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.

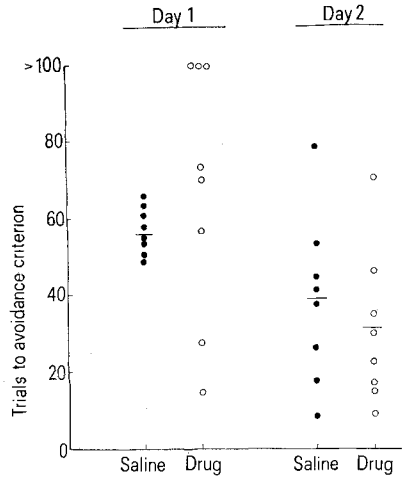

Fig. 2. Effect of brocresine (250 mg/kg, i.p.) and saline (1 ml/100 g) on the acquisition (day 1) and retention (day 2; no injections) of a CAR performance criterion of 90% avoidance.

[1] Supported in part by USPHS Grants Nos. MH-22570 and NS-10203. Brocresine dihydrogen phosphate was kindly provided by Lederle Laboratories.

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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

[1] This work was supported by Union of Scientific Medical Institutions of Serbia (Grant No. 85).

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sympathetic nervous activity[2,5]. Furthermore, immediately after the termination of the present study, BHARGAVA[7] reported that superfusion of 5-HT in the cat medullary pressor area elicits pressor response and tachycardia which are abolished by methysergide. The purpose of this investigation was to examine the general characteristics and the nature of cardiovascular response to i.vent. administration of 5-HT in rats.

Materials and methods. Albino rats of both sexes, weighing 220 to 320 g, were anaesthetized by urethane, 1.5 g/kg s.c. The left carotid artery and trachea were cannulated and then the rat was placed in a stereotaxic instrument. A 22 gauge stainless steel guide cannula was implanted stereotaxically into the left ventricle. The i.vent. injections were made via a 28 gauge stainless steel injector cannula inserted through the guide. The arterial blood pressure was recorded from the left carotid artery through a mercury manometer on a smoked kymograph paper and heart rate was recorded by the transistor-electrocardiograph Nek-2 (R.F.T.).

In one group of rats, 15–20 min prior to the 2nd injection of 5-HT, the cervical vagosympathetic trunk was cut bilaterally low in the neck. In other group of rats, under the same experimental conditions, the spinal cord was transsected between the 1st and the 2nd cervical vertebra. The latter rats were on artificial respiration. In some experiments, the pressor response to i.vent. administration of acetylcholine was used as a control. This response results from the activation of the central muscarinic receptors[8].

All compounds were dissolved in isotonic NaCl solution which afterwards was adjusted to pH 5.0–6.0. Drugs were administered i.vent. (in a volume of 2–10 µl). An exception to this was reserpine, which was injected i.p. (in a single dose of 5 mg/kg, 48 and 24 h before the experiment). In each particular experiment, 5-HT was administered i.vent. in the same volume, at the same rate, at intervals of 90 min. The following substances were used: 5-hydroxytryptamine creatinsulphate (Fluka), acetylcholine hydrochloride (Pliva), atropine sulphate (Lek), hexamethonium bromide (Merck), methysergide (Deseril®-Sandoz) and reserpine (Serpasil®-Ciba). All doses refer to the salts.

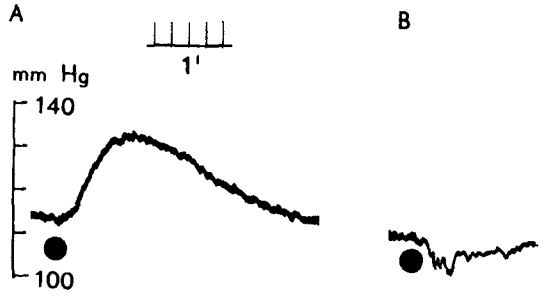

Fig. 1. The effect of methysergide on the pressor response to i. vent. administration of 5-HT in the rat (310 g). At dots, 5 µg of 5-HT was injected i. vent. and between A) and B), 10 ng of methysergide. The rat was treated by methysergide 8 min prior to the 2nd injection of 5-HT. Time interval between A) and B), 74 min. Time: 1 min intervals.

