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Pressor Action of Intracerebroventricular Nicotine and Muscarine in the Rabbit

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ABSTRACT

When administered intracerebroventricularly (icv), cholinergic nicotinic agents, nicotine and DMPP, as well as cholinergic muscarinic agents, muscarine and bethanechol, produced pressor responses in urethane-anesthetized vagotomized rabbits. The response patterns to nicotine and to DMPP were similar, while the bethanechol response resembled the muscarine pattern. The pressor response to nicotine and DMPP was markedly inhibited by icv mecamylamine but not by icv pirenzepine, whereas the response to muscarine and bethanechol was inhibited by icv pirenzepine but not by icv mecamylamine, suggesting that both nicotinic and muscarinic receptors in the brain are involved in the action.

Intravenous pretreatments of animals with regitine, reserpine, enalapril, saralasin, both regitine and enalapril, both regitine and saralasin, SK&F-100273 did not prevent the pressor response to nicotine and muscarine. Iv pretreatments with both regitine and SK&F-100273 inhibited the nicotine response without affecting the muscarine response, whereas pretreatments with three agents, regitine, enalapril and SK&F-100273, inhibited the muscarine response.

The nicotine-induced elevated blood pressure as well as the muscarine-induced were lowered by regitine but not by enalapril or by SK&F-100273. Enalapril was without effect on the nicotine hypertension in rabbits treated with regitine or both regitine and SK&F-100273, whereas SK&F-100273 lowered the nicotine hypertension in regitine-treated animals. Enalapril did not enhance the lowering effect of SK&F-100273 in regitine-treated ones, nor did it cause a fall of the muscarine hypertension induced in regitine-treated rabbits, but it did lower the blood pressure in animals treated with both regitine and SK&F-100273. Likewise, SK&F-100273 did not cause a fall of the muscarine hypertension induced in regitine-treated rabbits, but it did lower the blood pressure in animals treated with both regitine and enalapril.

These data suggest that the nicotine-induced hypertensive state is related to at least two systems in the periphery—sympathetic and vasopressin, whereas in the muscarine-induced hypertensive state three systems in the periphery are involved, i.e., the sympathetic, vasopressin and angiotensin system.

The hypotensive effect of regitine on basal arterial blood pressure levels of rabbits was not influenced by pretreatment with either of enalapril or SK&F-100273, but significantly potentiated by treating with both enalapril and SK & F-100273, suggesting participation of the sympathetic and the renin-angiotensin system as well as the vasopressin system in maintenance of arterial blood pressure.

Key Words: Rabbit blood pressure, Intracerebroventricular(icv) injection, Nicotine, Muscarine, Regitine, Enalarpril, SK&F-100273

INTRODUCTION

The presence of acetylcholine nicotinic receptors has been shown in the hypothalamus and brain stem which play an important role in the regulation of cardiovascular functions(Morley *et al.*, 1977; Segal *et al.*, 1978; Yoshida & Imura, 1979; Block & Billiar, 1981; Schwartz *et*

al., 1982). Cholinergic muscarinic receptors too are present in the hypothalamus and brain stem (Brezenoff *et al.*, 1981; Willette *et al.*, 1984; Punnen *et al.*, 1986; Benarroch *et al.*, 1986). Intracerebroventricular(icv) nicotine produced pressor responses in conscious dogs(Lang and Rush, 1973), cats(Pradhan *et al.*, 1967), goats (Vandeputte-Van Messom, 1981) and rats(Kubo & Misu, 1981a). A hypertensive response is evoked by central cholinergic activation by muscarinic agonists or acetylcholinesterase inhibitors in the unanesthetized cat(Day & Roach, 1977) and dog(Lang & Rush, 1973), in the anesthetized rabbit(Kim, 1990) and in the both conscious and anesthetized rat(Dirnhuber & Collumbine, 1955; Varagic 1955; Brezenoff & Rusin, 1974; Hoffman, 1979). As to the mechanism(s) of blood pressure responses following central nicotine as well as cholinesters, which have been shown to act on central nicotinic receptors, the activation of the sympathetic nervous system (Review by Kubo, 1985) and the release of vasopressin(Hoffman, 1979; Iitake *et al.*, 1986; Yamaguchi & Hama, 1989; Bhargava *et al.*, 1972; Cadnapaphornchai *et al.*, 1974; Bisset *et al.*, Castro De Souza, 1977) have been reported. The hypertension following icv muscarinic agonists or acetylcholinesterase inhibitors is mediated via augmented sympathetic outflow after the activation of central muscarinic receptors(Varagic & Vojvodic, 1962; Stamenovic & Varagic, 1970; Lang & Rush, 1973; Sinha *et al.*, 1967). In rabbits it is suggested that icv physostigmine activated both the sympathetic and renin-angiotensin system(Kim, 1990).

In this study, the author found that icv nicotine and muscarine elicited pressor responses in the rabbit, and attempted to elucidate the responsible pressor systems for these responses.

METHODS

Rabbits of either sex, weighing between 1.7 and 2.4 kg, were anesthetized with urethane(1 g/kg, sc). The trachea was cannulated. The animal was fastened prone with its head extended.

Blood pressure was taken from the left femoral artery and recorded on a physiograph. Blood pressure was expressed as mean arterial pressure(mean±S.E.M., mmHg). In some experiments heart rate was simultaneously recorded with blood pressure on a physiograph by means of biotachometer. Heart rate was expressed as beats per minute(mean±S.E.M., bpm).

