Ind. J. Physiol. Pharmac., Volume 33, Number 3, 1989

THE EFFECT OF β-ADRENOCEPTOR ANTAGONISTS ALONE AND IN COMBINATION WITH A GABA-ELEVATING AGENT ON ISONIAZID-INDUCED CONVULSIONS IN RATS

VANAJA PAUL* AND M. S. KRISHNAMOORTHY

**Department of Pharmacology and Environmental Toxicology,
PGIBMS, University of Madras,
Taramani, Madras - 600 113*

(Received on January 5, 1989)

Abstract : A delay in the onset of isoniazid-induced convulsions was found in rats pretreated with the β_2-adrenoceptor blocker, butoxamine and the nonspecific β–blocker, propranolol. In these animals the convulsive responses were inhibited in a dose dependent manner. These compounds were found to be effective even after the induction of convulsions. The β_1–blocker, acebutolol was able to protect rats only when injected prior to the challenge. The anticonvulsant effect of acebutolol and propranolol but not that of butoxamine was found to be enhanced in animals pretreated with a γ-aminobutyric acid (GABA) elevating agent, aminooxyacetic acid (AOAA). The findings indicate that the GABA-mediated anticonvulsant action of AOAA seems to be additive with that resulting from β_1 but not β_2–blockade.

Key words : butoxamine propranolol acebutolol isoniazid-induced convulsions aminooxyacetic acid

INTRODUCTION

Propranolol has been shown to inhibit convulsions induced by electroshock (1), hyperbaric oxygen (2), loud auditory stimulation (3) and pentylenetetrazol (PTZ, 4) in rodents. An impairment and an activation of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA) in the brain have reported to be involved in induction (5) and inhibition (6) of convulsive responses, respectively. In order to investigate whether the anticonvulsant action of propranolol is additive with that of a GABA-ergic agent, a preliminary study was designed to compare its effect with that produced by it in combination with a GABA elevating agent, aminooxyacetic acid (AOAA,7,8) against convulsions induced by the GABA synthesis inhibitor, isoniazid (INH, 9). An inhibition of PTZ-induced convulsions has been shown to result mainly from the β_2-blocking action of propranolol and compounds that possess this property (4). In order to characterize whether this anticonvulsant mechanism is additive with GABA, the results obtained with propranolol was compared with those shown by the selective β_1 and β_2–antagonists, acebutolol (10) and butoxamine (11), respectivelp.

METHODS

Adult Wistar strain male albino rats weighing 150-200 g were used. Food and water were withdrawn during the experiment. Acebutolol (May & Baker), butoxamine (Burroughs Wellcome), propranolol (Cipla, India) and AOAA (Sigma, U.S.A.)

*Corresponding Author

were dissolved in distilled water and injected ip. The convulsant, INH (Laba-Chemie Indoaustrano, India) was dissolved in distilled water and administered im. All solutions were freshly prepared prior to injection (0.2 ml/100 g).

Groups of rats injected with graded doses of the test drugs were challenged 30 min later with INH (250 mg/kg). In another study, the test drugs were injected 50 min after INH (after the onset of clonic convulsions).

In order to study their combined effect, animals treated 6 h previously (see 7, 8) with the least protective dose of AOAA (2 mg/kg, see Table II) were given the minimum effective doses of the drugs and 30 min later challenged with INH.

Immediately after INH injection, the animals were caged singly. The drug-pretreated rats were observed for 2 h. The latency to the first clonic movement was recorded in each rat. The number of rats showing clonic and tonic (full extension of fore and hindlimbs) seizures and mortality during the test period were recorded. Animals that received test drugs 50 min after INH (after the onset of clonic convulsions) were observed for 1 h. The latter two parameters were recorded in these animals.

The latency data were analyzed using the t-test. X^2 test was used to analyze other data.

