Cardiovascular actions of dopexamine in anaesthetized and conscious dogs

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1 Arterial blood pressure, heart rate and cardiac contractility were measured in pentobarbitone-anaesthetized mongrel dogs and in conscious, instrumented dogs.

2 In anaesthetized dogs ($n = 5$), dose-response curves were obtained by intravenous infusion of increasing doses of dopexamine ($5\text{--}20\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$). Infusions were administered three times to each animal to determine whether the responses were reproducible. Dopexamine increased heart rate and myocardial contractility and decreased blood pressure. The dose-response curves for dopexamine did not differ significantly over time.

3 In a second group of dogs ($n = 6$), dose-response curves ($5\text{--}20\text{ mg kg}^{-1}\text{ min}^{-1}$) were obtained as above and repeated after the administration of amitriptyline (2 mg kg^{-1} , i.v.). Amitriptyline caused a non-significant reduction in the inotropic and chronotropic responses to dopexamine.

4 Control dose-response curves for dopexamine ($5\text{--}50\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$) were similarly obtained in a third group of dogs ($n = 6$), and repeated after bilateral vagotomy and sympathetic denervation of the heart. In these animals, a third dose-response curve for dopexamine was obtained after the administration of ICI 118551 (0.2 mg kg^{-1} , followed by $0.2\text{ mg kg}^{-1}\text{ h}^{-1}$). The chronotropic response to dopexamine was significantly reduced after cardiac denervation. There was a small, non-significant reduction in the inotropic and depressor responses after denervation. Administration of ICI 115881 significantly reduced both the inotropic and chronotropic response to dopexamine and caused a non-significant reduction in the depressor response.

5 The effect of raclopride ($0.2\text{ }\mu\text{mol kg}^{-1}$, p.o.) was investigated by comparison of the dose-response curves for dopexamine in a control group of dogs ($n = 6$) to those obtained in dogs which had been pretreated with raclopride ($n = 5$). Raclopride had no significant effect on the cardiovascular responses to dopexamine.

6 In conscious, instrumented dogs ($n = 5$), pretreated with raclopride, dose-related positive inotropic and chronotropic and depressor responses to dopexamine infusions were recorded. The chronotropic responses in conscious animals were significantly greater than those in the anaesthetized animals.

7 The results of this study indicate that both the positive inotropic and chronotropic actions of dopamine are due to a combination of direct, β_2 -adrenoceptor-mediated effects and the baroreceptor reflex response to the depressor action of the drug.

Keywords: Dopexamine; β_2 -adrenoceptor agonists; amitriptyline; heart rate; ICI 115881; inotropic agents

Introduction

Dopexamine is a catecholamine which has been used in the acute treatment of low cardiac output states (Smith & Fileck, 1989). Responses to dopexamine in animals include a fall in blood pressure and increases in heart rate and myocardial contractility. The depressor effect is thought to result from the vasodilator response to stimulation of dopamine D_1 receptors in renal and mesenteric vascular beds and vascular β_2 -adrenoceptors (Brown *et al.*, 1985a; Smith *et al.*, 1987). Reduced noradrenaline release from sympathetic nerves, due to stimulation of prejunctional D_2 receptors may also contribute to the fall in blood pressure (Brown *et al.*, 1985a). There is some disagreement about the mechanism of the positive inotropic and chronotropic effects of dopexamine.

The increased cardiac activity may be due to stimulation of β_1 - and/or β_2 -adrenoceptors (Bass *et al.*, 1987; Smith *et al.*, 1987; Brodde, 1991). Dopexamine has also been shown to inhibit noradrenaline uptake₁ (Mitchell *et al.*, 1987) and it has been suggested (Bass *et al.*, 1987) that this may contribute to the positive inotropic and chronotropic response. These authors also showed that, in anaesthetized dogs, the cardiac response to dopexamine was markedly reduced after ganglion blockade and suggested that baroreceptor reflex

activity in response to the depressor effect was an important component of the increased rate and contractility. In other studies (Smith *et al.*, 1987), only the responses to low doses of dopexamine were attenuated by ganglion blockade; those to higher doses were not reduced and some were enhanced. The assessment of the importance of the reflex component of the response to dopexamine is further complicated by the observation that stimulation of D_2 -receptors by dopexamine inhibits the response to cardiac accelerans nerve stimulation (Brown *et al.*, 1985a). This action would tend to reduce the impact of baroreceptor reflex activation.

