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Pressor Action of Physostigmine in the Rabbit

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ABSTRACT

The effect of physostigmine (PS), which has been shown to act on the muscarinic receptors in the brains of the rat, dog and cat, on the arterial blood pressure (BP) was investigated in urethane-anesthetized rabbits.

Intravenous (iv) PS, 25~300 μg/kg, caused little change in BP. However, after treatment of rabbits with either of chlorisondamine (CS), hexamethonium, intracerebroventricular (icv) clonidine, icv xylazine and icv reserpine iv PS produced a pressor response. Spinalization of the rabbit also caused iv PS to increase BP.

The pressor effect of iv PS in CS-treated rabbits was markedly reduced after prazosin or pirenzepine. Iv PS inhibited the pressor response to McN-A-343 in CS-treated and in spinal rabbits; alternately during the infusion of McN-A-343 iv PS failed to produce the pressor response. The pressor response to DMPP was not affected by iv PS.

Icv PS, 12~200 μg/kg, produced a pressor response which was accentuated after CS-treatment. This pressor effect was inhibited, though not complete, by prazosin or by pirenzepine. A simultaneous treatment of rabbits with both [Sar^1, Ala^8]-angiotensin II, an angiotensin II antagonist, and prazosin or pirenzepine almost completely abolished the pressor effect of icv PS, whereas the angiotensin II antagonist did not enhance the inhibitory effect of pirenzepine and prazosin on the pressor response to iv PS. Icv pirenzepine blocked the pressor response to icv PS without affecting that to iv PS.

The present results show that the pressor response to iv PS in CS-treated and in spinal rabbits arises from stimulation of the muscarinic receptors in the sympathetic ganglia, whereas the pressor response by icv PS via activation of the muscarinic receptors in the brain which causes an enhancement in the outflow of sympathetic discharge and angiotensin. The results also suggest that iv PS is unable to produce a pressor response in the rabbit unless the sensitivity of the gangionic muscarinic receptors is altered by ganglionic nicotinic blockade, by the decrease of central sympathetic outflow on the sympathetic ganglia or by spinalization.

Key Words: Rabbit blood pressure, Muscarinic receptors, Physostigmine, McN-A-343, Pirenzepine, [Sar^1, Ala^8]-angiotension II.

INTRODUCTION

It has been shown that physostigmine (PS) given either intravenously or intracerebroventricularly evokes a pressor response in the rat (Varagic 1955; Brezenoff 1973; Brezenoff & Rusin 1974; Brezenoff *et al.*, 1982; Caputi *et al.*, 1980; Taira & Enero 1989). The dog too responds with a rise in blood pressure to intravenous (iv) and intracerebroventricular (icv) PS (Hilton 1960; Lang and Rush 1973; Sinnha *et al.*, 1967; Laubie *et al.*, 1974). In the cat, however, injection of PS into the vertebral artery produces hypotension (Wildt & Porsuis 1981a).

As to the mechanism of the pressor response in the rat, stimulation of muscarinic receptors in the central nervous system which mediates an increase in peripheral sympathetic activity has been shown (Varagic & Vojvodic 1962; Brezenoff and Rusin 1974; Buccafusco & brezenoff 1979; Caputi *et al.*, 1980; Taira and Enero 1985). In the dog the similar mechanism—participation of central muscarinic receptors—has been suggested (Lang & Rush 1973; Sinnha *et al.*, 1967; Laubie *et al.*, 1974). The hypotension in the cat has been attributed (Wildt & Porsuis 1981a; 1981b) to the central stimulation of muscarinic receptors which may give rise to a release of endogenous norepinephrine, resulting in a hypotensive

effect as described for clonidine.

In this study the effect of PS on the arterial blood pressure is investigated in the rabbit.

METHODS

Rabbits of either sex, weighing between 1.8 and 2.2kg, were anesthetized with urethane (1 g/kg, sc). The trachea was cannulated. The animal was fastened prone with its head extended.

Blood pressure (BP) was taken from the left femoral artery and recorded on a physiograph. Blood pressure was expressed as mean arterial pressure (mean ± SE).

Intravenous (iv) injections were made into the left ear vein in a volume of 0.5 ml/kg, and intravenous infusion into the right ear vein at a rate of 0.1 ml/kg/min.

Intracerebroventricular (icv) injections were performed through a thin polyethylene tube (3cm long and 1mm diameter) inserted into the lateral cerebral ventricle. Drugs were given in a volume of 0.05 ml/kg. The drug solutions were kept at 36~38°C. At the end of each experiment the position of the tube was confirmed by removing the parietal bone and dissecting the brain.

