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EFFECTS OF DOPAMINE ON SINUS RATE AND VENTRICULAR CONTRACTILE FORCE OF THE DOG HEART *in vitro* AND *in vivo*

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1 Experiments were carried out on dog isolated papillary muscle and sinus node preparations perfused with arterial blood from a donor dog. The chronotropic and inotropic effects of dopamine were analysed by using reserpine, desmethylimipramine (DMI), cocaine and phenoxybenzamine, and the relative chronotropic and inotropic effects defined, the results being compared with those for noradrenaline (NA).

2 The effects of dopamine administered intra-arterially into the isolated preparations were reduced by pretreatment of animals with reserpine both in the papillary muscle and sinus node. The chronotropic effects, however, were affected less by pretreatment with reserpine than were the inotropic effects.

3 Desmethylimipramine (DMI) reduced the inotropic and chronotropic effects of dopamine, and enhanced the effects of NA and nerve stimulation; the chronotropic effects of the amines were less affected than the inotropic effects.

4 Cocaine enhanced considerably the inotropic and chronotropic effects of NA, and decreased the inotropic but not the chronotropic effect of dopamine.

5 Phenoxybenzamine enhanced the inotropic effects of dopamine, NA and nerve stimulation, but did not affect the chronotropic effects of the amines.

6 When dopamine (1 to 300 μg/kg) was administered intravenously to the donor dog, it increased preferentially the contractile force of the ventricular myocardium with a comparatively small change of the sinus rate in the isolated preparations as well as in the heart *in vivo*. NA (0.1 to 10 μg/kg) caused effects similar to those of dopamine. The maximal inotropic responses to these catecholamines were reached with lower doses than the chronotropic ones.

7 It is concluded that both the positive inotropic and the positive chronotropic responses to dopamine are mediated partially by a direct and partially by an indirect stimulant effect on β-adrenoceptors in the dog heart. The present results suggest that the difference in activity of dopamine and NA between the ventricular myocardium and the sinus node may be ascribed to the unequal innervation with adrenergic nerve fibres of the atrium and the ventricle (Furnival, Linden & Snow, 1971). The sinus node which is densely innervated by adrenergic nerve fibres may inactivate noradrenaline and dopamine more effectively than the ventricular myocardium through the uptake into the nerve and thereby be less sensitive to the exogenous catecholamines.

Introduction

Dopamine has been shown to have both direct and indirect sympathomimetic actions on the heart in various species. In human subjects and in the dog, it increases myocardial contractile force at doses which have little effect on heart rate (Maxwell, Rowe, Castillo, Clifford, Afonso & Crumpton, 1960; Holmes & Fowler, 1962; Horwitz, Fox & Goldberg, 1962; McDonald & Goldberg, 1963). Goldberg (1972) concluded that dopamine differs from other catecholamines in this respect. However, Furnival, Linden & Snow (1971) have shown that noradrenaline caused a much greater inotropic change than isoprenaline for a given chronotropic

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change in the denervated dog heart. Tuttle (1970) has suggested that the positive chronotropic effect of dopamine is due to direct stimulation of β-adrenoceptors, whereas the positive inotropic effect is largely indirect. This assumption was based on the finding that in the anaesthetized dog, following vagotomy, the positive inotropic effect of dopamine, but not the positive chronotropic effect could be abolished with desmethylimipramine (DMI). This latter observation is at variance with the finding that the positive chronotropic response to dopamine is reduced by reserpine in the dog (Bejrablaya, Burn & Walker, 1958), the guinea-pig (Tsai, Langer & Trendelenburg, 1967), rabbit (Lee & Yoo, 1964) and cat (Farmer, 1966).

The present study was undertaken to elucidate further the mechanism of action of dopamine on the myocardium by the use of reserpine, DMI, cocaine and phenoxybenzamine, and the results were compared with those for noradrenaline (NA) on the isolated, blood-perfused papillary muscle (Endoh & Hashimoto, 1970a, b) and sinus node (Kubota & Hashimoto, 1973) preparations of the dog. Comparisons were made between the *in vitro* effects of dopamine and NA and the effects of the amines on myocardial contractile force and heart rate *in vivo* in the donor dog.

Methods

Mongrel dogs of either sex weighing between 7 and 14 kg were anaesthetized with sodium pentobarbitone (30 mg/kg i.v.). Each animal was given an intravenous dose of heparin (500 u/kg) and the heart removed. The ventricular septum together with the anterior papillary muscle of the right ventricle, and the right atrium containing the sinus node, were excised separately and placed in cold Tyrode solution gassed with 95% O_2 and 5% CO_2. The anterior septal artery and the sinus node artery respectively were cannulated and were perfused with arterial blood from a donor dog at a constant perfusion pressure of 100 mmHg using a rotating pump (Watson-Marlow Ltd., type MHRE 200). The venous effluent from the preparations was collected in a reservoir and returned to the donor dog through the jugular vein. The donor dog was anaesthetized with sodium pentobarbitone (30 mg/kg i.v.); heparin (500 u/kg) was given intravenously immediately before the perfusion began and subsequent doses of heparin (200 u/kg) given at intervals of 1 hour. The temperature of the tissues was maintained at 37-38° C. Details of the experimental procedures used in perfusion of the papillary muscle and the sinus node have been described previously (Endoh & Hashimoto, 1970a, b; Kubota & Hashimoto, 1973). The papillary muscle was driven at a rate of 120 beats/min with square wave pulses of 5 ms duration and a stimulus strength of 1 V (about 1.5 times the threshold voltage). The developed tension of the papillary muscle was measured isometrically with a force displacement transducer (Statham gold cell with microscale accessory Model UL5). The rate of the isolated sinus node was recorded by means of a cardiotachograph (Grass 7P4D) triggered by the electrogram of the sinus node region, using a unipolar silver electrode. The maximal rate of developed tension (dT/dt) and perfusion pressure of the preparation, together with the blood pressure and heart rate of the donor dog, were also constantly recorded and displayed on an inkwriting oscillograph (Grass Model 7B polygraph). The blood flow of the preparations was measured by collecting blood in a graduated cylinder or by means of an electromagnetic flow meter (Nycotron, Model 375).

