Br. J. Pharmac. (1983), **78**, 449–451

Effect of disopyramide on isolated aortic ring of the rat

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Disopyramide produces a contraction of the isolated aortic ring of the rat which is graded, develops slowly, and has a time course similar to the tonic phase of the noradrenaline response. This effect is not modified by α-adrenoceptor blockade (yohimbine) but is completely abolished by a Ca^{2+} antagonist (verapamil) or by removal of Ca^{2+} from the bathing solution. These results indicate that, in the rat aorta, disopyramide has a vasoconstrictor effect dependent on Ca^{2+} influx across the vascular smooth muscle membrane.

Introduction Disopyramide (DP), an antidysrthythmic drug with a quinidine-like action (Sekiya & Vaughan Williams, 1963) has been used for treating a number of atrial and ventricular arrhythmias (Vismara, Mason & Amsterdam, 1974). Haemodynamic studies in man have shown that it slightly increases arterial pressure, depresses myocardial contractility and increases peripheral vascular resistance (Navqui, Thompson, Morgan, Williams & Coltart, 1979). Electrophysiological studies in animals have shown that DP decreases the slope of phase 4 diastolic depolarization, depresses the maximum upstroke velocity of the action potential, decreases the conduction velocity and increases the action potential duration of Purkinje, atrial, ventricular and AV node fibres (Kus & Sasyniulk, 1975; Danilo, Hordof & Rosen, 1977). Although the various actions of DP on the heart are well established, little is known about its action on peripheral blood vessels and the present study was undertaken to evaluate this effect.

Methods Male Wistar rats (230–290 g) were killed by stunning and exsanguination. The thoracic aorta was immediately removed, cleaned of fat and connective tissue. Aortic rings, approximately 2 mm wide, were suspended by two platinum hooks in a 20 ml bath containing warm (37 °C) physiological salt solution gassed with 95% O_2 and 5% CO_2. A resting tension of 2 g was applied and the vessels were allowed to equilibrate for 2 h before starting the experiment. Changes in tension were recorded isometrically by a force displacement transducer (HP-FTA-10-1) coupled to a Hewlett-Packard Polygraph (Model 7702B).

Two bath fluids were used: (1) a polarizing salt solution (PSS) containing (mM): NaCl 118, KCl 4.7, $NaHCO_3$ 25, KH_2PO_4 1.2, $MgSO_4$ 1.2, $CaCl_2$ 2.5, glucose 10 and (2) a Ca^{2+}-free depolarizing salt solution (DSS) containing (mM): NaCl 17, KCl 100, $NaHCO_3$ 25, KH_2PO_4 1.2, $MgSO_4$ 1.2, EGTA 0.2 and glucose 10. All chemicals used to make the bath solutions were Merck products whilst the EGTA was from Sigma. The bath solutions were changed every 10 min. The following drugs were used: disopyramide phosphate (S.A. Roussel), (−)-noradrenaline bitartrate (Sigma), verapamil (Knoll), yohimbine (Merck). All drug doses are expressed as final bath molar concentrations. The volume of drug injected varied from 0.1–0.4 ml. Disopyramide (DP) and noradrenaline (NA) were left in contact with the tissue until a plateau contraction was reached whilst verapamil or yohimbine were added 30 min before addition of either DP or NA. Experiments performed with Ca^{2+}-free DSS had the following sequence: first a control response to DP or NA was obtained in normal PSS and after recovery the PSS was changed to Ca^{2+}-free DSS. DP or NA was subsequently added to the bath immediately after the end of the contraction induced by the depolarization had been achieved. The data were analysed by means of Student's *t* test and significance was set at $P < 0.05$. The results are expressed as means ± s.e.mean.

Results *Effect of disopyramide on rat isolated aorta* DP (10^{-6} to 10^{-4} M) produced a dose-dependent increase in the tone of the rat isolated aorta. The response started 15–60 s after adding the drug to the bath and developed slowly to take 7.9 ± 1.8 min to reach a plateau. The responses were reproducible provided that an interval of 45 min was allowed between consecutive doses.

