Effect of Buspiron on Formation of Acquired Helplessness

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By decreasing anxiety and emotional stress, buspiron in doses of 1 and 5 mg/kg decelerates the formation of instrumental defense reflex and increases the incidence of acquired helplessness in rats trained under conditions of highly indefinite environment. Buspiron in a dose of 0.5 mg/kg apparently does not affect the optimal emotional background, thus promoting attaining the goal of conditioned reflex activity and not leading to an increase in the incidence of acquired helplessness.

Key Words: *buspiron; instrumental reflex and training; acquired helplessness*

Investigation of neurasthenia and the chronic fatigue syndrome, to which experimental acquired helplessness (AH) corresponds best of all [12], is an important problem of general and systemic pathology. These states develop when it is difficult or impossible to attain a vitally important result and often under conditions of indefinite environment [7]. They are characterized by increased anxiety, extreme "isolation" of the organism from conditioned and even unconditioned signals, and areactivity involving visceral functions [6]. Behavior and its disorders are formed on the basis of neurochemical systems of the brain related to each other. Recent studies discovered an important role of the central serotoninergic structures in the development of anxiety in neurosis-like states [2,6].

The effects of buspiron and its analogs exerting selective anxiolytic effects [14] and activating presynaptic serotonin 1a-receptors in the midbrain suture nuclei [13] have been studied. The latter effect leads to selective depression of the serotoninergic neuron functions. Antidepressive and nootrope-like effects of low buspiron doses (0.5 and 1 mg/kg) and anxiolytic and neurolept-like effects of its high (5-10 mg/kg) doses in various behavioral tests were demonstrated [3].

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We studied the effect of buspiron on the formation of instrumental reflex and incidence of AH in rats under conditions of indefinite environment.

MATERIALS AND METHODS

Outbred male albino rats weighing 220-270 g were divided into 4 groups, 12 animals each. Instrumental defense reflex of pedal pressing in response to a conditioned light signal was trained. Unconditioned stimulus was electrocutaneous stimulation of the paws through the floor [6]. The probability of accidental correct reaction (PACR) was unfavorable for training in all groups, creating a highly indefinite environment [7]. PACR was determined as the ratio of duration of exposure to a conditioned signal (2 sec) to total duration of one cycle (duration of conditioned signal plus the interval between the stimuli); in our case PACR=2 sec/(2 sec+38 sec)=0.05.

Buspiron was injected in 40 min before training daily in intraperitoneal doses of 0.5, 1, or 5 mg/kg (volume 0.5 ml) to animals of groups 2, 3, and 4, respectively. Group 1 rats were injected with 0.5 ml isotonic NaCl. Conditioned reflex was considered trained at a statistically significant ($p<0.05$) excess in the number of correct reactions over an a priori level of their accidental correct reactions [5].

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RESULTS

The time course of instrumental reflex training is shown on Fig. 1. The period of training was divided into 5 intervals and the incidence of correct realizations was estimated in percentage of the total number of instrumental reactions for each interval. During the first 40-60% combinations, the frequency of pedal pressing in response to conditioned signal coincided with mathematically expected PACR in all groups except group 4 (Fig. 1).

On the other hand, not all animals developed the conditioned reflex. Some experimental rats pressed the pedal accidentally, without relation to the conditioned signal, and the number of pressings was far less than other animals needed for the formation of the reflex. A decrease in the general research activity and body weight, fur shedding, and augmented areactivity ("isolation") toward signals were observed in these animals, progressing with every experiment. They developed a stable AH state characterized by impaired ability to actively get rid of or passively avoid the damaging agent [12]. The incidence of AH development depended on the dose of buspiron. As Table 1 shows, 25% control animals developed AH, while in experimental groups these values were 33% in group 2 and 50% in group 3, and in group 4, administered the highest dose of buspiron, only two rats developed the reflex (AH in 80% animals).

Moreover, buspiron affected the rate of reflex formation: the reflex formed similarly in trained group 1 (control) and group 2 (0.5 mg/kg buspiron), as indicated by two independent parameters (Table 1). An increase in buspiron doses decelerated the development of conditioned reflex.

