Therefore, our results have shown that, in the rat liver 1. the synthesis of RNA was strongly reduced by α-amanitin until 6 h after poisoning; 2. there was a complete recovery of the synthesis of RNA between the 6th and the 10–12th h after α-amanitin treatment; 3. this recovery was hindered by the inhibition of protein synthesis with cycloheximide. Thus we can exclude the possibility that in the rat liver the recovery of the synthesis of RNA may be due to a dissociation of the α-amanitin-RNA polymerase complex. Our results fit reasonably well with the hypothesis that in the rat liver the recovery of the synthesis of RNA may be due to the synthesis of new molecules of RNA polymerase II.

The capability of the rat liver to synthesize the RNA polymerase II may be due to a long life of the mRNA for this enzyme. α-amanitin, by lowering the synthesis of extranucleolar RNA, induces also an inhibition of the mRNA synthesis[16]. Therefore, if the lifetime of the mRNA molecules is longer than the clearance time of α-amanitin from the organism, new enzyme molecules would not be inhibited by the toxin.

In conclusion, the difference in sensitivity between rats and mice to α-amanitin may be explained on this basis: liver RNA synthesis is inhibited by the toxin both in rats and in mice, but a longer life of mRNA in the rat prevents the inhibition of protein synthesis. This is in agreement with the finding that in mouse liver the protein synthesis, 18 h after α-amanitin poisoning, was reduced to the 50% level of the controls, whereas in rat liver it was practically unaffected. Moreover, this inhibition of protein synthesis was found to be due to a lack of mRNA[17].

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Effect of Brocresine on Conditioned Avoidance Behavior in Mice[1]

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Summary. Brocresine, an inhibitor of brain histamine biosynthesis, has been found to impair the ability of mice to avoid shock in a shuttle box CAR test; escape performance was unaffected in these studies.

An increasing body of evidence has appeared in recent years supporting the concept that histamine is a neurotransmitter in the central nervous system. Histamine is nonuniformly distributed in the brains of mammals and is synthesized in nerve endings, stored in synaptic vesicles and its release is enhanced by potassium-induced depolarization. The turnover rate of brain histamine has been estimated to be less than 1 h and this rate is reduced after barbiturate administration[2–4]. While the functional role of histamine is obscure at this time, its central administration has been reported to modify such vegetative functions as thermoregulation[5], water intake[6], water balance regulation[7] and the emetic response[8], as well as alter continuous (Sidman) avoidance[6] and self-stimulation[9] behaviors. This study was designed to determine whether brocresine-induced inhibition of histamine biosynthesis could modify the acquisition, retention and performance of a learned behavior (conditioned avoidance responding) in mice. Brocresine, an inhibitor of histidine decarboxylase[10,11], is capable of reducing rodent brain histamine levels by 40–50%[12].

Methods. Male albino CD-1 mice (18–25 g) were employed in these experiments in a typical shuttle box[13]. Animals were trained to perform a shuttle box conditioned avoidance response (CAR) as follows: the mouse was placed at one end of the box and, after a 5-sec environmental exposure period, 5 sec of buzzer was presented, followed by 15 sec of footshock (60 cycle alternating current; 2 milliamperes delivered through a shock scrambler) in the continued presence of buzzer. To avoid or escape a shock, the mouse was required to reach a 'safe area' platform placed at grid level at the opposite end of the shuttle box. Each mouse was given 10 trials in the morning and afternoon until the animal was able to avoid shock in 9 out of 10 consecutive trials. After achieving this 90% avoidance criterion, the test animal was used as its own control receiving saline and brocresine in the morning and afternoon, respectively, 30 min prior to testing. In experiments designed to evaluate drug effects on the acquisition of CAR, behaviorally naive mice were given up to 100 consecutive trials or until each animal achieved the 90% avoidance criterion.

Results and discussion. At doses up to 300 mg/kg, i.p. administered 5–120 min prior to testing, brocresine failed to induce minimal neurotoxicity or muscle incoordination when evaluated by the inability of mice to remain on a horizontal rod rotating at 6 rpm for 1 min. Greatest depression of spontaneous motor activity was observed 30–60 min after drug administration.

