Opioid Modulation of Oxytocin Release

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Analgesia or anesthesia is frequently used for women in labor. A wide range of opioid analgesics with vastly different pharmacokinetics, potencies, and potential side effects can be considered by physicians and midwives for laboring patients requesting pain relief other than a labor epidural. The past 50 years have seen the use of the classic mu opioid agonist morphine and other opioids diminish markedly for several reasons, including availability of epidural anesthetics, side effects, formulary restrictions, and concern for neonatal respiratory depression. Morphine is now primarily used in obstetrics to provide rest and sedation as appropriate for the stressed prodromal stages of a labor without sufficient cervical dilatation. This review discusses the scientific basis for opioid modulation of oxytocin release from the posterior pituitary and the practical implications of this relationship to explain well-known clinical observations of the effect of morphine on prodromal labor.

Keywords: *endogenous opioids; morphine; meperidine; mu-kappa-delta opioid receptors; oxytocin; parturition; vasopressin*

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The major hormone involved with parturition to stimulate uterine contractions is oxytocin. Russell et al[1] have reviewed the extensive literature on the complexity of the magnocellular oxytocin system. Endogenous opioids mechanisms inhibit oxytocin release as part of the multiple hormones involved, including relaxin, estrogen, progesterone, and autoinhibition by nitric oxide.

Oxytocin is produced in the hypothalamus and is released into systemic circulation via the posterior lobe of the pituitary gland. Specifically, oxytocin is made in magnocellular neurosecretory cells of the supraoptic nucleus and paraventricular nucleus of the hypothalamus. It is well established that oxytocin is involved in a positive feedback loop during parturition, in which oxytocin causes uterine contractions, which in turn lead to more oxytocin release. This feed-forward loop continues until parturition. Oxytocin is also released when an infant suckles at the nipple of a lactating mother and acts at the mammary glands, causing milk letdown. In view of the importance of the endogenous opioids system in modulating oxytocin release, it is of interest to note the use of exogenous mu opioids such as morphine and meperidine in human parturition.

Different forms of analgesia/anesthesia are needed for both the benefit of the woman in labor and her baby. In the United States today, about 1 in 3 women and their caretakers are opting for cesarean sections, typically as elective, scheduled surgery.[2] The Cochrane protocol for the use of parenteral opioids for maternal pain relief in labor is especially useful.[3] The availability of a wide range of analgesics with vastly different pharmacology, pharmacokinetics, milligram potencies, routes of administration, and side effects is impressive. Nevertheless, morphine use during labor has had a checkered pro and con history over the years. During its use to produce twilight sleep, it became clear that although analgesia and amnesia for the mother was desirable, some women became excited and delirious. In addition, newborns frequently showed apnea. Thus, twilight sleep was abandoned years ago. Its replacement with meperidine alone or in combination with promethazine also had a pro and con history of increased use to abandonment. Meperidine has a complex pharmacology in addition to having mu opioid analgesic properties. DeVoe et al[4] reported that meperidine alone or in combination with promethazine, although analgesic, did not decrease but actually increased uterine activity over control from about 7 to 20-30 Torr/min units of uterine activity over 10 to 30 minutes. Many other opioids have been used

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since, again with mixed results. Today, morphine is used in a subset of obstetrical patients to provide rest and sedation as appropriate for the stressed prodromal stages of a labor without sufficient cervical dilation with a fetus in no stress. This review provides a rational scientific basis to its current use and shows why it is useful for more than just rest and sedation for patients.

OPIOID RECEPTORS IN THE PITUITARY

Controversy exists over the nature of opiate binding in the posterior pituitary.[11] C-carfentanil (a selective mu opioid receptor agonist) is known to have relatively high binding potential in the human pituitary similar to classical opiate binding areas in the brain, but its clinical significance remains unknown.[5,6] However, positron emission tomography (PET) imaging does not distinguish whether binding is in the anterior or posterior lobes. Relatively large doses of naloxone (1 mg/kg) do not completely displace ^{11}C-carfentanil binding in the pituitary compared to other brain areas, indicating the presence of a nonopioid binding site.[5,6] One possibility is that a metabolite of ^{11}C-carfentanil such as ^{11}C-methanol may be involved.

