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Facilitation of Copulatory Performance in Male Rats by Naloxone: Effects of Hypophysectomy, 17α-Estradiol, and Luteinizing Hormone Releasing Hormone[1]

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MYERS, B. M. AND M. J. BAUM. *Facilitation of copulatory performance in male rats by naloxone: Effects of hypophysectomy, 17α-estradiol, and luteinizing hormone releasing hormone.* PHARMAC. BIOCHEM. BEHAV. 12(3) 365–370, 1980.—Three experiments were performed to explore the mechanism whereby systemic administration of the opiate receptor antagonist, naloxone hydrochloride (20 mg/kg) causes reductions in the frequency of intromissions preceding ejaculation and latency to ejaculation in sexually experienced male rats. Administration of naloxone to male rats which were hypophysectomized in addition to being castrated and implanted SC with 30 mm silastic capsules containing testosterone caused such behavioral changes, suggesting that these behavioral effects of naloxone do not result from interference with the binding of endorphin of pituitary origin. Surprisingly, a significant facilitatory effect of naloxone on sexual performance was absent in castrated controls bearing 30 mm testosterone implants. Recent evidence suggests that 17α-hydroxylated estrogens, which may be produced in gonadally intact males, possess appreciable affinity for opioid receptors. However, daily administration of 17α-estradiol (50 μg) to castrated, testosterone-implanted males failed to make them as behaviorally responsive to naloxone as gonadally intact animals. Administration of LHRH (1 μg given SC 1.5 hr prior to testing) caused a significant reduction in ejaculation latency in gonadally intact males but not in castrated males bearing 30 mm testosterone implants. It is suggested that the facilitatory effect of naloxone on masculine sexual performance results, in part, from a drug-induced release of LHRH.

Rat Sexual behavior Naloxone Endorphin Pituitary Luteinizing hormone releasing hormone

SEVERAL lines of evidence have implicated endorphins in the regulation of sexual behavior in the male rat, hamster, and human. For example, in sexually experienced rats, intraventricular injection of either β-endorphin [26] or (D-Ala²)-met-enkephalinamide [27] suppressed mounting behavior at doses which did not influence other aspects of motoric behavior. Administration of opiate receptor antagonists drugs, such as naloxone or naltrexone, caused reductions in intromission frequency prior to ejaculation coupled with reduced ejaculation latencies ([25,28] T. MacIntosh, personal communication, 1978). In other studies, administering naloxone to otherwise sexually inactive males caused a rapid onset of copulation in a large proportion of animals [13]. In a single male subject naloxone greatly reduced the time needed to achieve ejaculation by masturbation [14] and in another study [21] naloxone caused penile ejections in several men in the absence of any erotic context. The present studies were carried out in male rats to determine: (a) whether in affecting sexual behavior it is endorphin of pituitary origin whose action is antagonized by administering naloxone, (b) why naloxone more readily facilitates sexual performance in gonadally intact male rats than in castrated animals bearing 30 mm testosterone implants, and (c) whether some of the effects of naloxone on males' sexual performance could be duplicated by administering luteinizing hormone releasing hormone (LHRH).

METHOD

Subjects

Adult male rats (300–350 g) of the hooded Long-Evans strain were purchased from Charles River Breeding Farms and housed in groups of 4 in a room in which the lights were off between 12:00 and 24:00. Food and water were available ad lib. Prior to being used in any experiment the males had displayed at least one ejaculation in tests with sexually receptive females. These females were ovariectomized and made sexually receptive by SC injections of estradiol benzoate (5 μg/0.1 ml sesame oil) 48 hr prior to testing and progesterone (500 μg/0.1 ml sesame oil) 4 hr prior to testing.

