Modifications of Behavioral Effects of Corticoliberin Injected into the Neostriatum by Corticosteroids

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Behavioral effects of corticotropin-releasing factor (CRF-41) injected into the neostriatum are described. These effects are associated with functional state of the hypophyseal-adrenocortical system. CRF-41 markedly decreases horizontal motor activity of rats in the open field test. This effect was abolished by hydrocortisone which blocks hypophyseal-adrenocortical system.

Key Words: *neostriatum; hypophyseal-adrenocortical system; behavior; corticoliberin*

Adequate behavioral reactions in response to changes in the environment are the major manifestation of adaptation. Stress hormones and neurohormones, primarily catecholamines and corticosteroids, play an important role in behavioral responses homeostasis maintenance [10,12]. It was demonstrated that corticoliberin (CL) [14] activates hypophyseal-adrenal system during stress, thus contributing to the formation of the adaptive behavior, and acts at the level of hypothalamus and extrahypothalamic structures [9].

Our interest into the effects of CL is motivated by the fact that CL acts via the neostriatum, which is involved in regulation of simple and complex behavioral reactions [1,8]. Extensive morphological connections of the neostriatum with limbic system and with hypothalamic neurosecretory centers [4] indicate that this structure is involved in neuroendocrine functions which are closely related to stress reaction.

This study is an attempt to characterize behavioral effects of CL injected into the neostriatum and to demonstrate a relationship between these effects and functional state of hypophyseal-adrenocortical system.

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MATERIALS AND METHODS

Experiments were performed on adult male Wistar rats (body weight 200-250 g) maintained on standard diet with free access to water. For several days the rats were habituated to handling in the laboratory, then cannulas were implanted into the neostriatum under Ketalar anesthesia according to the following coordinates: F 0.5 mm from the bregma, L 2 mm from sagittal suture, H 4.5 mm from the skull surface. At the end of experiment, position of the cannulas was verified histologically. Four days after the surgery, group 1 rats (control) were intraperitoneally injected with normal saline 24 h before microinjection of CL into the neostriatum. Group 2 rats were given hydrocortisone (5 mg/100 g body weight intraperitoneally). This dose blocks hypophyseal-adrenocortical system and prevents stress-induced release of corticosteroids [7]. Corticoliberin (CRF-41, Serva) or its solvent (normal saline) was injected into the neostriatum in a dose of 0.25 μg (volume 0.5 μl) bilaterally 24 h after administration of hydrocortisone, when its blocking effect mas maximal.

Behavioral reactions were analyzed in the open field test [3]. For this purpose we used the standard Hall chamber: rectangular cell with the floor divided into 36 squares. Four squares in the center were illuminated with a 100 W bulb, and other squares

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were considered peripheral. After intrastriatal injections, horizontal motor activity was assessed by the number of crossed squares and vertical motor activity by the number of rearings; the durations of snuffings and freezings within the first 5 min each minute and the on the 10th and 15th min were also recorded.

It should be noted that the rats were kept in Hall chamber for 15 min, which provided a more objective evaluation of CL effect by eliminating the stressor effect of new environment. Results were analyzed using the Mann—Whitney nonparametrical test.

