Psychostimulant Effect of Synthetic Dermorphin Analog

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The effect of a dermorphin analog on learning was studied in a Wistar rat model of the complex food-seeking task. The preparation decreased the degree of anxiety in a dose-independent manner. In a dose of 50 μg/kg it increased the number of "well"-learning rats by intensifying the learning process in rats with initially suppressed cognitive activity. In a dose of 150 μg/kg, the opioid decreased the number of "well"-learning rats due to disturbance of motivation mechanisms, which was manifested in behavioral instability.

Key Words: *opioids; dermorphin analog; μ-receptors; psychostimulants; learning*

Extensive study of opioid peptides revealed a broad range of their effects on physiological systems as well as on emotion, memory, and learning [1,6, 13,14]. Therapeutic usage of neuropeptides stimulated the synthesis of a great variety of these peptides the analog of the endogenous opioid dermorphin among them. The study of biological activity of this preparation revealed its relation to peripheral and central opiate receptors [11]. There is evidence of high cholinolytic activity, participation in the metabolism of biogenic cerebral amines, and anti-alcoholic and morphine-like activities of this dermorphin analog [2-4]. Our aim was to study the effect of dermorphin synthetic analog on the learning of rats in an intricate problematic situation.

MATERIALS AND METHODS

Experiments were carried out on male Wistar rats with an initial weight of 200-220 g. The dermorphin analog H-Tyr-D-Ala-Phe-D-Ala-Tyr-Pro-Ser-NH-CH_3 was synthesized at the Laboratory of Peptide Synthesis of the Cardiology Research Center by the classical method in a solution [12]. The preparation was injected intramuscularly in 0.5 ml physiological saline (50 and 150 μg/kg) for 5 days prior to learning. The rats of the "active" control group were injected with physiological saline. Intact rats comprised the "passive" control group.

The zero level of psychic load was attributed to informative complexity of the medium in a "living room" (part of laboratory interior) where the rats could perform unrestrained motions for 3 h [7]. To simulate an increased psychic load, an original model was used which formed a complex instrumental task in the multichoice maze [10]. In the framework of this cognitive task a rat should occasionally leave the maze after reinforcement in it, then enter it again, and only in this case a new portion of food was placed into the feeding trough. The 13-min learning sessions were carried out daily according to the free choice method with a 22-h food deprivation. The recorded parameters were locomotor activity (LA, the number of crossed space zones per second, zone/sec), the number of entries into the maze, the number of reinforcements and errors, and the parameters of about twenty unconditioned reflexes subdivided into classes (*s*, orienting-exploratory; *z*, passive defensive; grooming, etc.). The portion of the reactions of each class (P_s, P_z) of the total number of all reactions exhibited by a rat during an experiment was calculated. Specially developed information analysis [5] was used to characterize the

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basic cognitive processes of perception, appraisal, and prediction. We considered perception as detection of 7 significant elements of the task, evaluation as finding the connections between them (42 semantic connections), and prediction as construction of the plan to solve the whole task. The intensity (I) of each process was calculated from the formula $I=100/N_t \times N_e$, where N_t is the number of trials at every stage, and N_e is the number of experiments.

RESULTS

Previously we showed that under the specified methodical conditions only 40% Wistar rats could solve the presented task, which were assigned to group of "well" learning (WL) animals [8,9,15]. Other 60% rats comprised the group of "badly" learning (BL) animals (Fig. 1). In these rats, the failure to learn was related predominantly to a low level of motivated excitement in them [8].

Injection of saline for 5 days increased the defensive component of behavior, which was manifested in a drastic decrease (by 2.3±1.4 times) in motor activity, domination of stupefaction reaction (P_Z=0.72±0.21), and inhibition of orienting-exploratory activity (P_S=0.21±0.11). It resulted in an increase of the number of BL rats to 80% (Fig. 2). Therefore, we used the intact rats for basic control.

Injection of dermorphin analog in the doses of 50 or 150 μg/kg significantly moderated the defense reactions due to possible analgesic effect of the preparation [2]. Its injection immediately caused prolonged (1-5 min) motoric inhibition, which was easily eliminated by biologically significant stimuli. This inhibition was replaced by normal activity under the "living room" conditions. After the 3rd injection of the opioid (50 μg/kg), its depressive effect was replaced by activation (LA_{mean}=0.8±0.3 p 6.3±1.8 zone/sec). The orienting-exploratory behavior was not accompanied by significant passive manifestations (P_S=0.64±0.22, P_Z=0.06±0.03). The depressive effect of the dermorphin analog (150 μg/kg) was observed during the entire period of injection (5 days), but the inhibitory phase was shorter (less than 1.7 min) during the repeated injections.

Different doses of the preparation induced diverse changes in the zoosocial structure of the group (10 rats). Initially, the population was composed of 30% dominant, 10% subdominant, and 60% subordinate rats. The zoosocial status is known to correlate with locomotor activity and the degree of space domination [8,15]. Injection of the opioid in a dose of 50 μg/kg changed the zoosocial structure of the population: the initially heterogeneous group

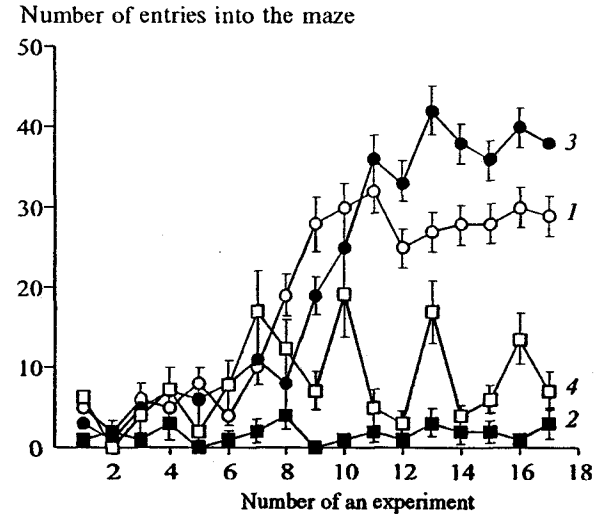

Fig. 1. Dynamics of learning in various experimental groups. Control: *1*) "well" and 2) "badly" learning rats. Experimental group: opioid dose *3*) 50 and *4*) 150 μg/kg.

