Comparison of the Effects of Yohimbine, Naloxone and 8-OH-DPAT on the Diminished Ejaculatory Capacity Induced by Repeated Ejaculation

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ABSTRACT

In various species, repeated ejaculation over a short period of time results in a marked decrease in the capacity of sexual responses and the activity of sexual arousal/motivation. The purpose of this study was to compare the effects of the α₂-adrenergic receptor antagonist yohimbine, the opioid receptor antagonist naloxone, and the 5-HT₆ receptor agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) (all of which have been shown to stimulate male sexual arousal/motivation in sexually exhausted rats), on the diminished ejaculatory capacity induced by repeated ejaculation in dogs. The data obtained show that both the decrease in the amount of ejaculate and the delay onset in ejaculation latency elicited by antecedent ejaculation were completely prevented by a low dose (0.1 mg/kg, i.p.) of yohimbine, but not naloxone (1.0–3.0 mg/kg, i.p.) and 8-OH-DPAT (0.01–0.1 mg/kg, i.p.). Unlike the effects on male sexual arousal/motivation, the present results suggest that yohimbine, naloxone, and 8-OH-DPAT, differentially affect on the diminished ejaculatory capacity and that yohimbine only may be effective for the treatment of ejaculatory dysfunction, which accompanies by the diminished ejaculatory capacity.

Behavioral studies have demonstrated that sexual arousal/motivation is also inhibited by coital ejaculations, together with the diminished ejaculatory capacity (1, 5). Recently, Rodriguez-Manzo et al. (5, 6) analyzed using the amount of ejaculate in response to manual penile stimulation as an index for a quantitative assessment of the ejaculatory capacity (10, 11). Using this model, we reported for the first time that systemically administered yohimbine, an α₂-adrenergic antagonist, can prevent and reverse the diminished ejaculatory capacity during a period of frequent ejaculation (11). A similar result was also obtained by other α₂-adrenergic antagonists that act in both the central and the peripheral nervous system, but not only the peripheral nervous system (14), indicating that the mechanism of diminished ejaculatory capacity elicited by repeated ejaculation may be involved in the activation of the central α₂-adrenergic receptors.
have demonstrated that the sexual arousal inhibition resulting from sexual exhaustion (repeated coital ejaculations) in male rats can be reversed by yohimbine, the 5-HT1A receptor agonist 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) or the opioid receptor antagonist naloxone, as evidenced for the increase in the proportion of satiated rats showing mounting, intromitting, and ejaculating behavior. These results suggest that the neural mechanisms regulating male sexual arousal/motivation are stimulated by yohimbine, 8-OH-DPAT or naloxone. However, it is unclear whether the diminished ejaculatory capacity elicited by repeated ejaculation can be prevented by 8-OH-DPAT and naloxone as well as yohimbine.

The purposes of the present study were (1) to compare the effects of yohimbine, 8-OH-DPAT and naloxone on the diminished ejaculatory capacity elicited by repeated ejaculation and (2) to examine the feature of the stimulating effect of yohimbine on ejaculation, using a dog model.

MATERIALS AND METHODS

Male beagle dogs weighing 12 to 18 kg were used. Prior to the experiments, all animals were tested for the reliable occurrence of ejaculation and penile erection in response to the manual penile stimulation. Dogs were individually housed in a temperature- and humidity-controlled room with a 14L:10D cycle (light on at 6:00 a.m.). Water and standard dog food (CD-1, CLEA, Japan) were available at all the times except during the experimental sessions. This study was reviewed and approved by the Animal Committee of Tohoku Pharmaceutical University.

Yohimbine HCl (Nacalai Tesque, Kyoto, Japan), naloxone HCl (Sigma, St. Louis, MO, USA) and 8-OH-DPAT ((±)-8-hydroxy-2-(di-n-propylamino)tetratin HBr; Research Biochemicals, Natick, MA, USA) were used in this study. Yohimbine was dissolved in sterile distilled water; naloxone and 8-OH-DPAT in sterile saline (0.9% NaCl). All drugs were prepared immediately prior to testing and were injected intraperitoneally (i.p.) in a volume of 0.2 ml/kg body weight.

