In conclusion the present study supports the suggestion that metabolites of sulphinpyrazone may be responsible for this drug's platelet inhibitory activity. The lack of effect of these metabolites on vascular prostacyclin generation could help clarify the mechanism of action of sulphinpyrazone as an antithrombotic agent.

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Dopamine acts peripherally on rat tail arteries

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There is much evidence supporting the concept that dopamine (DA) is a centrally acting amine. The central dopaminergic system may be involved in Parkinson's disease and probably in schizophrenia (Hornykiewicz 1977), in thermoregulation (Cox & Lee 1977), in intraocular pressure (Shannon et al 1976), in Huntington's disease (Reinse et al 1977). DA also exerts peripheral effects, e.g. in the cardiovascular as well as in the renal system, in shock (Goldberg 1977), and in the vas deferens (Simon & Van Maanen 1976). However, although the pharmacological basis for the clinical use of DA is increasing, the action of DA on peripheral arteries is still controversial. We have examined the activity of DA on peripheral arteries and compared it with the activity of noradrenaline (NA).

Male Wistar rats (250–300 g) were anaesthetized with urethane i.p. The rat tail artery was separated and perfused according to Nicholas (1969). The length of artery was standardized at 4–5 cm. The perfusion at a constant rate of 2 ml min^{-1} with oxygenated Krebs solution (37 °C) was maintained by a peristaltic roller pump. In all the arteries the perfusion was stabilized at a pressure between 20–30 mm Hg within 20–30 min. Vasoconstriction produced a rise in perfusion pressure which directly related to the intensity of the drug effect. Tested drugs were added to the external bath solution (10 ml) by discrete injection. Cumulative dose-response curves were constructed by increasing the dose in geometrical sequence according to van Rossum (1963). The maximum effect was reached for each dose within about 30 s. When a single response to a drug was observed, and maximum effect reached, the bath solution was replaced with Krebs solution (3 times). Cocaine HCl (3 mg $litre^{-1}$) was added to the Krebs solution (pH 7·4) to prevent the neuronal uptake of catecholamines (Pennefather 1976; Marshall 1977). Results are expressed as means with s.d. Student's *t*-test was used to evaluate differences between control and experimental groups.

Drugs used were: noradrenaline (Levonor, Polfa); dopamine (3-hydroxytyramine HCl, Serva Feinbiochemika); phentolamine (Regitine, Ciba-Geigy); dihydroergotamine methanosulphonate (Galenica); propranolol hydrochloride (Galenica); INPEA (*N*-isopropyl-*p*-nitrophenyletanolamine, Selvi); apomorphine HCl (Polfa); haloperidol (Gedeon Richter); imidazole (Flucka).

Experiments were carried out with both α- (phentolamine 5×10^{-7} M) and β-adrenergic (propranolol 10^{-6} M or INPEA 10^{-6} M) blocking drugs in the medium. DA constricted arteries in standard Krebs solution as well as in the presence of the adrenergic blocking drugs (Fig. 1). The cumulative dose-response curve indicates

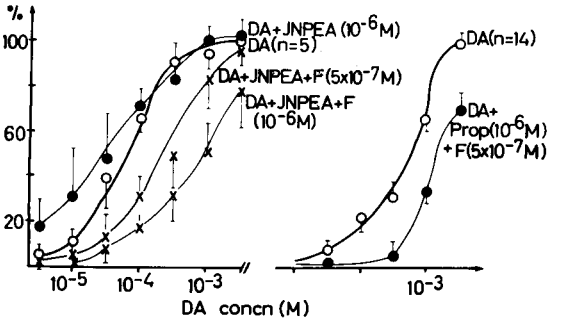

FIG. 1. The vasconstrictor response of rat isolated tail arteries to cumulative doses of dopamine (DA). Experiments were carried out according to van Rossum (1963). INPEA (10^{-6}M), Propr = propranolol (10^{-6}M). Fent = phentolamine (5×10^{-7} M).

* Correspondence.

