CENTRAL NERVOUS SYSTEM PHARMACOLOGY OF PROPRANOLOL

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Summary: In rats, propranolol potentiated alcohol and pentobarbitone hypnosis, but not barbital sleeping time, indicating enzyme inhibition as a possible mechanism of potentiation. Propranolol showed anticonvulsant effect on normal and reserpine treated rats by MES test, but showed dose related lowering of MET. Probable mechanisms are discussed.

Key words: propranolol anticonvulsants barbiturates alcohol narcosis reserpine

INTRODUCTION

Besides its beta-adrenergic blocking activity, propranolol produces several other actions which are not yet classified. For example, it remains to be pin-pointed whether the cardiac anti-arrhythmic action is a manifestation of beta-block, local anaesthetic activity or a non specific effect. Various central actions of propranolol have been reported; including potentiation of barbiturate sleeping time and anticonvulsant action(13,3). However, a large gap remains in our knowledge of the C.N.S. actions of propranolol. Hence this study was undertaken to clarify certain functions of propranolol on C.N.S.

MATERIALS AND METHODS

Potentiation of barbiturate and alcohol sleeping time: The effect of propranolol on sleeping time induced by barbitone and pentobarbitone was studied in male rats. The effect of propranolol on the sleeping time by ethyl alcohol was measured in male rats.

The effect of single dose of 10 *mg/kg* of propranolol administered 48 hr prior, on the pentobaritone and alcohol sleeping time was also studied.

Propranolol was administered at a dose of 10 *mg/kg*, twice daily for 3 days. 24 hr after the last dose, the duration of sleep produced by pentobarbitone and alcohol was studied.

Anticonvulsant action:

Minimum electroshock seizure threshold (MET): The effect of propranolol on MET in rats was studied by the method of Bapat *et al* (2).

Maximum electroshock seizure (MES): Shocks were delivered by a Techno model convulsiometer (150 mA, 0.2 sec, ear clip electrodes) and the anticonvulsant ED50 of pro-

pranolol was determined. The anticonvulsant action was defined as the abolition of hind limb extension component of the convulsions.

Audiogenic convulsions: Ability of propranolol to protect susceptible animals from audiogenic convulsions was tested as per the method previously described (6) and ED50 determined.

Reserpine antagonism: A slight modification of the method of Koslow and Roth (11) was used. Using a lower current strength (84 mA, 0.2 sec) large number of flexors were obtained and these flexors could be converted into extensors by administration of reserpine 0.5 *mg/kg* i.p. 5 hr prior. The ED50 of propranolol to convert the drug induced extensors, back into flexors was found out. ED50 of propranolol to antagonise the convulsions in reserpine treated animals receiving the usual current strength (150 mA, 0.2 sec) also was determined. Reserpine 0.5 *mg/kg* and 5 *mg/kg* were used, with the higher current strength.

Brain 5-HT determinations: One hr after administration of a single dose of 30 *mg/kg* of propranolol in rats, the animals were killed, the brain was removed, 5 HT extracted by the method of West (7) and estimated on rat fundus strip by Vane's technique (24).

Phenoxybenzamine pre-treatment: The percentage of rats protected by a standard dose of proparanolol (8 *mg/kg*) was compared with another set which had received a dose of phenoxybenzamine (15 *mg/kg*) also, 1 hr prior to propranolol. Phenoxybenzamine 1 *mg/kg* was investigated for any anticonvulsant activity.

RESULTS

Propranolol potentiated the sleeping time of alcohol and pentobarbitone, but not of barbitone. 1 *mg/kg* propranolol did not affect alcohol sleeping time (Table I). Administration of a

TABLE I: Effects of propranolol on narcosis induced by various hypnotics as measured by sleeping time (mts).

Pretreatment	*Barbital* 250 *mg/kg i.p.*	*Pentobarbitone* 25 *mg/kg i.p.*	*Alcohol* 14.5 *ml/kg i.p. as* 50% *solution*
Control	(30) 247 ± 8	89 ± 4.5	20.5 ± 2.2
Propranolol 10 *mg/kg* i.p. 30 mts prior to	(30) 264 ± 5	122 ± 6.2*	88 ± 3.8*
Propranolol 10 *mg/kg* i.p. 48 hrs prior to	(30) 258 ± 9	87.2 ± 4.7	18 ± 2.5
Propranolol 1 *mg/kg* i.p. 30 mts prior to	(10) ..	..	19.0 ± 1
Propranolol 25 *mg/kg* i.p. 30 mts prior to	(20) 254 ± 8	146 ± 4.8*	100 ± 6.3*

*Significant at $P < 0.01$
Figures in parenthesis indicate number of animals.

single dose of propranolol 48 hr prior does not change alcohol and pentobarbitone sleeping times (Table II). Administration of propranolol for 3 days had no effect on pentobarbitone and alcohol narcosis studied 24 hr after the last dose.

