD in 12 of 73 patients and a peak GH response to hypoglycemia below 3 mg/liter in around 15% of individuals in a study of patients with severe chronic pain using intrathecal opioids for a mean period of 27 months. This shows that some people, but not all, may experience severe GH insufficiency as a result of persistent opioid treatment. This reaction may be influenced by insulin sensitivity and levels as well as potential counterregulatory hormones. A research in human lymphoblastoid IM-9 cells demonstrated that morphine dramatically affected GH receptor gene expression and GH binding in a naloxone-reversible way, providing evidence that opioid receptors are involved in the influence of opioids on GH. It is unclear if the in vivo effects of opioids rely on dosage, the method of administration (oral or transdermal), or the potential contributions of pain, other drugs, or comorbid diseases. Additionally, it is unknown if GH medication could help people whose low GH is brought on by opiate.

Opioid antagonists were utilised in other experiments to look at how opioids affected GH. Despite the fact that basal levels of GH, IGF-I, and IGF binding protein-3 were unaffected in either group, chronic naltrexone administration (50 mg/ d for 4 wk) caused a 75% reduction in the GHRH-induced GH response in healthy premenopausal women (97) but a 3-fold increase in the GHRH-induced GH response in obese women. In polycystic ovarian syndrome (PCOS) patients, naltrexone administration had opposite results. Lean PCOS patients had an enhanced GH response following GHRH, but obese PCOS patients had no impact. The direction and extent of the effects of these variables are still not well understood, despite the fact that these results suggest that opioids modify the response of GH to GHRH and that body composition, sex hormones, and insulin resistance may also be involved.

Among patients with a range of disorders, several human investigations on the impact of opioids on GH levels have been carried out. Both acromegalics and healthy participants who took morphine had an increase in GH. Opioids have a positive modifying impact on GH secretion in individuals with active acromegaly, as evidenced by the fact that larger dosages of morphine were needed to induce GH secretion in normal participants than in acromegalic subjects. In contrast, GH secretion in acromegalic individuals can be more susceptible to the stimulatory effects of opioids. IGF-I levels and the GH response to insulin-induced hypoglycemia were considerably lower in patients taking intrathecal opioids for intractable pain in a retrospective investigation as compared to controls. The GH deficiency criteria were satisfied by 15% of these individuals.

3. A summary and an overview of how opioids affect GH

Overall, while acute opioid administration increases GH secretion, the effects of chronic opioid administration appear to be much more complex. For example, intrathecal opioids inhibit GH secretion in patients with chronic pain, while an opioid antagonist increases the GHRH-induced GH response in obese women. The possibility that opioids might cause GH deficit has to be further investigated, even if this reaction seems to be influenced by sex, body composition, and insulin resistance.

B. Prolactin

1. Animal studies

Typically, opioids and their analogues influence the hypothalamus to induce PRL secretion from the anterior pituitary (99). PRL release was unaffected by morphine or morphine analogues being directly incubated on isolated perfused pituitaries (1 00, 101). Nonetheless, it

has been demonstrated that a single systemic injection of an opioid agonist, such as DAMME or FK 33-824, reliably raises blood PRL concentrations across a variety of species (80, 82, 102) and that this effect is reversed by naloxone in both heifers and rats (103-105). In addition to their effects on PRL release, morphine and naloxone both reduced the levels of PRL mRNA in rats by 10% and 12%, respectively (89), showing that opioids have an impact on the expression of the morphine gene. Since dopaminergic pathways interact with the opioid system in rats and increase PRL release while decreasing serotoninergic pathways' ability to do so, the mechanism by which opioids affect PRL secretion is complicated. Moreover, the serotoninergic system does not become functional until 10 to 15 days after birth and is unable to regulate the effects of opioids on PRL production in neonatal rats, but the dopaminergic system does. In contrast, serotoninrgic pathways in monkeys increase PRL secretion whereas dopaminergic pathways have little effect. A hypothalamic location for opioid control of PRL secretion was also verified by this investigation. ln the dorsomedial arcuate nucleus of rats, it was discovered that nicotine, morphine, and a serotonin agonist [8-hydroxy-2-(di-n-propylamino) tetralin] all use the same synaptic route for PRL release (108). Most notably, this research (108) confirmed Bero and Kuhn's findings (106) that blocking of dopaminergic pathways is a key factor in how opioids induce PRL release. Even though these experiments using isolated rat pituitaries in culture are not physiological and do not take into account the interactions between the hypothalamus and pituitary, the administration of morphine, leu-enkephalin, and DAMME showed little effect on dopamine-induced inhibition of PRL secretion. Nevertheless, the -opioid receptor seemed to have a key role in mediating the action of opioids on PRL secretion, even though all three opioid receptors are engaged in the opioid-induced PRL stimulation. Mice lacking opioid receptors should be used to confirm these results.

Acute stress increased PRL, and the endogenous opioids -endorphin and dynorphin-A can control this impact.

Naloxone injection was said to boost the stress-induced rise in PRL secretion in one pig study, however this response was quite moderate and was not statistically supported. The majority of papers state that naloxone suppresses PRL release, which is the anticipated result. Endogenous opioid peptides may have a role in the neural transmission of genitosensory stimulation causing PRL secretion since they are implicated in the immediate response of

PRL release after mating in female rats. Moreover, female monkeys' medial basal hypothalamus -endorphin also controlled progesterone-induced PRL.

Contrary to GH, opioids have a wide range of effects on PRL secretion that depend on when they are taken, especially throughout the female cycle. Although acute morphine treatment enhanced PRL secretion in diestrous and proestrous rats, it had no effect on the levels of PRL in lactating rats, probably because the -opioid receptor was down-regulated. Contrarily, during lactation in female rats, -endorphin and a leu-enkephalin analogue raised PRL.