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(3 cm long and 1 mm diameter) inserted into the lateral cerebral ventricle. Drugs were given in a volume of 0.1 ml per animal. 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.

In all the animals employed in this study bilateral vagotomy was performed by cutting the vagal nerve trunks at the level of the neck 1 hr before experiments. It was noted in preliminary experiments that icv nicotine produced a marked decrease in heart rate along with an increase in blood pressure. In vagotomized rabbits, however, the decrease of heart rate was significantly attenuated and the increase of blood pressure became more marked, that is, in 4 non-vagotomized rabbits icv nicotine 100 μg produced an increase of 19±2.9 mmHg in blood pressure and a decrease of 141±16 bpm in heart rate, while in 4 vagotomized animals the same dose produced an increase of 44±5.7 mmHg and a decrease of 52±5 bpm.

Drugs. Nicotine hydrogen tartrate(Carl Roth), muscarine chloride(Sigma), DMPP(Sigma), bethanechol chloride(Sigma), methoxamine HCl (Sigma), mecamylamine HCl(Merck Sharp & Dohme), pirenzepine dihydrochloride(Sigma), regitine methanesulfonate(Ciba), reserpine(Ciba), enalapril maleate(Merck Sharp & Dohme), saralasin(Sigma), SK&F-100273([d(CH_2)$_5$Tyr-(Me)]-arginine-vasopressin, Smith Kline & French Lab), vasopressin(Sigma), angiotensin I (Sigma), angiotensin II(Sigma) and norepinephrine bitartrate(Sigma) were used. The drugs, except reserpine, were dissolved in saline. A stock 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 before use. All doses are expressed as weight of salt. The doses of drugs

given icv were expressed as μg per animal.

The Student's t-test was used in analysing the results statistically.

RESULTS

Responses to icv cholinergic drugs

Nicotine. 20 μg elicited a slight pressor response only in some animals. With 50 μg, however, a distinct pressor response was always seen and the response became larger with 100 μg. The rise of blood pressure by 100μg reached a plateau at about 1~2 min after injection and 2~3 min later blood pressure began to decline and returned to the preinjection levels in about 5 min(Fig. 1, 2). The second injection given at interval of 2~3 hr produced almost the same response, but the third one elicited a diminished response.

DMPP. 100 μg elicited a slight and inconsistent response. With 200μg the pressor response was distinct(Fig. 1) and the pattern of the response was similar to that to 50 μg nicotine. With higher doses no increase in the magnitude of the rise in blood pressure was observed. On repeated administrations of 200 μg at intervals of 2~3 hr the response was reproducible, while the response to the third dose tended to decrease.

Muscarine. 25 μg produced a distinct rise. The pressure began to rise in about 3 min after injection, reaching a plateau at 5~10 min, which lasted for a period of about 15 min, and then declined very gradually(Fig. 1, 3). With the dose reduced to one half, no pressor responses were noted in some animals, and even when the dose was doubled no increase in the response was seen. As seen in the cases of nicotine and DMPP, the blood pressure response to the second injection given at 2~3 hr later remained undiminished but the third dose produced much less response.

Bethanechol. 100 μg elicited a distinct pressor response. Doubling doses almost did not increase the response. The blood pressure rose gradually, reaching a plateau at about 5 min after injecion, which lasted over 10 min(Fig. 1). The second and third injections given at 2 hr intervals produced almost the same responses.

Effect of icv mecamylamine and pirenzepine on the responses to icv cholinergic drugs

The results of this study are summarized in Table 1.

About 3 min after an administration of icv mecamylamine and pirenzepine responses to cholinergic agents were examined.

Mecamylamine markedly inhibited the responses to nicotine and DMPP but did not inhibit those to muscarine and bethenechol, while pirenzepine inhibited the responses to musca-

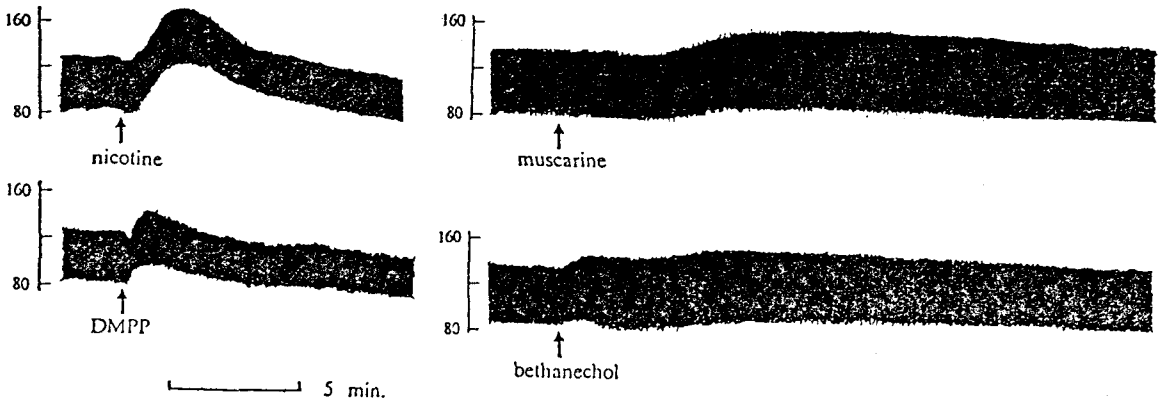

Fig. 1. Blood pressure tracing of rabbits. Left scales: mmHg. At arrow marks nicotine (100 μg), DMPP (200 μg), muscarine (25 μg) and bethanechol (200 μg) were administered intracerebroventricularly.