Drug solutions, in a volume of 0.01-0.03 ml, were injected into the rubber tubes connected to the arterial cannula of each of the isolated preparations. Injections were made over a period of 4 s with a microsyringe (Jintan Terumo Co.). Cocaine was infused at a rate of 0.01 ml/min into the base of the Y piece connecting the outflow from the donor dog to the two preparations.

Release of autonomic transmitters in response to field stimulation (FS) of the papillary muscle (Endoh & Hashimoto, 1970b) was obtained by raising the voltage of the driving pulse of the muscle from 1 V to 5 V or 10 V for 15 or 30 seconds. Perivascular nerve stimulation (PNS) of the papillary muscle (Endoh, Hashimoto & Kimura, 1972) was performed by applying a pulse of 1 ms duration and 3-20 V at 10-20 Hz for 15 or 30 s through bipolar silver electrodes attached around the septal artery.

In seven experiments, a left thoracotomy was performed in the donor dog. A Walton-Brodie strain-gauge arch was sutured to the surface of the right ventricle for the recording of myocardial contractile force, and the cervical vagi divided. Drugs were administered via a cannulated femoral vein. Chronotropic and inotropic responses to dopamine and NA were recorded from the intact heart of the donor dog and the isolated preparations, simultaneously. Inotropic effects were expressed either in absolute values (g in the papillary muscle and mm in the donor dog) or in percentage changes of the active tension.

Drugs used in these experiments were dopamine hydrochloride, (−)-noradrenaline bitartrate, tyramine hydrochloride, prindolol (Visken), reserpine, desmethylimipramine hydrochloride (DMI, Geigy), cocaine hydrochloride and phenoxybenzamine.

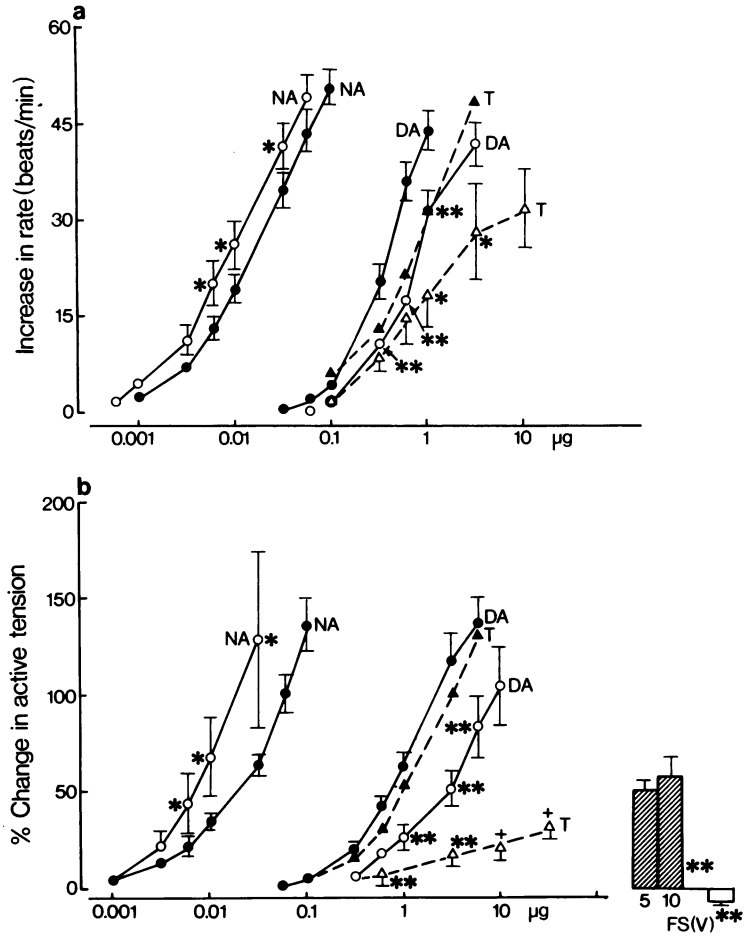

Figure 1 Effects of reserpine on mean responses to noradrenaline (NA), dopamine (DA), tyramine (T) and field stimulation (FS) in the dog. (a) Isolated sinus node preparation and (b) isolated papillary muscle. The sympathomimetic amines were directly injected into the sinus node or papillary muscle artery. Since the blood flow of the papillary muscle preparation is about 5 times that of the sinus node preparations, the concentration of the amines in the sinus node preparation is higher than that in the papillary muscle preparation. Closed symbols and hatched columns: preparations from untreated animals (n = 15 to 27 in NA, DA and FS; n = 6 in T); open symbols and open columns: preparations from reserpine-pretreated animals (n = 6); vertical bars show s.e. mean. *$P < 0.05$ compared with responses to the corresponding doses of amines and to nerve stimulation in preparations from untreated animals; **$P < 0.01$; +$P < 0.001$ compared with the response to 6 μg of tyramine.

