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Effects of Morphine, β-Endorphin and Naloxone on Catecholamine Levels and Sexual Behavior in the Male Rat

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McINTOSH, T. K., M. L. VALLANO AND R. J. BARFIELD. *Effects of morphine, β-endorphin and naloxone on catecholamine levels and sexual behavior in the male rat.* PHARMAC. BIOCHEM. BEHAV. 13(3) 435–441, 1980.—Intraperitoneal administration of the opiate antagonist naloxone hydrochloride (30 mg/kg) to sexually experienced male rats caused a significant reduction in mount and intromission latencies, number of mounts preceding ejaculation and ejaculation latencies. Intraperitoneal administration of naloxone (30 mg/kg) also stimulated persistant non-copulators to begin mating and to ejaculate within a twenty minute test period. Conversely, intraperitoneal administration of morphine sulphate (6 mg/kg) as well as intraventricular injection of the endogenous opiate β-endorphin (6 μg) produced a complete loss of copulatory behavior in male rats. The deficit in sexual behavior induced by β-endorphin was correlated with a significant increase in hypothalamic norepinephrine levels. It is suggested that the endogenous opiates may be involved in the mediation of sexual behavior via an interaction with central catecholaminergic systems.

Naloxone β-Endorphin Morphine Sexual behavior Catecholamine

THE recent discovery of the endogenously occurring opioid peptides (Enkephalins and Endorphins) has generated enormous interest in the possibility that these compounds are involved in other physiological mechanisms aside from pain perception and analgesia. The fact that binding sites for these peptides are distributed in the hypothalamus, neostriatum and limbic system [3] suggests that the endogenous opiates may play a role in mediating sexual and/or reproductive behavior as well as other important behavioral functions. In support of this hypothesis, Meyerson and Terenius [29] found that intraventricular injection of 1 μg of β-endorphin significantly reduced the display of mounting behavior in male rats. This effect of β-endorphin was abolished by pretreatment with the opiate antagonist naltrexone. Similarly, intravenous injection of 3 μg of (D-Ala^2)-met-enkephalinamide (a synthetic enkephalin analog) increased mount latencies in male rats [32], while 6 μg totally abolished copulatory behavior [15,32]. Hetta [19] also observed that administration of the opiate morphine (5 mg/kg IP) to male rats caused a decrease in mounting and intromission rates, whereas naltrexone (5 mg/kg IP) administered alone 30 min before testing increased the percentage of animals ejaculating within a five-minute test period. In addition, Myers and Baum [31] have recently demonstrated that increasing doses of naloxone hydrochloride produced an increase in the percentage of tests in which the males ejaculated, as well as a decrease in ejaculation latencies and the number of intromissions needed to achieve ejaculation.

It appears likely that endogenous opiate receptors are involved in the modulation of neurotransmitter activity within the brain. Several behavioral effects of the narcotic analgesics, including motor stimulation, circling behavior, catalepsy and analgesia may be correlated with the opiate's effects on central dopamine turnover [24]. De la Baume [12] found that the changes induced by long-term morphine treatments in the striatum are similar to the "disuse hypersensitivity" that is developed by interrupting dopaminergic transmission. Moreover, both morphine and β-endorphin inhibited the potassium-induced release of dopamine from striatal synaptosomes, *in vitro* [26]. *In vivo* studies have demonstrated that met-enkephalin inhibited the release of dopamine at synapses in the rat striatum; an effect which was antagonized by naloxone [2]. Because catecholamine levels within the brain are known to be important in the mediation of male sexual behavior, the present study was undertaken to more clearly elucidate the effects of morphine, β-endorphin and the opiate antagonist naloxone on masculine sexual behavior and related neurotransmitter activity.

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TABLE 1

EFFECTS OF MORPHINE AND NALOXONE ON THE SEXUAL BEHAVIOR OF MALE RATS

	Saline vehicle	Morphine (3 mg/kg)	Naloxone (10 mg/kg)	Naloxone (10 mg/kg) + morphine (3 mg/kg)
Mount latency	55 ± 0.20	128 ± 0.70	57 ± 0.10	67 ± 0.20
Intromission latency	103 ± 0.09	132 ± 0.09	123 ± 0.06	136 ± 0.06
Ejaculation latency	512 ± 0.3	449 ± 0.7	440 ± 0.30	438 ± 0.03
No. of mounts	9 ± 0.01	12 ± 0.05	10 ± 0.02	8 ± 0.05
No. of introm.	10 ± 0.10	9 ± 0.10	11 ± 0.20	10 ± 0.30
Post-ejaculatory interval	435 ± 13.7	446 ± 9.4	510 ± 10.1	441 ± 14.1
Inter-copulatory interval	60 ± 0.03	54 ± 0.06	43 ± 0.08	42 ± 0.10
% Tests in which ejaculation occurred	96 ± 2	96 ± 2	96 ± 2	92 ± 4

Values given are mean seconds ± SEM for the same 16 rats under different treatment conditions.

