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Influence of Metoclopramide on the Response of Blood Pressure in Rabbits**

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=Abstract=

가토의 혈압반응에 미치는 Metoclopramide의 영향**

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현재 임상에서 오심, 구토, 위하수증의 치료에 사용되어지고 있으며, dopamine 차단제로 알려진 metoclopramide(MCP)가 가토의 혈압 반응에 미치는 영향을 검토하고 그 기전을 규명코자 본 연구를 시행하여 다음과 같은 결과를 얻었다.

그 기전을 규명코자 본 연구를 시행하여 다음과 같은 결과를 얻었다.

MCP를 가토의 일측 대퇴정맥내에 주사 하였을때 용량 의존적으로 혈압 하강반응을 나타내었다. MCP의 혈압강하작용은 atropine이나 cyproheptadine의 전처치로 별다른 영향을 받지 않았다.

Prazosin, bethanidine, chlorisondamine으로 전처치 했을때 MCP의 강압반응은 현저히 억제되었으나 propranolol에 의해서는 영향을 받지 않았다. MCP를 4.0mg/kg/30min으로 가토의 정맥내 주입하였을때 norepinephrine의 승압반응은 상당히 감약되었으나 dopamine의 강압반응은 영향을 받지 않았다. 이상의 실험결과로 보아, MCP는 가토의 혈압 반응을 현저히 하강 시키며 이러한 강압 작용은 adrenergic-alpha receptors의 차단작용에 기인되는 것으로 사료된다.

KEY WORDS : Metoclopramide · Depressor action.

INTRODUCTION

There are now some reports on the effects of metoclopramide (MCP), a dopaminergic antagonist[1-3] employed presently in treating vomiting and gastroparesis, on the blood pressure response, but uncertainty still exists in regard to its precise mode of action. Recently published data from our laboratory[4] have shown that MCP causes markedly a dose-rela-

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ted faill in blood pressure in rat followed by secondary transient pressor respnses, that the hypotensive activity may be due to adrenergic alpha-receptors blocking action, and that pressor activity may be exerted throgh activation of cholinergic nicotinic receptors in autonomic ganglia. Some investigators[5-7] also reported that intravenous administration of MCP induced catecholamine release and a hypertensive crisis only in patients with pheochromocytoma.

However, it is known that MCP does not influeuce blood pressure and plasma catecholamines in normal, in moderate hypertension and in renovascular hypertension[7]. Abe et al[6] suggested that the mechanism of hypertensive crisis induced by MCP may be due rather to its presynatic dopaminergic blocking effect wihich would indirectly release CA than to the direct CA-releasing effect.

It has been tried against hiccup, vertigo, and orthostatic hypertension[3-8]. Kuchel et al[8] reported that MCP improved the postural hypotensin. This effect was known to due to inhibiting the vasodilatory and natriuretic action of the excessive release of dopamine[9] ; additional effect may have been due to shifting the adrenal medullary compensatory response from dopamine toward epinephrine[8].

It has been also shown that dopaminergic stimulation by bromocriptine produces hypotensive action[10] while dopaminergic inhibition by sulpiride induces the hypertensive action[11].

Therefore, this study was designed to investigate the effects of MCP on the arterial blood pressure in rabbits and to clarify the mechanism of its action.

Materials and Methods

Experimental Animals ;

White mature rabbits of both sexes, weighing 1.7~2.5kg, were used in these expeirments. The animals were housed individually in each cage and food (Cheil Animal Chow) and tap water were allowed ad libitum at least for a week to adapt to experimental circumstances. On the day of experiment, a rabbit was anesthetized with urethane(g/kg) subcutaneously. The tracheal cannula was inserted to the trachea of the rabbit which was tied in supine position on fixing panel to prevent rabbit movements. The body temperature was maintained at 37°~38℃ with a thermostatically controlled blanket and heating lamp.

Determination of Blood Pressure ;

The right common carotid artery was catheterized with artery cannula and connected to a pressure transducer and pulse pressure of mean arterial blood pressure was recorded on a physiograph (Beckman Co.) for continuous monitoring of arterial pressure. The artery cannula was filled with heparin solution (400 I.U.) to prevent the blood coagulation during experiment. Another cannulation with polyethylene tube(Gauge No. 23) was made into a femoral vein for injecting drugs. Each rabbit was left undisturbed for at least 30 minuted after completion of the operative procedures to permit cardivascular parameter to be stabilized.

