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ANALYSIS OF NEUROCHEMICAL MECHANISM OF ACTION OF PSYCHOTROPIC AGENTS DURING STATE-DEPENDENT LEARNING

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Summary. – *Chronic administration of phenazepam, cleregil or 3-hydroxypyridine in the course of learning induces in rats a state-dependent learning. Changes of maze behavior exhibited during phenazepam or 3-hydroxipiridine-induced state-dependent learning are almost entirely eliminated by the administration of calcium valproate and were aggravated by bicuculline. The central cholinolytic amysil and the cholinomimetic arecoline were without effect. The cholinergic component was predominant in cleregil-induced state-dependent learning.*

Riassunto (Analisi dei meccanismi neurochimici coinvolti nell'azione dei farmaci psicotropi durante lo "state-dependent learning"). – *La somministrazione ripetuta di fenazepam, cleregil e 3-idrossipiridina nella fase di apprendimento induce nei ratti uno "state-dependent learning". Le alterazioni del test nel labirinto che compaiono nel corso del trattamento con fenazepam o 3-idrossipiridina scompaiono quasi del tutto in seguito alla somministrazione di valproato di calcio e vengono potenziate dalla bicucullina. I farmaci ad azione centrale colinolitica (amysil) o colinomimetica (arecolina) non risultano attivi. La componente colinergica è prevalente nello "state-dependent learning" indotto da cleregil.*

During chronic administration of many centrally-acting drugs in the course of learning, an unusual form of behavior is observed in animals - a state-dependent learning, when a conditioned reflex or skill is only realized in the drug's presence, and is not realized without this drug [1-3]. It is known that ethanol, morphine, chlordiazepoxide and some others neuro-and psychotropic drugs can cause this phenomenon [1, 2, 4, 5]. Therefore, state-dependant learning is a suitable model for the investigation of the neurochemical mechanism of drug action.

The experiments were carried out on male albino rats weighing 180-280 g (animal farm "Stolbovaya"). The investigation has been carried out with the help of T-maze [3, 6]. State-dependent learning has been produced in the course of prolonged administration of benzodiazepine tranquilizer phenazem (2 mg/kg, i.p.), 3-hydroxypiridine (50 mg/kg, i.p.) and nootropic agent cleregil (deanol aceglumate) (150 mg/kg, i.p.) with parallel learning of a conditioned drinking reflex.

For the assessment of the role of neurochemical and receptor mechanisms in the realization of the drugs' effects, the animals with a formed state-dependent learning were challenged with different drugs using a replacement test [7].

The rats with drug-induced state-dependent learning could no longer perform this reflex upon drug withdrawal (the time of reflex is increased 10-fold). To analyze this neurochemical situation various drugs were administered: thiosemicarbazide (4 mg/kg. s.c.), bicuculline (1 mg/kg, s.c.), cleregil (150 mg/kg, i.p.), amysil (benactizine) (10 mg/kg, i.p.), atropine (25 mg/kg, i.p.), arecoline (5 mg/kg, s.c.), β-ethyldiphacil (10 mg/kg, i.p.), diazepam (5 mg/kg, i.p.), calcium valproate (200 mg/kg, i.p.), picrotoxin (2 mg/kg, i.p.), RO 15-1788 (10 mg/kg, i.p.).

Statistical analysis was performed calculating the arithmetical mean with standard error of the mean, where $p = 0.05$ [8].

Changes of maze behavior exhibited during phenazepam-or 3-hydroxypyridine-induced state-dependent learning were almost entirely eliminated by the administration of a GABA-positive agent such as calcium valproate and were aggravated by the specific GABA-receptor antagonist bicuculline or by the chloride channel blocking agent picrotoxin (Fig. 1 and 2). The benzodiazepine receptor antagonist RO 15-1788 was without effect on the state-dependent learning produced by 3-hydroxypyridine, however, it modified the animal's behavior under phenazepam-induced state-dependent learning.