The positive inotropic and chronotropic actions of dopexamine have also been demonstrated in conscious dogs (Brown *et al.*, 1985b). In these studies, the maximum dose of dopexamine which was administered was $10^{-7}\text{ mol kg}^{-1}\text{ min}^{-1}$ (approximately $43\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$). Dose limitation was imposed by dopexamine-induced stimulation of the D_2 receptors in the chemoreceptor trigger zone which led to panting, licking and emesis which was evident in some animals at doses of $3 \times 10^{-8}\text{ mol kg}^{-1}\text{ min}^{-1}$ ($13\text{ }\mu\text{g kg}^{-1}\text{ min}^{-1}$). It is possible that the cardiovascular responses to the lower doses of dopexamine were influenced by the sensations of nausea and most likely that responses to the higher doses were affected by vomiting.

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Thus the aims of the present experiments were to assess the importance of Uptake₁ blockade, baroreceptor reflex activity, D₂ receptor and β_2 -adrenoceptor stimulation in the response to dopexamine by the use of selective antagonists and to compare the actions of a wide range of doses of dopexamine in anaesthetized and conscious animals.

Methods

Acute experiments in anaesthetized dogs

Mongrel dogs ($n = 26$) (12–28 kg) were anaesthetized with sodium pentobarbitone (30 mg kg⁻¹, i.v.); supplementary doses were administered as required. The animals were intubated and mechanically ventilated (Ugo Basile dog ventilator 5025). Both femoral veins were cannulated for drug administration. Arterial pressure was monitored from the femoral artery (Statham P23AC pressure transducer) and heart rate was obtained from a tachograph (Grass 7P4D5) triggered by the QRS complex of the Lead II ECG.

The chest was opened by either a mid-sternal incision (where subsequent cardiac denervation was performed) or at the 4th intercostal space. A miniature pressure manometer (Konigsberg P6.5) was inserted into the left ventricular cavity. The first derivative of left ventricular pressure (dP/dt) was derived by electronic differentiation of the ventricular pressure signal using an active circuit with a time constant of 50 ms. The index of myocardial contractility used in this study was obtained beat by beat, by an on-line digital computer (Digital Decgraphic 11/40). Under programme control, the R-wave of the Lead II ECG initiates the sampling of left ventricular pressure and dP/dt until peak dP/dt is detected. At this time, the ratio of maximum dP/dt to the time integral of isovolumic pressure (the area under the left ventricular pressure curve) is computed and returned to the chart recorder as an analogue signal. Evaluation of this index ($dP/dt \div$ integrated isometric tension, units = s⁻²) as a measure of myocardial contractility has shown that, within a reasonable range, it is not influenced by changes in heart rate, preload or afterload (Goodman *et al.*, 1972).

All cardiovascular parameters were continuously recorded (Grass Model 7 Polygraph). Following instrumentation, the animals were allowed to stabilize for 30 min before recording of baseline cardiovascular variables.

Dose-response curves for dopexamine were obtained by infusion of increasing doses (IMED volumetric infusion pump 922). Infusion at each dose rate was continued until cardiovascular variables were maintained at a steady level and then the infusion rate was increased to administer the next dose. The cardiovascular variables were allowed to return to baseline.

Group 1 ($n = 5$) Reproducibility of responses to dopexamine The effect of dopexamine (5–20 $\mu\text{g kg}^{-1} \text{ min}^{-1}$) on the cardiovascular system was examined. The dose-response curve was repeated three times in each animal to determine whether reproducible responses could be obtained. Cardiovascular variables were allowed to return to baseline between trials.