Bilateral vagotomy was performed by cutting the vagal nerve trunks at the level of the neck 1 hr before experiments.

Spinal rabbits were prepared by transecting the cervical cord at the level of C1 under artificial respiration.

Drugs. Physostigmine sulfate (Merck), chlorisondamine chloride, (Ciba), hexamethonium bromide (Sigma), clonidine HCl (Boehringer Ingelherim), xylazine HCl (Bayer), reserpine (Ciba), prazosin HCl (Pfizer), pirenzepine dihydrochloride (Sigma), norepinephrine bitartrate (Sigma), McN-A-343 (RBI), DMPP (Sigma), angiotensin II (Sigma), [Sar^1, Ala^8]-angiotension II (Vega Biochemical), methoxamine HCl (Sigma) and yohimbine HCl (Merck) were used. The drugs, except reserpine, prazosin, norepinephrine and yohimbine, were dissolved in saline. The solution of reserpine (2.5 mg/ml) was prepared by dissolving in a mixture of benzylacohol, citric acid and Tween 80 which was further diluted with distilled water. Prazosin (1 mg/ml) was solubilized in 5% (W/V) dextrose containing 5% (W/V) glycerin. Norepinephrine (5 mg/ml) and yohimbine (5 mg/ml) were dissolved in acid saline and distilled water, respectively. These solutions were diluted with saline before use.

The Student's *t*-test was used to analyse the results statistically.

RESULTS

Responses to iv physostigmine

1) No prior treatment

In rabbits without any pretreatment, PS in doses ranging from 25 to 200 μg/kg produced no significant change in BP.

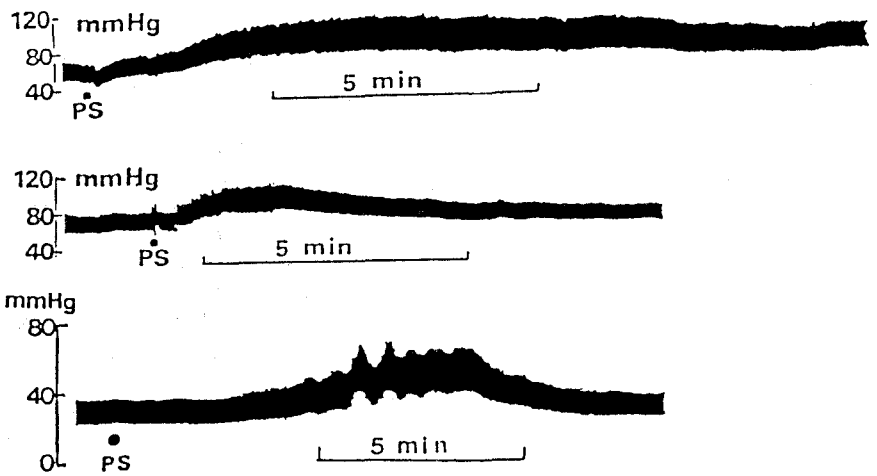

Fig. 1. Increase in arterial blood pressure (BP) by iv physostigmine (PS) in a chlorisondamine (CS)-treated (upper), a clonidine-treated (middle), and a spinal rabbit (lower). The dose of PS was 100 μg/kg in upper and middle, 500 μg/kg in lower.

