Central nervous system effects of four β-adrenergic receptor blocking agents

SIR,—Propranolol has been shown to possess marked central nervous system depressant and anticonvulsant properties. Leszkovszky (1965) suggested that these effects may be due to the presence of a naphthyl group in its molecule. We now report an investigation in which the CNS effects of three β-receptors blockers having a naphthyl group are compared to those effects produced by a highly specific β-adrenergic blocking agent (Somani & Lum, 1965) with different chemical structure, the 2-isopropylamino-1-(*p*-nitrophenyl)ethanol (INPEA). With the aim of separating CNS effects eventually related to β-inhibition from those due to independent pharmacological properties, the pure optical isomers of INPEA, the absolute configuration of which we recently determined chemically (to be published), and of which only the D(–) form has β-blocking properties, were used.

Adult NMRI mice of either sex were used. Median lethal doses were estimated by the subcutaneous route. All tests were run for 15 min after s.c. administration of drug. The convulsants or hexobarbitone were injected intravenously at the rate of 0·01 ml/sec. Hexobarbitone sodium toxicity was determined in mice pretreated with 0·2 LD50 of the drug to be tested. Ataxia was evaluated by the ability of mice to remain for 3 min on a rotating rod (7 rpm). Fighting behaviour was induced in male mice by footshock at 2 mA, 100 V stimulus intensity of 1 msec duration, and 1 shock/sec. The number of attacks in a 3 min test period subsequent to treatment with 0·2 LD50 of the agent under examination was registered and expressed as a percentage of the number of attacks observed in controls. Strychnine antagonism and nicotine antagonism were determined in mice challenged with a dose of strychnine sulphate (0·76 mg/kg), or nicotine hydrogen tartrate (2·70 mg/kg), which in controls proved to be lethal to 95–97% of the mice within 10 min; survival was considered to be a sign of protection. Leptazol antagonism was determined in animals treated with a lethal dose of the convulsant (45·0 mg/kg); inhibition of the tonic extensor phase of the hind legs was considered to be protection. Maximal electroshock seizures were elicited through cornea

TABLE 1. CNS EFFECTS OF 4 DIFFERENT β-ADRENERGIC BLOCKING AGENTS

Test	Results expressed in mg/kg	Propranolol	Pronethalol	Idrobutamine (1)	D-(−)-INPEA	L-(+)-INPEA
Toxicity, s.c.	LD50*	167·5 (187·3–149·8)	424·0 (534·2–336·5)	81·0 (94·8–69·2)	400·0 (457·6–349·7)	296·0 (327·0–267·9)
Hexobarbitone toxicity 65·6 (80·4–53·6)	LD50*	30·4 (37·4–24·7)	63·0 (74·3–53·4)	101·5 (113·9–90·5)	91·9 (101·6–83·2)	124·5 (140·1–110·7)
Effects on fighting behaviour	% of controls	31·5	2·3	124·7	115·1	98·3
Ataxia	ED50*	21·9 (29·9–16·0)	26·2 (48·0–14·3)	45·3 (50·2–40·9)	92·5 (113·6–75·3)	90·0 (125·9–64·3)
Duration of ataxia at 0·2 LD50	ET50†	138·5 (154·7–124·0)	20·6 (24·5–17·3)	0	0	0
Antagonism of tonic leptazol seizures	ED50*	18·9 (21·8–16·3)	23·6 (28·9–19·3)	>40<50	0	0
Antagonism of tonic electroshock seizures	ED50*	13·9 (18·4–10·5)	19·0 (26·0–13·9)	43·8 (48·7–39·3)	0	0
Antagonism of nicotine toxicity	ED50*	1·04 (2·06–0·52)	1·90 (3·75–0·96)	3·36 (7·39–1·53)	0	0
Antagonism of strychnine toxicity	ED50*	>20<30	>100<150	>40<60	0	0

(1) (Clin. Terap., **33**, 523 (1965).
* Results calculated from experimental data by the method of Litchfield & Wilcoxon (1949).
† Results calculated from experimental data by the method of Litchfield (1949).

electrodes at 100 V, using a pulse rate of 150/sec, and a pulse width of 0·5 msec, for 0·3 sec; abolition of the tonic extensor seizures of the hind legs was used as a criterion of protection.

Table 1 shows the results and it will be seen that given in non-toxic doses, propranolol and pronethalol have CNS-depressant properties. In fact, a direct depressant action on the CNS adequately explains the reduced fighting behaviour produced by both agents as well as the increase in acute hexobarbitone toxicity caused by propranolol. INPEA or 2-s-butylamino-1-(5,6,7,8-tetrahydro-2-naphthyl)ethanol hydrochloride (idrobutamine) on the other hand, evoke some central excitant effects in these tests. Propranolol, pronethalol and idrobutamine are capable of preventing death from strychnine-, nicotine-, or leptazol-induced convulsions and in modifying the pattern of maximal (tonic-clonic) electroshock convulsions. The compounds can be ranked in the following approximate order of decreasing activity: pronethalol, propranolol, idrobutamina. Protection against leptazol toxicity is not effected by elevation of the threshold for convulsion seizures nor so much by modification of the pattern of maximal (tonic-clonic) seizures induced by the convulsant, but rather by preventing death that normally occurs after repeated tonic episodes. Protection from nicotine toxicity is produced by prevention of the terminal convulsions; the typical tremors produced by the central action of nicotine are not abolished and the antagonistic action appears to be unrelated to sedation since non-sedative doses are highly effective. The protective effects of the compounds on spinal cord (strychnine-poisoning) are compatible with those on higher centres, but lower doses are effective centrally. Just as with CNS depression, the anticonvulsant properties possessed by propranolol, pronethalol and, to a much lesser degree idrobutamine, are not shared by INPEA which, on the contrary, causes some measure of CNS stimulation in these tests.

Thus our experimental analysis of the CNS effects of this series of β-blocking agents reveals striking differences between propranolol, pronethalol, and idrobutamine on the one hand, and INPEA on the other. By a process of exclusion it can therefore be concluded that the depressant action on the CNS or the anticonvulsant properties of the former agents, or both, may well be related to their particular chemical structure, but β-receptor blockade is not involved in these actions. Similar considerations apply to the CNS effects caused by INPEA. A complete dissociation of CNS stimulation from β-adrenergic receptor blockade is emphasised by the fact that the adrenergically inactive L-(+)-isomer is about equally active in causing CNS stimulation as is the β-adrenergic receptor blocker D-(−)-INPEA. Moreover, because of the much lower doses required to produce β-receptor blockade, there is some evidence that even the central excitatory effects of D-(−)-INPEA are unrelated to β-adrenergic blockade.

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