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Facilitation by Opiate Antagonists of Sexual Performance in the Male Rat

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MYERS, B M AND M J BAUM *Facilitation by opiate antagonists of sexual performance in the male rat* PHARMAC BIOCHEM BEHAV 10(4) 615–618, 1979 —Intraperitoneal administration of increasing doses (5 mg/kg or 20 mg/kg) of the opiate antagonists naloxone hydrochloride or naltrexone hydrochloride to sexually experienced male rats caused a significant reduction in the number of intromissions prior to ejaculation and ejaculation latency Mount and intromission latencies were significantly reduced following treatment with only the lower dose of each antagonist Ways are suggested whereby endorphins may modulate masculine sexual performance and thereby contribute to successful fertilization of female conspecifics

Sexual behavior Male rat Endorphins Naloxone Naltrexone

INTRAVENTRICULAR injections of as little as 1 μg β-endorphin have been found to significantly reduce the display of mounting behavior in male rats without reducing their inclination to pursue the estrous female [14]. In another experiment [15] intraventricular injection of 6 μg of the synthetic enkephalin analogue, [D-Ala^2]-met-enkephalin-amide caused an increase in the mount latencies of male rats, but affected no other variable once mounting had started In both of these experiments the effects of exogenous endorphin were reversed by prior administration of the opiate receptor antagonist naltrexone hydrochloride (1 mg/kg) In yet another study [10] Hetta found that administration of naltrexone hydrochloride (5 mg/kg) alone significantly increased the percentage of males which ejaculated in 5 minute tests Unfortunately, under Hetta's testing conditions it was not possible to determine whether naltrexone enhanced males' sexual arousal, their copulatory performance, or both factors [16]. One other experiment has employed opiate antagonist drugs to explore the possibility that endogenous opioids may modulate some aspect of masculine sexual behavior In that double-blind, cross-over study [9] the effect of IV infusion of up to 10 mg of naloxone hydrochloride on the ability of one human subject to masturbate to ejaculation was studied Although the authors concluded that naloxone had no overall effect on sexual arousal or orgasm, the results suggested that naloxone slightly retarded the achievement of full penile erection and greatly reduced the time needed to achieve ejaculation once full erection had been attained As the authors of that study pointed out, no final conclusions can be drawn on the basis of a single subject The present study was carried out using male rats in an attempt to define more precisely the effect of two opiate receptor antagonists, naloxone and naltrexone, on masculine sexual behavior In this way it was hoped to gain insight into the possible role played by endorphins in modulating this behavior

METHOD

Twelve male rats of the hooded Long-Evans strain were obtained from Charles River Breeding Farms and were housed in an environmental chamber in which the lights were off between 9 00 and 19 00 The males weighed approximately 350 g at the beginning of the experiment and 450 g at its conclusion Long-Evans rats were used because previous experience had shown that males of this hooded strain most consistently displayed high levels of masculine sexual behavior Food and water were available ad lib Twenty ovariectomized female rats of the Sprague-Dawley strain were maintained as stimulus animals for tests of males' sexual behavior These animals were made sexually receptive by SC injections of estradiol benzoate (5 μg/0 1 ml sesame oil) 48 hours prior to testing and progesterone (500 μg/0 1 ml sesame oil) four hours prior to testing Females of the Sprague-Dawley strain were used instead of Long-Evans females because past experience had shown that Sprague-Dawleys responded more consistently from week to week to the hormonal treatments used to induce sexual receptivity As such, these females served as highly consistent sexual stimuli over all tests All tests were given during the dark phase of the day/night cycle

New solutions of the opiate antagonists naloxone hydrochloride or naltrexone hydrochloride were prepared in 0 9% NaCL just prior to each day's testing session Each of these drugs were given at two dose levels (5 mg/kg or 20 mg/kg body weight in 0 5 ml saline) In an initial experiment male rats received naloxone hydrochloride or the saline vehicle 30 min before being tested with a sexually receptive female Tests and injections were given every other day, with saline and opiate antagonist being given alternately to the same animals All males received 2–4 tests with each dose of naloxone and the same number of tests with saline vehicle All tests using the lower dose of naloxone were