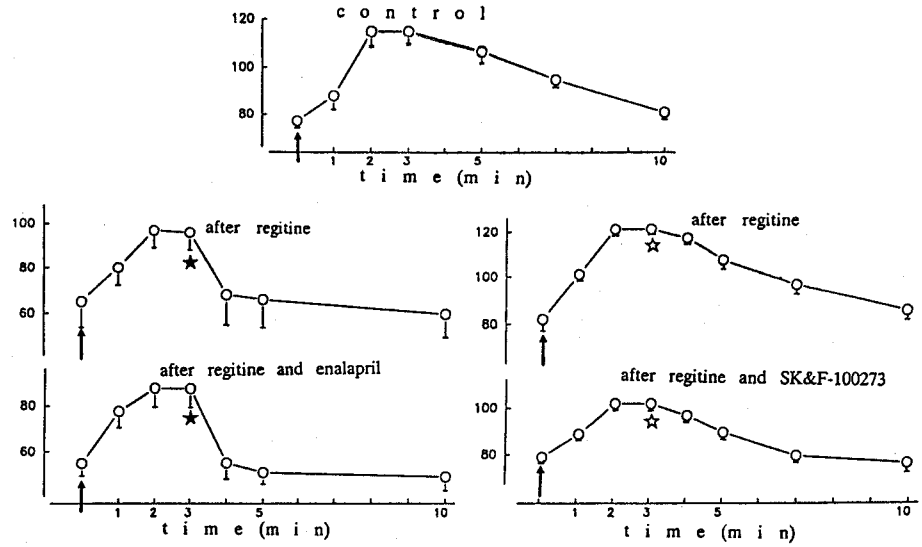

Fig. 2. Changes of blood pressure by SK&F-100273 and enalapril in nicotine (100 μg, icv)-induced hypertensive state in rabbits. Arrow marks: icv injection of nicotine (100 μg). Left scales: blood pressure (mmHg). Closed asterisks: iv injection of SK&F-100273 (20 μg/kg). Open asterisks: iv injection of enalapril (2 mg/kg). Upper curve was obtained from the rabbits without pretreatment. Two middle curves were from the regitine (1.5 mg/kg, iv)-pretreated rabbits. Left lower curve from the rabbits pretreated with regitine (1.5 mg/kgm iv) and enalapril (2 mg/kg, iv), right lower one from those pretreated with regitine (1.5 mg/kg, iv) and SK&F-100273 (20 μg/kg, iv). Data are the mean±S.E.M. for 4~6 animals

Note that SK&F-100273 produced a fall of the nicotine-induced elevated blood pressure in regitine-treated rabbits but enalapril did not.

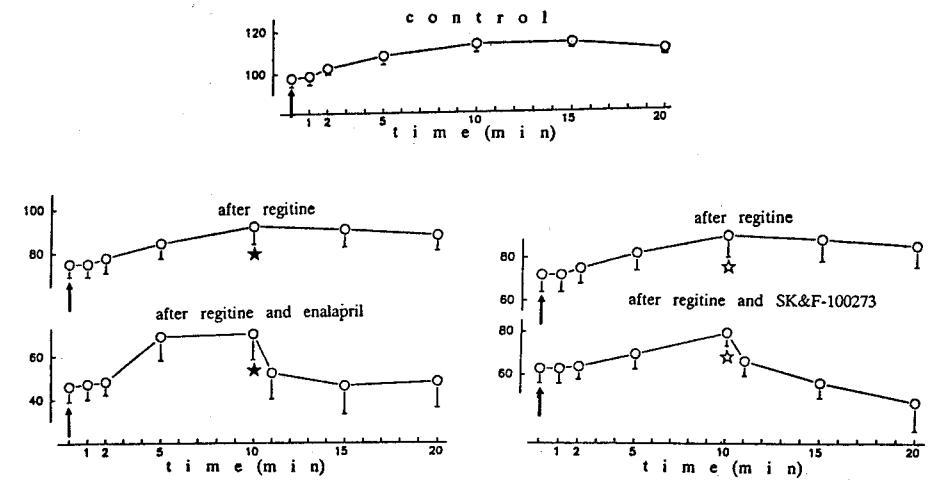

Fig. 3. Changes of blood pressure by SK&F-100273 and enalapril in the muscarine (25 μg, icv)-induced hypertensive state in rabbits. Legends are the same as in Fig. 2. Data are the mean±S.E.M. for 4~6 animals.

Note that SK&F-100273 and enalapril failed to produce a fall of the muscarine-induced elevated blood pressure in regitine-treated rabbits. SK&F-100273 and enalapril, however, produced a fall of the muscarine-induced elevated blood pressure in rabbits treated with regitine and enalapril and those treated with regitine and SK&F-100273, respectively.

