EFFECT OF INHIBITORS OF SEROTONIN AND NORADRENALIN SYNTHESIS ON LEARNING IN RATS WITH EMOTIONALLY DIFFERENT REINFORCEMENT

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The effect of inhibitors of serotonin and noradrenalin synthesis in the brain on learning in rats with emotionally different reinforcement was investigated. Parachlorophenylalanine (320 mg/kg) impaired learning in rats with food reinforcement but improved learning with pain reinforcement. Disulfiram (100 mg/kg) which significantly impaired learning with pain reinforcement, had no effect on learning with food reinforcement. α-Methyl-m-tyrosine inhibited both forms of learning. Comparison of these facts with previous observations confirms the hypothesis that the monoaminergic systems of the brain play the role of intermediary between the emotions and memory.

KEY WORDS: learning; emotions; parachlorophenylalanine; disulfiram; α-methyl-m-tyrosine.

Recent investigations have shown that an increase in the biogenic amine level in the brain has a significant effect on learning and memory in animals [1, 3, 5, 7]. The character of this effect has been shown to be determined by the biological role of the reinforcement used during learning [2, 5]. It was accordingly decided to compare the patterns of learning in rats during emotionally different reinforcement with the changes in the serotonin and noradrenalin levels in the brain of the aminals when synthesis of these substances was inhibited.

EXPERIMENTAL METHOD

Experiments were carried out on 100 male Wistar rats weighing 180-200 g. In the experiments of series I the effect of parachlorophenylalanine (PCPA) [8], which blocks serotonin synthesis at the hydroxylation stage in the brain [8], on learning was studied in rats during emotionally positive and emotionally negative reinforcement. In series II the effect of disulfiram, a specific blocker of noradrenalin synthesis at the hydroxylation stage from dopamine, and of α-methyl-m-tyrosine (αMMT), which lowers the catecholamine level in the brain through the formation of methylated metabolic products of the catecholamines, which behave as pseudomediators [6], was studied.

A suspension of PCPA was made up in physiological saline as described previously [8], using Tween-80, and a suspension of disulfiram was prepared in a 3% solution of gum arabic. α-MMT was dissolved in physiological saline acidified with hydrochloric acid. In all cases the pH of the solution was adjusted at the time of injection to 7.0.

PCPA was injected the first time 3 days before the beginning of the investigation and subsequently at intervals of 5 days. αMMT was injected daily 6-8 h before the experiment, and disulfiram daily 4 h before the experiment. The compounds were injected intraperitoneally. Control aminals received the equivalent volume of physiological saline.

In each series learning by the animals was accompanied by the use of emotionally positive and emotionally negative reinforcement. A conditioned active avoidance response (CAAR) of the animals to painful punishment by an electric shock applied to the wire floor of the cage, was used as the model of learning with emotionally negative reinforcement. A conditioned response of consecutive alternation of trips to the right or left sides of the cage to obtain food was used as the model of learning with emotionally positive reinforcement

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TABLE 1. Rate of Learning in Animals with Emotionally Different Reinforcement, under the Influence of Inhibitors of Serotonin and Noradrenalin Synthesis

Series	Learning with emotionally positive reinforcement			Learning with emotionally negative reinforcement		
	number of rats in group	rate of formation of conditioned active avoidance	persistence of habit after extinction	number of rats in group	rate of formation of conditioned active avoidance	persistence of habit after extinction
Control (physiological saline)	28	87,1±10,9	64%	34	62,8±22,5	15%
PCPA, 320 mg/kg	7	198,6±13,5‡	—	10	32,0±9,4†	63%
αMMT, 100 mg/kg	5	150,0±27,8‡	—	5	148,0±91,9*	—
Disulfiram, 100 mg/kg	5	92,0±13,6	26%	6	173,3±27,9 ‡	—

*P < 0.05.
†P < 0.01.
‡P < 0.001.