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Behavioral Testing and Data Analysis

All tests were carried out during the dark phase of the day/night cycle in a room lit only by a dim yellow light. Animals were tested in ten-gallon aquariums (25×47×29 cm) with sawdust bedding. Following adaptation to the test cage for 10 min, a receptive female was introduced and the male's copulatory behavior was scored by an observer using an Esterline-Angus event recorder. Following introduction of the female, males were given 15 min to achieve an initial intromission, and if this occurred, an additional 15 min to ejaculate. If neither of these events occurred the test was terminated. In the event of an ejaculation, males were left in the test arena until the initial intromission of a second copulatory series occurred, whereupon the test was stopped.

The following parameters of masculine sexual behavior were scored: (a) percentage of tests with ejaculation, (b) mount latency—the time elapsed between the introduction of the female and the first display of mounting, (c) intromission latency—the time elapsed between the introduction of the female and the first display of intromission, (d) postejaculatory interval—the time elapsed between an ejaculation and the first subsequent intromission, (e) intromission rate—the number of intromissions (including the ejaculatory intromission) divided by the ejaculation latency, (f) the number of intromissions preceding ejaculation, and (g) ejaculation latency—the time elapsed from the first intromission until the ejaculation. In each experiment males served as their own controls, with 3–5 tests with ejaculation providing the data base for each treatment condition. All data from males which ejaculated in fewer than three tests under any treatment condition were excluded from the data analysis of any given experiment. For each parameter, means were calculated for each animal under each treatment condition. Within groups comparisons were made using Mann-Whitney U tests, or Kruskal-Wallis one-way analysis of variance. As advocated by Ferguson [11], differences between or within groups were considered statistically significant when p was less than 0.05 in a unidirectional test.

EXPERIMENT 1. EFFECTS OF NALOXONE AFTER HYPOPHYSECTOMY, CASTRATION, AND TESTOSTERONE TREATMENT

β-endorphin is secreted by the intermediate and the anterior lobes of the rat pituitary gland [4], in addition to being formed in the brain itself. Although endorphins pass through the blood-brain barrier with great difficulty [7], recent evidence shows that β-endorphin is present in high concentrations in the portal vessels between the median eminence and the anterior pituitary gland [19]. This fact raises the possibility that β-endorphin of pituitary origin may reach the brain in high concentrations via retrograde flow along this vascular route. An experiment was conducted to see whether the facilitatory effects of naloxone on males' sexual performance result from blocking the action of endorphin of pituitary origin.

METHOD

Five castrated, hypophysectomized male rats were purchased from Charles River Breeding Farms and maintained in tubs with extra bedding and water containing 10% sucrose. Eight castrated males of the same age served as controls. All rats were implanted SC with 30 mm long silastic capsules (Dow Corning Medical-Grade tubing 0.062 ID × 0.125 in OD, sealed with medical-grade elastomer) containing crystalline testosterone (Steraloids Co., Wilton, NH). This particular implant was chosen because it had been shown to produce plasma levels of testosterone in castrated rats which were only slightly less than those of gonadally intact animals [9]. Beginning two weeks after hormone implantation, all males received pretests for sexual behavior. Subsequently, males were tested every 2 days one half hour after IP injection of either naloxone HCl (20 mg/kg in 0.2 ml physiological saline) or vehicle alone. This dose of naloxone had produced the most consistent facilitation of males' sexual performance in a previous study [25]. On each test day half of the rats in each group received naloxone whereas the other half received saline. Following the last behavioral test, all animals were killed with an overdose of ether, the brains removed and the sella turcica inspected under a dissecting microscope for the presence of pituitary reminants. Body and seminal vesicle weights (fluids expressed) were also recorded.

RESULTS AND DISCUSSION

Administration of naloxone to hypophysectomized, castrated male rats bearing 30 mm testosterone implants caused significant reductions ($p<0.05$) in frequency of intromission and ejaculation latency together with a significant ($p<0.05$) increase in postejaculatory interval (Fig. 1). Similar trends were present in castrated, testosterone-implanted males; however, these effects failed to reach statistical significance. No other parameters of sexual behavior were significantly affected by naloxone treatment in either group (data not shown), nor were there any significant between-groups differences for any parameter of sexual behavior. At the end of the experiment, hypophysectomized, castrated males weighed 197 ± 12 g (mean ± SEM) whereas castrated males weighed 394 ± 12 g ($p<0.01$). Despite their reduced body weights, hypophysectomized rats were alert and active. Seminal vesicle weights were also significantly lower ($p<0.01$) in castrated, (94 ± 4 mg/100 g body weight) than in castrated, hypophysectomized males (332 ± 45 mg/100 g body weight). No pituitary reminants were found in the sella turcica of any hypophysectomized animal.