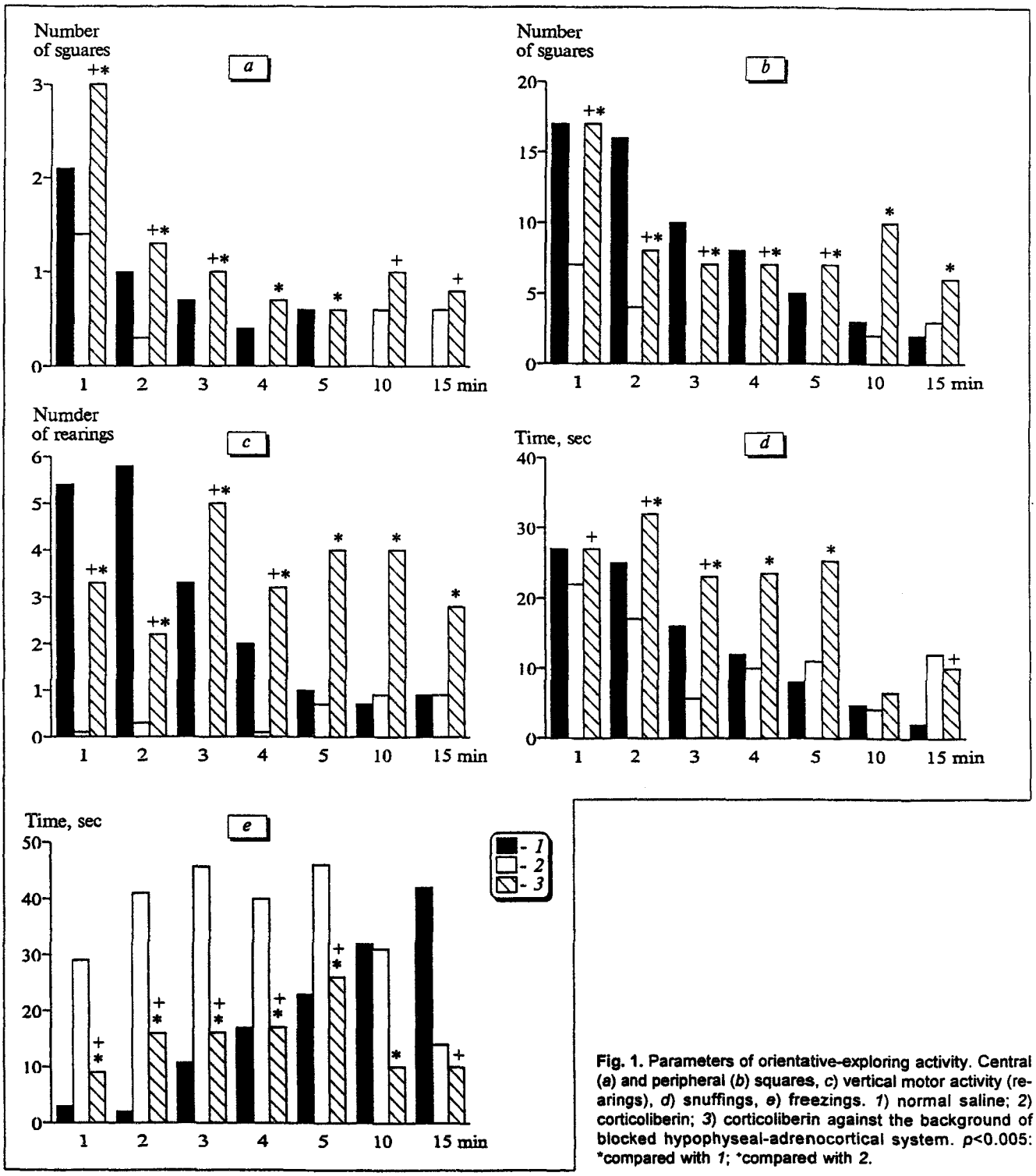

Fig. 1. Parameters of orientative-exploring activity. Central (*a*) and peripheral (*b*) squares, *c*) vertical motor activity (rearings), *d*) snuffings, *e*) freezings. *1*) normal saline; *2*) corticoliberin; *3*) corticoliberin against the background of blocked hypophyseal-adrenocortical system. $p<0.005$: *compared with *1*; +compared with *2*.

RESULTS

In control series, where normal saline was injected into the neostriatum before repeated placing of rat in the OF, we observed habituation to the environment: motor and exploring activities decreased by the end of testing (Fig. 1). This dynamics reflects normal behavior of rats in changed environment.

Microinjections of CL into the neostriatum strongly inhibited horizontal and vertical activities and markedly prolonged freezing periods in the beginning of test. The animals exhibited exploring activity between the 10th and 15th min of experiment (Fig. 1).

This suggests that CL suppresses orienting and exploring behavior and does not accelerate habituation. Freezing is a species-specific reaction of rodents and is induced by strong, potentially dangerous stimuli. Presumably, CL simulates these stimuli, particularly against the background of preceding stress caused by new environment. Bearing in mind the crucial role of the nigrostriatum system in the regulation of adaptive behavior [4,8] and the fact that the effect of CL is realized via the neostriatum, it can be hypothesized that CL plays an important role in the development of freezing. Since freezing reflects anxiety, it can be suggested that anxiogenic effect of CL, which always occurs in emotional stress, is realized at the level of neostriatum.

To check up this hypothesis, in the second series of experiments CL was injected into the neostriatum of rats in which hormonal stress reaction induced by new environment was blocked by hydrocortisone. In contrast to hydrocortisone-untreated rats, exploring activity of rats with blocked hypophyseal-adrenocortical system was increased and markedly surpassed that of control animals. Even by the 15th min in the OP no signs of habituation were observed: the behavior of rats was the same as in the beginning of test (Fig. 1).

Thus, it can be suggested that CL increases anxiety in animals if they respond to new environment by stress reaction with the release of corticosteroid hormones into circulation. If this reaction cannot develop due to blockade of hypophyseal-adrenocorticotropic system, the effect of CL is not realized and its anxiogenic activity is not exhibited. This may be explained by the fact that corticosteroids may change the functional state of neostriatal neurons, judging from the presence of receptors for corticosteroid hormones in the striatum [2,5]. We have shown that these receptors are located in the neostriatum on dopaminergic terminals [6] and may preterminally regulate the release of dopamine whose significance in adaptation has been well established.

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