Simantov and Snyder[7] reported the presence of mu opiate binding in bovine intermediate and posterior but very little in the anterior pituitary, where beta-endorphin is released.[8] Jordan et al[9] studied postmortem pituitaries from 5 human participants without neuroendocrine or neuronal disease. They used (^{125}I)-FK-33-824 for mu, (^{125}I)[D.Ala^2] Deltorphin-I for delta, and ^{3}H-U69,593 for kappa opioid sites. Quantitative in vitro autoradiography of pituitary sections with each radioactive ligand indicated the absence of significant labeling in the anterior lobe but high binding in the posterior pituitary. All 5 posterior pituitary specimens had significant mu and kappa binding sites that almost overlap completely but had no significant delta binding sites. These investigators further showed that both the mu and kappa opioid binding was competitively antagonized by other selective opioid ligands. The more recent PET study by Weerts et al[10] also demonstrated a specific mu opioid binding site in the human pituitary. These investigators studied mu as well as delta opioid brain and pituitary binding in recently abstinent alcohol-dependent participants treated with naltrexone. The naltrexone-treated subjects had decreased binding in the pituitary for both ^{11}C-carfentanil (mu) and ^{11}C-naltridole (delta). Delta opioid binding in the human brain and pituitary was present but minimal. This latter finding differs from other published animal and human pituitary data that indicated negligible delta opioid binding. Naltrindole has been found to bind to mu and kappa in addition to delta receptors,[11] which could account for the different conclusions.

MU OPIOID MODULATION OF POSTERIOR PITUITARY HORMONE RELEASE

Opioid binding in the posterior pituitary is important because of the effect on oxytocin and vasopressin release. Both mu and kappa opioid receptor agonists have been shown to affect posterior pituitary hormone release. Oxytocin secretion is inhibited centrally by both mu and kappa agonists or directly at the posterior pituitary via kappa receptors. Lutz-Bucher and Koch[12] isolated the rat neurointermediate as well as the neural lobe (posterior pituitary). Removal of the endogenous opiate-rich pars intermedia cells from the pars nervosa enhanced both oxytocin and vasopressin release. Morphine inhibited their release from both lobes, but the neurointermediate lobe needed a larger concentration. Naloxone reversed the effects of morphine, indicating a primarily mu opioid receptor action.

Clarke and Patrick[13] studied isolated rat pars nervosa with attached pars intermedia. They electrically stimulated the pituitary stalk to measure oxytocin and vasopressin release. Morphine inhibited both oxytocin and vasopressin release. Naloxone reversed morphine inhibition of oxytocin but not vasopressin release. Bicknell et al[14] found that oxytocin cells develop dependence with added morphine and eventually require morphine to function normally. When naloxone was given, the firing rate of oxytocin-secreting cells increased 360% and plasma oxytocin levels increased 100 times greater than in controls. No significant difference was observed in vasopressin levels. Zhao et al[15] also found in rats that naloxone increased oxytocin release 100% and 173% in 2 experiments and vasopressin release only 30% and 20%, respectively.

Pumford et al[16] showed that morphine depresses the firing rate of supraoptic oxytocin neurons when given intracerebroventricularly (ICV) and intravenously (IV). Both morphine tolerance and dependence developed in magnocellular oxytocin neurons during 5 days of ICV infusion. The researchers suggested that tolerance and dependence to endogenous opioids is important for oxytocin neurons during pregnancy, in preparation for parturition.

Ortiz-Miranda et al[17,18] reported that mu opioid receptors modulate rat neurohypophyseal terminals

by inhibiting R-type Ca^{2+} channels. The mu receptor agonist, [D-Ala^2, N-Me-Phe^4, Gly^5-ol]-enkephalin (DAMGO), inhibited oxytocin more than vasopressin release. The inhibitory actions of DAMGO were antagonized by the mu antagonist CTOP (D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr amide).

