Inhibition of propranolol-induced bronchospasm by sodium cromoglycate

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We have previously reported to the Society that the bronchospasm induced by β-adrenoceptor blocking drugs in guinea-pigs and rats is unrelated to the blockade of β-adrenoceptors in the airway smooth muscle (Maclagan & Ney, 1977). In the present experiments the effects of several pharmacological antagonists on the bronchospasm induced by (±)- and (+)-propranolol were studied.

Guinea-pigs and rats were anaesthetised with urethane (1.25 g/kg^{-1}) and allowed to breathe spontaneously. Airway resistance (R_{aw}) and dynamic lung compliance ($C_{d,n}$) were measured using the subtractor method described by Green & Widdicombe (1966). Intravenous injections of mepyramine (2 mg/kg), cimetidine (2 mg/kg), methysergide (1 mg/kg), phenoxybenzamine (2 mg/kg) and atropine (1 mg/kg) did not affect the increase in airway resistance produced by propranolol or its isomer (+)-propranolol.

In contrast, intravenous injection of sodium cromoglycate (100 μg kg to 2 mg/kg) 15–20 min before (±)- or (+)-propranolol (6×10^{-7} mol/kg to 10^{-6} mol/kg) resulted in an approximately 50% reduction in the propranolol-induced bronchoconstriction.

Jackson & Richards (1977) have shown that sodium cromoglycate can cause a reduction in the reflex response to irritant receptor stimulation mediated via the parasympathetic nervous system. However, such a modification of the reflex control of airway smooth muscle is unlikely to explain the present results because pretreatment with atropine (1 mg/kg) did not alter the inhibitory effect of sodium cromoglycate on propranolol-induced bronchospasm in guinea-pigs and rats.

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Does the hypoglycaemic effect of 5-hydroxytryptophan involve insulin?

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5-Hydroxytryptophan (5HTP) but not 5-hydroxytryptamine (5HT) produces hypoglycaemia in mice pretreated with monoamine oxidase inhibitors (MAOI). (Lundquist, Ekholm & Ericson, 1971; Furman, 1974). In large doses 5-HTP can also produce hypoglycaemia in *normal* mice, the effect being augmented by pretreatment with MAOI or by the concurrent administration of drugs known to inhibit the neuronal uptake of 5HT (Furman & Wilson, 1978). Some evidence has been presented suggesting that the hypoglycaemic effect of 5-HTP is mediated at least in part through some central nervous system effect of 5-HT (Darwish & Furman, 1974). Although insulin does not appear to mediate the hypoglycaemic effect of 5-HTP administered in small doses to MAOI pretreated mice, its role in 5-HTP induced hypoglycaemia in *normal* mice has not been reported and this is the subject of the present communication.

All experiments were made using white, male CFLP mice (20–25 g) fasted for 18 hours. Plasma glucose (Beckman Glucose Analyzer) and plasma immunoreactive insulin (IRI) (Hales & Randle, 1963) were determined in blood samples obtained from the femoral vein after anaesthetizing the mice lightly with ether at the desired time after drug injection.

5-HTP (100–400 mg/kg i.v. 30′ or 60′ before blood sampling) produced a dose dependent decrease in the plasma glucose concentration of normal fasted mice. This hypoglycaemia was accompanied by marked increases in the plasma IRI concentration detectable at 5′ after drug injection (e.g. control 6 ± 1 μU/ml; 5-HTP 200 mg/kg 55 ± 9 μU/ml $P < 0.001$). In *niala-mide pretreated* mice 5-HTP produced hypoglycaemia in doses as low as 2–5 mg/kg i.v. but no change in the plasma IRI concentration was detectable at any time. Induction of diabetes using alloxan (80 mg/kg i.v. 2 days beforehand) prevented or markedly reduced the hypoglycaemic effect of 5-HTP (400

mg/kg) in *normal* mice although such treatment is known to have no effect on the hypoglycaemic effect of lower doses of 5-HTP in MAOI pretreated mice (Lundquist, *et al.*, 1971, Furman, 1974).

In *normal* mice the combination of a threshold hypoglycaemic dose of 5-HTP (100 mg/kg) with drugs known to inhibit the neuronal uptake of 5-HT (ORG6582 25 mg/kg; fenfluramine 20 mg/kg, fluoxetine 20 mg/kg, clomipramine 25 mg/kg, or mazindol 25 mg/kg) produced marked hypoglycaemic responses although these drugs were themselves without effect on plasma glucose in normal mice. These responses were accompanied by increases in the plasma IRI concentration but these increases were no greater than those produced by 5-HTP alone.

The results suggest that 5-HTP has a dual action on plasma glucose. One effect appears to be mediated by a stimulation of insulin secretion and is seen when large doses of 5-HTP are given to normal mice. The second does not involve stimulation of insulin secretion and is evident when lower doses of 5-HTP are administered to MAOI pretreated mice or to normal mice in combination with drugs known to inhibit the neuronal uptake of 5-HT.

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Pharmacological control of corticosterone secretion in the intact rat

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Corticotropin releasing factor (CRF) in the rat has been shown *in vitro* to be under cholinergic and serotoninergic facilitatory and noradrenergic inhibitory control (Buckingham & Hodges, 1977; Jones, Hillhouse & Burden, 1976). In intact male Sprague-Dawley rats weighing 150–210 g, plasma corticosterone (CS) levels have been assayed to give a measure of CRF and adrenocorticotrophic hormone activity. In most experiments, drugs were administered intraperitoneally and blood was always collected by decapitation and collection of trunk blood into heparinised tubes.

The muscarinic agonist oxotremorine (Oxo-T) produced a dose related rise in plasma CS 15 min after injection in the dosage range 0.01–0.05 mg/kg. This dose response curve was shifted significantly to the right by pretreatment with atropine (1 mg/kg s.c.i.) one hour before Oxo-T treatment.

5-Hydroxy-L-tryptophan (5-HTP, 1–20 mg/kg) also produced a rise in plasma CS levels 30 min after injection. Both Oxo-T and 5-HTP begin to raise the plasma CS level at dosages below those needed to induce peripheral or behavioural effects. A number of putative serotonin antagonists have been studied for their effect on the 5-HTP induced plasma CS rise. Of these, methergoline (5 mg/kg) and methysergide (10 mg/kg) produced no change. Cyproheptadine (10 mg/kg), (−)-propranolol (20 mg/kg) and cinanserin (10 mg/kg) produced a slight depression of the plasma CS response to 5-HTP. Only mianserin (10 mg/kg) given one hour before 5-HTP produced a statistically significant suppression of the CS response. Pretreatment with atropine (2 mg/kg s.c.i.) did not inhibit the CS response to 5-HTP. Mianserin did not decrease significantly the CS response to Oxo-T.

Rats given α-methyl-para-tyrosine methyl ester (αMpT, 400 mg/kg) decreased their hypothalamic noradrenaline levels by 50% after 14–16 hours. At the same time, such rats exhibited a rise in plasma CS levels. This rise was suppressed one hour after injection of clonidine (0.01–0.05 mg/kg). This suppression could be decreased by piperoxane (5 mg/kg) given 15 min prior to blood collection. Clonidine at this dosage has no effect on basal plasma CS levels in rats not pretreated with αMpT. Apomorphine (5 mg/kg) produced no change in plasma CS levels in rats treated with αMpT.