Table 1. The influence of apomorphine, haloperidol and imizadole on the constrictor response of rat isolated tail arteries to dopamine (DA) and noradrenaline (NA). Apomorphine at 10^{-5} M inhibited the vasoconstrictor response to DA and NA by about 30%, but applied at the peak of the constrictor phase it did not change the perfusion pressure. Haloperidol at 10^{-8} and 10^{-7} M did not influence the vascoconstrictor response of arteries to NA. Imidazole 10^{-4} M did not change the DA effect, but at 10^{-4} and 10^{-3} M it enhanced the vasoconstriction induced by NA (Szadujkis-Szadurski 1977). The influence of applied drugs on DA vascoconstriction was the same in the standard Krebs solution and in the presence of both adrenergic blocking drugs.

Drugs	Perfusion pressure mmHg	Medium	Difference mmHg	Difference %
DA 3×10^{-3} M	41·3 s.d. 4·96	Krebs solution + phentolamine 5×10^{-7} M	−21·1	−48·8**
DA + apomorphine 1×10^{-4} M	20·16 s.d. 4·25			
DA 3×10^{-3} M	43·16 s.d. 7·19	+ propranolol 10^{-6} M	−15·5	−64*
DA + haloperidol 1×10^{-7} M	27·66 s.d. 4·49			
DA 3×10^{-3} M	48·5 s.d. 9.2	+ cocaine 3 mg litre^{-1}	−8·2	−17
DA + imidazole 1×10^{-3} M	40·2 s.d. 10·4			
NA 1×10^{-6} M	53·5 s.d. 9·46	Krebs solution + cocaine 3 mg litre^{-1}	−36·4	−68**
NA + apomorphine 1×10^{-4} M	17·1 s.d. 2.92			

Differences from comparative, control, values are significant at $^{**}P > 0.001$, and $^{*}P > 0.01$, paired t-test, number of experiments = 6.

that DA, in the external bath solution, caused constriction of arteries in a dose-dependent manner.

Phentolamine + propranolol or phentolamine + INPEA reduced the maximum DA response, the curve being shifted to the right. Phentolamine (5×10^{-7} M) in the presence of propranolol (10^{-6} M) had the same effect as phentolamine (10^{-6} M) in the presence of INPEA (10^{-6} M). These results do not exclude the possibility that the local anaesthetic action of propranolol was causing non-specific vasodilatation. On the other hand, INPEA did not change the maximum effect of DA and the curve was shifted to the left. ED50 for DA = $7{\cdot}38 \times 10^{-4}$ M, and for DA + INPEA = $2{\cdot}94 \times 10^{-5}$ M.

The use of α- and β-blocking agents has led to a better understanding of the effects encountered with DA. Therefore experiments were carried out with NA as a model for α-adrenoreceptor vasoconstrictor effects and the results were compared with those obtained after DA treatment. The influence of added blocking drugs on vasoconstriction and vasodilatation was observed on the single responses of arteries.

In standard Krebs solution a similar, submaximal, constriction of arteries was observed after both DA treatment (3×10^{-3} M) and NA treatment (10^{-6} M). The average perfusion pressure was 53·7 s.d. 24 (n = 43) and 56 s.d. 28 (n = 65) mm Hg respectively, Fig. 2a.

Phentolamine was applied from 5×10^{-8} to 5×10^{-6} M; a dose of 5×10^{-7} M almost completely inhibited the vascoconstrictor response of arteries to NA (n = 5), and to DA—by about 88% (n = 6), Fig. 2b.

Propranolol (10^{-6} M) did not significantly enhance the vasoconstrictor response of arteries to DA (by 24 s.d. 2·6 mm Hg (n = 6) (value statistically insignificant, t = 2 3949 unpaired t-test), and vasodilatation was not inhibited (Fig. 2d, upper trace). But, while at 10^{-6} M, it did not influence the vascoconstrictor effect of NA (Fig. 2d, lower trace), at 10^{-5} to 10^{-4} M it decreased the perfusion pressure by 12 s.d. 5 (n = 5) and by 18 s.d. 5·2 (n = 18) mm Hg respectively (Fig. 2e, trace B) and in all cases inhibited vasodilatation. Neither phentolamine nor dihydroergotamine (5×10^{-7} M) caused vasodilatation when applied at the maximum of vasconstrictor effect reached after NA + propranolol treatment.