The analysis of the involvement of cholinergic mechanism in the action of phenazepam and 3-hydroxypyridine has shown that the central M-choli-

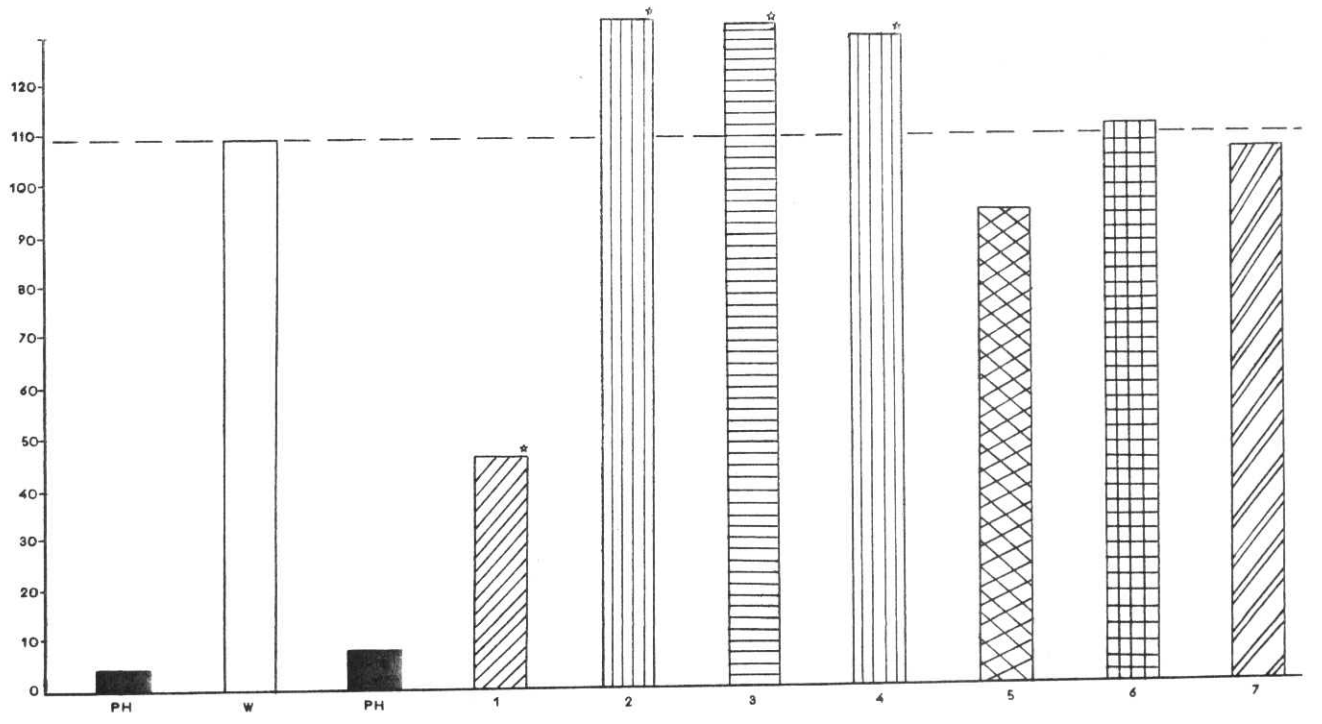

Fig. 1. – Mechanism of phenazepam-induced state-dependent learning.
Ordinate = reflex time (s)
Abscissa = Ph: phenazepam (2 mg/kg, i.p.)) W: withdrawal; 1: calcium valproate (200 mg/kg, i.p.); 2: thiosemicarbazide (4 mg/kg, s.c.); 3: bicuculline (1 mg/kg, s.c.); 4: picrotoxin (2 mg/kg, i.p.); 5: RO 15-1788 (10 mg/kg, i.p.); 6: amysil (10 mg/kg, i.p.); 7: cleregil (150 mg/kg, i.p.) * $p < 0.05$ (Student's t test)

nolytic amysil and the M-cholinomimetic arecoline were without effect on state-dependent learning of animals (Fig. 1, 2). On the other hand the cholinergic component was predominant in the mechanism of cleregil-induced state-dependent learning (Fig. 3) since calcium valproate and β-ethyldiphacil had no effect on behavioral abnormalities, whereas arecoline aggravated them.