Table 1. Effects of pretreatment with icv mecamylamine and pirenzepine on the pressor respones to icv cholinergic drugs in rabbits[@]

Cholinergic agents (Doses per animal)	No pretreatment			Pretreatment with					
				Mecamylamine (100μg, icv)			Pirenzepine (25μg, icv)		
	n	* initial	**increase	n	initial	increase	n	initial	increase
Nicotine (50 μg)	6	85±3.8	16±2.4	4	92±3.8	5±2.3*	5	90±4.2	18±3.6
(100 μg)	9	93±2.4	40±5.7	6	96±4.5	15±3.5*	5	95±5.3	38±6.8
DMPP (200 μg)	14	97±2.9	18±2.8	5	86±4.6	5±1.2*	4	90±2.0	15±1.2
Muscarine (25 μg)	8	99±2.8	17±1.0	4	99±4.5	19±0.9	4	89±4.9	8±1.3*
Bethanechol (200 μg)	6	93±3.5	14±1.2	4	99±1.5	11±1.6	4	88±3.4	2±1.1*
Methoxamine**(1 mg)	5	87±6.4	20±4.1	5	88±3.4	21±7.1	4	90±2.9	16±3.3

[@] Vagotomized rabbits were employed.
Initial*: level of blood pressure (mmHg, mean±S.E.M) before cholinergic agents.
Increase**: mean±S.E.M (mmHg) of differences between blood pressure before cholinergic agents and maximum blood pressure achieved by cholinergic agents.
* Statistical significant differences ($P < 0.01$) from the increase in "no pretreatment".
** Icv mecamylamine and pirenzepine did not affect the increases of blood pressure by methoxamine.

rine and bethanechol but did not offset those to nicotine and DMPP. By contrast, both mecamylamine and pirenzepine had no effect on the pressor response of methoxamine.

Effect of various pharmacological agents on the responses to icv nicotine and muscarine

The results of this study are summarized in Table 2.

Regitine. At about 3 min after iv regitine(1.5 mg/kg), the increase of blood pressure by norepinephrine(3 μg/kg) was reduced to 6±2.6 mmHg from the control increase of 30±5.6 mmHg. At 10 min after the injection, however, the pressor response to norepinephrine was 18± 3.7 mmHg, indicating a significant decline of the regitine action. Therefore icv nicotine and muscarine were given at 2~3 min after iv regitine.

Basal blood pressure levels were lowered by iv regitine(Fig. 4). The pressor effect of nicotine and muscarine was not modified by regitine.

Reserpine. Pretreatment with reserpine(1 mg/kg, iv 24hr before experiment) too did not affect the pressor responses to the nicotine and muscarine.

Enalapril. At about 3 min after enalapril(2 mg/kg, iv) the increase of blood pressure by angiotensin I(3 μg/kg) was reduced to 5±0.7 mmHg from the control increase of 42±5.5 mmHg. This inhibitory effect of enalapril on angiotensin I lasted over 1 hr.

Basal blood pressure levels were not lowered by enalapril. Enalapril was without effect on the pressor responses to nicotine and muscarine.

Saralasin. During an infusion of this angiotensin II-antagonist(5 μg/kg/min) nicotine and muscarine produced pressor responses as in the control animals without saralasin infusion.

Regitine and enalapril. Regitine was given at about 5 min after enalapril and then effect of nicotine and muscarine was examined. No significant alterations in the activity of nicotine and muscarine were observed.

Regitine and saralasin. While continuing an infusion of saralasin, regitine was given and then the effects of nicotine and muscarine were examined. The response to nicotine was not af-

Table 2. Effects of pharmacological agents on the pressor responses to icv nicotine (100 μg) and muscarine (25 μg) in rabbits*

Pretreatment* (dose/kg)	Nicotine			Muscarine		
	n	initial*	increase**	n	initial	increase
None	9	93±2.4	40±5.7	8	99±2.8	17±1.0
Regitine (1.5 mg)	9	76±5.9	43±4.4	6	75±3.1	20±2.8
Reserpine (1 mg, 24hr before)	4	61±4.1	30±2.6	4	62±9.2	24±8.0
Enalapril (2 mg)	4	98±6.1	42±8.0	5	85±4.5	16±4.0
Saralasin (5 μg/min)	4	90±3.0	36±5.6	4	86±1.9	21±4.2
Regitine (1.5 mg) and Enalapril (2 mg)	4	57±2.4	30±3.4	7	52±5.4	15±2.8
Regitine (1.5 mg) and Saralasin (5 μg/min)	4	72±3.0	40±9.3	4	62±6.1	13±4.0
SK&F-100273 (20 μg)	5	86±6.9	41±5.7	5	86±4.2	16±4.6
Regitine (1.5 mg) and SK&F-100273 (5 μg/min)	7	78±4.0	20±2.6**	10	65±5.6	15±1.8
Regitine (1.5 mg), Enalapril (2 mg) and SK&F-100273 (20 μg)	4	47±6.7	18±3.8**	4	35±2.5	3±0.7**

* Vagotomized rabbits were employed.
* The drugs except reserpine and saralasin were given intravenously 3-10 min before icv nitocine and muscarine. Reserpine (iv) was given 24 hr before experiment, and saralasin was infused (5 μg/kg/min).
* and ** denote the same as in Table 1.
** Statistical significant differences ($P < 0.01$) from the increase in "None".

fected. The response to muscarine tended to become smaller, though insignificant.

