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Relaxant effects of dopamine and isoprenaline on canine isolated coronary arteries – relationship to cyclic AMP production

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We have previously shown (Al-Jeboory & Marshall, 1977) that the relaxant effects of dopamine in porcine coronary artery strips are not due to stimulation of either β-adrenoceptors or specific 'dopamine receptors' but may result from inhibition of cyclic nucleotide phosphodiesterase. We have extended these studies to examine the relaxant effects of dopamine, isoprenaline and the phosphodiesterase inhibitor (±)-4-(3-butoxy-4-methoxy benzyl)-2-imidazolidininone (Rö 1724) on greyhound isolated coronary artery strips bathed in Krebs-Hensleit solution (37°C) bubbled with 95% oxygen – 5% CO_2 mixture and have attempted to correlate these effects with changes in cyclic AMP levels measured with an assay kit (Amersham) using a modification of Brown's method (Brown, Albano, Ekins & Sghergzi, 1971). In all experiments coronary artery strips were incubated for 60 min with phenoxybenzamine (1.6×10^{-5} M) to exclude effects on α-adrenoceptors.

In such treated strips contracted with submaximal concentrations of either K^+ (10–30 mM) pr PGE_2 ($0.2–1.6 \times 10^{-6}$ M), dopamine ($0.7–6.5 \times 10^{-4}$), isoprenaline ($0.2–8.0 \times 10^{-6}$M) and Rö 1724 (0.4–6.2 10^{-7} M) all caused dose-dependent relaxations of the tissue and increases in cyclic AMP (Table 1). Pretreatment of the tissues with propranolol (3×10^{-6} M) abolished both the pharmacological and the biochemical effects of isoprenaline but left those of dopamine and Rö 1724 unaffected. The relaxant responses to dopamine were also unaffected by the prior administration of either atropine, cyproheptadine, indomethacin or morphine thus excluding a role for acetylcholine, histamine or prostaglandins in these responses. In addition, pretreatment of the tissue with 'dopamine antagonists' like haloperidol or α-flupenthixol did not affect either the relaxations or increases in cyclic AMP produced by dopamine (Table 1). Further evidence that the dopamine-induced relax-

Table 1 Increases in cyclic AMP levels (picomoles/mg wet tissue) produced by dopamine and isoprenaline in canine coronary artery strips. Values are mean ± s.e.mean of at least six determinations

	Controls	*+ Propranolol* (3×10^{-6} M)	*+ Haloperidol* (3×10^{-6} M)	*+ α − Flupenthixol* (9.8×10^{-6} M)	*+ Imidazole* (7×10^{-5} M)
Dopamine (M)					
7×10^{-5}	3.3 ± 0.3	3.7 ± 0.3	3.4 ± 0.2	3.9 ± 0.4	0.6 ± 0.1*
2.1×10^{-4}	4.0 ± 0.3	3.8 ± 0.2	3.8 ± 0.5	—	0.6 ± 0.1*
7×10^{-4}	5.5 ± 0.3	5.3 ± 0.1	4.9 ± 0.5	5.1 ± 0.4	0.7 ± 0.2*
Isoprenaline (M)					
2×10^{-7}	4.1 ± 0.3	0.3 ± 0.2*	—	—	1.1 ± 0.3*
10^{-6}	4.3 ± 0.3	0.3 ± 0.2*	—	—	2.1 ± 0.2*
4×10^{-6}	5.6 ± 0.5	0.5 ± 0.2*	—	—	3.3 ± 0.2*

*Significantly different from control $P < 0.05$.

ations were related to cyclic AMP formation was obtained by the observation that imidazole (0.7×10^{-4} M) inhibited both the relaxations and the increases in cyclic AMP produced by dopamine, isoprenaline or Rö 1724 but did not alter the responses to adenosine.

These results suggest that a good quantitative and temporal relationship exists between the relaxant effects of dopamine, isoprenaline and Rö 1724 and their ability to generate cyclic AMP in isolated coronary vascular smooth muscle. In addition, as previously reported for pig coronary arteries, the effects of dopamine are more readily explained by an inhibition of cyclic nucleotide phosphodiesterase than by stimulation of hypothetical 'dopamine receptors'.

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References

AL-JEBOORY, A. & MARSHALL, R.J. (1977). The effects of dopamine and dobutamine on isolated coronary vascular smooth muscle of the pig. *Br. J. Pharmac.* **59**, 514P.

BROWN, B.L., ALBANO, J.D.M., EKINS, R.P. & SGHERZI, A.M. (1971). A simple and sensitive saturation method for the measurement of adenosine 3',5'-cyclic monophosphate. *Biochem. J.* **121**, 561–562.

The actions of indoramin on isolated artery preparations

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The isolated perfused ear artery of the rabbit was used to study the effects of indoramin on vascular tissue. At dose levels between 10^{-4} mM and 10^{-3} mM, indoramin competitively antagonized the vasoconstriction produced by noradrenaline (pA_2 7.7) and antagonized non-competitively the effects of 5-hydroxytryptamine and histamine. To investigate the possibility of non-specific vasodilator activity, tone was induced in six arteries by the use of excess potassium (4 times normal concentration) in the perfusing Krebs solution. This resulted in a sustained rise in baseline pressure. Indoramin, either as a bolus injection (2 μg) or added to the perfusing fluid (5×10^{-3} mM), failed to cause any fall in perfusion pressure. Injections of papaverine (1 μg), however, caused falls in perfusion pressure which were sustained for up to 20 minutes. Preliminary experiments on human temporal arteries obtained from autopsy specimens 4–6 h after death indicate that indoramin also antagonizes the effects of 5-hydroxytryptamine and noradrenaline on this tissue. These observations combined with reports of the use of indoramin in migraine (Wainscott, Volans, Wilkinson & Faux, 1975) have led us to conduct a 3-month clinical trial, the results of which showed that indoramin caused ⩾50% reduction in frequency and severity of migraine headaches in 9 out of 10 patients.

Reference

WAINSCOTT, G., VOLANS, G.N., WILKINSON, M. & FAUX, G.A. (1975). Indoramin in prevention of migraine. *The Lancet*, **ii**, 32–33.