Removal of the pituitary source of endorphin did not attenuate the behavioral effects of naloxone; instead it heightened them. This finding argues against the notion that the facilitatory effect of naloxone on males' sexual performance results from a blockade of the binding by opiate receptors of endorphin of pituitary origin. Given our previous finding of reduced intromission frequency and ejaculation latency following naloxone administration to gonadally intact males [25], it was puzzling to find no significant effect in castrated males bearing 30 mm testosterone implants. Seminal vesicle weights were considerably greater in castrated, hypophysectomized males than in castrated animals, suggesting that the circulating levels of testosterone were greater in the former group. However, it seems unlikely that this difference can account for the differential ability of naloxone to influence copulatory performance in the two groups. First, there were no significant differences between the groups in any aspect of sexual performance during saline tests. Second, Damassa *et al.* [9] found no significant differences in any parameter of masculine sexual performance in castrated rats bearing testosterone implants ranging from 5–60 mm in length. Thus, provided a minimal degree of steroidal stimulation is present, there is no relationship be-

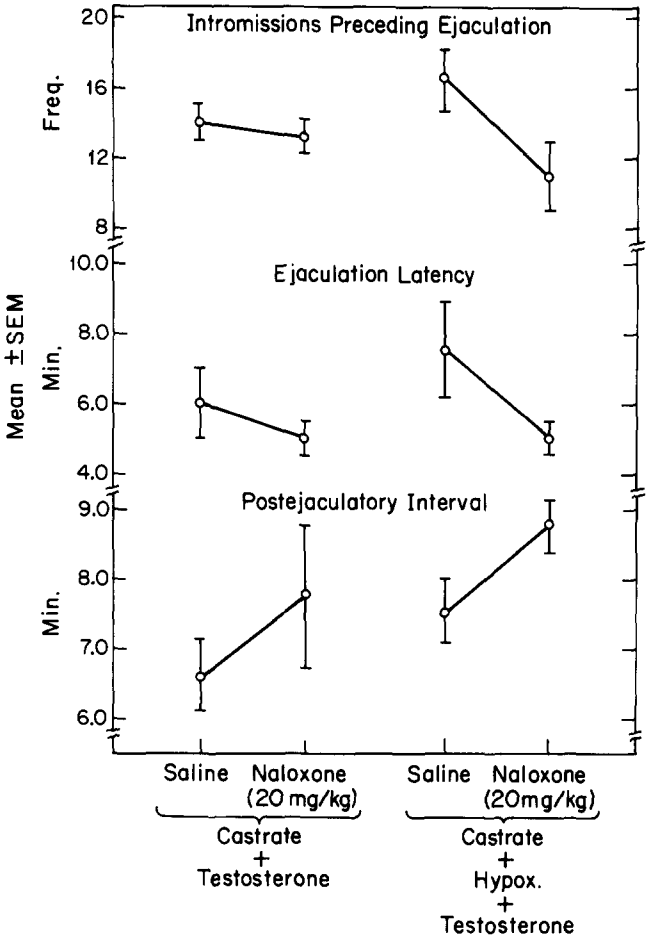

FIG. 1. Effects of administering naloxone HCl or saline vehicle 0.5 hr prior to behavioral testing on sexual performance of male rats which were either castrated and implanted with 30 mm testosterone capsules (n=8) or castrated, hypophysectomized (Hypox.) and implanted with 30 mm testosterone capsules (n=5).

tween circulating levels of testosterone and males' copulatory performance.

