ELSEVIER

Pharmacology, Biochemistry and Behavior 70 (2001) 141–147

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

α_2-Adrenoceptor antagonists: effects on ejaculation, penile erection and pelvic thrusting behavior in dogs

Akihiko Yonezawa[a,*], Ryuichiro Ando[b], Chizuko Watanabe[b], Seiichi Furuta[a], Motoharu Kutsuwa[a], Shinobu Sakurada[a], Yukio Kimura[c]

[a]*Department of Physiology and Anatomy, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan*
[b]*Center for Laboratory Animal Science, Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai 981-8558, Japan*
[c]*Towada Urology Hospital, 1-3-8 Motomachi-Higashi, Towada City 034-0003, Japan*

Received 6 February 2001; received in revised form 3 May 2001; accepted 10 May 2001

Abstract

We previously reported that systemic administration of yohimbine, an α_2-adrenoceptor antagonist, exerts a biphasic effect (stimulating and suppressing) on ejaculation in dogs, when this function is analyzed using the amount of ejaculated semen in response to genital stimulation. To clarify the effect of α_2-adrenoceptor blockade on male sexual function, we investigated the effects of four selective α_2-adrenoceptor antagonists, rauwolscine, idazoxan, RX821002 and mydaglizole, on sexual responses (ejaculation, penile erection and pelvic thrusting behavior) elicited by manual penile stimulation in dogs. Rauwolscine (intraperitoneal, 30 min before the testing) caused a biphasic effect on ejaculation; the amount of ejaculated semen produced by the stimulation was significantly increased by the lower doses (0.1 and 0.3 mg/kg), whereas it was decreased by the higher doses (1.0 and 2.0 mg/kg). The higher doses of rauwolscine also markedly inhibited both penile erection and pelvic thrusting behavior. Idazoxan and RX821002, at doses of 0.1 and 0.3 mg/kg, caused a significant increase in the amount of ejaculated semen without affecting other sexual functions. RX821002 (2.0 mg/kg), but not idazoxan (2.0 mg/kg), moderately inhibited both penile erection and pelvic thrusting behavior. Mydaglizole, a peripherally acting α_2-adrenoceptor antagonist, did not affect the sexual responses at any doses (0.1–4.0 mg/kg). In the ejaculatory declining test, all α_2-adrenoceptor antagonists (0.1 mg/kg), except for mydaglizole, completely prevented the decrease in ejaculatory capacity produced by antecedent ejaculation. These results indicate that, though the range of the effective dose is narrow, the α_2-adrenoceptor antagonists that can block the central α_2-adrenoceptors have the stimulatory effects on ejaculatory function. The difference of the sexual effects may be based on the action except for the α_2-adrenoceptor blockade.

Keywords: α_2-Adrenoceptor antagonist; Ejaculation; Penile erection; Pelvic thrusting behavior; Dog

1. Introduction

There is a considerable evidence supporting the stimulatory effect of α_2-adrenoceptor antagonists in the modulation of male sexual behavior. For example, treatment of male rats with yohimbine, a prototype of α_2-adrenoceptor antagonist, facilitates several components of copulatory behavior (Clark et al., 1984, 1985a; Sala et al., 1990; Smith et al., 1987a) and causes a considerable improvement in a variety of hyposexual conditions such as castration (Clark et al., 1985b) and age-related sexual deficiencies (Smith and Davidson, 1990). However, it was shown that the dose range of yohimbine, which causes the sexual promoting effect, is very narrow. Recent studies have reported that a more potent and selective α_2-adrenoceptor antagonists also can stimulate sexual behavior in rats (Tallentire et al., 1996) and monkeys (Linnankoski et al., 1992) over a wide dose-range. This suggests that the α_2-adrenoceptor antagonist may possess an aphrodisiac property, and that central α_2-adrenoceptor may be involved in the modulation of male sexual behavior.

With regard to the effects of α_2-adrenoceptor antagonists on male sexual functions, especially ejaculation, pharmaco-

* Corresponding author. Tel.: +81-22-234-4181; fax: +81-22-275-2013.
E-mail address: yonezawa@tohoku-pharm.ac.jp (A. Yonezawa).

0091-3057/01/$ – see front matter
PII: S0091-3057(01)00584-6

logical research has been hampered by the lack of a suitable animal model. Recently, we found the stability of the amount of ejaculated semen in response to genital stimulation in dogs and established a simple method for evaluating the drug effects on ejaculation (Yonezawa et al., 1991a). Using this method, we reported for the first time that systemically administered yohimbine affects the ejaculatory capacity in dogs in a biphasic fashion; low doses increase the amount of ejaculated semen, whereas higher doses diminish the ejaculatory capacity (Yonezawa et al., 1991a). Furthermore, we clearly demonstrated that yohimbine, at lower doses, prevents the diminution of ejaculatory capacity during frequent ejaculation in dogs and that the diminished ejaculatory capacity is restored to an almost normal level (Yonezawa et al., 1991b,c). These results suggest the possibility that α_2-adrenoceptor antagonists have a stimulating effect on the ejaculatory function.