SK&F-100273. About 3 min after an injection of this drug(20 μg/kg) vasopressin 50 mIU, which caused a rise of 21±2.3 mmHg(n=4), almost did not produce pressor responses. This inhibitory effect lasted over 1 hr. This vasopressin-antagonist did not affect basal blood pressure levels as well as the pressor responses to nicotine and muscarine.

Regitine and SK&F-100273. At about 5 min after SK&F-100273, regitine was injected, and then the effects of nicotine and muscarine were checked. The pressor response to nicotine was significantly inhibited($P<0.01$), but that to muscarine was not affected.

Regitine, enalapril and SK & F-100273. At 3 min after an injection of regitine following administration of enalapril and SK&F-100273, the pressor responses to both nicotine and muscarine were markedly inhibited($P<0.01$ each).

Effect of regitine, enalapril and SK&F-100273 on hypertensive state induced by nicotine and muscarine

Regitine. This drug caused a fall of the blood pressure which had been elevated by either of nicotine and muscarine, although it did not pre-

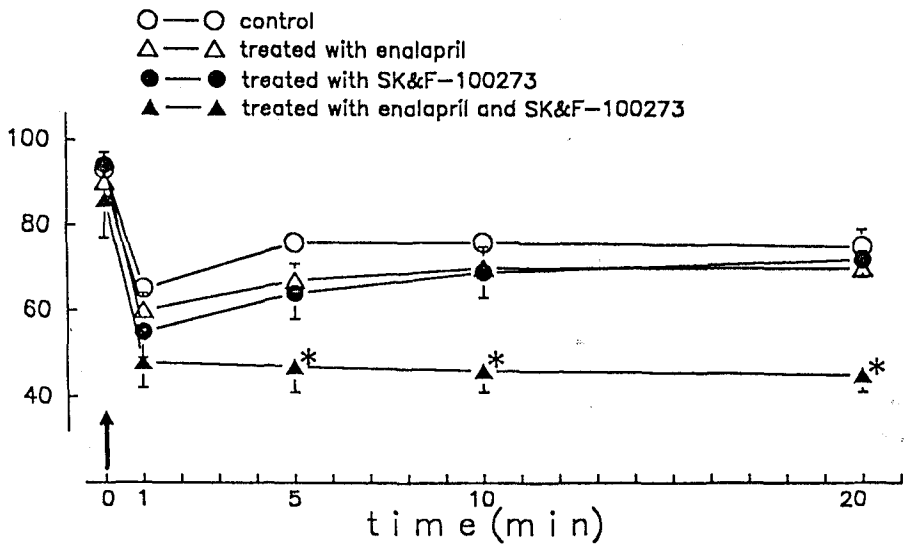

Fig. 4. Influence of enalapril and SK&F-100273 on the hypotensive effect of regitine in rabbits. Arrow mark: iv regitine (1.5 mg/kg). Left scale: blood pressure (mmHg). Data are the mean±S.E.M. for 4~6 animals.
* Significant difference ($P < 0.01$) from the above 3 values at the corresponding time.

vent the pressor responses of nicotine and muscarine.

Enalapril. This converting enzyme inhibitor did not cause a fall of the elevated blood pressure by nicotine in the animals treated with regitine or with both regitine and SK&F-100273 as in non-treated animals(Fig. 2).

The muscarine-induced hypertensive state after regitine also was not affected by this inhibitor. The similar hypertensive state in the animals treated with both regitine and SK&F-100273, however, was lowered by this drug(a fall of 16±3 mmHg within 1 min after administration, n=4) (Fig. 3).

SK&F-100273. This vasopressinergic antagonist did not cause a fall of blood pressure which had been elevated by either of nicotine or muscarine in non-treated animals. However, this drug produced a distinct fall of the nicotine-elevated blood pressure in the animals treated either with regitine alone or with both regitine and enalapril(Fig. 2). The magnitude of the fall in regitine-treated rabbits(28±4.1 mmHg within 1 min after injection, n=5) was not different from that in both regitine and enalapril-treated ones(32±3.5 mmHg within 1 min after injection, n=4).

In regitine-treated animals the muscarine-induced hypertensive state was not affected by this antagonist, whereas the elevated blood pressure in the animals treated with both regitine and enalapril was lowered by this drug(a fall of 20±4 mmHg, n=4) (Fig. 3).

Influence of enalapril and SK&F-100273 on hypotensive effect of regitine

On injecting regitine(1.5 mg/kg, iv) an abrupt fall of blood pressure ensues almost invariably. And then, partial recovery follows, as shown in Fig. 4. This pattern was also observed in rabbits treated with either enalapril(2 mg/kg) or SK&F-100273(20 μg/kg). The treatment of rabbits with both enalapril and SK&F-100273, however, changed the pattern into one, in which no partial recovery takes place(Fig. 4).

DISCUSSION

Sites of pressor action of nicotine, DMPP, muscarine and bethanechol

The pressor response to icv nicotine and DMPP, cholinergic nicotinic agonists, was inhibited by prior icv injection of mecamylamine,

a cholinergic nicotinic antagonist, but not icv pirenzepine, a cholinergic muscarinic antagonist, whereas the pressor response to icv muscarine and bethanechol, cholinergic muscarinic agonists, was inhibited by pirenzepine but not by mecamylamine. Icv mecamylamine and pirenzepine did not affect the pressor response to icv methoxamine which has been shown to act on α-adrenoceptors(Kim *et al.*, 1982). In addition, the response patterns to the two nicotinic agonists were similar and those to the two muscarinic agonists resembled each other. These findings suggest the presense of two distinct types of cholinergic receptors in the rabbit brain, both of which participate in the regulation of blood pressure.

