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Stimulation of Opioid Receptors Suppresses Penile Erectile Reflexes and Seminal Emission in Rats

JULIO GOMEZ-MARRERO, MANUEL FERIA AND MANUEL MAS*[1]

*Departamentos de Farmacologia y *Fisiologia, Facultad de Medicina*
Universidad de La Laguna, 38320 Tenerife, Spain

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GOMEZ-MARRERO, J., M. FERIA AND M. MAS. *Stimulation of opioid receptors suppresses penile erectile reflexes and seminal emission in rats.* PHARMACOL BIOCHEM BEHAV 31(2) 393–396, 1988.—The effects of several doses of morphine and naloxone, given alone or in combination, on ex copula tests for rat penile erectile responses and seminal emission were studied. Morphine (0.1, 0.5, 1 and 5 mg/kg IP, 30 min before the test) reduced the proportion of animals showing erections in a dose-related fashion. Seminal emission was apparently more sensitive to opioid inhibition than erectile responses, since it was virtually suppressed by all the doses of morphine tested. Naloxone given alone (0.1, 1 and 10 mg/kg IP, 15 min before testing) was largely ineffective on these genital responses although a significant decrease in the display of erection was observed with the lowest dose. Naloxone (1 mg/kg) efficiently antagonized the effects of morphine (1, 5 and 25 mg/kg) on erectile responses and all but the largest dose of the opiate agonist on seminal emission. These results indicate that, in addition to the well-documented effects of opioids on sexual drive, their effects on the genital reflex potential could play a major role in the sexual deficits associated to opiate intake.

Morphine Naloxone Penile reflexes Seminal emission

THE deleterious effects of opioids on human sexuality have long been recognized [see (17) for a comprehensive review]. Studies in laboratory animals consistently support this view, especially in the male. Thus, treatments with several opioid agonists have been repeatedly reported to impair male copulatory activity (8, 10, 14, 17, 22). The specificity of these effects was verified in some instances by their effective reversal by opioid antagonists (8, 10, 17, 22). Treatments with antagonists alone have been also given extensively to assess the role of endogenous opioid systems in the modulation of sexual behavior. Their effects, however, have been found far less consistent than those of the agonists [reviewed in (17)].

Furthermore, the relative impact of opiates on different components of the male sex behavioral pattern such as arousal/motivation, erection and ejaculation remains largely unexplored. Most of the experimental studies to date on the effects of opiates on male sexual behavior have relied exclusively on the observation of mating wirh receptive females. This test gives some generally accepted indices of sexual arousal such as the intromission latency and intercopulatory intervals. Yet its value for the assessment of drug effects on genital responsiveness, particularly the erectile and ejaculatory capacities, is more controversial, since their dispaly in the mating situation depends on adequate arousal. These phenomena can be better assessed, at least in the rat, by specific ex copula tests for penile erectile reflexes and seminal emission (5, 11, 12, 18, 20). The use of these tests in recent years has extensively documented that several neuroactive drugs can have specific and differential effects on those aspects of male sexual responsiveness (4, 11, 12, 19–21). They were used in the present study to assess the possible influences of opioid agonist-antagonist interactions on male genital reflex potential.

METHOD

Fifty-five adult, sexually inexperienced, male Sprague-Dawley rats were used for this experiment. They were housed 3 to a cage under a 14:10 light:dark cycle. Food and water were available ad lib.

Drugs (morphine sulphate and naloxone hydrochloride) were dissolved in 0.9% saline and injected intraperitoneally in a volume 1 ml/kg body weight. Injections were given either 30 min (morphine) or 10 min (naloxone) before the test. Each treatment or control group consisted of 10 animals. Five doses of morphine and three doses of naloxone, given alone and/or in combination (specified in the Results section) were studied. Control animals received

[1]Requests for reprints should be addressed to Prof. M. Mas, Departamento de Fisiologia, Facultad de Medicina, E-38320 Tenerife, Spain.

