THE EFFECT OF DOPAMINE ON PERIPHERAL VASCULATURE OF THE RAT

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Many investigators have reported that the effect of dopamine on the peripheral vasculature apparently varies and is dependent on the species. Holtz and Credner (1) observed that dopamine produced depressor effects in blood pressure of guinea pigs and rabbits while pressor effects were produced in cats and dogs. In the anesthetized cat and dog, dopamine causes vasodilatations in the superior and inferior mesenteric, gastric, and renal arteries and vasoconstrictions in the hepatic and splenic arteries (2, 3).

Ebel (3) reported that the action of dopamine on the systemic blood pressure was the result of balance between these vasoconstrictions and vasodilatations. It is also reported that dopamine has a direct sympathomimetic action on the heart (2, 4-7), while some reports suggest that dopamine acts on the sympathetic nerve terminals since its effect is reduced by reserpine, cocaine (8) and ephedrine (9). On the other hand, Tsai (10) observed that dopamine has both actions on cat nictitating membrane and on guinea pig heart.

In order to analyse the pressor effect of dopamine in the rat, experiments herein were designed to study (a) the modification of dose-response curve of dopamine on the rat blood pressure by several drugs and (b) the local vasculature effects of dopamine at the hind limb and kidney.

MATERIALS AND METHODS

Wistar male rats 250-300 g were anesthetized with urethane (1.5 g/kg s.c.). A tracheal tube was inserted to facilitate respiration. In most experiments, the vagus nerves were cut high in the neck. Systemic blood pressure was measured with a transducer (Nihon Kohden MP-4T) connected to a cannula in the left carotid artery. Drugs were administered into the external juglar vein. In the case of hind limb perfusion experiment, following the method of Brody (11), the abdominal aorta was doubly cannulated with the external circuit which was constructed with a Tygon tube having an inside diameter of 1/16 inches and a wall thickness of 1/16 inches. Polyethylene tubes (Hibiki NO. 3) 3-4 cm in length were inserted into the both ends of Tygon tube and were used for cannulation of the aorta. After cannulation, Tygon tube was set in a Model T-8 Sigma motor pump. Flow rate was adjusted so that perfusion pressure was essentially equivalent to blood pressure. Systemic blood pressure and perfusion pressure were recorded from the proximal aortic
cannula and the distal one respectively. In the case of kidney perfusion the same method was used as hind limb perfusion. One cannula was inserted into the carotid artery and another into the renal artery. When the rate of flow was constantly adjusted, the change in perfusion pressure was directly proportional to the change in vascular resistance. Intravenous injection was made into the external jugular vein, and the intraarterial injection was given into the rubber tube connected to the shank of the polyethylene cannula. The volume of intraarterial injection was maintained at less than 10 μl by using a microsyringe (Terumo Microsyringe MSN-10).

Agents used were: dopamine hydrochloride (Tokyo Kasei), 1-norepinephrine hydrochloride (Sigma), tyramine hydrochloride (Tokyo Kasei), l-ephedrine hydrochloride (Taisho), 1-α-methyldopa (Taisho), dl-α-methyl-p-tyrosine (Aldrich), reserpine (Takeda), rescinnamine (Boehringer Mannheim), ergotamine tartrate (Tokyo Kasei), disulfiram (Tokyo Kasei), morphine hydrochloride (Sankyo), haloperidol (Dainihon), dl-propranolol (Sumitomo), atropine sulphate (Tokyo Kasei), and 6-hydroxydopamine hydrobromide.

Disulfiram (800 mg/kg) was injected intraperitoneally twice (24 hr and 1 hr before experiments, respectively). Reserpine (5 mg/kg) and rescinnamine (5 mg/kg) were injected intraperitoneally 24 hr before experiments. In some cases reserpine was injected for four days (2 mg/kg/day on the first two days and 1 mg/kg/day on the next two days). Alpha-methyldopa (400 mg/kg) and α-methyl-p-tyrosine (400 mg/kg) were injected intraperitoneally 24 hr before experiments. Six-hydroxydopamine (100 mg/kg) was dissolved immediately before injection in 0.001 N HCl saline solution which had been gassed with nitrogen for 10 min and injected intravenously 2–3 weeks before experiments.

The statistical significance of difference between means was calculated using Student t test.

RESULTS

1. Hind limb perfusion experiment

The perfusion pressure of hind limb was hardly affected by intravenous injections of dopamine (300 μg/kg) and norepinephrine (5 μg/kg) but raised with intraarterial injections of these drugs (Fig. 1. a).

2. Kidney perfusion experiment

Intraarterial injections of dopamine (6, 10, and 20 μg/kg) and norepinephrine (20, 60, and 100 ng/kg), caused monophasic vasoconstrictions (Fig. 1. b).

