EFFECT OF PSYCHOTROPIC DRUGS ON EMOTIONAL BEHAVIOR INDUCED IN CATS BY INJECTION OF ACETYLCHOLINE INTO THE CENTRAL GRAY MATTER

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The effect of psychotropic drugs (chlorpromazine, trifluoperazine, haloperidol, meprobamate, librium, benactyzine, imipramine, morphine, atropine) on the rage response and the accompanying encephalographic picture following injection of acetylcholine into the central gray matter was studied in chronic experiments on cats. The results indicate that chlorpromazine and trifluoperazine, in certain doses, facilitate the behavioral manifestations of the response; haloperidol has no such property. The response studied, unlike that described previously to hypothalamic stimulation, is not blocked by the M-cholinolytics benactyzine and atropine.

The writers have previously demonstrated the cholinergic nature of the rage response which is formed at the level of the anterior hypothalamus in cats [3] and have studied the effects of psychotropic drugs on its behavioral and electroencephalographic manifestations [6]. However, besides the hypothalamus, the structures of the mesencephalon, notably the central gray matter surrounding the cerebral aqueduct [12, 16, 4], are also known to play an important role in emotional responses. Chemical stimulation (carbachol) of this region of the brain evokes an emotional response resembling the rage response to stimulation of the hypothalamus in cats [10].

In the investigation described below the effect of psychotropic drugs of different classes were studied on the emotional rage response induced by injecting acetylcholine into the central gray matter in cats.

EXPERIMENTAL METHOD AND RESULTS

Chronic experiments were carried out on 12 male cats under conditions of free behavior. The effect of chlorpromazine (3-6 mg/kg), trifluoperazine (0.75-4 mg/kg), haloperidol (2-4 mg/kg), librium (5-10 mg/kg), meprobamate (30-60 mg/kg), benactyzine (1-3 mg/kg), imipramine (6-12 mg/kg), morphine (1.5-3 mg/kg), and atropine (1-2 mg/kg) was studied by methods described fully previously [6].

Characteristic pendulum-like movements of the tail, salivation, and tachypnea appeared 30-60 sec after injection of 5 μl 10% acetylcholine solution into the central gray matter of the cat (Fig. 1), and the animal lowered its head to the floor, stepped backward, and made a rumbling noise. Strengthening of the vocal responses (conversion of the rumbling into hissing) could be provoked by applying an extra stimulus, such as by touching the animal with the hand or with a paper pellet. The cat attacked the stimulus by striking it with its paws and attempted to seize the paper with its teeth. The electroencephalographic picture at the time of the maximal behavioral manifestations showed desynchronization in the cortex and mesencephalic reticular formation and bursts of high-amplitude activity at a frequency of 30/sec in the amygdala. Absence of the theta-rhythm in the hippocampus distinguished this electroencephalographic picture from

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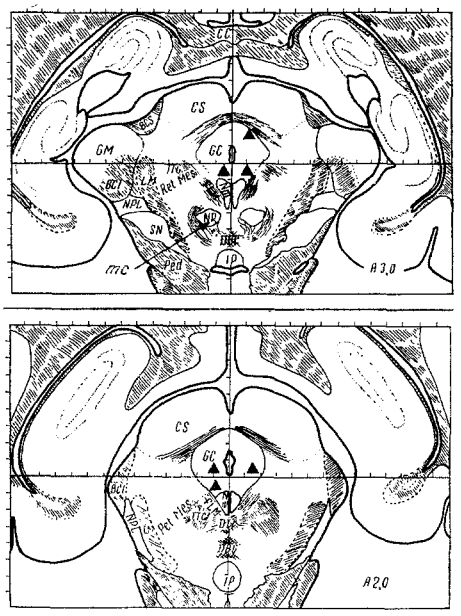

Fig. 1. Region of central gray matter of cat, stimulation of which by acetylcholine evokes an emotional rage response (from the atlas of Snider and Niemer [17]).

that described in response to hypothalamic stimulation [6]. The behavioral and electroencephalographic manifestations of the response ceased after 10-15 min.