DMI and phenoxybenzamine were dissolved in 30% ethanol solution; close arterial injection of 0.01 ml of 30% ethanol solution caused small negative inotropic and negative chronotropic effects lasting for only 1 to 2 minutes.

Reserpine was given in a dose of 3 mg/kg subcutaneously to 9 animals 24 h before the experiment. Six of these animals were used to provide the isolated preparations, 3 were donor animals.

Doses of prindolol, phenoxybenzamine and reserpine refer to the base; doses of the other drugs refer to the corresponding salt.

All experimental values are given as means with s.e. mean. Statistical comparisons were performed by means of Student's t test. The test for paired

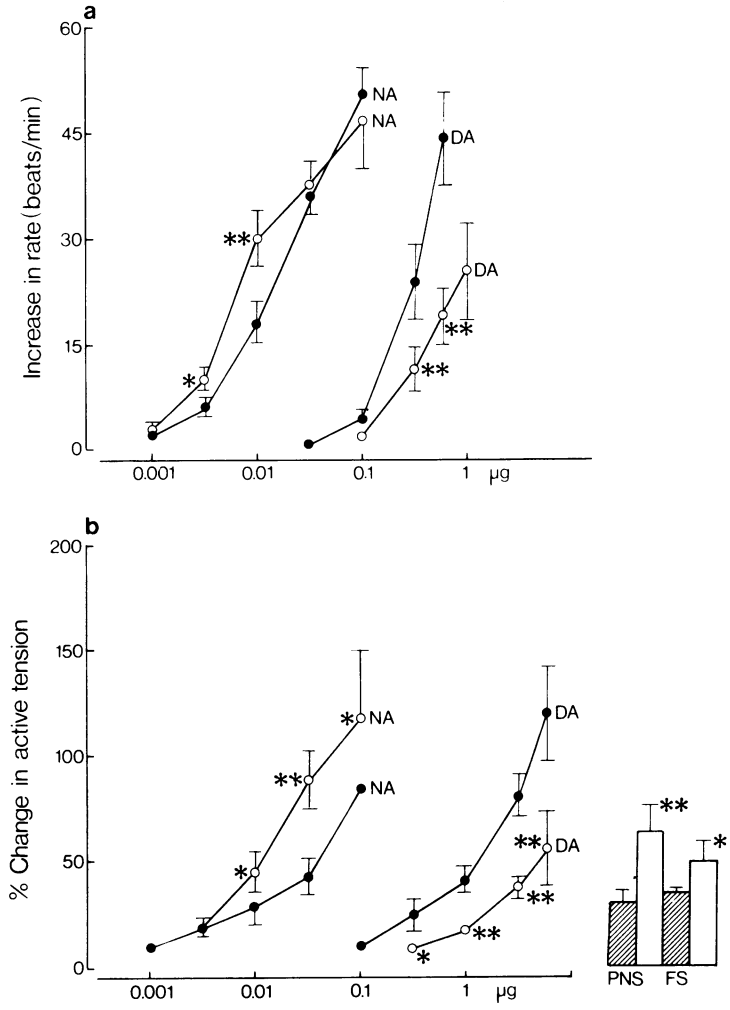

Figure 2 Effects of desmethylimipramine (DMI) on mean responses to noradrenaline (NA), dopamine (DA), perivascular nerve stimulation (PNS) and field stimulation (FS) in dog (a) isolated sinus node preparation and (b) isolated papillary muscle. Closed symbols and hatched columns: control responses; open symbols and open columns: following administration of DMI 100 μg; n =3 to 6; vertical bars show s.e. mean. *$P < 0.05$ compared with responses to the corresponding doses of NA and dopamine, and to nerve stimulation in the absence of DMI-treatment; **$P < 0.01$.

comparison was used when applicable. A P value of less than 0.05 was considered to be significant.

Results

Effects of noradrenaline and dopamine on sinus rate and active tension in the isolated preparations

NA and dopamine injected directly into sinus node or papillary muscle artery increased the rate of contraction of the sinus node preparation and increased active tension in the papillary muscle preparation over a wide range of doses. The responses were dose-dependent; the dose-response curve for the two catechlamines were parallel; NA was approximately 50 times more potent than dopamine on both preparations, when they were compared in molar doses (Figure 1). Since the effects of NA and dopamine on the maximum rate of developed tension (dT/dt) in the papillary muscle were similar to the effects on active