Group 2 ($n = 6$) Effect of amitriptyline on dopexamine dose-response curves A control dose-response curve (5–20 $\mu\text{g kg}^{-1} \text{ min}^{-1}$) was obtained in each animal. The cardiovascular variables were allowed to return to baseline and then amitriptyline (2 mg kg⁻¹, i.v.) was administered. The effectiveness of Uptake₁ blockade by this dose of amitriptyline was tested by the administration of tyramine (25 $\mu\text{g kg}^{-1}$) before and after amitriptyline. The dose-response curve for dopexamine was then repeated. The test dose of tyramine was injected at the end of the experiment to test whether Uptake₁ blockade was still effective.

Group 3 ($n = 6$) Effect of autonomic denervation and β_2 -adrenoceptor blockade on cardiovascular responses to dopexamine Control dose-response curves for dopexamine (5–50 $\mu\text{g kg}^{-1} \text{ min}^{-1}$) were obtained as above. The vagi were then cut and sympathetic denervation of the heart was achieved by bilateral crushing of the *ansae subclavia*. The completeness of the denervation was assessed by comparing the cardiac response to 15 s bilateral carotid occlusion before and after denervation. The infusion of increasing doses of dopexamine was then repeated. When the cardiovascular variables had returned to baseline, the selective β_2 -adrenoceptor antagonist, ICI 118551 (0.2 mg kg⁻¹ bolus followed by 0.2 mg kg⁻¹ h⁻¹) was administered and the dose-response curve to dopexamine was repeated.

Group 4 ($n = 11$) Effect of raclopride on dopexamine dose-response curves Dose-response curves for dopexamine were obtained in six anaesthetized animals. In five other animals, the selective D₂ receptor antagonist, raclopride (Ross & Jackson, 1989) was administered (0.2 $\mu\text{mol kg}^{-1}$, p.o.) 30 min before anaesthesia. A dose-response curve for dopexamine was obtained in these animals following instrumentation.

Experiments in conscious dogs

Konigsberg micromanometers were implanted in the left ventricles of mongrel dogs ($n = 5$) under halothane anaesthesia. The animals were allowed at least 6 weeks to recover before any experimental procedures were conducted. During the experiments, the dogs lay unrestrained on a mattress. Lead II ECG was recorded using surface leads attached to the paws. Cardiac contractility was measured, as above, using the signal from the implanted micromanometer. Systemic blood pressure was measured with a Critikon Dynamap Vital Signs Monitor. Dose-response curves to dopexamine were obtained by the intravenous infusion of increasing doses of dopexamine (1–50 $\mu\text{g kg}^{-1} \text{ min}^{-1}$), as described above. In order to prevent the emetic effect of higher doses of dopexamine in conscious animals, the dogs were dosed with raclopride (0.2 $\mu\text{mol kg}^{-1}$, p.o.) approximately 2 h before dopexamine infusions.

Analysis of results

Dose-response curves to dopexamine were compared by repeated measures analysis of variance. Paired *t* tests were used to test for the significance of the effects of Uptake₁ blockade, denervation and β_2 -adrenoceptor blockade on resting levels of cardiovascular variables in anaesthetized animals. Unpaired *t* tests were used to compare resting cardiovascular variables in anaesthetized and conscious animals which had been pretreated with raclopride. Results were considered to be significant when $P < 0.05$.

Results

Acute experiments

Group 1: Reproducibility of dopexamine dose-response curves Infusion of increasing doses of dopexamine increased cardiac contractility and heart rate and decreased blood pressure (Figure 1). The drug had a rapid onset of action, taking 2–10 min to reach steady state, depending on the rate of infusion. The effects wore off within 20 min of the termination of infusion. Analysis of variance indicated that there were no significant ($P > 0.05$) differences in any of the cardiovascular responses over time.

Group 2: Effect of amitriptyline on the dose-response curves to dopexamine Amitriptyline abolished the response to tyramine and remained effective after the dopexamine infusion.

Figure 1 Effect of doxamine on (a) blood pressure, (b) heart rate and (c) myocardial contractility (●) and on the same parameters when infused a second (▲) and third (■) time. Points shown represent the mean ($\pm$ s.e.mean) of responses in six dogs.

Figure 2 Effect of doxamine on (a) blood pressure, (b) heart rate and (c) myocardial contractility before (■) and after (●) administration of amitriptyline (2 mg kg^{-1}). Points shown represent the mean ($\pm$ s.e.mean) of responses in six dogs.

