Antidepressant Properties of Antibodies to Serotonin, Brain-Specific S100 Protein, and Delta Sleep-Inducing Peptide

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Potentiated antibodies to delta sleep-inducing peptide and S100 protein produced an antidepressant effect in Wistar rats. This effect was more pronounced after combined treatment with these antibodies. It can be assumed that these antibodies modulate neurobiological mechanisms of positive emotional reinforcement and, therefore, affect the resistance to depression associated with psychoemotional stress.

Key Words: *antidepressant activity; ultralow doses; antibodies; delta sleep-inducing peptide; S100 protein; behavior*

Medical and biological studies of mechanisms underlying the influence of potentiated substances (ultralow doses obtained using homeopathic potentiation technique) on humans and animals at the informational level are a perspective and important trend in modern medicine. The informational principle is widely used in various fields of science and technology. In modern physiology and medicine, considerable attention is given to studies of nature at the supramolecular (informational) level. Information provides the basis for self-organization and self-regulation of vital activity [1,9,13].

Published data show that antidepressant drugs affect the central nervous mechanisms involved in evaluation of environmental factors and formation of purposeful behavior [5]. A key role in the organization of this behavior is played by reinforcement mechanisms [7]. Activation of neuromolecular engrams after previous reinforcements is realized via motivations associated with the dominant need [6]. Substances with antidepressant activity are involved in the mechanisms of reinforcement (award) [8]. The brain mechanism of reinforcement depends on the interaction between emotional, motivational, and memory components [12]. Functional activity of various components of the brain reinforcement systems and antidepressant properties of pharmacological agents can be evaluated in some behavioral paradigms (*e.g.*, place preference test and reaction of self-stimulation) [10,11,14].

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In the present work antidepressant activity of potentiated antibodies to delta sleep-inducing peptide (AB-DSIP), brain-specific S100 protein (AB-S100), and 5-hydroxytryptamine (AB-HT) administered perorally to rats was evaluated by their positive reinforcing effect.

MATERIALS AND METHODS

Experiments were performed on 80 male outbred rats weighing 180-200 g and obtained from the Central Nursery of Laboratory Animals (Andreevka, Moscow region). The animals were adapted to vivarium conditions at the P. K. Anokhin Institute of Normal Physiology for 7 days. Emotional status was evaluated using the open-field test. To this end the following parameters were recorded: the latency of the first movement, latency of entry into the center of the open field, number of crossed peripheral and central squares, number of peripheral and central rearing postures, exploratory activity (exploration of holes), time of grooming, and defecation rate (parameter characterizing the balance between the sympathetic and parasympathetic systems). Tests were performed at 10.00-13.00 to minimize the effect of circadian rhythms on animal behavior [4].

The open field was a round area (diameter 90 cm) with 40-cm walls illuminated with a 100 W lamp. The area was divided into 37 squares. Locomotor activity in the open field was recorded using a computer (Open Field software). The index of activity was calculated for each rat by the formula N/t_1+t_2, where N is the number of squares crossed over 3 min; and t_1 and t_2

0007-4888/03/supp-0023$25.00

are latencies of the 1st and 2nd crossings, respectively. Depending on the index of activity, the rats were active, ambivalent, and passive.

Highly and low active rats (index of activity above 3.75 and below 0.25) were excluded from the experiment. Further experiments were performed only on animals that were intermediate between the rats highly resistant and low resistant to emotional stress.

The rats were divided into 6 groups (12 animals each). Antidepressant and anxiolytic properties of AB-HT, AB-S100, and AB-DSIP were evaluated by animal behavior in the place preference test (time spent by rats in various compartments of a modified experimental chamber [4] and the total behavioral profile). The chamber consisted of start compartment, compartment with metal wire floor, and compartment with fiberglass floor. Electric current can be applied to wire floor when the rat entered this compartment. Electric current was selected individually for each animal (0.3-1.5 mA). The rats receiving electrical shock avoid the compartment with wire floor.

The rats were placed into the start compartment. The behavior and time spent in each compartment of the chamber were recorded for 10 min. Three rats were simultaneously monitored in three identical individual chambers. On days 1-5 of the experiment all rats received 20 µl H_2O and the baseline behavioral parameters were recorded. Various compounds were administered on day 6 (the animal was kept 10 min the nonpreferred compartment) and on days 7-11 (before placing into the start compartment). The animals received 20 µl AB-DSIP (control group), 20 µl AB-S100 (group 2), 20 µl AB-HT (group 3), 40 µl amitriptyline (Lechiva, group 4 [2]), or 20 µl of AB-DSIP+AB-S100 mixture (1:1, group 5). The behavioral profile of rats was estimated by the ratio between exploratory, comfort, passive defense, and other types of behavior.

