Antiaggressive Activity of Antibodies to S-100 Protein in Ultralow Doses

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Experiments on rats demonstrated antiaggressive activity of ultralow doses of antibodies to S-100 protein in tests of motivated and unmotivated aggression. The effect of ultralow doses of antibodies to S-100 protein in single and course treatment was not inferior to that of benzodiazepine anxiolytic diazepam.

Key Words: *aggression; anxiety; depression; antibodies to S-100 protein; ultralow doses*

The preparation containing ultralow doses (ULD) of antibodies to S-100 protein (ULD of anti-S100) exhibits both anxiolytic and antidepressant activities [3]. Clinical studies demonstrated the efficiency of ULD of anti-S100 (tenoten) in the treatment of anxious disorders [8]. The anxiolytic effect of ULD of anti-S100 is determined by GABA-agonistic effect of the preparation [4]. Moreover, GABA-B and serotoninergic systems participate in the realization of anxiolytic and antidepressant effects of ULD of anti-S100 [6,7]. Thus, the mechanisms underlying the effects of ULD of anti-S100 are mediated by the influence of the preparation on GABA- and serotoninergic systems, which determines the presence of anxiolytic and antidepressant properties in the spectrum of its pharmacological activity.

Aggression is a result of chronic stress and often accompanies anxious and depressive disorders. The spectrum of pharmacological activities of anxiolytic and antidepressant preparations often includes antiaggressive effect. Thus, GABAergic (benzodiazepine anxiolytics) and serotoninergic (buspirone) preparations exhibit antiaggressive activity [1,9].

Here we studied possible antiaggressive effects of ULD of anti-S100.

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MATERIALS AND METHODS

Experiments were carried out on 120 outbred albino male rats weighing 200-250 g. ULD of anti-S100 in a dose of 2.5 ml/kg, diazepam (Polfa) in a dose of 5 mg/kg, and distilled water in a volume of 2.5 ml/kg were intragastrically administered once 40 min before testing or 2 times a day for 4 days (9.00 and 17.00, last dose was given 40 min before testing). One half of rats in each group were tested in the test with unmotivated aggression (UA), and the rest rats were tested in the test with motivated aggression (MA).

In the UA test, the threshold of aggressive reaction of two rats on an electrode floor was measured by gradually increasing the stimulating voltage according to Manual on Experimental (Preclinical) Study of New Pharmacological Substances (2005) [5].

Two rats were placed in a standard perspex chamber (27.5×27.5×40 cm) with electrode floor and alternating current of increasing voltage (starting from 15 V) was delivered to the floor (3-sec stimulations with 1-sec intervals). If no aggressive reaction appeared after presentation of 3 stimuli of the same intensity, the voltage was increased by 1 V and the stimulation was continued until the development of aggression in response to not less than 3 stimuli of the same intensity. This voltage was considered as the threshold

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voltage. Rat behavior when they stood up on their hind paws face to face and tried to bite and to strike each other with their fore and hind paws was considered as the aggressive reaction. The antiaggressive effects of the preparations were evaluated by the increase in the threshold of aggressive reaction.

In the MA test, the intensity of aggressive reaction in two rats caused by their attempts to avoid punishments on a narrow safe bench was studied [2]. The experiment was carried in two stages. On day 1, the rats were trained to avoid painful stimulation (conditioning). To this end, they were trained to jump on the safe bench placed in the center of the chamber with electrode floor. The rat was placed in the chamber and after 5-min adaptation 3-sec pulses of alternating current (35 V) were delivered to the electrode floor with 1-sec intervals. After successful avoidance, the rat was allowed to stay on the bench for 30 sec and then was returned to the home cage; the procedure was repeated after 2 min. Training was stopped after attaining learning criterion (100% avoidance with a latency <10 sec). On the next day, the rats in pairs were placed in the chamber and their behavior was observed for 2 min. The control animals started fighting for the safe bench (the size of the bench was enough for 2 rats). After administration of the preparations with antiaggressive effect, the rats sat together on the safe bench. The effect was assessed by the time of co-avoidance.

The significance of differences between the groups was evaluated using Student *t* test.

RESULTS

In the UA test, ULD of anti-S100 exhibited antiaggressive properties in both single and course treatment. The effect of the preparation did not depend on the duration of treatment and was not inferior to diazepam. For instance, the threshold of aggressive reaction increased by 23.1% ($p<0.05$ compared to the control) after single administration of ULD of anti-S100 and by 34.9% ($p<0.05$ compared to the control) after 4-day treatment, while diazepam increased the threshold of aggressive reaction by 26.3 и 31.3% ($p<0.05$), respectively (Fig. 1).