Table 1 Resting levels of blood pressure, heart rate and myocardial contractility before and after administration of amitriptyline

	Control	Amitriptyline
Blood pressure (mmHg)	121 ± 10	127 ± 7
Heart rate (min^{-1})	158 ± 4	155 ± 11
Myocardial contractility (s^{-2})	1580 ± 100	1600 ± 100

Values shown are mean ($\pm$ s.e.mean).

The resting levels of blood pressure, heart rate and contractility before and after the administration of amitriptyline are shown in Table 1 where it can be seen that amitriptyline had no significant ($P > 0.05$) effect on the resting cardiovascular parameters. The mean of the responses to increasing doses of doxamine before and after amitriptyline are shown in Figure 2. Analysis of variance indicated that although there was a trend to reduced chronotropic responses and enhanced depressor responses to doxamine after amitriptyline, the shifts in the dose-response curves were not significant ($P > 0.05$). The reduction in inotropic responses to doxamine after amitriptyline just failed to reach significance ($P < 0.06$).

Group 3: Effect of autonomic denervation and β_2 -adrenoceptor blockade on cardiovascular responses to doxamine Resting levels of blood pressure, heart rate and contractility in this group of dogs were similar to those in Group 2 (Tables 1 and 2). Cardiac denervation abolished the chronotropic response to bilateral carotid occlusion. After denervation there was a significant decrease in heart rate ($P < 0.005$; t test, 10 d.f.) and contractility ($P < 0.001$; t test, 10 d.f.) but there was no significant change in blood pressure ($P > 0.05$) (Table 2). Dose-response curves for doxamine before and after cardiac denervation are shown in Figure 3. Analysis of variance indicated that only the chronotropic response was significantly reduced by denervation ($P < 0.05$).

Administration of the β_2 -adrenoceptor antagonist, ICI 118551 caused a further small, but significant ($P < 0.05$; t test, 10 d.f.), reduction in heart rate and an insignificant ($P > 0.05$) increase in contractility (Table 2). After receptor blockade, the inotropic dose-response curve to doxamine was significantly reduced when compared to the results in the denervated animals ($P < 0.01$; ANOVA). Although the depressor and chronotropic responses appeared to be reduced, these effects were not statistically significant ($P > 0.05$). The difference between the chronotropic dose-response curve in the control period and that after ICI 11851 was significant ($P < 0.01$, ANOVA).

Group 4: Effect of raclopride on cardiovascular responses to doxamine The resting levels of blood pressure, contractility and heart rate in the groups of dogs which received

dopexamine alone and dopexamine after pretreatment with raclopride are shown in Table 3. Raclopride had no significant effect on any of these parameters. The mean of the responses to increasing doses of dopexamine in the animals pretreated with raclopride and those with no pretreatment are shown in Figure 4. Analysis of variance indicated that

Table 2 Resting levels of blood pressure, heart rate and myocardial contractility before and after denervation and administration of ICI 118551

	Control	Denervation	ICI 118551
Blood pressure (mmHg)	128 ± 10	118 ± 3	130 ± 5††
Heart rate (min ⁻¹)	158 ± 6	127 ± 4*	119 ± 5†
Myocardial contractility (s ⁻²)	1820 ± 80	1360 ± 170**	1500 ± 180

Values shown are mean (± s.e.mean).

*Significantly different from control ($P < 0.05$);

**Significantly different from control ($P < 0.01$);

†Significantly different from denervation ($P < 0.05$);

††Significantly different from denervation ($P < 0.005$).

Figure 3 Effect of dopexamine on (a) blood pressure, (b) heart rate and (c) myocardial contractility before (●) and after (■) cardiac denervation and after (▲) administration of ICI 118551 (0.2 mg kg⁻¹, followed by 0.2 mg kg⁻¹ h⁻¹). Points shown represent the mean (± s.e.mean) of responses in six dogs.

raclopride had no significant effect on any of the responses in the anaesthetized animals.