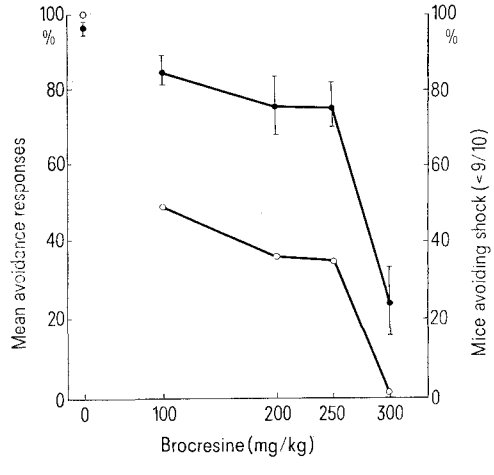

Fig. 1. Effect of brocresine and saline on avoidance responding in CAR trained mice. ●, mean percent avoidance responses ± SEM out of a total of 80 trials at each dose of brocresine; each of 8 animals was used as its own control. ○, percent of 8 mice avoiding shock less than 9 times in 10 trials. All doses of brocresine significantly ($p < 0.05$) impaired performance.

Brocresine significantly impaired the ability of trained mice to avoid shock, but did not interfere with the ability of any mouse to escape to the 'safe area' after the commencement of shock. Avoidance failures of 15, 24 and 75% out of a total of 80 trials were elicited by drug treatments of 100–300 mg/kg (Figure 1). With increasing doses of brocresine a greater number of mice failed to avoid shock at least 9 times in the 10 trials (Figure 1), and the time required for mice to reach the 'safe area' was increased by 20–63% in a dose-related manner.

The effects of saline and brocresine (250 mg/kg) pretreatment on the ability of mice to acquire and retain CAR behavior was compared in 2 groups of 8 mice each. 30 min after injection, each mouse was given repeated trials until attaining the 90% avoidance criterion or a maximum of 100 trials. While saline-pretreated mice required 50–64 trials, drug-treated animals required 15–74 trials, with 3 mice not attaining this 90% criterion after 100 trials. 24 h after injection both groups were re-tested and found to manifest equivalent CAR performance (Figure 2).

To date only a few studies have utilized inhibitors of histamine biosynthesis or antihistamines as tools to probe the behavioral role of brain histamine. Brocresine (200 mg/kg) has been recently shown to reduce the susceptibility of mice to pentylenetetrazol-induced minimal (clonic) seizures, while increasing the risk of these animals to maximal (tonic) convulsions; many, but not all antihistamines (H_1 antagonists) and intraventricularly administered metiamide (H_2 antagonist) increased the susceptibility of mice to minimal seizures[14]. The histidine decarboxylase inhibitor thiazol-4-ylmethoxyamine has been reported to reduce motor activity, food intake and REM sleep in rats[15]. The central stimulating and depressing effects of H_1 antagonists have been demonstrated in human and animal studies[6,14,16–18]. The results of neurochemical and neuropsychopharmacological studies suggest that histamine may have a physiological and/or neurotransmitter function in the mammalian brain.

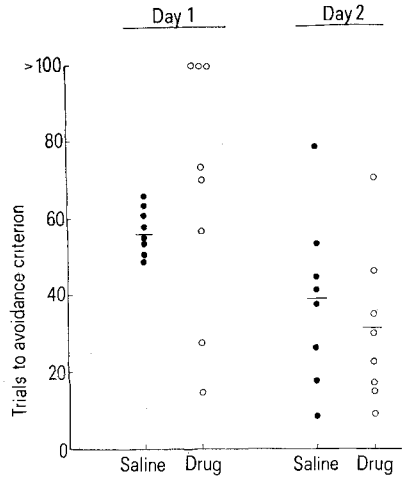

Fig. 2. Effect of brocresine (250 mg/kg, i.p.) and saline (1 ml/100 g) on the acquisition (day 1) and retention (day 2; no injections) of a CAR performance criterion of 90% avoidance.

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Hypertension Mediated by the Activation of the Rat Brain 5-Hydroxytryptamine Receptor Sites[1]

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Summary. 5-Hydroxytryptamine (5-HT) administered intraventricularly (i.vent.) in rats produced hypertension without considerable changes in heart rate. After transsection of the spinal cord or i.vent. administration of methysergide, 5-HT failed to produce the pressor effect. Thus, the hypertension results from the activation of 5-HT receptor sites of the rat brain.

It has been demonstrated that 5-HT injected into a lateral cerebral ventricle of the dog causes hypotension and bradycardia[2,3]. Ginzel[4] failed to observe the vasomotor effects on i.vent. administration of 5-HT in the cat. However, recently it was reported that 5-HT injected into the cat lateral ventricle or cisterna magna produces a decrease in arterial blood pressure and heart rate[5,6]. These effects, in the dog as well as in the cat, probably result from a centrally-induced decrease in

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