(in respect of locomotor and exploratory activity) became homogeneous. The variation coefficient of the considered parameters was no more than 10.5% instead of 74.4% in the control: LA_{mean}=8.2±0.7 zone/sec instead of 5.1±4.5 zone/sec; portion of visited zones P_{zone}=0.89±0.9 instead of 0.530±31. When applied in the dose of 150 μg/kg, the drug increased the number of scarcely active rats to 90% (LA_{mean}=0.6±0.4 zone/sec, P_{zone}=0.15±0.04).

The drug-induced modification of free behavior was more pronounced in learning. Five 50 μg/kg doses of dermorphin analog drastically increased the number of WL rats (to 90%), while injection of the same preparation in a dose of 150 μg/kg decreased the fraction of such rats to 20% (Fig. 2). Irrespective of the dose, in all the rats the number of passive defense reactions in an unknown environment (P_Z= 0.12±0.05 as compared to P_Z=0.34±0.18 in control) decreased, while both locomotor and orienting-

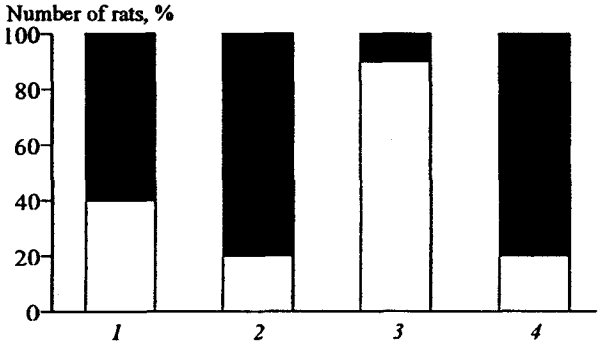

Fig. 2. The effect of the opioid on the ratio between the number of "well" (white bars) and "badly" (dark bars) learning rats. *1*) intact rats; *2*) injection of physiological saline ("active" control); *3*) opioid in the dose of 50 μg/kg; *4*) opioid in the dose of 150 μg/kg.

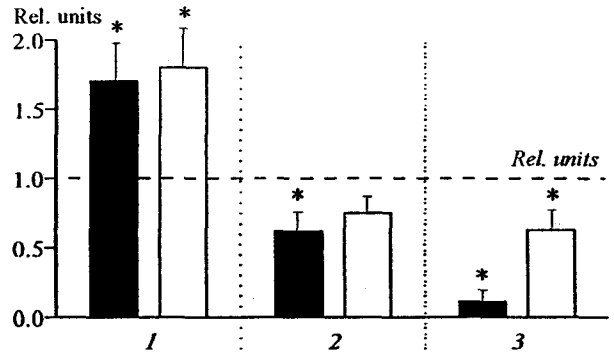

Fig. 3. Intensity of the processes of *1*) perceptive, 2) appraising, and 3) predictive activity of the rats in various experimental groups. White bars: opioid, 50 μg/kg; solid bars: 150 μg/kg. *$p<0.05$ in comparison with the control group.

exploratory activity increased in comparison with the control (LA_{mean}=6.1±1.1 zone/s; P_S=0.47±0.16 and LA_{mean}=3.4±2.1 zone/s; P_S=0.29±0.12, respectively).

The opioid changed significantly the character of cognitive activity, the direction of these changes being dose-dependent. The learning dynamics in the rats treated with 50 μg/kg was similar to that of WL rats in the control conditions (Fig. 1): to learn the task, the opioid-treated rats needed 99.3±19.8 trials and 9.7±3.2 sessions, while the corresponding values for the control rats were 79.7±14.1 trials and 7.8±2.4 sessions. However, the information analysis revealed a markedly incresed perception intensity in the "opioid" rats (Fig. 3), which at the same time had retarded appraising and predictive (generalizing) abilities. The dermorphin analog (150 μg/kg) provoked a highly unstable behavior which was maintained throughout the entire observation period (Fig. 1). Notwithstanding the higher (relative to the control) orienting-explorative activity (LA_{mean}=3.2±0.6 zone/sec; P_S=0.28±0.11 instead of LA_{mean}=0.2±0.1 zone/sec; P_S=0.12±0.3) and a decreased level of passive defense reactions (P_Z=0.21±0.09 instead of P_Z=0.68±0.18), the intensity of all cognitive processes in the opioid-treated rats was low. At 150 μg/kg, the preparation widened the gap between perception and subsequent generalization (i.e., appraisal and prediction): the informative perception was facilitated, while formation of the problem solution plan was significantly retarded (Fig. 3). Similar to the rats injected with 50 μg, these rats went to the feeding troughs rather quickly and demonstrated a reliable learning of the task as early as in the 3rd session. However, in contrast to the rats treated with a low opioid dose the food-seeking behavior in these experiments was not formed (20 sessions).

The observed psychostimulant effect of synthetic dermorphin analog was clearly dose-depending. The small dose (50 μg/kg) decreased anxiety and intensified the cognitive processes in the rats with initially decreased motivated excitement (BL rats). Application of the opioid in a dose of 150 μg/kg caused a mismatch between the intensity of cognitive processes and activity of physiological and biochemical substrate underlying these processes, which was manifested in behavior as a marked instability, disturbance in the motivation status, and the lack of self-organization.

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