Drugs ;

The following durgs were used ; metoclopramide hydrochloride, dopamine HCI, norepinephrine bitartrate (Sigma Chemical Co.), atropine sulfate (Merk Co.), chlorisondamine chloride (CIBA Co.), propranclol HCI(ICI Co.), prazosine HCI(Phizer Co.) and bethanidine sulfate (Samil Pharm. Co.). These drugs were prepared in 0.9% sodium chloride solution on the day of experiment and stored in a refrigerator except norepinepbrine and dopamine. Norepinephrine and tyramine were dissolved in 0.9% acidic saline (PH=4.0), respectively. Doses were expressed as the base. All drugs were adminstered into a femoral vein except infusion experiments of MCP which was infused into a jugular vein at a given rate.

Statistical Analysis ;

Statistical significance between groups was determined utilizing the Student's "t" test. Data obtained from animals which served as own control were analyzed for significance using t-test for unpaired observations. A p-value for $p<0.05$ was considered to represent a significant change unless specifically noted in the text. Values given in the text refer to means with standard error(S.E.).

RESULTS

Effect of MCP on the response of blood pressure ;

Rabbits were allowed to stabilize at least for 30 min before experimental protocols were initiated. When cardiovascular parameters became stabilized, MCP was injected into a femoral vein of the rabbit, resulting in a dose-related fall in blood pressure as shown in Fig. 1.

In 13 rabbits, MCP of 1.0mg/kg given intravenously produced depressor responses by -6.9 ± 0.94mmHg from pre-injection level. Higher doses of MCP at 2.0 and 4.0mg/kg given intravenously induced the marked and immediate decrease in blood pressure, which were -9.4 ± 1.41 and -18.2 ± 2.2mmHg, respectively, as shown in Table 1, Fig. 2 shows representative tracing of blood pressure evoked by MCP.

This hypotensive activity of MCP was very similar to that evoked by MCP in rats in which was followed by secondary increase in blood pressure[4].

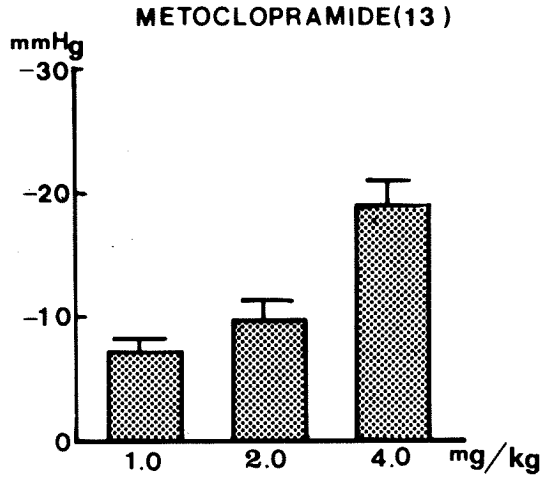

Fig. 1. Effects of MCP(metoclopramide) on the blood pressure of the rabbits. Ordinate ; changes of blood pressure in mmHg. Abcissa ; doses of MCP in mg/kg. Vertical bars on top of the column indicate standard errors of means. Numerals in upper bracket represent number of animals used in this experiment.

The effect of atropine on MCP-evoked responses of blood pressure. ;

Since it has been found that atropine reduces or abolishes its upper gastrointestinal smooth muscle action evoked by MCP[12,14].

Atropine, 3.0mg/kg, i.v. was used in the present work to block peripheral muscarinic receptors[15]. Preliminary studies showed that this dose of atropine blocked vasodepressor effect of muscarine. In the presence of atropine along with bilateral vagotomization, MCP administered intravenously at all of

Table 1. Effect of metoclopramide (MCP) on the response of blood pressure of rats

Administration routes	Dose of MCP (mg/kg)	Changes of Blood Pressure (mmHg from pre-injection level)	Number of Animals
Intravenous injection	1.0	-6.9 ± 0.94	13
	2.0	-9.4 ± 1.44	13
	4.0	-18.2 ± 2.12	13

These data are expressed with Mean± S.E.

