EFFECT OF ADRENERGIC BLOCKING AGENTS ON TOXICITY OF AMPHETAMINE IN MICE KEPT IN GROUPS OR IN ISOLATION

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Phentolamine, tropaphen, and propranolol reduced the toxicity of amphetamine in mice whether kept in isolation or in groups. Pronethalol was effective only in relation to isolated mice. All four adrenergic blocking agents prevented to some extent the increase in body temperature of the animals produced by amphetamine. It is postulated on the basis of these results that the central effects of the drugs studied are not dependent on their adrenergic blocking properties.

The stimulant effect of amphetamine is a convenient model for evaluating the effect of pharmacological agents on central adrenergic processes, because it is assumed that this effect is the result of excitation of the adrenergic structures of the brain stem [3, 5, 8]. The α- and β-adrenergic blocking agents are interesting as possible amphetamine antagonists, but their central action has received inadequate study and what results have been obtained are contradictory [4, 10].

The object of this investigation was to compare some α- and β-adrenergic blocking drugs by their effect on the phenomenon of the "group toxicity" of amphetamine, in the genesis of which an important role is ascribed to central adrenergic processes [9]. For comparison, it was also interesting to study the effect of these substances on the toxicity of amphetamine in isolated mice.

EXPERIMENTAL METHOD

Male albino mice weighing 20-24 g were used in the investigation, and at least 10 animals were tested with each dose of the drugs. In the experiments to study group toxicity, the mice were kept in groups of ten in plastic cages measuring 14 × 14 × 14 cm. The animals had an adequate air supply and could obtain food and water freely. The temperature inside the cages was kept at 23-24°. The results of the toxicity experiments were read after 24 h. Every 30 min the rectal temperature of the mice in the groups was recorded by means of a "Biotherm" electrothermometer. The value of LD_{50} was determined by the method of Litchfield and Wilcoxon, and other parameters were treated by calculation of the mean and of its confidence limits at $P = 0.05$.

Phentolamine and tropaphen were used as adrenergic blocking agents of the α-type, and pronethalol and propranolol as agents of the β-type. The drugs were injected intraperitoneally 30 min before injection of amphetamine or of 0.9% NaCl solution.

EXPERIMENTAL RESULTS AND DISCUSSION

The results given in Table 1 show that the α-adrenergic blocking drugs phentolamine and tropaphen and the β-blocking agent propranolol prevent the phenomenon of increased toxicity in mice kept in groups almost completely. LD_{50} of amphetamine, determined in groups of mice after the preliminary administra-

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TABLE 1. Effect of Adrenergic Blocking Substances on Toxicity of Amphetamine in Mice

Agent	Dose (in mg/kg)	Toxicity of amphetamine (LD_{50} with confidence limits at P = 0.05)	
		mice in groups	isolated mice
0.9% NaCl solution		13 (10–16)	42 (28–63)
Phentolamine	15	35 (26–48)	125 (91–173)
Tropaphen	15	50 (32–72)	190 (140–258)
Propranolol	15	32 (22–46)	195 (155–246)
Pronethalol	15	15*	105 (81–137)

*Confidence intervals not calculated.

tion of these drugs , and LD_{50} in experiments on isolated intact animals were statistically indistinguishable (P = 0.05). The other β-adrenergic blocking agent which was used (pronethalol) did not change the toxicity of amphetamine in the groups of mice, possibly because this drug possesses an adrenomimetic action [11].

The toxicity of amphetamine for isolated mice was much reduced by the action of all adrenergic blocking agents, although in this case also the effect of pronethalol was weaker. A definite parallel was observed between the degree of the change in LD_{50} in grouped and isolated mice during the action of adrenergic blocking agents. For instance, after administration of phentolamine, LD_{50} of amphetamine in the grouped mice was increased on the average by 2.7 times, and in the isolated mice by about 3 times.

Because of reports in the literature that an important factor in the development of increased toxicity of amphetamine in animals in groups may be the hyperthermia developing under these circumstances [6], it was decided to study the action of adrenergic blocking agents in this direction.

In the first series of experiments in which the action of adrenergic blocking agents on intact mice was studied, these drugs had no significant effect on the rectal temperature. Only phentalamine reduced the rectal temperature on the average by 1.3° 2 h after administration.

