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PHARMACOLOGY

Effect of Amiridin and Piracetam on Memory Disturbances Induced by Experimental Stress

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The preparation amiridin was developed for the treatment of nervous and mental diseases [2,15]. In particular, it has proved highly effective in the treatment of senile dementia. However, experimental studies performed so far on the effects of amiridin on higher nervous activity have been confined to the methodology of passive avoidance [2,4]. The influence of the drug on more complex behavior has not yet been investigated.

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The present study was aimed at a comparative investigation of the effect of amiridin and piracetam on the formation of the avoidance response (AR) in the norm and after its functional impairment.

MATERIALS AND METHODS

The study was performed on 94 mongrel male rats with a body weight of 180-220 g in 4 series of experiments. In each series 3 groups of animals were used. Animals of group 1 received amiridin injections (1 mg/kg), while those of the second group received piracetam injections (300 μg/kg). The preparations

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were administered intraperitoneally 30 min before the experiment in a 0.9% isotonic NaCl solution (1 ml per 100 g body weight). The equivalent volume of isotonic solution was injected into the animals of the control group. In series I of the experiments, group 1 consisted of 10 rats, group 2 of 8 rats, and group 3 of 10 animals. The avoidance response was developed in all animals in a shuttle box over 5 days with 25 daily presentations of the stimuli. Sound (10 sec) served as the conditioned stimulus and an electrical current (10 sec) was the unconditioned stimulus. As the animals passed from the first section of the box into the other one through a hole in the distal part of the partition, both stimuli were switched off. In the second series of experiments, group 1 included 6 rats and group 2 and 3 each included 8 animals. The AR was developed in all animals in the shuttle box over 6 days, as described above. After the 6th experiment, the hole in the distal part of the partition was closed and another hole at the opposite end of the partition was opened. The AR level was tested on the same day during 10 presentations of the stimuli. In series III, groups 1 and 2 contained 6 rats each and group 3 consisted of 8 animals. First, an AR was developed in all animals as described above. After the 6th experiment, a functional reversible impairment of the AR was achieved as earlier described [9]. According to this method, the response of the animals did not lead to the switching off of the stimuli: despite the relationships formed between the stimuli, response, and its consequences, the animals were shocked as they passed into the other section of the chamber (in all 5 times). After the 5th time, the current was switched off immediately and the sound 2 sec later. The position of the hole in the partition was changed on the same day and the AR level was tested. In series IV, group 1 contained 12 animals and group 2 and 3, 6 animals each. First, an AR was developed in all animals in a Skinner box over 7 days. The experiments were performed according to the standard methodology. Sound served as the conditioned stimulus, and an electrical current (10 sec) was added 5 sec later. The sound and the current were switched off when the lever situated in the distal third of the side wall was pressed. After the 7th experiment, the lever was installed in the proximal third of the wall and the AR was tested during 10 presentations of the stimuli. The experimental data were processed using the nonparametric Wilcoxson and Kolmogorov-Smirnov tests.

RESULTS

The experimental data provide evidence that neither amiridin nor piracetam promoted AR development in the first series of experiments. Analogous results were obtained in the series II and III. There are no indications in the literature concerning the effect of amiridin on AR formation in a shuttle box, while the neutral effect of piracetam observed in this study in good agreement with published data [5,6].

The switch of the hole position in the second series of experiments led to a marked impairment of the conditioned response. The AR was completely extinguished at the first presentation immediately after the switch; later on, in the blocks of presentations from the 2nd to the 5th and from the 6th to the 10th, restoration of the AR was observed, its rate being highest against the background of amiridin injections and lowest in the control animals. Analysis of the deliverance responses (DR) also reveals that disturbances were minimal after amiridin. In addition, when we changed the position of the hole, we registered a many-fold increase in the number of intersignal reactions, which points to an increase in pragmatic uncertainty and emotional tension [13].

As demonstrated, amiridin promoted AR transformation: motor reactions directed toward the former position of the hole faded more rapidly and became completely extinguished by the end of the experiment, while avoidance and deliverance responses were more rapidly established. Since the impairment of conditioned responses is used for assessing the flexibility (lability) of nervous processes [14], we conclude that amiridin improves this index. The same conclusion, though to a lesser extent, may be applied to piracetam.

As mentioned above, we did not register any positive effect of the preparations on the rate of AR formation in the third series of experiments. Combination of two stressogenic factors (impairment of the response and switch of the hole) in series III led to even more dramatic disturbances than those provoked by moving the hole. In the control group even DR disappeared at the first presentation of the stimuli; after presentations 2-5, the AR remained suppressed and only a few DR were observed. At the next stage of testing we registered 10% AR. The restoration of the conditioned response proceeded most rapidly and fully after amiridin pretreatment: following presentations 2-5 the AR level was 3.3 times higher than that against the background of piracetam.

Analysis of the experimental data allows us to trace the following correlation: the more pronounced the functional disturbance is, the better psychotropic effect the tested preparations exhibit.

Studies on AR formation in a Skinner box did not reveal any effect of the preparations. Transfer of the lever position induced disturbances of the conditioned response that were most marked in the control animals. In comparison with the control, in both experimental groups the fading of responses to the

former lever position as well as the formation of deliverance and avoidance responses proceeded statistically more rapidly.

What are the reasons for the observed positive effect of the preparations on memory disturbed by stress influences? In our opinion, two explanations may be offered.

Amiridin is known to be effective in the treatment of Alzheimer's disease [2], disturbances of memory, including spatial memory, being one of its major characteristics. Changes in the position of the hole and lever may serve as a test for assessing the effect of amiridin on the spatial component of memory. The preparation may influence either the durability (strength) of the formed memory trace or mastery of the new position. The first effect may be judged from the number of responses to the former position of the hole or lever immediately after it was changed, while the second effect may be assessed from the number of deliverance and avoidance responses. Both indexes proved significantly higher in the experimental animals than in the controls, indicating a positive effect of the preparations on spatial memory.

Why, then, did the preparations not promote AR formation in series I-III, even though the spatial orientation was undoubtedly significant under those conditions as well? We are inclined to believe that at the early stages of AR formation the contribution of the spatial memory component is not great, since connections must be established between the conditioned stimulus (sound and current; current, response, and switching off of current; sound and response, etc.) [8,16,17]. The specific share of the spatial memory component among others is rather small. However, after the position of the hole is changed, learning its new position becomes the primary requirement for solving the task, since all other established connections remain unchanged. Under such conditions the role of the spatial memory component acquires decisive significance and the preparations are given the possibility to exhibit their influence on it.

The change in the position of the hole or lever, like any change in the conditions of an experiment, is a stress factor which interferes with a formed conditioned response [1]. As is well known, nootropics enhance resistance to response impairment in rats [9-11]. As was described above, we also observed an increased emotional tension, especially in series III, which was significantly lower after pretreatment with the preparations, including amiridin.

Earlier, the effect of nootropics and tranquilizers (piracetam and phenazepam) were convincingly differentiated under conditions of disturbed deliverance response to a stress situation [12].

Although the accomplishment of this reaction is determined by both the emotional reactivity and ability to realize the integral act leading to deliverance, it was established that piracetam displays a unique ability to eliminate the injurious effect of cycloheximide.

It seems likely that the pharmacological activity of each of these preparations includes their ability to affact the spatial memory component as well as ability to increase resistance to stress.

Thus, the experiments performed did not reveal any positive effect of either amiridin or piracetam on AR development. However, both preparations did produce a positive effect on AR restoration after it was destroyed by functional stress influences. In this respect, amiridin proved more effective.

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