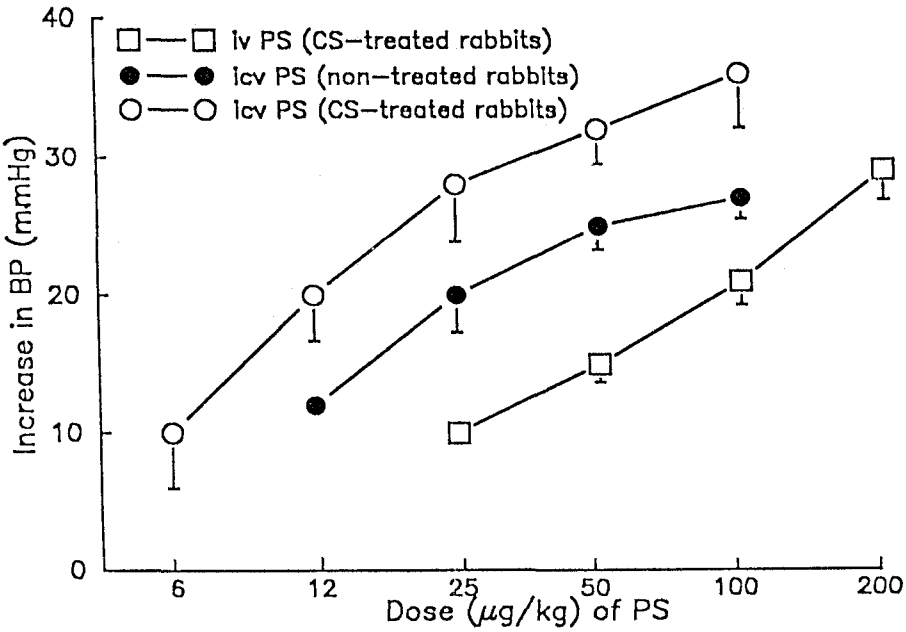

Fig. 2. Increase in BP (Y-axis) by iv and icv PS (X-axis) in rabbits. Each point (mean ± SE) was obtained from 6 to 18 rabbits.

2) Pretreatment with ganglionic nicotinic blockers

(1) Chlorisondamine-treated rabbits. In hypotensive state (50~80 mmHg) following administration of chlorisondamine (CS, 0.4 mg/kg) PS elicited a dose-related increase in BP (Fig. 2). BP began to rise gradually, reached a plateau at about 3~4 min after an injection, was sustained for a period of 5 to 10 min, and then slowly declined to the initial level in about 10 min (Fig. 1). The pressor response to 100 and 200 μg/kg PS was reproducible when injections were made at interval of about 1.5 hr, whereas the response became weaker or was abolished when repeated at shorter intervals—30 min or less. In the present experiments 0.4 mg/kg of CS was given every 2 hr in order to maintain the state of ganglionic nicotinic blockade.

(2) Hexamethonium-treated rabbits. PS elicited a pressor response in the hypotensive state produced by hexamethonium (10 mg/kg) as in CS-treated rabbits. The magnitude and pattern of the BP rise were the same as those in CS-treated ones.

3) Pretreatment with some agents which produce a decrease in the central sympathetic outflow

(1) Clonidine. This drug has been shown to act on the α_2-adrenoceptors in the brain stem to cause a decrease in the central sympatehtic outflow (Reviews by Van Zwieten, 1975). In 10 rabbits BP was lowered to 53 ± 3.7 mmHg at about 10 min after icv administration (15 μg/kg) from the initial level of 88 ± 2.7 mmHg. In this state all the rabbits tested responded with an increase in BP (15 ± 2.1 mmHg) to 100 μg/kg PS (Fig. 1). The increase appeared gradually, reaching a maximum within 1 to 2 min, was maintained for a period of 2 to 3 min, and then slowly declined to the preinjection levels.

(2) Xylazine. It was shown that xylazine and clonidine affect rabbit BP in a similar way (Kim 1985). To substantiate the pressor action of PS in clonidine-treated rabbits, experiments were conducted in 4 rabbits treated with icv xylazine (0.2 mg/kg). In the hypotensive state (34 ± 4.2 mmHg) induced by xylazine PS (100 μg/kg) produced a rise of BP (18 ± 5.0 mmHg). The pattern of the rise was almost the same as in clonidine-treated animals.

(3) Reserpine. When icv reserpine (0.1 mg/kg) was given BP did not show significant change until about 2 hr after injection, but then tended to decrease, downed to 75 ± 6.2 mmHg (n = 5) at about 3 hr after the administration. In this state an injection of PS (100 μg/kg) elicited an increase in BP (16 ± 5.0 mmHg). The pattern of the increase was similar to that in clonidine-treated rabbits.

Table 1. Effects of prazosin, pirenzepine, [Sar¹, Ala⁸]-angiotensin II, prazosin plus [Sar¹, Ala⁸]-angiotensin II, and pirenzepine plus [Sar¹, Ala⁸]-angiotensin II on the pressor responses to iv and icv PS in CS-treated rabbits

	n	iv PS (100 μg/kg)		n	icv PS (50 μg/kg)	
		initial	increase in BP		initial	increase in BP
			Prazosin (100 μg/kg) alone			
before	4	60±3.5	25±3.8	6	54±2.2	29±2.6
after		44±2.0	8±1.6@		43±4.4	18±2.2@
			Pirenzepine (30 μg/kg) alone			
before	6	50±3.6	23±2.5	4	50±3.2	26±2.2
after		42±0.7	10±2.4@		45±1.8	20±4.4^{NS}
			Pirenzepine (100 μg/kg) alone			
before	5	57±5.1	27±3.2	6	54±4.0	30±37
after		50±4.8	11±1.7@		46±4.7	20±3.9^{NS}
			Pirenzepine (300 μg/kg) alone			
before	4	56±4.2	24±2.6	4	50±3.0	30±2.9
after		46±5.6	5±1.7@		41±2.4	10±2.2@
			[Sar¹, Ala⁸]-angiotensin II (5 μg/kg/min) alone			
before	4	52±4.2	31±4.0	4	57±3.6	26±2.5
after		43±5.0	24±6.5^{NS}		56±3.1	23±4.4^{NS}
			Prazosin (100 μg/kg) plus [Sar¹, Ala⁸]-angiotensin II (5 μg/kg/min)			
before	4	58±4.0	34±3.8	4	56±3.3	27±2.2
after		40±4.2	10±2.2@		42±3.6	9±0.5@*
			Pirenzepine (100 μg/kg) plus [Sar¹, Ala⁸]-angiotensin II (5 μg/kg/min)			
before	4	52±4.2	31±3.0	4	57±3.6	26±2.5
after		39±5.4	13±3.3@		53±3.1	3±1.9@**

