EFFECT OF HALOPERIDOL ON AMPHETAMINE STEREOTYPY

É. B. Arushanyan, V. A. Baturin, and L. V. Shishlyannikova

UDC 615.214.22:547.829].015.23:615.214.31

KEY WORDS: haloperidol; amphetamine stereotypy.

Amphetamine-induced behavioral stereotypy can be used as an experimental model of a psychopathological form that is easily abolished by neuroleptics. From the neurophysiological standpoint, one possible cause of the stereotype is functional insufficiency of the corpus striatum and of its leading component — the caudate nucleus. Meanwhile, there is indirect evidence that the antipsychotic properties of neuroleptics may depend on activation of striatal mechanisms [1, 2, 9]. If this is so, the inhibitory action of neuroleptics on amphetamine stereotypy must be determined by mobilization of the striatum.

To test this hypothesis two approaches were used in the investigation described below. First, an attempt was made to discover how injury to the striatum influences the improvement brought about by haloperidol in certain indices of avoidance behavior in rats receiving amphetamine. Second, the action of the neuroleptic on stereotypy was studied in conjunction with artificial triggering of striatal influences. Behavioral inhibition arising after termination of repeated electrical stimulation of the caudate nucleus in cats was used as the model state for this purpose [6].

EXPERIMENTAL METHOD

There were two series of experiments. In series I experiments were carried out on 30 noninbred albino rats of both sexes weighing 200-250 g. Avoidance behavior was studied in a Y-maze by the method described previously [3]. The animals were divided into two groups: Rats of one group were given amphetamine (5 mg/kg), those of the other group received a combination of amphetamine with haloperidol (0.1 mg/kg). The drugs were injected intraperitoneally. The experiments were repeated twice at weekly intervals, but the second time the corresponding volume of physiological saline was injected, and these results were compared with the experimental data (Student's t-test, $P < 0.05$). The effect was evaluated by the same method in the early (7th-14th days) and late (28th-35th days) stages after bilateral electrolytic injury to the corpus striatum (a direct current of 2 mA was passed for 25 sec through a silver electrode 0.2 mm in diameter).

The experiments of series II were carried out on 6 cats (48 experiments) of both sexes weighing 2.2-3.4 kg. Stable behavioral changes were obtained after the termination of long-term low-frequency (2.5 min, 2 Hz, 3-4 times at intervals of 10 min) stimulation of the head of the caudate nucleus through previously implanted electrodes [6]. The results of control experiments (injection of physiological saline) were compared with those of injection of amphetamine (0.5-1 mg/kg) and a combination of amphetamine with haloperidol (0.03-0.06 mg/kg body weight). The drugs were injected intraperitoneally in this series also, with intervals of 3-4 days.

EXPERIMENTAL RESULTS

In the dose tested amphetamine evoked stereotyped behavior in all the animals in the form of a set of automatic actions (sniffing, chewing, turning the head). The avoidance behavior in the maze worsened at the same time. In agreement with earlier observations [4] the number of incorrect responses increased, the animals were more unrestrained, they frequently left the correctly chosen safe compartment, and took longer to correct their mistakes.

Department of Pharmacology, Medical Institute, Chita. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, pp. 296-298, September, 1980. Original article submitted December 12, 1979.

 0007-4888/80/9009-1210$07.50 © 1981 Plenum Publishing Corporation

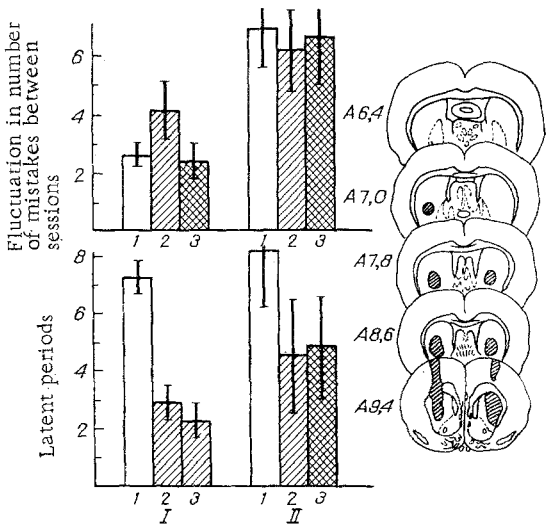

Fig. 1. Weakening of ability of haloperidol to reduce fluctuations between number of mistakes made per session by rats receiving amphetamine after bilateral injury to corpus striatum. Series of frontal brain sections on right shows typical location of destruction of nucleus in one animal. I) Intact rats; II) striatectomized rats. 1) Normal; 2) amphetamine; 3) haloperidol plus amphetamine.

Because the behavioral task used in the present investigation was more complex and required reorganization of the previously formed trajectory of the avoidance response, it was able to reveal another important fact. Under the influence of the drug, the paths of the rats through the maze became definitely preservative in character when the animals preferred to follow them in one particular direction. For this reason, the reorganization of the motor skill was disturbed drastically and fluctuations in mistakes between sessions increased. These changes took place against the background of shortening of latency of the responses (Fig. 1).

