PHARMACOLOGY AND TOXICOLOGY

Effect of Haloperidol and Amphetamine on Conditioning and Functional Disturbances in Avoidance Reaction

A. N. Inozemtsev, S. B. Bokieva, A. B. Spinei, T. A. Voronina, and N. A. Tushmalova

Translated from *Byulleten' Eksperimental'noi Biologii i Meditsiny*, Vol. 125, No. 1, pp. 56-58, January, 1998
Original article submitted July 30, 1996

We compared the effects of haloperidol and amphetamine on the conditioning of the avoidance reaction in rats and its reversible disturbances by delivering electrical stimuli conflicting with the established relation between stimulation, responses, and their consequences. Amphetamine accelerates conditioning of avoidance reaction and diminishes the impact of functional disturbances. Haloperidol in a dose of 0.1 mg/kg completely inhibits avoidance but not intersignal reactions; in animals injected with 0.01 mg/kg haloperidol, avoidance reactions can be conditioned but less effective than in control animals. Functional disturbances inhibit avoidance and increase the number of intersignal reactions. These findings suggest that haloperidol in low doses activates generalized motor activity and does not improve adaptive reactions timed with conditioning stimulus and ensuring escape from electrical footshock.

Key Words: *haloperidol; amphetamine; avoidance reaction; functional disturbance*

Functional disturbances in the central nervous system are a very helpful instrument for understanding the action of some psychotropic agents. Previously [4], we revealed some peculiarities of the effect of nootropics and tranquilizers using the model of functional disturbance of the avoidance reaction (AR), which allowed us to assume that similar effects of these preparations, i.e., normalization of behavioral parameters through reduction of emotional stress, are achieved via different mechanisms. Tranquilizers reduce emotional stress by acting directly in the emotional sphere, while the effects of nootropics are mediated through activation of mnestic and cognitive processes. It seems interesting to evaluate behavioral effects of the psychostimulant amphetamine and the neuroleptic haloperidol in this model.

Laboratory of Evolution of Memory Mechanisms, Biological Faculty of M. V. Lomonosov Moscow State University; Laboratory of Psychopharmacology, Institute of Pharmacology, Russian Academy of Medical Sciences, Moscow

MATERIALS AND METHODS

Experiments were carried out on male random-bred rats weighing 180-210 g. The rats were divided into 4 groups. The effects of 0.02 mg/kg amphetamine and 0.1 and 0.01 mg/kg haloperidol were studied on rats of groups 1 (n=16), 2 (n=7), and 3 (n=16), respectively. Group 4 rats (n=16) served as controls.

Group 1, 3, and 4 animals were trained AR in a shuttle box for 6 days (25 presentations per day) according to the following scheme: acoustic signal followed 10 sec later by electrical stimulation. Both

0007-4888/98/0001-0047$20.00©1998 Plenum Publishing Corporation

stimuli were switched off by animal transition to the opposite chamber. The intersignal pause was 30 sec. On day 6, a reversible functional disturbance of AR [5] was induced by introducing the following change: transition to the opposite compartment in response to conditioned or unconditioned stimulus did not switch off both stimuli during three transitions, so that the animal received footshock. After the third response electrical current was immediately switched off, while acoustic stimulation persisted for additional 2 sec. Thereafter, AR was tested in 20 presentations under the initial conditions. The drugs were injected intraperitoneally 30 min prior to the experiment. The data were processed statistically using the Wilcoxon test.

RESULTS

Haloperidol in a dose of 0.1 mg/kg considerably suppressed learning: AR could not be conditioned. Moreover, starting from the 2nd experiment the escape score decreased from 100 to 90.2%, i.e., although the animal received footshock it did not run to the opposite compartment. In addition, intersignal reactions (ISR) appeared. A decrease in the dose to 0.01 mg/kg allowed for AR conditioning, but it was less effective than in the control (Fig. 1). The number of ISR did not significantly differ from the control, except for day 5. Unlike haloperidol, amphetamine increased both AR and IRS (Fig. 1).

Haloperidol in a dose of 0.01 mg/kg aggravated functional disturbances and reduced AR performance in presentations 1-5 and 6-10. The number of ISR under these conditions significantly increased ($p<$ 0.001). By contrast, amphetamine diminished functional disturbances and improved AR immediately after injection (presentations 1-5) in comparison with the control. The number of ISR during this period did not differ from the control (Fig. 2). Starting from presentation 6, the number of ISR in treated animals surpassed the control level.