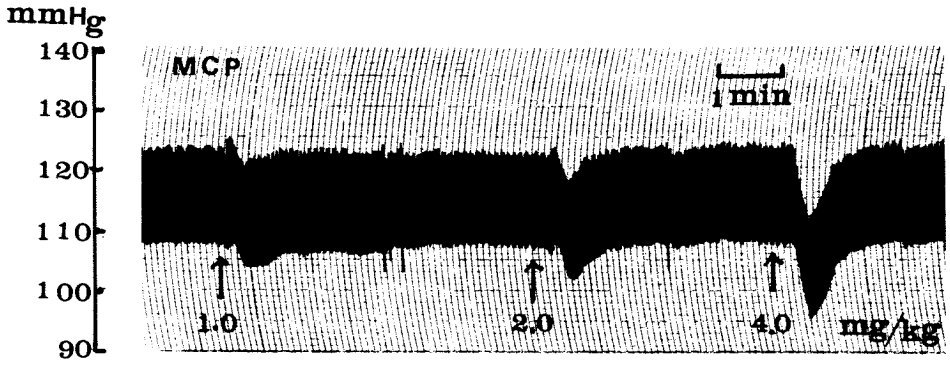

Fig. 2. The tracing of blood pressure evoked by MCP in a whole rabbit(Expt. 16, 2.2kg).
At arrow marks, the indicated doses of MCP(1.0, 2.0 and 4.0 mg/kg) were injected into a femoral vein, respecitively. Time ; 1 min.

Table 2. Effects of some blocking agents on MCP-induced changes of blood pressure

Blockade	Dose of MCP (mg/kg)	Changes of Blood Pressure (mmHg from pre-injection level)		Statistical Significances
		BEFORE	AFTER	
Atropine(8)	1.0	−6.4± 0.90	−6.0± 0.35	NS
	2.0	−10.8± 1.06	−9.7± 1.32	NS
	4.0	−15.5± 1.64	−14.5± 2.50	NS
Chlorisondamine(6)	1.0	−7.3± 0.61	−2.1± 0.08	$P<0.05$
	2.0	−11.5± 0.92	−5.3± 0.72	$P<0.05$
	4.0	−18.7± 1.48	−7.5± 0.50	$P<0.05$
Prazosin(10)	1.0	−6.5± 1.35	−3.2± 0.60	$P<0.05$
	2.0	−12.8± 1.02	−6.9± 0.16	$P<0.01$
	4.0	−18.5± 1.40	−10.1± 0.86	$P<0.01$
Bethanidine(8)	1.0	−9.7± 1.32	−4.7± 0.41	$P<0.01$
	2.0	−14.9± 1.09	−7.0± 0.92	$P<0.01$
	4.0	−18.9± 1.86	−7.6± 1.40	$P<0.01$
Propranolol(5)	1.0	−8.5± 0.93	−9.3± 1.09	NS
	2.0	−16.1± 1.76	−15.9± 1.84	NS
	4.0	−21.9± 2.08	−22.6± 2.48	NS
Cyprohepadine(7)	1.0	−8.1± 0.18	−8.8± 1.68	NS
	2.0	−12.5± 1.97	−11.4± 2.86	NS
	4.0	−21.5± 2.72	−19.3± 2.01	NS

"BEFORE" and "AFTER" indicate changes of blood pressure evoked by MCP after administration of blocking agent. Atropine (3.0mg/kg), chlorisondamine (1.0mg/kg), prazosin(1.0mg.kg), bethanidine (3.0mg/kg), propranolol (2.0mg/kg) and cyproheptadine (2.0mg/kg) were given intravenously after obtaining each corresponding control value, respectively. Statistic al differences were calculated by comparing the response of "BEFORE" with
that of "AFTER". Numerals in the bracket denote number of animals used in the present work.