Numbers: mean ± SE (mmHg)

NS: nonsignificant difference from the corresponding "before"-value; @: significant difference from the corresponding "before" value ($p<0.01$). * and ** are significantly different from the "after" value in prazosin alone and that in pirenzepine alone, respectively ($p<0.01$).

4) Spinal rabbits

BP of spinal rabbits ranged from 25 to 40 mmHg. PS below 100 μg/kg elicited little change in BP, 200 μg/kg produced a negligible increase (n = 5, 5 ± 3.3 mmHg), and 500 μg/kg an increase of 13 ± 4.1 mmHg (n = 12). BP showed very gradual rise after injection, reaching a peak within 5 to 8 min, was sustained for a period of 3 to 5 min, and then declined (Fig. 1). CS-pretreatment did not potentiate the response to PS

5) Relations with peripheral sympathetic system

In CS-treated rabbits, response to 100 μg/kg PS was examined at 3 to 10 min after injection of 100 μg/kg prazosin, and after 30, 100 and 300 μg/kg of pirenzepine. As shown in Table 1 both drugs markedly reduced the pressor response.

With this dose of prazosin the increase of BP by norepinephrine (1 or 5 μg/kg) was reduced to 14 ± 1.6 mmHg from the control increase of 38 ± 2.6 mmHg (n = 4). The inhibitory effect of pirenzepine on the increase of BP by McN-A-343 was shown by Yoo (1989) in this laboratory.

6) Interaction of physostigmine and McN-A-343

(1) CS-treated rabbits. In order to find a hint to the site of action of PS, effect of PS on the pressor response to McN-A-343 was examined. McN-A-343 was injected when the elevated BP by PS almost declined to the preinjection levels. As seen in Fig. 3 the dose-response curves of McN-A-343 were shifted to the right parallelly, indicating competitive inhibition by PS of response to McN-A-343.

Alternately the response to PS was examined under the influence of McN-A-343. An infusion of

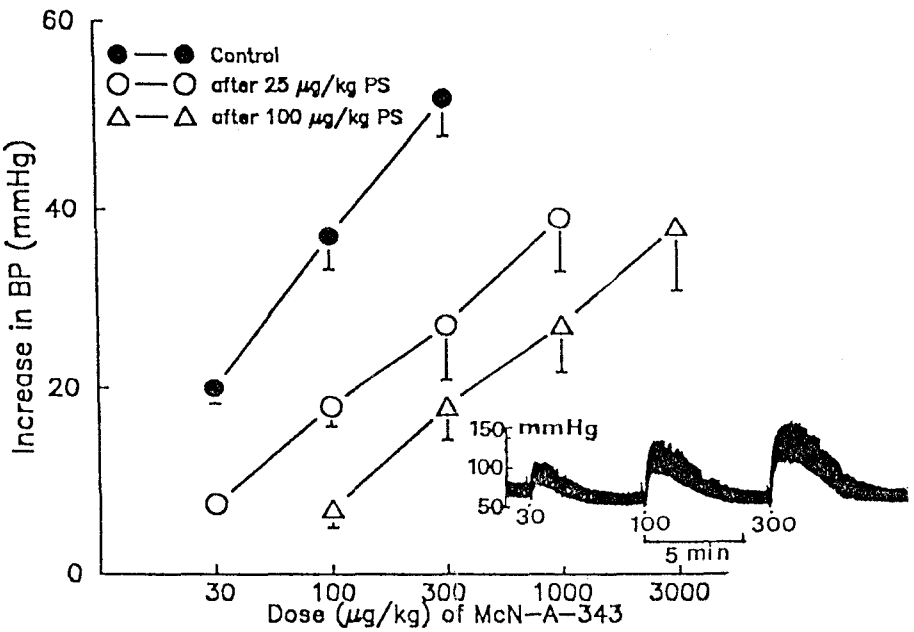

Fig. 3. Antagonistic effect of iv PS (25 and 100 μg/kg) on the pressor response (Y-axis) to McN-A-343 (X-axis) in CS-treated rabbits. Each point (mean ± SE) was obtained from 4 to 18 rabbits. Right lower: A tracing of BP in a CS-treated (control)rabbit, showing pressor responses to iv McN-A-343 (30, 100 and 300 μg/kg) given at interval of 15 min.

