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INTERACTION OF ASARONE WITH MESCALINE, AMPHETAMINE AND TREMORINE*

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The potent tranquilizing property shown by asarone and β-asarone, active principles obtained from the volatile oil of Acorus calamus Linn has been reported. In rats, these active principles reduced the motor activity, blocked the conditioned avoidance response in a specific manner and produced a taming influence on hostile cats (1). Further studies showed that asarone reduced anxiety in rats trained for choice discrimination behavior, caused a long-lasting calming effect in monkeys and antagonized the stimulant action of a number of central nervous system stimulants (2). Asarone also potentiated some of the actions of reserpine and chlorpromazine (3).

These encouraging observations demanded further studies, and the present communication reports the influence of pretreatment of asarone on the effects produced by mescaline, amphetamine and Tremorine in experimental animals.

METHODS

Solution of asarone for injection was prepared by dissolving it in a few drops of absolute alcohol and then adding warm 3 percent

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polysorbato-80 to make up the requisite volume. The alcohol content of this solution never exceeded 5 percent v/v. Mescaline hydrochloride, d-amphetamine sulfate and Tremorine dihydrochloride were dissolved in distilled water. Control experiments were simultaneously performed using the alcohol-polysorbate-80 mixture. All the injections were made intraperitoneally unless otherwise stated.

Mescaline-induced hallucinations in rats :

Albino rats (Haffkine strain) of either sex weighing between 150 and 200 g. were employed in 3 groups of 6 animals each. To the first group, the solvent mixture was administered, followed 30 minutes later by mescaline hydrochloride in a dose of 100 mg/kg. The second group was pretreated with asarone in a dose of 3 mg/kg and 30 minutes later, the same dose of mescaline was administered. The third group of rats received 3 mg/kg. dose of chlorpromazine followed 30 minutes later by mescaline. The animals were observed for 2 hours and the scoring was done using a double-blind technic.

Amphetamine toxicity in aggregated mice :

Albino mice (Haffkine strain) of either sex weighing between 20 and 30 g. were divided into three groups of ten animals each distributing males and females equally in each group. These were kept aggregated in three metallic cages (25cm x 13cm x 12cm) having wire-meshed walls. To one group of mice the solvent mixture was administered followed 30 minutes later by d-amphetamine sulfate in a dose of 20 mg/kg. The second and third groups of mice were pretreated with asarone (1 mg/kg) and chlorpromazine (1 mg/kg) respectively,and after 30 minutes the same dose of d-amphetamine was administered.All these injections were made subcutaneously. These groups of aggregated mice were observed at intervals for 18 hours, the dead animals being removed at the time of observation. At the end of the experi-

-ment, the number of animals surviving in each group was noted.

Tremorine-induced tremors in mice :

Albino mice (Haffkine strain) of either sex, weighing between 18 and 25 g. were divided into 4 groups of 15 animals each. The first group was treated with the solvent, the second and third groups received asarone in doses of 3 mg/kg and 10 mg/kg respectively. Atropine sulfate was used as the reference standard and was administered to the fourth group of mice in a dose of 3 mg/kg. Thirty minutes after the pretreatment, Tremorine dihydrochloride in a dose of 25 mg/kg was administered to all the groups of mice. These animals were observed for the following 4 hours and the intensity of tremors, rigidity, salivation and lacrymation induced by Tremorine in the different groups was observed and compared.

RESULTS

Mescaline-induced hallucinations :

The control group of (solvent-treated) rats exhibited marked hyperactivity, moved about with an abnormal gait, occasionally standing on their hindlimbs and were aggressive. Chlorpromazine could reduce these effects markedly, but the rats still showed restlessness and piloerection. On the other hand, asarone completely antagonized all the effects of mescaline.

Amphetamine toxicity in aggregated mice :

The results are given in Table-i. In a dose of 20 mg/kg. amphetamine caused 100 percent mortality in aggregated mice. Twenty percent of the animals died within 2 hours and the rest were found dead after 5 hours. In a dose of 1 mg/kg chlorpromazine reduced the mortality rate by 50 percent and also delayed the onset of death in animals. The same dose of asarone offered complete protection to aggregated mice treated with amphetamine. The antagonism was so

complete that at no stage, the animals were stimulated in contrast to chlorpromazine in which case most of the animals were hyperactive, but much less than the unprotected control group of mice.