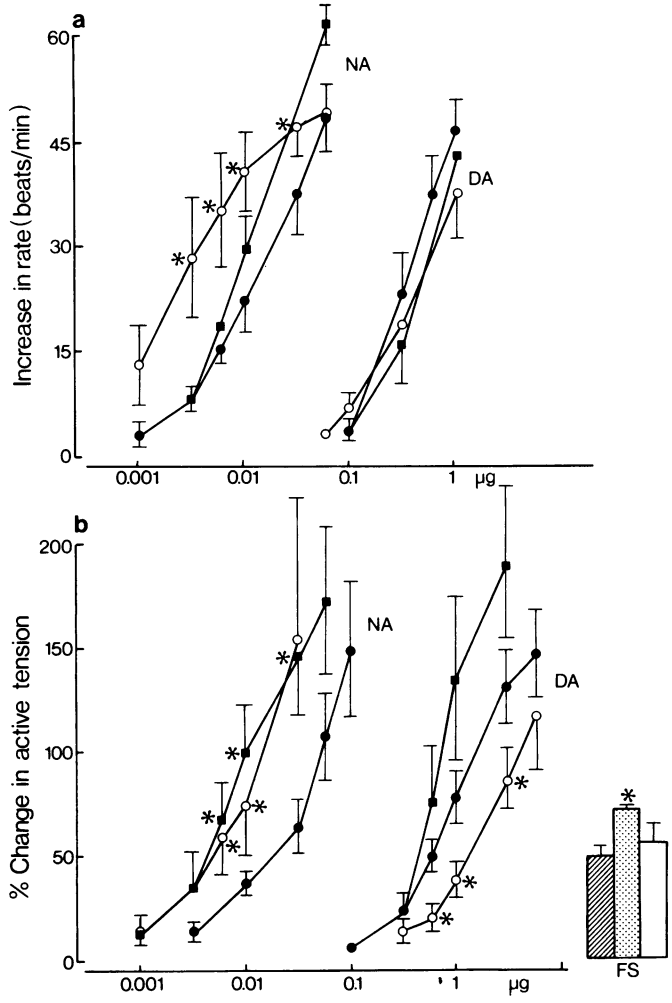

Figure 3 Effects of cocaine on mean responses to noradrenaline (NA), dopamine (DA) and field stimulation (FS) in dog (a) isolated sinus node preparation and (b) isolated papillary muscle. (●) and hatched column: control responses; (■) and dotted column: during infusion of cocaine 3 μg/min; (○) and open column: during infusion of cocaine 10 μg/min; $n = 3$ to 8 in NA and dopamine; $n = 2$ to 7 in field stimulation; vertical bars show s.e. mean. $^*P < 0.05$ compared with responses to the corresponding doses of NA and DA, and to nerve stimulation before infusion of cocaine.

tension, only the effects on active tension will be described.

The responses to dopamine (0.3 to 1.0 μg) as well as noradrenaline (0.01 to 0.1 μg) and field stimulation could be abolished by the β-adrenoceptor blocking agent prindolol, 10 μg, administered to each preparation. Prindolol has previously been shown to exert a long-lasting block of β-adrenoceptors with little stimulant or depressant actions in a study of seven β-blocking agents tested in the present preparations (Hashimoto, Ohkuda, Chiba & Taira, 1969; Hashimoto, Endoh, Tamura & Taira, 1970).

Effect of reserpine

The dose-response curves obtained in tissues from animals pretreated with reserpine showed a shift to the left in the case of NA whereas the dose-response curves for dopamine and tyramine were displaced to the right (Figure 1). The effect of pretreatment with reserpine on responses to NA, dopamine and tyramine were more marked on the papillary muscle than on the sinus node. The dose-response curves in the control and reserpine-pretreated preparations were compared in the part where curves are substantially parallel, i.e. increase