McN-A-343 at a rate of 100 μg/kg/min caused a rise of BP to 70~100 mmHg within 2 to 3 min from the initial levels of 57~69 mmHg (n = 4), and then BP fell gradually to the preinjection levels, in spite of continued infusion. At about 10 to 15 min after the start of the infusion, an injection of PS 100 μg/kg did not produce a pressor response in all 4 rabbits.

(2) Spinal rabbits. These responded with a rise of BP to McN-A-343 as did to PS : 30 μg/kg produced a rise of 12 ± 3.2 mmHg (n = 7), and 100 μg/kg 26 ± 1.9 mmHg (n = 30). McN-A-343, however, produced a much smaller rise after PS-treatment; 100 μg/kg McN-A-343, given when the elevated BP by PS almost returned to the initial level, caused a rise of 16 ± 2.9 mmHg (n = 8) after 100 μg/kg PS, and 7 ± 13 mmHg (n = 8) after 500 μg/kg PS.

7) Effect of physostigmine on the pressor response to DMPP

Inorder to test whether PS acts on nicotinic receptors, effect of PS on the pressor response to DMPP was examined.

(1) Whole rabbits. In vagotomized rabbits (It was noted in our laboratory that the rabbit showed more pronounced pressor responses to DMPP in vagotomized state), DMPP (200 μg/kg) produced an increase of BP preceded by a slight fall. The increase was not significantly affected following PS-treatment (50 μg/kg); in 4 rabbits the control rise was 41 ± 4.0 mmHg, the rise after PS 31 ± 6.3 mmHg.

(2) Spinal rabbits. The pressor response to 100 μg/kg DMPP before and after PS (200 μg/kg) was 40 ± 5.9 mmHg and 33 ± 5.0 mmHg (n = 4), respectively, showing little difference.

Responses to icv physostigmine

1) No prior treatment

Icv PS (12~100 μg/kg) caused a dose-related pressor response. With 100 μg/kg PS, BP began to rise in about 2 min after an injection, reaching a plateau at about 5 min, was sustained for a period of 5 to 10 min, and then gradually declined (Fig. 4). With lower doses, the magnitude of the rise in BP was smaller and the duration of the plateau period shorter.

On repeated administrations at interval of about 2 hr, the response was reproducible. In some rabbits the response to the second injection was somewhat bigger than that to the first one, but in all rabbits tested the resonses to the third and fourth dose were almost the same as that to the second one.

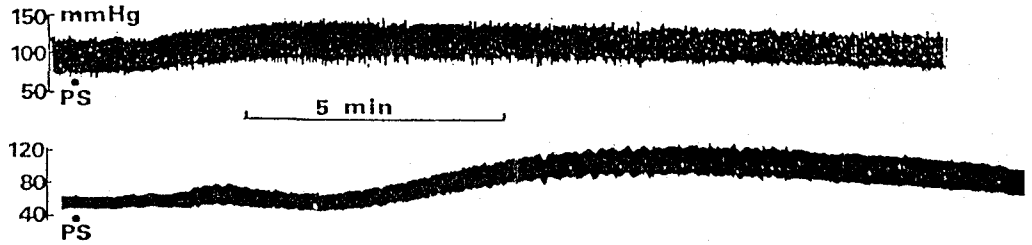

Fig. 4. Increase in BP by icv PS (50 μg/kg) in a rabbit. Upper: before CS (non-treated). Lower: after CS-treatment. Lower panel was obtained 2 hr after upper panel.

2) Pretreatment with a ganglionic nicotinic blocker

In the hypotenisve state following CS (0.4 mg/kg, iv), the magnitude of the pressor response became larger (Fig. 2) but a longer time (about 10 min) was needed to attain the maximum BP rise. In some rabbits a slight rise of BP (about 10 mmHg) was preceded by the sustained rise.

3) Relations with peripheral sympathetic system

As seen in Table 1 prazosin inhibited the pressor response to icv PS as it did the response to iv PS, but the inhibition on icv PS was less pronounced than on iv PS; pirenzepine 30 and 100 μg/kg which markedly reduced the response to iv PS did not reduce the response to icv PS significantly. But raising the dose to 300 μg/kg inhibited the response to icv PS.