The purpose of the present study was to investigate the effects of four selective α_2-adrenoceptor antagonists on ejaculation elicited by manual penile stimulation in dogs. Penile erection and pelvic thrusting behavior induced by the stimulation were also observed to accurately evaluate the effects of these antagonists on male sexual functions.

2. Materials and methods

2.1. Animals

Fourteen adult male beagle dogs weighing 11–16 kg were used. Before the drug experiments, all animals were tested for the reliable occurrence of penile erection and ejaculation in response to manual penile stimulation. They were individually housed in a dog's room at a temperature of 22–24°C and 50–60% relative humidity, and adapted on a reverse light–dark cycle (light on: 6:00 a.m.–8:00 p.m.). Water and standard dog food (CD-1, CLEA, Japan) were available at all times except during the experimental sessions. This study was reviewed and approved by the Animal Committee of Tohoku Pharmaceutical University.

2.2. Drugs

Rauwolscine HCl (Carl Roth), idazoxan HCl (Sigma), RX821002 HCl (Research Biochemicals) and mydaglizole (donated by Daiichi Pharmaceutical, Tokyo) were used in this study. Drugs were dissolved in physiologic saline or sterile distilled water (also used as control solution) immediately prior to testing and were injected intraperitoneally in a volume of 3 ml/animal 30 min before the testing. The doses of the drugs were calculated as the salt.

2.3. Testing procedure

The testing procedure for evaluating the drug effects on male sexual functions were similar to those reported previously (Yonezawa et al., 1991a). For all experimental sessions, dogs were transferred to an experimental room 15–30 min before the testing and then injected the appropriate drugs or vehicle. Ejaculation and penile erection were elicited by continuous manual stimulation of the penis (Experiment 1 for 5 min, Experiment 2 for 10 min), which applied light pressure and gently rubbed the body of the penis just behind the bulbus glandis. To assess ejaculation, the expelled semen from the urethra was collected with a preweighed plastic beaker during a period of the stimulation and then weighed on an electro-millibalance (Sartorius Type 1413). To assess penile erection, the latency to full erection from the start of the stimulation was measured. If the animals failed to exhibit full erection, test duration was assigned as the response latency and the changes of erectile potency were simultaneously scored according to the following grades of intensity: score 0, no reaction; score 1, slight increase of the size of the bulbus glandis and pars longa glandis; score 2, the glans penis largely engorgement,

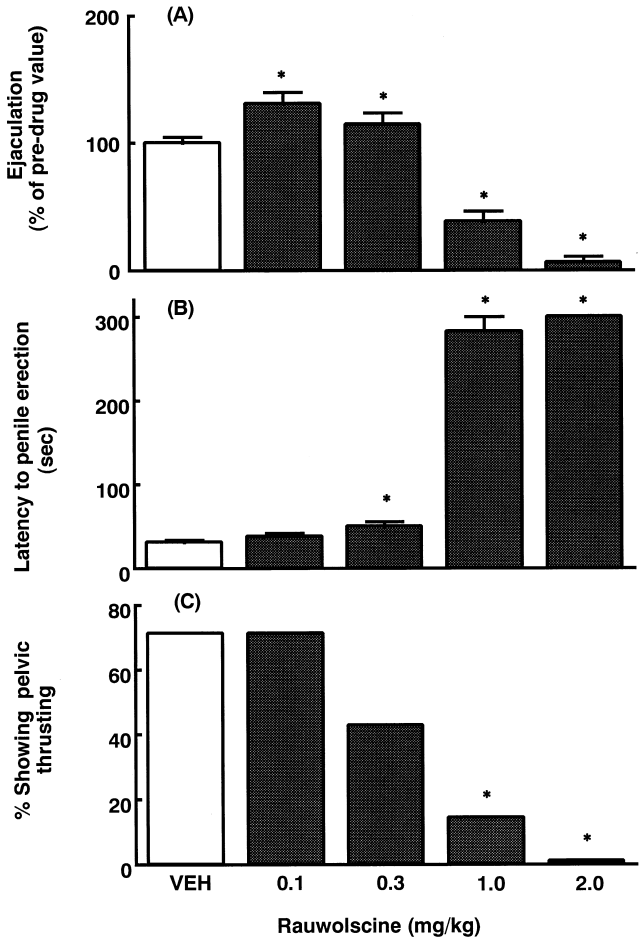

Fig. 1. Effects of rauwolscine on ejaculation (A), penile erection (B) and the incidence of pelvic thrusting behavior (C) elicited by manual penile stimulation in dogs. Rauwolscine was injected intraperitoneally 30 min before the testing. The symbol (*) indicates a significant difference ($P<.05$) from vehicle (VEH)-treated animals ($n=7$).

