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Role of β-adrenoceptors in the anticonvulsant effect of propranolol on leptazol-induced convulsions in rats

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High levels of cyclic (c)AMP are observed in brain after the production of seizures by drugs or electroshock in animals (Sattin 1971; Ferrendelli & Kinscherf 1977; Clarenbach et al 1978) or in the cerebrospinal fluid of epileptic patients following a fit (Myllyla et al 1975). The catecholamines, noradrenaline (NA) and isoprenaline (ISO) are capable of producing seizures (Walker et al 1974) and increased brain cAMP levels, an effect antagonized by the β-adrenoceptor antagonist propranolol (Tsang & Lal 1978).

Propranolol has significant anticonvulsant properties in animals (Leszkovszky & Tardos 1965; Murmann et al 1966; Yeoh & Wolf 1968; Madan & Barar 1974; Anlezark et al 1979) and also prevents leptazol (pentetrazol)-induced elevation of cAMP (Gross & Ferrendelli 1979) but the exact mechanism of action is not well understood. However, the reported relationship between seizures and high cAMP levels suggests that it may act by antagonizing stimulation of brain adenylate cyclase. We report that the anticonvulsant effect of propranolol may in part be due to an antagonist action at central β-adrenoceptors.

Experimental convulsions were produced in fed Sprague-Dawley rats (male or female, 150–200 g) by injection of leptazol (50 mg kg^{-1} i.p.). Propranolol was administered either in repeated doses or acutely by gavage. In the first study (±)-propanolol (20 mg kg^{-1}) was given twice daily for 4 days and once on the fifth day at least 1 h before leptazol challenge. In the acute studies the same dose of (±)-propranolol was given either 30, 40, or 60 min before leptazol whereas (+)- and (−)-isomers of propranolol (0·05–1·0 mg kg^{-1}) were administered 40 min before leptazol. The doses of propranolol used were chosen to give plasma concentrations which would produce effective β-adrenoceptor blockade (Gugler et al 1979). In addition, propranolol is concentrated some 10 times in brain relative to blood (Schneck et al 1977).

The following parameters were noted; time of onset of myoclonic jerk and generalized seizure; duration of seizure and subsequent period of unconsciousness, characteristics of the seizure (tonic/clonic) and the recovery time for each rat. All time measurements were made with a stopwatch. Subsequently rats were decapitated and plasma and brain samples frozen at −20 °C for propranolol assay by a modification of the method of Ambler et al (1974). Results are expressed as mean ± standard error of the mean (s.e.m.). Significance of differences between means are assessed by Student's *t*-test. Correlation between brain propranolol levels and anticonvulsant effect was examined using a Spearman-Rank test.

Repeated administration of propranolol significantly decreased the duration of seizures and unconsciousness in rats. In 9 of 23 rats seizures were abolished (Table 1). The onset of seizures was not altered by propranolol in those animals that convulsed with leptazol, but the characteristics of the seizure were altered. The tonic component of the seizure, present in all control rats, was present in only two treated rats. Propranolol concentrations were measured in brain and plasma of all rats at the conclusion of the experiment. In the animals which did not convulse following leptazol the brain and plasma concentrations were 8·5 ± 1·7 μg g^{-1} and 0·45 ± 0·08 μg ml^{-1} (n = 9) whereas in the animals that did convulse the values were respectively 5·8 ± 0·7 μg g^{-1} and 0·26 ± 0·04 μg ml^{-1} (n = 14). In the group of animals which did have seizures there was a significant correlation between brain propranolol