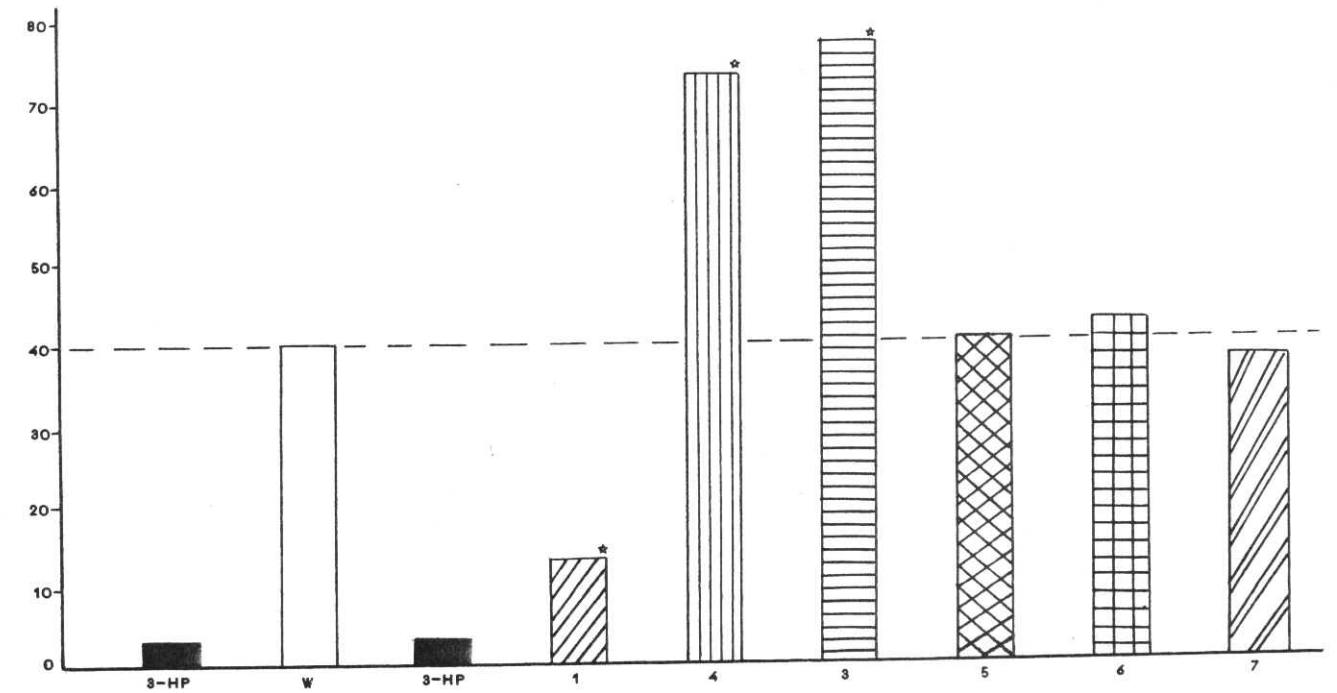

Fig. 2. – Mechanism of 3-hydroxypyridine - induced state-depemdent learning
Ordinate = reflex time (s)
Abscissa = 3-hp: 3-hydroxypyridine; W: withdrawal; 1: calcium valproate (200 mg/kg, i.p.); 3:bicuculline (1 mg/kg, s.c.); 4: picrotoxin (2 mg/kg, i.p.); 5: RO 15-1788 (10 mg/kg, i.p.); 6: amysil (10 mg/kg, i.p.); 7: cleregil (150 mg/kg, i.p.) * $p < 0.05$ (Student's t test)

According to the most widely acknowledged hypothesis, the cholinergic system plays the predominant role in the intimate mechanism of state-dependent learning [2]. The data obtained suggest that this mechanism is far from being exhaustive and even not always predominant and that other neurotransmitter systems are involved in the realization of this phenomenon.