Effect of Psychotropic Drugs on Behavior. Phenothiazine derivatives chlorpromazine and trifluoperazine, in doses of 6 and 4 mg/kg, respectively, facilitated the behavioral components of the rage responses. This effect was reflected in a two-fold increase in the duration of the response and intensification of its vocal manifestations: the muffled rumbling noise heard in the control animals was replaced by a loud rumbling sound, changing into spontaneous and repeated hissing, after administration of these neuroleptics. With a decrease in the doses of the phenothiazine derivatives, signs of depression of the response appeared. Chlorpromazine in a dose of 3 mg/kg and trifluoperazine in a dose of 0.75 mg/kg had a marked depriming effect, increasing the latent period of the response (for 60 sec in the control to 90 sec), considerably shortening its duration (from 15 to 9 min), and inhibiting the vocal and autonomic components. Hissing could not be evoked even by the use of a provocative stimulus. A further decrease in the doses of these neuroleptics caused disappearance of their effect on the group of changes in the animals' behavior described above. The animal's aggressiveness, as reflected in its attack on the outstretched hand during attempts to stroke it, was not produced by chlorpromazine or trifluoperazine in any of the doses used. Haloperidol (4 mg/kg) considerably lengthened the latent period of the response (from 60 to 450 sec) and almost halved its duration. Marked inhibition of the autonomic and vocal components and complete suppression of the animal's aggressiveness were observed. This effect of haloperidol was considerably weakened if the drug was given in a dose of 2 μg/kg, with the exception of the persistent "anti-aggressive" action. The behavioral components of the rage response were not altered by administration of librium (5-10 mg/kg) or meprobamate (30-60 mg/kg). Benactyzine (3 mg/kg) and atropine (2 mg/kg) increased the latent period of the response by three times without affecting its duration. The response showed absence of salivation and tachypnea, but the vocal components were unchanged. The animals' emotional tension, as judged by the character of the pendulum-like movements of the tail, was not abolished by benactyzine and atropine. Complete suppression of the autonomic manifestations and a slight decrease in the intensity of the vocal responses were observed after administration of imipramine (12 mg/kg). Morphine (3 mg/kg) increased the salivation and tachypnea and evoked restless movements and a state of alertness in the animals. In a dose of 1.5 mg/kg it reduced the autonomic manifestation, but did not prevent the onset of the vocal responses (the rumbling and hissing).

Electroencephalographic Changes Following Administration of the Psychotropic Drugs. Desynchronization in the cortex and mesencephalic reticular formation accompanying the rage response was replaced in the control animals by synchronization after administration of chlorpromazine and haloperidol. It is interesting to note that chlorpromazine exhibited this property not only in a dose of 3 mg/kg, but also in a dose of 6 mg/kg, when it facilitated the behavioral components of the response. The synchronizing effect of trifluoperazine in relation to the rhythms of these brain structures was exhibited only in a dose of 0.75 mg/kg, in which it caused a decrease in the intensity of the behavioral changes in the animals described above. Phenothiazine derivatives blocked the spindle activity in the amygdala only in doses which had a depriming effect on the behavioral components of the rage response: chlorpromazine – 3 mg/kg, trifluoperazine – 0.75 mg/kg. Haloperidol had no effect on amygdalar activity in any of the doses used. Meprobamate, librium, and morphine did not prevent desynchronization in the cortex and reticular formation or the paroxysmal activity in the amygdala. Against the background of the action of benactyzine, atropine, and imipramine, the reduced behavioral manifestations were accompanied by high-amplitude low-frequency electrical activity in the above-mentioned brain structures.

The results of these experiments reveal certain distinctive effects of the psychotropic drugs used on the animals' behavior evoked by injection of acetylcholine into the cat's central gray matter. One such

effect is the absence of the blocking effect of the M-cholinolytics benactyzine and atropine on the vocal components of the response and the pendulum-like movements of the tail. At the same time, these drugs were clearly capable of suppressing salivation and tachypnea. Comparison of these facts suggest activation by acetylcholine not only of the M-cholinergic mechanisms participating in the behavioral changes of this response. The validity of this hypothesis was demonstrated in experiments in which microinjections of 10 μl of 10% nicotine solution were given (nicotine simulates such components of the response to acetylcholine as pendulum-like movements of the tail, hissing, attacking the paper pellet, and the animal's state of alertness). The results of the experiments with nicotine confirmed earlier reports of its ability to evoke similar changes in the cat's behavior when injected into structures of the mesencephalon [9] and of the existence of nicotine-like cholinergic systems in this part of the central nervous system [5]. The results of these experiments and data in the literature suggest that the rage response studied is produced by nicotine-like cholinergic systems of the central gray matter in cats.

