Effect of Interleukin-1β on the Behavior of Rats during Mild Stress in the Open-Field Test

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Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 148, No. 11, pp. 488-490, November, 2009
Original article submitted July 13, 2009

We studied the effect of interleukin-1β on the behavior of rats with different individual typological characteristics during mild stress in the open-field test. Intraperitoneal injection of interleukin-1β (5 μg/kg, 108 U/mg) was followed by a decrease in orientation and exploratory activity of passive and, particularly, of active animals in the open field. As differentiated from rats receiving physiological saline, the initial differences in behavioral characteristics of active and passive animals were not revealed in the repeated test after injection of interleukin-1β. We conclude that interleukin-1β abolishes the behavioral differences between active and passive specimens in the open field. These data suggest that administration of interleukin-1β to rats leads to reorganization of the mechanisms for emotional evaluation of adverse emotiogenic factors under conditions of mild stress in the open-field test.

Key Words: *interleukin-1β; active and passive rats; behavior; mild stress; open-field test*

The open-field test is extensively used for evaluation of animal resistance to emotional stress before conflict situation [9]. Activity of rats in the open field is a reliable prognostic criterion for the resistance of animals to stress exposure [3]. Behaviorally active rats are more resistant to adverse consequences of emotional stress than passive specimens.

Many investigators believe that open field testing is a mild stress for rats [7,13-15]. According to some reports, open-field testing of animals is followed by changes typical of the stress response. They include an increase in the number of c-Fos-positive cells in brain structures [11], decrease in the cytotoxicity of natural killer cells in the blood and spleen [15], elevation of blood pressure and heart rate [13], and hyperthermia [10,12].

Previous studies showed that immunomodulatory compounds play a role in the formation of biological motivations and emotional reactions (main components in the systemic organization of human and animal behavior) [6]. Special attention is paid to interleukin-1β (IL-1β), one of the major triggers of a cascade of immune processes in the organism [2]. IL-1 has at least 50 biological functions. The cells of nearly all organs and tissues serve as the target for this compound. A large body of evidence exists that IL-1β is involved in the pathogenesis of emotional stress in mammals [8]. IL-1β produces a specific effect on the cytokine profile of blood serum [5] and functional state of lymphoid structures in the gastrointestinal tract of active and passive rats under stress conditions [1]. Hence, this cytokine plays a particular role in the stress response in animals with different emotional reactivity.

Here we studied the effect of IL-1β on the behavior of rats with various individual typological characteristics during mild stress in the open field test.

MATERIALS AND METHODS

Experiments were performed on 85 male Wistar rats weighing 346.8±4.1 g. The animals were housed in cages (4-5 specimens per cage) at 20-22°C and artifi-

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0007-4888/09/1485-0735

cial light/dark cycle (8.00-20.00, lightness; 20.00-8.00, darkness). They had free access to water and food. The animals were adapted to laboratory conditions for 5 days after delivery to the laboratory. The experiment was conducted in accordance with the "Rules of Studies on Experimental Animals" (approved by the Ethics Committee of the P. K. Anokhin Institute of Normal Physiology; protocol No. 1, 3.09.2005), requirements of the World Society for the Protection of Animals (WSPA), and European Convention for the Protection of Experimental Animals.

Individual typological characteristics of rats were evaluated in the first session of the open field test over 3 min [3]. The open field was a round area (90 cm in diameter) surrounded by walls (40 cm in height). There were 8 vertical bars (13 cm in height) on the floor. The area was divided into 19 central squares and 18 peripheral squares. It was illuminated with a 100 W lamp. To calculate the index of activity, the sum of crossed peripheral and central squares, peripheral and central rearing postures, and explored objects was divided by the sum of the latency of the first movement and entry into the center of the open field.

Depending on the initial behavior in the open-field test, the animals were divided into groups of active (n=35), passive (n=23), and intermediate specimens (n=27). These animals differed in the mean index of activity: passive rats, 0.51±0.04; intermediate rats, 1.35±0.07; and active rats, 4.12±0.49. Further experiments were performed on active and passive animals with the "extreme" patterns of behavioral activity.