Major pressor systems and the pressor responses to nicotine and muscarine

The regulatory systems thought to be primarily responsible for the support of blood pressure are the sympathetic nervous system, the renin-angiotensin system and the vasopressin system. In this study the contribution of these systems to the pressor responses to nicotine and muscarine was evaluated by observing the effect on these responses of pharmacological agents that block each of the systems.

Neither the decrease of the activity of the sympathetic nervous system with regitine(an α-adrenoceptor antagonist) or reserpine(a catecholamine depletor), nor the removal of activity of the renin-angiotensin system with saralasin (an angiotensin II antagonist) or enalapril(a converting enzyme inhibitor), nor the blockade of the pressor action of vasopressin with SK&F-100273(a vasopressinergic antagonist) did prevent the pressor responses to nicotine and muscarine. Even the simultaneous inactivation of the sympathetic nervous system and the renin-angiotensin system with regitine and saralasin (or enalapril) was unable to inhibit the pressor responses. These findings may easily lead one to an erroneous conclusion that the three major systems are not related to the pressor action of nicotine and muscarine(see later).

However, further observations clearly indicate that the contrary is true. The nicotine response was weakened by the simultaneous blockade of the sympathetic nervous system and the vasopressin system, suggesting that the pressor action is indeed related to the sympathetic and vasopressin system. The muscarine response was not affected even with both α-adrenoceptor antagonist and vasopressinergic antagonist but almost abolished when the three systems were blocked at the same time, indicating the participation of the three systems in the pressor action.

On the other hand, the blockade of α-adrenoceptors lowered the blood pressure which had been elevated by nicotine and muscarine, whereas neither the inhibition of the converting enzyme nor the blockade of the vasopressinergic receptors did suppress the pressure. When the sympathetic system was inactive, however, the nicotine-induced hypertension was lowered by the blockade of the vasopressin system, suggesting that the hypertension in this state was vasopressinergic in origin. The attenuated pressor respones to nicotine following the inactivation of both the sympathetic and vasopressin system was not further inhibited by the inactivation of the renin-angiotensin system, indicating no role of angiotensin in this response. The muscarine-induced hypertension after sympathetic blockade was not affected by the inactivation of either of the renin-angiotensin or the vasopressin system. However, the muscarine hypertension in the state of decreased activity of both the sympathetic and renin-angiotensin system was inhibited by the vasopressinergic blockade, indicating that vasopressin was responsible for this response. The hypertension in decreased activity of the sympathetic and vasopressin system was suppressed by the inhibition of the converting enzyme, indicating that angiotensin II was contributing to this increase in blood pressure. These data suggest that central nicotine activated the sympathetic nervous system and the vasopressin system, whereas central muscarine stimulated the sympathetic nervous system, the renin-angiotensin system and the vasopressin system.

Basal blood pressure levels and major pressor systems

Regitine lowered basal blood pressure but enalapril and SK&F-100273 did not. Also on the hypertensive states induced by nicotine and muscarine the three drugs produced the same response as in normal rabbits. In the dog similar

phenomena have been observed(Fejes-Toth *et al.*, 1985; Hiwatari *et al.*, 1985; Schwartz & Reid, 1983). These findings indicate the greatest potential of the sympathetic nervous system in controlling blood pressure. The hypotensive effect of regitine on blood pressure was not affected by the treatment of animals with either enalapril or SK&F-100273. However, in animals pretreated with both enalapril and SK&F-100273 the partial recovery of the lowered blood pressure following regitine did not occur and the hypotension was accentuated. These indicate that both the renin-angiotensin and vasopressin system participate in the partial recovery following sympathetic blockade. Brand *et al.* (1988) suggested that during autonomic ganglionic blockade, blood pressure was supported by both angiotensin II and vasopressin, and that sympathetic function was not essential for maintenance of blood pressure in resting dogs.

Conclusively, all three pressor systems, i.e the sympathetic, the renin-angiotensin and the vasopressin are responsible for maintanance of basal blood pressure as well as for the hypertensive response to muscarine. For occurrence of the nicotine hypertension both the sympathetic and vasopressin system are responsible. This may be plausibly accounted for, if one assumes that acute removal of the activity of any of the pressor systems is quickly counteracted by enhanced activity of the other systems. The inability of regitine-pretreatment to affect the nicotine pressor responses, for example, may not be due to the failure of blockade of adrenergic receptors but result from enhanced activities of the renin-angiotensin and vasopressin systems in response to the adrenergic blockade, as well as from the release of vasopressin via the stimulation of central nicotinic receptors.

Others

Although the pressor responses to nicotine showed significant decrease by a combined pretreatment of regitine and SK&F-100273, part of the pressor responses persisted(Table 2). It might be due to some other pressor factor(s) than catecholamine, angiotensin II and vasopressin as suggested in adrenal regeneration hypertension and pressor responses to icv hypertonic NaCl by Foulkes *et al.* (1988) and Takata *et al.* (1988).