Effect of angiotensin II antagonist on the pressor response to PS

Although the results of experiments with prazosin and pirenzepine indicated that the pressor response to PS, icv as well as iv, was related to the activity of the peripheral sympathetic nervous system, it was noted that the inhibitory effect of these two drugs on the response to icv PS seemed to be less potent than on that to iv PS. This could be interpreted as a participation of other factors than the sympathetic system in this pressor response. As there exists evidence for the presence of brain angiotensin II neural system in rats (Changaris *et al.*, 1978; Buccafusco and Serra 1985; Nicoletta *et al.*, 1983), and possible interaction between angiotensin and cholinergic system centrally has been suggested (Elie & Panniset 1970; Nicoletta *et al.*, 1983; Severs & Daniel-Severs 1973), it was attempted to investigate the effect of angiotensin II antagonist, [Sar^1, Ala^8]-angiotensin II (Bravo *et al.*, 1976), on the pressor responses to iv and icv PS.

Procedures of experiments. CS-treated rabbits were used. Responses to angiotensin (2 μg/kg) and PS were checked before and during the infusion of the antagonist (5 μg/kg/min), and then while continuing the infusion prazosin (100 μg/kg) or pirenzepine (100 μg/kg) was injected, and at 3 to 10 min after the injection, responses to PS were rechecked. The interval between injections of PS was 2 hr.

Angiotensin II. In 8 rabbits the control rise of BP was 77 ± 1.4 mmHg. This was reduced to 14 ± 1.3 mmHg during the infusion of the antagonist.

Iv PS. The pressor response to iv PS was not affected by the antagonist. The combination of the antagonist and either of prazosin or pirenzepine produced almost the same degree of reduction in the pressor response as prazosin or pirenzepine alone did (Table 1).

Icv PS. The antagonist was without effect on the pressor response to icv PS, too. However, treatment of rabbits with both the antagonist and prazosin or pirenzepine inhibited the pressor response much more markedly than prazosin or pirenzepine alone did (Table 1).

Effect of icv pirenzepine on the pressor response to PS

As shown in Table 2, icv pirenzepine almost abolished the pressor response to icv PS, whereas it did not affect the response to iv PS. The pressor responses to icv methoxamine which has been shown to act on central α_1-adrenoceptors (Kim *et al.*, 1981) and to icv yohimbine acting on central α_2-adrenoceptors (Cho *et al.*, 1989) were not inhibited by icv pirenzepine, indicating the selectivity of this drug on the muscarinic receptors.

Table 2. Effects of icv pirenzepine on the pressor responses to PS, methoxamine and yohimbine in rabbits

Pressor agents	n	control		after pirenzepine	
		initial	increase in BP	initial	increase in BP
		icv pirenzepine (10 μg/kg)			
PS (icv) 50 μg/kg	5	59±4.5	30±2.8	65±1.4	16±4.2*
		icv pirenzepine (25 μg/kg)			
PS (icv) 50 μg/kg	4	60±2.6	28±3.7	53±3.1	4±1.6**
PS (iv) 200 μg/kg	4	57±3.3	30±5.4	47±5.6	27±3.4^{NS}
Methoxamine (icv) 1 mg/kg	4	79±3.5	32±6.5	73±3.1	34±7.2^{NS}
Yohimbine (icv) 125 μg/kg	4	93±3.9	17±3.7	83±2.2	19±2.9^{NS}

Numerals: mean±SE (mmHg)

NS denotes nonsignificant difference from the corresponding control increase in BP; significant difference is denoted by * ($p<0.05$) and ** ($p<0.01$). The pressor responses to PS were examined in CS-treated rabbits.

DISCUSSION

Site of pressor action of iv PS

Iv PS produced pressor effect after treatment of rabbits with CS, a ganglionic nicotinic receptor antagonist, and the effect was markedly reduced after either pirenzepine, a ganglionic muscarinic receptor antagonist or prazosin, an α-adrenoceptor antagonist. These suggest that PS activates the peripheral sympathetic pathways through the ganglionic muscarinic receptors. PS competitively inhibited the pressor response to McN-A-343, a ganglionic muscarinic receptor agonist, of CS-treated and of spinal rabbits, and McN-A-343 blocked the pressor response to PS in CS-treated rabbits. These findings further support that iv PS acts on the muscarinic receptors where McN-A-343 acts.