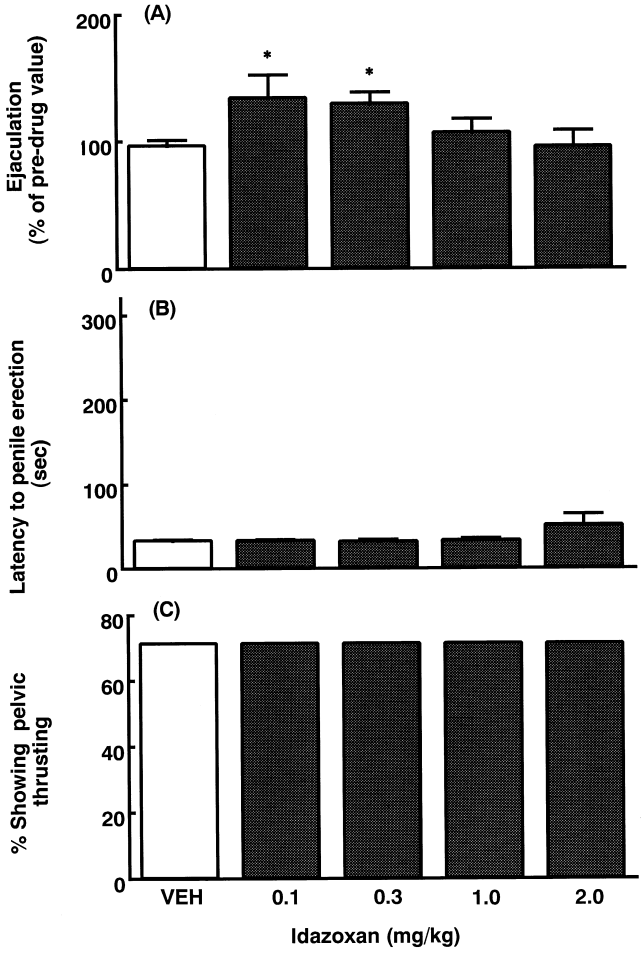

Fig. 2. Effects of idazoxan on ejaculation (A), penile erection (B) and the incidence of pelvic thrusting behavior (C) elicited by manual penile stimulation in dogs. Idazoxan was injected intraperitoneally 30 min before the testing. The symbol (*) indicates a significant difference ($P < .05$) from VEH-treated animals ($n = 7$).

but not fully erect. Some dogs appeared copulatory behavior-like components such as pelvic thrusting and alternate stepping of the hind legs induced by the stimulation. In the present study, therefore, the incidence of these components was also observed to accurately assess the drug effects on male sexual functions. Manual penile stimulation and observation of each sexual function was carried out by the same observer.

2.3.1. Experiment 1

Each animal served as his own control, because the amount of ejaculated semen produced by manual penile stimulation varied considerably among individual animals (Yonezawa et al., 1991a). The time interval between semen collections was 4–5 days. To determine the basal ejaculate value, the semen collection was made three to five times prior to the testing and the mean weight of ejaculates was calculated in each animal (pre-drug value). All data for ejaculation were represented as a percentage of the pre-drug value. After the determination of the pre-drug value, each dog was administered vehicle or four doses of each α_2-adrenoceptor antagonist. The order of administration was rauwolscine, idazoxan, RX821002 and mydaglizole. The time interval between the drug administrations was 4–5 days.

2.3.2. Experiment 2

Our previous study showed that the amount of ejaculated semen produced by manual penile stimulation was drastically reduced during a period of frequent ejaculation (Yonezawa et al., 1991b,c). Indeed, the amount of ejaculated semen obtained by the second stimulation was decreased drastically. To assess the stimulatory action of α_2-adrenoceptor antagonists on the ejaculatory function, therefore, each α_2-adrenoceptor antagonist was injected immediately after the first stimulation (for 10 min) and the data were represented as a ratio against the weight of the first ejaculated semen. The experimental sessions on a given animal were repeated at 7–10-day intervals.