3. Effects of several drugs on dopamine action in systemic arterial blood pressure

a) Effects of pharmacological blocking agents

Pressor action induced by dopamine was reversed by adrenergic-α-blocking agent, ergotamine. This depressor component was not influenced by propranolol (0.2 mg/kg), atropine (0.5 mg/kg), morphine (10–30 mg/kg), and haloperidol (0.1–0.3 mg/kg) (Fig. 2).

b) Effect of disulfiram

As dopamine is the immediate precursor of norepinephrine, the effect of conversion into norepinephrine was researched. Rats were pretreated with disulfiram, dopamine-β-
FIG. 1. Effects of dopamine (DA) and norepinephrine (NE) on the hind limb (a) and kidney (b) perfusion pressure in rats.

BP; blood pressure, PP; perfusion pressure

FIG. 2. Effect of ergotamine on pressor action of dopamine.

(a) before and (b) after administration of ergotamine 2.5 mg/kg.
FIG. 3. Effect of disulfiram on pressor action induced by dopamine.
Solid line; untreated, broken line; disulfiram treated. Ordinate; change of blood pressure, abscissa; doses of dopamine. Values are means $\pm$ S.D. of seven experiments.

FIG. 4. Effect of cocaine on pressor actions induced by dopamine and tyramine.
Closed circle; dopamine, open circle; tyramine. Solid line; untreated, broken line; cocaine treated. Ordinate; change of blood pressure, abscissa; doses of dopamine and tyramine. S; statistical significance between means (p<0.01). Values are means $\pm$ S.D. of seven experiments.
FIG. 5. Effect of ephedrine on pressor action induced by dopamine. Ephedrine was injected up to 15 (●—●), 30 (○—○), and 60 (▲—▲) mg/kg. Ordinate; change of blood pressure, abscissa; doses of dopamine. Values are mean ± S.D. of seven experiments.

FIG. 6. Effect of α-methyldopa on pressor actions induced by dopamine and tyramine.
Close circle: dopamine, open circle: tyramine. Solid line: untreated, broken line: α-methyldopa treated. Ordinate; change of blood pressure, abscissa; doses of dopamine and tyramine. S; statistical significance between means (p<0.01). Values are mean ± S.D. of seven experiments.
hydroxylase inhibitor (24, 25). The dose-response curve of dopamine did not change with disulfiram (Fig. 3).

c) Effects of cocaine and ephedrine

The pressor action evoked by dopamine was reversed in the small dose range and reduced in the large dose range by cocaine and ephedrine. Cocaine (5 mg/kg) was administered intravenously for 5–6 min. Inhibition with cocaine was significant ($p<0.01$) in doses from 10 μg/kg to 1 mg/kg of dopamine (Fig. 4). On the other hand, the pressor action induced by tyramine was more greatly reduced than that caused by dopamine especially in the high dose range. Ephedrine (5–10 mg/kg) was injected repeatedly at intervals of 15–20 min. Fig. 5 shows the shift of dose-response curve of dopamine with the doses of 15, 30, and 60 mg/kg of ephedrine. These three dose-response curves treated by ephedrine were not significantly different ($p>0.05$).

d) Effects of α-methyl-p-tyrosine and α-methyldopa

Pressor actions produced by dopamine and tyramine were partially reduced by α-
methyldopa (Fig. 6), while the pressor actions of these amines were reduced by α-methyl-
p-tyrosine (Fig. 7).

e) Effect of 6-hydroxydopamine

Pressor action evoked by dopamine was significantly potentiated by 6-hydroxydopamine, while that of tyramine was markedly reduced (Fig. 8).

f) Effects of reserpine and rescinnamine

Figs. 9 and 10 show the dose-response curves of dopamine and tyramine in rats pre-
treated by reserpine and rescinnamine. The potentiation of pressor action of dopamine
by reserpine was significant (p<0.01) in a dose range from 10 μg/kg to 300 μg/kg, while
the action of tyramine was markedly reduced. The pressor action of norepinephrine was
not potentiated in rats treated with reserpine 24 hr before experiments. It was potentiated
however, in rats treated for four days (2 mg/kg on the first two days and 1 mg/kg on the next
two days) (Fig. 11).

g) Effect of ephedrine in reserpine treated rats

Fig. 12 illustrates the effect of ephedrine on pressor action of dopamine in the reserpine
treated rats. Depressor component of dopamine was greatly reduced by treatment of
reserpine (5 mg/kg i.p. 24 hr before experiments).
FIG. 11. Effect of reserpine on pressor action induced by norepinephrine. Closed circle ; untreated, open circle and broken line ; reserpine treated 24 hr before, open circle and solid line ; reserpine treated for four days. Ordinate ; change of blood pressure, abscissa ; doses of norepinephrine. S ; statistical significance between means (p<0.01). Values are means ± S.D. of seven experiments.

