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Comparative β-adrenoceptive stimulant properties of salbutamol (AH 3365), orciprenaline and soterenol (MJ 1992)

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The activities of the β-adrenoceptive receptor stimulants salbutamol, soterenol and orciprenaline have been examined on *in vitro* and *in vivo* preparations of the guinea-pig for potency, duration and selectivity of action. Salbutamol and orciprenaline have been the subject of previous reports (Brittain, Farmer, Jack, Martin & Simpson, 1968; Engelhardt, Hoefke & Wick, 1961).

Salbutamol (0.02–0.5 μg/ml.), soterenol (0.02–0.5 μg/ml), and orciprenaline, (0.25–10 μg/ml.) inhibited responses of the isolated guinea-pig trachea to transmural electrical stimulation. Increases in the force of contraction of guinea-pig left atria which were isolated and electrically driven were obtained with salbutamol, (1–50 μg/ml.), soterenol (5–100 μg/ml.) and orciprenaline (0.25–10 μg/ml.). The cumulative dose-response curves for salbutamol and soterenol on isolated trachea and isolated atria were less steep and had lower maxima than those obtained with isoprenaline. The dose-response curves for orciprenaline were similar in shape and height to those for isoprenaline on both these tissues.

In anaesthetized guinea-pigs intravenous doses producing a 60% inhibition of the bronchoconstrictor response to acetylcholine were: salbutamol, 18 μg/kg, soterenol, 32 μg/kg and orciprenaline, 447 μg/kg. At equipotent doses all three drugs were longer-acting than isoprenaline.

In conscious guinea-pigs both salbutamol and soterenol (5 mg/kg orally) prolonged by a factor of 4 the time taken to onset of dyspnoea caused by an acetylcholine aerosol. The effect lasted more than 6 hr with salbutamol and 2–4 hr with soterenol. At the same dose level soterenol caused a greater increase in heart rate than salbutamol. Orciprenaline at 20, 50 and 100 mg/kg gave inconsistent results but in no instance was there a pronounced increase in the time to dyspnoea. When given by aerosol (0.1 mg/ml. for 1 min) both salbutamol and soterenol caused a 4-fold increase in the time to onset of dyspnoea. The effects of both drugs lasted for about 1 hr. Orciprenaline, in aerosol form, was less potent; 1 mg/ml. solution sprayed for 1 min caused a 2-fold increase in the time to onset of dyspnoea and this effect lasted 7 min. At 10 mg/ml. there was a 3–4-fold increase which lasted for 30 min. In aerosol form all compounds were without effect on heart rate at the concentration used.

The *in vitro* results show that both salbutamol and soterenol possess a selectivity for β-receptors in bronchial smooth muscle relative to those in cardiac muscle. This

selectivity was not observed with orciprenaline. *In vivo* salbutamol and soterenol were many times more active than orciprenaline as bronchodilator agents when given intravenously, orally, or by aerosol. At effective bronchodilator doses salbutamol had less activity on the heart than soterenol. The selectivity shown by salbutamol and soterenol further substantiates the hypothesis of Lands & Brown (1964), who suggested that β-receptors can be divided into two distinct groups, β_1 and β_2.

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Structure-activity studies on the *Helix* dopamine receptor

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Walker, Woodruff, Glaizner, Sedden & Kerkut (1968) studied the effects of α- and β-receptor blocking agents on the inhibition produced by dopamine in neurones of the *Helix* brain and concluded that the dopamine receptor in this preparation resembles the α-receptor for adrenaline.

The problem remains as to whether dopamine acts on the classical α-receptor or whether there are, in the *Helix* brain, specific dopamine receptors. The present investigation is concerned with a study of structure-activity requirements for dopamine-like activity in specific neurones of *Helix aspersa*.

The electrical activity was recorded from identifiable cells in the right parietal ganglion of the isolated snail brain, using methods similar to those previously described (Walker *et al.*, 1968). All the cells used in this study were hyperpolarized and inhibited by dopamine, applied by addition to the bath (0.005 to 0.025 μ-mole) or by iontophoretic injection (100 to 200 nA).

Five of the compounds tested showed dopamine-like activity and caused inhibition of cell firing rate. The potency of these compounds was expressed as the ratio of the molar doses of the compound and of dopamine required to produce the same period of inhibition. The most suitable dose of dopamine was usually 0.005 μ-moles. N-methyldopamine was equipotent with dopamine with a range of 0.5 to 2.2. 5-methoxydopamine and (−)-noradrenaline had mean equipotent molar ratios of 16.5 (range 8.5 to 34.0) and 17.3 (range 0.6 to 57.5) respectively. (+)-α-methyldopamine had a mean equipotent molar ratio of 30.7 (range 0.9 to 183.5) while (−)-adrenaline had a mean equipotent molar ratio of 91.8 (range 22.8 to 113.9). The number of observations ranged from seven to twelve for each compound.

The other compounds tested included isoprenaline, isoetharine, orciprenaline, (±)-octopamine, tyramine, (−)-metaraminol, (±)-oxedrine, hydroxyamphetamine, 3-methoxydopamine, *p*-methoxyphenylethylamine, apomorphine, 3,4-dimethoxyphenylethylamine and methoxamine. None of these compounds had any dopamine-like activity in doses of up to 1,000 times the effective dose of dopamine.