Pharmacological Analysis of Dopamine Action on the Isolated Dog Atrium

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CHIBA, S. *Pharmacological Analysis of Dopamine Action on the Isolated Dog Atrium*. Tohoku J. exp. Med., 1975, 115 (4), 355-360 — The isolated right atrium of the dog was perfused with arterial blood introduced from a carotid artery of a support dog. The selective injection of dopamine, tyramine and norepinephrine into the cannulated sinus node artery induced dose-relatedly positive chronotropic and inotropic effects. However, for an equal increase in sinus rate, dopamine caused less increase in tension development than norepinephrine. Tyramine caused least increase in contractility. Effects induced by dopamine were not blocked by treatment with tetrodotoxin which blocked those induced by nicotine. Desmethylinipramine treatment significantly suppressed dopamine-induced effects and completely blocked tyramine-induced ones but rather enhanced norepinephrine-induced ones. Alprenolol inhibited effects of dopamine, tyramine and norepinephrine.

From these results, it is concluded that positive chronotropic and inotropic effects of dopamine are partly due to tyramine-like effect which causes the release of norepinephrine from sympathetic storage sites. ——— dopamine; tyramine; desmethylinipramine; tetrodotoxin; isometric tension development

It is well recognized that dopamine has a cardiac stimulating property which partly by acting directly on beta-adrenergic receptors and partly by releasing norepinephrine from sympathetic storage sites (McDonald and Goldberg 1963; Goldberg 1972; Chiba et al. 1973, 1974). On the other hand, it has been reported that dopamine causes a smaller increase in heart rate at an equivalent increment in cardiac contractile force than other catecholamines (Black and Rolett 1966, 1968; Harrison et al. 1969; Wintroub et al. 1969). In 1970, Tuttle suggested that the disparity between heart rate and contractility induced by dopamine may be due to a small direct effect of dopamine on the SA node.

In the present study, it was attempted to investigate effects of dopamine, tyramine and norepinephrine on atrial rate and contractility, using the blood-perfused, isolated atrium preparation of the dog (Chiba et al. 1975a, b) which was originally developed by Chiba et al. (1972). Furthermore, these effects were pharmacologically analyzed by use of desmethylinipramine (Chiba 1974), tetrodotoxin (Hashimoto and Chiba 1969) and alprenolol. A preliminary report of part of these results has been published (Chiba 1975).

METHODS

Twenty-five mongrel dogs were anesthetized with i.v. sodium pentobarbital. After treatment with sodium heparin, the right atrium was excised. The sinus node artery was cannulated and perfused with arterial blood led from the heparinized support dog. The details of preparation have been described in the previous papers (Chiba et al. 1975a, b; Chiba 1975). The electrogram, atrial rate, perfusion flow rate, isometric tension development and the maximum rate of the developed tension (dT/dt) were measured and recorded on an ink-writing rectigraph. The perfusion flow rate was 2 to 4.5 ml/min, and the atrial rate was approximately 100 beats/min in this study.

The drugs used were dopamine hydrochloride (Kyowa Hakko), norepinephrine hydrochloride (Sankyo), tyramine hydrochloride (Wako), tetrodotoxin (Sankyo), desmethylinipramine (Fujisawa), alprenolol (AB Hässle) and nicotine (base). The drug solution was intra-arterially injected into the cannulated sinus node artery in a volume of 0.01 to 0.03 ml over a 4 sec period.

RESULTS

Effects of dopamine on the blood-perfused, isolated atrium preparation

When dopamine was injected into the cannulated sinus node artery, a positive chronotropic and an inotropic effect were simultaneously induced even in a small dose level of $0.1 \mu\text{g}$ of dopamine. This indicates that the threshold dose level of dopamine for inducing a positive chronotropic and an inotropic effect is almost the same. Fig. 1 shows typical responses to increasing doses of norepinephrine, dopamine and tyramine on atrial rate and atrial contractile force. The positive inotropic response to dopamine was smaller than that to norepinephrine in doses which produced the same grade of the positive chronotropic response. The response to tryamine was smallest. The ratios of ED_{50} of norepinephrine, dopamine and tyramine on the tension development are roughly 1:30:100, respectively, as reported previously (Chiba 1975). The order of the duration of the same grade of positive inotropic action is tyramine > dopamine > norepinephrine.

Fig. 1. Effects of increasing doses of norepinephrine, dopamine and tyramine on sinus rate and the tension development in the blood-perfused, isolated atrium preparation of the dog.

Effects of tetrodotoxin on responses to dopamine and nicotine

When tetrodotoxin was injected into the cannulated sinus node artery, negative chronotropic and inotropic responses were induced dose-relatedly. The positive chronotropic and inotropic responses to dopamine were not inhibited by treatment with tetrodotoxin while those to nicotine were suppressed by it. Fig. 2 shows that 3 μg of tetrodotoxin inhibits effect of 10 μg of nicotine but does not suppress that of 0.1 μg of dopamine. Summarized data are shown in Table 1.

TABLE 1. *Effects of tetrodotoxin (TTX) on positive chronotropic and inotropic responses to dopamine and nicotine in 4 isolated atrium preparations*

Compound	TTX treatment (1–3 μg)			
	Before		After	
	PCE (% increase)	PIE (% increase)	PCE (% increase)	PIE (% increase)
Dopamine 0.1–0.3 μg	15 $\pm$ 5.8	78 $\pm$ 22.6	14 $\pm$ 5.8*	87 $\pm$ 28.9*
Nicotine 3–10 μg	29 $\pm$ 8.1	119 $\pm$ 27.4	3 $\pm$ 1.3†	16 $\pm$ 11.6†

Results are given as mean $\pm$ SEM.