PS thus exerts pressor activity by acting on the same site as McN-A-343 does; however, the patterns of their responses are quite dissimilar. The response to McN-A-343 was more intensive but shorter in duration than the PS response (Fig. 1 and Fig. 3). These suggest that PS acts on the ganglionic muscarinic receptors as a partial agonist-antagonist, resulting in the inhibition of the McN-A-343 response. On the other hand, an infusion of the small dose of McN-A-343 (100 μg/kg/min) caused a moderate increase in BP (20~30 mmHg) but the increase decayed gradually in spite of the continued infusion, during which PS failed to produce a pressor response. This finding suggests that McN-A-343, when it interacts with the receptors persistently, acts as an antagonist for the muscarinic receptors. Such antimuscarinic activity of McN-A-343 is shown in the rat adrenal medulla (Wakade *et al.*, 1986) and in the isolated rabbit intestine (unpublished data in our laboratory).

The pressor response to DMPP, a ganglionic nicotinic receptor agonist, of whole and of spinal rabbits was little affected by PS, indicating the selectivity of PS on the muscarinic receptors in the ganglia.

The fact that icv pirenzepine which almost completely blocked the response to icv PS did not affect the iv PS response (Table 2) indicates that iv PS does not act centrally in producing this effect.

Site of pressor action of icv PS

In contrast to the inability of iv PS to produce a pressor response in rabbits without nicotinic ganglionic blockade, icv PS elicited a pressor response and the amount of icv PS needed to elicit this response was much smaller than that of iv PS in CS-treated rabbits (Fig. 2), indicating the pressor response to icv PS being central in origin. The fact that icv pirenzepine selectively and almost completely abolished the pressor response to icv PS and that the pressor effect was not reduced by CS but inhibited, though not complete, by iv pirenzepine and by iv prazosin suggest that icv PS acts selectively on the central muscarinic receptors which mediates an increase in peripheral sympathetic activity through the stimulation of ganglionic muscarinic pathway. In the rat and dog, too, the central muscarinic receptors have been shown to be the site of pressor action of PS and other cholinomimetics (Brezenoff & Rusin 1974; Buccafusco & Brezenoff 1979; Caputi *et al.*, 1980; Taira & Endo 1985; Lang & Rush 1973; Laubie

et al., 1974) and the central muscarinic pressor effect in the rat has been shown to be mediated by enhanced sympathetic outflow (Stamenovic & Varagic 1970; Varagic & Vojdovic 1962; Buccafusco & Brezenoff 1979).

The present results show that pirenzepine 30 and 100 μg/kg which produced a marked inhibition of the pressor effect of iv PS did not affect the icv PS response significantly, but that a simultaneous treatment of rabbits with both [Sar^1, Ala^8]-angiotensin II and 100 μg/kg of pirenzepine or prazosin almost completely abolished the icv response (Table 1). Thus it is suggested that in rabbits, in addition to enhanced sympathetic activity, the increase in BP by the central muscarinic stimulation may associate with an activation of the angiotensin system. In the present experiment, however, the angiotensin antagonist alone failed to inhibit the icv PS response; this would be probably due to a minor role in eliciting this response of the angiotensin system compared with the cholinergic system, and also to a complementary interaction of the two systems. In contrast to this finding in the rabbit, it has been shown in the rat that the brain renin-angiotensin systme does not participate in the cardiovascular effect induced by cholinergic stimulation in the brain (Nicoletta *et al.*, 1983). On the other hand, it has been reported that in the cat central angiotensin can enhance the release of acetylcholine in the brain (Elie & Panniset 1970) and that in the rat the central pressor effect of angiotensin is mediated through brain acetylcholine acting on central muscarinic receptors (Nicoletta *et al.*, 1983). Icv atropine has also been reported to block drinking behaviour in rats after subsequent administration of angiotensin II (Severs & Daniel-Severs 1973). These data seem to suggest the possible interaction between angiotensin and the cholinergic system centrally.

The present report demonstrates that even though both iv and icv injection of PS evoke the same responses, the mechanisms involved in these effects are different. The finding that the pressor responses to iv and icv PS occurred via completely different pathways has been reported in rats (Brezenoff 1973).

Does PS act directly on the muscarinic receptors?

From the data available in the present study, it is difficult to state whether iv and icv PS act directly on the muscarinic receptors or whether they act through endogenous acetylcholine. The fact that iv PS discriminated the muscarinic receptors and the nicotinic receptors in the ganglia by inhibiting the McN-A-343's effect without affecting the DMPP's may suggest the direct action of iv PS, since it is not conceivable that endogenous acetylcholine could differentiate the two receptors. The finding that PS and other cholinesterase inhibitors act directly on acetylcholine receptors has been reported (Pascuzzo *et al.*, 1983; Slater *et al.*, 1986; Sadoshima *et al.*, 1988; Kim *et al.*, 1990). By contrast, it has been shown that acetylcholine in brain mediates the hypertensive response to PS in rats (Brezenoff & Giuliano 1982; Brezenoff & Rusin 1974).