EXPERIMENT 2. EFFECTS OF NALOXONE IN CASTRATED MALES RECEIVING 17α-ESTRADIOL PLUS TESTOSTERONE

In Experiment 1 administration of naloxone failed to reduce significantly intromission frequency and ejaculation latency in castrated males maintained with SC testosterone implants, whereas such changes had previously been obtained in gonadally intact males [25]. Estradiol-17α causes considerable displacement of (^{3}H) naloxone from binding sites in membrane preparations of rat brain, and this steroid possesses mixed agonist-antagonist activity at these sites [18]. The biochemical pathways are present in rat for formation of 17α hydroxylated estrogens, either from 17β estradiol, which is secreted in appreciable quantities by the rat testes [10], or from androstenedione (via epitestosterone), which is also secreted by the testes. It seemed possible that naloxone affected sexual performance in gonadally intact males, but not in castrates given testosterone, because intact males produce more 17α-hydroxylated estrogens.

METHOD

Twenty-four male rats were divided into three groups. Following pretests to gain sexual experience, two groups (n=8) were castrated and implanted SC with 30 mm silastic capsules containing testosterone whereas the third group (n=8) was sham-operated. One group of castrated, testosterone-implanted males received daily SC injections of 17α-estradiol (Steraloids Co., Wilton, N.H., 50 μg/0.01 ml sesame oil) for 10 consecutive days before resumption of behavioral testing, and each day thereafter for the rest of the experiment. Males in the other two groups received daily injections of oil vehicle. All injections were given in the morning, four hr prior to the behavioral tests. All males were tested with receptive females every 48 hr, with naloxone (20 mg/kg) and saline vehicle being given on alternate test days, one half hr prior to the behavioral test. On each test day, half of the rats in each group received naloxone whereas the other half received saline. At the end of the experiment all males, except those treated with 17α-estradiol, were saved for use in Experiment 3. Two rats from each group ejaculated in fewer than 3 tests with naloxone treatment; thus their data were discarded.

RESULTS AND DISCUSSION

Administration of naloxone to gonadally intact males caused significant ($p<0.05$) reductions in frequency of intromission preceding ejaculation and in ejaculation latency (Fig. 2), whereas no such effects occurred in castrated, testosterone-implanted males, regardless of whether or not they received 17α-estradiol. Postejaculatory intervals were significantly longer following naloxone treatment ($p<0.05$) in both groups of castrated males, but not in gonadally intact males. There were no other statistically significant effects of naloxone on parameters of masculine sexual behavior in any of the three groups (data not shown). Between-groups comparisons carried out separately for saline and naloxone tests revealed no statistically significant differences on any behavioral parameter.

The results of the present experiment confirm our previous finding [25] that administration of naloxone to gonadally intact male rats reduced intromission frequency and ejaculation latency. In the present experiment, as in Experiment 1, naloxone had no such effects when administered to castrated males implanted with 30 mm testosterone capsules. Furthermore, administering 17α-estradiol to such animals failed to augment the ability of naloxone to cause these behavioral changes, suggesting that an interaction of 17α hydroxy estrogens with opiate receptors in gonadally intact males plays no role in the behavioral effect of naloxone.

EXPERIMENT 3. EFFECTS OF LUTEINIZING HORMONE RELEASING HORMONE IN GONADALLY INTACT AND CASTRATED, TESTOSTERONE-IMPLANTED MALES

Administration of either naloxone or naltrexone to adult male rats causes a rise in serum luteinizing hormone (LH) levels with a latency of less than one-half hour, which likely reflects increased release of LHRH by hypothalamic neurons into the hypothalamic-hypophyseal portal blood system [6]. In some preliminary experiments Moss *et al.* [23] reported that SC injections of LHRH caused a reduction in ejaculation latency in gonadally intact male rats, as well as in