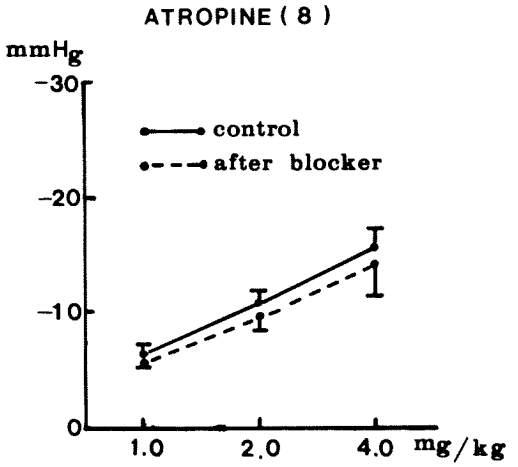

Fig. 3. Effects of atropine on MCP-evoked changes of blood paessure. Atropine(3.0mg/kg) was given intravenously after obtaining the corresponding control values. The methods and other legends are the same as in Fig. 1.

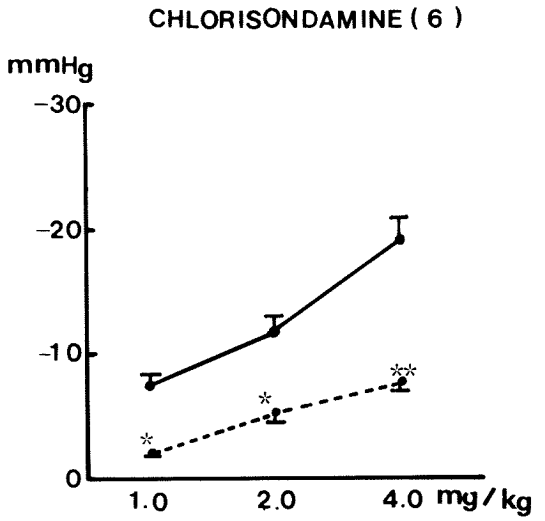

Fig. 4. Effects of chlorisondamine on MCP-evoked changes of blood pressure. Chlorisondamine(1.0mg /kg) was administered intravenously after obtaining control responses. The methods and other legends are the same as in Fig. 1. * ; $p<0.05$, ** ; $p<0.01$

the forementioned doses(1.0, 2.0 and 4.0mg/kg) still evoked depressor responses as showin in Table 2. Fig. 3 also represents the effect of atropine on MCP-evoked changes of blood pressure.

The effect of chlorisondamine on MCP-evoked changes of blood pressure. ;

Intravenous injection of chlorisondamine[15] (1.0 mg/kg), a ganglionic blocking agent, into a femoral vein of the rabbit inhibited significantly the depressor effect of MCP (Table 2). In 6 rabbits, the changes of blood pressure at 1.0, 2.0 and 4.0 mg/kg, i.v. of MCP before the administration of chlorisondamine were -7.3 ± 0.61, -11.5 ± 0.92 and -18.7 ± 1.48mmHg, respectively, but the changes after chlorisondamine treatment were attenuated markedly to -2.1 ± 0.08 ($p<0.05$), -5.3 ± 0.72 ($p<0.05$) and -7.5 ± 0.50mmHg ($p<0.01$), respectively, as shown in Fig. 4.

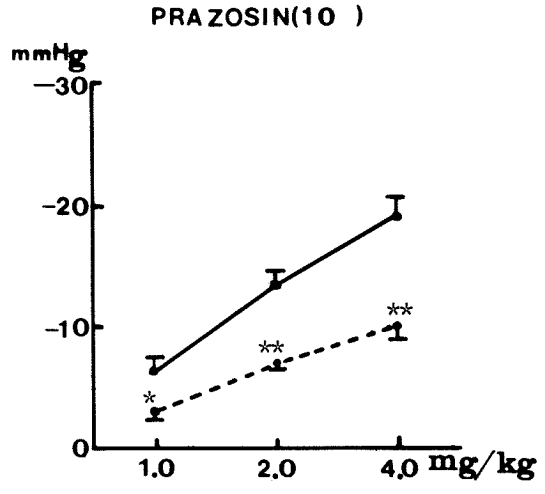

Fig. 5. Effects of prazosin on MCP-induced changes of blood pressuure. Prazosin(1.0mg/kg) was administered intravenously after obtaining control values. The methods and other legends are the same as in Fig. 1.
** ; $p<0.01$.