Another fact which deserves attention is that neuroleptics (chlorpromazine and trifluoperazine), in certain doses, can facilitate the behavioral components of the response to injection of acetylcholine into the central gray matter in cats. The explanation to this phenomenon must probably be sought in the functional properties of this part of the mesencephalon. It has been shown by chemical stimulation that the central gray matter participates in the regulation of sleep and the emotional behavior of animals, and also that it is closely connected functionally and morphologically with the structures of the forebrain, particularly with the septo-hippocampal region [1, 13, 15]. The system of the septo-hippocampal mechanisms has both a facilitatory and an inhibitory influence on the effector zones of structures responsible for the emotional behavior of animals. An illustration of one of these influences is given by results showing the strengthening of emotional responses of different origin after destruction of the hippocampus [1, 14]. Meanwhile, there is evidence in the literature that the hippocampus may be the neuronal substrate on which certain neuroleptics and, in particular, the phenothiazine derivatives, act. It has been shown that chlorpromazine and trifluoperazine have a direct effect on synaptic transmission in the hippocampus [8], modify the activity of its flavine and pyridine enzymes [7], suppress the arousal reaction evoked by hippocampal stimulation, and facilitate the spread of paroxysmal discharges from the hippocampus to other brain structures and, in particular, to the neocortex [2]. It can be assumed that the facilitatory effect of chlorpromazine (6 mg/kg) and trifluoperazine (4 mg/kg) on the behavioral components of the rage response observed in these experiments is the result of a disturbed effect of the hippocampus on the mechanism of this response formed at the level of the central gray matter in cats.

LITERATURE CITED

1. L. Kh. Allikmets and M. E. Ditrikh, Zh. Vyssh. Nervn. Deyat., No. 1, 86 (1965).
2. L. Kh. Allikmets and F. P. Vedyaev, Zh. Vyssh. Nervn. Deyat., No. 4, 659 (1967).
3. Yu. V. Burov and I. G. Kurochkin, Zh. Vyssh. Nervn. Deyat., No. 4, 668 (1971).
4. A. V. Val'dman and M. M. Kozlovskaya, in: Neuropharmacology of Processes of Central Regulation [in Russian], Leningrad (1969), p. 83.
5. V. A. Krauz, Farmakol. i Toksikol., No. 1, 3 (1971).
6. I. G. Kurochkin and Yu. V. Burov, Farmakol. i Toksikol., No. 1, 21 (1971).
7. V. A. Markin, in: Modern Psychotropic Drugs [in Russian], No. 3, Moscow (1970), p. 126.
8. R. U. Ostrovskaya, G. N. Krolevets, and V. V. Markovich, in: Modern Psychotropic Drugs [in Russian], No. 3, Moscow (1970), p. 137.
9. A. T. Selivanova, The Action of Cholinergic Drugs on Higher Nervous Activity [in Russian], Leningrad (1969).
10. B. L. Baxter, Exp. Neurol., 21, 1 (1968).
11. B. L. Baxter, Exp. Neurol., 23, 220 (1969).
12. A. Fernandez de Molina and R. W. Hunsperger, J. Physiol. (London), 160, 200 (1962).
13. R. Hernandez-Peon, G. Chavez-Ibarra, P. J. Morgane, et al., Exp. Neurol., 8, 93 (1963).
14. D. P. Kimble, J. Comp. Physiol., 56, 273 (1963).
15. W. J. H. Nauta, Brain, 81, 319 (1958).
16. F. M. Skultety, Arch. Neurol., 8, 608 (1963).
17. R. S. Snider and W. T. Niemer, Stereotaxic Atlas of the Cat Brain, Chicago (1961).