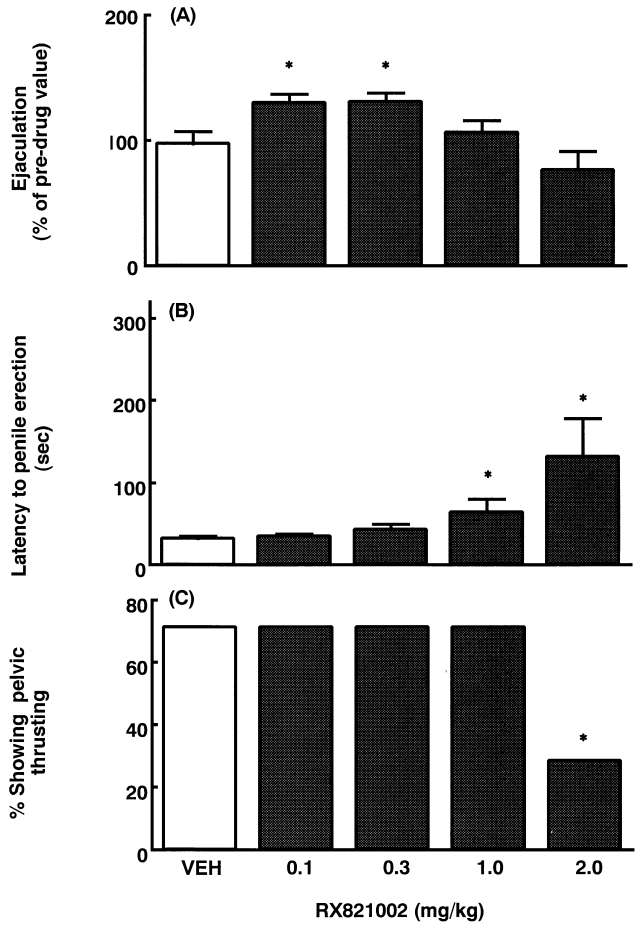

Fig. 3. Effects of RX821002 on ejaculation (A), penile erection (B) and the incidence of pelvic thrusting behavior (C) elicited by manual penile stimulation in dogs. RX821002 was injected intraperitoneally 30 min before the testing. The symbol (*) indicates a significant difference ($P < .05$) from VEH-treated animals ($n = 7$).

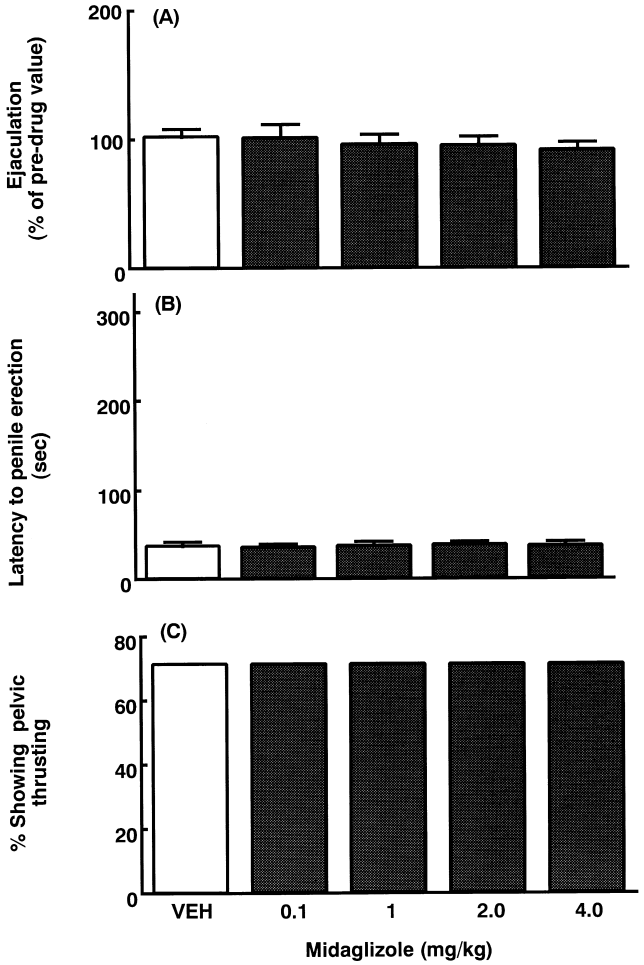

Fig. 4. Effects of mydaglizole on ejaculation (A), penile erection (B) and the incidence of pelvic thrusting behavior (C) elicited by manual penile stimulation in dogs. Mydaglizole was injected intraperitoneally 30 min before the testing. The symbol (*) indicates a significant difference ($P<.05$) from VEH-treated animals ($n=7$).

2.4. Data analysis

Nonparametric statistics were used throughout. Overall differences were analyzed using the Friedman two-way analysis of variance. When significant differences ($P<.05$) were obtained, the Wilcoxon-matched pairs signed-ranks test was applied to identify significant differences between the treatments. For analysis of percentages, the Binomial test for significance of change was used. Data are presented as the mean ± S.E.M.