Opioids may also affect early reproductive systems, which might lead to impairments in adulthood. When given to young female rats, morphine inhibited suckling-induced PRL secretion in maturity, but had no effect on other parental behaviours. As a result, adolescent opioid usage has a permanent impact on PRL secretion.

2. Human studies

In addition to euthyroid and hypothyroid participants, males also had higher serum PRL concentrations after receiving acute morphine treatment. In postmenopausal women, acute morphine treatment similarly raised PRL levels. A single dosage of intravenous morphine enhanced PRL and lowered LH in postmenopausal women, indicating that morphine may have an effect on a single receptor or neurotransmitter that regulates both PRL and LH production from the anterior pituitary. Morphine continued to raise PRL following the administration of a submaximal dosage of the dopamine agonist metoclopramide, but not after the administration of a maximum dose of the drug. This implies that the effects of opioids on PRL release in humans and animals are mediated by dopaminergic pathways.

Little is known about how long-term opioid administration would affect PRL. In both male and female chronic pain patients who took opioids either intravenously or orally, PRL levels were normal. In contrast, after receiving therapy with the dopamine agonist bromocriptine for 30 days, baseline PRL levels in male opioid addicts participating in a methadone maintenance programme declined. In Iran, the PRL levels of 87% of opium users were increased. It's possible that there are inherent differences between individuals using painkillers and heroin users, or that there are particular effects of methadone on PRL secretion that account for the discrepancy between the methadone research and other studies showing increased PRL following opiates. Naloxone, an opioid receptor antagonist, has an unclear impact on PRL. Naloxone did not affect baseline PRL levels or its release after stimulation with TRH in

healthy males. Nevertheless, naloxone was able to lessen the rise in PRL following buprenorphine injection in a similar sample of males. In two trials that concluded that naloxone had no effect on PRL levels, men and women were tested jointly.

The effects of opioids on PRL in women may possibly be modulated by sex steroid hormones. Menopausal women, hypogonadal women, or normal women in the early follicular or late luteal phase of their menstrual cycle did not respond to naloxone in terms of basal PRL production. However when given to healthy women for 7 days during the luteal phase of the menstrual cycle, naloxone did cause PRL release as seen by an increase in LH and PRL pulse frequencies. Naloxone injections given to postmenopausal estrogen-treated women revealed lower plasma PRL concentrations than the untreated control group of women of reproductive age. These papers demonstrate that oestrogen levels (as indicated by the phase of the cycle or by exogenous oestrogens) modify the effects of opioids on PRL levels in women and hint to an interaction between LH and PRL that is mediated by opioids.

3 Generalized mechanisms of how opioids affect PRL

Acute opioid injection boosted PRL levels in both rats and people, although this impact seems to be mediated through hypothalamic mechanisms rather than the pituitary directly. Circulating sex hormones influence the response. Dopaminergic pathways increase the opioid-induced PRL release whereas serotoninergic pathways lower it. Both the effects of prolonged opioid medication and the effects of naloxone on PRL levels can vary. Naloxone has been shown to lower PRL levels in certain studies, an action that may be influenced by circulating sex hormones. Sometimes, chronic opioid administration increases PRL levels; this impact may depend on the particular opioid used. The clinical effects of persistent opioids on PRL levels require more research.

IV. Future Research Topics

The aforementioned research demonstrate how opioids impact the endocrine system, yet many unanswered concerns remain. It is unclear if all opioid effects are dosage-dependent or if there is a certain opioid dose below which effects do not manifest. Instead of being prospective research, a lot of studies are cross-sectional comparisons, and the presence of additional illnesses or medications can often skew the results. The degree and/or direction of the opioid effects on hormone secretion may vary depending on the mode of administration, such as intrathecal vs. oral or transdermal. It is unknown how partial opioid agonists, such as buprenorphine, affect the endocrine system in comparison to complete opioid agonists and

antagonists. lnsufficient explanations are given for the diverse ways that acute and chronic opioids affect people. Even if long-term opiate usage results in hypogonadism, gender-related variations must be validated and explained to the fullest degree possible. The long-term implications of opioid-induced hypogonadism, such as on bone density, sexual function, and fertility, are also not well understood.

Studies on cardiovascular events and risk factors of opioid users are necessary because hypogonadism is clearly caused by long-term opioid use and is associated with an increased risk for cardiovascular events, particularly because these patients already have a high prevalence of other risk factors like immobility and nicotine abuse. In general, prospective studies on the impact of prolonged opioid medication on the endocrine system are required. Since pain has numerous impacts on the endocrine system, these studies will need proper controls for intensity and maybe distinct types of pain.

V. CONCLUSION

Exogenous opioids, opioid analogues, and endogenous opioid peptides all have a variety of effects on the endocrine system. While the AVP findings are inconsistent, opioids often raise GH and PRL and reduce LH, testosterone, estradiol, and OT in both animals and humans. Although opioids raise TSH in humans, they lower TSH in animals. Little is known regarding how opioids affect AVP and ACTH. The capacity of the opioids to impact these endocrine hormones depends in large part on the activation of specific receptors and the time of delivery. However, there are many different ways that opioids work since they influence both the expression of endogenous opioid peptide genes and receptors in endocrine glands.

Hypogonadism, especially in men, is the main problem in those who take opioids. In addition to the frequency of this disorder's impact on sexual function, users and abusers need to be mindful of how opioids affect other hormones in their bodies, which can have negative long-term repercussions. Other endocrine conditions including hyperprolactinemia and hyperthyroidism may also be brought on by opioid usage. To further understand the incidence of these and other endocrine problems linked to opiate use and misuse, more study must be conducted.

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