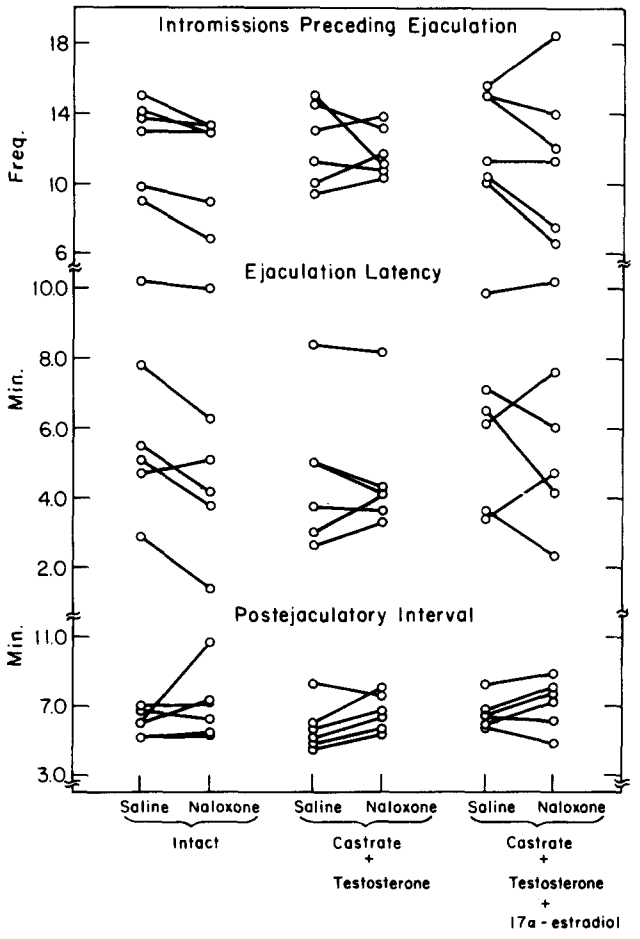

FIG. 2. Effects of administering naloxone HCl (20 mg/kg) or saline vehicle 0.5 hr prior to behavioral testing on sexual performance of male rats which were either gonadally implanted with 30 mm testosterone capsules and given daily 50 μg injections of 17α-estradiol (n=6) or of sesame oil vehicle (n=6). Values shown are means for each treatment condition for each individual subject.

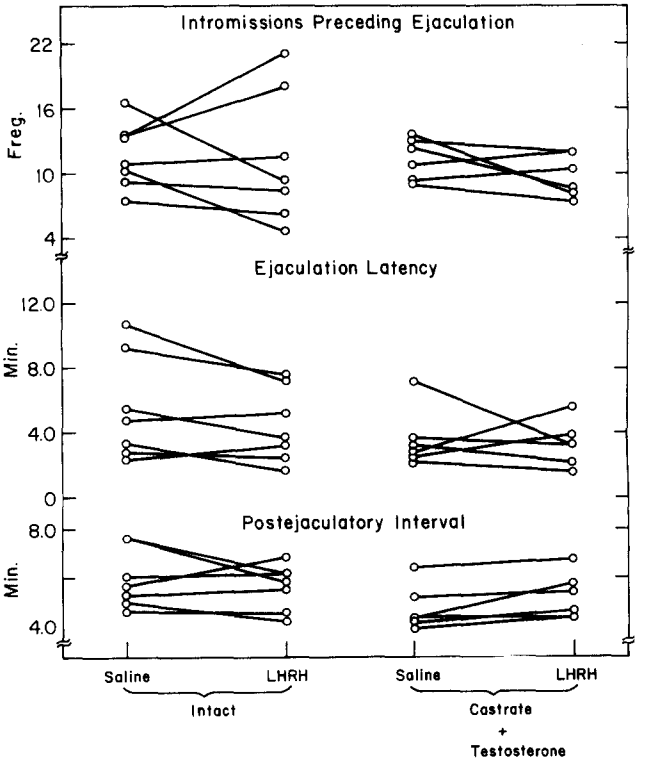

FIG. 3. Effects of administering LHRH (1 μg/rat) 1.5 hr prior to behavioral testing on sexual performance of male rats which were either gonadally intact or castrated and implanted with 30 mm testosterone capsules. Values shown are means for each treatment condition for each individual subject.

