This activation also explains why noradrenaline is more pressor than adrenaline in the cat—their α- and β_1-actions are similar but usually (see later) only adrenaline has an appreciable depressor (β_2-) influence. Corroborative signs of substantial β_2-adrenoceptor stimulation are the depressor effects of low doses of adrenaline and secondary hypotensive phases following the initial pressor responses to higher doses. With noradrenaline, the above signs only occurred, and even then infrequently, in three cats and one rabbit (see later). In these animals alone noradrenaline reversal sometimes happened (Karim, 1964).

In the rabbit, adrenaline reversal is uncommon (Harvey & Nickerson, 1953) yet β_2-effects (diastolic BP falls) undoubtedly occur with isoprenaline. In 5 out of 8 New Zealand White rabbits (i.p. urethane, 2 g/kg), the β_2-activation produced by adrenaline was negligible and adrenaline and noradrenaline were equipressor. But, in the other 3 rabbits, adrenaline had a stronger β_2-action so that low doses were depressor and pressor effects less than those of noradrenaline: these rabbits were the only ones to show adrenaline reversal.

Therefore, in both cats and rabbits, 'adrenaline reversal' is invariably linked with the extent of β_2-adrenoceptor stimulation, and is explicable solely as a phenomenon of α-adrenoceptor blockade unveiling a β_2-action which intrinsically exceeds the corresponding β_1-effect.

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45-Calcium uptake in rat peritoneal mast cells

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When sensitized rat peritoneal mast cells are challenged with antigen, the resulting secretion of histamine is dependent upon calcium in the external medium (Foreman & Mongar, 1972). Calcium entry into the cell appears to provide the trigger for histamine release (Foreman, Mongar & Gomperts, 1973). Indirect evidence suggests that calcium entry as well as histamine release is blocked by dibutyryl cyclic AMP (Foreman, Mongar, Gomperts & Garland, 1975).

Changes in the amount of calcium associated with the cell have been measured in a purified suspension of rat peritoneal mast cells from Lister Hooded rats, sensitized with egg albumin and *Bordetella pertussis* adjuvant 2-3 weeks previously. The cells were purified by centrifugation through a human serum albumin gradient (20% and 26% albumin). The pellet contained 70-90% mast cells. After washing, the cells were incubated for 5 min in 100 μl Tyrode solution, containing 45-calcium chloride, above 100 μl silicon oil in a micro-centrifuge tube. The tubes were spun for 30 s at 15,000 g to separate the cells from the radioactive medium. The pellet, after removal by freezing and cutting off the bottom of the micro-centrifuge tube, was dissolved in Triton-X—100 and the radio-activity measured by liquid scintillation counting.

On average antigen caused 94 nmol histamine release and 0.3 nmol calcium uptake per million cells. With unstimulated cells the corresponding values were 28 nmol histamine release and 0.55 nmol calcium uptake. When pre-incubated with metabolic inhibitors, antimycin A and cyanide, histamine release was abolished but calcium uptake was only slightly reduced (Figure 1). In the absence of inhibitors part of the calcium uptake is possibly due to the increase in surface area of the cells that accompanies histamine release. When this is inhibited a small inhibition of calcium uptake may occur. With dibutyryl cyclic AMP both histamine release and 45-calcium uptake were inhibited.

These results suggest that the increase in 45-calcium associated with cells after antigen challenge is due to an increase in membrane permeability to calcium. Opening of the calcium

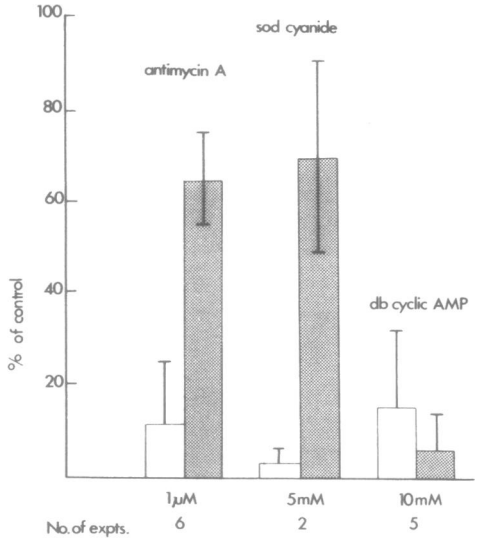

Figure 1 The effect of metabolic inhibitors and dibutyryl cyclic AMP on 45-calcium uptake (hatched columns) and histamine release (open columns). Vertical bars show standard error of mean.

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.

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

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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