Differential effects of prazosin on the pre- and postsynaptic α-adrenoceptors in the rat and dog

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The heart rate decreases and blood pressure increases seen with i.v. clonidine administration to pithed rats, in which their basal heart rates have been elevated by continuous selective electrical stimulation of the thoracic spinal cord, are attributed to a respective activation of pre- and postsynaptic α-adrenoceptors (Drew, 1976). We have performed a biokinetic analysis for both responses and found that the rates of onset and dissipation of the clonidine induced hypertension were much quicker than those for the heart rate reductions.

The effects of phentolamine (1.0 mg/kg, i.v.) and prazosin (1.0, 5.0 mg/kg, i.v.) on the pre- and postsynaptic actions of clonidine were compared. Phentolamine effectively antagonized both the hypertensive and heart rate lowering responses of clonidine. However, prazosin selectively blocked the clonidine induced pressor responses without affecting the heart rate.

Using pentobarbital anaesthetized dogs untreated or treated with desipramine, Lokhandwala & Buckley (1976) reported that phentolamine (2.0 mg/kg) potentiated the chronotropic responses to cardioaccelerator nerve stimulation by inhibiting presynaptic α-adrenoceptors at the level of the cardiac pacemaker.

We have observed that in spinal dogs desipramine (1.0 mg/kg, i.v.) effectively inhibited the tachycardia to tyramine (50 μg/kg, i.v.) and increased the positive chronotropic effects to both i.v. noradrenaline (0.2 μg/kg) and stimulation of the cardioaccelerator nerve (supramaximal voltage for 15 s at frequencies 0.25–2.0 Hz and pulse duration of 0.5 msec). After phentolamine (0.3, 1.0 mg/kg, i.v.) the tachycardias seen with cardioaccelerator stimulation were further increased whereas pressor effects of i.v. noradrenaline were reduced. However, contrary to the finding of Lokhandwala & Buckley (1976), we could not show a potentiation of the tachycardias to stimulation of the cardioaccelerator with phentolamine in the absence of desipramine. Both desipramine and phentolamine caused increases in the basal heart rate levels.

In the spinal dog prazosin (0.3, 1.0 mg/kg, i.v.) increased, as did phentolamine the basal heart rate and potentiated the positive chronotropic responses to cardioaccelerator stimulation only when given after desipramine. At the same time it antagonized the pressor responses to i.v. noradrenaline.

In conclusion, phentolamine inhibited both pre- and postsynaptic α-adrenoceptors in the rat and dog. Prazosin showed a definite selective antagonism for postsynaptic α-adrenoceptors only in the rat. These results suggest that there may be a species difference for the cardiac presynaptic α-adrenoceptors.

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Investigation of the bronchoconstriction induced by β-adrenoceptor blocking drugs in guinea-pigs and rats

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β-Adrenoceptor blocking drugs are known to cause bronchospasm in man, especially in asthmatic subjects but this effect has rarely been reported in animals.

In the present experiments, the effects on airways resistance of β-adrenoceptor blocking drugs have been investigated in guinea-pigs and rats using the sensitive method of Green & Widdicombe (1966). Animals were anaesthetized with urethane (1.25 g/kg, i.p.) or pentobarbitone sodium (40 mg/kg, i.p.) and total lung resistance (TLR) and dynamic lung compliance (C_{dyn}) were measured for each inspiration during spontaneous breathing. The resting values in rats and guinea-pigs ranged from 10.5 to 72.5 cm H_2O l^{-1} s^{-1} for TLR and from 0.22 to 1.68 ml/cm H_2O for C_{dyn}.

In guinea-pigs histamine acid phosphate (0.5 to 5 μg/kg, i.v.) produced a short-lasting increase in inspiratory resistance and a corresponding decrease in compliance. This effect was greatly reduced by pretreatment with atropine sulphate (1 mg/kg, i.v.) indicating that the response was reflexly mediated. The

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-