Previous findings demonstrate a relationship between the rate of training in accidental environment and formation of AH, on the one hand, and PACR values, on the other [7]. This may be due to easier or impeded informational relationships between the organism and the environment at optimal or pessimal (extremely high or low) PACR values, respectively. At low PACR values (0.05 in our experiment) animals get positive support (no electrocutaneous stimulation) extremely rarely, because the overwhelming majority of instrumental reactions are not related to the conditioned signal. This decreases the efficacy of research activity and promotes neurotization, eventuating in formation of AH in some animals. On the other hand, a deficiency of information about the environment can be compensated for by a high research activity, promoting the formation of a reflex.

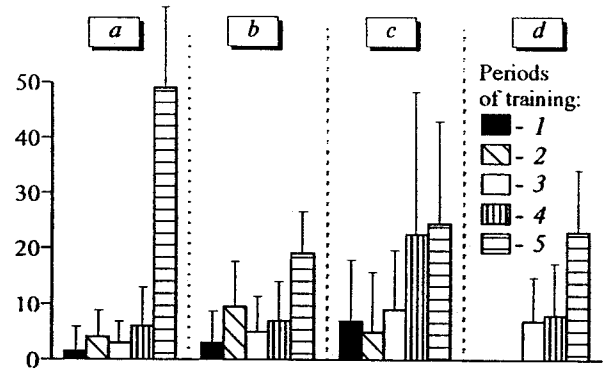

Fig. 1. Incidence of correct instrumental reactions at different periods of training after buspiron treatment. *a*) Group 1 (control); *b*) group 2 (0.5 mg/kg buspiron); *c*) group 3 (1 mg/kg buspiron), *d*) group 4 (5 mg/kg buspiron). Ordinate: the ratio of the incidence of correct instrumental reactions to their total number, % (p=0.05).

Clinically [8] buspiron and its analogs hepiron and insaperon exert no negative effects on the cognitive capacity, this permitting us to consider them as optimal tranquilizers. The spectrum of buspiron effects is similar to that of the day-time tranquilizers, because it possesses no soporific and sedative activities. According to the EEG data, the drug in doses of 5-10 mg/kg acts as a nonsedative anxiolytic [1]. Under conditions of a classical conflict situation, buspiron in doses of 2.5-5.0 mg/kg facilitates drinking behavior of rats as effectively as diazepam [10]. In a dose of 3 mg/kg the drug suppresses the development of conditioned active avoidance reflex and prolongs the period of reaction development [9]. The influence of the drug on memory is ambiguous. It was reported that in a dose of 1 mg/kg buspiron impairs the reproduction of the choice

TABLE 1. Relationship between Training Process and Buspiron Dose ($M \pm m$)

Group	Number of animals with acquired helplessness	Number of trained animals	Number of instrumental reactions needed for training	Number of combinations needed for training
1	3	9	95.7±25.9	105.4±24.1
2	4	8	92.7±22.9	117.5±35.3
3	6	6	145.5±32.4	154.3±14.0
4	10	2	139.2±40.2	168.4±60.2

habit [11] or improves it [15]. These findings suggest that buspiron in different doses differently affects various components of conditioned reflex activity.

In our experiment the deterioration of training after higher doses of buspiron may be explained by a lower research activity, which was most pronounced in group 4 (Fig. 1). The deficiency of the information about the environment can be compensated by a higher research activity supported by an appropriate emotional strain. Research activity notably increases during transfer from constant to probable support (25 and 50%), as was shown in experiments on dogs. Further decrease of support probability (to 5 and 10%) does not stimulate research activity, but decreases it [4]. Emotional strain increases extremely, as evidenced by pronounced autonomic reactions (inadequately high conditioned reflectory changes in gastric motoricity, irregular cardiac and respiratory rhythms), behavioral deviations (avoidance of experimental chamber, whining, refusal from food, and muscular tremor).

"Optimal" emotional strain conducive to attaining the goal of a conditioned reflex act may be needed for training under conditions of indefinite environment. Low doses of buspiron decreasing the level of anxiety maintain the required emotional strain and adequate research activity. An increase in buspiron dose may decrease fear and anxiety and suppress the emotional state needed for a reflex formation, thus leading to the development of AH.

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