Effect of α-adrenoceptor blockade on the responses to disopyramide and noradrenaline The contractions to DP and NA were recorded before and after incubation of the tissue with yohimbine (5×10^{-6} M) for 30 min. The control responses to DP (5×10^{-6} M) and NA (10^{-8} M) were 0.53 ± 0.13 g and 0.90 ± 0.21 g, respectively ($n = 6$). After treatment with yohimbine, the response to DP (0.54 ± 0.12 g)

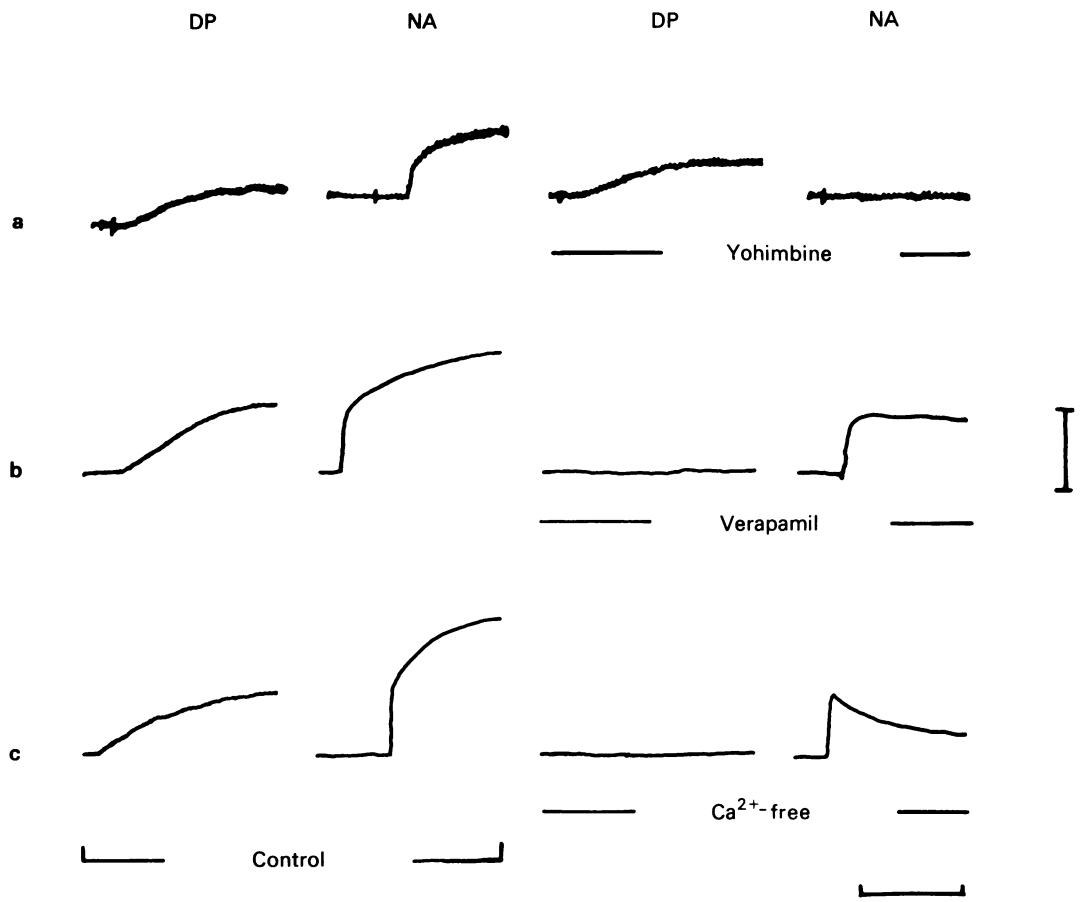

Figure 1 Experimental records of the contractile responses of the rat isolated aortic ring to disopyramide (DP) or noradrenaline (NA) before (left control columns) and after (right columns) incubation with (a) yohimbine (5×10^{-6} M), (b) verapamil (10^{-6} M) and (c) Ca^{2+}-free solution. The test doses of DP were either 10^{-5} M (b,c) or 5×10^{-6} M (a), whilst those of NA were either 10^{-7} M (b,c) or 10^{-8} M (a). The vertical calibration represents 1.0 g and the horizontal calibration 5.0 min.

was not significantly different from the control value but the response to NA was completely blocked (see Figure 1a).

