ACTION OF SOME PSYCHOSTIMULANTS ON LEARNING AND MEMORY IN RATS

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UDC 615.214+615.276.4.015.4:
612.821.1/3

KEY WORDS: psychostimulants; centrophenoxin; TP-1; learning; memory.

Previous investigations have shown that tuftsin (Thr-Lys-Pro-Arg tetrapeptide) and its analog TP-1 have a stimulating action on investigative behavior of animals [1, 2, 5, 6]. We also know that orienting-investigative reactions of animals are the beginning of adaptive goal-directed behavior, a higher form of which is conditioned-reflex activity [3]. The level of investigative activity in an open field has been shown to correlate clssely with the ability of animals to learn [4, 7, 8], and administration of CNS stimulants to the animals before the beginning of learning significantly increases the stability of the skill formed [9, 10].

The aim of the present investigation was a comparative study of the effects of psychostimulants, namely centrophenoxin and the new peptide compound TP-1 (synthesized at the Institute of Molecular Genetics, Academy of Sciences of the USSR, in the Laboratory of Biopolymer Synthesis, Head of Laboratory V. N. Nezovibat'ko) on the processes of formation and preservation of a conditioned-reflex food-getting motor response (CRFMR) formed in animals in the course of a single experimental session.

EXPERIMENTAL METHOD

Experiments were carried out on 15 male Wistar rats divided into three groups, with five rats in each group. The animals were trained in the course of one experimental session, consisting of 30 separate training exercises in a chamber (150 × 16 × 23 cm), divided into three compartments: start, neutral, and target. Photoelectric cells were mounted in the walls of the chamber between the compartments, to record the time spent by the animals in each compartment. A CRFMR was formed in the animals placed in the start chamber, in response to opening of the door and initiating going into the target compartment and pressing on a shelf with the forelimbs. The maximal duration of the response during training was 90 sec. If during this time the animal did not respond independently, it was considered to be faulty. Preservation of the skill was tested after 24 h, 7 days, and 1 month: in these experiments the rats were able to make 20-10 visits, each lasting not more than 30 sec. The substances were injected into the animals in a single dose during training after the first 10 training exercises. Rats of control group 1 were given an injection of 0.5 ml of physiological saline, and their training was resumed 15 min later. Rats of group 2 were given an injection of PT-1 (300 μg/kg intraperitoneally), and their training also was resumed 15 min later. Rats of group 3 were given an injection of centrophenoxin (50 mg/kg, intraperitoneally), and their training was resumed 30 min later.

During analysis of the animals' learning and memory attention was paid to the average time of performance of the CRFMR, the number of mistakes, and the ratio (in %) between the number of conditioned-reflex and mistaken responses. The experimental results were subjected to statistical analysis by Student's t test.

EXPERIMENTAL RESULTS

According to the initial parameters of learning recorded before injection of the substances, there was no difference between animals of the control and experimental groups. Injection of TP-1 or centrophenoxin was accompanied by shortening of the fully developed response performance time and reduction of the number of mistaken responses. The effect of

Institute of Biological Physics, Academy of Sciences of the USSR, Pushchino. Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 106, No. 8, pp. 161-163, August, 1988. Original article submitted July 21, 1987.

0007-4888/88/0008-1099$12.50

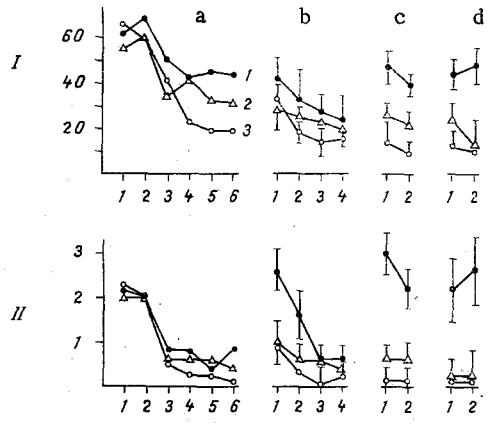

Fig. 1

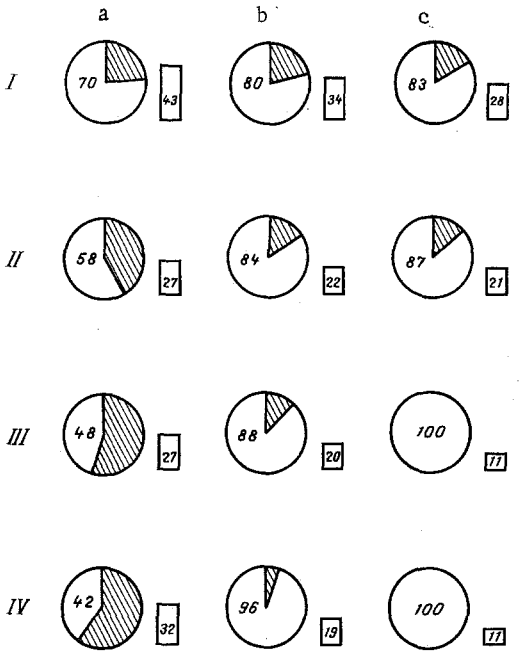

Fig. 2

Fig. 1. Characteristics of formation (a) and preservation of CRFMR in animals of control and experimental groups and its preservation after 1 (b), 7 (c), and 30 days (d) CRFMR found in control and experimental animals. Abscissa, consecutive numbers of sets of five visits; ordinate: I) mean response performance time (in sec) and standard error of mean; II) number of mistaken responses, averaged for five visits. 1) Control group; 2) animals receiving TP-1; 3) animals receiving centrophenoxin. Arrow indicates time of injection of substance.