RESULTS

As reported previously (12), INH produced a sequence of clonic convulsions after a latent period of 40–60 min. The clonic convulsions occurred intermittently with the animals showing normal behaviour in between the episodes. A severe and persistent clonic phase proceeded to tonic seizure which invariably resulted in death of the animal.

retreatment of rats with butoxamine or propranolol resulted in a prolongation of convulsive latency (Table I A). A reduction in tonic seizures and mortality rate was found in these animals. The convulsive latency was not prolonged in acebutolol pretreated animals, but in them a does-dependent inhibition of tonic convulsions and mortality was found (Table I A) Butoxamine and propranolol were able to control the pretriggered convulsive responses too Acebutolol failed to show this effect (Table I B).

TABLE I : Effect of β-adrenoceptor antagonists on isoniazid-induced convulsions in rats.

	Dose (mg/kg)	*Latency (min) to clonic convulsion*	*Number of rats in each group (n=10) exhibiting*		
			Clonus	*Tonus*	*Mortality*
(A) Distilled water		48.8±4.8	10	10	10
Acebutolol	2.0	49.5±3.0	10	8	8
	4.0	48.5±5.3	10	6	5
	8.0	51.1±6.2	10	3+	1++
Butoxamine	0.5	59.6±6.3	10	9	9
	1.0	63.7±2.3*	10	6	6
	2.0	68.8±7.1*	9	2+	0++
Propranolol	0.5	61.0±2 2	10	8	7
	1.0	63.2±5.6*	10	4+	3+
	2 0	73.2±6.5*	7	0++	0++
(B) Distilled water				10	10
Acebutolol	4.0			10	10
	8.0			10	10
Butoxamine	0.5			10	10
	1.0			9	8
	2.5			4+	4+
Propranolol	0.5			9	9
	1.0			7	7
	2.0			4+	3+

The test drugs were injected ip 30 min before (A) or 50 min after (B) INH (250 mg/kg im); latency data are shown as $\bar{X} \pm$ SEM of the number of rats showing clonic convulsions.

*P<0.05 (t-test)

+P<0.05, ++P<0.01 (X^2 test).

A dose-dependent protection was found in AOAA pretreated rats. Acebutolol and propranolol but not butoxamine produced a greater protective effect in animals dosed previously with a least protective dose of AOAA (Table II).

TABLE II : Effect of β-adrenoceptor antagonists on isoniazid-induced convulsions in rats pretreated with AOAA.

Pretreatment	*Drug*	*Latency (min) to clonic convulsions*	*Number of rats in each group (n=10) exhibiting*		
			Clonus	*Tonus*	*Mortality*
Distilled water		50.2±4.6	10	10	10
AOAA-mg/kg					
2.0		58.2±6.8	10	9	9
4.0		52.2±4.8	10	6	6
8.0		66.4±5.2*	8	4+	3+
Distilled water	Acebutolol	49.8±8.2	10	8	8
AOAA	Acebutolol	77.2±9.4*	5	0+	0++
Distilled water	Butoxamine	52.6±6.2	10	9	8
AOAA	Butoxamine	55.8±8.2	10	9	7
Distilled water	Propranolol	56.8±7.2	10	7	7
AOAA	Propranolol	84.2±6.8*	4+	0++	0++

Rats received AOAA 6 h prior to INH (250 mg/kg im). For the combined effect, 6 h after AOAA, acebutolol (2 mg kg), butoxamine (0.5 mg/kg) or propranolol (0.5 mg/kg) was injected and 30 min later challenged with INH: latency data are shown as $\bar{X} \pm$ SEM of the number of rats showing clonic convulsions.

*$P<0.05$ compared to the respective distilled water pretreated control group (t-test).

+$P<0.05$, ++$P<0.01$ compared to the respective distilled water pretreated control group (X^2 test).