KAPPA OPIOID MODULATION OF POSTERIOR PITUITARY HORMONE RELEASE

Zhao et al,[15,19] Bicknell et al,[20] Kato et al,[21] and Russell et al[22] emphasized the importance of functional kappa receptors on oxytocin and vasopressin rat posterior pituitary terminals, with a greater inhibition on oxytocin than vasopressin release. Mu agonists do not have as great of an effect as kappa agonists at oxytocin and vasopressin nerve terminals.[22,23] Russell et al[22] found that the kappa agonist U50,488 inhibited electrically stimulated oxytocin release in rats, but morphine had no effect. U50,488 had no effect on mammary gland sensitivity to oxytocin, whereas morphine decreased sensitivity. These results suggest that mu receptors located on the posterior pituitary are not coupled to mechanisms regulating release of oxytocin but are rather responsible for inhibition of the firing rate of oxytocin neurons, whereas kappa agonists act directly at oxytocin secretory terminals to decrease secretion.

Van de Heijning et al[24] used both naloxone and its quaternary methylnaloxone given either subcutaneously (SC) or ICV to water-deprived rats to alter plasma oxytocin and vasopressin levels. Both opioid antagonists given SC increased plasma oxytocin. Given ICV, both equally antagonized coadministered dynorphin A (an endogenous predominant kappa receptor agonist). When either beta-endorphin or dynorphin A were given ICV, the quaternary antagonist was less effective than tertiary naloxone. This indicated a more central action inside the brain for antagonism of ICV opioid agonist inhibition of hormone release. Interestingly, dynorphin A ICV inhibition of oxytocin release was equally antagonized by both opioid antagonists, suggesting an action outside of the blood-brain barrier (ie, in the posterior pituitary). In a different experiment, Van de Heijning et al[25] again found that mu and kappa but not delta opioid receptors are involved in the modulation of vasopressin and oxytocin release in rats. The mu opioid receptor agonist DALDA (H-Tyr-D-Arg-Phe-Lys-NH_2) given SC and ICV inhibited both vasopressin and oxytocin release. The kappa opioid receptor agonist U-69,593 inhibited the release of vasopressin and oxytocin when given SC but not when given ICV, again indicating action at the posterior pituitary for a kappa agonist. Both kappa (norbinaltorphimine) and mu (naloxone) but not delta (naltrindole) antagonists increased oxytocin levels, but when given ICV, only the kappa antagonist enhanced both oxytocin and vasopressin release.

Dayanithi et al[26] used rat neural lobes and isolated nerve terminals to show kappa agonist inhibition of oxytocin more than vasopressin release as well as antagonism by naloxone. There were a number of inconsistencies and evoked changes in intracellular calcium $[Ca^{2+}]_i$. The investigators concluded that opioid molecules may have a doubtful physiological role in controlling neurohypophyseal secretion. Kato et al[21] also used isolated nerve terminals from rat neurohypophysis to study the effects of kappa opioid effects on secretion of oxytocin and vasopressin. Dynorphin A 1-11 inhibited K^+-evoked oxytocin more than vasopressin release. It did not inhibit the rise in intracellular Ca^{2+} even though kappa receptors are coupled to $[Ca^{2+}]_i$. An unknown alternative mechanism may be involved in posterior pituitary nerve endings.

Brown et al[27] reviewed the complexity of opioid modulation of the magnocellular hypothalamic cells whose axons terminate in the posterior pituitary to release oxytocin and vasopressin. Endogenous opioid peptides inhibit their release both within the hypothalamus and at their terminals in the pituitary itself. Furthermore, the co-localization in neurosecretory granules and subsequent co-release of the kappa agonist, dynorphin, with vasopressin appears to reduce oxytocin release from the latter's axon terminals. Oxytocin cells also synthesize dynorphin and enkephalins. The co-release of endogenous opioids appears to reduce oxytocin release more than vasopressin. Bicknell and Leng[28] concluded that endogenous opioid receptor agonists only act to inhibit oxytocin release, with no effect on vasopressin release in rat posterior pituitary. Also in rats, Bondy et al[29] found that dynorphin A (an endogenous predominant kappa receptor agonist) inhibits the electrically stimulated release of oxytocin but not vasopressin from the terminals of the posterior pituitary. However, Shuster et al[30] conclude from their studies in guinea pigs that dynorphin-vasopressin co-release only acts to inhibit further vasopressin release, with the kappa opioid receptor as an autoreceptor.