In a dose of 15 mg/kg, amphetamine produced marked hyperthermia in the mice (Fig. 1). The development of amphetamine hyperthermia after preliminary administration of adrenergic blocking agents is also shown in this figure. All adrenergic blocking agents to some extent reduced the hyperthermia due to amphetamine, although none of these drugs completely prevented the hyperthermia.

Propranolol slightly retarded its development. Tropaphen was less active in preventing amphetamine hyperthermia, but in this case also, the difference between the body temperature of the control and experimental mice was statistically significant.

The results of these experiments thus show that no basic differences could be found between the action of adrenergic blocking agents of α- and β-types on the phenomenon of group toxicity or that of hyperthermia produced by amphetamine. It is also easy to see that no complete parallel exists between the effects of the drugs on group toxicity, on the one hand, and on amphetamine hyperthermia on the other: tropaphen, which reduced the toxicity of amphetamine more strongly than the other drugs, was least active in preventing hyperthermia; pronethalol neither modified the group toxicity of amphetamine nor significantly reduced the hyperthermia. These results do not agree with the observations of Clark et al. [6], who consider that hyperthermia is the dominant factor in the manifestation of increased toxicity of amphetamine in groups of mice.

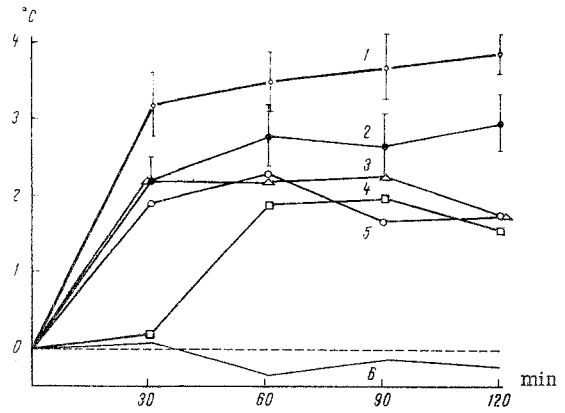

Fig. 1. Effect of adrenergic blocking agents on amphetamine hyperthermia in albino mice. Abscissa: time (in min) after injection of amphetamine; ordinate: changes in rectal temperature (in deg); 1) amphetamine 15 mg/kg; 2) tropaphen 15 mg/kg + amphetamine; 3) pronethalol 15 mg/kg + amphetamine; 4) propranolol 15 mg/kg + amphetamine; 5) phentolamine (15 mg/kg) + amphetamine; 6) control.

It is interesting to compare these results with those of the writers' previous investigation [1] of the same drugs, which showed that α-adrenergic blocking agents reduce, while β-blocking agents increase the action of amphetamine on the motor activity of mice. It thus follows that the increase in motor excitation, like the hyperthermia, cannot be the dominant factor in the phenomenon of group toxicity. It is evident that exhaustion of the reserves of catecholamines as a result of the action of amphetamine plays a more important role in the genesis of the increased mortality among the mice kept in groups. In the light of these ideas, the protective effect of adrenergic blocking agents can be regarded as the result of their ability to prevent exhaustion of the central catecholamines, as has been demonstrated for phenoxybenzamine [9]. The possibility of acceleration of the synthesis of endogenous catecholamines by adrenergic blocking agents likewise cannot be ruled out [7].

Comparison of these results with those previously published shows the absence of any selectivity in the effect of α- and β-adrenergic blocking agents on the group and individual toxicity of amphetamine and on the hyperthermia produced by it. Tropaphen, a peripheral adrenolytic [2], behaved in these experiments as an active antagonist of the central effects of amphetamine. One of the β-adrenergic blocking agents, propranolol, behaved in the same way. The other similar β-adrenergic blocking agent, pronethalol, was ineffective as regards the group toxicity of amphetamine.

It can be concluded from these findings that the protective effect of phentolamine, tropaphen, and propranolol against the action of toxic doses of amphetamine is the result of their specific effect on the central nervous system. This effect does not correlate with the ability of these drugs to block adrenergic structures of α- and β-types.

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