The anticonvulsant action of the (−)- and (+)-enantiomers of propranolol

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The threshold for electrically—or chemically—induced seizures in rodents can be raised by β-adrenoceptor antagonists, such as propranolol (Murmann et al 1966; Yeoh & Wolf 1968).

An exacerbation of chemically-induced seizures by (±)-propranolol has also been reported (Kilian & Frey 1973; Madan & Barar 1974). A convulsant action of β-adrenoceptor antagonists is consistent with the evidence for β-adrenoceptors in the cerebellum, cerebal cortex and hypothalamus (Conway et al 1978) at which noradrenaline has an inhibitory action (Bevan et al 1977). However, propranolol and some other β-adrenoceptor antagonists are also potent 5-HT antagonists as judged by both behavioural tests (Green & Grahame-Smith 1976; Weinstock et al 1977) and in vitro membrane studies (Middlemiss et al 1977). Drugs acting on 5-hydroxytryptaminergic mechanisms can readily modify seizure thresholds (Meldrum 1978).

Propranolol also possesses membrane stabilizing properties as indicated by a local anaesthetic or quinidine-like action on nerve and heart cell membrane, decreasing excitability and prolonging refractoriness (Basset & Hoffman 1971; Hellenbrecht et al 1973).

This stabilizing effect is probably related to inhibition of calcium binding at a plasma membrane site (Feldman & Weinhold 1977). Some central effects of β-blockers (or their dextroenantiomers) can be attributed to a membrane stabilizing effect on brain-stem neurons (Bousquet et al 1978). Whereas the effects on β-adrenoceptors and 5-hydroxytryptaminergic receptors show a high degree of stereospecificity, the (−)-enantiomer being 10–100 times as potent as the (+)-enantiomer (Green & Grahame-Smith 1976; Weinstock et al 1977; Conway et al 1978), the membrane stabilizing effect by the two enantiomers is shown to be approximately equal (Bassett & Hoffman 1971; Bousquet et al 1978).

To clarify the role of the different actions of (±)-propranolol on seizure threshold we have studied the effect of (+)- and (−)-propranolol on seizure responses induced in DBA/2 mice by loud auditory stimulation.

Groups of 9–13 DBA/2 mice (bred in the laboratory from supplier's stock) were used at 19–26 days old (weight range 7–13 g).

The enantiomers of propranolol were dissolved in 0·9% NaCl solution to give a maximum volume equivalent to 1% of the body weight of a mouse, and were injected intraperitoneally, 45 min before testing.

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Mice were exposed to auditory stimulation as previously described (Anlezark et al 1976) for 60 s or until tonic extension occurred and the incidence of seizure phases (wild running, clonus, tonus and respiratory arrest) noted. Statistical comparisons were made using Fisher's exact probability test.

Significant protection against the tonic phase of the seizure response was seen following (−)-propranolol, 16 mg kg^{-1}. No protection was seen after this dose of (+)-propranolol, but the tonic and respiratory arrest phases of the audiogenic seizure were absent after (+)-propranolol, 32 mg kg^{-1} (Table 1). Apparent increases in seizure response occurred following (−)-propranolol, 4 and 8 mg kg^{-1}, and (+)-propranolol 8 and 16 mg kg^{-1}, but these did not reach significance (Table 1). (In a further experiment using 35-day old mice, (−)-propranolol, 6 mg kg^{-1}, and (+)-propranolol, 6 or 12 mg kg^{-1}, produced a similar increase in seizure responsiveness).

No toxic behavioural changes were seen after any dose of either enantiomer, although the highest dose of (−)-propranolol induced slight piloerection.