The effects of kappa opioid receptor agonists can be biphasic. Grell et al[31] injected bremazocine (a kappa receptor agonist) into rats and measured subsequent plasma oxytocin levels. The researchers found a decrease in oxytocin 30 minutes after injection,

much like in other studies. However, after 4 hours, oxytocin levels increased 20-fold. Two possible explanations for this phenomenon were given: (1) inhibition of oxytocin release from the posterior pituitary, combined with increased water excretion and the ensuing elevation of plasma sodium, caused the late rise in oxytocin, and (2) downregulation of opioid receptors. This biphasic effect of opioids on oxytocin release could have important clinical implications related to pregnancy and parturition. The clinical effect of initial decreased oxytocin levels may be exploited in pregnant women with a dysfunctional pattern of labor contractions. Obstetricians occasionally empirically give morphine for a period of rest. When the effects of the drug wear off, normal uterine contractions often follow perhaps due to increased endogenous oxytocin release. Theoretically, a mu agonist such as morphine would be preferred because of the dysphoric and psychotomimetic properties of kappa opioid receptor agonists.[32]

CLINICAL USE OF OPIOIDS IN OBSTETRICS

A wide range of opioid analgesics can be considered by physicians and midwives for laboring patients requesting pain relief outside of when a labor epidural is available. The opioid analgesic meperidine was previously a popular narcotic in this field. However, it has been restricted in many hospitals due to a variety of dangerous side effects (confusion, anxiety, hallucinations, tremors, and seizures), a shorter analgesic period than morphine, and potentially fatal interactions with monoamine oxidase inhibitors.[33-35]

Intrathecal and epidural administration of opioids by anesthesiologists is a common analgesic method used in active labor. Sufentanil and fentanyl are widely used for this purpose.[36,37] However, labor epidurals are given only in active labor (greater than or equal to 4 cm dilation). This leaves a relatively lengthy window of time in labor when the patient may ask for options for pain relief outside of a labor epidural. It is during those times of latent or prodromal labor that morphine may be prescribed. Morphine provides women in latent labor with analgesia and rest, and contractions may ease soon after injection. In 1955, Friedman[38] noted from observations of 46 patients with uterine inertia that almost half were due to excessive medication. Unfortunately, his article did not specify the medication(s) given. Most women awaken from "therapeutic rest" from morphine in active labor.[39] Of course, respiratory depression of the newborn can be an issue when large doses of morphine are used.

BASIC SCIENCE MODELS OF CLINICAL OBSERVATIONS

Russell et al[22] demonstrated in a rat model that morphine could be used to delay parturition. Morphine given ICV on days 17 to 18 of pregnancy delayed the start of parturition by 4 hours. Once parturition was established, however, it was not affected by morphine, indicating tolerance to morphine inhibition of oxytocin secretion.