Pressor response to i. vent. administration of 5-HT (3–5 µg) in rats

Latent period[a] (sec)	Duration of injection (sec)	Pressor response	
		Height (mm Hg)	Duration (min)
16 ± 0.73 (47)[b]	14 ± 0.57 (47)	16 ± 0.66 (65)	13 ± 0.5 (65)

Values are means ± SEM.
[a] Time interval from the beginning of the injection to the beginning of the pressor response. [b] Numbers of experiments.

Results and discussion. 5-HT (1.5–6 µg) injected i.vent. after a latent period of 10 to 30 sec from the beginning of administration, caused a blood pressure rise (Figure 1). The hypertensive effect varied in height from several to 30 mm Hg, and in duration from 4 to 25 min. In the majority of experiments, 5-HT injected in a dose of 3 to 5 µg produced a pressor response which was suitable in magnitude for the pharmacological analysis (Table). When 5-HT was administered at intervals of 90 min, there was no tachyphylaxis to the hypertensive effect of the drug (7 experiments). The increase in arterial blood pressure was dose-dependent. There was a linear relationship between the logarithm of the 3 increasing doses of 5-HT (1.5, 3 and 6 µg) and the magnitude of the blood pressure rise (Figure 2).

In the majority of experiments, the heart rate was not considerably altered by i.vent. administration of 5-HT. During the rise of arterial blood pressure produced by 5-HT (3–5 µg), different heart responses were obtained: in 28 out of 59 experiments the heart rate was decreased (by 18 beat/min ± 2.15; mean ± SEM), in 14 experiments increased (by 12 beat/min ± 2.42), in 4 experiments initially increased and afterwards decreased, and in 13 experiments unchanged.

Bilateral cutting of the cervical vagosympathetic trunk did not considerably modify the pressor response to i.vent. administration of 5-HT (5 experiments). However, the pressor response to 5-HT was abolished after the spinal cord transsection (6 experiments), indicating that the hypertension results from the activation of the brain vasomotor zones. In these 2 groups of rats, 5-HT only slightly decreased or increased the heart rate, and therefore it was difficult to make any reliable conclusion concerning the effect of the vagosympathetic trunk cutting and the spinal cord transsection on the heart response to this amine.

Atropine (5 µg) did not affect the pressor response to 5-HT (5 experiments). However, in a separate experimental group, atropine (2–4 µg) abolished the hypertensive response to acetylcholine (5 experiments). Hexamethonium (7.5–10 µg) did not appreciably change the

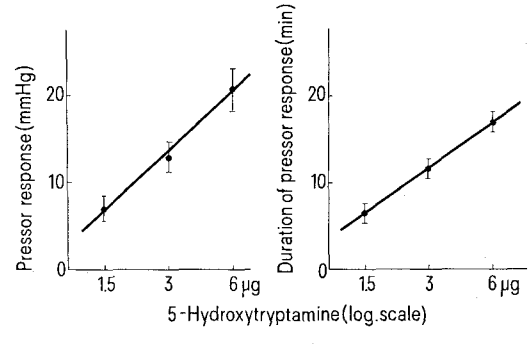

Fig. 2. Relationship between doses of 5-HT and magnitude of the pressor response. All the 3 doses of 5-HT were injected in the same rat i. vent., at intervals of 90 min. Every point represents mean of 5 experiments ± SEM.

pressor response to 5-HT (8 experiments). Furthermore, it is known that central injection of hexamethonium, in a similar dose range as in the present experiments, blocks the pressor response to centrally injected carbachol in rats[9]. On the other hand, all doses of methysergide between 7 and 10 ng abolished the hypertensive effect of 5-HT (Figure 1; 6 experiments). However, in a separate experimental group, methysergide (7–10 ng) did not appreciably affect the increase in arterial blood pressure caused by acetylcholine (6 experiments). Accordingly, the pressor response to i.vent. administration of 5-HT was selectively blocked by methysergid.

The preliminary experiments have shown that the pressor response to 5-HT was not appreciably altered in reserpinized rats (6 experiments). However, further experiments are necessary in order to establish the real nature of the peripheral mechanism mediating the hypertensive response to 5-HT.

