Myocardial effects of phentolamine

P. K. DAS and J. R. PARRATT*, *Department of Pharmacology, University of Strathclyde, Glasgow, C.*1

The main rationale for the use of α-adrenoceptor blocking drugs in clinical shock has been that, by antagonizing sympathetic vasoconstrictor tone, they increase peripheral tissue perfusion. It has been suggested that this is achieved at the expense of a diversion of blood from the heart and brain (Perlroth & Harrison, 1969), although Grayson & Mendel (1961) have demonstrated that in normotensive rabbits phentolamine increased myocardial blood flow. In normal human subjects phentolamine substantially increases cardiac output and it has been presumed that this is a reflex response to hypotension, perhaps involving sensitization and potentiation of the carotid sinus reflex (see Taylor, Sutherland, MacKenzie, Staunton & Donald, 1965). More recently, however, Gould (1969) has drawn attention to a myocardial stimulant effect of phentolamine. The present study is an attempt to analyse the mechanism of action of phentolamine in increasing myocardial blood flow and contractile force.

Sixteen cats, anaesthetized with pentobarbitone sodium (30 mg/kg) were used. Left ventricular pressure and dp/dt, descending aortic pressure and dp/dt, heart rate and right atrial pressure were measured (McInnes & Parratt, 1969). Changes in myocardial blood flow were assessed by a heat clearance technique (Grayson & Mendel, 1961; McInnes & Parratt, 1969) and cardiac output was measured by thermodilution. Phentolamine was given by infusion for a period of 5 min in doses of 0·01, 0·02, 0·05 or 0·1 (mg/kg)/min. There was a reduction in systolic ejection time and increases in left ventricular maximum dp/dt (+ve and −ve, without a change in end-diastolic pressure), descending aortic dp/dt, heart rate, myocardial blood flow and cardiac output. In some animals these effects were seen in doses of 0·01 and 0·02 (mg/kg)/min; in others only with the higher doses. Similar effects were seen in cats in which the heart had been depressed by large doses of pentobarbitone. Phentolamine-induced myocardial stimulation had the following characteristics:

(1) Maximal responses were usually seen towards the end of the infusion period and the effects sometimes lasted for 20–30 min.

(2) With the lower doses, which had little or no α-adrenoceptor blocking effect, myocardial stimulation occurred without a reduction in blood pressure; in some animals a pressor response was observed. This suggests that the increase in cardiac output is not a reflex response to systemic hypotension.

(3) Phentolamine-induced myocardial stimulation was prevented by the β-adrenoceptor blocking drug alprenolol (0·5 mg/kg). However, recovery from block was considerably slower than with adrenaline or noradrenaline.

It is concluded that phentolamine stimulates the myocardium by a mechanism involving the sympathetic nervous system, perhaps by protecting released noradrenaline against "tissue inactivation" (Gillespie & Kirpekar, 1965).

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Cardiovascular effects of pentazocine in rabbits

M. FOGARTY, D. GILL, P. HILL* and J. PETTIT (introduced by P. J. CANNON), *Department of Pharmacology, University College, Dublin*

After the intravenous injection of pentazocine in man some workers (Lal, Savidge & Chhabra 1969) have recorded a transient fall in arterial pressure followed by a rise to levels higher than those of the control period. Others (Jewitt, Maurer & Hubner, 1970) did not observe the initial fall but noted a transient reduction in cardiac output followed by a prolonged rise in systemic and pulmonary arterial pressures. These haemodynamic changes are unexplained.

In decerebrate rabbits or in rabbits anaesthetized with chloralose–urethane, rapid intravenous injection of pentazocine in doses of 0·5, 1·0 and 2·0 mg/kg also caused a transient fall and subsequent rise in arterial pressure. The degree and duration of the fall in pressure were related to the dose given and were greater and longer lasting after cutting the vagus and sympathetic in the neck. In conscious animals, doses of pentazocine (1–2 mg/kg intravenously) caused an increase in heart rate, prolongation of the QT interval, a marked reduction in voltage with widening of the QRS complex and abnormalities of the T wave. Ventricular tachycardia occurred in two animals.

Pentazocine reduced the force of contraction of the heart isolated from the rabbit, the dose required to produce a 50% reduction being approximately 350 μg; with this dose the maximum effect occurred within 30 s and wore off gradually over 6–7 min. The heart rate was slowed but this effect was less marked and of shorter duration than the effect on contractile force. Coronary flow was measured as a drop rate; this slowed very briefly, recovering completely within 30 s.

Apart from its effects on the heart, pentazocine also had local anaesthetic properties and acted as a non-competitive anatagonist of acetylcholine and histamine on the guinea-pig ileum.

It is suggested that the cardiovascular effects of intravenous pentazocine in the intact animal are due to a direct depressant action of the drug on the myocardium modified by secondary reflex sympathetic activity.

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Cardiovascular actions of Wy 21901, a new hypotensive and anti-arrhythmic agent

B. J. ALPS*, E. S. JOHNSON and A. B. WILSON, *Department of Pharmacology, Wyeth Institute of Medical Research, Taplow*

β-Adrenoceptor blocking drugs are well known as anti-arrhythmic agents, and have