Comparison of the relaxant effects of isoprenaline and tolbutamide on uterine and tracheal muscle

The stimulatory effects of both isoprenaline and hypoglycaemic sulphonylureas on insulin secretion are inhibited by β-adrenoceptor blocking agents such as propranolol (Porte, 1967; Sirek, Vigas & others, 1969; Majid, Saxton & others, 1970; Massara, Strumin & others, 1971). It has therefore been suggested that the release of insulin by sulphonylureas depends on their ability to stimulate β-adrenoceptors (Sirek & others, 1969). Using the dual β-receptor classification (Lands, Arnold & others, 1967; Lands, Luduena & Buzzo, 1967), Loubatières, Mariani & others (1971) have suggested that the pancreatic receptors are of the β_2-type. It therefore seemed of interest to find out whether hypoglycaemic sulphonylureas could stimulate β_2-adrenoceptors in other tissues.

The kitten isolated uterus and the guinea-pig tracheal chain were the test preparations. Kittens, 500–700 g, were anaesthetized with ether. The uteri were removed and placed in McEwen (1956) solution and stored at 4° for 24 h before use in order to reduce spontaneous activity in the preparations. The uteri were then suspended under a tension of 500 mg in oxygenated McEwen solution maintained at 31°. Guinea-pig tracheal chain preparations were set up as described by Chahl & O'Donnell (1967). Both test preparations developed tone and when this became constant drug-induced relaxations were assessed using isometric strain gauges coupled to an ink writing pen recorder. In uterine preparations the effects of single doses of drugs were examined whereas in tracheal preparations drug activity was assessed using cumulative concentration-effect curves.

In six preliminary experiments in the uterine preparations it was found that molar potency ratios calculated from concentrations producing 50% of the maximal relaxation (50% E_{max}) were (±)-isoprenaline 4337 ± 1029; salbutamol 1743 ± 630: (−)-adrenaline 1341 ± 272: (−)-noradrenaline 1. After β-adrenoceptor blockade with propranolol (10^{-6}M), doses of the agonists which had previously produced maximal relaxation of the uterus failed to contract the preparation suggesting that they did not cause significant α-adrenoceptor stimulation. Foster (1966) has shown that the molar potency ratio of the β-agonists (−)-isoprenaline, (−)-adrenaline and (−)-noradrenaline in guinea-pig tracheal preparations is 174:10·2:1 respectively and that there are few excitatory α-adrenoceptors in this tissue. The high potency of isoprenaline and the very low potency of noradrenaline relative to the other adrenoceptor agonists in both of these preparations are in accordance with the β_2-type classification of Lands & others (1967a, b).

The sodium salt of tolbutamide was found to relax the uterus at concentrations greater than 10^{-3}M, and the tracheal chain at concentrations greater than $0{\cdot}25 \times 10^{-3}$M. The relaxations produced by tolbutamide were somewhat slower than those produced by isoprenaline, however similar maximal relaxant effects were obtained. The tolbutamide induced effects were reversible on washing the preparations. It was found that in each of 4 uterine preparations and in 3 out of 4 tracheal preparations the two drugs produced parallel log concentration-effect curves (analysis by method of Moore & Edwards, 1965). Tolbutamide was 3×10^6 and 5×10^5 times less active than isoprenaline in the uterine and tracheal preparations respectively. When the tissues were exposed to propranolol 1×10^{-6}M for 30 min and the effects of the two drugs were re-examined in the presence of the β-adrenoceptor blocking agent, responses to isoprenaline were inhibited whereas those to tolbutamide were enhanced. At 50% E_{max}, dose ratios for isoprenaline were $1{\cdot}24 \pm 0{\cdot}52 \times 10^3$ and $4{\cdot}24 \pm 0{\cdot}35 \times 10^3$ in uterus and trachea respectively while those for tolbutamide were 0·77 ± 0·06

and $0{\cdot}48 \pm 0{\cdot}15$. Thus tolbutamide does not appear to produce relaxation of uterine or tracheal muscle through stimulation of β_2-adrenoceptors.

In contrast, the sodium salt of glibenclamide, which is some 500 times more potent than tolbutamide as a hypoglycaemic sulphonylurea, did not produce any significant effects on the uterus in doses up to $0{\cdot}25 \times 10^{-4}$M while doses of $0{\cdot}25 \times 10^{-8}$ to $0{\cdot}25 \times 10^{-4}$M only produced extremely slow and irreversible decreases in the tone of the tracheal chain. Limitations of solubility precluded the testing of higher concentrations.

The conclusion of Loubatières & others (1971) that the pancreatic adrenoceptors involved in insulin secretion were of the β_2-type was based on experiments with β-adrenoceptor agonists and antagonists which have been widely used to differentiate β_1- and β_2-adrenoceptors. The pancreatic β_2-adrenoceptor might therefore be expected to respond similarly to β_2-adrenoceptors in other tissues. The inactivity of glibenclamide on the uterus and trachea and the failure of tolbutamide to stimulate β_2-adrenoceptors in these tissues therefore indicate that hypoglycaemic sulphonylureas are unlikely to cause insulin release due to stimulation of β_2-adrenoceptors in the pancreas. If this is the case, the inhibitory effect of β-adrenoceptor blocking agents on insulin secretion provoked by sulphonylureas is probably also independent of adrenergic mechanisms. Bressler, Vargas-Cordon & Brendel (1969), for example, have suggested that since β-adrenoceptor blocking agents possess local anaesthetic activity they may inhibit the influx of calcium into islet cells which is coupled with insulin secretion.

The similarity in the response of uterine and tracheal muscle to β_2-agonists and tolbutamide may be due to the fact that they can both raise intracellular levels of cyclic AMP (Robison, Butcher & Sutherland, 1967; Lasseter, Levey & others, 1972).

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