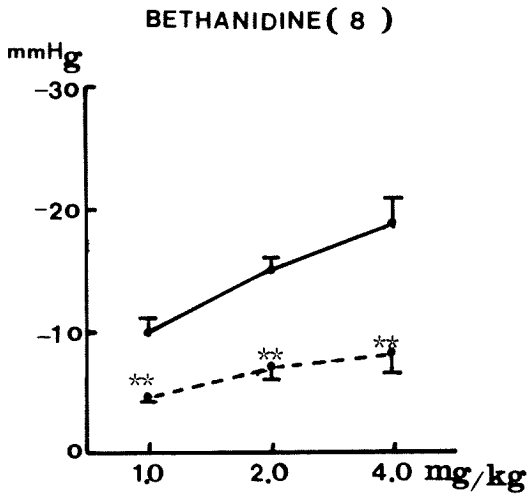

Fig. 6. Effects of bethanidine on MCP-evoked changes of blood pressure. Bethanidine (3.0mg/kg) was injected into a femoral vein after obtaining control value. The methods and other legends are the same as in Fig. 1. ** ; $p<0.01$.

The effect of prazosin on MCP-evoked changes of blood pressure. ;

Prazosin[15-17] (1.0mg/kg), an adrenergic alpha-receptor blocking agent presently employed in treating hypertension, given intravenously produced the significant inhibition of vasodepressor responses induced by MCP. In the experiments of 10 rabbit, the hypotensive activities of MCP at doses of 1.0, 2.0 and 4.0mg/kg before pretreatment with prazosin were -6.5 ± 1.35, -12.8 ± 1.02 and -18.5 ± 1.40 mmHg, respectively.

After prazosin they were reduced markedly to -3.2 ± 0.60 ($p<0.05$), -6.9 ± 0.16 ($p<0.01$) and -10.1 ± 0.86 ($p<0.01$) mmHg, respectively as shown in Table 2, Fig. 5 shows the effect of prazosin on MCP-evoked changes of blood pressure.

The effect of bethanidine on MCP-evoked changes of blood pressure. ;

After blockade of responses to sympathetic adrenergic neurons and to indirect acting sympathomictic amines (E.G., tyramine and amphetamine) by pretreatment with bethanidine[15], the vasodepressor actions evoked by MCP were greatly reduced (Table 2).

As shown in Fig. 6 depressor responses of MCP at doses of 1.0, 2.0 and 4.0mg/kg after pretreatment of bethanidine were clearly attenuated from -9.7 ± 1.32, -14.9 ± 1.09 and -18.9 ± 1.86mmHg of the control before bethanidine to -4.7 ± 0.14 ($p<0.01$), -7.0 ± 0.92 ($p<0.01$) and -7.6 ± 1.40 ($p<0.01$) mmHg, respectively.

Table 3. Effects of MCP-infusion on the responses of blood pressure evoked by norepinephrine and dopamine

Agents	Dose of MCP (μg/kg)	Changes of Blood Pressure (mmHg from pre-injection leve)		P-value
		BEFORE	AFTER	
Norepinephrine(5)	0.3	-9.8 ± 1.37	-8.6 ± 2.09	NS
	1.0	-19.6 ± 1.89	-13.0 ± 1.99	$P<0.05$
	3.0	-28.9 ± 2.42	-18.4 ± 1.52	$P<0.05$
Dopamine(5)	1.0	-6.0 ± 0.41	-6.4 ± 0.85	NS
	3.0	-8.1 ± 1.27	-9.3 ± 1.78	NS
	10.0	-15.7 ± 2.49	-14.6 ± 2.79	NS

MCP was infused into a jugular vein of the rabbit at a rate of 4.0mg/kg/30min for 30min after obtaining the control value. Other legends are the same as in Table 2

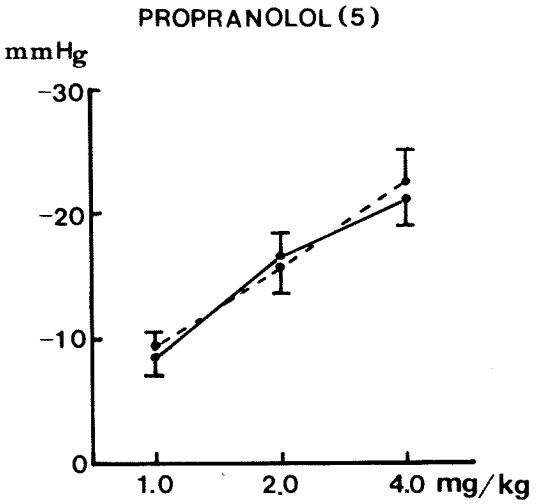

Fig. 7. Effects of propranolol on MCP-evoked changes of blood pressure. Propranolol(2.0mg/kg) was injeted into a femoral vein after obtaining control values. The methods and other legends are the same as in Fig. 1.