TABLE 1

Showing the effect of Chlorpromazine and Asarone on Amphetamine Toxicity in Aggregated mice.

Drug and Dose	No.of animals in each group	No. of animals dead within				Mortality
		2 hr.	3 hr.	5 hr.	18 hr.	
Control (Solvent+amphetamine) 20 mg/kg	10	3	7	-	-	10/10
Chlorpromazine(1 mg/kg) + amphetamine(20 mg/kg)	10	0	3	2	0	5/10
Asarone (1 mg/kg) + amphetamine(20 mg/kg)	10	0	0	0	0	0/10

Tremorine-induced tremors in mice :

The results obtained are shown in Table 2. Tremorine produced profound tremors of the head and limbs of mice. In addition, the animals moved about slowly, showed muscular rigidity and were less active.

Asarone, when given to mice in doses of 3 mg/kg and 10 mg/kg before Tremorine, completely prevented tremors but muscular rigidity was only slightly reduced. Salivation and lacrymation were increased in the asarone treated animals receiving Tremorine. In contrast to this, atropine sulfate completely antagonized all the effects of Tremorine.

TABLE 2

The effect of Asarone and Atropine on Tremorine-induced Tremors in mice.

Drug and Dose	No.of animals	Tremors	Muscular rigidity	Salivation	Lacrimation
Tremorine 25 mg/kg	15	++++	++++	++	++
Asarone 3 mg/kg + Tremorine	15	0	++	+++	+++
Asarone 10 mg/kg + Tremorine	15	0	++	+++	+++
Atropine 3 mg/kg + Tremorine	15	0	0	0	0

Key - 0 Absent; ++ Mild; +++ Moderate; ++++ Marked

DISCUSSION

It is known that mescaline produces hyperactivity and hallucination in man and experimental animals. It has already been reported that asarone antagonized the stimulant effects of d-amphetamine, methylphenidate, lysergicacid diethylamide and iproniazid in mice (2). Mescaline is of interest, more especially due to its close structural similarity with asarone, both being simple trimethoxybenzene derivatives. Asarone completely antagonized all the effects of mescaline in rats, but since the stimulant effects of other drugs with widely differing chemical structures have also been antagonized by asarone, the mechanism of mescaline antagonism may not be due to a competitive blockade of the receptors by asarone. Further work may have to be carried out to probe this possibility.

The marked increase in the toxicity of amphetamine when mice are aggregated was explained on the basis that grouped mice showed excessive excitement which in turn increased the mortality (4). Later, this effect of amphetamine was developed as a basis for the evaluation of the tranquilizing effect of drugs (5) when it was shown that reserpine and chlorpromazine significantly decreased the mortality rates in aggregated mice treated with amphetamine. The dramatic effect shown by asarone is in agreement with its tranquilizing property (1,2) and on a weight basis it is much more effective than chlorpromazine in reducing amphetamine toxicity.

Previous studies have shown the anticholinergic effects of asarone on isolated skeletal and smooth muscles (6). On this basis it was anticipated that asarone might antagonize the experimental tremors in animals, in which case it could be used in the treatment of parkinsonism, the tranquilizing effect being an additional advantage. But in these experiments with Tremorine, the effect shown by asarone was not very marked, since only partial antagonism was observed in contrast to the total protection offered by atropine against all the effects of Tremorine.

The antagonistic effect of asarone to mescaline and amphetamine offers additional evidence for its tranquilizing action.

SUMMARY

Asarone, one of the active principles obtained from the volatile oil of Acorus calamus Linn. antagonized the hyperactivity and hallucinogenic effects of mescaline in rats and also offered complete protection to aggregated mice treated with d-amphetamine. On a weight basis asarone was found to be much more effective than chlorpromazine in both these experiments. These findings offer

additional evidence for the tranquilizing effect of asarone.Asarone also partially antagonized Tremorine-induced tremors in mice but was found to be inferior to atropine in this respect. It appears that the tranquilizing effect of asarone is responsible for its antagonism to mescaline and amphetamine, whereas the anticholinergic effect accounts for the partial protection offered to Tremorine treated mice.

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