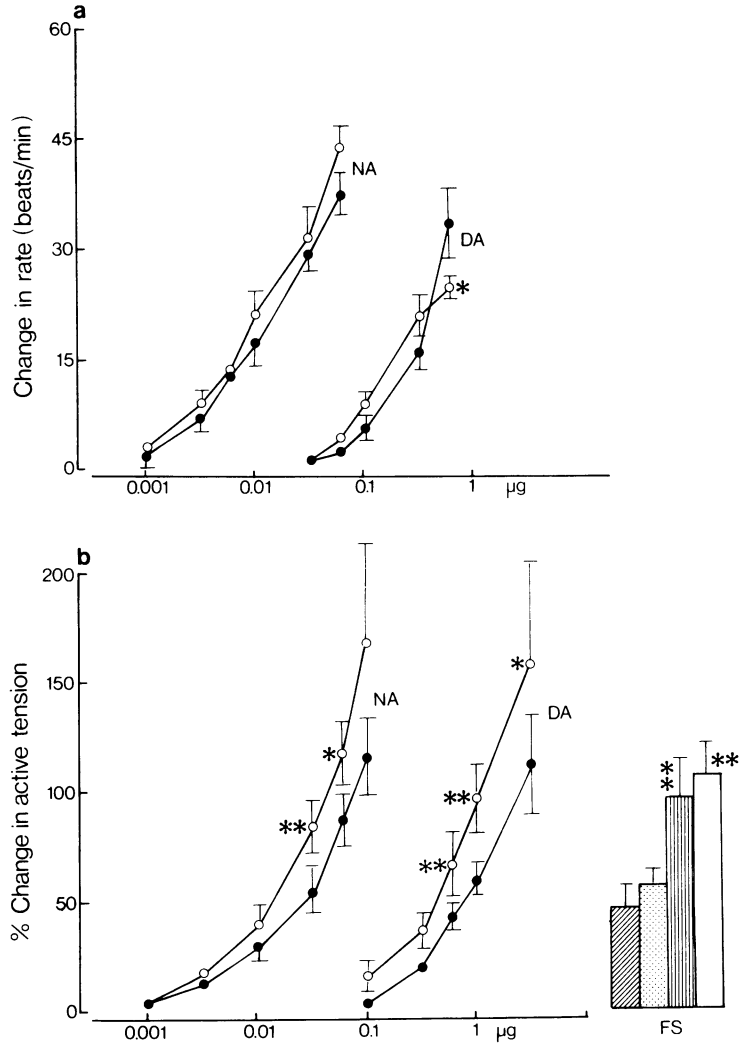

Figure 4 Effects of phenoxybenzamine on mean responses to noradrenaline (NA), dopamine (DA) and field stimulation (FS) in dog (a) isolated sinus node preparation and (b) isolated papillary muscle. (•) and diagonally hatched column: control responses; dotted column: responses following phenoxybenzamine 100 μg; vertically hatched column: following phenoxybenzamine 300 μg; (○) and open column: following phenoxybenzamine 1000 μg; $n = 4$ to 8; vertical bars show s.e. mean. $^{*}P < 0.05$ compared with responses to the corresponding doses of NA and dopamine, and to nerve stimulation before the administration of phenoxybenzamine; $^{**}P < 0.02$.

of 25 beats/min in the sinus node and 80% increase of active tension in the papillary muscle preparation. The curves for NA were shifted to the left by a factor of 2.2 in the sinus node and 3.2 in the papillary muscle; the shift of curves for dopamine to the right was 2.6 in the sinus node and 4.0 in the papillary muscle. Reserpine completely abolished the positive inotropic response to field stimulation: field stimulation in these preparations induced a reduction in active tension, a response which could be blocked by atropine (Endoh & Hashimoto, 1970b).

Effects of desmethylimipramine (DMI) and cocaine

Close-arterial injections of 100 μg of DMI to the sinus node or papillary muscle caused transient negative followed by positive chronotropic or inotropic responses lasting from 5 to 10 min,

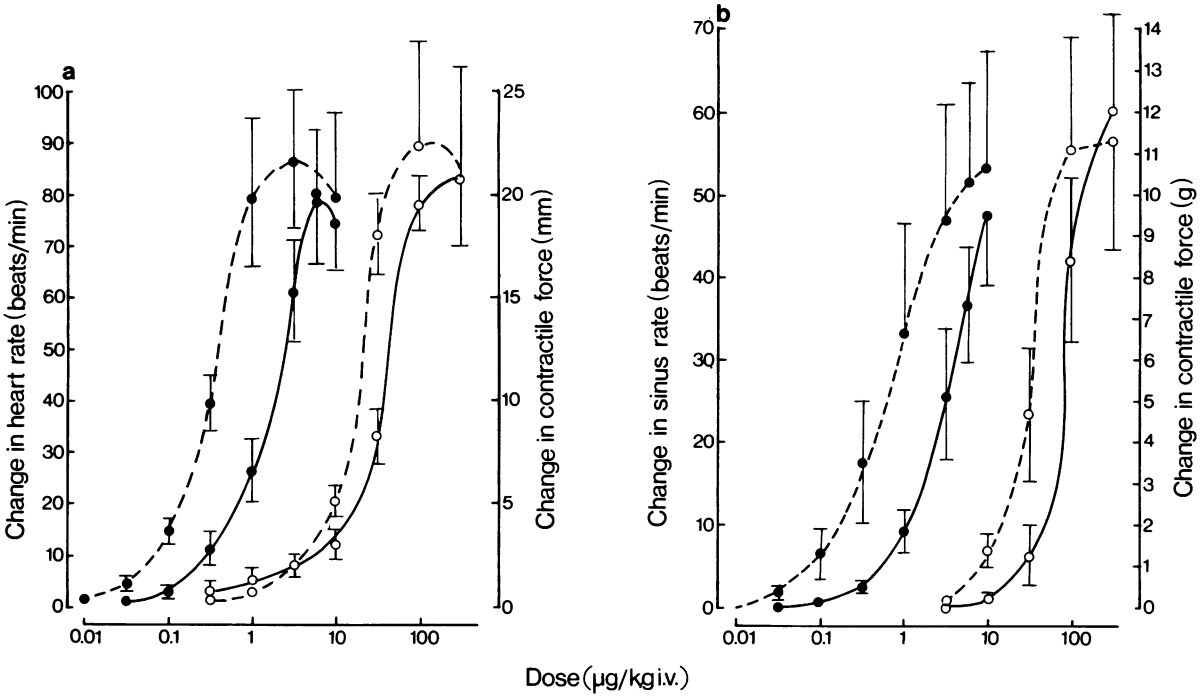

Figure 5 Effects of noradrenaline (NA) (•) and dopamine (○) administered intravenously into the vagotomized donor dog on the sinus rate (solid lines) and the contractile force (dotted lines). (a) Donor dog (n = 7); (b) isolated preparations (n = 4). Vertical bars show s.e. mean.

which could be abolished by prindolol. Subsequent responses to NA in both preparations and positive inotropic responses to perivascular nerve stimulation and field stimulation were enhanced; in contrast, responses to dopamine were smaller (Figure 2). The shift of the dose-response curves for NA to the left and for dopamine to the right occurred to the same degree, i.e. by a factor of 2 in the sinus node and 4 in the papillary muscle.

