Anti-arrhythmic and local anaesthetic activity of some β-receptor blocking compounds

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The ability of propranolol, 1-(isopropylamino)-3-(*o*-phenoxyphenoxy)-2-propanol, HCl (Ph QA 33) (Hermansen, 1968), and 2-isopropylamino-1-(*p*-nitrophenyl) ethanol HCl (INPEA) to abolish ouabain-induced ventricular fibrillations in guinea-pigs was compared with their local anaesthetic and β-receptor-blocking potency.

INPEA has previously been reported to be devoid both of local anaesthetic activity and of an effect against ouabain-induced ventricular tachycardia (Somani & Lum, 1965). With a different technique we found that INPEA has a significant reversing action on ouabain-induced fibrillations and also some local anaesthetic effect. The following values were obtained with the three compounds: antiarrhythmic effect (ED50 I.V.): propranolol 0.3 mg/kg, Ph QA 33 0.5 mg/kg, INPEA 1–3 mg/kg; local anaesthetic effect (ED50): propranolol 1.2 mg/ml., Ph QA 33 3.5 mg/ml., INPEA 18 mg/ml.; beta-receptor blocking effect (ED50 I.V.): propranolol 8.0 μg/kg, Ph QA 33, 7.5 μg/kg, INPEA 1–3 mg/kg. The order of potency demonstrates the close relationship between local anaesthetic activity and effect against non-catecholamine-induced arrhythmia. Furthermore, the results confirm the lack of correlation between anti-arrhythmic and β-receptor blocking effect as also shown with some other β-receptor antagonists.

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On the mechanism of the pressor response due to propranolol

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Occasional rises of systemic blood pressure with small doses of propranolol, and rise of perfusion pressure in the hind limb of the dog have been observed by various workers (Kayaalp & Kiran, 1966; Kayaalp & Turker, 1967). We have observed a consistent and moderate rise of blood pressure following propranolol (1–20 μg) in the rat (380 to 430 g) anaesthetized with urethane. The pressure was recorded from the common carotid artery with a Condon manometer; all injections were made into the cannulated femoral vein in volumes of 0.1 ml., followed by 0.2 ml. of normal saline.

The response on the blood pressure was immediate—the peak rise varied from 15 mm to 30 mm Hg. With propranolol (1–2 μg) the duration of the pressor response was 5 to 15 min; with 20 μg, the response was persistent and rarely returned to the pre-injection level, even after an hour or more. Development of tachyphylaxis occurred with repeated doses, the greater the dose, the earlier being the loss of response.

There was also a slight increase in the heart rate lasting for about 10–15 min (with 3 μg, 336–348/min). A positive inotropic and a slight chronotropic effect was also obtained with propranolol (0.4 μg) on Langendorff's preparation of the rabbit's heart. Thus the pressor response may be partly due to a direct or indirect effect on the heart.

The pressor response with propranolol was not prevented when the rats were treated with hexamethonium bromide (15 mg/kg I.V.). The response was also consistently obtained when the α-receptors for adrenaline had been blocked with phenoxybenzamine

hydrochloride (15 mg/kg I.V.). The pressor responses to propranolol and tyramine hydrochloride (100 μg) were not seen when the animals had been pretreated with reserpine, 10 mg/kg I.P., 48 hr and 24 hr before the experiment. A slow intravenous infusion of noradrenaline (10–15 μg in 20–30 min) in the presence of bretylium tosylate (1 mg/kg I.V.) as suggested by Clark & Leach (1968), restored the response to tyramine but not to propranolol. The response due to propranolol was also lost by pithing the rat by the method of Shipley & Tilden (1947).

It may therefore be concluded that the pressor response due to small doses of propranolol is mediated partly through a peripheral β-receptor stimulating action on the heart but also via a central mechanism, since pithing or reserpinization prevents the response. The failure of α-receptor blockade to prevent the pressor response to propranolol may reflect the ability of this drug to restore the response to noradrenaline after α-receptor blockade. The persistence of the pressor response despite ganglion blockade by hexamethonium is rather difficult to explain.

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Adrenergic mechanisms in hypertension

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The effectiveness of anti-adrenergic drugs in hypertensive animals and man has focused a great deal of attention on the role of adrenergic mechanisms such as increased activity of vasoconstrictor neurones, supersensitivity of vascular smooth muscle (Doyle & Frazer, 1961), increased cardiovascular reactivity (McCubbin & Page, 1963), decreased uptake or increased elimination rate of noradrenaline (Champlain, Krakoff & Axelrod, 1966), at reduced tissue noradrenaline content (Gitlow, Wilk, Wolf & Nafthi, 1964).

We have studied some aspects of the role of adrenergic mechanisms in experimental hypertension. In conscious dogs with nephrogenic or neurogenic hypertension, the pressor responses to tyramine and angiotensin are significantly greater than in normal dogs. Angiotensin appears not to release catecholamines from the adrenal to any great extent under these conditions because the dimethylphenylpiperazinium (DMPP) and noradrenaline pressor responses remain unchanged. The enhancement of tyramine and angiotensin but not of noradrenaline shows that supersensitivity of vascular smooth muscle to noradrenaline is not the cause of the tyramine and angiotensin potentiation.

The supersensitivity may be due to changes in vessel wall characteristics. In rats with nephrogenic hypertension the non-inulin space, Na^+, K^+ and water content of the hypertensive vessel is increased. Furthermore the membrane potential of the vascular smooth muscle cell is raised. This suggests a shift of Na^+, K^+ and water to the paracellular ground substance and not to the smooth muscle cell. There would then be an increased wall volume, decreased elasticity and reduced vessel diameter as suggested by Jones,