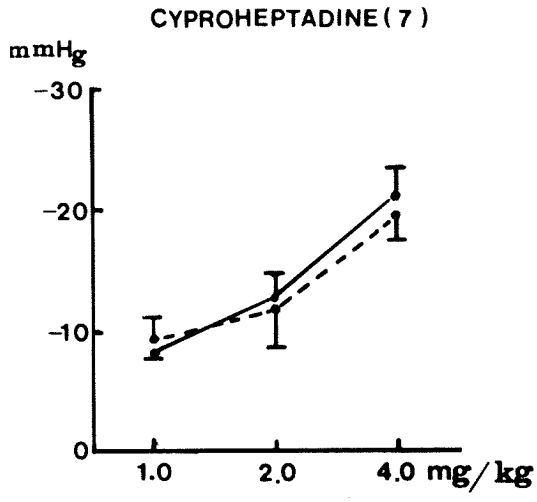

Fig. 8. Effects of cyproheptadine on MCP-induced changes of blood pressure. Cyproheptadine(2.0mg/kg) was injected intravenously after obtaining the control pressure. The methods and other legends are the same as in Fig. 1.

The effect of propranolol and cyproheptadine on MCP-evoked changes of blood pressure. ;

Propranolol[15] 2.0mg/kg, an adrenergic beta-receptors blocking agent, and cyroheptadine, an antiserotonin and antihistaminic agent were used in this study to block peripheral beta-adrenoceptors, and histaminergic and serotonergic receptors. In preliminary studies, we observed that these doses of propranolol and cyproheptadine blocked vasodepressor responses induced by isoproterenol, histaminine and and 5-hydroxytrytamine, respectively. As shown in Table 2, administration of either propranolol or cyproheptadine did not produce any changes in the responses of blood pressure evoked by MCP at doses of 1.0, 2.0 and 4.0mg/kg when compared with the corresponding control group. Fig. 7 and 8 show the effects of propranolol and cyproheptadine on MCP-evoked changes of blood pressure, respectively.

The effect of MCP on the responses of blood pressure induced by norepinephrine and dopamine. ;

In the light of the fact that MCP evoked vasodepressor response was greatly diminished by pretreatment with prazosin, bethanidine and chlorisondamine as shown in Fig. 4, 5 and 6, MCP could produce hypotensive action primarily by blockade of adrenergic nerve. It is therefore of particular interest to study the effect of MCP on the pressor resonses of norepinephrine.

The results of this experiments are shown in Table 3. Each observation was made in five rabbits, respectively. Fig. 9 shows that the pressor effect of norepinephrine was distinctively inhibited during infusion of MCP. Norepinephrine at doses of 0.3, 1.0 and 3.0 ug/kg given intravenously before infusion of MCP evoked the elevation in blood pressure of 9.8± 1.37, 19.6± 1.89 and 28.9± 2.42mmHg, respectively.

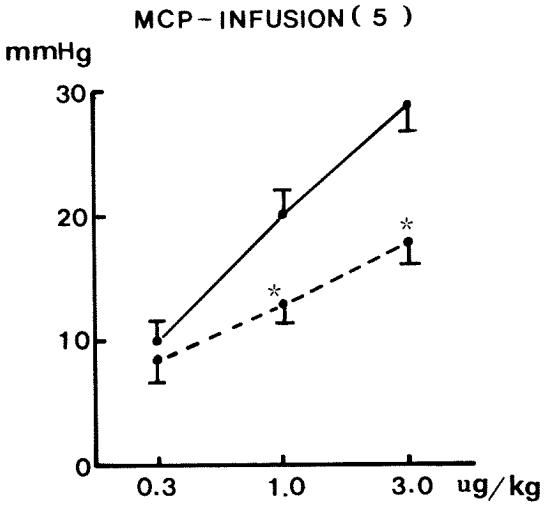

Fig. 9. Effects of MCP-infusiong on norepinephrine-evoked pressor responses. MCP was infused into a jugular vein at a rate of 4.0mg/kg/30min for 30 min after obtaining control values. The methods and other legends are the same as in Fig. 1. *; $p<0.05$

