The effects of dopamine and dobutamine on isolated coronary vascular smooth muscle of the pig

A. AL-JEBOORY & R.J. MARSHALL

Department of Physiology and Pharmacology, University of Strathclyde, Glasgow

Goldberg (1972) has postulated the presence of specific dopamine receptors in renal and mesenteric vascular smooth muscle. There is also some evidence that such receptors may also play a role in the coronary dilator effects of dopamine (Schuelke, Mark, Schmid & Eckstein, 1971; Toda & Goldberg, 1975). We have examined this possibility by comparing the effects of dopamine, dobutamine, noradrenaline and isoprenaline on pig isolated coronary artery strips bathed in Krebs-Henseleit solution (37°C) bubbled with carbogen.

In strips contracted with submaximal concentration of K^+ (10–30 mM) dopamine ($0.2–5 \times 10^{-3}$ M), dobutamine ($0.3–9 \times 10^{-6}$ M) and noradrenaline ($0.5–7.5 \times 10^{-7}$M) caused further dose-dependent increases in vascular tone. After blockade of α-adrenoceptors with phenoxybenzamine (1.6×10^{-5} M) these three agonists caused dose-dependent relaxations of the tissue. Isoprenaline ($0.3–5.6 \times 10^{-6}$ M) and the phosphodiesterase inhibitor DL-4-(3 butoxy-4-methoxy benzyl)-2-imidazolidinone (Ro1724) ($0.4–6.2 \times 10^{-7}$M) also caused dose-dependent relaxations. Pretreatment of the tissues with propranolol (3×10^{-6} M) caused parallel shifts to the right of the dose-response curves to isoprenaline and noradrenaline but left the responses to dopamine, dobutamine and Ro1724 unaffected. The relaxant responses to dopamine and dobutamine were also unaffected by pretreatment with either atropine (4×10^{-6} M), apomorphine (3×10^{-6} M) or ergometrine (2×10^{-6} M), were significantly potentiated by haloperidol (3×10^{-6} M) and pimozide (2×10^{-6}M) and were abolished by the phosphodiesterase stimulant, imidazole (1.5×10^{-4} M).

In concentrations which did not themselves produce a measurable response both dopamine (1.3×10^{-4} M) and Ro1724 (0.2×10^{-7} M) caused a significant (7-fold) shift to the left of the isoprenaline dose-response curves.

These results suggest that the direct vasodilator actions of dopamine and dobutamine in large coronary vessels in the pig do not involve stimulation of either β-adrenoceptors or specific dopamine-receptors, but may result from inhibition of cyclic nucleotide phosphodiesterase. Detailed analysis of the time-course of the coronary vasodilator actions of dopamine and dobutamine also suggest an intracellular mechanism rather than interaction with a membrane-bound receptor.

References

GOLDBERG, L.I. (1972). Cardiovascular and renal actions of dopamine; potential clinical applications. *Pharmac. Rev.*, **24**, 1–29.

SCHUELKE, D.M., MARK, A.L., SCHMID, P.G. & ECKSTEIN, J.W. (1971). Coronary vasodilatation produced by dopamine after adrenergic blockade. *J. Pharmac. exp. Ther.*, **176**, 320–327.

TODA, N. & GOLDBERG, L.I. (1975). Effects of dopamine on isolated canine coronary arteries. *Cardiovasc. Res.*, **9**, 384–389.

Prazosin, a selective antagonist of post-synaptic α-adrenoceptors

D. CAMBRIDGE, M.J. DAVEY & R. MASSINGHAM

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

Among its pharmacological effects, the antihypertensive drug prazosin can bring about a functional blockade of α-adrenoceptors quite unlike the occupancy block caused by conventional α-adrenoceptor blocking agents (Constantine, McShane, Scriabine & Hess, 1973). Similarly, unlike conventional α-adrenoceptor blocking agents, prazosin did not cause tachycardia or renin release in dogs (Constantine *et al.*, 1973; Massingham & Hayden, 1975).

In light of the realization that at the terminal ramifications of sympathetic C fibres local control mechanisms operate which modulate transmitter output through positive and negative feedback mechanisms, we decided to compare the effects of prazosin with phenoxybenzamine on pre- and post-synaptic α-adrenoceptors (Langer, 1974; Starke, Endo & Taube, 1975).