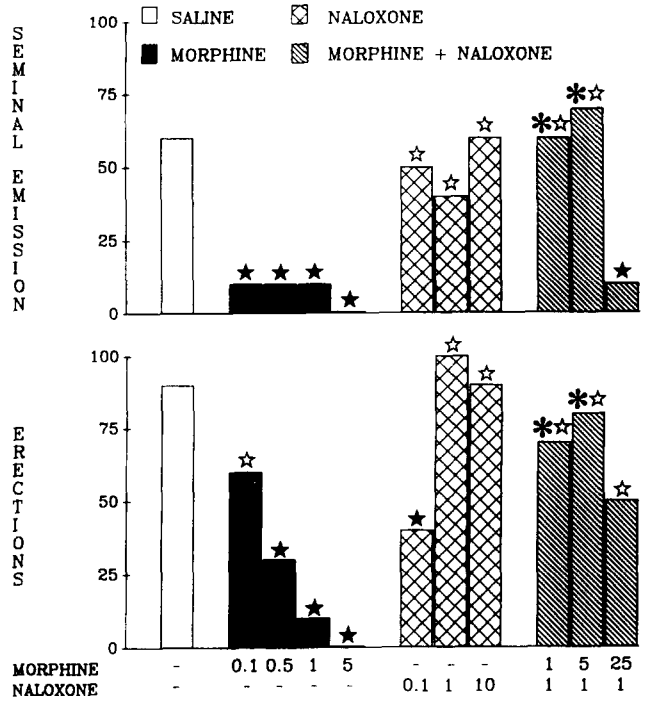

FIG. 1. Percentage of rats showing penile erections and seminal emisssion after administration of morphine, naloxone and a combination of both. Doses of the drugs are indicated at the bottom as mg/kg. See text for further details. ★: Significant vs. saline-injected control group; *: significant vs. the corresponding dose of morphine; ☆: not significant vs. saline control.

saline injections. Each animal received two of these treatments, given in random order, with a 10–12 day interval.

The penile reflexes test was performed during the lights on period. It was done as previously described (11,12) with some modifications. Briefly, the animal was held in a supine position on a wooden flat surface and restrained with a screw-tightened black cloth. This device is based on the one described by Owen *et al.* (16) for analgesia testing. According to our experience, it is apparently less stressful and gives more consistent results in the penile reflexes test than the usual plastic cylinder. A second modification consisted of initially keeping the animals in the restrainer for 10 min without retracting the penile sheath. This was found by Smith *et al.* (20) to result in a high incidence of seminal emission. The seminal emissions displayed in this test situation show the same circadian pattern as that observed in the three day long "corset" tests (11,20). There is apparently no relationship between such episodes of seminal emission and the display of erectile reflexes afterwards. The glans penis was then extruded and the test continued for 20 minutes after the first erection or for 15 min if no reflexes occurred. The following penile responses were recorded: erections, cups (erection with flaring of the glans) and flips (dorsal movements of the penis). Differences between groups were analyzed by chi square and Fisher tests for the percentage data and Kruskal-Wallis and Mann-Whitney tests for latencies and number of events. Significance levels were set at p values of 0.05 or less.

RESULTS

As shown in Fig. 1, morphine treatments (0.1, 0.5, 1 and 5 mg/kg) resulted in a dose related reduction in the proportion of animals displaying penile erectile responses. Seminal emission was apparently more sensitive to inhibition by morphine since it was virtually suppressed even by the smallest dose of the opiate tested.

Naloxone given alone did not influence significantly the occurrence of seminal emission at any of the dose levels (0.1, 1 and 10 mg/kg) studied. A similar lack of effects was found on the display of erectile reflexes except at the lowest dose which resulted in a significant decrease of this response.

The intermediate dose of naloxone (1 mg/kg) was also given in conjunction with morphine (1, 5, and 25 mg/kg). Figure 1 shows that the opioid anatgonist completely reversed the inhibitory effects of the low and intermediate doses of morphine on the display of both erectile responses and seminal emission. This dose of naloxone could also antagonize the predictable suppression of both responses by 25 mg/kg of morphine on the display of erections but not seminal emission.

The effects of the different treatments on the latencies to the display of erectile responses and numbers of events are summarized in Table 1. No significant differences in these parameters could be demonstrated between the different groups. The small number of animals showing any of these responses in the morphine-treated groups would make it difficult to reach significance levels. Nevertheless, the latencies and number of events displayed by those animals showing reflexes in all groups were quite similar to the values of the control group. That suggests that the strong inhibitory effects of morphine on seminal emission and penile responses as well as the efficient reversal of these phenomena by naloxone occurred in an all-or-none fashion.

DISCUSSION

These results clearly show that morphine treatment decreases the potential for both penile erectile responses and seminal emission within the range of doses tested. The opioid specificity of these actions of morphine is evidenced by their highly efficient reversal by naloxone. The mechanisms for seminal emission seem to be more sensitive than the erectile responses to the inhibitory actions of opiates. That is suggested by both the significant inhibitions of the former by a smaller dose of morphine as well as the relative inability of 1 mg/kg naloxone to counteract its suppression by the largest dose (25 mg/kg) of the opiate. The efficient inhibition of seminal emission by morphine is consistent with its reported ability to block the ejaculation ex copula induced by dopamine agonists (2).