We have previously demonstrated that nootropic agents (piracetam) diminished functional disturbance of AR [4-6]. Piracetam improves cerebral metabolism and activates energy-dependent processes in neurons, since it enhances ATP synthesis and turnover, as well as DNA and RNA synthesis in the brain. Administration of piracetam results in accelerated glucose utilization, activates phospholipase A_2, phosphatidylcholine and phosphatidylethanolamine metabolism, and improves energy supply of the brain in stress [3,11-15]. It should be noted that piracetam activates dopamine and norepinephrine metabolism in the brain.

The psychostimulant amphetamine improved organism's capacity to work through mobilization of

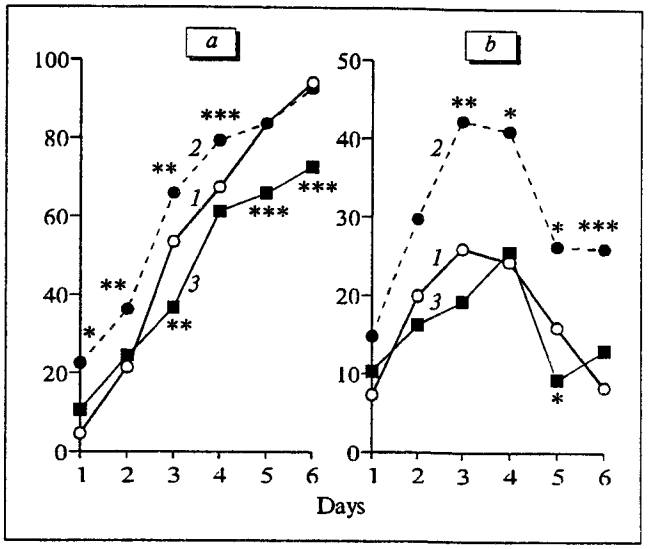

Fig. 1. Effects of amphetamine and haloperidol on the conditioning of avoidance reaction (*a*) and intersignal reactions (*b*), 1) control; 2) amphetamine; 3) haloperidol. Here and in Fig. 2.: ordinate: mean score, % of presentation. *$p<0.05$, **$p<0.01$, ***$p<0.001$ compared with the control.

reserves. From the neurochemical point of view, in the context of our experimental paradigm it should be noted that amphetamine by its chemical structure is similar to dopamine and norepinephrine and induces the release of these transmitters from presynaptic terminals. Thus, amphetamine and piracetam modulate the content of these transmitters in the brain.

On the other hand, neuroleptics (haloperidol) block dopamine and norepinephrine receptors and inhibit their release from nerve endings. Our findings suggest that these catecholamines participate in the adaptive reactions under conditions of functional disturbance.

Haloperidol in a dose of 0.1 mg/kg completely inhibits conditioning of AR, but does not suppress ISR. Similar results were obtained with a lower dose of haloperidol (0.01 ng/kg): it increased ISR against the background of suppressed AR. It is known that enhancement of generalized motor activity indicates activation of defense reserves in the organism in the presence of danger [2,7,9,10]. In this context, the observed increase in ISR suggests the presence of an activating component in the psychotropic spectrum of haloperidol. This assumption is consistent with previously demonstrated activating effect of low doses of haloperidol in both clinical [1] and experimental [8] studies. However, our experiments have shown a peculiar nature of this activation: haloperidol activates only ISR and has no effect on goal-directed reactions.

Thus, in animals injected with haloperidol, stimulation of generalized motor activity (in the form of ISR) in response to changes in experimental con-