It has been shown that anesthetized cats (Armitage & Hall, 1967a 1967b) and rats(Kubo & Misu, 1981b) responded with hypotension to icv nicotine. In the present study hypotensive responses were hardly observed. The species difference may explain this phenomenon.

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REFERENCES

Armitage AK and Hall GH: *Effects of nicotine on the systemic blood pressure when injected into the cerebral ventricles of cats.' Int J Neuropharmacol 6: 143-149, 1967a*

Armitage AK and Hall GH: *Further evidence relating to the mode of action of nocotine in the central nervous system. Nature 214: 977-979, 1967b*

Benarroch EE, Granata AR, Ruggiero DA, Park DH and Reis DJ: *Neurons of C1 area mediate cardiovascular responses initiated from ventral medullary surface. Am J Physiol 250: R932-R945, 1986*

Bhargava KP, Kulshrestha VK and Srivastava YP: *Central cholinergic and adrenergic mechanisms in the release of antidiuretic hormone. Br J Pharmacol 44: 617-627, 1972*

Bisset GW, Feldberg W, Guertzenstein PG and Rocha E Silva M Jr: *Vasopressin release by nicotine: The site of action. Br J Pharmacol 54: 463-474, 1975*

Block GA and Billiar RB: *Properties and regional distribution of nicotinic cholinergic receptors in the rat hypothalamus. Brain Res 212: 152-158, 1981*

Brand PH, Patricia JM and Steven LB: *Support of arterial blood pressure by major pressor systems in conscious dogs. Am J Physiol 255: H483-H491, 1988*

Brezenoff HE and Rusin J: *Brain acetylcholine mediates the hypertensive response to physostigmine in the rat. Eur J Pharmacol 29: 262-266, 1974*

Brezenoff HE, Carney K and Buccafusco JJ: *Potentia-*

tion of the carotid artery occlusion reflex by a cholinergic system in the posterior hypothalamic nucleus. Life Sci 30: 391-400, 1981

Cadnapaphornchai P, Boykin JL, Berl T, McDonald Schrier RW: *Mechanism of effect of nicotine on renal water excretion. Am J Physiol 27: 1216-1220, 1974*

Castro De Souza EM and Rocha E Silva M Jr: *The release of vasopressin by nicotine: Further studies on its site of action. J Physiol 265: 297-311, 1977*

Day MD and Roach AG: *Cardiovascular effects of carbachol and other cholinomimetics administered into the cerebral ventricles of conscious cats. Clin Exp Pharmacol Physiol 4: 431-442, 1977*

Dirnhumber P and Cullumbine H: *Effect of anticholinesterase agents on rats blood pressure. Br J Pharmacol 10: 12-15, 1955*

Fejes-Toth GA, Naray-Fejes-Toth and Ratge D: *Evidence against role of antidiuretic hormone in support of blood pressure during dehydration. Am J Physiol 249: H42-H48 1985*

Foulkes R, Gardine SM and Benett T: *The cardiovascular responses to sequential inhibition of α-adrenoceptors, the renin-angiotensin system and vasopressin in rats with adrenal regeneration hypertension. J Hypertens 6: 305-310, 1988*

Hiwatari M, Nolan PL and Johnston CI: *The contribution of vasopressin after autonomic blockade. Hypertension Dallas 7: 547-553, 1985*

Hoffman WE: *Central cholinergic receptors in cardiovascular and antidiuretic effects in rats. Clin Exp Pharmacol Physiol 6: 373-380, 1979*

Iitake K, Share L, Ouchi, Y, Crofton JT and Brooks DP: *Central cholinergic control of vasopressin release in conscious rats. Am J Physiol 251: E146-E150, 1986*

Kim JB: *Pressor action of physostigmine in the rabbit. Korean J Pharmacol26: 117-127, 1990*

Kim, YI, Baik YH, Kang SS and Kim JH: *Effects of α-adrenoceptor antagonists administered intraventricularly on central hypotensive action of clonidine and on central hypertensive action of methoxamine in rabbits. Arch Int Pharmacodyn 257: 66-76, 1982*

Kubo T and Misu Y: *Increased pressor responses to nicotine in spontaneously hypertensive rats. Jap J Pharmacol 31: 221-226, 1981a*

Kubo T and Misu Y: *Cardiovascular responses to intracisternal administration of nicotine in rats. Can J Physiol Pharmacol 59: 615-617, 1981b*

Kubo T: *Brain nicotinic acetylcholine receptors and their functions in special reference to central cardiovascular regulation. Folia Pharmacol Japon 85: 425-433. 1985*

Lang WJ and Rush ML: *Cardiovascular responses to injections of cholinomimetic drugs into the cerebral ventricles of unanesthetized dogs. Br J Pharmacol 47: 196-205, 1973*

Morley BJ, Lorden JF, Brown GB, Kemp GE and Bradley RJ: *Regional distribution of nicotinic acetycholine receptor in rat brain. Brain Res 134: 161-166, 1977*

Pradhan SN, Bhattacharya IC and Atkinson KS: *The effects of intraventricular administration of nicotine on blood pressure and some somatic reflexes. Ann N Y Acad Sci 142: 50-56, 1967*

Prnnen S, Willette, RN Krieger AJ and Sapru HN: *Medullary pressor area: Site of action of intravenous physostigmine. Brain Res 383: 178-184, 1986*