castrated males maintained on very low doses of testosterone propionate (TP) given by injection. More recently, Evans and Distiller [11] reported that IM injections of LHRH to normal men tended to reduce the time needed to achieve ejaculation by masturbation. A similar effect of naloxone was previously reported by Goldstein and Hansteen [14]. In light of these findings, an experiment was carried out to determine the extent to which LHRH could duplicate the effects of naloxone both in gonadally intact and in castrated male rats implanted with 30 mm testosterone implants.

METHOD

The eight castrated males bearing 30 mm testosterone implants (not having received 17α estradiol) and eight gonadally intact males used in Experiment 2 were used in a final experiment, which began two weeks after the end of Experiment 2. All animals received SC injections of either LHRH (1 μg/0.02 ml physiological saline) or vehicle 1.5 hr prior to behavioral testing. This dosage of LHRH and time interval between injection and testing were chosen with the aim of maximizing any behavioral effect of the peptide, based on the work of Moss and McCann [21], and Pfaff [26], showing that LHRH augmented lordosis behavior in ovariectomized, estrogen-primed female rats. Animals were tested once every 48 hr, with LHRH or saline vehicle being given alternately to half the rats in each group. Immediately after the final test all animals were killed with an overdose of ether, and body and seminal vesicle weights were recorded.

One gonadally intact and one castrated male died before the end of the experiment. An additional castrated male ejaculated in fewer than 3 tests when given LHRH. Data from all these rats were discarded.

RESULTS AND DISCUSSION

Administration of LHRH caused a significant ($p<0.05$) reduction in ejaculation latency in gonadally intact males (Fig. 3) but not in castrated, testosterone-implanted animals. The only other within-groups comparison for any of the behavioral parameters measured which reached statistical significance was that of the postejaculatory interval in castrated, testosterone-implanted males, which was significantly longer ($p<0.01$) in tests with LHRH. At the end of the experiment body weights were 435 ± 18 g and 395 ± 12 g in gonadally intact and castrated rats, respectively. The difference was not statistically significant. Seminal vesicle weights were 135 ± 7 mg/100 g body weight in gonadally intact males and 170 ± 13 mg/100 g in castrated, testosterone-implanted males ($p<0.025$). The presence of heavier seminal vesicles in castrated males implanted with this particular length of tes-

tosterone capsule than in gonadally intact males confirms a previous report by Damassa *et al.* [8].

In the present experiment LHRH caused a small, but statistically significant reduction in ejaculation latencies of gonadally intact males, thus duplicating in part (intromission frequency was not reduced in the present study) the effects of giving either naloxone or naltrexone ([25]; Experiment 2). It seems possible that SC administration of LHRH failed to mimic completely the behavioral effects of opiate receptor antagonists because LHRH penetrates the blood-brain barrier with great difficulty. Considerably more endogenous LHRH could be released at neural sites of action in response to naloxone, which passes readily into the brain.

In Experiment 1 hypophysectomy of castrated, testosterone-implanted males, augmented naloxone-induced reductions in intromission frequency and ejaculation latency. It has been suggested that the pituitary gonadorophins normally exert a tonic, inhibitory, "short-loop" feedback control over the release of LHRH. In light of the effect of LHRH on ejaculation latency found in the present experiment as well as by Moss *et al.* [23], it seems possible that the behavioral effects of hypophysectomy observed in Experiment 1 may have resulted from increased tonic secretion of LHRH. Damassa *et al.* [8] have shown that the 30 mm silastic implants of testosterone used in the present studies effectively suppress circulating LH (and by inference, the release of LHRH into the hypophyseal portal system) below the levels present in gonadally intact rats. In Experiment 1 hypophysectomy of castrated males bearing such implants may have increased the pool of LHRH in brain available for release in response to acute administration of naloxone.

