Effect of Monoamino Oxidase Inhibitors on Audiogenic Seizures

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This study attempts to demonstrate that monoamino oxidase inhibitors possess anticonvulsant activity as evaluated by their effects on audiogenic seizures in mice.

A RECENT STUDY of iproniazid and pheniprazine in rats indicated that the two agents inhibit the tonic extensor component of convulsions induced by electroshock (1). The present study is concerned with the effects of several inhibitors on audiogenic seizures in mice.

EXPERIMENTAL

Methods.—The apparatus employed in the study has been described in earlier reports by Plotnikoff (2, 3). Essentially, the apparatus consisted of a metal auditory-test chamber placed inside a sound-deadened plywood box. The sound source consisted of two common doorbells attached to the inner wall of the metal test chamber. The test procedure consisted of placing a single animal inside the metal chamber and exposing it to auditory stimulation for 1 minute. The sole criterion used to measure protection in this study was the presence or absence of tonic extension. Each drug was tested at three or more dose levels with ten mice tested per dose. The dose that reduced tonic extension responses to 50% of the control values (PD_{50}) and its standard error were estimated by the technique of Miller and Tainter (4). The drugs were administered by the intraperitoneal route. The animals used for this study were random bred male Swiss mice susceptible to audiogenic seizures.[1]

Studies on convulsions induced by electroshock were based on the maximal electroshock seizure test (M.E.S.) in mice reported by Swinyard, *et al.* (5), for maximal electroshock (50 *mA*). Normal albino Swiss mice (18–22 Gm.) nonsusceptible to audiogenic seizures were used for the M.E.S. test.

Results.—The anticonvulsant effects of several monoamino oxidase inhibitors are shown in Table I. The first agent to be reported upon is iproniazid which was shown to have an anticonvulsant effect (inhibition of both tonus and clonus) 30 minutes after administration in a dose range from 130 to 200 mg./Kg. The protective dose in 50% of the animals (PD_{50}) was found to be 163 ± 8.5 mg./Kg.

The second agent, tranylcypromine, was found to have anticonvulsant activity (inhibition of tonic extension) 1 hour after administration in a dose range from 10 to 40 mg./Kg. The protective dose in 50% of the animals was found to be 16.5 ± 2.2 mg./Kg.

The third agent, pheniprazine, was found to be active (inhibition of tonic extension) 16 hours after administration in a dose range from 5 to 20 mg./Kg. The protective dose in 50% of the animals was found to be 11.0 ± 1.6 mg./Kg.

Etryptamine was found to be the most active agent against audiogenic seizures (inhibition of tonic extension), with a PD_{50} of 4.1 ± 0.6 mg./Kg. It was tested in a range from 1.25 to 20.0 mg./Kg. 2 hours after being administered.

Phenelzine also prevented tonic extension with a PD_{50} dose of 19.0 ± 3.0 mg./Kg., and was tested in a range from 15 to 60 mg./Kg.

Nialamide exerted protection against tonic extension and was found to have a PD_{50} dose of 8.7 ± 1.1 mg./Kg. and was tested in a range from 5 to 40 mg./Kg.

Comparative anticonvulsant studies were carried out in normal mice (not susceptible to audiogenic seizures) by maximal electroshock. The results are shown in Table II. Iproniazid was evaluated over a time period of 15 minutes to 8 hours after injection and found to be ineffective in preventing tonic extension. Tranylcypromine and pheniprazine exerted partial protection against tonic extension only at high doses. Phenelzine and nialamide were also found to be ineffective in preventing tonic extension. Mortality following maximal electroshock was not significantly different from that found in controls. Etryptamine exterted significant protection against tonic extension in a dose range from 5 to 40 mg./Kg. The PD_{50} was estimated to be 13.5 ± 1.8 mg./Kg.

