EVIDENCE FOR CENTRAL $\alpha_2$ — ADRENERGIC MECHANISM OF CLONIDINE-INDUCED EJACULATORY DISTURBANCE IN DOGS

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In order to clarify the central mechanism of clonidine (CL)-induced sexual dysfunction such as erectile and ejaculatory disturbances, we examined the effects of intracerebroventricularly (i.c.v.) administered CL on erection and ejaculation in male dogs. CL (0.5–5 $\mu$g/kg) produced a dose-related inhibition of ejaculation but not significant inhibition of erection by the manual stimulation of the penis. Sperm was not found in the urine drawn from the urinary bladder, suggesting that the inhibitory effect of CL on ejaculation was not due to retrograde ejaculation. The ejaculatory disturbance elicited by CL (5 $\mu$g/kg) was antagonized by an $\alpha_2$-adrenoceptor antagonist, yohimbine (1–10 $\mu$g/kg, i.c.v.) in a dose-related manner. In contrast to the effect of yohimbine, it was unaffected by an $\alpha_1$-adrenoceptor antagonist, prazosin (3 and 10 $\mu$g/kg, i.c.v.).

These results indicate that i.c.v. administered CL may selectively inhibit the ejaculatory response, which is presumably mediated through the stimulation of $\alpha_2$-adrenoceptors.

Keywords — sexual dysfunction; ejaculation; erection; clonidine; central $\alpha_2$-adrenoceptor

INTRODUCTION

Clinical investigations have suggested that sexual dysfunction is a relatively common complication of antihypertensive drug therapy. Clonidine (CL), a centrally acting antihypertensive drug, has been also noted to produce sexual dysfunction in both human and experimental animals.1,2) In man, the disorders associated with this drug include impotence, decreased libido and impaired ejaculation. It has been proposed that the sexual dysfunction elicited by CL may be involved with the central effect of the drug.1) However, there has been no systematic study in relation to these disorders. The present study was performed with two aims in mind. The first was to investigate the effects of intracerebroventricularly (i.c.v.) administered CL on penile erection and ejaculation in male dogs. The second was to determine the contribution of $\alpha$-adrenoceptor subtypes to the effects elicited by i.c.v. administered CL, using selective $\alpha$-adrenoceptor antagonists.

Twenty-seven male adult mongrel dogs (9–20 kg) were used. The animals were maintained individually in a dog’s room under controlled light (14 h light, 10 dark, light on at 6:00) and constant temperature (22–24 °C) and humidity (50–60%). Under pentobarbital anaesthesia (30 mg/kg i.p.), a stainless steel cannula with an external diameter of 1.2 mm was stereotaxically implanted into the lateral ventricle according to the atlas of Lim et al.3) The cannula was lowered to a depth of approximately 15 mm below the dura, the depth being determined by monitoring pressure changes in the cannula. The cannula was fixed to the skull with dental cement. Before use in the experiments, the implanted animals were allowed to recover for at least 1 week. CL (Sigma) was dissolved in a volume of 0.01 ml/kg of isotonic saline (also used as control solution) and i.c.v. injected through an internal cannula (external diameter 0.8 mm) protruding from the guide cannula by 0.5 mm (injection rate 0.1 ml/min). Yohimbine (YOH, Sigma) and prazosin (PRZ, Pfizer Taito) were dissolved in the same volume of distilled water and injected in the same route.
The observational conditions were similar to those described previously. The experimental sessions on a given animal were repeated at 7–10 d intervals. The changes of penile erection and ejaculation by manual stimulation (approximately 5 min) of the penis were observed 10 min, 1, 3, 5 and 24 h after i.c.v. administration of CL. Penile erection and ejaculation were given one of four scores according to the grade of occurrence based on the following criteria: erection; 3 — perfect erection, 2 — weak, 1 — slight increase of the size of glans penis and exposure of the glans, 0 — no reaction; ejaculation; 3 — frequent ejaculation, 2 — several, 1 — few, 0 — no reaction. The scores of the changes of erection and ejaculation after i.c.v. administration of the drugs were compared. To examine retrograde ejaculation, the animals treated with CL (5 μg/kg i.c.v.) were anesthetized (pentobarbital 30 mg/kg i.p.) after the experiments and urine was drawn from the bladder with a syringe. The urine was centrifuged at 500 rpm, for 5 min and observed for detection of sperm with a microscope (×200). The interactions between CL and α-adrenoceptor antagonists were statistically analyzed by an analysis of variance (ANOVA) followed by Duncan's new multiple range test.

Figure 1 shows the time course changes of the grade of both erection (A) and ejaculation (B) after i.c.v. administration of CL. CL, at doses of 0.5, 1.5 and 5.0 μg/kg, was without significant effect on erection at various observation times. In contrast to the effect on erection, CL produced a dose-related inhibition of ejaculation. The highest dose of CL gave the maximal inhibitory effect on ejaculation 1 h post-injection with recovery in about 5 h. Furthermore, sperm was not found in the urine 1 h post-injection, suggesting that the inhibitory effect of CL on ejaculation was not due to retrograde ejaculation. I.c.v. administration of control solution was without effect on both sexual functions.