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Hexobarbital Action in Rats with Flavonoid-Deficiency

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Summary. In flavonoid-deficient rats, hexobarbital-sleeping times are prolonged. The hexobarbital concentrations in brain, liver and plasma are increased. These results are discussed as a consequence of an impaired drug metabolism.

Feeding rats a diet lacking flavonoids raises the pentobarbital-induced sleeping time (Földi and Földi-Börcsök[1]). The problem arose as to whether the action other drugs with effects on the central nervous system is also changed.

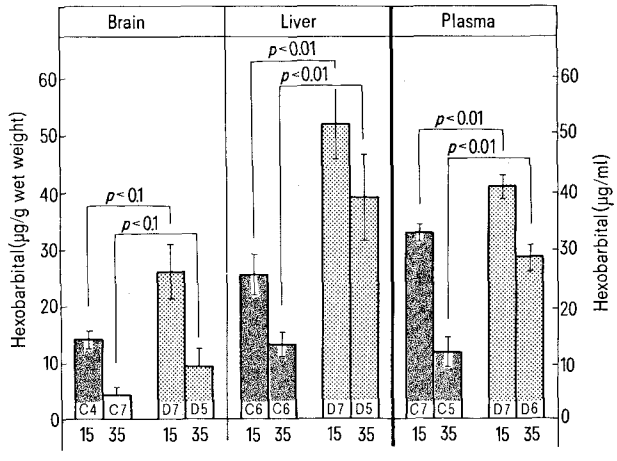
Therefore rats on a diet lacking the flavonoids were injected with hexobarbital. Their sleeping times were estimated, and 15 and 35 min after the injection measurements of the barbiturate in brain, liver and plasma were performed. Such measurements give some information about the disappearance of the drug from these 3 compartments, and therewith about the metabolic rate leading to the inactivation of the hexobarbital (Bush and Weller[2]).

Materials and methods. In the course of September 1975, experiments were performed on male Sprague-Dawley rats with a body weight of 425 ± 10 g ($\bar{x} \pm s_{\bar{x}}$, $n = 26$). The ages and the body weights of flavonoid-deficient (FD) and control rats, respectively, did not differ. The FD-animals were fed for more than 4 months with the diet. These rats, as well as the control animals on a standard diet, were kindly given by Prof. M. Földi. The detailed conditions of their nutrition are described by Földi and Földi-Börcsök[1].

The rats were injected with hexobarbital-Na in a dose of 50 mg/kg i.e. 1 ml/kg into a tail vein. The injection time was about 15 sec. The time interval from the end of the injection till the moment when the rats where put on one side, turned back on their hind legs, was measured and called sleeping time.

Estimations of hexobarbital in brain, liver and plasma were performed by a gaschromatographic procedure (for details see Endell and Seidel[3]). Results are given as mean ± standard error of mean ($\bar{x} \pm s_{\bar{x}}$). Statistical analysis of the significance of differences between two means was performed using the *t*-test.

Results. FD-rats treated i.v. with hexobarbital slept longer than the controls. While the sleeping time in the latter group was 13.4 ± 0.9 min ($n = 7$) 4 of 6 FD-animals still slept when they were decapitated 35 min after the injection of the barbiturate. The sleeping times in the two other FD-animals were 24.6 and 17.6 min, respectively.



Concentrations of hexobarbital in brain, liver and plasma of rats 15 and 35 min, respectively, after injection (50 mg/kg i. v.). Number in the columns: animals/group. C, normally fed animals; D, flavonoid-deficient animals.

The hexobarbital concentrations in brain, liver and plasma 15 and 35 min, respectively, after the administration of the hexobarbital, are shown in the Figure. The FD-animals revealed higher concentrations which decreased more slowly than those in the controls. As hexobarbital is eliminated mainly by metabolic degradation in the liver (Bush and Weller[2]), this may indicate an impaired hexobarbital metabolism.

The means of the quotients 'hexobarbital concentration in brain divided by the concentration in plasma' of single FD-rats, as well as of the controls, were in the same range [15 min: 0.63 ± 0.09 ($n = 7$) versus 0.54 ± 0.14 ($n = 4$); 35 min: 0.37 ± 0.12 ($n = 5$) versus 0.46 ± 0.15 ($n = 5$)].

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