METHOD

Male Long-Evans rats (300–350 g) were obtained from Charles River Breeding Farms and housed individually in steel wire-mesh cages. Sexually active males were selected through a screening procedure and caged singly under reversed lighting condition (dark phase; 9:30–21:30). Food (Purina Rat Chow) and water were available ad lib.

Fresh solutions of morphine sulphate and naloxone hydrochloride were prepared in 0.9% NaCl daily. In Experiment 1, morphine was administered at a dose of 3 mg/kg or 6 mg/kg body weight in 0.1 ml saline IP while naloxone was administered in a dose of 10 mg/kg or 30 mg/kg weight in 0.1 ml saline IP. In Experiments 2 and 3, β-endorphin (6 μg) was dissolved in saline and injected intraventricularly in a volume of 6 μl.

In all experiments, each animal received the preferred drug treatment 30 min before being tested with a sexually receptive female. The females were ovariectomized Long-Evans rats injected with 50 μg of estradiol benzoate 54 hours before the test, and 500 μg of progesterone 6 hours before testing with the male. All tests were performed during the dark phase of the light-dark cycle under red illumination. The test cage was a glass bottom aquarium (40×26×29 cm). Animals were allowed to adapt to the test chamber for at least five minutes prior to the introduction of a receptive female. The occurrence of standard items of sexual behavior was recorded manually on a pushbutton-activated Rustrak event recorder. An ultrasonic microphone fixed at the top of the testing chamber was connected to a Holgate bat detector which monitored 22 kHz ultrasonic vocalizations emitted by the males during the refractory period. The following measures were derived from the raw data: Intromission Frequency (IF—the number of intromissions prior to ejaculation), Mount Latency (ML—the time from the introduction of the female to the first mount), Intromission Latency (IL—the time from the introduction of the female to the first intromission), ICI (a measure of copulatory rate found by dividing EL/no. of intromissions), Ejaculation Latency (EL—the time from the first intromission to ejaculation), Vocalization Latency (VL—the time from ejaculation to the beginning of the 22 kHz vocalization), Vocalization Termination (VT—the time from ejaculation until the end of the 22 kHz vocalization), Post-Ejaculatory Interval (PEI—the time from ejaculation until the first intromission of the next copulatory series). For each parameter, means were calculated for each subject based on their performance in tests given under each drug dose. The data presented are grand means (±SEM) calculated from the means of individual subjects. The data were analyzed using a one-way analysis of variance for repeated measures.

EXPERIMENT 1

METHOD

Sixteen sexually experienced Long-Evans male rats were used as subjects. Each animal received a single IP injection of either (1) morphine (3 mg/kg) 30 min prior to testing, (2) naloxone (10 mg/kg) 30 min prior to testing, (3) saline, 30 min prior to testing and (4) naloxone (10 mg/kg) 60 min prior to testing followed by morphine (3 mg/kg) at 30 min prior to testing. Animals were tested once each week for four weeks with each animal receiving each treatment.

RESULTS

Table 1 demonstrates that administration of morphine (3 mg/kg), naloxone (10 mg/kg) or both naloxone and morphine had no significant effect on any parameter of sexual behavior studied when compared to the saline-injected control group. Morphine (3 mg/kg) did appear to lengthen mount latencies, but the effect was not statistically significant. Based on the possibility that these concentrations were too low to influence the mechanisms controlling sexual behavior, we decided to increase the dosages employed.

TABLE 2

EFFECTS OF MORPHINE AND NALOXONE ON THE SEXUAL BEHAVIOR OF MALE RATS

	Saline vehicle	Morphine (6 mg/kg)	Naloxone (30 mg/kg)	Naloxone (30 mg/kg) + morphine (6 mg/kg)
Mount latency	82 ± 0.03	—	28 ± 0.05†	78 ± 0.03
Intromission latency	126 ± 0.05	—	15 ± 0.06†	132 ± 0.01
Ejaculation latency	442 ± 0.40	—	220 ± 0.20*	284 ± 0.20
No. of mounts	9 ± 0.20	—	3 ± 0.30†	8 ± 0.60
No. of introm.	12 ± 0.70	—	10 ± 0.70	9 ± 0.70
Post-ejaculatory interval	338 ± 14.1	—	315 ± 10.2	344 ± 11.0
Inter-copulatory interval	40 ± 0.40	—	22 ± 0.30*	39 ± 0.60
% Tests in which ejaculation occurred	94 ± 2	0 ± 0.0	100 ± 0.0	100 ± 0.0

Values are mean sec ± SEM for the same 16 rats under different treatment conditions.

