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 α-adrenoceptors, and vasodilatation by activating specific dopamine receptors.

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

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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 chronotropic 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 (5×10^{-5} to 5×10^{-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 5×10^{-5} M. In addition, UK-14,275 (5×10^{-5} 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 5×10^{-4} M) did not affect the activity of guinea-pig heart adenyl 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 (6.6×10^{-8} M)

reduced the maximum inotropic response to UK-14,275. Attenuation of the inotropic responses to UK-14,275 was also seen in tissues which had been pretreated with syrosingopine or reserpine. This partial dependence of the activity of UK-14,275 on catecholamines is compatible with phosphodiesterase inhibition, since catecholamines increase the rate of cAMP synthesis.

UK-14,275 is a novel, orally active inotropic agent which preferentially increases force as opposed to frequency of contraction. This unusual property is shared only by the cardiac glycosides to which it bears no structural or mechanistic resemblance. Studies to date suggest that the major part of its activity is mediated *via* the inhibition of phosphodiesterase. Clinical evaluation of UK-14,275 as an agent for the treatment of congestive heart failure is in progress.

Histamine-induced changes in heart rate in anaesthetized cats

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Histamine increases the rate of beating of isolated cardiac preparations due to interaction with histamine H_2-receptors (Black, Duncan, Durant, Ganellin & Parsons, 1972). Histamine also increases heart rate in anaesthetized animals (e.g. Tucker, Weir, Reeves & Grover, 1975; Powell & Brody, 1976) although the response has not been characterized. Tachycardia due to interaction with histamine H_2-receptors has not been demonstrated *in vivo*. Doses of histamine which increase heart rate also lower blood pressure and can release catecholamines from chromaffin tissue (Burn & Dale, 1926), both mechanisms which might elicit tachycardia independent of histamine H_2-receptors. Experiments have been made to characterize the mechanism of tachycardia after administration of histamine to anaesthetized cats.

Cats, of either sex, were anaesthetized by intraperitoneal injection of chloralose (60 mg/kg) and urethane (700 mg/kg). The trachea was cannulated. Blood pressure was measured from one femoral artery and heart rate measured using a rate meter triggered by the blood pressure pulse. Drugs were administered via catheters in each brachial vein.

Histamine caused dose-dependent depressor responses and tachycardia over the dose range 1×10^{-9} to 1×10^{-7} mol/kg. Tachycardia persisted after treatment with mecamylamine (5 mg/kg), to block autonomic ganglia and prevent reflex increases in heart rate associated with the depressor responses to histamine.

Tachycardia caused by histamine up to 1×10^{-7} mol/kg, in ganglion-blocked cats could be reduced or abolished by treatment of cats with either propranolol (1 mg/kg) or mepyramine (5 mg/kg) suggesting that the tachycardia caused by these doses of histamine was due to release of catecholamines from chromaffin tissue, a histamine H_1-receptor phenomenon (Emmelin & Muren, 1949). Increasing the dose of histamine to 1×10^{-6} mol/kg in mepyramine-treated cats restored tachycardia. This response to larger doses of histamine was refractory to propranolol or further doses of mepyramine but antagonized by metiamide, 0.5 mg kg^{-1} min^{-1} indicating that these large doses of histamine can cause tachycardia by interaction with histamine H_2-receptors.

These experiments indicate that histamine can cause tachycardia in anaesthetized cats independent of reflex responses to falls in blood pressure. After low doses of histamine this response is due to release of catecholamines whereas larger doses of histamine can also cause tachycardia by interaction with histamine H_2-receptors.

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