Striatectomy itself could be the cause of disturbance of the avoidance responses and, in particular, it could lead to stable motor perservation [3]. In conjunction with amphetamine, injury to the brain led to a marked increase in the fluctuation in the number of responses between sessions and to an increase in the number of times the animals left the safe compartment. Meanwhile the character of the stereotype changed, and most frequently it became less organized.

According to data published previously [5, 8], isolated injection of the neuroleptics haloperidol and chlorpromazine optimizes avoidance behavior in rats. This is reflected in a decrease in the total number of incorrect responses, a decrease in the number of times the animals leave the safe compartment, and a clear decrease in fluctuations in the number of mistakes between sessions. Meanwhile, the latent periods of avoidance showed a tendency to lengthen. Optimization of this sort was particularly demonstrative in animals which could not be well retrained in the control, and it was absent in rats which coped well with the task initially. Despite the fact that the striatectomized animals resembled in several parameters of their avoidance behavior animals which were poorly retrained, the optimizing action of the neuroleptics on these animals disappeared. The changes were quite specific, for they were not observed in two control rats with bilateral injuries to the parieto-occipital cortex.

In conjunction with amphetamine, haloperidol modified the picture of the amphetamine stereotypy somewhat, but did not suppress it completely. The general mobility of the rats increased, they ceased to chew, but continued to sniff. Meanwhile the neoroleptic completely abolished defects in retraining due to amphetamine, and fluctuations in the number of errors between sessions and the number of times the animals left the safe compartment decreased significantly. A paradoxical shift of latency also was observed: Instead of the usual lengthening, a tendency toward further shortening was observed.

Against the background of striatectomy, haloperidol lost its ability to modify the outward manifestation of amphetamine stereotypy and the accompanying defects of avoidance behavior. This action was exhibited particularly clearly in the late stages (28-35th days) after brain injury.

The defects in retraining of the rats under the influence of amphetamine and also after striatectomy could be explained by difficulties in the construction of a program of an adequate behavioral response. Haloperidol can evidently abolish such defects by activating

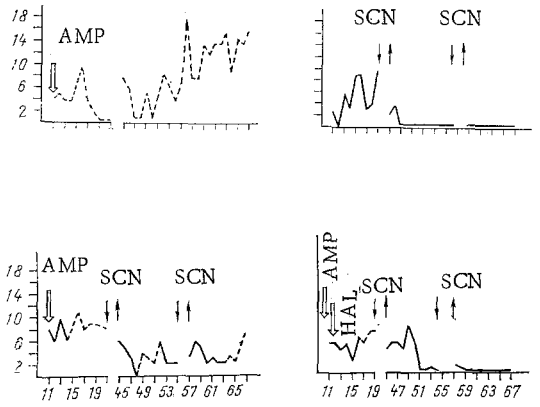

Fig. 2. Potentiation by haloperidol of inhibition of amphetamine stereotypy arising after termination of stimulation of caudate nucleus in a cat. Haloperidol, given 15 min after amphetamine, was injected in a low dose (0.03 mg/kg) when no changes were present in caudate inhibition or in the pattern of amphetamine stereotypy in a given animal. Results of third stimulation of caudate nucleus (2 Hz, 2.5 min) are illustrated. Abscissa, time of recording behavior (in min); ordinate, number of heat movements (in different directions), by means of which cat's activity was judged. AMP) amphetamine; SCN) stimulation of caudate nucleus; HAL (haloperidol).

the striatum by blocking the nigro-striatal system which restrains it [1]. That is probably why striatectomy abolishes the optimizing action of the neuroleptic in normal rats and also in animals poisoned with amphetamine.

Stable behavioral inhibition serves as the widespread state arising after discontinuation of repeated electrical stimulation of the caudate nucleus in cats. In its origin, it resembles more closely than evoked responses the natural state of the brain, but at the same time, it differs from ordinary sleep in several criteria. According to previous investigations [6], caudate inhibition is extremely similar to drug-induced neurolepsy. It can thus be regarded as an adequate experimental model suitable for the purposes of psychopharmacological experiments.

In agreement with previous observations [17], against the background of doses of amphetamine at the threshold level for stereotypy (0.5-1.0 mg/kg), after 3 to 5 stimulations of the dorsomedial zones of the nucleus, disorganization of stereotypy took place. The cats turned their heads more slowly and less frequently, they often stood and stared, or they could lie on the floor. Caudate inhibition, to judge from responses of the cats to test stimuli, made those responses more adequate.

After isolated injection of small doses of haloperidol (0.03-0.06 mg/kg), not significantly changing the cats' spontaneous behavior, the onset of caudate inhibition was speeded up and its duration increased. Meanwhile the intensity of trace activation phenomena (turning the head, grooming), sometimes preceding inhibition, was reduced. Yet in the doses tested, haloperidol had no appreciable effect on the pattern of amphetamine stereotypy.