*$p<0.001$ 1-way Analysis of Variance.

†$p<0.05$ 1-way Analysis of Variance.

METHOD

Sixteen sexually experienced Long-Evans male rats were again used as subjects. Each animal received an IP injection of either (1) morphine (6 mg/kg) 30 min prior to testing, (2) naloxone (30 mg/kg) 30 min prior to testing, (3) saline, 30 min prior to testing and (4) naloxone (30 mg/kg) 60 min prior to testing followed by morphine (6 mg/kg) at 30 min prior to testing. Animals were tested once each week for four weeks with each animal receiving each treatment.

RESULTS

Table 2 demonstrates that the administration of morphine at a dose of 6 mg/kg virtually eliminated all mating responses. The morphine-treated animals had no locomotor difficulties, and in fact, were quite active. These animals displayed vigorous ano-genital investigatory behavior yet all failed to initiate mounting behavior, thereby causing the percentage of tests in which the males ejaculated to drop to zero. Prior treatment of the animals with naloxone (30 mg/kg) reversed the effects of morphine on sexual behavior. All copulatory parameters returned to control levels when naloxone was administered 1/2 hour before morphine. However, ejaculation latencies of this treatment group were significantly shorter when compared to control values.

Table 2 also demonstrates that mount latencies, intromission latencies, ejaculation latencies, number of mounts preceeding ejaculation and the intercopulatory intervals were all significantly reduced following administration of naloxone (30 mg/kg) alone. Both the naloxone alone and the naloxone+morphine treatments also produced an increase in the percentage of tests in which the males ejaculated.

Because of these dramatic effects, we injected 8 males who would not mate in any of the screening tests with naloxone (30 mg/kg). It was subsequently discovered that this dosage of naloxone induced all 8 subjects to begin mating and to ejaculate within a 20 min period. Furthermore, upon re-testing these males without naloxone one week later, 6 out of 8 males again showed a total absence of any copulatory behavior.

EXPERIMENT 2

The dramatic effects of morphine and the opiate antagonist naloxone on sexual behavior obtained in Experiment 1 suggested to us that the endogenous opiates may be directly involved in the modulation of sexual behavior. Experiment 2 was performed to confirm this hypothesis and to extend the findings obtained in Experiment 1.

METHOD

Twelve sexually experienced male Long-Evans rats were used as subjects. Before the experiment began, each animal was anesthetized with Chloropent and a permanent guide cannula was implanted into the right lateral ventricle of the brain (coordinates: A-P 5.6; L 1.7; D-V 3.0; from Pellegrino and Cushman [33]. When tested post-operatively, all subjects showed consistently high levels of sexual behavior.

Beta-Endorphin (Beckman) was dissolved in saline immediately prior to use and injected into the lateral ventricle at a concentration of 6 $\mu g/\mu l$ 30 min before behavioral testing. Each animal received either: (1) an IV injection of β-endorphin (6 μg) 30 min before testing, (2) an IP injection of naloxone (30 mg/kg) 60 min prior to testing followed by an injection into the lateral ventricle of β-endorphin (6 μg) 30 min before testing or (3) an IV injection of saline (6 μl). Animals were tested once each week for three weeks with each animal receiving each treatment.

TABLE 3

EFFECTS OF INTRAVENTRICULAR ADMINISTRATION OF B-ENDORPHIN ON SEXUAL BEHAVIOR IN MALE RATS

	Saline control	B-endorphin (6 μg IV)	Naloxone (30 mg/kg IP) + B-endorphin (6 μg IV)
Mount latency	68 ± 0.07	—	75 ± 0.06
Intromission latency	110 ± 0.09	—	88 ± 0.06
Ejaculation latency	440 ± 0.3	—	501 ± 0.3
No. of mounts	12 ± 0.10	—	9 ± 0.30
No. of introm.	10 ± 0.60	—	10 ± 0.40
Post-ejaculatory interval	376 ± 8.9	—	322 ± 9.5
Inter-copulatory interval	56 ± 0.01	—	48 ± 0.02
% Tests in which ejaculation occurred	96 ± 2.0	0 ± 0.0	98 ± 1.0

Values are mean sec ± SEM for the same 12 rats under different treatment conditions.