Control atrial rate is 96.7 $\pm$ 3.3 (mean $\pm$ SEM) beats/min in 4 preparations.

PCE, positive chronotropic effect; PIE, positive inotropic effects.

* not significantly different from the control values ($P>0.05$).

† significantly different from the control values ($P<0.05$).

Fig. 2. Effects of 3 μg of tetrodotoxin on actions of 10 μg of nicotine and 0.1 μg of dopamine in the blood-perfused, isolated atrium preparation of the dog.

Effects of desmethylimipramine on responses to dopamine, tyramine and norepinephrine

When desmethylimipramine was injected into the cannulated sinus node artery, initially negative chronotropic and inotropic responses followed by rela-

Fig. 3. Effects of 30 μ g of desmethylinipramine (DMI) on actions of 0.3 μ g of dopamine (DA) and 0.01 μ g of norepinephrine (NE) in the blood-perfused, isolated atrium preparation of the dog.

TABLE 2. Effects of desmethylinipramine (DMI) on positive chronotropic and inotropic responses to dopamine, tyramine and norepinephrine

Compound	Number of prep.	DMI treatment (10–30 μ g)			
		Before		After	
		PCE (% increase)	PIE (% increase)	PCE (% increase)	PIE (% increase)
Dopamine 0.3–1 μ g	7	49 $\pm$ 10.4	186 $\pm$ 35.1	21 $\pm$ 5.7*	94 $\pm$ 16.7*
Tyramine 0.3–1 μ g	5	47 $\pm$ 7.6	93 $\pm$ 12.6	9 $\pm$ 6.4†	10 $\pm$ 4.0‡
Norepinephrine 0.01–0.03 μ g	9	39 $\pm$ 8.6	135 $\pm$ 37.6	42 $\pm$ 13.3	234 $\pm$ 68.2

Results are given as mean $\pm$ SEM.

Control atrial rate is 99.2 $\pm$ 5.7 (mean $\pm$ SEM) beats/min in 9 isolated atrium preparations.

PCE, positive chronotropic effect; PIE, positive inotropic effect.

* significantly different from control values ($P<0.05$).

† significantly different from control values ($P<0.02$).

‡ significantly different from control values ($P<0.01$).

vely long-lasting positive chronotropic and inotropic ones were dose-relatedly induced. However, the positive chronotropic response was predominantly induced and the positive inotropic one was occasionally unclear.

The positive chronotropic and inotropic responses to tyramine were markedly inhibited by treatment with desmethylinipramine, and those to dopamine were significantly suppressed by that as shown in Fig. 3. On the other hand, those to norepinephrine were rather enhanced by desmethylinipramine treatment. Summarized data are shown in Table 2.

Effects of alprenolol on dopamine action

When alprenolol, an adrenergic beta-blocking agent, was injected into the cannulated sinus node artery, negative chronotropic and inotropic responses were dose-relatedly induced at a dose level of 0.3 to 10 μ g. Effects of dopamine were inhibited by treatment with alprenolol both in chronotropism and in inotropism.

DISCUSSION

Previously Chiba et al. (1973) reported that dopamine induced a long-lasting positive chronotropic effect as compared with norepinephrine or epinephrine when injected into the sinus node artery of the in situ dog heart. In addition, Chiba et al. (1974) also reported that the positive chronotropic effect of dopamine was significantly suppressed by treatment with desmethyylimipramine, although it was not influenced by tetrodotoxin. Those results suggested that the positive chronotropic action of dopamine is tyramine-like partly due to release of norepinephrine, because tyramine action was blocked by treatment with desmethyylimipramine (Chiba et al. 1974), although it was not influenced by tetrodotoxin (Hashimoto and Chiba 1969). However, the inotropic action of dopamine has not been examined yet on the dog atrium by reason of the difficulty of the measurement of the tension development. Recently, the blood-perfused, isolated atrium preparation of the dog heart, arranged by Chiba et al. (1972), was modified for measuring the contractile force (Chiba et al. 1975a, b). In that arrangement, both atrial rate and the tension development persisted unchanged over 5 hr in all 5 control experiments (Chiba et al. 1975b). In the present study, using this preparation dopamine action was investigated not only on chronotropism but also on inotropism. Even in inotropism, dopamine action was not influenced by treatment with tetrodotoxin and it was suppressed by desmethyylimipramine treatment, i.e., dopamine-induced positive chronotropic and inotropic effects were not modified by tetrodotoxin which blocked nicotine action, and these were significantly suppressed by desmethyylimipramine which markedly blocked tyramine action but slightly potentiated norepinephrine action.

In 1970, Tuttle reported that the positive inotropic response of the dog ventricle to dopamine is more predominant than the positive chronotropic one. In the present study, dopamine did not show more predominant inotropic response than the positive chronotropic one on the dog atrium. As demonstrated previously, the inotropic action of dopamine was rather smaller than chronotropic one, i.e., the order to the ratios of the inotropism/chronotropism was norepinephrine > dopamine > tyramine (Chiba 1975). The difference from Tuttle's result (1970) which indicated predominant inotropic effect of dopamine may be due to reasons as follows: 1) this preparation is completely isolated from extracardiac factors but the preparation used by Tuttle is not completely excluded from the influence of the reflex mechanism, and 2) in this study dopamine exerts its inotropic effect on the dog atrium but not on the dog ventricle.

Acknowledgments

I am very grateful for the technical assistance of Mr. Shoji Hayashi. These experiments were supported in part by a grant from Eisai Co.

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