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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