The effect of IL-1β on behavioral characteristic of rats during mild stress in the open field was studied on day 30 after the first test. IL-1β in a dose of 5 μg/kg (activity 10^8 U/mg) was dissolved in 1 ml sterile physiological saline. Physiological saline (1 ml) or IL-1β was injected intraperitoneally 1 h before the repeated session in the open field. The animals were divided into the following 4 groups: group 1, active rats receiving physiological saline (n=15); group 2, active rats receiving IL-1β (n=20); group 3, passive rats receiving physiological saline (n=10); and group 4, passive rats receiving IL-1β (n=13). Human recombinant IL-1β was obtained from the State Research Institute of Highly Pure Biopreparations (Federal Medical and Biological Agency of Russia).

The significance of between-group differences was evaluated by nonparametric Mann–Whitney test. The data are presented as M±m.

RESULTS

During the first session in the open field, the activity index of behaviorally active rats was 8.08-fold higher than that of passive animals (4.12±0.49 and 0.51±0.04, respectively, p<0.01; Fig. 1).

The activity index of active rats receiving physiological saline was shown to decrease during the repeated open-field testing (by 3.01 times compared to the baseline, 1.37±0.46, p<0.05). These changes were not observed in behaviorally passive animals of the corresponding group (activity index 0.55±0.22).

Administration of IL-1β was followed by a significant decrease in the open-field behavior of rats. The index of behavioral activity during the repeated session was reduced in passive (by 2.04 times, 0.25±0.06, p<0.05) and, particularly, in active rats receiving IL-1β (by 12.87 times, 0.32±0.12, p<0.01). After injection of IL-1β, the activity index of active (p<0.05) and passive rats was much lower than that of animals receiving physiological saline (by 4.28 and 2.20 times, respectively).

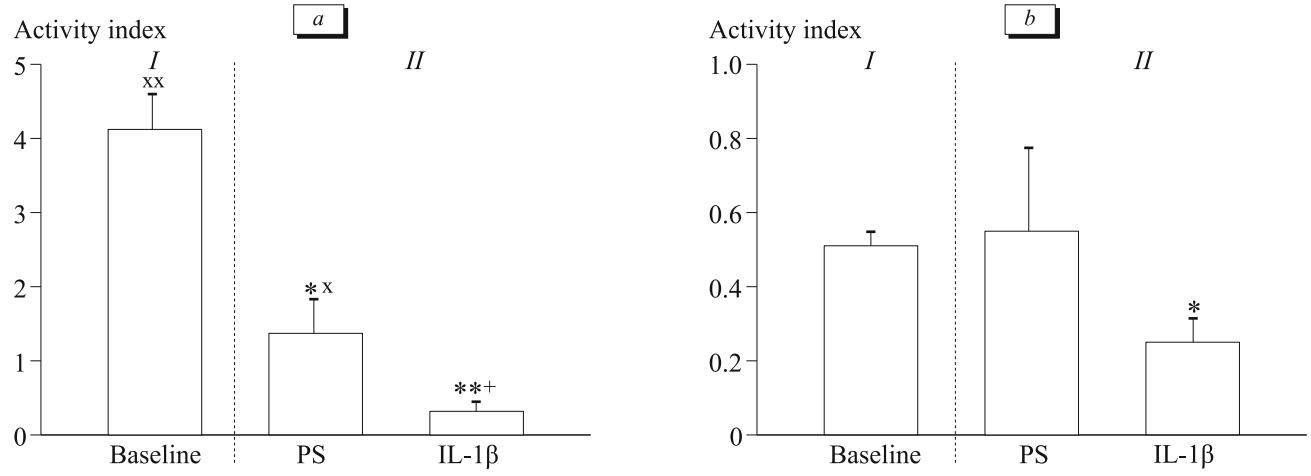

Fig. 1. Behavior of active (*a*) and passive rats (*b*) during the first (*I*) and repeated test (*II*) in the open field after single injection of physiological saline (PS) or IL-1β. *p<0.05 and **p<0.01 compared to the first test; ^{+}p<0.05 compared to physiological saline; ^{x}p<0.05 and ^{xx}p<0.01 compared to passive rats.