The effect of verapamil The contractile responses to DP and NA were measured before and after incubation with the Ca^{2+} channel blocker verapamil (10^{-6} M) for 30 min ($n = 6$). The response to DP (10^{-5} M) was 0.82 ± 0.19 g before verapamil but afterwards was completely abolished. The two phases of the contractile response to NA were analysed. Whilst the initial phasic contraction induced by NA (10^{-8} M) before verapamil (0.68 ± 0.17 g) was not significantly affected by treatment, (0.60 ± 0.16 g), the secondary tonic responses to NA was completely blocked by verapamil (see Figure lb).

Effect of Ca^{2+}-free solution on the responses to disopyramide and noradrenaline Control responses to DP (10^{-5} M) and NA (10^{-7} M) were obtained while the aortic rings were bathed in PSS; 30 min after removal of the agonist the bathing solution (PSS) was changed to Ca^{2+}-free DSS and, immediately after the end of the contraction induced by the depolarization, the responses to DP and NA were re-examined. The response to DP, while the aorta was bathed in PSS, was 0.63 ± 0.10 g ($n = 11$) but in Ca^{2+}-free DSS no contractile effect was observed. In PSS the phasic and tonic contractions of NA were 0.96 ± 0.14 g and 0.61 ± 0.16 g, respectively. However, when the bath fluid was changed to Ca^{2+}-free DSS, the phasic component was significantly reduced to 0.70 ± 0.10 g ($P < 0.05$) and the tonic component of the contraction was abolished (see Figure 1c).

Discussion The intravenous injection of DP in patients without signs of cardiac failure produces an increase in diastolic and mean arterial pressure (Navqui *et al.*, 1979). In anaesthetized dogs, DP produces an increase in arterial blood pressure that is not blocked by phenoxybenzamine (Walsh & Horwitz, 1979). Haemodynamic studies in man have shown that DP increases peripheral vascular resistance and decreases cardiac output (Navqui *et al.*, 1979). As DP has a negative inotropic effect, the elevation of arterial blood pressure may be due to an increase in peripheral vascular resistance. Walsh & Horwitz (1979) suggested that DP may directly stimulate vascular smooth muscle or sensitize it to the actions of endogenous vasoactive substances. Our results partly confirm that suggestion, since we have shown that DP causes an increase in the tone of the isolated aorta of the rat. Moreover, our results show that in the rat isolated aorta the effects of DP are quite different from that of NA. Brodie, Bohr & Smit (1959) revealed that the time course of the response to NA on the rat isolated aorta could be divided into initial, fast and secondary, slow components. Subsequent analysis suggested that the fast phase depended on the release of Ca^{2+} from intracellular pools whilst the slow phase was due to Ca^{2+} influx from the extracellular fluid (Godfraind & Kaba, 1969). In the present experiments the time course of the DP response was similar to the slow, second component of the NA response in this tissue, suggesting that DP might increase vascular smooth muscle tone by modulating Ca^{2+} increase across the vascular smooth muscle membrane. Verapamil, a Ca^{2+} influx antagonist, blocked the slow phase of the response to NA and completely abolished the effect of DP. This, together with the finding that aortic rings suspended in Ca^{2+}-free DSS did not respond to DP, supports our conclusions that Ca^{2+} movements are involved in the vascular effects of DP in this tissue.

The vascular effects of DP persisted after α-adrenoceptors were blocked with yohimbine, so that any possible indirect adrenergic effect can be ignored. It appears, therefore, that DP has different actions on vascular smooth muscle from the heart. In the heart, DP decreases the inotropic effect of Ca^{2+} (Chiba, Kobayashi & Furukawa, 1979), but in vascular smooth muscle it achieves its contractile effect in a way dependent upon Ca^{2+} fluxes. The treatment of cardiac arrhythmias with DP in hypertensive patients has, in view of these differential actions, to be performed with caution.

This work was supported in part by CNPq and CEPG.

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(Received December 1, 1982.)