RESULTS

Table 3 demonstrates that intraventricular injection of β-endorphin (6 μg) completely eliminated mating behavior in all subjects tested. As with the morphine-treated animals, these males displayed consistently vigorous ano-genital investigatory behavior, yet mounting behavior was never initiated. Pre-treatment of the animals with naloxone (30 mg/kg) reversed the effects of β-endorphin on sexual behavior.

EXPERIMENT 3

Because a dynamic interaction exists between endogenous opiates and monoaminergic neurons in both the hypothalamus and the corpus striatum [22], Experiment 3 was designed to determine whether the effects of opiates and opiate antagonists on sexual behavior are correlated with changes in central catecholamine levels in these brain regions.

METHOD

Fifty sexually active male Long-Evans rats were used as subjects. Behavioral testing was performed as in the previous experiments. Ten subjects received unilateral implants of a permanent guide cannula as described in Experiment 3. Post-operative testing demonstrated consistently high levels of sexual behavior. Two weeks following surgery the 50 animals were divided into 5 groups (N=10/group). Thirty minutes following the injection of either (1) morphine (6 mg/kg), (2) naloxone (30 mg/kg), (3) naloxone (30 mg/kg) given 30 min prior to the injection of morphine (6 mg/kg) (4) intraventricular injection of β-endorphin (6 μg in 6 μl volume) or (5) saline, the animals were sacrificed in a microwave apparatus (General Medical Engineering Corporation) in order to maximize recovery of hypothalamic and striatal catecholamines [10].

Hypothalamic norepinephrine and dopamine levels and striatal dopamine content were measured according to the method of Zschaeck and Ramirez [44]. Briefly, the method involved radioenzymatic methylation of norepinephrine and dopamine, extraction, and separation of the methylated amines by cation exchange chromatography. The mean and standard error of control and experimental groups were calculated. The differences between the means were analyzed for statistical significance by the Students *t*-test.

TABLE 4

EFFECTS OF OPIATES ON HYPOTHALAMIC AND STRIATAL CATECHOLAMINE LEVELS

Treatment	Hypothalamus		Striatum
	NEPI (μg/g tissue)	DA (μg/g tissue)	DA (μg/g tissue)
Saline control	2.4 ± 0.2	2.0 ± 0.2	4.5 ± 0.4
Morphine (6 mg/kg)	2.8 ± 0.2	2.3 ± 0.2	5.4 ± 0.4
B-Endorphin (6 μg)	3.5 ± 0.4*	2.5 ± 0.3	5.1 ± 0.5
Naloxone (30 mg/kg)	2.3 ± 0.2	2.7 ± 0.3	4.3 ± 0.2
Naloxone (30 mg/kg) + morphine (6 mg/kg)	2.7 ± 0.3	1.7 ± 0.2	4.7 ± 0.6

Values respresent mean ± SEM of at least 5 determinations.
*$p<0.05$ compared to control.

RESULTS

Table 4 demonstrates the effects of morphine, β-endorphin and naloxone on hypothalamic norepinephrine and dopamine levels and on striatal dopamine levels. A significant increase in hypothalamic norepinephrine levels was

observed in response to the intraventricular administration of β-endorphin, while naloxone was without effect, suggesting that norepinephrine release may be inhibited by the concentration of β-endorphin that also inhibited male copulatory behavior. Moreover, a trend towards increased hypothalamic norepinephrine content was produced by morphine, although this enhancement was not statistically significant.

In the present experiment, regional brain content of dopamine and norepinephrine is employed as an index of neuronal activity. It is known that treatments which inhibit impulse flow and catecholamine release from dopaminergic neurons result in increased intrasynaptosomal dopamine levels [41,42]. Administration of morphine to rats at doses which inhibit dopaminergic function and release will also cause an increase in intrasynaptosomal dopamine levels [18]. Similarly, an inverse relationship exists between acetylcholine release from cholinergic neurons and intrasynaptosomal levels of acetylcholine [36]. The use of neurotransmitter turnover rate as an index of neuronal activity has been discouraged [22] since increased transmitter turnover is associated with both increased and decreased neuronal activity. For the above reasons, regional brain content was favored as the method for determination of catecholamine release in the present study.