Figure 2 shows the effects of i.c.v. administration of two selective α-adrenoceptor antagonists, YOH (α1) and PRZ (α2), on the ejaculatory disturbance elicited by CL (5 μg/kg). Pretreatment with YOH (1–10 μg/kg) which had no effects on erection and ejaculation by itself, antagonized the CL-induced ejaculatory disturbance in a

**FIG. 1. The Effects of Intracerebroventricular Administration of Clonidine (0.5–5.0 μg/kg) on Penile Erection (A) and Ejaculation (B) by Manual Stimulation of Penis**

Each value represents the mean ± S.E.M. of the score in 4–6 animals. I.c.v. administered saline solution was without effect on both sexual functions at all observation times (data not shown).

∇, 0.5 μg/kg; ●, 1.5 μg/kg; ○, 5.0 μg/kg.

**FIG. 2. The Effects of Pretreatment with α1-(Prazosin; PRZ) and α2-(Yohimbine; YOH) Adrenoceptor Antagonists on the Ejaculatory Inhibition Induced by Clonidine (CL; 5 μg/kg i.c.v.)**

The effects were determined 60 min after clonidine injection, while the effects of each antagonist itself and saline (SAL) were determined 100 min after the i.c.v. injection. Each antagonist was injected 20 min before the i.c.v. administration of CL. Each value represents the mean ± S.E.M. of the score in 4–6 animals. The symbol a) indicates \( p < 0.01 \) compared to the CL (5 μg/kg i.c.v.)-treated group.
dose-related manner. However, pretreatment with PRZ had no effect on the ejaculatory disturbance at the two doses tested (3 and 10 μg/kg).

The present experiment clearly demonstrates that i.c.v. administration of CL to male dogs produced a dose-related inhibition of ejaculation but had no significant effect on erection. Our previous results showed that systemic administration of CL significantly inhibited both ejaculation and erection. The different results from i.c.v. and systemic administrations on erection suggest that CL-induced erectile disturbance may be due to peripheral rather than central effect of the drug. Furthermore, this disturbance is not secondary to a change in blood pressure since i.c.v. administration of CL significantly lowers blood pressure in dogs.

Previous studies indicated that chemical and surgical sympathectomy of the male accessory organs produced no significant effect on the penile erection in dogs and rats. Therefore, it seems apparent that CL-induced erectile disturbance is not due to the inhibition of noradrenaline release from sympathetic nerve endings.

It is generally accepted that penile erection is mediated primarily via a reflex response through the parasympathetic nervous system. The erectile disturbance elicited by systemic CL may result from an acute impairment in parasympathetic nerve transmission, since the drug inhibits the release of acetylcholine from cholinergic nerve endings.

In contrast to its effect on erection, the fact that i.c.v. administration of CL effectively inhibited the ejaculatory response suggests that the site of this disturbance elicited by systemically administered CL may be partially involved in the central nervous system. There was no evidence of seminal fluid from regurgitation into the urinary bladder after i.c.v. administration of CL, suggesting that the inhibitory effect on ejaculation results from functional impairment of the mechanism underlying seminal emission and/or ejaculation, without acting on the closure of the internal urethral orifice.

In the present experiment, the ejaculatory disturbance was antagonized dose-dependently by centrally administered YOH, an α2-adrenoceptor antagonist, but not PRZ, an α1-adrenoceptor antagonist. These results indicate that α-adrenoceptor mainly mediating the ejaculatory disturbance elicited by i.c.v. administered CL is of the α2-subtype, which may be concerned with central regulation of the ejaculation. This view was supported by the finding that YOH given alone facilitated ejaculation as well as other sexual components in sexually inactive male rats. Additionally, our previous results indicated that i.c.v. administered α-methylnoradrenaline, an α2-adrenoceptor agonist had the same effect with CL on both sexual functions. Since it is well known that i.c.v. administered α2-adrenoceptor agonists produce a significant fall in blood pressure, it cannot be denied that the α2-adrenoceptor agonists which can induce ejaculatory disturbance may be secondary to the change in blood pressure. However, the hypotensive effect of i.c.v. administered CL was equipotently attenuated by either YOH or PRZ administered i.c.v. in cats. Therefore, it seems that CL-induced ejaculatory disturbance and hypotensive effect may, at least in part, be regulated by a different neuronal mechanism in the central nervous system. Further studies are needed to clarify the propriety of this consideration.

In conclusion, the present experiment suggests that i.c.v. administration of CL may selectively inhibit the ejaculatory but not erectile response, which is presumably mediated through the stimulation of α2-adrenoceptors.

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