TABLE 1

EFFECTS OF TWO OPIATE RECEPTOR ANTAGONISTS ON THE SEXUAL BEHAVIOR OF MALE RATS

	Saline Vehicle	Naloxone Hydrochloride 5 mg/kg	Naloxone Hydrochloride 20 mg/kg	F (2,22)
% Tests in which Ejaculation Occurred	70 ± 6	96 ± 2§	83 ± 7	5 21*
Mount Latency (min)	0 80 ± 0 20	0 30 ± 0 03‡	50 ± 0 06	4 71*
Intromission Latency (min)	1 00 ± 0 20	0 30 ± 0 03§	0 60 ± 0 09	4 33*
Postejaculatory Interval (min)	6 50 ± 0 30	6 60 ± 0 40	6 00 ± 0 30	1 71
No Intromissions Before Ejaculation	11 00 ± 0 70	10 90 ± 0 80	7 30 ± 0 70§	17 84†
Intromission Rate (intromissions/min)	2 40 ± 0 10	2 9 ± 0 20	3 1 ± 0 30§	3 79*
Ejaculation Latency (min)	5 30 ± 0 5	4 00 ± 0 30§	2 50 ± 0 30§	22 97†

Values given are Means ± SEM for the same 12 rats under different treatment conditions
For F value *$p<0$ 05, †$p<0$ 01
For Newman Keuls comparison with saline control condition ‡$p<0$ 05, §$p<0$ 01

completed before those with the high dose were given. Beginning one month after the completion of the experiment with naloxone, the same males were used in an identical experiment in which two doses of the longer acting opiate receptor antagonist, naltrexone hydrochloride, or its saline vehicle were given

Tests of the males' sexual behavior were carried out in a darkened room, lit only by a dim yellow light The testing cages consisted on ten gallon aquariums (25×47×29 cm) with sawdust on the floor All males were tested with receptive females four times over a two-week period prior to the administration of opiate antagonist All males ejaculated in at least one of these tests Individual males were placed in the test cages for a ten min adaptation period after which a receptive female was placed in each cage and the male's copulatory behavior was scored using an Esterline Angus event recorder A record was kept of males' mounts with pelvic thrusting, intromission responses, and ejaculations [5] Males were given 15 min to achieve an initial intromission and an additional 15 min to achieve ejaculation in the event that intromission occurred. In the latter instance, males rarely failed to achieve ejaculation within this allotted time Following an ejaculation, males were left with the female until a subsequent intromission occurred, whereupon the test was stopped

The following parameters of masculine sexual behavior were calculated for each testing condition (a) percentage of tests with ejaculation, (b) mount latency—the time elapsed between introduction of a female and the first mount, (c) intromission latency—the time elapsed between introduction of a female and the first intromission, (d) the postejaculatory interval—the time elapsed between an ejaculation and the first subsequent intromission, (e) intromission rate—the number of intromissions preceeding an ejaculation divided by the ejaculation latency, and (f) the ejaculation latency—the time elapsed between the initial intromission and the subsequent ejaculation For each parameter, means were calculated for each male based on their performance in tests given under each drug dose Within each experiment there were no significant differences among individual blocks of saline control tests, thus these data were combined. The data presented are grand means (± SEM) calculated from the means for individual males. For all variables except the percentage of tests with ejaculation, means for individual males are based only on data from tests in which ejaculation occurred The data were analyzed using a one-way analysis of variance for repeated measures Individual comparisons of the results with each dosage of opiate antagonist with the respective saline control condition were made using *a posteriori* Newman-Keuls tests [18]

RESULTS AND DISCUSSION

Administering increasing doses of naloxone hydrochloride caused a significant increase in the percentage of tests in which males ejaculated (Table 1), thus confirming the results of Hetta [10] In the present study administration of naltrexone hydrochloride had no significant effect on ejaculation, probably because the incidence of the response was already maximal during saline control tests Table 1 shows that the latencies to first mount and first intromission were significantly reduced following administration of only the lower doses of either naloxone or naltrexone Although mount and intromission latencies have previously been taken as indices of sexual arousal in the male rat, many students of rat sexual behavior consider the post-ejaculatory interval to

TABLE 1 (Con't)