At the doses employed, hypothalamic dopamine content was unaffected by the opiates. Thus, levels of dopamine in the hypothalamus in response to the administration of opiates agonists and antagonists did not correlate well with narcotic induced changes in sexual behavior.

Although striatal dopamine content was not significantly altered in response to the treatments utilized, a trend towards increased striatal dopamine levels (indicating an inhibition of dopamine release) with both β-endorphin and morphine was apparent, whereas naloxone alone and the naloxone-morphine treatment resulted in dopamine levels which were indistinguishable from control levels.

DISCUSSION

The results of the present experiments demonstrate that administration of naloxone hydrochloride (30 mg/kg) reduced the number of mounts occurring before ejaculation, ejaculation latencies and the inter-copulatory interval (a measure of copulatory rate). This enhancement of copulation was also reported by Myers and Baum [31] who observed a decrease in EL and in the number of intromissions prior to ejaculation following administration of increasing doses of naloxone (a significant decrease in the number of intromissions was not found in our study). In the present experiment, naloxone increased the percentage of animals ejaculating, thereby confirming the results obtained in several other recent studies [15, 19, 31].

Mendelson *et al.*,[28] recently reported that the opiate antagonist naltrexone was capable of influencing sexual function in human male subjects. By giving an acute dose (50 mg PO) of naltrexone, three subjects reported spontaneous penile erections. This enhancement of sexual function correlates well with the results of the present study. Our results also agree with a clinical report on a single human subject [17] concerning the effects of intravenous infusion of increasing doses of naloxone on the ability of this subject to masturbate to ejaculation. Although naloxone inhibited the ability of the subject to achieve penile erection to some extent, the drug reduced the time needed to achieve ejaculation once erection had been attained. The authors warn that a conclusion on the basis of a single subject must be considered tentative, but similarities between this study and the animal research is intriguing.

Administration of morphine (6 mg/kg) and the endogenous opiate β-endorphin (6 μg) completely eliminated all mating behavior without impairing other motor or investigatory responses. Prior treatment of the subjects with naloxone (30 mg/kg) completely reversed the inhibitory effects of both morphine and β-endorphin on sexual behavior, indicating that this effect is most likely mediated by the "classical" opiate receptor. Meyerson and Terenius [29] also observed a dramatic decrease in male sexual behavior following IV injection of 3 μg β-endorphin which was reversed by pre-treatment with the opiate antagonist naltrexone. Additionally, a recent study indicated [15] that IV administration of 6 μg of D-alanine-methionine-enkephalinamide (a synthetic analog of Met-enkephalin) produced a complete loss of copulatory behavior in male rats. These authors also found, as we did, that administration of naloxone to sexually sluggish or inactive rats caused a significant increase in the number of animals displaying all aspects of copulatory behavior.

A large body of existing evidence implies that increased release of brain catecholamines, particularly dopamine, facilitates male sexual behavior, while diminution of central dopamine release inhibits such behavior [7, 16, 27, 39]. Evidence also supports the existence of presynaptic opiate receptors on dopaminergic terminals in striatal [34] and mesolimbic areas [35]. Furthermore, both morphine and β-endorphin inhibit the potassium-induced release of dopamine from rat striatal slices *in vitro* [26]. Because of the functional and anatomical interaction between opiates and neurotransmitter systems, it is quite possible that the inhibitory effects of the exogenous and endogenous opiates on sexual behavior are related to a direct interference with dopamineergic transmission. Indeed, narcotic analgesics including methadone and morphine share certain pharmacological and biochemical properties with dopaminergic antagonists [8, 12, 24, 37]. Conceivably, the dramatic facilitation of sexual behavior induced by naloxone administration results from the ability of that compound to block the inhibitory effects of the endogenous opiates on dopamine release.

Although the results were not statistically significant, our data display a trend towards increased striatal dopamine content in subjects which were treated with 6 mg/kg of morphine or 6 μg of β-endorphin relative to control values, which implies that these narcotic agonists inhibited striatal dopamine release. Simon *et al.*, [38] observed significant increases in rat striatal dopamine levels following the administration of 5 mg/kg of morphine, while injection of higher doses of the drug did not alter dopamine levels. An increase in striatal dopamine synthesis in response to acute opiate administration [2] may account for the restoration of striatal dopamine levels to control values. Possibly, the narcotics exert a dual effect on central dopamine systems; an excitatory effect on dopamine cell soma, and an inhibitory action on dopamine release from the presynaptic dopamine terminals [13] which complicates data interpretation considerably.