Cocaine alone had little effect on either preparation at the infusion rates used (3 and 10 μg/minute). Responses to dopamine, NA and nerve stimulation were obtained before and again from 10 min after beginning an infusion of cocaine. Mean results are shown in Figure 3. Responses to NA were considerably enhanced during infusion of both doses of cocaine: the shift of the dose-response curves for NA to the left during infusion of the high dose of cocaine was by a factor of about 4 in both preparations. The inotropic response to dopamine was enhanced slightly but not significantly during infusion of the low dose of cocaine and decreased significantly at the higher dose: the dose-response curve for dopamine was shifted to the right by a factor of 2.5. In the sinus node preparation, however, response to dopamine was not significantly changed during infusion of cocaine at either rate.

Effect of phenoxybenzamine

Phenoxybenzamine in doses of 100, 300 and 1000 μg, injected close-arterially into the sinus node or papillary muscle artery, caused positive chronotropic or inotropic responses lasting between 10 and 30 minutes. After the rate of contraction of the sinus node preparation and the developed tension of the papillary muscle had returned to the control level, the effects of dopamine, NA and nerve stimulation were examined in each preparation. The positive inotropic effect of field stimulation was enhanced dose-dependently by phenoxybenzamine (Figure 4). The positive inotropic responses to dopamine as well as to NA were significantly enhanced after treatment with 1000 μg of phenoxybenzamine: the shift of curves for both amines was about 2-fold. In contrast, the positive chronotropic effects of NA and dopamine were affected less than inotropic effects of the amines. The chronotropic response to a high dose of dopamine (0.1 μg) was significantly decreased (Figure 4).

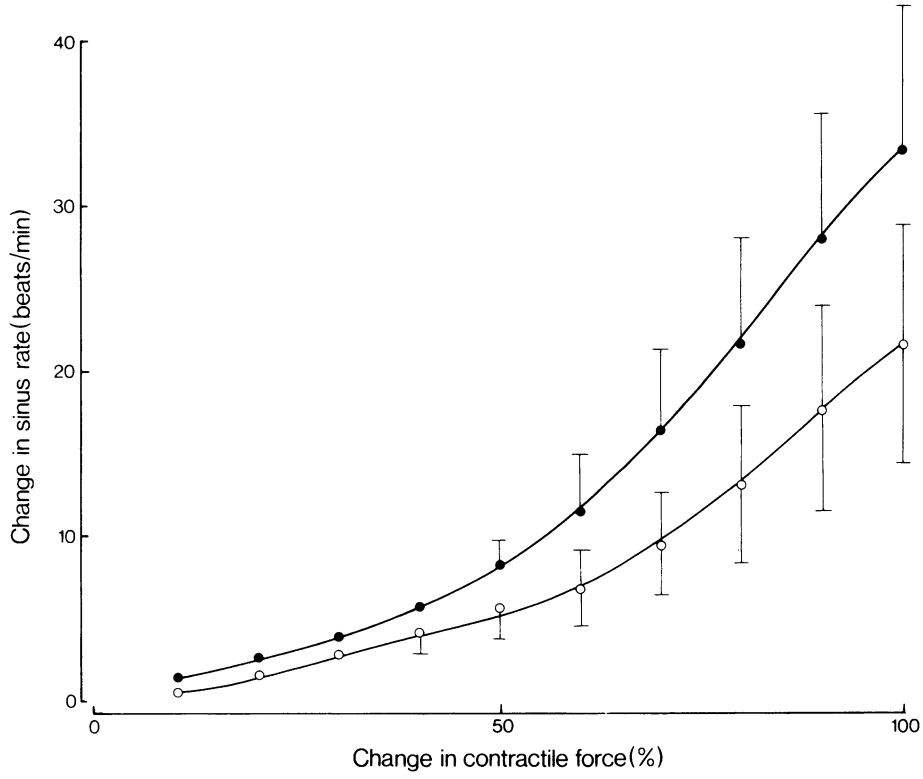

Figure 6 Inotropic-chronotropic relationships of noradrenaline (•) (NA) and dopamine (○) in the isolated preparations ($n = 4$). Increases in the rate (ordinate in beats/min) of the isolated sinus node preparation in response to intravenous doses of NA and dopamine which caused equal positive inotropic effects in the papillary muscle preparations are estimated. Vertical bars show s.e. mean.