3. Results

3.1. Ejaculation, penile erection and pelvic thrusting behavior by manual penile stimulation

In control experiment, the ejaculation occurred within 0.5 min after the start of manual penile stimulation, and subsequently occurred intermittently when the stimulation was continued. The weight of ejaculated semen produced by the stimulation varied considerably among individual dogs, as previously reported (Yonezawa et al., 1991a). The basal value (pre-drug value) in each animal obtained by regular semen collection (3–5 times at 4–5-day intervals) ranged from 3.58 to 12.31 g. However, the time to time variations in the weight of ejaculated semen is little changed in each of 14 dogs. The coefficients of variation within animals ranged from 5.6% to 13.4% with an average of 10.3%. A rapid penile tumescence and pelvic thrusting behavior was also simultaneously occurred by the stimulation, and all animals showed a full erection within 1 min after the start of the stimulation.

3.1.1. Experiment 1

Fig. 1 shows the dose-dependent effects of rauwolscine on ejaculation, penile erection and the incidence of pelvic thrusting behavior elicited by manual penile stimulation. Rauwolscine at a low dose (0.1 mg/kg) caused a significant increase in the amount of ejaculated semen without affecting the latency to full erection and the incidence of pelvic thrusting behavior. Conversely, the higher doses (1.0 and 2.0 mg/kg) of the drug markedly attenuated the sexual responses by the stimulation (mean erectile potency was 1.4, $n=7$). At 1.0 mg/kg dose of rauwolscine also produced a marked autonomic and behavioral effect such as diarrhea, salivation and restless. It seems unlikely that the decrease in semen caused by rauwolscine may be due to retrograde ejaculation, since sperm was not found in the urine drawn from the urinary bladder.

As shown in Figs. 2 and 3, idazoxan (0.1 and 0.3 mg/kg) and RX821002 (0.1 and 0.3 mg/kg), which were equipotent, caused a significant increase in the amount of ejaculated semen without affecting other sexual responses. Unlike rauwolscine, the highest dose (2.0 mg/kg) of idazoxan did

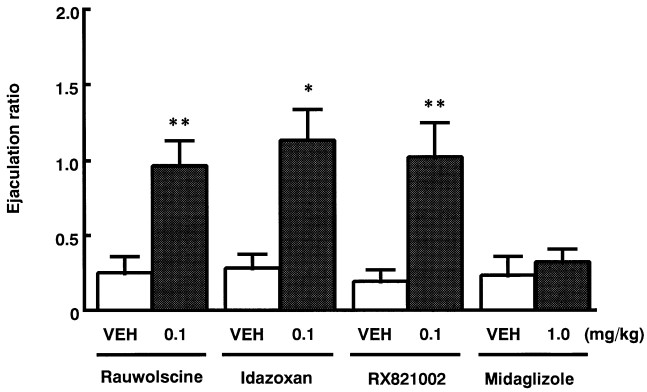

Fig. 5. Effects of rauwolscine, idazoxan, RX821002 and mydaglizole on the diminution of ejaculatory capacity in dogs following ejaculation (first stimulation). The restimulation (second stimulation) was done 30 min after the first stimulation. Ejaculatory capacity is represented as a ratio against the ejaculated semen obtained by the first stimulation (for 10 min). Each drug was injected intraperitoneally immediately after the first stimulation. * $P<.05$, ** $P<.01$ when compared to VEH-treated animals ($n=7$).

not show an inhibitory effect on all sexual responses. RX821002, at the dose 2.0 mg/kg, showed only the significant extension in the latency to full erection and decrease in the incidence of pelvic thrusting behavior.

In contrast to the above three α_2-adrenoceptor antagonists, mydaglizole (0.1–4.0 mg/kg), a peripherally acting α_2-adrenoceptor antagonist, did not affect the sexual responses at any doses (Fig. 4).

3.1.2. Experiment 2

Fig. 5 shows the effects of rauwolscine, idazoxan, RX821002 and mydaglizole on the diminution of the ejaculatory capacity induced by antecedent ejaculation. Although the weight of the first ejaculated semen varied considerably among individual animals (range from 4.80 to 8.14 g), the degree of reduction in ejaculated semen induced by the second penile stimulation was not related to the weight of the first ejaculated semen. When administered immediately after the first stimulation (for 10 min), rauwolscine, idazoxan and RX821002, at the dose 0.1 mg/kg, completely and equivalently prevented the decrease in ejaculated semen produced by subsequent penile stimulation. However, mydaglizole was without effect on the diminution of the ejaculatory capacity.