There is now abundant evidence suggesting that while the enkephalins and their receptors are distributed widely throughout the brain in numerous groups of cell bodies with very short neurons [21], significant amounts of endorphin are found in discrete areas of the brain including the pituitary and hypothalamus [3, 4, 5]. Hypothalamic neurons shown to

contain endorphin and endorphin-like compounds appear to be localized in the arcuate nucleus and basal hypothalamus [6, 14, 43]. The hypothalamus is also known to contain the tuberoinfundibular dopaminergic system (projecting from cell bodies in the arcuate and periventricular nuclei into the intermediate lobe of the pituitary and median eminence) as well as the incerto-hypothalamic dopaminergic system (connecting the dorsal and posterior hypothalamus with the dorsal anterior hypothalamus and lateral septal nucleus) [11]. In addition, the hypothalamus receives noradrenergic projections from cell bodies originating in the locus coeruleus, a region containing a high density of opiate receptors. We thought it possible that the inhibitory actions of β-endorphin and morphine and the stimulatory action of naloxone on sexual behavior may be mediated by influencing hypothalamic catecholaminergic systems. Consequently, we analyzed the hypothalamus for changes in both dopamine and norepinephrine following injections of β-endorphin, morphine and naloxone.

The results indicate that opiates do not significantly alter steady-state hypothalamic dopamine levels at the doses employed. Possibly, the facilitatory effects of naloxone on male copulatory behavior and ejaculation is mediated by its ability to block opiate-induced inhibition of dopamine release in areas other than the hypothalamus, such as the caudate-putamen, limbic system and/or spinal cord (areas known to contain opiate receptors). These areas have all been implicated in the control of masculine sexual behavior (see ref. [25] for review). Finally, measurement of steady-state hypothalamic dopamine levels may not accurately reflect opiate effects on dopaminergic neurotransmission since an increase or decrease in biosynthetic enzyme activity in response to opiate agonist or antagonist administration could potentially mask an effect on release.

In the present experiment norepinephrine content in the hypothalamus was significantly increased by β-endorphin, and appeared to be elevated by morphine administration, suggesting to us that norepinephrine release may be inhibited by the endogenous opiates. Administration of naloxone alone or naloxone followed by morphine did not significantly alter hypothalamic norepinephrine content. In support of the opiate-norepinephrine anti-release concept, morphine and enkephalins inhibited the firing rate of norepinephrine containing cell bodies in the locus coeruleus in a naloxone-reversible fashion [23]. Additionally, narcotic analgesics inhibit release of norepinephrine from electrically-stimulated rat brain slices [30] while enkephalins have been found to cause presynaptic inhibition of central noradrenergic transmission [40]. The inhibition of norepinephrine release may play a key role in the suppression of copulatory behavior induced in this study with administration of morphine and β-endorphin. Caggiula *et al.* [6] found that the degree of telencephalic norepinephrine depletion following lesions of the medial forebrain bundle was positively correlated with an impairment of sexual behavior in male rats. It has also been observed that deficits in the copulatory behavior of male rats lesioned with 6-OHDA are directly related to depletions of 78–81% cortical norepinephrine and 56–62% hypothalamic norepinephrine [7].

The results obtained with administration of both morphine and β-endorphin suggest that the endogenous opiates may play a functional role in the control of sexual behavior by influencing noradrenergic transmission within the hypothalamus. Two groups of β-endorphin immunoreactive neurons are located within the basal hypothalamus. One is located between the dorsolateral and arcuate nuclei, the other is located more anterior and lateral to the basal hypothalamus [3]. According to these authors, "long and thick varicose processes" project from these nuclei to the anteriolateral hypothalamus and median eminence. Because noradrenergic terminals have been found in the lateral part of the external layer of the median eminence, possibly localized at sites where the secretion of hypothalamic releasing factors may be influenced [20], it is tempting to speculate that sexual dysfunction may be related to endogenous endorphin release in this area.

In the rat, it has been demonstrated that if ejaculation is preceded by too few intromissions and occurs too rapidly, pregnancy is largely inhibited [1]. Myers and Baum [31] have suggested that activation of opiate receptors in the male brain during copulation may modulate the pattern of copulatory behavior in a way that prolongs the time needed for the male to achieve ejaculation. Perhaps by interfering with catecholaminergic transmission within the CNS, the interaction of β-endorphin with opiate receptors may regulate the pacing of male copulatory behavior to insure successful impregnation of the female. Clearly, however, the numerous effects of opiates on neuroendocrine and neurotransmitter systems within the CNS precludes a simple explanation as to their mechanisms of action.

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