DISCUSSION

The present study raises several questions regarding the efficacy of comparing anticonvulsant effects of drugs on seizures induced by audiogenic stimuli and electroshock. Most of the animals susceptible to audiogenic seizures are between 21 and 25 days of age, whereas mice used for electroshock are between 25 and 30 days of age. Thus, audiogenic-seizure-susceptible mice may be more sensitive to the effects of various drugs because of their age. A similar observation with known anticonvulsants was recently

TABLE I.—EFFECT OF MONOAMINO OXIDASE INHIBITORS ON AUDIOGENIC SEIZURES IN MICE

Drug	Time Tested After Drug Administration, hr.	Protective Dose 50%, mg./Kg.
Iproniazid	1/2	163.0 ± 8.5
Tranylcypromine	1	16.5 ± 2.2
Pheniprazine	16	11.0 ± 1.6
Etryptamine	2	4.1 ± 0.6
Phenelzine	2	19.0 ± 3.0
Nialamide	2	8.7 ± 1.1

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[1] Animal suppliers: Flora O'Grady, 2336 Gunther Avenue, New York, N. Y., and Simonsen Laboratories, Day Road, Gilroy, Calif.

TABLE II.—EFFECT OF MONOAMINO OXIDASE INHIBITORS ON CONVULSIONS INDUCED BY ELECTROSHOCK IN MICE

Drug	Time Tested After Drug Administration	Dose, mg./Kg.	Number with Tonic Extension/Number Tested	Mortality
Iproniazid	Controls		10/10	3/10
	15 min.	400	10/10	4/10
	30 min.	400	10/10	2/10
	1 hr.	400	10/10	0/10
	2 hr.	400	10/10	1/10
	4 hr.	263	10/10	1/10
	6 hr.	263	10/10	3/10
	8 hr.	263	10/10	0/10
	15 hr.	240	9/10	1/10
	15 hr.	288	10/10	2/10
	15 hr.	345	9/10	0/10
	15 hr.	414	9/10	3/10
Tranylcypromine	Controls		18/19	2/19
	1 hr.	10	20/20	5/20
	1 hr.	20	16/17	6/17
	1 hr.	40	9/23	7/18
Pheniprazine	Controls		20/20	5/20
	2 hr.	40	10/10	1/10
	4 hr.	40	10/10	1/10
	6 hr.	15	9/10	2/10
	6 hr.	30	9/10	6/10
	6 hr.	60	7/10	1/10
	8 hr.	40	6/10	1/10
	10 hr.	40	6/10	2/10
Etryptamine	Controls		10/10	3/10
	2 hr.	5	9/10	5/10
	2 hr.	10	8/10	3/10
	2 hr.	20	2/10	3/10
	2 hr.	40	0/10	3/10
Phenelzine	Controls		10/10	4/10
	30 min.	20	10/10	4/10
	1 hr.	20	10/10	0/10
	2 hr.	20	10/10	4/10
	4 hr.	20	10/10	2/10
Nialamide	Controls		10/10	1/10
	2 hr.	25	8/10	2/10
	2 hr.	50	10/10	2/10
	2 hr.	100	10/10	1/10

reported by Swinyard (6). Although both stimuli (electroshock and auditory) produce the very same kind of convulsion (clonic-tonic), there may be a difference in stimulus spread in the central nervous system. Thus, the anticonvulsant effects of monoamino oxidase inhibitors in mice with audiogenic seizures and on normal animals may vary considerably. The latter were employed for evaluation of agents against convulsions induced by maximal electroshock. Nevertheless, such comparisons are useful for studying anticonvulsant drug responses. In the present study, the monoamino oxidase inhibitors did not exert significant anticonvulsant effects in mice experiencing convulsions induced by maximal electroshock. An exception was etryptamine which protected animals from tonic extension. The anticonvulsant mechanisms involved may be related to levels of central amines, although recently Lehmann (7) reported that there was not a complete parallelism between anticonvulsant effects and serotonin brain levels. Perhaps a more complete correlation can be established between other central intermediates such as norepinephrine, pyridoxal 5-phosphate, dihydroxyphenylalanine, or dopadecarboxylase.

SUMMARY

Mice susceptible to audiogenic seizures and normal mice were employed to evaluate the anticonvulsant activity of monoamino oxidase inhibitors. This study has demonstrated that tranylcypromine, pheniprazine, etryptamine, phenelzine, and nialamide inhibit the tonic extensor component of audiogenic seizures in mice. Iproniazid was found to inhibit both the tonic and clonic components of audiogenic seizures in mice. With the exception of etryptamine, all of the inhibitors were inactive in preventing convulsions induced by electroshock (M.E.S. test).

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