4. Discussion

The major finding of the present study is that a low dose (0.1 mg/kg) of α_2-adrenoceptor antagonists, rauwolscine, idazoxan and RX821002, has a stimulatory effect on the ejaculatory function in dogs. In fact, the amount of ejaculated semen produced by manual penile stimulation was significantly increased by these drugs without affecting the penile erection and the incidence of pelvic thrusting behavior. Furthermore, 0.1 mg/kg dose of rauwolscine, idazoxan and RX821002 completely prevented the diminution of the ejaculatory capacity elicited by antecedent ejaculation. Our previous study showed that administration of yohimbine (0.01–0.30 mg/kg ip), a prototype of α_2-adrenoceptor antagonist, results in a stimulatory effects as assayed by both ejaculation tests used in the present study (Yonezawa et al., 1991a,b), which is in line with the present data that of rauwolscine, idazoxan and RX821002. These results, taken together, suggest that a low dose of α_2-adrenoceptor antagonists exerts the stimulating effect on the ejaculatory function under either a normal or diminished state of the ejaculatory capacity in dogs.

In contrast to above three α_2-adrenoceptor antagonists, mydaglizole (0.1–4.0 mg/kg) did not have any significant effects on ejaculation, penile erection and the incidence of pelvic thrusting behavior. This drug has been reported to be a selective α_2-adrenoceptor antagonist, which possesses blocking activities on peripheral α_2-adrenoceptors, but lacks the blocking activity on central α_2-adrenoceptors when administered systemically (Hirohashi et al., 1990). In fact, the central α_2-adrenoceptor-mediated fall in blood pressure and pupillary dilation induced by clonidine and B-HT 920, the α_2-adrenoceptor agonists, can be blocked by yohimbine and idazoxan, whereas mydaglizole is ineffective (Hirohashi et al., 1990). Furthermore, the ejaculatory suppression induced by clonidine cannot be blocked by mydaglizole, whereas yohimbine and idazoxan are effective (Yonezawa et al., 1986, 1992). Based on these pharmacological findings, it is probable that the stimulating effects of rauwolscine, idazoxan and RX821002 on ejaculation may be related to blockade of the α_2-adrenoceptors in the CNS rather than in the peripheral site.

The stimulatory effects of the α_2-adrenoceptor antagonists on ejaculation is in contrast with previous findings (Smith et al., 1987b) that treatment with the antagonists, especially idazoxan, to male rats abolished spontaneous seminal emission. The discrepancy may be explained by the differences of species and experimental conditions that in our study ejaculation was elicited by continuous tactile stimulation of the penis in dogs, while in the rat study it was elicited without stimulating the genital organs. In fact, there is a paper that the doses of idazoxan that inhibit the spontaneous seminal emission facilitate the elicitation of behavioral ejaculation following the intromission (Smith et al., 1987a). These results, therefore, suggest that the afferent sensory input may be necessary for the elicitation of ejaculatory stimulation by α_2-adrenoceptor antagonists.

One particularly interesting finding in the present study is that the levels of increase in the amount of ejaculated semen elicited by administration of α_2-adrenoceptor antagonists were significantly greater in animals having diminished ejaculatory capacity (Experiment 2, Fig. 5) than in those having normal ejaculatory capacity (Experiment 1, Figs. 1–3). Thus, the activation of the α_2-adrenergic mechanism may be related to the decrease in ejaculatory capacity produced by antecedent ejaculation. Reduction in the amount of ejaculate semen during the course of repeated ejaculation is generally ascribable to either a low storage or a decrease in secretion capacity in the male accessory glands, or a combination of both (Rui et al., 1984). The α_2-adrenoceptor antagonists may directly stimulate the prostatic secretion and thereby prevent the diminished ejaculatory capacity in dogs. However, this possibility seems unlikely for the following reasons. (1) Pilocarpine (0.1 and 0.3 mg/kg ip), which is known to stimulate prostatic secretion, did not prevent the reduction of ejaculated semen during repeated ejaculation (Yonezawa et al., 1994). (2) Yohimbine (0.03–1.00 mg/kg ip) did not exert a pilocarpine-like stimulating effect on the prostatic secretion in anesthetized dogs, at any doses (Yonezawa et al., 1994). Thus, the promoting effects of α_2-adrenoceptor antagonists on ejaculation cannot be regarded as being secondary to increase the resting prostatic secretion. Our previous studies clearly showed that seminal emission and ejaculation induced by electrical stimulation of the hypogastric nerves are unaffected by repeated stimulus given within a short

period (Kimura, 1972; Yonezawa et al., 1991c). These results led to suggest that administration of rauwolscine, idazoxan and RX821002 to male dogs may facilitate the ejaculatory reflex arc, which is triggered by the tactile stimulation. Electrophysiological studies have demonstrated that the activity of pre- and postganglionic sympathetic nerves are increased by yohimbine and other α_2-adrenoceptor antagonists (McCall et al., 1983; Ramage and Tomlinson, 1985).

