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Relative blocking effectiveness of propranolol and of practalol [4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide] on isoprenaline in β-1 receptor mediated calorigenesis*

Barrett, Crowther & others (1968) have shown practalol [ICI 50172; 4-(2-hydroxy-3-isopropylaminopropoxy) acetanilide] to be about one third as effective as propranolol in blocking isoprenaline in previously defined (Arnold, McAuliff & others, 1966; Lands, Arnold & others, 1967) β-1 receptor mediated lipolytic or cardiac effects. However, practalol was only about 1/100 as effective as propranolol in antagonizing reference catecholamines in previously defined (Arnold & others, 1966; Lands & others, 1967) β-2 receptor mediated bronchodilatation or vasodepression. Since we have shown (Arnold & McAuliff, 1968) that calorigenesis (non-shivering thermogenesis) in the rat, based on oxygen uptake, is β-1 receptor mediated, we were prompted to compare the blocking effectiveness of propranolol and of practalol on isoprenaline under these *in vivo* conditions.

The method we used was modified slightly from that of MacLagan & Sheahan (1950) for mice. Briefly, groups of three, 60 to 90 g, *ad libitum* fed, conscious rats were placed in a small but adequate sized wire basket which was placed, in turn, in a 10-inch dessicator at 28°. The dessicator previously had been flushed with oxygen for a few minutes. The oxygen uptake of the rats was monitored by an appropriately inter-connected Med Science Electronics (St. Louis) Model 160 Spirometer. The comparisons are based on the oxygen taken up over the 10- to 25-min period after administering a test compound, a 10 min equilibration having been judged to be adequate.

Table 1. *Comparison of blockade of (—)-isoprenaline in calorigenesis in the rat by propranolol or by practalol. Three rats per trial*

Isoprenaline* (μg/kg)	Blocking agent† (mg/kg)	No. of trials	O_2 Uptake Mean ± s.e. (cc/100 g/min)	O_2 Uptake % Control
None	None	6	3·57 ± 0·13	
Isoprenaline, 4	None	5	4·45 ± 0·25	125
Isoprenaline, 12	None	6	6·21 ± 0·53	170
None	None	4	3·19 ± 0·12	
Isoprenaline, 12	Propranolol, 3·16	4	4·39 ± 0·53	140
Isoprenaline, 12	Propranolol, 10·0	4	3·46 ± 0·17	110
None	None	8	2·91 ● 0·18	
Isoprenaline, 12	Practalol, 31·6	4	4·20 ± 0·12	140
Isoprenaline, 12	Practalol, 100	3	3·19 ± 0·10	110

* Test agents as base. Compounds used as the hydrochlorides. Test agents given s.c.
† Blocking agent given ½ h before isoprenaline.

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The blocking agents were given subcutaneously in the back of the neck a half hour before administration of isoprenaline by the same route.

Isoprenaline, 12 μg/kg, increased oxygen uptake well above 50% of the control intake (Table 1). At 4 μg/kg there was a 25% increase in oxygen uptake over the control value. Propranolol at 10·0 mg/kg or practalol at 100 mg/kg antagonized the effect of isoprenaline, 12 μg/kg, almost completely. Lesser amounts, propranolol 3·16 mg/kg, or practalol 31·6 mg/kg, had an intermediate antagonizing effect. Neither propranolol nor practalol alone manifested any effect on the oxygen uptake of the rats. On the basis of this comparison, we conclude practalol to be about 1/10 as effective as propranolol in antagonizing the effect of a modestly calorigenic dose of isoprenaline (12 μg/kg).

Barrett & others (1968) indicated that practalol was less effective in blocking isoprenaline-effected tachycardia in conscious dogs than in anaesthetized animals. The use of conscious rats in the present comparisons, accordingly, may explain the practalol/propranolol ratio, on a weight basis, of about 1/10 noted here compared with the ratio of about 1/3 indicated by Barrett & others (1968) on the basis of lipolytic and cardiac effect comparisons. Burns, Salvador & Lemberger (1967) noted that butoxamine {α-[1-(t-butylamino)ethyl]-2,5-dimethoxybenzaldehyde alcohol} antagonized the effect of isoprenaline on heart rate in conscious dogs but not in anaesthetized animals.

By way of contrast with the relatively similar effectiveness of propranolol and of practalol in antagonizing catecholamines in β-1 receptor mediated effects (lipolysis, heart rate and force, calorigenesis) compared with their significantly unequal effect in blocking catecholamines in β-2 receptor mediated effects (bronchodilatation, vasodepression), may be mentioned the converse findings of Moran (1966). He noted that DCI, dichloroisoprenaline [3,4-dichloro-α-(isopropylaminomethyl) benzyl alcohol] and α-methylDCI were essentially equally effective in antagonizing the vasodilator effect of isoprenaline in the dog. However, α-methylDCI was only about 1/15 as effective as DCI in blocking the effect of isoprenaline on heart rate.

Thus, evidence is at hand to support the view previously proposed (Arnold & others, 1966; Lands & others, 1967) that adrenergic receptor mediated-effects are readily explainable by a three receptor concept. This view is based both on studies with agonists (Arnold & others, 1966; Lands & others, 1967) as well as with antagonists (Barrett & others, 1968; Moran, 1966) along with the above antagonist comparison.

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