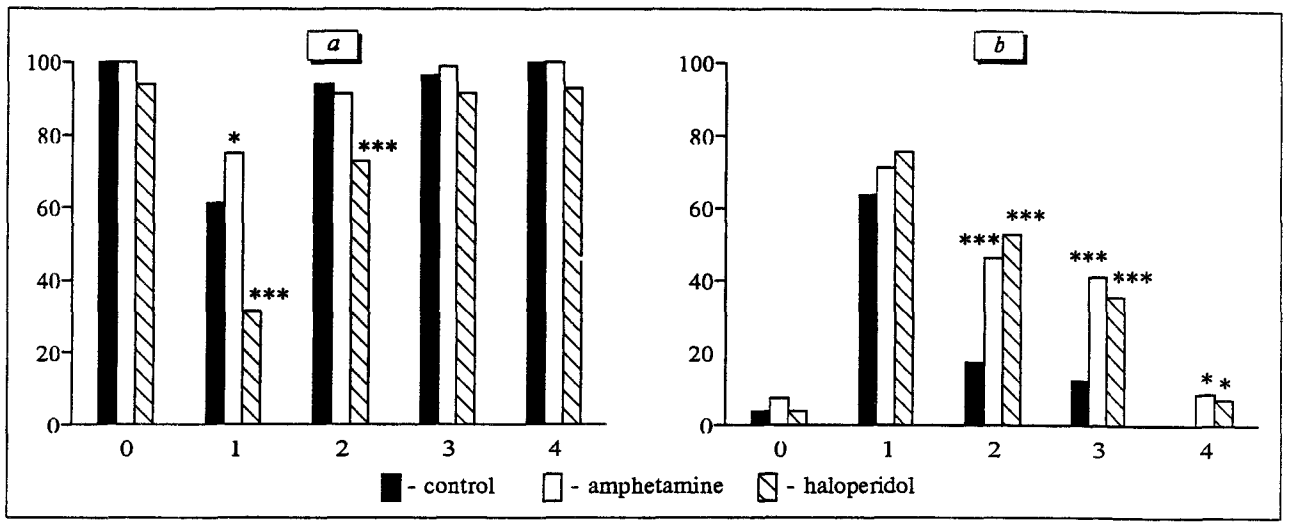

Fig. 2. Effects of amphetamine and haloperidol on avoidance reactions (*a*) and intersignal reactions (*b*) before and after functional disturbance. O: 5 presentation prior to disturbance, 1, 2, 3, and 4 series of 5 presentation after disturbance.

ditions does not enhance adaptive reaction related to conditioning stimulus and ensuring the escape from electrical footshock, which probably reflects impaired cortical control. This may be due to haloperidol-induced modulations of catecholaminergic mechanisms of subcortical structures and reticular formation, which alters their interaction with the cortex.

The study was supported by Automated Medico-Biological Systems Scientific and Technological Program of the Russian State Committee on Higher Education.

REFERENCES

1. Yu. A. Aleksandrovskii, *Heloperidol in the Treatment of Schizophrenia. Author's Abstract of PhD Thesis*, Moscow (1965).
2. P. K. Anokhin, *Biology and Neurophysiology of Conditioned Reflex* [in Russian], Moscow (1968).
3. B. B. Borisyul and V. I. Kresyun, in: *Pharmacology of Nootropic Agents. Experimental and Clinical Studies* [in Russian], Moscow (1989), pp. 8-19.
4. A. N. Inozemtsev, S. B. Bokieva, T. A. Voronina, and N. A. Tushmalova, *Byull. Eksp. Biol. Med.*, **122**, No. 8, 152-155 (1996).
5. A. N. Inozemsev and L. L. Pragina, *Zh. Vyssh. Nervn. Deyat.*, **39**, No. 4, 764-766 (1989).
6. A. N. Inozemtsev, L. L. Pragina, F. A. Firova, et al., *Farmakol. Toksikol.*, **58**, No. 3, 15-16 (1995).
7. V. B. Kennon, *Physiology of Emotions* [in Russian], Leningrad (1927)
8. G. M. Molodavkin, *Byull. Eksp. Biol. Med.*, **91**, No. 1, 48-50 (1981).
9. P. V. Simonov, *Emotional Brain* [in Russian], Moscow (1981).
10. K. V. Sudakov, in: *System Behavioral Mechanisms* [in Russian], Moscow (1990), pp. 9-38.
11. S. Tuneva, Ts. Tencheva, N. Tyutyulkova, and M. Nikolova, *Med. Biol. Information*, No. 6, 8-11 (1980).
12. N. A. Tushmalova, N. G. Bezlepkin, F. F. Kokaeva, and A. I. Gaziev, *Dokl. Acad. Nauk SSSR*, **320**, No. 9, 761-763 (1991).
13. O. Benesova, N. Dloholkova, A. Pavlik, *Act. Nerv. Super.* (Praha), **27**, No. 4, 284-285 (1985).
14. V. J. Nikolson and O. L. Wolthuis, *Brain Res.*, **113**, 616-619 (1976).
15. J. P. Pede, L. Schimpfessel, R. Crocoett, *Arch. Int. Physiol. Biochim.*, **79**, No. 5, 1036-1037 (1971).