In the presence of phentolamine + propranolol the vascoconstrictor response of arteries to DA remained (Fig. 2e, trace A) although the DA effect was lower than in the standard Krebs solution. In the same conditions the contractile activity of arteries to NA was abolished.

To verify the effect of DA on arteries, apomorphine—an agonist of DA in the c.n.s. (Kafi & Gaillard 1976; Maj 1977) and in the frog skin (Wiglusz & Korolkiewicz 1979), haloperidol—an antagonist of DA in the c.n.s. (Burt et al 1976; Gnegy et al 1976), and imidazole—an antagonist of DA in the frog skin (Wiglusz & Korolkiewicz 1979) were studied (Table 1).

Haloperidol inhibited DA effects while the influence of imidazole was statistically insignificant. But haloperidol did not influence, while imidazole increased (Szadujkis-Szadurski 1977) the NA-induced constriction of arteries. Apomorphine inhibited the vasoconstrictor response to NA as it did to DA.

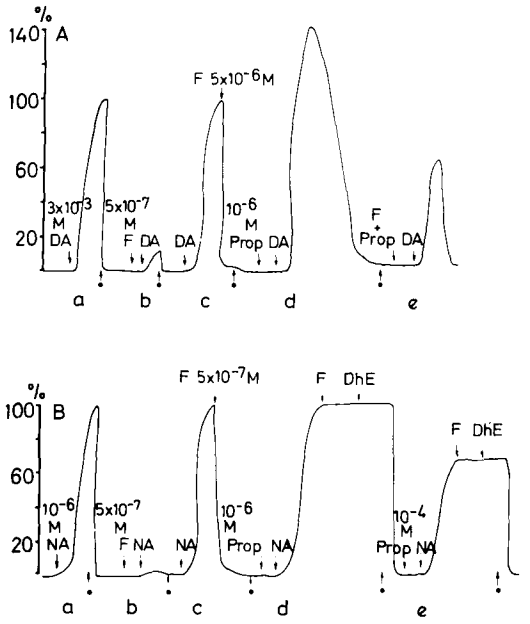

FIG. 2. The influence of dopamine (DA) and noradrenaline (NA) on the single contraction of isolated rat tail arteries. After DA treatment (3×10^{-3} M) the average arterial pressure was 53·7 s.d. 24 mm Hg (N = 43) which was taken as 100% (upper trace). After NA treatment (10^{-6} M) the average arterial pressure was 56 s.d. 28·5 mm Hg (n = 65) which was assumed as 100% (lower trace). F = phentolamine (5×10^{-7} M), Prop = propranolol (10^{-6} M), DhE = dihydroergotamine (5×10^{-7} M), ● = washing with the standard Krebs solution.

Rat tail arteries have been studied as a model for the influence of DA on peripheral arteries. The data presented add to the evidence that DA has an influence on arteries by a mechanism different from that for NA because DA constricted arteries during blockade of both α- and β-adrenoceptors whereas NA induced vasoconstriction in the presence of phentolamine + propranolol only when applied at $10^2 \times$ the concentration that it produced vasoconstriction without the blocking drugs. The sensitivity of arteries to DA was greater in the presence of propranolol or INPEA; this was not so for NA.

The dose-response curve for DA in the presence of adrenoceptor blocking agents indicates that phentolamine is responsible for the non-competitive diminution of DA contractile activity. On the other hand, DA effect could be influenced by haloperidol receptor systems as in the c.n.s. (Brown et al 1976) since haloperidol antagonized DA induced vasoconstrictor responses but did not change those of NA.

The vasodilatation due to DA was not influenced by propranolol, thus this effect is not connected with the activity of β-adrenoceptors as it is with NA.

Different responses of arteries to DA and NA in the presence of haloperidol and imidazole indicate that DA effects cannot be identified with those of NA. Moreover, the peripheral influence of DA on arteries indicates that this differs in some respect from DA's influence on the c.n.s. since apomorphine, an agonist of DA in c.n.s., appeared to be an antagonist of DA in rat tail arteries.

On the basis of this study we assume that there are putative DA receptors in the rat tail artery.

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