Among α_2-adrenoceptor antagonists used in this study, the higher doses (1.0 and 2.0 mg/kg) of rauwolscine strongly inhibited ejaculation, penile erection and the incidence of pelvic thrusting behavior. A similar effect has been also reported in the high dose (1.0 mg/kg) of yohimbine (the isometric form of rauwolscine) (Yonezawa et al., 1991a), suggesting the common suppressive mechanism(s) that are not due to the blockade of the α_2-adrenoceptor between these indole alkaloids. Winter and Rabin (1992) clearly showed that yohimbine and rauwolscine have high affinity for 5-HT_{1A} receptor and these two drugs, but not idazoxan, generalizes to the stimulus effect of 5-HT_{1A} agonist in drug discrimination studies. Kawai et al. (1992) also showed that yohimbine acts as a full agonist at 5-HT_{1A} receptors in the second messenger studies. Furthermore, electrophysiological study demonstrated that high doses of yohimbine inhibit sympathetic nerve activity via 5-HT_{1A} receptor agonist action (McCall et al., 1991). These results suggest that the effects of higher doses of these indole alkaloids may be mediated by 5-HT_{1A} receptors. Indeed, it has been shown that 5-HT_{1A} receptor agonists such as 8-OH-DPAT and buspirone inhibits seminal emission and penile erection when administered systemically or intrathecally in genital reflex test (Mathes et al., 1990; Schnur et al., 1989). 8-OH-DPAT also caused the decrease in seminal plugs obtained by copulatory behavior (Schnur et al., 1989). These results, taken together, suggest that the suppressive effect of rauwolscine and yohimbine on male sexual functions may be related to an interaction with the 5-HT_{1A} receptor. This is supported by our recent finding that the 5-HT_{1A} receptor agonist 8-OH-DPAT can also inhibit ejaculation, penile erection and the incidence of pelvic thrusting behavior (unpublished data). Another explanation for the mechanism of the ejaculatory inhibition may be related to an α_1-adrenergic blocking action of these alkaloids at high doses. Further investigations are, however, necessary to elucidate these inhibitory mechanisms.

The fact that α_2-adrenoceptor antagonists have a stimulating effect on ejaculation, especially the diminished state of the capacity, is in accord with clinical findings. Brindley (1994) 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, the α_2-adrenoceptor antagonist may be effective for the treatment of ejaculatory failure, which accompanies by the decrease in the ejaculated semen. In addition, the α_2-adrenoceptor antagonist may have a great potential for alleviation of male sexual dysfunction, because recent research on erection has shown that the antagonist is also the effectiveness in various erectile disorder (Munoz et al., 1994; Reid et al., 1987).

In conclusion, we have presented evidence that though the range of the effective dose is narrow, selective α_2-adrenoceptor antagonists have the stimulating effect on the ejaculatory function under either a normal or diminished state of the ejaculatory capacity in dogs. The difference of the sexual effects in the high dose of the antagonists may be based on the action except for the α_2-adrenoceptor mechanisms.

Acknowledgments

The authors are grateful to Daiichi Pharmaceutical (Tokyo, Japan) for their gift of mydaglizole.

References

Brindley GS. Impotence and ejaculatory failure. In: Rushton DN, editor. Handbook of neuro-urology. New York: Marcel, 1994. pp. 329–48.

Clark JT, Smith ER, Davidson JM. Enhancement of sexual motivation in male rats by yohimbine. Science 1984;225:847–9.

Clark JT, Smith ER, Davidson JM. Testosterone is not required for the enhancement of sexual motivation by yohimbine. Physiol Behav 1985a;35:517–21.

Clark JT, Smith ER, Davidson JM. Evidence for the modulation of sexual behavior by α-adrenoceptors in male rats. Neuroendocrinology 1985b; 41:36–43.

Hirohashi M, Tanaka M, Suzuki I, Akashi A. α_2-Adrenoceptor-blocking properties of mydaglizole (DG-5128) in rats. Arch Int Pharmacodyn 1990;306:75–86.

Kawai N, Yamamoto T, Baba A, Yamamoto H, Moroji T, Kumamoto H. Properties of yohimbine and its stereoisomers as a 5-hydroxytryptamine$_{1A}$ receptor agonist. Mol Neuropharmacol 1992;2:283–8.

Kimura Y. On peripheral nerves controlling ejaculation. Tohoku J Exp Med 1972;30:177–85.