DISCUSSION

Although evidence for its entry into the brain has not been shown experimentally, the ability of butoxamine, like propranolol, to inhibit electrically-induced convulsions in rats (13) indicates its central action. The powerful anticonvulsant effect of butoxamine is evident from the data showing its ability, unlike acebutolol, to prolong the convulsive latency and to inhibit pre-induced convulsions of INH. This finding is in support of previous investigations (4) which show that β_2-selectivea ntagonists are highly protective than β_1-blockers against PTZ-induced convulsions, that the blockade of centrally located β_2-adrenoceptor is mainly involved in the anticonvulsant action of agents that possess this property. The results obtained with acebutolol, however, indicate that a weaker anticonvulsant action may result from adrenergic β_1-receptor blockade.

Since an anticonvulsant action and an increase in the synaptosomal GABA content was found to occur 6 h after AOAA administration (7, 8), a GABA-ergic action has been proposed to involve in its dose-dependent protective effect in the present study against INH-induced convulsions. The greater protection shown by acebutolol and not butoxamine in AOAA pretreated animals indicates that the anticonvulsant mechanism of AOAA and that mediated through β_1-blockade seems to be additive. In support of this suggestion propranolol which is known to block these receptors nonselectively, has, like butoxamine, showed both a prolongation of convulsive latency and an inhibition of preinduced convulsions. Also it has produced an additive action, like acebutolol, with the GABA-ergic agent AOAA.

ACKNOWLEDGEMENTS

The authors thank Mr. C. Azhaganambi for assistance.

REFERENCES

1. Leszkovszky G, Tardos L. Some effects of propranolol in the central nervous system. *J Pharm Pharmacol* 1965; 17 : 518-9.
2. Wood JD, Watson WJ, Stacey NE. A comparative study of hyperbaric O_2-induced and drug-induced convulsions with particular reference to GABA metabolism. *J Neurochem* 1966; 13 : 361-70.
3. Anlezark G, Horton R, Meldrum B. The anticonvulsant action of the (−)-and (+)-enantiomers of propranolol. *J Pharm Pharmacol* 1979; 31 : 482 3.
4. Louis WJ, Papanicoloau J, Summers RJ, Vajda FJE. Role of central β-adrenoceptors in the control of pentylenetetrazol-induced convulsions in rats. *Br J Pharmacol* 1982; 75 : 441-6.

5. MacDonal RL, Barket JL. Specific antagonism of GABA-mediated postsynaptic inhibition in cultured spinal cord neurons: a common mode of convulsant action. *Neurology* 1978; 28 : 325-30.

6. MacDonald RL, Barker JL. Enhancement of GABA-mediated postsynaptic inhibition in cultured mammalian spinal cord neurons : a common mode of anticonvulsant action. *Brain Res* 1979; 167 : 323-6.

7. Gale K, Iadarola MJ. Seizure protection and increased nerveterminal GABA : Delayed effects of GABA-transaminase inhibition. *Science* 1980; 208 : 288-91.

8. Loscher W, Frey HH. Aminooxyacetic acid : correlation between biochemical effects, anticonvulsant action and toxicity in mice. *Biochem Pharmacol* 1978; 27 : 103-8.

9. Wood JD, Peesker SJ. The role of GABA metabolism in the convulsant and anticonvulsant action of GABA. *J Neurochem* 1973; 20 : 379-83.

10. Marmo E, Spaziante G, Pentimalli D, Marfella A, Ruggiero E, DeCarla R, Ruta R, Mastero G. Specific and nonspecific action of acebutolol, atenolol, metoprolol and propranolol. Comparative experimental studies. *Int J Clin Pharmacol Res* 1982; 2 : 41-8.

11. Levy B. The adrenergic blocking activity of N-tertbutyl-methoxamine (butoxamine). *J Pharmacol Exp Ther* 1966; 151 : 413 22.

12. Czuczwar SJ, Turski L, Kleinrok Z. Diphenylhydantoin potentiates the protective effect of diazepam against pentylenetetrazol but not against bicuculine and isoniazid-induced seizures in mice. *Neuropharmacology* 1981; 20 : 675 9.

13. Iyer KS, Thampuran RVA. β-blockade and anticonvulsant activity of propranolol. *Ind J Physiol Pharmac* 1978; 22 : 293-5.