and (±)-amphetamine on efflux by inhibiting the efflux of amine across the neuronal plasma membrane. In other studies, we have demonstrated that the increases in noradrenaline efflux produced by ouabain, omission of K^+ or metabolic inhibition are similarly inhibited by cocaine or desipramine.

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Some actions of bradykinin on mouse isolated ileum

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Superfusion techniques are used to detect or assay many biologically active substances; the choice of donor species and tissue depending on the sensitivity of response to the agent in question. In studying the suitability of mouse tissues for bioassay purposes we found that bradykinin produced biphasic responses in the isolated ileum and that the contractile component was reduced by AH 5158, a drug which blocks both α- and β-adrenoceptive receptors (Farmer, Kennedy, Levy & Marshall, 1972). Experiments were undertaken to assess whether the release of endogenous materials by bradykinin might be responsible for its actions in this tissue.

Isotonic or isometric recordings were made from 1·5 cm lengths of mouse distal ileum, under 0·5 g tension, over which McEwen's solution at 32° C, saturated with a mixture of 95% O_2 and 5% CO_2, flowed at a rate of 1 ml/min. Agonist drugs were applied for 30 s (optimal contact time) generally on a 4 min cycle. When the actions of antagonists were assessed they were present continuously in the superfusing medium except during the 30 s agonist contact period.

Bradykinin caused an initial decrease in the tone and the pendular movements of the ileum followed within 12 s by a contraction. The threshold concentration for this biphasic effect was about 1·0 ng/ml; the maximum relaxation occurred with 82 ± 11 ng/ml and maximum contraction with 670 ± 48 ng/ml (means ± S.E. of means). The inhibitory action of AH 5158 (10 to 100 μg/ml) on submaximal contractions was confirmed and no antagonism of the bradykinin-induced relaxation was seen in this concentration range. This action of AH 5158 would appear to be non-selective since it caused similar reductions in the intestinal contractions produced by furmethide, 5-HT or PGE_2. Neither propranolol (up to 10 μg/ml) nor phentolamine (up to 30 μg/ml) produced a selective inhibition of the bradykinin-induced responses and we concluded that it was unlikely that released catecholamines were responsible for the peptide's actions.

Non-steroidal anti-inflammatory drugs can reduce some of bradykinin's effects (Collier, Dinneen, Johnson & Schneider, 1968; Collier, James & Piper, 1968) and it has recently been shown that members of this group of drugs may also prevent the biosynthesis and/or release of prostaglandins, or like materials, from certain tissues (Piper & Vane, 1969; Gryglewski & Vane, 1972a, 1972b). Using sodium meclofenamate as an example, we found that this drug had dose-dependent anti-bradykinin activity (0·1 to 10 μg/ml) while leaving unchanged the responses to other agonists. Both the relaxant and contractile components of the bradykinin response were reduced by this drug. If sodium meclofenamate owes its anti-bradykinin activity to an inhibition of prostaglandin production then it would be necessary to demonstrate the release of two, or more, prostaglandin-like substances having opposite effects on the mouse ileum.

Experiments are currently being performed to determine whether prostaglandin release by bradykinin could be responsible at least for the slowly developing contractile response.

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Inhibitory effect of propranolol on insulin secretion

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Inhibition of glucose-stimulated insulin secretion by propranolol occurs in man (Cerasi, Luft & Efendić, 1972) but the mechanism involved is unknown.

Fasted male rats were anaesthetized with pentobarbitone sodium (60 mg/kg I.P.), and a femoral artery and vein were cannulated for blood sampling and drug administration respectively. The animals were heparinized (100 u I.V.). Plasma glucose was determined by a glucose oxidase method (Beckman glucose analyser) and plasma immunoreactive insulin (IRI) was determined by the method of Hales and Randle (1963).

(±)-Propranolol (0·5 mg/kg I.V., 15 min prior to glucose administration) caused a significant reduction in both plasma glucose and plasma IRI concentrations following glucose injection (0·5 g/kg I.V.). The increase in IRI concentrations caused by sulphonylurea administration (glibenclamide 2 mg/kg or tolbutamide 200 mg/kg I.V.) was similarly reduced although their hypoglycaemic effect was not significantly altered. The hyperglycaemia and increase in IRI concentrations produced by isoprenaline administration (175 μg/kg by slow I.V. injection) were completely prevented by (±)-propranolol (0·5 mg/kg) as was isoprenaline-induced tachycardia. (+)-Propranolol (0·25 mg/kg I.V.) exerted similar effects on the plasma glucose and plasma insulin changes caused by each of the above agents but did not modify isoprenaline tachycardia.

(±)-Propranolol (0·5 μg/ml; $1{\cdot}7\times10^{-6}$ M) caused a marked suppression of the increased IRI secretion stimulated by glucose (3 mg/ml: $1{\cdot}7\times10^{-2}$ M) or tolbutamide (200 μg/ml; $7{\cdot}4\times10^{-4}$ M) from pieces of chopped pancreas incubated *in vitro* according to the method of Coore and Randle (1964).

(±)-Propranolol up to 20 μg/ml ($2{\cdot}8\times10^{-5}$ M) did not affect the determination of human insulin in protein buffer solutions, suggesting that inhibition of IRI secretion by the drug is a real effect and is not due to interference of the drug with the assay system.

We conclude that the inhibitory effect of propranolol on IRI secretion is exerted directly on the islets of Langerhans and is not meditated through primary effects on plasma glucose or on pancreatic blood flow. The lack of specificity of the inhibitory effect of (±)-propranolol to any of the three agents tested, together with the similar effects of (+)-propranolol, suggests that the effect may not be mediated by β-adrenoceptor blockade. The effect may be meditated through the membrane stabilizing action of propranolol or by an action on some other component of the insulin secretory mechanism common to the insulinotropic effect of all three agents.

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