histamine-induced bronchoconstriction was also reduced by isoprenaline sulphate (1 μg/kg, i.v.).

Intravenous injection of β-adrenoceptor blocking drugs produced a rapid increase in inspiratory resistance accompanied by a fall in compliance. The maximum response occurred 2 min after the injection and the effect lasted 15 to 30 minutes. A reduction in heart rate, which followed a similar time course to the bronchoconstriction, was also recorded.

In eight experiments using (±)-propranolol, a dose of 100 μg/kg produced a mean increase in TLR of 32.7 ± 8.5%. With 1 mg/kg the increase was 46.0 ± 17.6%. Practolol had a similar effect. The bronchoconstriction was not affected by atropine sulphate nor was it influenced by the choice of general anaesthetic.

The β-adrenoceptor blocking drugs also caused potentiation of the histamine-induced bronchoconstriction. The potentiation lasted for several hours.

Injection of (+)-propranolol, which has only weak β-adrenoceptor blocking activity, produced an increase in airways resistance indistinguishable from the effect of the racemate. After injection of (+)-propranolol (100 μg/kg) which caused a 47.7% increase in TLR, isoprenaline was still effective in reducing histamine-induced bronchoconstriction, indicating minimal β-adrenoceptor blockade in the airway smooth muscle under these conditions.

In rats which have no sympathetic innervation to the bronchial smooth muscle (Fillenz & Woods, 1970) β-adrenoceptor blocking drugs produced the same effects on airways resistance and potentiated 5-HT-induced bronchoconstriction. These effects were also obtained in rats with de-medullated adrenal glands.

These results suggest that in guinea-pigs and rats, the bronchoconstriction induced by β-adrenoceptor blocking drugs may be unrelated to blockade of β-adrenoceptors and due to some other mechanism. The fact that atropine does not alter the bronchospasm produced by these drugs suggests that stimulation of parasympathetic constrictor nerves either by an action on irritant receptors or an action on the central nervous system is unlikely to be involved.

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The inhibition of human heart monoamine oxidase

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Largely from the use of a range of different substrates and selective irreversible inhibitors such as clorgyline, it appears that the monoamine oxidase (MAO) activity of many animal tissues exists in more than one form. The form of the enzyme that is very sensitive to inhibition by clorgyline has been designated MAO-A, and that which is less sensitive as MAO-B (Johnston, 1968; Hall, Logan & Parsons, 1969). In addition an amine oxidizing activity that is resistant to inhibition by clorgyline has also been reported in rat and chick hearts (Lyles & Callingham, 1975; Fowler & Callingham, 1977). Here an attempt has been made to identify the components responsible for the activity of human heart MAO.

Tissues from the left ventricles of human hearts were obtained within 48 h of sudden death, and homogenized mechanically either in ice-cold 1 mM potassium phosphate buffer, pH 7.8, or in 0.25 M sucrose/10 mM potassium phosphate buffer. After low-speed centrifugation to remove cell débris and nuclei, crude homogenates in buffer were used for assay, while washed mitochondrial fractions were made from the homogenates in sucrose. MAO activity was assayed radiochemically with [^{3}H]-tyramine, [^{3}H]-5-HT, [^{3}H]-benzylamine and [^{14}C]-β-phenylethylamine as substrates.

The effects of clorgyline, (+)-amphetamine, desipramine and debrisoquine were measured *in vitro* by addition to aliquots of the tissue homogenates, 20 min before the addition of substrate. All incubations were carried out in an atmosphere of oxygen at 37°C, with material from 6 subjects.

When clorgyline was used in a range of concentrations from 5×10^{-11} M to 5×10^{-2} M, the MAO activity towards 5-HT was inhibited by very low concentrations. A single sigmoid log concentration-

inhibition curve was produced that gave an IC_{50} of 6×10^{-9} M. With benzylamine and β-phenylethylamine as substrates, the inhibition curves were still sigmoid in shape, but the concetrations of clorgyline needed to inhibit the activity were much greater, with IC_{50} values of about 10^{-5} M. With tyramine a double sigmoid inhibition curve was produced, with a central plateau region separating the two sigmoidal components, which would indicate that this substrate is metabolized by both MAO-A and -B in the human left ventricle. No evidence could be found, with any of the substrates used, for the presence of a clorgyline-resistant amine oxidase.

Both (+)-amphetamine and desipramine were found to be competitive inhibitors of the MAO activity in washed mitochondrial fractions when 5-HT was used as substrate. The K_i values were 3.4×10^{-6} M and 1.0×10^{-4} × for (+)-amphetamine and desipramine respectively. Debrisoquine with 5-HT was a reversible non-competitive inhibitor with a K_i of 2.0×10^{-6} M. With benzylamine and β-phenylethylamine as substrates all three inhibitors were much less potent. This suggests that, in the human heart, these inhibitors are selective for the MAO-A type of activity as they appear to be in other animal tissues.

These results indicate that the MAO activity in the left ventricle of the human heart can be resolved into two components that appear to be MAO-A and -B as defined by Johnston (1968), but the clorgyline-resistant component has not been found.

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The effect of some dopamine agonists and antagonists on the rat anococcygeus muscle *in vitro*

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It is now widely accepted that dopamine (DA) is a neurotransmitter in the CNS. Recently, however, it has been postulated that DA may also function as an important neurotransmitter in the peripheral nervous system, affecting both gastrointestinal and cardiovascular activity (Thorner, 1975; Greenacre, Teychenne, Petrie, Calne, Leigh & Reid, 1976). Such hypotheses rely heavily on the degree of selectivity of the various DA agonists and antagonists employed. It was of interest therefore to observe the effects of some of these drugs on the rat anococcygeus muscle, a recently described smooth muscle preparation, closely associated with the colon, and possessing a dense noradrenergic innervation (Gillespie, 1972).

Pairs of anococcygeus muscles were dissected and set up in organ baths as described previously (Gillespie, 1972). Antagonists were left in contact with the muscle for 30 min, prior to measurement of agonist sensitivity.

The muscle responded to DA with a contraction, the characteristics of which were similar to those produced by noradrenaline (NA). Indeed, the muscle was only slightly less sensitive to DA than to NA. However, cocaine (100 ng/ml) produced a much greater leftward shift of the dose response curve to NA (50-fold) than that to DA (5-fold). The responses to both NA and DA were reduced by haloperidol (1 μg/ml), and by a similar degree.

The DA agonist apomorphine also contracted the muscle. However, a dose-response curve could not be obtained, since apomorphine produced an 'all-or-none' type of contraction, with a threshold of around 1 μg/ml. Unlike NA or DA, apomorphine often resulted in large oscillations in tone which persisted even after washout of the agonist. These appeared to be myogenic since they were not abolished by tetrodotoxin (5 μg/ml).

Bromocriptine, also believed to be a DA agonist,