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The action of β-receptor antagonists on intracellular cardiac potentials.

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Dohadwalla, Freedberg & Vaughan Williams (1969) have reported that in isolated rabbit atria, 60 min exposure to (−)-, (+)- and (±)-propranolol and practolol (I.C.I. 51072) greatly reduced the rate of rise (MRD) of the intracellularly recorded action potential at concentrations which had no significant effect on contractility, repolarization time and other cardiac parameters. They concluded that the MRD "was by far the most sensitive test of the activity of the drugs on cardiac function".

In the present experiments, (±)-propranolol ($1{\cdot}0\times10^{-5}$M) after 10 and 20 min exposure decreased the MRD and amplitude of the action potential and depressed contraction in rabbit atria, which agrees with the above results. However, in some experiments (±)-propranolol ($1{\cdot}0\times10^{-6}$M) caused a significant increase in MRD and action potential amplitudes in spite of a significant depression of the contractile response.

In other experiments, however, notably with 10^{-6}M propranolol on spontaneously beating guinea-pig atria, and with 10^{-5}M practolol on driven guinea-pig atria, MRD was reduced to a greater extent than contractions. Similar results were obtained with (±)-propranolol ($1{\cdot}0\times10^{-6}$M) in guinea-pig atria driven at 60/min (left atria) and at 180/min (combined right and left atria). At a higher concentration ($1{\cdot}0\times10^{-5}$M) of (±)-propranolol there were no differences in the electrophysiological parameters from control values in these preparations.

Practolol and oxprenolol, two other β-receptor blocking agents, had almost no effect (even at concentrations much greater than that necessary to cause substantial ß-receptor blockade) on MRD, action potential size, or configuration of the action potential when tested on guinea-pig left atria.

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The effects of intravenous acetylcholine on the cardiovascular system of the anaesthetized dog.

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The fall in systemic blood pressure following the intravenous administration of acetylcholine was found not to be associated with a direct effect of acetylcholine on resistance in the femoral vasculature.

Rapid intravenous injections of acetylcholine (2–5 μg/kg in 0·1–0·25 ml) were made via a polyethylene cannula introduced through a femoral vein into the inferior vena cava. Femoral arterial flow was measured on the other side using an electromagnetic flowmeter. A mass ligature was tied around that leg, passing under the femoral artery and vein; the sciatic and femoral nerves were cut.

A fall in femoral flow during the fall of blood pressure was observed in all eight experiments with acetylcholine and the calculated resistance during these early seconds was slightly increased. A rise in femoral flow during the period of decreased systemic blood pressure occurred following the intravenous administration of isoprenaline (1–2 μg/kg) and the resistance was decreased. It appeared that intravenous isoprenaline reached the leg but that intravenous acetylcholine did not. Vane (1969) has suggested that acetylcholine is unlikely to have a significant role as a circulating hormone, not only because of rapid destruction in blood, but also because of pulmonary inactivation.

When the hind leg was perfused with a Sigmamotor pump the close intra-arterial injection of acetylcholine (10–50 ng/kg) induced a fall in perfusion pressure and femoral resistance. When the point of intra-arterial injection was moved distally by 2 inch increments, thus prolonging contact time with the blood, this vasodilator effect was progressively reduced. When the intra-arterial injection was in contact with the blood for an additional 13–16 s the acetylcholine did not affect the femoral resistance.

The start of the precipitous fall in systemic blood pressure in these experiments was 4–6 s after intravenous injection; the blood pressure started to return about 15 s after the injection. Thus, blood pressure began to fall at a time before acetylcholine could have reached the periphery and began to recover at a time when, if not totally inactivated in the blood, acetylcholine might have had a direct vasodilating effect.

It is suggested that effects of intravenous injections of acetylcholine on peripheral resistance that contribute to the fall in systemic blood pressure are not the result of a direct action of acetylcholine because: (1) acetylcholine is inactivated too quickly in the circulation and (2) the blood pressure effects occur before acetylcholine could reach the periphery. These effects may be, therefore, (1) neurogenic in origin and/or (2) the result of an autoregulatory reaction to a decreased pressure resulting from a decreased cardiac output.

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Cholinergic mechanism in the perfused vessels of the rabbit ear.

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Thompson & Tickner (1953) and Grant & Thompson (1963) have demonstrated the presence of cholinesterases in the rabbit ear and its blood vessels and Bernheim & Bernheim (1938) and Hobbiger & Lessin (1955) have discussed the presence and variability of atropine esterase in rabbits but not with particular regard to the ear.

We have studied the effects of temperature on the dilator response induced by acetylcholine (ACh) in the rabbit isolated ear perfused with Krebs solution. Preliminary results were reported at the Fourth International Congress on Pharmacology (Al Tai & Graham, 1969).