Experiments in conscious dogs

Resting levels of contractility in the conscious dogs (1570 ± 180 s⁻²) were similar to those in the anaesthetized animals which had been pretreated with raclopride, although heart rate (78 ± 3 min⁻¹) and mean arterial pressure (80 ± 2

Table 3 Resting levels of blood pressure, heart rate and myocardial contractility in anaesthetized dogs before and after administration of raclopride

	Control (n = 6)	Raclopride (n = 5)
Blood pressure (mmHg)	102 ± 7	120 ± 3
Heart rate (min ⁻¹)	149 ± 8	148 ± 8
Myocardial contractility (s ⁻²)	1610 ± 150	1630 ± 130

Values shown are mean (± s.e.mean).

Figure 4 Effect of dopexamine on (a) blood pressure, (b) heart rate and (c) myocardial contractility in control anaesthetized dogs (■) ($n = 6$), anaesthetized dogs pretreated with raclopride ($n = 5$) (▲) and conscious dogs pretreated with raclopride ($n = 5$) (●). Points shown represent the mean (± s.e.mean) of responses in each group.

mmHg) were significantly lower (heart rate: $P < 0.001$; t test, 8 d.f.; blood pressure: $P < 0.001$, t test, 8 d.f.). Dopexamine produced dose-related increases in both heart rate and contractility and reductions in blood pressure; the dose-response curves obtained in the conscious animals are shown in Figure 4. From this figure, it can be seen that the inotropic and chronotropic responses to dopexamine in the conscious animals were more marked than those in anaesthetized animals, while the depressor effect was similar. The difference in chronotropic responses were shown to be statistically significant when the data from anaesthetized animals which had been pretreated with raclopride were compared (ANOVA) to those from conscious animals. The differences between inotropic responses in anaesthetized and conscious animals failed to reach statistical significance. This was probably due to the greater variability in dose-response curves in the conscious animals.

Discussion

The effects of dopexamine on the cardiovascular system of anaesthetized dogs in the present experiments were similar to those reported by Smith *et al.* (1987) and Bass *et al.* (1987). As in these reports, the changes in blood pressure and heart rate in response to dopexamine in the present experiments were not as marked as the increase in cardiac contractility. In conscious animals, dopexamine also had positive inotropic and chronotropic actions and lowered blood pressure; responses which were qualitatively similar to those reported by Brown *et al.* (1985). In the present study, the animals were pretreated with raclopride and thus it was possible to administer higher doses of dopexamine without inducing panting, licking and emesis, which could all have influenced the cardiovascular system. It was assumed that raclopride did not alter the responses to dopexamine observed in conscious animal since the responses in anaesthetized dogs were shown to be unaffected by pretreatment with this selective D_2 -antagonist.

It has been shown that dopexamine inhibits noradrenaline Uptake₁ (Mitchell *et al.*, 1987; Smith & O'Connor, 1988), and it has been suggested that this action contributes to the cardiac response to dopexamine (Bass *et al.*, 1987). The doses of dopexamine used in this study are effective in blocking Uptake₁ in dogs (Smith & Naya, 1987) and the resting heart rate of the anaesthetized animals indicates a high background level of sympathetic tone. Thus, the cardiac stimulant action of dopexamine in these animals could involve a potentiation of endogenous noradrenaline. If Uptake₁ blockade were a significant factor, the effects of dopexamine should be reduced in animals treated with an Uptake₁ blocker, such as amitriptyline. However, in the present experiments, although the abolition of the response to tyramine indicated effective Uptake₁ blockade, treatment with amitriptyline did not significantly alter the resting levels of the cardiovascular variables. Furthermore, despite a trend towards reduced responses in the amitriptyline-treated animals, the inotropic and chronotropic dose-response curves after blockade were not significantly different from those in the control period. It is unlikely, therefore, that the inhibition of Uptake₁ by dopexamine is of major importance in its cardiac stimulant action.

