REPRODUCTION OF AUDIOGENIC CONVULSIONS IN ANIMALS RECEIVING PRELIMINARY INJECTIONS OF AMIDOPYRIN

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Audiogenic convulsions have many points of resemblance to convulsions in man [4], yet in experimental noninbred rats and mice they develop in only 2-3% of cases [3, 4]. The object of this investigation was to find a method of increasing the sensitivity of small laboratory animals to audiogenic stimuli, as a result of which this model of audiogenic convulsions could be used more widely for experimental purposes.

EXPERIMENTAL METHOD

To increase the sensitivity of mice and rats to audiogenic stimuli, subcutaneous injections of amidopyrin were used. In large doses this drug induces convulsions [2]. Experiments were conducted on 159 albino mice and 88 albino rats. Animals sensitive to auditory stimulation were first identified, for which purpose the rats and mice were placed in a box, measuring 100 × 40 × 30 cm, with a movable glass lid, and a loud electric bell inside the box was switched on for 30 sec. Audiogenic convulsions developed in 4 mice (of which one died) and 2 rats; in addition, in 2 mice and 1 rat motor excitation was observed (running reaction).

The animals which did not react by convulsions to the sound of the electric bell were given a subcutaneous injection of a 4% aqueous solution of amidopyrin in doses of 175, 200, 225, and 250 mg/kg, and placed in a chamber for reproduction of audiogenic convulsions. When 10-15 min had elapsed after the injection, the electric bell was switched on for 30 sec. The significance of the convulsive or anticonvulsive effect was calculated by the χ^2 method by comparison with control investigations.

EXPERIMENTAL RESULTS

Amidopyrin in doses of 175-200 mg/kg caused slight restlessness among the animals, and in doses of 225 mg/kg, and especially 250 mg/kg, isolated convulsive spasms were observed in some of the mice and rats. The frequency and severity of the audiogenic convulsions were greatly increased after the injection of amidopyrin, and depended on the dose of the drug and also, to some extent, on the species of animal (Table 1).

In mice audiogenic convulsions appeared 1, 5, and 10 sec after the beginning of the action of the electric bell, and took the form of a strong motor reaction (the running reaction), followed by transition to a phase of clonico-tonic convulsions, terminating in death of most of the animals.

In rats the reaction to auditory stimulation differed slightly from that in mice. During the action of the sound of the electric bell, after a latent period of 2, 10, and 15 sec the rats developed motor excitation: the animals ran around the box or exhibited strong spasms and jumps, alternating with clonic convulsions, and aggressiveness. Only in individual rats was the transition to the tonic phase complete, with the development of opisthotonus, after which the convulsion passed into a phase of coma. The motor excitation and state of aggressiveness which arose in response to the action of the auditory stimulation were maintained, in those rats which did not develop tonic convulsions, for 2-5 min, and sometimes for 6-12 min after the bell was switched off. The convulsions terminated only rarely in death of the rats.

TABLE 1. Changes in the Frequency of Onset of Audiogenic Convulsions in Mice and Rats After Injection of Amidopyrin

Dose of amidopyrin (in mg/kg)	Total number of animals		No. of animals developing audiogenic convulsions		Criterion of significance of development of audiogenic convulsions χ^2 at P = 0.05	
	mice	rats	mice	rats	mice	rats
175	28	17	8	6	19.0	17.2
200	48	29	41	22	133.7	53.1
225	52	23	49	20	164.7	68.2

These experiments showed that the preliminary injection of large doses of amidopyrin into rats and mice facilitates the development of audiogenic convulsions in the animals, and that this type of convulsion develops more easily in mice.

This model of amidopyrin-audiogenic convulsions was studied in order to test its suitability as a means of detecting substances possessing an anticonvulsant action. Trials were made of substances exhibiting a marked anticonvulsant effect in experimental and clinical conditions. The drugs were given by mouth in doses effective against other types of experimental convulsions. Amidopyrin, in a dose of 200 or 250 mg/kg, was injected 1.5-2 h after administration of the drugs to be tested. The results of these experiments are given in Table 2.

TABLE 2. Comparative Characteristics of Anticonvulsive Activity of Preparations in Amidopyrin-Audiogenic Convulsions

Preparation tested	Dose of preparation (in mg/kg)		Dose of amidopyrin (in mg/kg)	Total no. of animals		No. of animals developing audiogenic convulsions		Criterion of significance of anticonvulsant effect (χ^2)	
	mice	rats		mice	rats	mice	rats	mice	rats
Phenytoin*	90	100	200	7	8	1	1	11.9	16.0
	45		250	12		4		15.0	
Phenobarbital*	100		200	10		0		19.1	
Primidone	200		200	6		0		17.5	
	350		250	7		0		37.0	
Troxidone	400	350	200	7	9	0	0	10.8	12.7
	300	500	250	6	7	0	0	19.5	14.7
Acetazolamide	200		200	6		5		1.46	
Beclamide	200		200	15		10		3.34†	

* The drug intensified the convulsant action of amidopyrin.

† The anticonvulsant effect was significant if $\chi^2 > 3.84$ at P = 0.05.

Three types of result were obtained from the trials of these preparations: 1) absence of convulsive reaction to auditory stimulation and weakening of convulsant action of amidopyrin (troxidone and primidone); 2) absence or a significant weakening of the convulsive reaction to the sound of the bell and an increase in the sensitivity of the animals to the convulsant action of amidopyrin (in some animals lethal amidopyrin convulsions developed, whereas in the control animals the doses of amidopyrin given failed to produce convulsions); this type of action was characteristic of phenytoin and, to a lesser extent, of phenobarbital; 3) absence of anticonvulsant action against audiogenic convulsions (acetazolamide and beclamide).

The differences in the anticonvulsant activity of the drugs tested in this manner may point to differences in the mechanism of the anticonvulsant action of preparations belonging to different chemical groups.

The simplicity and demonstrativeness of the method of reproduction of audiogenic convulsions by the preliminary injection of amidopyrin enable it to be used in investigations aimed at discovering anticonvulsant preparations and determining the mechanism of their action.

SUMMARY

Subcutaneous injection of amidopyrin in nonconvulsive doses considerably increased the sensitivity of rats and mice to the effect of sound stimulus. Following amidopyrin injection (175-225 mg/kg) bell ringing provoked fatal convulsive attacks in most of the albino mice, and convulsions and motor excitation (for 6-12 min) in rats.

Troxidone and primidone totally prevented the audiogenic convulsions, whereas beclamide produced but a mildmild effect, while Acetazolamide proved to be ineffective. phenytoin and phenobarbital prevented the appearance of audiogenic convulsions intensifying, however, the convulsive effect of amidopyrin.

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