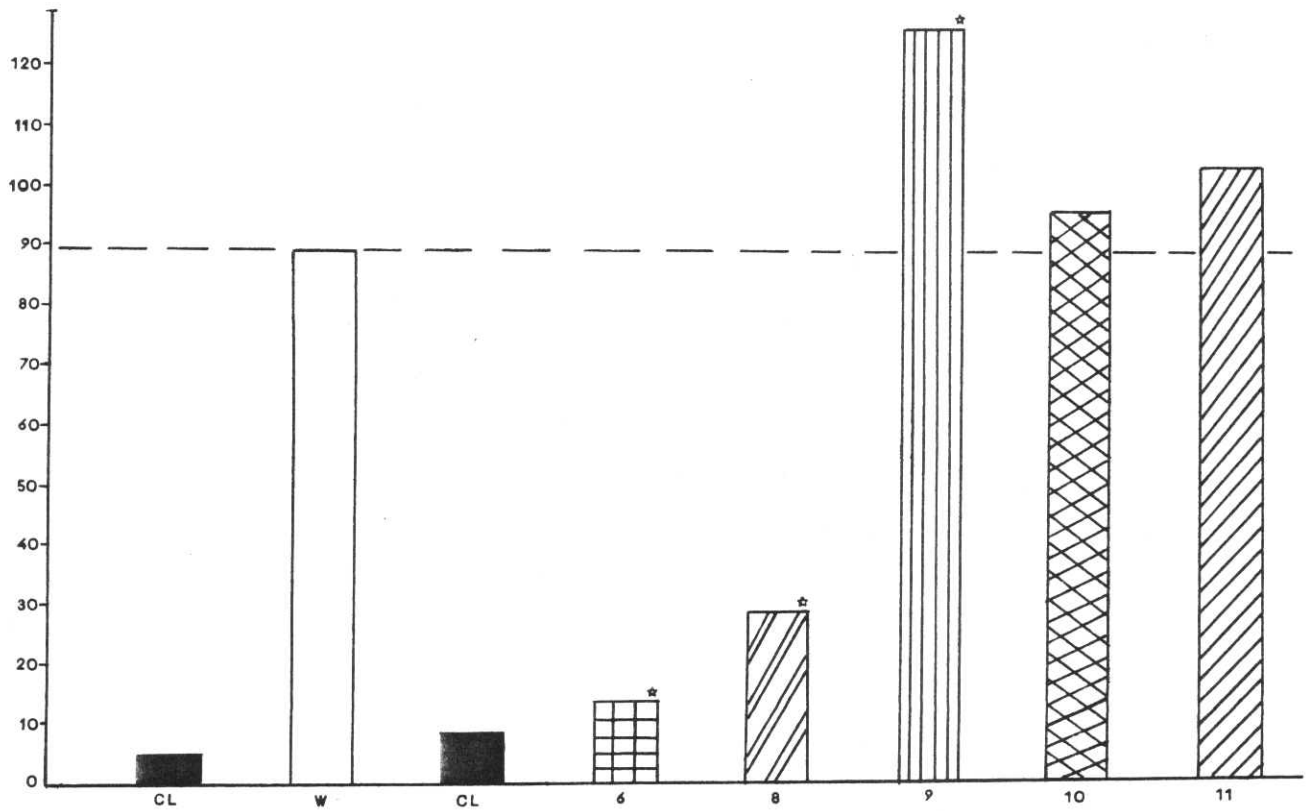

Fig. 3. – Mechanism of cleregil-induced state-dependent learning

Ordinate = reflex time (s)

Abscissa = Cl: cleregil (150 mg/kg,i.p.); W: withdrawal; 6: amysil (10 mg/kg, i.p.); 8: atropine (25 mg/kg, i.p.); 9: arecoline (5 mg/kg, s.c.); 10: B-ethyldiphacil (10 mg/kg, i.p.); 11: diazepam (5 mg/kg, i.p.) * $p < 0.05$ (Student's t test)

REFERENCES

1. OVERTON, D.A. 1966. State-dependent learning produced by depressant and atropine-like drugs. *Psychopharmacologia* **10**: 6-31.

2. AZARACHVILI, 1981. *Investigation of memory mechanism by use of physiologically active compounds.* Science, Moscow. 184 pp. (in Russian).

3. VORONINA, T.A. & GARIBOVA, T.L. 1983. Phenazepam-induced dissociation learning-reversible amnesia. *Bull. Exp. Biol. Med.* **45**: 49-52 (in Russian).

4. OVERTON, D.A. 1976. Discriminable effects of benzodiazepines. *Psychopharmacol. Commun.* **2** (4): 339-343.

5. KRIMMER, E.C. & BARRY, H. 1980. Effect of dosage on discrimination of morphine from saline. *Pharmacol. Biochem. Behav.* **13**: 313-316.

6. GARIBOVA, T.L. & VORONINA, T.A. 1986. Characteristics and mechanisms of tolerance to benzodiazepines. In: *Drug dependence and emotional behavior. Neurophysiological and neurochemical approaches.* A.V. Valdman (Ed.). Consultants Bureau, New York, London. pp. 453-478.

7. OVERTON, D.A. 1982. Comparison of the degree of discriminability of various drugs using the T-maze drug discrimination paradigm. *Psychopharmacology* **76**: 385-395.

8. BELENKY, M.Z. 1959. *Elements of quantitative evaluation of pharmacological effect.* Editing house "Academia Scientiarum of Latvian SSR" Riga. pp. 9-187 (in Russian).