MET was significantly reduced by propranolol in a dose related manner (Table II). Anticonvulsant ED50 is given in Table III.

TABLE II: Effect of propranolol, administered i.p. 1 hr prior to shock, on the minimum electroshock seizure threshold.

	MET mA means ±SE	*Significance*
Control	18.8 ± 0.4	—
Propranolol 1 *mg/kg*	17.8 ± 0.35	N.S.P > 0.3
,, 2 *mg/kg*	14.5 ± 0.36	P < 0.01
,, 8 *mg/kg*	12.6 ± 0.4	P < 0.001
,, 10 *mg/kg*	9.6 ± 0.45	P < 0.001

TABLE III: The ED50 of propranolol against various types of convulsions in rats.

MES	5.0 ± 0.42
Audiogenic convulsions	9.3 ± 0.80
After reserpine 0.5 *mg/kg*	10.0 ± 0.4
After reserpine 5.0 *mg/kg*	9.33 ± 0.28
Conversion of drug induced extensions back into flexors	10.0 ± 0.8

Propranolol was administered i.p. one hr prior to and reserpine 5 hr prior to test.

Phenoxybenzamine antagonised the anticonvulsant effect of propranolol. 8 *mg/kg* propranolol protected 70% rats but prior treatment with phenoxybenzamine reduced the rate of protection to 23% ($P < .01$). Phenoxybenzamine had no anticonvulsant effect. Proparnolol did not alter brain 5HT.

DISCUSSION

Propranolol potentiated the sleeping time induced by pentobarbitone and alcohol but not by barbitone. Barbitone is not metabolised in the body and has been suggested as the ideal drug to study the influence of other drugs on barbiturate sleeping time (21). Since barbtione is not potentiated, propranolol possibly mediates its effect by inhibition of hepatic enzymes. Reports on the influence of beta blockers on pentobarbitone hypnosis are available and inhibition of hepatic microsomal enzymes has been suggested as a possible mechanism (17), the beta blocking properties being entirely unrelated to this function (3). This view gets support

from the present study. The antagonism of alcohol narcosis by low doses of propranolol reported in mice (22) could not be confirmed in rats.

The beta blockers produce several actions on CNS like sedation, potentiation of barbiturate anaesthesia, reduction in spontaneous motor activity (3,13,17). Phenoglycodol, chlorpromazine, glutethimide etc which possess these properties antagonise pentobarbitone hyponsis (9) and alcohol narcosis (14) when administered in a single dose, 48 hr prior to the test. Induction of enzyme has been suggested as the possible mechanism. Drugs which produce a preliminary inhibition of enzymes act as enzyme-inducers 12 hr after administration and this induction is more marked after repeated administration (18). Propranolol, however, did not antagonise pentobarbitone hypnosis or alcohol narcosis and hence is not an enzyme inducing agent.

Propranolol shows anticonvulsant activity as determined by the MES test. This is not unusual since chlorpromazine lowers the MET (23) but consistently produced a dose related increase in flexion time/extension time ratio in our hands (unpublished). This increase in F/E ratio is considered as an index of anticonvulsant activity (8). Other substances such as secondary and tertiary alcohols and isatin showed anticonvulsant effect by MES test but had no effect on MET (4,10).

Increase in the brain 5-HT concentration has been correlated with the activity of anticonvulsant drugs (5). However, this correlation has been questioned (1). The absence of change due to propranolol in brain 5 HT is in concurrence with an earlier report (12).

Reserpine facilitates convulsions by inducing an extensor component in rats which show only a flexor phase by the MES test and acetazolamide has been investigated for its antagonism of this facilitation (11). Propranolol antagonised the reserpine-induced facilitation. ED50 of propranolol antagonising reserpine-facilitated convulsions is only twice its normal ED50 whereas with acetazolamide and phenytoin, the ED50 rises several fold (11,19), and hence propranolol may be more specific than the other anticonvulsants in this regard. However, involvement of biogenic amines in the facilitation of convulsions by reserpine is disputed (11,19).

Since phenoxybenzamine (PBZ) antagonises the anticonvulsant effect of phenytoin, chlordiazepoxide and acetazolamide (20), a non-specific facilitation of convulsions by PBZ or still better, a non-specific antagonism of anticonvulsants appears probable. An antagonism between alpha and beta blocking agents has been reported in other tissues (16). However, anticonvulsant action is not related to the beta blocking effect (15). This mechanism requires further elucidation.

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