EFFECTS OF TWO OPIATE RECEPTOR ANTAGONISTS ON THE SEXUAL BEHAVIOR OF MALE RATS

	Saline Vehicle	Naltrexone Hydrochloride 5 mg/kg	Naltrexone Hydrochloride 20 mg/kg	F (2,22)
% Tests in which Ejaculation Occurred	94 ± 4	83 ± 7	100	2 95
Mount Latency (min)	0 30 ± 0.03	0 20 ± 0 03‡	0.30 ± 0 03	6 50*
Intromission Latency (min)	0 40 ± 0 07	0 20 ± 0 06§	0.40 ± 0 09	7.03†
Postejaculatory Interval (min)	5.50 ± 0 20	5 30 ± 0 30	5 50 ± 0 30	0 48
No Intromissions Before Ejaculation	10.20 ± 0 70	9 60 ± 0 60	7.50 ± 0 70§	8 40†
Intromission Rate (intromissions/min)	3 30 ± 0 30	3 30 ± 0 30	3.40 ± 0 20	0 05
Ejaculation Latency (min)	4 00 ± 0 5	2 90 ± 0.20‡	2 50 ± 0 30‡	6 04†

Values given are Means ± SEM for the same 12 rats under different treatment conditions
For F value. *$p<0$ 05, †$p<0.01$
For Newman Keuls comparison with saline control condition ‡$p<0$ 05, §$p<0$ 01

be a more reliable index of this process (received in [16]). In the present experiment post-ejaculatory intervals were not affected by any drug treatment.

Much evidence suggests that separate neural mechanisms control the processes of sexual arousal and copulatory performance in the male [6,16]. The present results suggest that opiate receptor antagonists more reliably affected the mechanism concerned with copulatory performance. Administration of the higher dose of either naloxone or naltrexone caused a significant reduction in the number of intromissions which preceded ejaculation. Intromission rates were not consistently affected by drug treatments whereas ejaculation latencies were significantly reduced after administration of each dose of both opiate receptor antagonists. In so far as they are comparable, the present results are in agreement with those of Goldstein and Hansteen [9] who reported that in a single human subject naloxone affected the time needed to achieve penile erection (index of sexual arousal) only slightly whereas it clearly tended to reduce the time needed to achieve ejaculation by masturbation (an index of sexual performance).

In the present experiments the higher (20 mg/kg) dose of opiate antagonists yielded the most consistent behavioral effects. This dose of either naloxone or naltrexone is much in excess of the amount normally required to block the interaction of opiate alkaloids or exogenously administered endorphins with opiate receptors; however, it has been suggested that comparatively large amounts of antagonist must be given in order to reverse the action of endogenous opioids [17]. Furthermore, the clear dissociation in the effects of both naloxone and naltrexone on indices of copulatory performance as opposed to sexual arousal suggests that even at high doses these drugs acted in a specific fashion

Autoradiographic studies carried out in rats using (^{3}H) diprenorphine have demonstrated that opiate receptors are localized in layers I and II of the dorsal horn of the spinal cord [2], at several midbrain sites [3], as well as in the amygdala, caudate-putamen, and nucleus accumbens [4]. Immunohistochemical experiments have demonstrated a distribution of Met-enkephalin-like immunoreactivity in both the rat brain and spinal cord which corresponds in many respects to this distribution of opiate receptors [12]. Opiate receptor antagonists could facilitate masculine sexual performance by acting at any of several possible neural sites, including spinal cord and the caudate putamen. Afferent somatosensory inputs contribute to the occurrence of ejaculation, and nigrostriatal and/or mesolimbic dopaminergic mechanisms have been implicated in the control of masculine sexual behavior by several studies [8]. Available evidence suggests the enkephalins may normally exert an inhibitory influence on the activity of primary afferent neurons in the spinal cord [11] as well as on the release of dopamine at synapses in the caudate-putamen [7,13] Antagonism of either of these effects might enhance masculine sexual performance.

During normal copulation the activation by enkephalins of opiate receptors in the male brain may be essential for producing a pattern of copulatory behavior which optimally

insures successful impregnation of the female. Working with rats, Adler [1] has shown that if ejaculation occurs too quickly and is preceded by too few intromissions, pregnancy is significantly inhibited This failure to conceive is probably due either to incomplete functional activation of the corpora lutea or to inadequate transport of sperm into the uterus and oviducts As such, the modulation of the male rat's copulatory performance by endorphins may contribute to this species' reproductive success.

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