Linnankoski I, Gronroos M, Carlson S, Pertovaara A. Increased sexual behavior in male *Macaca arctoides* monkeys produced by atipamezole, a selective α_2-adrenoceptor antagonist. Pharmacol Biochem Behav 1992;42:197–200.

Mathes CW, Smith ER, Popa BR, Davidson JM. Effects of intrathecal and systemic administration of buspirone on genital reflexes and mating behavior in male rats. Pharmacol Biochem Behav 1990;36:63–8.

McCall RB, Margaret R, Schuette SJ, Humphrey RAL, Barsuhn C. Evidence for a central sympathoexitatory action of alpha-2 adrenergic antagonists. J Pharmacol Exp Ther 1983;224:501–7.

McCall RB, Harris LT, King KA. Sympatholytic action of yohimbine mediated by 5-HT_{1A} receptors. Eur J Pharmacol 1991;199:263–5.

Munoz M, Bancroft J, Beard M. Evaluating the effects of an alpha2 adrenoceptor antagonist on erectile function in the human male: 2. The erectile response to erotic stimuli in men with erectile dysfunction, in relation to age and in comparison with normal volunteers. Psychopharmacology 1994;115:471–7.

Ramage AG, Tomlinson A. The effect of yohimbine, WY26392 and idazoxan on sympathetic nerve activity. Eur J Pharmacol 1985; 109:153–60.

Reid K, Surridge DHC, Morales A, Condra M, Harris C, Owen J, Fenmore J. Double blind trial of yohimbine in the treatment of psychogenic impotence. Lancet 1987;2:421–3.

Rui H, Gerhardt P, Mevag B, Thomassen Y, Purvis K. Seminal plasma characteristics during frequent ejaculation. Int J Androl 1984;7:119–28.

Sala M, Braida D, Leone MP, Calcaterra P, Monti S, Gori E. Central effect of yohimbine on sexual behavior in the rat. Physiol Behav 1990; 47:165–73.

Schnur SL, Smith ER, Lee RL, Mas M, Davidson JM. A component analysis of the effects of DPAT on male rat sexual behavior. Physiol Behav 1989;45:897–901.

Smith ER, Davidson JM. Yohimbine attenuates aging-induced sexual deficiencies in male rats. Physiol Behav 1990;47:631–4.

Smith ER, Lee RL, Schnur SL, Davidson JM. α_2-Adrenoceptor antagonists and male sexual behavior: I. Mating behavior. Physiol Behav 1987a; 41:7–14.

Smith ER, Lee RL, Schnur SL, Davidson JM. α_2-Adrenoceptor antagonists and male sexual behavior: II. Erectile and ejaculatory reflexes. Physiol Behav 1987b;41:15–9.

Tallentire D, McRae G, Spedding M, Clark R, Vickery B. Modulation of sexual behavior in the rat by a potent and selective α_2-adrenoceptor antagonist, delequamine (RS-15385-197). Br J Pharmacol 1996; 118:63–72.

Winter JC, Rabin RA. Yohimbine as a serotonergic agent: evidence from receptor binding and drug discrimination. J Pharmacol Exp Ther 1992;263:682–9.

Yonezawa A, Ando R, Tadano T, Kisara K, Miyamoto A, Kimura Y. Evidence for central α_2-adrenergic mechanism of clonidine-induced ejaculatory disturbance in dogs. J Pharmacobiodyn 1986;9:1032–5.

Yonezawa A, Kawamura S, Ando R, Tadano T, Nobunaga T, Kimura Y. Biphasic effects of yohimbine on the ejaculatory response in the dog. Life Sci 1991a;48:103–9.

Yonezawa A, Kawamura S, Ando R, Tadano T, Nobunaga T, Kimura Y. Diminution of ejaculatory capacity induced by frequent ejaculation in dogs: prevention and reversal by yohimbine. Andrologia 1991b;23: 71–4.

Yonezawa A, Kawamura S, Ando R, Tadano T, Nobunaga T, Kimura Y. Diminution of ejaculatory capacity in dogs by frequent ejaculation: involvement of central alpha-2 adrenergic mechanism. In: Yoshikawa M, Uono M, Tanabe H, Ishikawa S, editors. New trends in autonomic nervous system research. Amsterdam: Elsevier, 1991c. pp. 505–11.

Yonezawa A, Kawamura S, Ando R, Tadano T, Kisara K, Kimura Y. Chronic clonidine treatment and its termination: effect on penile erection and ejaculation in the dog. Life Sci 1992;51:1999–2007.

Yonezawa A, Kawamura S, Ando R, Tadano T, Kimura Y. Diminution of ejaculatory capacity in dogs by frequent ejaculation: differential effects of yohimbine and pilocarpine. J Tohoku Pharm Univ 1994;41:239–45 (in Japanese).