In the MA test, ULD of anti-S100 also exhibited pronounced antiaggressive activity. The time of co-avoidance increased by 3.4 times ($p<0.05$ compared to the control) after single administration of ULD of anti-S100, while the reference preparation diazepam increased this parameter by 3.1 times ($p<0.05$ compared to the control). Course treatment with the preparations increased the time of co-avoidance by 3.8 and 3.3 times, respectively ($p<0.05$ compared to the control, Fig. 2). The antiaggressive effect of diazepam was not inferior to that of ULD of anti-S100.

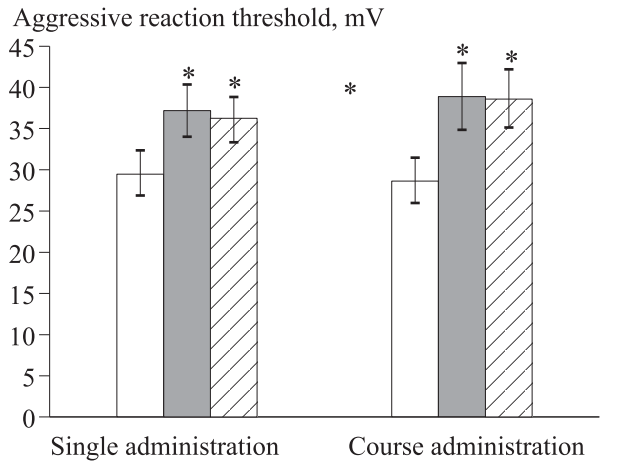

Fig. 1. Antiaggressive effect of ULD of anti-S100 and diazepam in UA test. Here and on Fig. 2: Open bars: control; dark bars: diazepam; hatched bars: ULD of anti-S100. *$p<0.05$ compared to the control.

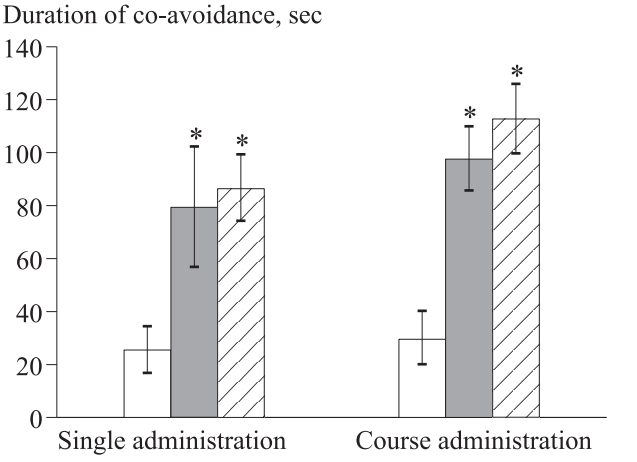

Fig. 2. Antiaggressive effect of ULD of anti-S100 and diazepam in MA test.

Thus, our study demonstrated antiaggressive activity of ULD of anti-S100 in tests with MA and UA. The presence of the antiaggressive effect in the spectrum of pharmacological activity of the preparation is probably determined by its influence on the GABA-ergic and serotoninergic neurotransmitter systems.

REFERENCES

1. N. P. Bondar' and N. N. Kudryavtseva, *Neirofarmakologiya*, **66**, No. 4, 12-16 (2003).
2. Yu. V. Burov and R. M. Salimov, *Byull. Eksp. Biol. Med.*, **81**, No. 5, 64-67 (1976).
3. T. A. Voronina, O. I. Epshtein, G. M. Molodavkin, *et al., Radioekologiya*, **43**, No. 3, 291-293 (2003).
4. T. A. Voronina, G. M. Molodavkin, S. A. Sergeeva, and O. I. Epshtein, *Byull. Eksp. Biol. Med.*, Suppl. 1, 37-39 (2003).

5. *Manual on Experimental (Preclinical) Study of New Pharmacological Substances*. Ed. R. U. Khabriev [in Russian], Moscow (2005).
6. I. A. Kheyfets, Yu. L. Dugina, T. A. Voronina, *et al., Byull. Eksp. Biol. Med.*, **143**, No. 5, 535-537 (2007).
7. I. A. Kheyfets, G. M. Molodavkin, T. A. Voronina, *et al., Ibid.*, **145**, No. 5, 552-554 (2008).
8. O. I. Epshtein, *Ultralow Doses (A History of One Investigation)* [in Russian], Moscow (2008).
9. F. Humble and M. Berk, *Hum. Psychopharmacol.* **18**, No. 6, 423-436 (2003).