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Action of prostaglandin E_1 on the longitudinal muscle of the guinea-pig isolated colon

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Segments of guinea-pig colon, 6–15 cm from the anal margin, were suspended in Krebs solution maintained at 37° and bubbled with 5% carbon dioxide in oxygen. Isotonic contractions of the longitudinal muscle were recorded by a frontal-writing lever on a kymograph. Prostaglandin E_1 (2–100 ng/ml., twenty-six experiments) in contact with the tissue for 30 or 60 sec caused slow contractions which reached a maximum in 0.5–2.5 min. Relaxation after wash-out was even slower (3–15 min).

The mechanism of action of prostaglandin E_1 was studied by assessing the effects of other drugs on the contractions which it produced. The nerve-blocking drug tetrodotoxin (0.25 or 0.5 μg/ml.) virtually abolished the effect of nicotine without altering the response to acetylcholine ; it reduced the contractions caused by prostaglandin E_1 by 35–90% (average 60% ; nine experiments). When tetrodotoxin was washed out of the bath, the response to prostaglandin E_1 usually returned within a few minutes whereas the effect of nicotine was depressed for much longer, often for more than an hour. Hyoscine in doses (0.1–5 μg/ml.) more than sufficient to prevent the effect of added acetylcholine, did not depress the response to prostaglandin in eleven experiments, although it caused reduction in two others. Morphine (0.1–0.2 μg/ml.), which prevents the release of acetylcholine from nerves, had no effect on the response to prostaglandin E_1 in four experiments, although it caused a reduction in four others.

These results suggested that prostaglandin E_1 stimulated receptors on or in the muscle cells, and also activated non-cholinergic excitatory nerves. Electrical stimulation experiments by Ambache & Freeman (1968) have demonstrated the presence of such nerves in guinea-pig ileum. We have obtained similar results in the guinea-pig colon, and we have also found that nicotine and dimethylphenylpiperazinium iodide produce contractions in the presence of hyoscine. The experiments with tetrodotoxin indicated a neurogenic action of prostaglandin E_1 but this mechanism of action was not confirmed with local anaesthetic drugs. Cocaine or lignocaine in concentrations (20–50 μg/ml., five experiments) which substantially reduced the response to nicotine, did not alter the effect of prostaglandin E_1. The efficacy of

local anaesthetics in blocking intramural nerves of isolated intestine may, however, be questioned because cocaine in doses which inhibited the response to nicotine had little effect on electrically stimulated contractions of guinea-pig ileum (Bennett, 1965). Although we favour the idea that prostaglandin E_1 acts partly by stimulating non-cholinergic excitatory nerves, the possibility that tetrodotoxin acts atypically, for example by interfering with the excitation of prostaglandin receptors on the muscle, cannot be excluded.

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The effect on intracellular atrial potentials of bretylium in relation to its local anaesthetic potency

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Bretylium has been reported to have anti-arrhythmic properties, (Leveque, 1965 ; Bacaner, 1968 ; Ellis, Barnes & Cozzi, 1968). Earlier studies revealed that several anti-arrhythmic compounds had some features in common. In the isolated rabbit auricle, they greatly reduced the rate of rise and the height of the intracellularly recorded action potential and decreased conduction velocity, but did not significantly affect either the resting potential or the duration of the action potential (Vaughan Williams, 1958, 1966 ; Szekeres & Vaughan Williams, 1962). In addition most of these compounds were shown to possess local anaesthetic activity. It was therefore of interest to compare the cardiac and local anaesthetic actions of bretylium with those of other anti-arrhythmic agents.

In isolated rabbit atria, electrically driven at a rate of 180/min, therapeutic concentrations of bretylium (5–20 mg/l.) did not significantly affect the transmembrane potentials. A marked decrease in the rate of rise was only observed at a concentration as high as 1,200 mg/l. The latter effect was associated with some reduction in the height of the action potential, but the resting potential was not significantly altered. Similar changes can be produced by procaine at 7.5 mg/l. or propranolol at 0.3 mg/l. In some experiments, bretylium induced a small transient increase in the height and rate of rise of the action potential and a small initial increase in atrial rate, contractility, conduction velocity, and maximum driving frequency, as well as a short-lasting reduction in the electrical threshold. Bretylium (1,200 mg/l.) after 60–180 min exposure, slightly reduced the atrial rate, conduction velocity, maximum driving frequency and increased the electrical threshold, but did not reduce the contractility.

On the desheathed sciatic nerve of the frog bretylium proved to be about 90 times less potent than procaine as a local anaesthetic, and was approximately 300 times less active than propranolol.