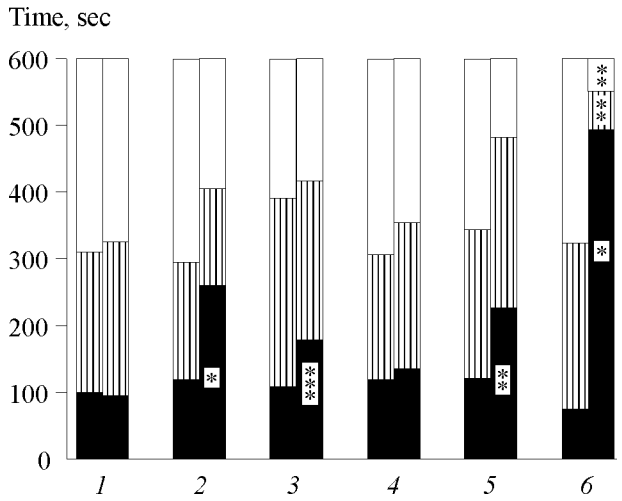

Fig. 1. Effects of distilled water (*1*), antibodies to delta sleep-inducing peptide (*2*), S100 protein (*3*), and 5-hydroxytryptamine (*4*), amitriptyline (5), and mixture of antibodies to delta sleep-inducing peptide and S100 protein (*6*) on the time spent in a nonpreferred compartment. Light bar: preferred compartment; shaded bar: start compartment; dark bar: nonpreferred compartment. Left and right parts: before and after administration of the compound, respectively. *p<0.001, **p<0.01, and ***p<0.05 compared to animals before treatment.

RESULTS

Peroral administration of antibodies in a dose of 20 µl produced specific changes in rat behavior in the place preference test (Fig. 1) Distilled water did not modulate behavioral parameters.

AB-DSIP changed the preferred place in 7 of 12 rats (58%, p<0.001, Fig. 2). It should be emphasized that in rats receiving AB-DSIP the mean duration of grooming increased more than by 25-30% compared to the control (Fig. 2, *a*).

AB-S100 produced similar, but less pronounced changes (Fig. 2). The preparation changed place pre-

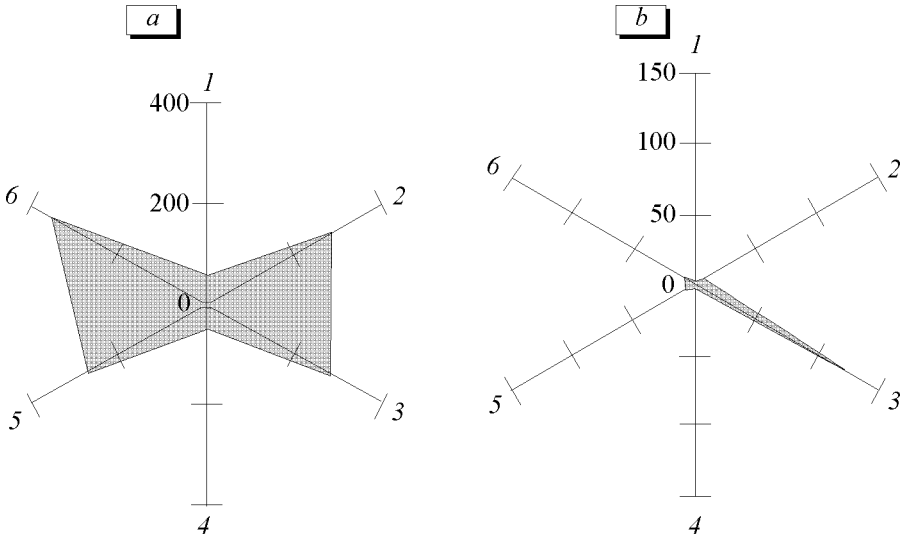

Fig. 2. Effects of distilled water (*1*), antibodies to delta sleep-inducing peptide (*2*), S100 protein (*3*), and 5-hydroxytryptamine (*4*), amitriptyline (5), and mixture of antibodies to delta sleep-inducing peptide and S100 protein (*6*) on the duration of comfort behavior (*a*) and sexual grooming (*b*). Ordinate: time, sec.

ference in 9 of 12 rats (75%). AB-S100 not only increased the duration of grooming (similarly to AB-DSIP), but also induced the appearance of sexual grooming. This type of behavior took 50% of the total duration of grooming (Figs. 2, *a*, *b*).

Administration of AB-HT changed behavioral characteristics and place preference in the experimental chamber in none of 12 rats (Fig. 1). The animals were inert and sleepy.

Amitriptyline changed place preference in 75% rats (Fig. 1). Animal behavior in this group was similar to that observed after AB-S100 administration (except sexual component of grooming, Fig. 2).

The mixture of AB-DSIP and AB-S100 changed the behavioral profile in 11 of 12 rats (91.7%). We revealed significant changes in the place preference and time spent in various compartments of the chamber (Fig. 1). The duration of comfort behavior increased by 25% (Fig. 2). Therefore, the mixture of these antibodies produced a positive reinforcing effect.

Our results show that antibodies in ultralow doses possess high physiological activity at the behavioral level. Changes observed after peroral administration of AB-DSIP and AB-S100 were similar to those produced by antidepressant amitriptyline, which attested to antidepressant activity of the test preparations [9-13]. However, in our experiments AB-HT produced no antidepressant effect.

Antidepressant activity of the AB-DSIP and AB-S100 mixture surpassed that of individual preparations and amitriptyline, which attested to mutual potentiation of their effects.

Our results and published data indicate that potentiated AB-DSIP and AB-S100 possess antidepressant properties. Probably, these antibodies modulate the neurobiological mechanism of positive emotional reinforcement and affect the resistance to depression associated with psychoemotional stress.

AB-DSIP, AB-S100, and their mixture hold much promise for the use in clinical practice.

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