The anticonvulsant effect we observed after (−)-propranolol, 16–32 mg kg^{-1}, is comparable to the protection previously reported against seizures induced by hyperbaric oxygen in mice ((−)-propranolol, 8–16 mg kg^{-1} i.v., Levy et al 1976), or against maximal electroconvulsive shock ((±)-propranolol 22 mg kg^{-1}, (+)-propranolol 25 mg kg^{-1}, orally, Greenwood 1977, personal communication), or leptazol ((±)-propranolol 19 mg kg^{-1}, Murmann et al 1966). The greater apparent potency of the (−)-propranolol agrees with the report of Ngai et al (1976). However, it is possible that the entry of (+)-propranolol into the brain is slower

Table 1. The effects of (+) and (−)-propranolol on audiogenic seizures in 19–26 day old DBA/2 mice. Mice were injected i.p. with (−)- or (+)-propranolol at the stated doses and exposed to auditory stimulation 45 min later. Statistical differences in seizure response from concurrent saline-injected controls are expressed as follows: $*P < 0.05$; $**P < 0.01$; n = number of mice in each group.

Drug and dose (mg kg^{-1})		% Response				
		Running	Clonus	Tonus	Resp. arrest	n
Saline		87	80	73	64	45
(−)-Propranolol	2	85	69	62	39	13
	4	92	92	92	46	13
	8	100	92	92	77	13
	16	100	67	42*	25**	12
	32	77	31**	0**	0**	13
(+)-Propranolol	2	83	50	42	33	12
	4	92	67	67	50	12
	8	92	58	58	42	12
	16	100	92	92	75	12
	32	85	85	0**	0**	13

than that of (−)-propranolol (Levy et al 1976). With such a selective rate of entry our results are compatible with the two enantiomers having the same potency in the brain.

These results are inconsistent with the anticonvulsant effect being attributable to an action on either β-adrenergic or 5-hydroxytryptaminergic receptors. The membrane stabilizing effect probably accounts for the protective effects of (±)-propranolol.

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Haemodynamic effects of systemic administration of clonidine in the anaesthetized spontaneously hypertensive rat

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The intravenous administration of clonidine produces an initial pressor response followed by a sustained decrease in arterial blood pressure and heart rate in both man and laboratory animals (Kobinger & Walland 1967; Onesti et al 1969). The accompanying changes in regional blood flow have been described for the conscious normotensive monkey by Bolme et al (1975) who reported that blood flow was maintained or increased in the hepatic and renal arteries despite the fall in cardiac output at the expense of the skin, skeletal muscle and brain. Similar observations were made in the same preparation after the administration of α-methyldopa (Forsyth et al 1978) which has been postulated to have a similar action to clonidine on central adrenergic pathways (Fuxe et al 1975). However, in renal hypertensive dogs clonidine produces decreases in blood flow through the splanchnic and femoral arteries as well as to the heart, brain and kidneys (Laubie & Schmitt 1969). Unfortunately, no comparison of the actions of clonidine in normotensive and hypertensive animals has been made in the same species so it is not possible to determine whether the differences in the actions of clonidine are due to species or hypertension. Since Hiley & Yates (1978) have observed different resting patterns of cardiac output distribution in anaesthetized spontaneously hypertensive rats (SHR) relative to normotensive Wistar controls (NR), it is important to establish whether the actions of clonidine on regional blood flow are different in hypertension. Accordingly we have compared the haemodynamic effects of intravenous clonidine in these two strains of rat.

Groups of age-matched male normotensive rats from our own colony and Okamoto strain spontaneously hypertensive rats (OLAC 1976, Ltd, Bicester, Oxfordshire) were anaesthetized with ketamine (120 mg kg^{-1} i.p.).

The right carotid artery was cannulated and, with the aid of pressure monitoring, the tip of the cannula was manipulated into the left ventricle. 60 000–80 000 carbonized plastic microspheres (15 ± 5 μm) labelled with ^{141}Ce (3M Co., St Paul, Minnesota, U.S.A.) and suspended by ultrasonication in 0·6 ml 0·9% NaCl containing 0·02% Tween 80 were injected through the left ventricular cannula over 20 s. Simultaneously, and for 70 s after injection, blood was withdrawn from a femoral artery with a syringe withdrawal pump (Perfusor IV, Braun, Melsungen, Germany). Arterial blood pressure was recorded from the other femoral artery by means of a pressure transducer (Bell and Howell type 4–422–0001) and a pen recorder (Grass Model 79 polygraph). A fourth cannula was placed in the right femoral vein. The injection of microspheres was made 15–20 min after intravenous administration over 30 s of either clonidine (20 μg kg^{-1}) or 0·3 ml

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