It must be noted that in the present experiment LHRH caused a significant lengthening of postejaculatory intervals in castrated males implanted with testosterone, but not in gonadally intact animals. In Experiment 1 a similar trend was present in castrated, testosterone implanted males following naloxone treatment, and this trend attained statistical significance when animals were hypophysectomized in addition to being castrated and implanted with testosterone. In Experiment 2 naloxone again caused significant lengthening of postejaculatory males, but not in gonadally intact animals. In our previous study [25] as in the study by Pellegrini-Quarantotti *et al.* [28], no change in postejaculatory interval was noted in gonadally intact male rats following administration of either naloxone or naltrexone, although other workers [31,32] have found lengthened postejaculatory intervals in gonadally intact males following several doses of naloxone. We cannot explain these discrepant findings in gonadally intact males. Likewise, we know of no obvious explanation for the consistent increases in postejaculatory intervals currently observed in castrated, testosterone-implanted males but not in gonadally intact animals in response to naloxone or LHRH.

GENERAL DISCUSSION

Opioid receptors and endorphin-containing neurons have been identified at a wide variety of sites in the rat brain and spinal cord, and it would be naive to assume that the effects of naloxone on masculine sexual performance derive exclusively from an interaction of the antagonist drug with receptors on LHRH secreting neurons. For example, evidence suggests the enkephalins normally inhibit the release of dopamine at synapses in the rat caudate-putamen [3,20] and the nigrostriatal dopaminergic system has been implicated in the control of masculine sexual behavior [5]. It seems unlikely, however, that naloxone hastens the occurrence of ejaculation by acting on this particular system [28], in so far as administering a low dose (100 μg/kg) of the dopamine receptor blocker, pimozide, actually intensified the facilitatory effects of naloxone on males' sexual performance instead of inhibiting it [2]. Much evidence suggests that enkephalins normally inhibit activity in the primary sensory afferent neurons of the spinal cord [15] and afferent signals originating from such neurons with each mount and intromission most certainly contribute to the occurrence of ejaculation [30]. More work is needed to test the possibility that naloxone facilitates the occurrence of ejaculation by partially antagonizing the inhibitory effects of enkephalin on the transmission of sensory impulses generated with successive intromissions.

Although other possible mechanisms exist, the present results suggest that at least some of the effects of opioid receptor antagonists on sexual performance in the male rat are mediated by a drug-induced release of LHRH in the brain. Obviously, additional studies need to be carried out in which LHRH is administered either intraventricularly or into particular brain sites in attempting to demonstrate more dramatic effects of this peptide on masculine sexual performance. In addition, it will be necessary to determine whether the effects of naloxone or naltrexone on males' sexual performance can be attenuated by blocking the drug-induced release of LHRH.

While acknowledging the need for additional supportive data, we wish to propose the following hypothesis about the role played by enkephalins and opioid receptors in controlling masculine sexual performance in the rat. Data from several rodent species, including rat, suggest that if ejaculation occurs too quickly and is preceded by too few intromissions, pregnancy is less likely to occur [1]. Activation of opiate receptors by endorphins during copulation may contribute to the pacing of males' intromissions and the occurrence of ejaculation in a manner which maximizes the changes of successful impregnation of the female. Several studies suggest that simply exposing the male rat to an estrous female stimulates the secretion of LHRH into the hypophyseal portal system [16,17] and may cause the release of this peptide at other brain sites as well. Results of the present studies, as well as those of Moss *et al.* [23], suggest that LHRH facilitates the occurrence of ejaculation. We propose that the release of endorphin, perhaps in response to the sensory stimulation associated with each mount and intromission, attenuates the ongoing release of LHRH, thereby prolonging the time which the male needs to achieve ejaculation. The present results further suggest that β-endorphin of pituitary origin is not involved in this process. Whatever the source of endorphin and the site(s) of opioid receptor activation, the resulting modulation of the male's copulatory performance may contribute to its reproductive success.

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