If, however, the neuroleptic was used after preliminary administration of amphetamine, subsequent stimulation of the caudate nucleus had a more distinct effect in abolishing stereotypy (Fig. 2). It began to be disturbed sooner and the disturbance was stronger than after isolated stimulation of the nucleus or isolated action of the neuroleptic. It is very important to note that under these circumstances adequate responses of the cats to sensory and biologically meaningful stimuli were restored, evidence not only of external normalization of behavior, but also of improvement of the animal's mental state.

Small doses of haloperidol, not by themselves suppressing amphetamine stereotypy and not disturbing the motor activity of cats, thus potentiate inhibition of stereotyped behavior observed after discontinuation of electrical stimulation of the caudate nucleus. Caudate inhibition cannot be completely identified with natural sleep or with motor inactivation. An important place in its genesis is occupied by changes in the emotional-motivational sphere, resembling neurolepsy [6]. It can accordingly be suggested that the specific antipsychotic action of neuroleptics may be due to triggering of striatal mechanisms. The results of the experiments of series I on rats support this hypothesis.

LITERATURE CITED

1. É. B. Arushanyan, Farmakol. Toksikol., 36, 481 (1973).
2. É. B. Arushanyan, Farmakol. Toksikol., No. 2, 221 (1977).
3. É. B. Arushanyan and V. A. Baturin, Byull. Éksp. Biol. Med., No. 11, 5 (1975).
4. É. B. Arushanyan and V. A. Baturin, Zh. Vyssh. Nerv. Deyat., No. 3, 535 (1975).

5. É. B. Arushanyan and V. A. Baturin, Farmakol. Toksikol., 42, 230 (1979).
6. É. B. Arushanyan and L. V. Shishlyannikova, Zh. Vyssh. Nerv. Deyat., 29, 80 (1979).
7. É. B. Arushanyan and L. V. Shishlyannikova, Byull. Éksp. Biol. Med., No. 6, 518 (1979).
8. V. A. Baturin, Farmakol. Toksikol., No. 3, 261 (1977).
9. É. B. Arushanyan (E. B. Arushanian) in: Advances in Pharmacology and Therapeutics, Vol. 5, C. Dumont, ed., New York (1978), p. 107.

EFFECT OF GAMMA-AMINOBUTYRIC AND GAMMA-HYDROXYBUTYRIC ACIDS ON RATE OF ^{14}C-LEUCINE INCORPORATION INTO PROTEINS OF THE GASTRIC MUCOSA AND HYPOTHALAMUS

S. A. Mirzoyan,* A. T. Tatevosyan, and G. A. Gevorkyan

UDC 612.32+612.826.4].015.348:547.466.26].014.46:[547.466.3+547.473.2

KEY WORDS: experimental ulcer; gamma-aminobutyric acid; gamma-hydroxybutyric acid; ^{14}C-leucine.

Gamma-aminobutyric acid (GABA), the mediator of inhibition in the central nervous system [1, 6-8] of vertebrates, performs at the same time general metabolic functions in the brain and effector organs [2, 3]. GABA has the property of increasing the blood supply to the brain [4], of protecting animals against experimental gastric ulcers [5], and of exerting a stronger anti-ulcerative effect in conjunction with gamma-hydroxybutyric acid (GHBA).

The choice of the experimental approach described below was dictated by the whole course of our previous work. Renewal of proteins in the hypothalamus and gastric mucosa, in animals with experimental ulcers under the influence of GABA and GHBA was investigated with the aid of ^{14}C-leucine and the distribution of radioactive GABA in the body was studied.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred rats. A gastric ulcer was induced in the animals by crushing the pyloroduodenal region for 10 min.

From the time of infliction of mechanical trauma, the experimental animals of one group began to receive GABA in a dose of 40 mg/kg three times a day, whereas rats of another group received GHBA in a dose of 100 mg/kg by the same scheme. On the second day all the experimental and control animals were given an injection of 50 μCi of ^{14}C-leucine (specific radioactivity 240 mCi/mmole). The animals were decapitated 3 h later and the peritoneal cavity opened. Weighed samples of tissues were taken for examination from the gastric mucosa and the hypothalamus. Protein obtained from the tissues was solubilized in 0.5 ml of Protosol (from New England Nuclear Corp., USA). After complete solubilization of the residue, radioactivity was measured quantitatively on an SL-30 scintillation spectrometer (from Intertechnique, France), in accordance with a program designed to count ^{14}C against an external standard. The counting efficiency of ^{14}C was 95%. In a special series of experiments, in order to study the distribution of radioactive GABA in the organs of the rats, ^{14}C-GABA was injected intraperitoneally in a dose of 50 μCi into intact and control animals, and 3 h later its concentration was determined on the SL-30 scintillation spectrometer in tissue homogenates from the gastric mucosa, liver, and hypothalamus. The results were expressed in cpm/g wet weight of tissue.

*Corresponding Member, Academy of Sciences of the Armenian SSR.

Department of Pharmacology, Erevan Medical Institute. Institute of Biochemistry, Academy of Sciences of the Armenian SSR. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 90, No. 9, pp. 299-300, September, 1980. Original article submitted February 20, 1980.

0007-4888/80/9009-1213$07.50 © 1981 Plenum Publishing Corporation