FIG. 12. Effect of ephedrine on pressor action induced by dopamine in reserpine treated rats. Reserpine was injected 24 hr before experiments. Right side numbers indicate ephedrine dosage. Closed circle and solid line ; control, closed circle and broken line ; ephedrine treated, open circle and solid line ; reserpine treated, open circle and broken line ; reserpine and ephedrine treated. Ordinate ; change of blood pressure, abscissa ; doses of dopamine. Values are means ± S.D. of seven experiments.

DISCUSSION

It has been reported that local vasculature responses to dopamine differ depending on the vascular bed, that is dopamine dilates the renal vascular bed and constricts the femoral vascular bed in dog (11-13), but constricts both vascular beds similar to norepinephrine in rat. These observations suggest that the nature of the renal vascular bed in the rat is different from that of the dog concerning response to dopamine. It has been demonstrated that the depressor component of dopamine in rabbit, guinea pig, cat, and dog was not blocked by adrenergic-β-blocking, anticholinergic, and antihistaminic agents (14-16). In the present investigation, the depressor component of dopamine in rats also was not influenced by these classical blocking agents. According to van Rossum (17) and Dhasmana (18), the depressor action after treatment of adrenergic-α-blocking agent in cats and dogs was blocked by haloperidol and morphine, respectively. The depressor action of dopamine, however, was not affected by these agents in rats. Consequently, rats may
have a specific natural dopamine receptor different from cats or dogs.

Cocaine and ephedrine are known as uptake inhibitor of catecholamines (19-21, 23) and ephedrine is the releaser of endogenous norepinephrine (22). From this point of view, the observation that pressor action of dopamine was reduced by cocaine and ephedrine like tyramine which is a typical indirectly acting sympathomimetic amine (26), suggests that dopamine may have some indirect sympathomimetic action to rat vasculature with the major part having direct action, as the rate of inhibition is considerably less than that of tyramine. This reasoning may be supported by the observation that α-methyl-p-tyrosine which is a catecholamine depleting agent reduced not only the pressor action of tyramine but that of dopamine. It has been observed that norepinephrine is not potentiated by reserpine administered 24 hr before experiment (28, 29). Our results were in agreement with this observation. The pressor action of norepinephrine was potentiated in the rats reserpinized for four days, but not for 24 hr. On the other hand, the pressor action of dopamine was potentiated in rats reserpinized for 24 hr. Moreover, the reducing effect of ephedrine to dopamine in reserpinized rats was significantly less than control animals. Reserpine and indirectly acting sympathomimetic amines (e.g. ephedrine, tyramine) were thought to release norepinephrine from a different pool of stores, respectively (32). Trendelenburg reported that reserpin impairs retention of catecholamine at the intragranular reserve pool but does not block the uptake process across the axoplasmic membrane from the extracellular fluid to the cytoplasmic mobile pool (30), that is, reserpine does not block the norepinephrine displacing effect of ephedrine from the cytoplasmic mobile pool. Therefore it is considered that the potentiation of pressor action of dopamine with reserpine is due to inhibition of depressor component of dopamine by reserpine. Thoenen (31) reported that denervation supersensitivity to catecholamines induced by 6-hydroxydopamine was fully developed 2-3 weeks after administration. In this experiment 6-hydroxydopamine markedly reduced pressor action of tyramine but potentiated that of dopamine even at 3 mg/kg of this drug. Inhibition of uptake is not fully applicable in explaining the mechanism of potentiation to dopamine. In spite of the uptake inhibitor, cocaine reduced the pressor action of dopamine. The result of this experiment suggests that 6-hydroxydopamine not only inhibits the uptake process of catecholamine but increases the sensitivity of dopamine receptor.

Since disulfiram had no significant effect on the dose-response curve of dopamine, conversion of dopamine into norepinephrine apparently does not contribute to the response of peripheral vasculature to dopamine.

SUMMARY

Effects of dopamine on the peripheral perfusion pressure and blood pressure were investigated in the anesthetized rats, with the following results:

1. Dopamine caused vasoconstriction in the hind limb and kidney vascular beds.
2. Pressor action of dopamine was reversed by ergotamine and this depressor component was not influenced by propranolol, atropine, haloperidol, and morphine.
3. Pressor action of dopamine was reduced by cocaine, ephedrine, α-methyldopa, and α-methyl-p-tyrosine.

4. Pressor action of dopamine was potentiated by reserpine, rescinnamine, and 6-hydroxydopamine.

5. The depressor component of dopamine after treatment of ephedrine was reduced by reserpine.

These results suggest that the vasoconstrictive effect of dopamine is predominant in the rat peripheral vasculature and this effect is partly dependent on indirect sympathomimetic action. Potentiation with reserpine may be the result of reduction in the depressor component of dopamine with reserpine, and potentiation with 6-hydroxydopamine the result of not only uptake inhibition but increase in sensitivity of the dopamine receptor.

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