The affinity of prazosin and phenoxybenzamine for pre-synaptic receptors was estimated by measuring

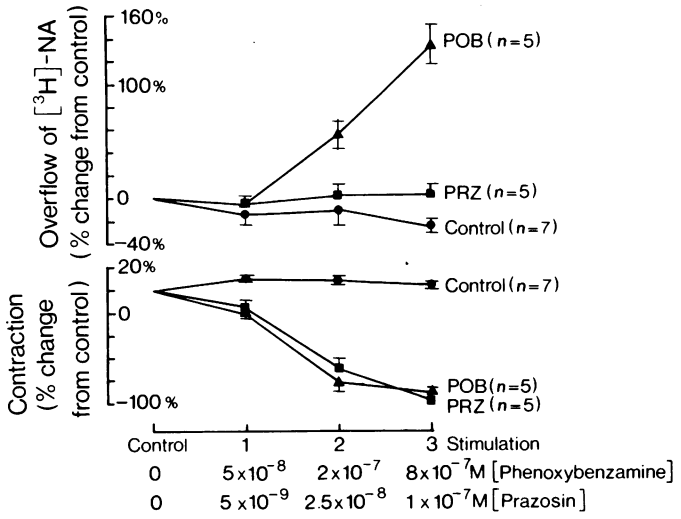

Figure 1 Effect of prazosin and phenoxybenzamine on contraction and ^{3}HNA overflow in rabbit pulmonary artery after blockade of uptake 1 and uptake 2. The control stimulation is the mean of 2 responses.

the stimulation-induced overflow of tritiated noradrenaline, whilst affinity for post-synaptic α-adrenoceptors was estimated by measuring the changes in tension elicited by nerve stimulation in superfused rabbit pulmonary artery preparations as described by Su & Bevan (1970).

The effects of prazosin and phenoxybenzamine were studied both in the absence and presence of desipramine (0.6 μM) and normetanephrine (10 μM) since phenoxybenzamine is known to block both neuronal and extraneuronal uptake of catecholamines (Iversen, 1971). In fact, similar results were obtained both in the presence and absence of uptake inhibitors.

The figure shows that prazosin has a remarkable specificity for post-synaptic adrenoceptors with little or no affinity for pre-synaptic. Prazosin, in concentrations which produce similar antagonism of post-synaptic events, caused virtually no increase in the overflow of tritiated noradrenaline whilst phenoxybenzamine caused a marked increase.

It is concluded that prazosin possesses specificity for post-synaptic α-adrenoceptors and that this provides an explanation for its apparent lack of tachycardia, tolerance and renin release which are observed with conventional α-adrenoceptor blocking agents.

References

CONSTANTINE, J.W., McSHANE, W.K., SCRIABINE, A. & HESS, H.-J. (1973). Analysis of the hypotensive action of prazosin. In *Hypertension: Mechanisms and Management*, eds. Onesti, G., Kim, K.E. & Moyer, J.H., pp. 429–444. Grune and Stratton Inc.

IVERSEN, L.L. (1971). Role of transmitter uptake mechanisms in synaptic neurotransmission. *Br. J. Pharmac.*, **41**, 571–591.

LANGER, S.Z. (1974). Presynaptic regulation of catecholamine release. *Biochem. Pharmac.*, **23**, 1793–1800.

MASSINGHAM, R. & HAYDEN, M.L. (1975). A comparison of the effects of prazosin and hydrallazine on blood pressure, heart rate and plasma renin activity in conscious renal hypertensive dogs. *Eur. J. Pharmac.*, **30**, 121–124.

STARKE, K., ENDO, T. & TAUBE, H.D. (1975). Relative pre- and post-synaptic potencies of α-adrenoceptor agonists in the rabbit pulmonary artery. *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **291**, 55–78.

SU, C. & BEVAN, J.A. (1970). The release of 3HNA in arterial strips studied by the technique of superfusion and transmural stimulation. *J. Pharmac. exp. Ther.*, **172**, 62–68.