Fig. 2. Ratio between numbers of conditioned-reflex and mistaken response (in %) during training and testing of skill preservation after 24 h and 7 and 30 days, in control rats (a) and rats receiving TP-1 (b) or centrophenoxin (c). In pie charts: unshaded part represents number of conditioned-reflex responses (in % of total number of training exercises), shaded part represents mistaken response. Average conditioned reflex performance time (in sets) indicated in columns. I) Training; II, III, IV) testing after 1, 7, and 30 days, respectively.

TP-1 on skill formation, incidentally, was weaker than that of centrophenoxin and was exhibited only as a tendency (Fig. 1a).

When preservation of the response was tested after 24 h statistically significant differences were found between animals of the control and experimental groups, especially during performance of the first 10 visits (Fig. 1b). For instance, whereas the response performance time in animals of the control group at the beginning of testing was 40 sec, in the experimental rats it was 28 and 32 sec ($p < 0.01$). The control animals made an average 2.6 mistakes, the experimental rats one mistake ($p < 0.05$).

Differences in stability of preservation of the skill was exhibited to an even greater degree when tested after 7 and 30 days, with respect to both parameters, as is clear from Fig. 1c, d. Analysis of the performance time of individual components of the CRFMR (leaving the start compartment, going through the central compartment and performing the final response in the target compartment) shows that differences between the behavior of the animals of the control and experimental groups are exhibited most significantly in the initial stages of response, i.e., at the stage of afferent synthesis and decision making.

The positive effect of both preparations on formation and preservation of the CRFMR is also clearly revealed by comparison of the relative numbers of conditioned-reflex and mistaken responses (Fig. 2). In the control animals, reproduction of the conditioned reflex response worsened with time. The number of correct responses of these animals fell from 76 to 48-42% on testing 7 and 30 days after training. In rats of the experimental groups, the

final stages of whose training took place after administration of the psychostimulants, not only did the number of reflex responses not decrease, but it actually had a tendency to increase: from 80 to 96% in rats receiving the peptide and from 83 to 100% in the rats receiving centrophenoxin.

The results are thus evidence that a single injection of psychostimulants (centrophenoxin or peptide TP-1) is sufficient to bring about statistically significant improvement of the memory trace provided that the substance is given when the consolidation process has already begun. Under these circumstances, the effect of the peptide is comparable in strength with the effect of a typical CNS stimulator.

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COMPARATIVE STUDY OF RELATIVE LIPOPHILICITY OF SOME DIALKYLAMINOALKYL AND DIALKYLAMINOACYL DERIVATIVES OF PHENOTHIAZINE AND THEIR INTERACTION WITH BOVINE STRIATAL DOPAMINE RECEPTORS

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UDC 615.31:547.869.2].033.813.2

KEY WORDS: dialkylaminoacyl derivatives of phenothiazine; lipophilicity; dopamine receptors.

The difference between the chemical structure of dialkylaminoacyl (DAC) derivatives of phenothiazine and that of typical neuroleptics is replacement of the dialkylaminoalkyl (DAL) group attached to the cyclic nitrogen atom in position 10 of the tricyclic phenothiazine nucleus by DAC [2]. This type of modification leads to a significant change in the pharmacological properties of these compounds. For instance, neuroleptic activity characteristic of DAL representatives disappears or is considerably reduced in DAC derivatives and, at the same time, a number of cardiotropic and, in particularly, antiarrhythmic properties appear [2]. Differences in the pharmacological activity of these two groups of compounds may be associated primarily with the change in their physicochemical properties, which determine the action of the drug at all the principal stages of its existence in the organism [3, 4]. For instance, physicochemical properties play an important role in interaction of the drug with different receptor systems [3, 7]. The principal physicochemical characteristics of a compound which determines its biological activity are its relative hydrophobicity or lipophilicity (LP) and its donor-acceptor and steric properties [9].

The aim of the present investigation was to compare LP and donor-acceptor properties of DAC and DAL derivatives of phenothiazine and also their effect on specific binding of ^{3}H-

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(Presented by Academician of the Academy of Medical Sciences of the USSR A. V. Val'dman.) Translated from Byulleten' Éxperimental'noi Biologii i Meditsiny, Vol. 106, No. 8, pp. 163-165, August, 1988. Original article submitted June 18, 1987.