Others

Without any pretreatment of rabbits, iv PS did not produce a pressor response in contrast to a pressor response in rats and dogs (Varagic 1955; Hilton 1960). As demonstrated in the present study, the pretreatment of rabbits with either of CS, hexamethonium, clonidine, xylazine, reserpine, and spinalization of rabbits enabled iv PS to elicit a pressor response. In other words, either of the block of ganglionic nicotinic receptors, or the decrease of central sympathetic outflow to the sympathetic ganglia, or the removal of tonic influence of the brain on the spinal cord seemed to contribute to the elicitation of the pressor effect by iv PS. These suggest that sensitivity of the muscarinic receptors in the sympathetic ganglia can be altered by reducing the activity of the nicotinic receptors in the ganglia. A similar finding has been shown with a sympathetic muscarinic agonist McN-A-343 (Yoo 1989). The inhibitory effect of nicotinic synaptic potentials on the muscarinic excitatory transmission in the sympathetic ganglia has been suggested (Brown 1983; 1984). Accordingly,the inability of iv PS as well as of McN-A-343 to produce a pressor effect may be due to too low muscarinic synaptic activity in rabbits, compared with that in rats and dogs.

PS fails to produce a pressor response in spinal rats and the pressor response to iv PS in the rat arises from an activation of central nervous sympathetic mechanisms (Gokhale *et al.*, 1964, Varagic 1955; Lesic & Varagic 1961). These indicate the difference in the action mechanisms of PS between rats and rabbits, and also suggest the difference in the characteristics of the blood-brain barrier system between the two species.

Conclusions

In rabbits, iv PS failed to produce a pressor reponse unless the sensitivity of the ganglionic muscarinic receptors is altered by ganglionic nicotinic

blockade, by the decrease of central sympathetic outflow on the sympathetic ganglia or by spinalization. The pressor response to iv PS in CS-treated and in spinal rabbits arises from stimulation of the musacrinic receptors in the sympathetic ganglia, whereas the pressor response by icv PS via activation of the muscarinic receptors in the brain which causes an enhancement in the outflow of sympathetic discharge and angiotensin.

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= 국문초록 =

토끼에 있어서의 Physostigmine의 혈압상승작용

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흰쥐, 개, 고양이의 뇌내의 머스커린수용체에 작용함이 알려져 있는 physostigmine(PS)의 동맥혈압에 미치는 효과를 urethane마취토끼에서 조사하였다.

정맥내(iv) PS 25~250μg/kg은 혈압변동을 일으키지 않았다. 그러나 토끼를 chlorisondamine(CS), hexamethonium, 뇌실내(icv) clonidine, icv xylazine, icv reserpine으로 처리후 또는 척수이단후에는 승압반응을 일으켰다.

CS처리토끼의 iv PS승압반응은 prazosin 또는 pirenzepine처리후에는 현저히 약화되었다. Iv PS는 CS처리나 척수이단토끼에서 일어나는 McN-A-343의 승압효과를 억제하였고 또 McN-A-343주입시에는 iv PS는 승압을 일으키지 않았다. DMPP의 승압효과는 iv PS의 영향을 받지 않았다.

Icv PS 12~100μg/kg은 승압반응을 일으켰고 이는 CS처리로 강화되었다. 이 승압효과는 완전치는 않으나 prazosin 또는 pirenzepine으로 억제되었다. Angiotensin II 길항약인(Sar^1, Ala^8)-angiotensin II와 prazosin 또는 pirenzepine으로 토끼를 처리할때는 icv PS승압효과는 거의 볼 수 없었다. 그러나 이 angiotensin II 길항약은 prazosin, pirenzepine의 iv PS승압반응에 대한 억제효과는 항진시키지 않았다. Icv pirenzepine은 icv PS승압반응은 차단하였으나, iv PS승압효과에는 영향을 미치지 않았다.

본실험성적은 CS처리 및 척수이단토끼에서 볼 수 있는 iv PS승압은 교감신경절의 머스커린수용체의 흥분으로 일어나고, icv PS승압은 뇌내의 머스커린수용체의 흥분으로 교감신경계 및 angiotensin계의 활성도가 높아져서 일어남을 가리키고 있다. 또한 토끼에서는 교감신경절니코틴수용체차단, 교감신경절에 미치는 중추 교감신경의 지배력의 감소 또는 척수이단등으로 교감신경절 머스커린수용체의 감수성이 바꾸어지지 않은한 iv PS는 승압반응을 일으키지 못함을 시사하고 있다.