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Differentiation of β-adrenoreceptors by the use of blocking agents

There is evidence that the β-adrenoreceptor population is comprised of at least two types designated as β-1 and β-2 (Lands, Arnold & others, 1967; Lands, Luduena & Buzzo, 1967). This sub-division was proposed to account for the differing structural requirements of catecholethanolamines for initiating β-sympathomimetic actions in different organs. The sub-division so proposed has been further supported by the recent discovery of β-agonists, such as salbutamol, with selective β-2 actions (Cullum, Farmer & others, 1969).

If β-adrenoreceptors differ significantly in their structural requirements for agonists then it is reasonable to suppose that such receptors could have different structural requirements for antagonists. Thus experiments have been made to measure quantitatively the β-adrenoreceptor blocking action (by use of pA_2 measurements) of two compounds, propranolol and ICI 50 172 (against isoprenaline) at typical β-1 and β-2 type receptors. Previous workers have shown that tissues with similar receptors can be expected to give the same pA_2 with a given antagonist (Arunlakshana & Schild, 1959). ICI 50 172 was chosen in addition to propranolol because some selectivity of blocking action for this compound has been described (Dunlop & Shanks, 1968).

Table 1. pA_2 *values for propranolol and ICI* 50 172 *on isolated tissues of the guinea-pig, rabbit and rat. Isoprenaline was used as an agonist*

Species	Preparation	Receptor type	Propranolol	ICI 50 172
Guinea-pig	Atria-force rate	β-1	8·8	7·3
Rabbit	Ileum	β-1	8·6	7·3
Guinea-pig	Trachea	β-2	8·7	5·4
"	Vas deferens	β-2	8·9*	6·8*
Rat	Uterus	β-2	8·5	5·0

* pA_2 value determined in the presence of 2 μg/ml cocaine.

Table 1 gives pA_2 values for propranolol and ICI 50 172 on isolated tissues of the guinea-pig, rabbit and rat. The pA_2 measurements were made by the method of Arunlakshana & Schild (1959) and each value was the mean of three determinations. The β-adrenoreceptor of the guinea-pig vas deferens although not previously classified, is, on the basis of work done in this laboratory, a β-2 type. Propranolol gave similar pA_2 values at both β-1 and β-2 type receptors and thus showed no selectivity in its blocking action. However, ICI 50 172 had a selective blocking action but did not always differentiate between β-1 and β-2 types since the compound showed highest activity on heart (β-1) and vas deferens (β-2) and much lower activity on ileum (β-1) and trachea (β-2).

These results agree with the concept of Lands and others that there are different β-receptor mechanisms in different tissues but are difficult to reconcile with their simple two receptor hypothesis.

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Antagonistic effects of dopa and propranolol on brain glycogen

We have reported previously that propranolol raises the glycogen content of the brain (Estler & Ammon, 1966, 1967), but we could not decide whether this effect was attributable to the anti-adrenergic effect of propranolol, which, by lowering the cyclic 3′,5′-AMP content of the brain, should inhibit glycogen breakdown and favour glycogen synthesis, or to the central depressant properties of propranolol, described by Leszkovsky & Tardos (1965), Murmann, Almirante & Saccani-Guelfi (1966) and Estler & Ammon (1969), that could likewise depress glycogenolysis. A decision seemed to be possible, however, on the assumption that the blockade of the adrenergic receptors is competitive (Wang, 1967) and should be overcome by large amounts of catecholamines. Experiments were therefore made on mice treated simultaneously with propranolol, and dopa which was chosen since unlike catecholamines, it crosses the blood brain barrier and penetrates into the brain where it is converted to dopamine and noradrenaline (Hornykiewicz, 1966; Marley, 1966). Dopa should thus antagonize the anti-adrenergic effects of propranolol if given in sufficient amounts.

Female NMRI-mice, kept at 25°, were treated with (±)-propranolol (5 μg/g, i.p.) or with (±)-dopa (300 μg/g, i.v.) or with both. 30 or 60 min later they were killed by immersion in liquid air. The brains were removed while still frozen and glycogen was measured (Kemp & Kits van Heijningen, 1954). Motility was measured in circular activity cages (Estler & Ammon, 1969).

As in our previous experiments (Estler & Ammon, 1966, 1967), propranolol did not significantly affect the spontaneous motor activity of single mice, but the glycogen content of the brain was increased (Table 1). The behavioural effect of dopa may range from central stimulation to central depression, depending on the species, dose and experimental condition (Boissier & Simon, 1966; Hornykiewicz, 1966). In our experiments 300 μg/g of dopa much reduced the motor activity of mice and temporarily lowered the glycogen content of the brain, a decrease probably attributable to the glycogenolytic action of catecholamines derived from dopa. After 1 h, brain glycogen concentrations returned to normal. In this way the effects of dopa are in contrast to those of other central depressants, which raise the glycogen content of the brain (Ammon, Estler & Heim, 1965), but resemble those of ethanol