Effects of intravenous administration of dopamine and noradrenaline

The mean changes in ventricular contractile force and heart rate in response to a wide range of doses of dopamine and NA administered intravenously to the donor dog are shown in Figure 5. The threshold doses for inducing the positive inotropic responses were lower than those for eliciting the positive chronotropic responses. In the donor dogs, 0.1 μg/kg of NA increased ventricular contractile force by 39.2 ± 9.6% ($P < 0.001$; calcu-

Table 1 The ED_{50} and ED_{100} for noradrenaline (NA) and dopamine (DA) administered intravenously to the donor dog (μg/kg)

		Donor dog			*Isolated preparations*		
		PIA	*PCA*	*PCA/PIA dose-ratio*	*PIA*	*PCA*	*PCA/PIA dose-ratio*
NA	ED_{50}	0.36	1.6	4.5	0.63	> 2.9	> 4.6
	ED_{100}	3	6		10	–	
DA	ED_{50}	22	39	1.8	35	> 74	> 2.1
	ED_{100}	100	300		300	–	

PIA: positive inotropic action; PCA: positive chronotropic action; ED_{100} and ED_{50}: doses required for eliciting the maximal and half of maximal response, respectively; PCA/PIA dose-ratio was calculated from doses which induce the half of maximal responses.

lated as a percentage change from the value in mm in Figure 5). A significant increase in heart rate (10 ± 3 beats/min; $P < 0.025$) was first obtained following 0.3 μg/kg of NA. In the isolated papillary muscle, 0.3 μg/kg of NA increased developed tension by $18.0 \pm 4.9\%$ ($P < 0.02$); the rate of the isolated sinus node was first significantly increased with 1.0 μg/kg of NA by 9 ± 2 beats/min ($P < 0.02$). Dopamine, 30 μg/kg, increased developed tension in the papillary muscle significantly by $46.7 \pm 12.1\%$ ($P < 0.02$); the rate of the isolated sinus node was first significantly increased with 100 μg/kg of dopamine by 35 ± 11 beats/min ($P < 0.05$).

The dose-response curves for NA and dopamine in the contractile force and sinus rate are substantially parallel both in the donor dog (Figure 5a) and in the isolated preparations (Figure 5b). The maximal inotropic responses to NA and dopamine were reached both in the isolated papillary muscle and the heart *in vivo*, while the maximal chronotropic responses were achieved only in the donor dog but not in the isolated sinus node. The ED_{50} and the ED_{100} for NA and dopamine are given in Table 1. NA as well as dopamine showed greater activity in the ventricular myocardium than in the sinus node *in vivo* and *in vitro*: NA and dopamine were more potent in the inotropic action by factors of 4.5 and 1.8 or more, respectively, than in the chronotropic action.

In order to analyse the relative chronotropic and inotropic effects of dopamine and NA more precisely, increases in the rate of the isolated sinus node preparation in response to intravenous doses of NA and dopamine which caused equal positive inotropic effects in the papillary muscle were estimated from the dose-response curve in each experiment. Figure 6 shows the inotropic-chronotropic relationships of NA and dopamine in the isolated preparations. The sinus node preparation was less sensitive to both catecholamines: when the developed tension in the papillary muscle was increased by 50% with NA and dopamine, respectively, increases in the rate of contraction of the sinus node preparation were less than 10 beats/minute.

Discussion

Mechanism of action of dopamine

In the *in vitro* experiments described here, responses to dopamine were inhibited in both the sinus node and papillary muscle preparations, and responses to NA potentiated in tissues obtained from animals pretreated with reserpine. Responses of the sinus node to dopamine and to NA were affected less by reserpine-pretreatment than were those of the papillary muscle. Also the chronotropic response to tyramine was only partially inhibited by reserpine-pretreatment, whereas the positive inotropic response of the papillary muscle to field stimulation was completely blocked and the positive inotropic response to tyramine was greatly reduced by reserpine-pretreatment. Tuttle (1970) showed in the anaesthetized, vagotomized dog that the chronotropic response to dopamine was also more resistant to DMI than that of ventricular contractile force; the present findings in the dog isolated heart preparations that the shift to the right caused by DMI in the dose-response curve for dopamine in the papillary muscle was twice that in the sinus node are consistent with the results of Tuttle. He concluded that the chronotropic effect of dopamine was due to a direct action on β-adrenoceptors and that much of the inotropic effect depended on NA release. However, in the present study not only the inhibitory effect of DMI on the response to dopamine but also the enhancing effect of DMI on the response to NA was less in the sinus node than in the papillary muscle preparation. These observations indicate that the sinus node preparation is more resistant to the blocking effect of DMI on the neuronal uptake of the amines (Iversen, 1967) as well as to depletion of NA by reserpine: the effect of dopamine on the sinus node is fundamentally not different from that on the papillary muscle. Thus, findings with reserpine and DMI support the view (Bejrablaya *et al.*, 1958; Lee & Yoo, 1964; Farmer, 1966; Tsai *et al.*, 1967; Chiba, Hashimoto & Hashimoto, 1973; Neuvonen & Westermann, 1973) that both the positive inotropic and the positive chronotropic responses to dopamine are mediated partially by a direct and partially by an indirect stimulant effect on β-adrenoceptors.

The infusion of cocaine (10 μg/min) greatly enhanced the positive chronotropic and inotropic effects of NA, while the positive chronotropic effect of dopamine was not changed significantly and the positive inotropic effect of dopamine was reduced significantly but to a lesser extent compared with the enhancement of responses to NA. Trendelenburg (1959, 1961), using the nictitating membrane of the spinal cat, observed that the injection of a small amount of cocaine (0.2 mg/kg) increased the contractile response to tyramine and NA, and assumed that the enhancement was due to a pronounced sensitization by cocaine of the effector organ to endogenously liberated NA and of a slight reduction of the releasing effectivity of tyramine. The present effects of cocaine (10 μg/min) on responses to

dopamine and NA, and of the low dose (3 μg/min) to enhance the positive inotropic response to dopamine, are compatible with findings of Trendelenburg (1959, 1961): cocaine may cause supersensitization of the postsynaptic effector cells of the sinus node and the papillary muscle.

