23°C the considerable reduction in calcium flux caused by D600 is more effectively antagonized by isoprenaline than by adrenaline. It is possible that at 6°C the greater potency of adrenaline may reflect the development of an alternative pathway for the adrenergic response. In addition, calcium transmembrane flux may contribute less to the contractile response at 6°C since D600 effects a much smaller work output reduction.

References


Responses of the sympathetically-innervated hepatic arterial vascular bed of the dog to intra-arterial injections of dopamine

P.D.I. RICHARDSON & P.G. WITHRINGTON

Department of Physiology, The Medical College of St. Bartholomew’s Hospital, Charterhouse Square, London ECTM 6BQ

The hepatic arterial vascular responses to intra-arterial (i.a.) noradrenaline and adrenaline have been studied in the dog (Andrews, Hecker, Maegraith & Ritchie, 1955; Richardson & Withrington, 1976a, 1977) and have been shown to involve stimulation of both α- and β-adrenoceptors. The third naturally occurring catecholamine, dopamine, has been shown to produce both vasodilatation and vasoconstriction in the dog (Yeh, McNay & Goldberg, 1969; Sampson, Scroop & Louis, 1974), effects which may be due to stimulation of both α- and β-adrenoceptors in addition to a specific dopamine receptor. The responses of the sympathetically-innervated hepatic arterial bed of the dog to dopamine, noradrenaline and adrenaline have been compared and the receptors mediating the dopamine effects examined.

In 6 chloralose-urethane anaesthetized dogs (Richardson & Withrington, 1976c), weighing 11.9 ± 1.9 kg (mean ± s.d.), under control conditions the hepatic arterial blood flow was 183.6 ± 46.8 ml/min (mean ± s.d.), and the perfusion pressure 121.3 ± 13.4 mmHg; the calculated hepatic arterial vascular resistance (HAVR) was 0.72 ± 0.28 mmHg ml⁻¹ min, or expressed in terms of the liver weights (272.0 ± 44.4 g), 1.87 ± 0.63 mmHg ml⁻¹ min 100 grams.

Dopamine was injected i.a. over the range 100 ng to 1 mg to construct 8 dose-response curves in 6 experiments: each injection produced an initial increase in calculated HAVR (vasoconstriction) followed by a secondary fall in HAVR (vasodilatation). The threshold for the vasoconstrictor response was 5–50 μg, the mean dose required to double the HAVR, 6.2 × 10⁻⁷ mol, being much greater than the corresponding doses for noradrenaline, adrenaline and phenylephrine (1.1, 2.7 and 6.9 × 10⁻⁸ mol respectively). The threshold for the vasodilator response (0.1–10 μg) was lower than that for the vasoconstrictor effect, the maximum reduction in HAVR of 25.7 ± 2.5% (mean ± s.e. mean) occurred at between 10 and 200 μg in different experiments.

These responses to dopamine were similar to those to adrenaline and noradrenaline, the secondary vasodilator effects of which have been shown to be due to β-adrenoceptor activation (Richardson & Withrington, 1976b, 1977).

In three experiments, the dose-response curves for both the vasoconstrictor and vasodilator responses to dopamine were constructed before and after propranolol (0.25 mg/kg i.v.). In common with adrenaline and noradrenaline, the vasoconstrictor dose-response curve to dopamine was shifted to the left, but in contrast to adrenaline and noradrenaline, the vasodilator dopamine dose-response curve was also shifted to the left, and at one dose level of dopamine (5.3 × 10⁻⁸ mol), this potentiation was statistically significant (P < 0.05, paired t-test).
These observations suggest that the hepatic arterial dilator responses to dopamine do not involve the same receptors as those which induce vasodilatation to adrenaline or noradrenaline, a conclusion supported by preliminary experiments with haloperidol (1.0 mg/kg i.v.) which markedly antagonized the hepatic arterial dilator effects to dopamine without affecting those to adrenaline or noradrenaline. Moreover the vasoconstrictor responses to both dopamine and phenylephrine were antagonized by haloperidol.

These results accord with the view that dopamine causes hepatic arterial vasoconstriction by stimulating \(\alpha\)-adrenoceptors, and vasodilatation by activating specific dopamine receptors.

This study was supported by the MRC.

References


UK-14,275, a novel orally-active cardiac stimulant

C.T. ALABASTER, K.J. BLACKBURN, J.R. JOICE, R. MASSINGHAM & P.C. SCHOLFIELD

Biological Research Group, Pfizer Central Research, Pfizer Limited, Sandwich, Kent

UK-14,275, 1-butyl-3-[1-(6,7-dimethoxyquinazolin-4-yl)piperidin-4-yl] urea, was selected for further evaluation from a structurally novel series of cyclic nucleotide phosphodiesterase inhibitors that were found to stimulate preferentially the force as opposed to the frequency of cardiac contraction.

In spontaneously beating guinea-pig atria, UK-14,275 (10^{-6} to 10^{-4} M) displayed dose-related positive inotropic activity coupled with negative chronotrophic activity. In this respect it resembled ouabain (10^{-7} to 10^{-6} M) but differed from isoprenaline (10^{-9} to 10^{-7} M) and theophylline (5 \times 10^{-3} to 5 \times 10^{-4} M) which increased force and frequency of contraction in parallel.

Intravenous injections (0.1 to 1.0 mg/kg) or infusions (0.05 to 0.5 mg kg^{-1} min^{-1} for periods up to 1 h) of UK-14,275 produced dose-dependent positive inotropic effects in anaesthetized and conscious dogs. Increases in heart rate were produced, but were markedly less than those evoked by an equally inotropic dose of isoprenaline.

Oral administration of UK-14,275, at doses above 5 mg/kg, evoked positive inotropic effects lasting from 3 to 6 h coupled with small increases in heart rate.

UK-14,275 was twenty times more potent than theophylline as an inhibitor of beef heart cyclic AMP phosphodiesterase in vitro, and was shown to increase tissue cyclic AMP levels in electrically driven guinea-pig left atria at a concentration of 5 \times 10^{-3} M. In addition, UK-14,275 (5 \times 10^{-3} M) potentiated both the inotropic response and the increase in tissue cyclic AMP levels evoked by isoprenaline in driven guinea-pig left atria. In contrast to isoprenaline, UK-14,275 (10^{-6} to 5 \times 10^{-4} M) did not affect the activity of guinea-pig heart adenylyl cyclase. Furthermore, unlike ouabain, UK-14,275 (10^{-8} to 10^{-4} M) had no effect on Na^{+}–K^{+} ATPase activity.

In driven cat left atria, propranolol (6.6 \times 10^{-8} M)