supersensitivity to reserpine we therefore used dosage regime (c). This dosage, however, satisfactorily depleted catecholamines since the indirectly acting sympathomimetic β-phenylethylamine was virtually ineffective in a dose that produced a significant response in untreated atria. The supersensitivity to schedule (b) was found to be non-selective since it was also demonstrated to histamine.

Salbutamol, a sympathomimetic amine having partial agonist properties in the heart (Brittain, Jack & Ritchie, 1970) was then compared with isoprenaline. In untreated atria salbutamol was almost a full agonist on rate but only a partial agonist on the tension with a mean maximum response only 10.8% (± 2.0%, $n = 4$) that of isoprenaline. However, in atria from animals receiving treatment (b) and (a), the maximum tension response was raised to 24.0% (± 6.8%, $n = 4$) and 52.5% (± 9.61, $n = 4$) respectively.

This study therefore demonstrates non-selective supersensitivity to isoprenaline by reserpinization on both rate and tension, the latter being more pronounced. Furthermore, a partial agonist on tension can be progressively shifted towards full agonist activity.

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Is ATP an inhibitory neurotransmitter in the rat stomach?

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Burnstock (1972) has postulated a neurohumoral role for ATP or a related nucleotide in 'purinergic' inhibitory nerves of the gastrointestinal tract.

The rat stomach has been shown to contain non-adrenergic inhibitory neurones from which release of the transmitter substance could not be demonstrated. After a wide range of potential neurotransmitters had been examined, only ATP and adenosine merited further investigation (Heazell, 1974). The hypothesis that the rat stomach contained purinergic inhibitory fibres was studied pharmacologically by comparing the effect of certain drugs upon the responses to exogenous ATP and adenosine with those to nerve stimulation.

A rat fundal strip (Vane, 1957) was placed in oxygenated Krebs solution at 32°C containing hyocine (1×10^{-6} M), 5-HT (3×10^{-7} M) to maintain tone and sodium metabisulphate (5×10^{-3} M) as an antioxidant. Sequential dose-response curves were obtained to ATP and adenosine.

The nature of response to a low dose of ATP (1×10^{-6} M) was not consistent although with higher doses up to 2×10^{-3} M, small relaxations were obtained sometimes followed by a contraction. Adenosine (1×10^{-5}-1×10^{-4}M) also caused a variety of effects, higher doses resulting in relaxation.

Dipyridramole and hexobendine (Satchell, Lynch, Bourke & Burnstock, 1972) which have been shown to potentiate 'purinergic' transmission increased the inhibitory response to exogenous purine. By contrast, responses to field stimulation with pulses of 30 V cm^{-1} (measured in Krebs solution), 0.2 ms duration at frequencies to produce maximal and sub-maximal effects were slightly reduced by dipyridamole and not significantly different following hexobendine.

2-2′ Pyridylisatogen tosylate, a specific antagonist of ATP (Hooper, Spedding, Sweetman & Weetman, 1974), reduced the inhibitory effects of ATP and adenosine. The response to electrical stimulation was reduced but was not significantly lower than the control; some of this reduction was due to the decline in muscle tone following addition of drug.

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On the basis of these observations, the non-adrenergic inhibitory innervation of the rat stomach is unlikely to be purinergic.

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Comparison of the effects of selective α- and β-receptor agonists on intracellular cyclic AMP levels and glycogen phosphorylase activity in guinea-pig liver

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(−)-Isoprenaline (a selective β-receptor agonist) and (±-amidephrine (a selective α-receptor agonist) have been shown to increase glucose release from guinea-pig liver slices (Haylett & Jenkinson, 1972a,b). The effects of these agents on intracellular cyclic AMP levels and glycogen phosphorylase activity have now been measured under similar experimental conditions. The slices were exposed to the agonists for 2 min, at which time increased glucose release was substantial but not maximal. Cyclic AMP was determined by a protein binding technique (Tovey, Oldham & Whelan, 1974) in samples extracted from slices by TCA precipitation of acid insoluble material, after freezing the tissue in liquid nitrogen. The supernatant was passed through a 3.0 x 0.5 cm column of Dowex 50 (H^+ form) to remove the TCA and substances that might interfere with the cyclic AMP assay. Glycogen phosphorylase activity was measured by the method of Danforth, Helmreich & Cori (1962). Glucose release was measured by the procedure of Park & Johnson (1949).

Doses of agonist which cause near maximal glucose release–isoprenaline 20 nM, amidephrine 20 μM–both produce comparable increases in phosphorylase activity. However while the cyclic AMP level in slices treated with this dose of isoprenaline was significantly greater than the control values ($P < 0.05$), there was little change in the cyclic AMP level in slices treated with amidephrine (Figure 1). Glucose release in the 2 min exposure to amidephrine was 53.8 ± 11.8% ($n = 16$) above control release, as compared with 25.9 ± 8.1% ($n = 15$) after isoprenaline. The increase in phosphorylase activity was shown to be dose-related between 4 and 20 μM amidephrine. The response to 20 μM amidephrine, but not that to 20 nM isoprenaline, was abolished in the presence of 40 μM phentolamine.

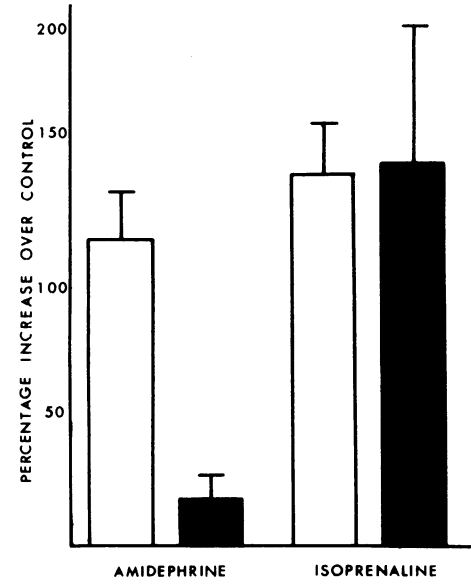

Figure 1 Effect of amidephrine (20 μM) and isoprenaline (20 nM) on glycogen phosphorylase activity (□) and tissue level of cyclic AMP (■). Each histogram represents the mean of at least 7 experiments; the vertical bar represents one s.e. mean.