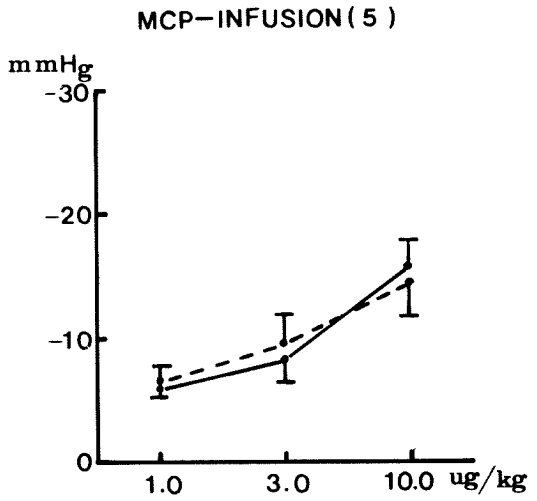

Fig. 10. Effects of MCP-infusion on dopamine-induced depressor responses. The methods and other legends are the same as in Fig. 1 and 8.

Repetitive injection of the same doses of norepinephrine after MCP injusion at a rate of 4.0mg/kg for 30 min resulted in significantly reduced responses of 8.6± 2.09, 13.0± 1.99 ($p<0.05$) and 18.4± 1.52 ($p<0.05$) mmHg, respectively. Intravenous dopamine at doses of 1.0, 3.0 and 10.0 ug/kg elicited no change in depressor responses from −6.0± 0.41, −8.1± 1.27 and −15.7± 2.49 mmHg before MCP-infusion to −6.4± 0.85, −9.3± 1.78 and −14.6± 2.79 mmHg, respectively, as shown in Fig. 10.

DISCUSSION

In the present study, MCP administered into a femoral vein of the rabbit produced a marked, dose-dependent fall in blood ressure.

The vasodepressor responses evoked by MCP were significantly inhibited by pretreatment with prazosin, bethanidine or chlorisondamine while were unaffected by atropone, propranolol and cyproheptadine. MCP also showed inhibitory effects on responses to the pressor activity evoked by norepinephrine but no effect on responses to depressor effects of dopamine. These experimental findings suggest that intravenous MCP causes vasodepressor activity in rabbits through the blockade of peripheral adrenergic alpha receptors with partly central action.

In view of the fact that MCP-evoked hypotensive action was markedly attenuated by pretreatment with chlorisondamine[15], a ganglionic blocking agent, it is felt that the site of depressor action evoked by MCP may be the autonomic ganglia or higher center. However, in unpublished experiments, MCP given intraventricularly produced no change in the response of blood pressure. This finding suggests that MCP has no central effect in evoking vasodepressor activity. Furthermore, bethanidine also inhibited MCP-evoked depressor actions. MCP attenuated significantly pressor reponses evoked by a adrenergic alpha-receptor agonist, norepinephine, while did not affect the depressor of dopamine.

In general, it is known that both chlorisondamine[18] and bethanidine[19] potentiates the pressor activity of norepinephrine in rabbits. In the present work,

these apparent contradictory findings can be explained that the MCP-evoked hypotension is neither due to blockade of autonomic ganglia or adrenergic nerve ending and nor through dopaminergic receptors.

Moreover, the finding that vasodepressor evoked by MCP was clearly reduced by pretreatment with prazosin[15], a postsynaptic alpha I-adrenergic blocker in blood vessel, demonstrates that MCP acts by interfering with peripheral sympathetic function. The superiority of prazosin over other alpha-receptor blocking drugs is attributed to its greater affinity for post synaptic α_1 receptors than for presynaptic alpha 2-adrenergic receptors. Since prazosin has little action on presynaptic receptors, norepinephrine concentrations do not increase and reflex sympathetic activity(for example, tachycardia) is less likely to occur[16-17].

Among the drugs which interefere with peripheral sympathetic function, alpha adrenoceptor blocking agents alone cause reversal of the epinephrine pressor response[20].