It is noteworthy that the inhibitory effects of morphine on erectile responses and seminal emission reported here were observed with doses of the opiate much smaller than those seemingly required to impair sexual arousal. According to the literature, systemic doses of morphine below 5 mg/kg do not suppress the initiation of mating in intact male rats (8,10). This would explain some findings from mating tests showing impaired copulatory efficiency, suggested by the increased number of mounts preceding an ejaculation, following opiate treatments (14, 17, 22). These data suggest altogether a differential sensitivity of specific components of the sex behavioral pattern to the inhibitory actions of opioids. The seminal emission/ejaculation mechanism seems to be the most sensitive followed by erectile reflexes, whereas the arousal sys-

TABLE 1

EFFECTS OF MORPHINE AND NALOXONE ON PENILE REFLEXES AND SEMINAL EMISSION

	Dose (mg/kg)	Latency to First Erection (min)	Number of Events			
			Erections	Cups	Flips	Seminal Emission
Saline		8.40 ± 1.47	10.11 ± 0.66 (9)	3.57 ± 0.84 (7)	3.14 ± 0.55 (7)	2.0 ± 0.49 (5)
Morphine	0.1	9.21 ± 2.60	9.66 ± 6 (6)	2.0 ± 0.7 (2)	2.66 ± 0.98 (3)	1 (1)
	0.5	10.25 ± 4.8	9.0 ± 2.16 (3)	7.0 (1)	4.50 ± 0.85 (2)	1 (1)
	1	7.21	14 (1)	— (0)	3 (1)	1 (1)
	5	—	— (0)	— (0)	— (0)	— (0)
Naloxone	0.1	9.94 ± 1.8	8.50 ± 3.13 (4)	— (0)	4.00 ± 1.41 (2)	1.5 ± 0.35 (5)
	1	9.63 ± 2.0	10.90 ± 1.72 (10)	4.43 ± 0.85 (7)	2.71 ± 0.52 (7)	1.5 ± 0.25 (4)
	10	7.08 ± 1.43	15.11 ± 2.90 (9)	3.62 ± 0.63 (8)	4.00 ± 0.35 (7)	2.3 ± 0.30 (4)
Naloxone 1 mg/kg plus morphine	1	6.54 ± 1.88	12.71 ± 4.50 (7)	3.00 ± 0.53 (3)	10.5 ± 4.40 (4)	1.6 ± 0.40 (6)
	5	10.26 ± 2.48	10.37 ± 2.25 (8)	1.50 ± 0.50 (2)	1.75 ± 0.64 (4)	2.1 ± 0.24 (7)
	25	7.02 ± 2.77	20.20 ± 7.33 (5)	2.25 ± 1.09 (4)	8.50 ± 9.20 (2)	1 (1)

Values are the mean ± S.E.M. Number of animals showing each response in parentheses.

tem would be more resistant to such an inhibition. This is consistent with findings in human male opiate addicts in which delayed ejaculation is the commonest sexual deficit. According to clinical reports the sexual dysfunction associated to chronic opiate intake in humans follows a well-defined temporal pattern including first anorgasmia and then erectile impotence and decreased libido; at the withdrawal these symptoms usually revert in an opposite sequence (3,17).

The mild morphine-like inhibitory effects on erectile responses of the lowest dose of naloxone tested is reminiscent of findings from studies in the field of analgesia (7,23). In an attempt to explain the latter it has been suggested that naloxone at low doses could be acting as a partial agonist for a particular subpopulation of opioid receptors (23). Studies on female sexual behavior have also documented such phenomena as U-shaped dose-response curves (1) and dual site-dependent effects (9) of opioid antagonists on lordosis quotients in rats. This reflex is known to be susceptive to differential modulation by several opioid receptor subtypes (17). That could be also the case for male genital reflexes. The observed lack of effect of the other doses of naloxone (1 and 10 mg/kg) given alone on penile reflexes is in agreement with the findings at Sach *et al.* (19). These latter data would speak against a prominent role for endogenous opiates in the control of genital reflexes of the male rat, at least in this specific test situation. Yet the high efficiency of both the inhibition of these responses by morphine and its blockade by naloxone suggests a physiological substrate for these actions. It is possible that, as has been proposed for arousal (15), an opiatergic system inhibitory of penile reflexes could operate only during periods of sexual activity contributing to the pacing of intromissions and ejaculation.

The sites of action of opioids for these inhibitory effects on erectile and ejaculatory reflexes cannot be established by the present experiment. Indirect evidence, however, points out the spinal cord as a likely candidate. The reflex mechanisms for penile erections and seminal emission have their essential constiuents in the lumbosacral cord (5, 12, 18, 21). This region contains the sexually-dimorphic, androgen-sensitive nuclei of the bulbocavernous and ischiocavernous muscles, the activity of which mediates the display of specific components of the penile reflex pattern, respectively cups and flips (5,18). According to immunocytochemical studies the lumbosacral cord contains and intrinsic (since it remains after spinal transection) enkephalinergic innervation, especially dense in these sexually dimorphic motor nuclei (13). Furthermore, the intrathecal infusions of morphine into the lumbosacral perispinal have been reported to increase the number of intromissions necessary for achieving an ejaculation (22), a finding consistent with the inhibitory effects of opioids on the genital reflex potential described here. Pharmacological and lesion studies indicate that the modulatory influence of the brain on the spinally-based reflexes for penile erection and seminal emission are exerted, at least in part, through descending monoaminergic pathways (12,21). It is possible that, similarly to the well-

documented phenomena in the field of analgesia [e.g., (6)], opioid-monoamine interactions could modulate the spinopeptal pathways controlling male genital reflexes.

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