The decrease in locomotor activity of rats during repeated open-field test reflects natural extinction of orientation and exploratory behavior, which is highest in a novel environment. The observed changes can be associated with repeated exposure of animals to stressogenic factors (bright light, reduced freedom of movement, *etc*.) under these conditions. The initial differences in behavioral characteristics of active and passive specimens were also observed during the repeated session in the open field.

Our findings are consistent with the results of behavioral experiments with rats under conditions of the natural light/dark cycle [4]. As differentiated from passive animals, the total locomotor activity of active rats was significantly reduced in the repeated open-field test during the daytime period (14th day after the first test).

We showed that IL-1β produces various effects on rats with different behavioral patterns during mild stress in the open field. The decrease in locomotor activity after injection of IL-1β was more pronounced in active animals than in passive specimens. As differentiated from rats receiving physiological saline, the initial differences in behavioral characteristics of active and passive animals were not revealed in the repeated test after IL-1β injection. We conclude that IL-1β abolishes the intergroup behavioral differences between active and passive specimens in the open field.

The results of our study and published data suggest that administration of IL-1β to rats is followed by reorganization of the mechanisms of emotional evaluation of adverse emotiogenic factors under conditions of mild stress in the open field test. In particular, it is manifested in a decrease in orientation and exploratory activity of animals in the open field.

This work was supported by the grant of the President of Russian Federation for Support of Leading Scientific Schools of Russian Federation (grant No. NSh-3232.2008.4).

REFERENCES

1. E. A. Ivanova, S. S. Pertsov, E. V. Koplik, and A. S. Simbirtsev, *Byull. Eksp. Biol. Med.*, **140**, No. 10, 377-382 (2009).
2. S. A. Ketlinskii and A. S. Simbirtsev, *Cytokines* [in Russian], St. Petersburg (2008).
3. E. V. Koplik, *Vestn. Nov. Med. Tekhnol.*, **9**, No. 1, 16-18 (2002).
4. S. S. Pertsov, *Ros. Fiziol. Zh.*, **91**, No. 7, 802-809 (2005).
5. S. S. Pertsov, E. V. Koplik, V. L. Stepanyuk, and A. S. Simbirtsev, *Byull. Eksp. Biol. Med.*, **148**, No. 8, 161-165 (2009).
6. K. V. Sudakov, *Individual Resistance to Emotional Stress* [in Russian], Moscow (1998).
7. A. E. Baum, L. C. Solberg, G. A. Churchill, *et al.*, *Behav. Brain Res.*, **169**, No. 2, 220-230 (2006).
8. A. Gadek-Michalska, A. J. Bugajski, and J. Bugajski, *J. Physiol. Pharmacol.*, **59**, No. 3, 563-575 (2008).
9. C. S. Hall, *J. Comp. Physiol.*, **18**, 385-403 (1934).
10. P. Johnson Rowsey, Y. L. Yang, and C. J. Gordon, *J. Appl. Physiol.*, **92**, No. 2, 789-794 (2002).
11. I. Klejbor, B. Ludkiewicz, B. Domaradzka-Pytel, *et al.*, *J. Physiol. Pharmacol.*, **57**, No. 1, 149-164 (2006).
12. T. Oka, K. Oka, and T. Hori, *Psychosom. Med.*, **63**, No. 3, 476-486 (2001).
13. M. van den Buuse, *Stress*, **5**, No. 3, 227-231 (2002).
14. C. G. Van Reenen, N. E. O'Connell, J. T. Van der Werf, *et al.*, *Physiol. Behav.*, **85**, No. 5, 557-570 (2005).
15. D. Wrona, M. K. Jurkowski, and J. Tokarski, *J. Neuroimmunol.*, **150**, Nos. 1-2, 88-97 (2004).