When epiephrine is administered to untreated animals, its alpha agonist properties predominate, resulting in a rise in mean arterial pressure. However, in the presence of alpha adrenoceptor blockade, the peripheral β_2-agnoist properties of epinephrine predominate and a fall in arterial pressure or reversal of the pressor response is observed.

In contrast the pressor responses to norepinephrine are impaired by alpha adrenoceptor blockade, but are not reversed[21], as this agent possesses little $\beta_2$gonist activity[22].

Thus, the inhibitory effect of MCP in response to pressor action evoke by norepinephrine may be taken to show the specific adrenergic alpha$_1$-receptor blockade. These observations suggest that the hypotensive activity of MCP appears to be very simlar to that of prazosin. On the other hand, it has been reported that dopamine and apomorphine inhibits synaptic transmission in the lumbar praravertebral ganglia, inducing vasodilation in the isolated hindleg or gracilis muscle of the dog, and the this ganglionic inhibitory effect is antagonized by haloperidol and alpha-adrenoceptor blocking agents[23].

Myers et al[24] also showed that ganglion cells were found in arteriols of skeletal muscles.

Although several investigators have implicated the involvement of postsynaptic dopamine receptors in the initial vasodilator action of small doses of dopamine, this postulation is mainly based on the observation that administration of a dopamine receptor antagonist prevents this vasodilator action of dopamine[25,26]. However, recent studies indicate that dopamine receptors are also located at the sympatheitic ganglia as well as postganglionic sympathetic nerve terminals and activation of either one of these receptors by a suitable agonist results in the inhibition of sympathetic neurotransmission and subsequent vasodilatation[27-32]. Therefore, it is likely that a dopamine receptor blocking agent would be able to inhibit the vasodilator action of dopamine by antagonizing either the postsynatic, presynatic and/or ganglonic dopamine receptors. Lokhandwala and Jandhyala[33] (1979) have shown that the fact that automic ganglionic blockade prevented the vasodilator action of dopamine in a group of dogs with intact sympathetic nervous system suggests that the depressor action of dopamine involved a neurogenic mechanism and was mediated via the activation of dopamine receptors.

In the present study, however, it is thought that the failure of MCP to produce a change in response to the depressor action evoked by dopamine suggested that this effect of MCP is not associated with dopaminergic pathway.

In view of the fact that atropine did not affect the vasodepressor action of MCP, it is very difficult to interpret the effect of MCP in relation to the muscarinic receptors. Therefore, cholinergic muscarinic could be ruled out.

These findings also indicate that the mechanism

of MCP evoked hypotensive action seems to be different from that of contraction of upper gastrointestinal smooth muscle[12-14], in which this contraction is reduced or abolished by atropine-pretreatment.

Furthermore, it is also felt that MCP-evoked depressor activity is not associated with histamine, serotonin or adrenergic beta-receptors stimulation because the effect of MCP was not affected or no changed by pretreatment with cyproheptadine[15] and propranolol[15]. In the present work, it is thought that there is species difference in response to the blood pressure evoked by MCP between the rat and the rabbit.

As forementioned in introduction, MCP given intravenously in rats[4] produced depressor response followed by secondary pressor response, while MCP in rabbits induced only depressor activity.

While the present study has established a pharmacological effects of MCP on the response of blood pressure under normal physiological condition and some mechanism of its action, the participation of this mechanism when this agent is used for treatment of various pathophysiological conditions and more detailed relationship between MCP and dopamine in the vascular actions remain to be determined in the future.

SUMMARY

This study was attempted to investigate the effects of metoclopramide(MCP), a selective dopaminergic antagonist presently employed in treating nausea and vomiting and gastroparesis, on blood pressure of the rabbit and to elucidate the mechanism of its action.

MCP, given into a femoral vein, elicted a dose-related marked fall in blood pressure.

The depressor response evoked by MCP was not affected by pretreatment with atropine or cyproheptadine. The MCP-induced hypotensive effect was inhibited clearly by pretreatment with prazosin, bethanidine or chlorisondamine, while was not modified by propranolol. MCP, when infused intravenously at rate of 4.0mg/kg/30min., resulted in reduction in pressor responses evoked by norepinephrine, but had no effect on depressor responses induced by dopamine.

From these experimental results, it is thought that MCP causes significant reduction in blood pressure of the rabbit, and that this deppressor action may be due to the inhibition of adrenergic alpha-receptors.

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