Schwartz RD, McGee R Jr and Kellar KJ: *Nicotinic cholinergic receptors labeled by [^{3}H] acetylcholine in rat brain. Mol Pharmacol 22: 56-62, 1982*

Schwartz J and Reid LA: *Role of vasopressin in blood pressure regulation in conscious water-deprived dogs. Am J Physiol 244: R74-R77, 1983*

Segal M, Dudai Y and Amsterdam A: *Distribution of an α-bungarotoxinbinding cholinergic nicotinic receptor in rat brain. Brain Res 148: 105-119, 1978*

Sinnha JN, Dhawan KN, Chandra O and Gupta GP: *Role of acetycholine in central vasomotor regulation. Canad J Physiol Pharmacol 45: 503-507, 1967*

Stamenovic BA and Varagic VM: *The effect of eserine on the efferent neuronal activity in the cervical sympathetic of the rat. Neuropharmacology 9: 561-566, 1970*

Takata Y, Yamashita Y, Takishita S and Fujishima M: *Mechanisms of pressor responses to intra-cisternal administration of hypertonic NaCl in conscious, unrestrained normotensive and spontaneously hypertensive rats. Clin Exp Hypertension [A]: 10 Suppl 1, pp 281-287, 1988*

Vandeputte-Van Messon G: *Effect of intracerebroventricular injection of nicotine and acetylcholine on renal water and salt excretion in conscious goats. Arch Int Pharmacodyn Ther 253: 52-67, 1981*

Varagic VM: *The action of eserine on the blood pressure of the rat. Br J Pharmacol 10: 349-353, 1955*

Varagic VM and Vojvodic N: *Effect of guanethidine, hemicholinium and mebutamate on the hypertensive response to eserine and catecholamines. Br J Pharmacol 19: 451-457, 1962*

Willette RN, Punnen, S, Krieger AJ and Sapru HN: *Cardiovascular control by cholinergic mechanisms in the rostral ventrolateral medulla. J Pharmacol Exp Ther 231: 457-463, 1984*

Yamaguchi K and Hama H: *Evaluation for roles of periventricular cholinoceptors in vasopressin secre-*

tion in response to angiotensin II and on osmotic stimulus. Brain Res 496: 345-350, 1989
Yoshida K and Imura H: *Nicotinic cholinergic receptors in brain synaptosomes. Brain Res 172: 453-459 1979*

= 국문초록 =

가토 측뇌실내 Nicotine 및 Muscarine의 혈압상승작용에 관하여

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이 충 경

미주신경절단 가토에서 니코틴성약물인 nicotine과 DMPP뿐아니라 무스카린성 약물인 muscarine과 bethanechol은 측뇌실내 투여로 모두 혈압상승작용을 나타냈다. Nicotine과 DMPP에 대한 승압반응은 측뇌실내 mecamylamine처리로 현저히 감약되었으나 측뇌실내 pirenzepine처리에 의해서는 영향받지 않았고, muscarine과 bethanechol에 대한 승압반응은 pirenzepin에 의해서는 억제되나 mecamylamine에 의해서는 영향받지 않았다. 이는 뇌내의 니코틴성 수용체 및 무스카린성 수용체가 모두 혈압상승에 관여함을 가리키고 있다.

Nicotine과 muscarine에 대한 승압반응은 regitine, reserpine, enalapril, saralasin, SK&F-100273, regitine과 enalapril, regitine과 saralasin의 정맥내 처리에 의해서는 억제되지 않았으며 nicotine에 대한 승압반응은 regitine과 SK&F-100273 두약물의 병용처리에 의해서 억제되었고 muscarine에 의한 승압반응은 regitine, enalapril과 SK&F-100273의 세가지 약물의 병용처리에 의해서만 억제되었다.

Nicotine이나 muscarine에 의한 혈압상승상태에서 정맥내 regitine의 투여는 혈압하강을 일으켰으나 enalapril이나 SK&F-100273은 혈압하강을 일으키지 못하였다. Enalapril은 regitine처리나 regitine과 SK&F-100273병용처리 가토에서 nicotione에 의해 상승된 혈압을 하강시키지 못하였으나 SK&F-100273은 regitine처리 가토에서 nicotine에 의한 상승된 혈압을 하강시켰다. Enalapril은 이러한 SK&F-100273의 혈압하강작용을 강화시키지 못하였다. Enalapril은 regitine처리 가토에서 muscarine에 의하여 상승된 혈압은 하강시키지 못하였으나, regitine과 SK&F-100273병용처리 가토에서 muscarine에 의해 상승된 혈압은 하강시켰다. SK&F-100273은 regitine처리 가토에서 muscarine에 의해 상승된 혈압을 하강시키지 못했으나 regitine과 enalapril병용처리 가토의 상승된 혈압은 하강시켰다.

이상의 성적은 뇌실내 nicotine에 의한 혈압상승에는 말초에서 교감신경계와 vasopressin이 관여하며 muscarine에 의한 혈압상승에는 교감신경계, vasopressin 및 angiotensin계가 관여함을 시사하고 있다.

Regitine의 정상 가토 혈압하강작용은 enalapril이나 SK&F-100273의 단독처리에 의해서는 영향받지 않았으나 이 두약물을 병용처리시에는 유의하게 강화되었고, 이는 가토 동맥압의 유지에 교감신경, renin-angiotensin 및 vasopressin계가 관여함을 시사하고 있다.