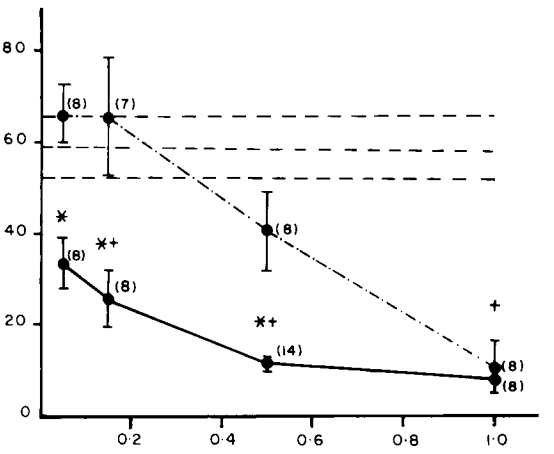

FIG. 1. Effect of (+)-propranolol (– · – ·) and (−)-propranolol (——) on leptazol-induced seizures in rats. The broken lines (– –) indicate the duration of seizures in the control (0·9% NaCl-pretreated) animals ± s.e.m. (n = 25). Asterisks (*) refer to significant differences in duration of seizures between the two isomers and crosses (+) between pretreated animals and control (in all cases $P < 0.001$). Numbers of animals used are given in parentheses. Ordinate: duration of seizure (s). Abscissa: dose (mg kg^{-1}).

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Table 1. The effect of repeated administration of (±)-propranolol (20 mg kg^{-1} orally twice daily) on leptazol-induced seizures in rats. The duration of the seizure and duration of unconsciousness are expressed as a mean value in seconds ±s.e.m. The asterisk (*) indicates a significant difference between saline treated controls and propranolol-pretreated rats ($P < 0.001$).

	Control (n = 25)	Treated (n = 23)
Mean duration of seizure (s)	43·1±4·4	6·2*±1·8
Mean duration of unconsciousness (s)	12·2±1·6	0·8*±0·4
Numbers of animals that underwent seizures	25	14
Animals with tonic seizures	25	2

concentrations and anticonvulsant effect (r = 0·85, $P < 0.05$).

In acute experiments propranolol (20 mg kg^{-1}) was given at various times before leptazol challenge. Administration 40 min before leptazol gave the highest brain and plasma propranolol concentrations (0·82 ± 0·2 μg g^{-1} and 0·06 ± 0·02 μg ml^{-1} respectively, n = 11), the lowest duration of seizure and unconsciousness and was adopted for subsequent experiments. The protective effect of propranolol was apparent with both isomers but at low doses the effect was stereoselective. The anticonvulsant effect of (−)-propranolol was observed at dose levels between 0·05–1 mg kg^{-1} whereas with the (+)-isomer it was apparent only at dose levels greater than 0·5 mg kg^{-1} (Fig. 1). Comparison of the dose levels of the (−)- and (+)-isomers which produced a 50% reduction in duration of seizures shows that the (−)-isomer is 7 times more potent than the (+)-isomer of propranolol. This relatively low degree of stereoselectively (cf. 20–100 in other tissues) probably reflects the anticonvulsant effect of (+)-propranolol produced by membrane stabilization. Although this may play a part in the anticonvulsant effect of (−)-propranolol at high dose levels it cannot explain its effectiveness at low doses (0·05–0·5 mg kg^{-1}). The tonic phase of the seizure was abolished at all dose levels of (−)-propranolol but only by doses of (+)-propranolol greater than 0·5 mg kg^{-1}. Neither brain nor plasma concentrations of the (+)- and (−)-isomers of propranolol at all 4 dose levels were significantly different, indicating that the difference in anticonvulsant potency was not due to differences in absorption and distribution.

This study indicates that propranolol has anticonvulsant activity against leptazol-induced seizures and that at least two mechanisms, membrane stabilization and β-adrenoceptor blockade are involved. Membrane stabilization is probably the principal mechanism involved in previous studies utilizing dose levels of (±)-, (+)- or (−)-propranolol greater than 1 mg kg^{-1} (Levy et al 1976; Anlezark et al 1979; Jaeger et al 1979). In the present study it was possible to separate membrane stabilization from β-adrenoceptor blockade. At low dose levels, only (−)-propranolol was effective. It is unlikely that the observed effects are due to metabolites of propranolol since the appearance and decline of metabolites in brain does not correlate with anticonvulsant activity after acute propranolol (Saelens et al 1977).

In conclusion, propranolol has significant anticonvulsant activity against leptazol-induced convulsions. At low dose levels the effect is stereoselective indicating that it is due to β-adrenoceptor blockade. At high dose levels (+)-propranolol has anticonvulsant activity probably related to membrane stabilization.

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