The testing procedure for evaluating the drug effects on ejaculation was similar to that employed previously (14). For all experimental sessions, animals were transferred to an experimental room 15–30 min before the testing. Ejaculation was elicited by continuous manual stimulation of the penis (for 10 min), which applied light pressure and gently rubbed the body of the penis just behind the bulbus glandis. This stimulation could easily produce a rapid onset of ejaculation, and subsequently occurred intermittently when the stimulation was continued. To produce a diminished ejaculatory capacity, the stimulation was done twice with a 30 min (Fig. 1 and 2), or 3 h and 6 h (Fig. 2) interval and the following parameters were recorded: (1) the amount of ejaculate collected during a period of the stimulation (data were represented as a ratio against the amount of ejaculate produced by the first stimulation), (2) ejaculation latency (time from the start of the stimulation to the first ejaculation). Each animal served as his own control and the experimental sessions on a given animal were repeated at 7-10-day intervals. Manual penile stimulation and observation of each parameter were carried out by the same observer.

Nonparametric statistics were used throughout. Overall differences were analyzed using the Friedman two-way analysis of variance. When significant differences (P < 0.05) were obtained, the Wilcoxon-matched pairs signed-rank test was applied to identify significant differences between the treatments. Data are presented as the mean ± S.E.M (the amount of ejaculate) or the median (ejaculation latency).

RESULTS

Fig. 1 shows the effects of yohimbine, naloxone and 8-OH-DPAT on the diminished ejaculatory capacity of dogs elicited by repeated ejaculation. When the penis was restimulated 30 min after the first stimulation, the amount of ejaculate produced by the stimulation was drastically decreased in vehicle-treated animals (the ratio against the amount of ejaculate by the first stimulation was 0.28 ± 0.11). Moreover, the ejaculation latency was prolonged by this manipulation (the median of ejaculation latency for the first stimulation was 5s). When administered immediately after the first stimulation, yohimbine produced a biphasic dose response curve for the diminished ejaculatory capacity; both the decrease in the amount of ejaculate and the delay in ejaculation latency elicited by the second stimulation were completely prevented by a low dose (0.1 mg/kg) of yohimbine, while the highest dose (1.0 mg/kg) resulted in a significant reduction of the ejaculation capacity. By contrast, 8-OH-DPAT (0.01–0.1 mg/kg) more decreased the amount of ejaculate, which was not statistically significant. However, 8-OH-DPAT at 0.1 mg/kg caused a significant delay in ejaculation.
Drugs and Ejaculatory Capacity in Dogs

AB

2.0

1.0

0.0

VEH 0.03 0.1 0.3 1.0
Yohimbine

Naloxone

8-OH-DPAT

0.01 0.03 0.1

Fig. 1 Effects of yohimbine, naloxone and 8-OH-DPAT on the diminished ejaculatory capacity (A; the amount of ejaculate, B; ejaculation latency) of dogs elicited by repeated (twice) ejaculation. The penis was restimulated 30 min after the first stimulation. Ejaculation ratio is represented as a ratio against the amount of ejaculate obtained by the first stimulation. Each drug was injected i.p. immediately after the first stimulation. *P < 0.05 when compared to vehicle (VEH)-treated animals (n = 8).

Fig. 2 shows the feature of the stimulating effect of yohimbine (0.1 mg/kg) on the process for the recovery of the diminished ejaculatory capacity elicited by antecedent ejaculation. Vehicle-treated animals gradually recovered the capacity and returned to the initial level at 6.0 h after antecedent ejaculation. When administered immediately, or 2.5 h and 5.5 h after the first stimulation, yohimbine significantly increased the amount of ejaculate in subsequent stimulation, at any of the administration times. Especially, the most striking effect was obtained when the drug was administered immediately after the first stimulation.

DISCUSSION

Behavioral studies have shown that sexual arousal inhibition resulting from repeated coital ejaculations (i.e., sexual exhaustion) in rats can be reversed by systemic administration of yohimbine, naloxone, and 8-OH-DPAT (5, 6). The present results, however, show that the diminished ejaculatory capacity of dogs induced by repeated ejaculation is differently affected by these drugs. Thus, when administered immediately after ejaculation, yohimbine at a low dose (0.1 mg/kg) completely prevented both a decrease in the amount of ejaculate and a delay in ejaculation latency in subsequent ejaculation, whereas naloxone and 8-OH-DPAT failed to exert such effects. Recently, we tested the ability of these drugs to stimulate ejaculation using dogs with normal ejaculatory capacity, and showed the ejaculatory stimulation (i.e., an increase in the amount of ejaculate) can be observed only in yohimbine-treated animals (15). These results, taken together, indicate that the drugs which stimulate male sexual arousal/motivation do not show the identical effects for the sexual responses, particularly ejaculation. In line with our observations, Schnurer et al. (9) reported that systemically administered 8-OH-DPAT stimulates sexual arousal and lowers the behavioral-ejaculatory threshold but inhibits both the ejaculation and penile erection.