Endogenous opioids, such as prodynorphin and its end products, are co-secreted with oxytocin and vasopressin and act via kappa opioid receptors to provide feedback inhibition.[40] This feedback mechanism via the kappa opioid receptor is less effective late in pregnancy.[41] The specific opioid system responsible for the control of oxytocin secretion during pregnancy until parturition changes with time. Douglas et al[41] found that on days 15, 18, and 21 of pregnancy in rats, naloxone caused a significant increase in plasma oxytocin levels, suggesting endogenous opioid inhibition of oxytocin release. Naloxone failed to cause a significant increase in oxytocin levels in nonpregnant, early pregnant, and postpartum rats. The kappa agonist U50,488 was less effective at inhibiting electrically stimulated release of oxytocin from posterior pituitaries from 16- and 21-day pregnant rats than in nonpregnant rats. This indicates desensitization of oxytocin nerve terminals to endogenous kappa opioid suppression late in pregnancy. Douglas et al[41] also found that posterior pituitary content of Met-enkephalin significantly decreased by the 21st day of pregnancy, suggesting increased release at this time. Posterior pituitary dynorphin A levels and prodynorphin mRNA expression in the supraoptic nucleus did not change during pregnancy. The researchers concluded that a product of proenkephalin A is likely responsible for autoinhibition of oxytocin release during pregnancy.

The kappa antagonist norbinaltorphine (norBNI) has also been used to investigate oxytocin suppression during pregnancy in rats. Leng et al[42] found that norBNI increased secretion of oxytocin in pregnant rats, whereas naloxone had no effect, suggesting the kappa receptor was involved. However, late in pregnancy, norBNI was no longer effective in increasing oxytocin levels, again indicating that endogenous kappa opioid receptors are downregulated. Other research suggests that mu opioid receptors mediate oxytocin release at the time of parturition. Kutlu et al[43] studied oxytocin levels in pregnant and parturient rats given ICV morphine (mu agonist), U50,488H (kappa agonist), clocinnamox (mu antagonist), and norBNI (kappa antagonist). Parturient rats had

increased levels of oxytocin and decreased levels of beta-endorphin compared to 20-day pregnant rats. Clocinnamox raised oxytocin levels, whereas U50,488H decreased oxytocin levels. An important finding was that only clocinnamox elevated norepinephrine in the supraoptic nucleus and the paraventricular nucleus. Norepinephrine has a stimulatory effect on oxytocin neurons.[44] Thus, Kutlu et al[43] concluded that endogenous mu opioid agonists cause tonic inhibition of oxytocin neurons at presynaptic norepinephrine terminals in the hypothalamus—tonic because only cloccinnamox raised oxytocin levels, and morphine had no effect. The decrease in oxytocin levels produced by U50,488H were likely due to actions directly on the posterior pituitary.

In addition, hypothalamic mu opioid receptor concentrations increase in rats during pregnancy, being significantly higher on days 15 to 22 of pregnancy than on the day of estrus. Receptor concentrations return toward control levels after parturition.[45] Hypothalamic beta-endorphin levels followed the same pattern in this study—an increase up to the point of parturition and a subsequent decrease back to normal levels 12 to 18 hours afterward. The increase in mu opioid receptors and beta-endorphin levels in the hypothalamus is likely responsible for control of oxytocin during pregnancy. Dondi et al[45] suggest that the decrease in hypothalamic mu opioid receptor and beta-endorphin concentrations after parturition is important for the development of maternal behavior and for the control of oxytocin release. Oxytocin is important in controlling lactation. Thus, opioid suppression of oxytocin release must be decreased for lactation to occur properly. Boersma et al[46] and Douglas and Russell[47] have emphasized neural-glial interactions in the release of oxytocin, vasopressin, ACTH, and the role of opioids and other peptides. In addition, endogenous opioids regulate intracerebral release of oxytocin in a region-specific manner.[48] In addition, the important role of infant-mother attachment involves contributions from opioids and oxytocin as well as norepinephrine.[49]

CONCLUSION

Both mu and kappa opioid receptor agonists can be used to decrease oxytocin levels in humans and animals. Their mechanisms and sites of action involve both the brain and pituitary. The clinical observation that morphine gives patients rest from contractions and delays childbirth is likely due to inhibition of oxytocin release. As the drug wears off or as opioid receptors are downregulated, oxytocin levels rebound significantly, and the patient finds herself in active labor or return to baseline uterine activity without labor. Morphine in proper doses can safely be administered to a patient in latent labor. If required, the mu opioid antagonist naloxone can be administered if needed to counteract newborn complications caused by the use of too much morphine administered to the mother.

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