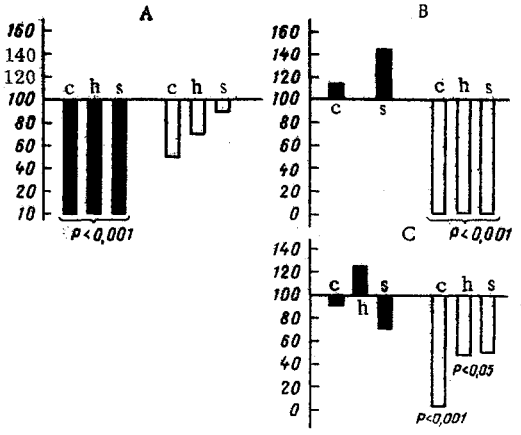

Fig. 1. Changes in serotonin and noradrenalin level in various brain structures of rats after administration of inhibitors of their synthesis. Black columns denote serotonin, white columns noradrenalin. After administration of: A) PCPA, B) αMMT, C) Disulfiram. c) Cortex, h) hypothalamus, s) caudal portion of brain stem. Ordinate, concentration of biogenic amines in brain (concentration in brain of trained animals receiving injections of physiological saline taken as 100%).

[4]. The criterion of the state of learning was obtaining a 70% level of performance of the response on two successive days in the first case and an 80% level in the second case. To test the stability of the habit thus formed in animals achieving the criterion of learning, an extinction test was carried out.

At the end of the experiment the animals were decapitated and the brain dissected. The region of the neocortex, hypothalamus, and the caudal portion of the brain stem was removed. The serotonin and noradrenalin concentrations were determined by Welch's method with a Hitachi fluorometer [9].

EXPERIMENTAL RESULTS

Injection of PCPA greatly disturbed the rats' ability to learn with food reinforcement. The animals did not achieve the criterion of learning despite 200 trips, whereas in the control 87.1 trips were needed (Table 1). The animals in these experiments showed increased motor activity and increased manifestations of stereotyped forms of behavior, such as sniffing, standing up on their hind limbs, and so on. A different picture was found in the case of learning by rats receiving PCPA with nociceptive reinforcement: a CAAR was formed in these animals twice as easily, and the habit formed was more resistant in the extinction experiments than in the control (Table 1).

Biochemical analysis of the monoamine concentration showed that injection of PCPA completely inhibited serotonin synthesis in all the brain structures tested. Some decrease in the noradrenalin level, most marked in the neocortex, also was observed (Fig. 1A).

Administration of αMMT and disulfiram to the animals reduced their ability to form a CAAR (Table 1). By contrast, the formation of the response to food reinforcement took place tactically identically after administration of disulfiram as in the control rats, although αMMT inhibited it. In all animals the level of motor activity was depressed.

Analysis of the biochemical data showed total inhibition of noradrenalin synthesis as a result of αMMT in all structures of the brain. Administration of disulfiram caused total inhibition of noradrenalin synthesis only in the neocortex, whereas in the hypothalamus and the caudal portion of the brain stem its concentration was halved (Fig. 1B, C).

The results thus indicate that selective inhibition of the activity of the brain serotoninergic system correlates with facilitation of learning by animals with nociceptive reinforcement and with its impairement with food reinforcement.

Meanwhile, depression of the activity of the noradrenergic system was accompanied by severe impairment of learning with nociceptive reinforcement. The fact that learning by the animals took place more slowly with both forms of reinforcement after administration of αMMT was evidently connected with blocking of the synthesis not only of noradrenalin, but also of dopamine [6], the leading mediator of the striopallidal system, the highest stage of regulation of motor function. This seems all the more likely because in a similar experimental situations the selective lowering of the noradrenalin level by means of disulfiram did not give this effect. Comparison of these facts with those obtained by the writers previously supports the view that monoaminergic systems of the brain act as intermediaries between the emotions of memory.

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