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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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

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