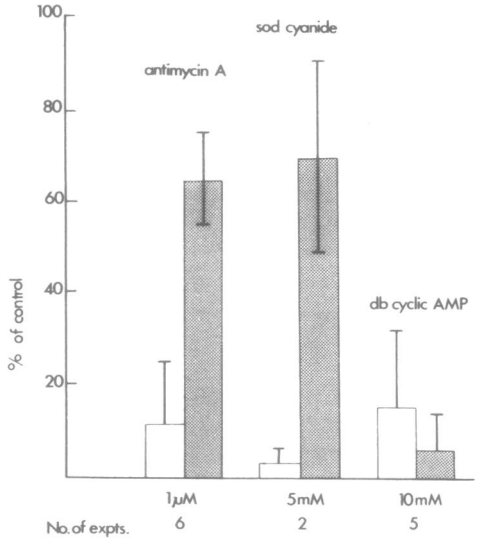

Figure 1 The effect of metabolic inhibitors and dibutyryl cyclic AMP on 45-calcium uptake (hatched columns) and histamine release (open columns). Vertical bars show standard error of mean.

channels is not dependent upon ATP production, but appears to be opposed by cyclic AMP. Further evidence for this mechanism is provided by the correlation ($r = 0.85$, $n = 14$) between cell sensitization (measured by uninhibited histamine release, 5-35% of cell content) and 45-calcium uptake.

MBH thanks the MRC for a training award.

References

FOREMAN, J.C. & MONGAR, J.L. (1972). Activation of anyphylactic histamine release by calcium and strontium ions. *Br. J. Pharmac.*, **44**, 326P.

FOREMAN, J.C., MONGAR, J.L. & GOMPERTS, B.D. (1973). Calcium ionophores and movements of calcium ions following the physiological stimulus to a secretory process. *Nature*, **245**, 249-251.

FOREMAN, J.C., MONGAR, J.L., GOMPERTS, B.D. & GARLAND, L.G. (1975). A possible role of cyclic AMP in the regulation of histamine secretion and the action of cromoglycate. *Biochem. Pharmac.*, **24**, 538-540.

Reserpine-induced supersensitivity to the rate and tension responses to isoprenaline and salbutamol of guinea-pig atria

K.J. BROADLEY & P. LUMLEY*

Department of Applied Pharmacology, Welsh School of Pharmacy, University of Wales Institute of Science and Technology, Cardiff CF1 3NU

Reserpine, as well as depleting neuronal catecholamines produces a non-specific supersensitivity (Trendelenburg, 1963). This has been demonstrated in isolated cardiac preparations where both the positive inotropic (McNeill & Schulze, 1972) and chronotropic responses (Westfall & Fleming, 1968) to noradrenaline were potentiated by reserpinization. However, Crout, Muskus & Trendelenburg (1962) failed to produce supersensitivity to the rate responses and Taylor, Westfall & Fleming (1974) have recently claimed that it is only the rate responses that are potentiated. To clarify these divergences of opinion, we have examined the effect of a range of reserpine pretreatment regimes upon both the inotropic and chronotropic responses to isoprenaline as the agonist.

Separated left and right guinea-pig atria were suspended in Krebs-bicarbonate solution at 38°C gassed with CO_2: O_2, 5%:95%. The left atrium was paced electrically at 2.5 Hz and isometric tension recorded on a Devices M19 polygraph for the inotropic responses. Chronotropic responses were obtained by means of a ratemeter triggered by the isometric tension signal of the spontaneous right atrium. Two cumulative dose response curves to isoprenaline were obtained and the second used for plotting purposes. In some experiments comparisons were made between this curve and a third curve to another agonist.

Isoprenaline in untreated atria was more selective for rate in that the rate dose response curve was to the left of that for tension. Isoprenaline was then examined in atria taken from guinea-pigs receiving the following reserpinization schedules; (a) 5 mg/kg at 72 h, 3 mg/kg at 48 h and 3 mg/kg at 24 h, (b) 5 mg/kg at 24 h and (c) 0.5 mg/kg at 24 h before sacrifice. Both the rate and tension dose response curves were displaced to the left by the three day pretreatment (a) suggesting the possibility of supersensitivity. However, the tension curve was shifted more, so that the selectivity for rate previously seen in untreated atria was reduced. As the severity of the reserpinization became less, so the supersensitivity declined and the separation of rate and tension curves became more apparent and comparable with the untreated situation. To avoid

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.

This work was supported jointly by a CAPS grant from SRC and Allen & Hanburys Ltd.

References

BRITTAIN, R.T., JACK, D. & RITCHIE, A.C. (1970). Recent β-adrenoceptor stimulants. *Adv. in Drug Res.*, 4, 197-253.

CROUT, J.R., MUSKUS, A.J. & TRENDELENBURG, U. (1962). Effect of tyramine on isolated guinea-pig atria in relation to their noradrenaline stores. *Br. J. Pharmac.*, 18, 600-611.

McNEILL, J.H. & SCHULZE, S. (1972). Reserpine-induced supersensitivity to histamine activated cardiac phosphorylase and cardiac contractility. *Res. Comm. Chem. Pathol. Pharmac.*, 3, 339-346.

TAYLOR, D.A., WESTFALL, D.P. & FLEMING, W.W. (1974). The effect of reserpine treatment on the chronotropic and inotropic sensitivities of the perfused guinea-pig heart to norepinephrine and calcium. *Eur. J. Pharmac.*, 29, 102-108.

TRENDELENBURG, U. (1963). Supersensitivity and subsensitivity to sympathomimetic amines. *Pharmac. Rev.*, 15, 225-276.

WESTFALL, D.P. & FLEMING, W.W. (1968). The sensitivity of the guinea-pig pacemaker to norepinephrine and calcium after pretreatment with reserpine. *J. Pharmac. exp. Ther.*, 164, 259-269.

Is ATP an inhibitory neurotransmitter in the rat stomach?

M.A. HEAZELL[1]
(introduced by A.K. BANERJEE)

Department of Physiology, Royal Veterinary College, London

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.

[1] Present address: Research Institute, May & Baker Ltd., Dagenham, Essex, RM10 7XS