Dopexamine reduces blood pressure by a vasodilator action at β_2 -adrenoceptors and dopamine receptors and it has been suggested that the baroreceptor response to the fall in pressure is 'a major contributor' to the increase in heart rate and cardiac contractile force produced by dopexamine (Bass *et al.*, 1987). This claim was based on experiments in anaesthetized dogs in which the cardiac response to bolus doses of dopexamine were almost abolished after ganglion blockade. Others, however, found that although the cardiac effects of infusion of low doses of dopexamine were reduced after ganglion blockade, the responses to higher doses were not

affected or were even potentiated (Smith *et al.*, 1987). One explanation for this apparent discrepancy is the difference in the method of drug administration. The baroreceptor response is most pronounced during changes in blood pressure and would be expected to be of greater significance in the experiments where bolus doses were given. In those experiments where infusions were used, the baroreceptors 'adjust' to the new, lower pressure and their influence declines. Thus, in the steady state, the importance of the baroreceptor input would be reduced. Infusion of dopexamine was used as the method of administration in the present experiments since it is the route used clinically and thus is of most relevance.

In order to evaluate the contribution of the baroreceptors to the dopexamine response in anaesthetized dogs, the drug was administered to dogs after surgical removal of autonomic innervation to the heart. This technique has the advantage of maintaining the autonomic tone in the circulation, thus minimizing changes which may occur secondary to the very low blood pressure seen after pharmacological ganglion blockade. The resting heart rate and myocardial contractility were reduced after denervation since animals under pentobarbitone anaesthesia tend to have increased sympathetic tone.

Denervation significantly reduced the chronotropic response to dopexamine and the shift of the dose-response curve reflects the importance of the baroreceptor component in this response. It should be noted that after denervation dopexamine still produced a significant dose-related increase in heart rate. Thus, it has some direct chronotropic activity. The results from this group of dogs also suggest that the baroreceptors are not of major significance in the inotropic response in anaesthetized animals, since denervation produced only a slight and non-significant reduction in the increase in contractility due to dopexamine.

The contribution of the baroreceptor reflex to the cardiac response to dopexamine was likely to have been far greater in the conscious animals, where no anaesthetic was present to depress reflex activity. Indeed, it is quite likely that this was the main reason for the marked difference in the chronotropic responses in anaesthetized and conscious animals. As in the denervation studies in anaesthetized animals, the contribution of the baroreceptor reflex to the inotropic response appeared to be less marked.

The effect of dopexamine at neuronal D_2 receptors and β_2 -adrenoceptors also requires consideration. The positive inotropic or chronotropic response may be attenuated by a reduction in noradrenaline release mediated *via* presynaptic D_2 receptors (Kohli *et al.*, 1983; Brown *et al.*, 1985b). If this were the case, blockade of D_2 receptors by raclopride would significantly affect the response to dopexamine and the response in denervated animals, in which there is no noradrenaline release, should be greater than that in the control animals. Since raclopride had no effect on the dose-response curves and the effect of denervation was to reduce the cardiac response to dopexamine, it is unlikely that presynaptic effects modulate the cardiac stimulant action of dopexamine. It also appears from the present results that D_2 receptor-induced reduction of neuronal release of noradrenaline does not contribute significantly to the depressor effect of dopexamine. It is also possible that in the presence of sufficient concentrations of dopexamine, stimulation of prejunctional β_2 -adrenoceptors could facilitate release of noradrenaline. Appropriately designed studies of transmitter release are required to evaluate definitively the contribution of these prejunctional effects to the cardiovascular responses to dopexamine.

The cardiac effects of dopexamine in the denervated animals were abolished by ICI 118551. These results confirm the conclusions that the direct inotropic and chronotropic responses are mediated *via* β_2 -adrenoceptors in the heart (Smith *et al.*, 1987). The depressor response appeared to be reduced by ICI 118551, although the difference was not statistically significant. The reduction in blood pressure which occurred after β_2 -adrenoceptor blockade was presumably due to vaso-

dilatation mediated *via* dopamine D₁ receptors in the renal vascular bed.

The results of the present study confirm the positive inotropic and chronotropic effects of dopexamine and its vasodepressor activity. The fall in blood pressure has been shown to be largely due to β_2 -adrenoceptor stimulation. The positive inotropic effect is predominantly due to direct

stimulation of cardiac β_2 -adrenoceptors. Both a direct, β_2 -adrenoceptor-mediated response and the baroreceptor reflex contribute to the tachycardia.

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