The present results are in accord with our previous findings (10) that systemic administration of yohimbine produces a biphasic dose-response effects (stimulating/inhibiting) on the ejaculatory response in dogs. Similar biphasic dose-response effect of yohimbine have been observed for male sexual behavior, social contacts and spontaneous ejaculations in rats (8). There is both direct and indirect evidence
Fig. 2  Effects of the stimulating dose (0.1 mg/kg) of yohimbine on the process for the recovery of the diminished ejaculatory capacity elicited by antecedent ejaculation. The penis was restimulated 30 min, 3.0 h or 6.0 h after the first stimulation. Ejaculation ratio is represented as a ratio against the amount of ejaculate obtained by the first stimulation. Each drug was injected i.p. 30 min before the stimulation. **P < 0.01 when compared to vehicle-treated animals (n = 14).

that the stimulating effects of yohimbine are mediated via the blockade of \( \alpha_2 \)-adrenergic receptor in the central nervous system. Thus, the inhibition of ejaculation induced by centrally or systemically administered clonidine, an \( \alpha_2 \)-adrenergic receptor agonist, is completely antagonized by pretreatment with systemic administration of a low dose (0.1 mg/kg) of yohimbine (12, 13). Furthermore, the selective \( \alpha_2 \)-adrenergic receptor antagonists that possess the blocking activity on both central and peripheral \( \alpha_2 \)-adrenergic receptors, have also a stimulatory effect on ejaculation, whereas a peripherally acting \( \alpha_2 \)-adrenergic receptor antagonist failed to produce such effects (14). The inhibitory effect of the high dose (1.0 mg/kg) of yohimbine on ejaculation (i.e., a decrease in the amount of ejaculate and a delay in ejaculation latency) has been proposed an interaction with either the \( \alpha_2 \)-adrenergic receptors or the 5-HT\(_{1A}\) receptor, or a combination of both (14). A part of this hypothesis is supported by the present finding that the 5-HT\(_{1A}\) receptor agonist 8-OH-DPAT inhibits the ejaculatory capacity. Furthermore, electrophysiological study has also demonstrated that the higher doses of yohimbine have the 5-HT\(_{1A}\)-mediated sympathoinhibitory properties that could be blunted by the \( \alpha_2 \)-adrenergic antagonist sympathoexcitatory properties of the drug (3, 4).

It is noteworthy that yohimbine at 0.1 mg/kg is an adequate dose for inducing stimulatory effect on the decrease in the amount of ejaculate and the delay in the ejaculation latency induced by antecedent ejaculation. In fact, the most striking effect was obtained when the drug was administered immediately after ejaculation. These results support the hypothesis (10, 14) that activation of the \( \alpha_2 \)-adrenergic, but not the opiodergic and the 5-HT\(_{1A}\) receptor mechanism, may play an important role in the expression and the maintenance of the diminished ejaculatory capacity produced by repeated ejaculation.

The fact that yohimbine has a stimulating effect on ejaculation, especially the diminished state of the capacity, is in accord with clinical findings. Brindley (2) has indicated that the vibrator stimulation is effective for the treatment of patients with primary anorgasmia, which lack ejaculation and orgasm, and that the administration of yohimbine (< 0.4 mg/kg) prior to applying the tactile stimulation is more effective in this therapy. Thus, yohimbine and other
α-adrenergic receptor antagonists may be effective for the treatment of ejaculatory failure which accompanies by the diminished ejaculatory capacity.

In conclusion, the present study indicates that unlike the effects on male sexual arousal/motivation in rats, administration of yohimbine, naloxone, and 8-OH-DPAT to dogs differentially affect the diminished ejaculatory capacity.

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