Phenoxybenzamine enhanced the positive inotropic effects of dopamine and NA to the same degree in the papillary muscle; this effect of phenoxybenzamine may be ascribed to its blocking action on the extraneuronal uptake of the amines (Iversen, 1967). On the other hand, the positive chronotropic effects of the amines are not affected by phenoxybenzamine. It is assumed that the extraneuronal uptake of amines is less in the sinus node than in the papillary muscle, because of anatomical differences between these tissues *viz.* the group of sinus node cells are perfused with a single main sinus node artery in the dog (Hashimoto, Tanaka, Hirata & Chiba, 1967), while the papillary muscle is perfused with many small branches of the septal artery (Endoh & Hashimoto, 1970b). The reason for inhibition by phenoxybenzamine of the positive chronotropic effect of a high dose of dopamine is unknown: it is not explained by the effect of phenoxybenzamine on the neuronal uptake of amines, because the effect of NA was not affected.

The relative chronotropic and inotropic effects of dopamine

Since it is evident that the chronotropic response to drugs in the heart *in situ* is modified by extracardiac factors, and furthermore that drug effects on ventricular contractile force are affected by changes in heart rate (Furnival, Linden & Snow, 1970), it is difficult to state exactly the inotropic-chronotropic relationship of drugs in the heart *in situ*. On the other hand, the isolated sinus node and papillary muscle preparations were perfused with the same concentration of drugs, and were not affected by extra-cardiac factors or frequency-dependent effects of drugs on contraction. It has been shown that the isolated preparations reflected well the blood level of the drugs, catecholamines and ouabain, in the donor dog (Hashimoto, Kimura & Kubota, 1973). Furthermore, if the donor dog is maintained carefully, the response to catecholamines injected close-arterially remains constant for several hours (Hashimoto *et al.*, 1970; Endoh, Kimura & Hashimoto, 1972): the amount of drugs required to cause responses in the isolated preparations is so small that re-circulation in the donor dog is negligible.

Dopamine given by the intravenous route to the donor dog caused marked increases in myocardial contractile force with comparatively little change in heart rate *in vivo* and in the isolated preparations. These results are in agreement with the findings reported for man and the dog (Maxwell, Rowe, Castillo, Clifford, Afonso & Crumpton, 1960; Holmes & Fowler, 1962; Horwitz *et al.*, 1962; McDonald & Goldberg, 1963). This differential effect on heart rate and contractile force has been considered to be specific for dopamine (Goldberg, 1972), although there has been no satisfactory comparison between the cardiac effects of dopamine and other catecholamines. Recently, Furnival *et al.* (1971) have shown that NA also produced less rise in heart rate than does isoprenaline for a similar increase in contractile force in the denervated dog heart. In the present experiments, the effects of dopamine on heart rate and contractile force were compared with those of NA. Intravenous administration of NA resulted in very similar effects to those observed with dopamine. The dose-response curves obtained for NA were parallel to those for dopamine. NA was approximately 50 times more potent than dopamine both in its effects on contractile force and heart rate. A similar potency ratio was found in the *in vitro* experiments. These experiments clearly show that the effects of dopamine on heart rate and contractile force are not specific for dopamine, but are shared by NA.

The question arises as to the reason for the difference in activity of NA and dopamine between the ventricular myocardium and the sinus node. It is known that the uptake mechanism of amines plays an important role in inactivating the exogenous and endogenous NA: Iversen (1967) has shown that there are two different mechanisms for uptake of NA, i.e. uptake into the nerve endings ($uptake_1$) and uptake into tissues other than nerve ($uptake_2$). On the other hand, the atrium, especially the right atrium, contains more transmitter substance, NA, than the ventricular myocardium in various species of animals (Muscholl, 1959; Cervoni, Kirpekar & Schwab, 1966). In the dog, Shore, Cohn, Highman & Maling (1958) have found that the sinus node region contains 2.3 μg/g NA, while the right papillary muscle contains 1.5 μg/gram. Angelakos, Fuxe & Torchiana (1963) have further shown histochemically that the catecholamines were located in nerve structures and that a high density of fluorescent fibre bundles were found in the sinus node region of the rabbit. Since it is commonly considered that the indirectly acting sympathomimetic amines are probably taken into adrenergic neurones by a common amine transfer system (Starke, 1972), the sinus node which is densely innervated by adrenergic fibres may have a larger capacity to inactivate the exogenous NA and dopamine by

taking up these amines more actively into the nerve and thereby show a lower sensitivity to these amines than the ventricular myocardium. This view has already been put forward by Furnival *et al*..(1971) on the basis of their findings that NA produced less rise in heart rate than did isoprenaline for a similar increase in contractile force, while the relative chronotropic and inotropic effect of NA equalled that of isoprenaline after the blockade of neuronal uptake by cocaine in the denervated dog.

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