EXPERIMENTAL STEREOTYPY INDUCED BY DISTURBANCE OF GABA-ERGIC MECHANISMS IN THE CAUDATE NUCLEI

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Stereotypy was produced in rats by the formation of generators of pathologically enhanced excitation (GPEE) during local disturbance of inhibitory mechanisms in the rostral part of the caudate nuclei (CN) as a result of bilateral injection of tetanus toxin. Microinjections of gamma-aminobutyric acid (GABA) into the region of GPEE and systemic administration of haloperidol suppressed the stereotyped behavior of the animals. It is concluded that the stereotypy may be based on the formation of a GPEE as a result of disturbances in the presynaptic component of the GABA-ergic system of CN, the operant part of which consists of dopaminergic neurons.

KEY WORDS: caudate nucleus; disturbance of GABA-ergic mechanisms; generator of pathologically enhanced excitation; dopaminergic neurons; stereotypy.

Generators of pathologically enhanced excitation (GPEE) arising in the presence of local insufficiency of inhibitory mechanisms in the corresponding parts of the CNS, are the pathogenetic basis of neuropathological syndromes characterized by hyperactivity of systems [1]. An effective method of creation of GPEE for the reproduction of neuropathological syndromes is microinjection of tetanus toxin (TT) [1, 3], for TT disturbs various types of inhibition in the CNS [2, 4, 6, 7, 10, 11]. The effect of TT develops slowly and lasts a long time, so that it is possible to study in detail the development of the pathological process and its clinical manifestations in an unrestrained animal.

It has been shown that the characteristic and early syndrome arising after microinjection of TT into the rostral part of the head of both caudate nuclei (CN) is a stereotypy [3]. Since this syndrome could be interpreted as the result of disinhibition of CN cells under the influence of TT, the question arises which elements of CN, when disinhibited, cause stereotyped behavior, and what are the inhibitory mechanisms in CN whose disturbance leads to the appearance of stereotypy.

To study these problems an experimental analysis was made with the aid of specific neurotropic drugs.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred male albino rats weighing 200-280 g. To cause a local disturbance of inhibition in CN TT was injected stereotaxically, bilaterally, in doses of 1-3 MLD for rats (in volumes of 0.2×10^{-4} to 0.15×10^{-3} ml) in one microinjection (by means of glass micropipets with a tip 20-30 μ in diameter). GABA (0.2M) was injected in volumes of 6 μl in the course of 5-6 min into both CN through cannulas for intracerebral injection implanted previously. The region of injection of the drugs corresponded to coordinates AP 2.0, L 2.5, H 4.0 of a stereotaxic atlas [12]. The microinjection of TT and insertion of the cannulas were carried out under hexobarbital anesthesia (100 mg/kg, intraperitoneally). The animals were kept in individual cages. The stereotypy was assessed visually. At the same time a recording was made of stereotyped behavior in a transparent plastic cage measuring $40 \times 40 \times 40$ cm, the floor of which, which rested on rubber shock-absorbers, was rigidly connected to a high-frequency seismic detector, on an automatic ink-writer with a tape winding speed of 1 mm/sec. No changes in behavior developed in the control rats

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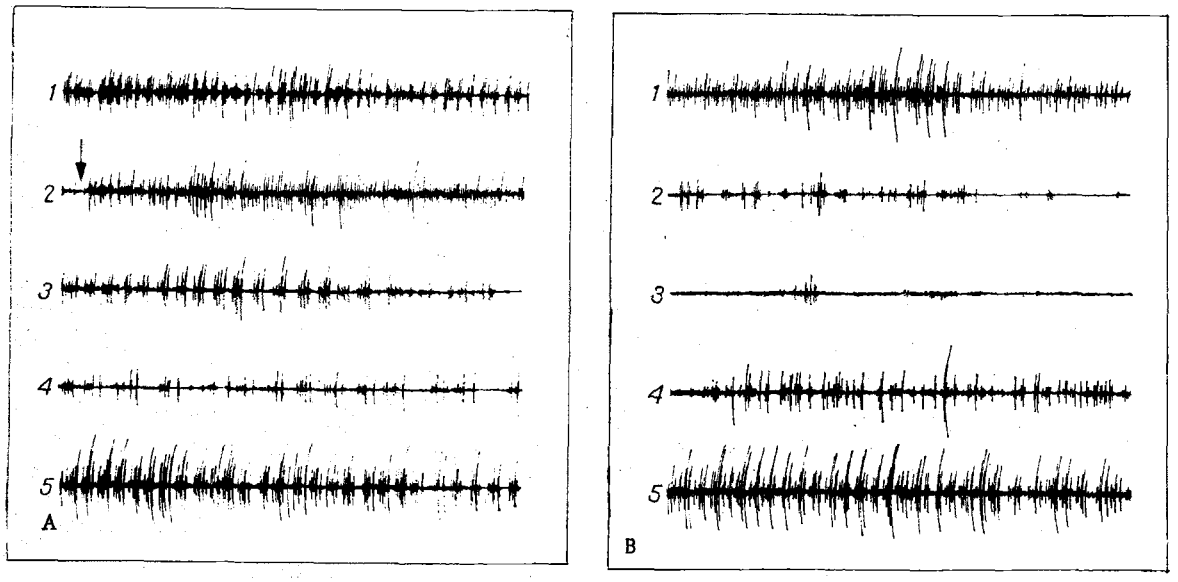

Fig. 1. Effect of various doses of haloperidol on stereotypy induced in rats by microinjection of TT into head of both CN. A) Effect of 1.0 mg/kg haloperidol. Stereotypy before (1) and immediately after (2) injection of haloperidol (time of injection indicated by arrow). At 20th-25th minute (3) and 35th-40th minute (4) after injection of haloperidol a decrease in frequency of stereotyped complexes and progressive decrease in intensity of stereotypy can be seen. Restoration of stereotypy at 70th-750th minute (5) after injection of haloperidol. B) Effect of 2.5 mg/kg haloperidol. Stereotypy before (1) injection of drug. Considerable decrease in frequency and intensity of stereotypy at 10th-15th minute (2) and complete cessation of stereotypy by 20th-25th minute (3) after injection of haloperidol. Restoration of stereotypy at 80th-85th (4) and 120th-125th minutes after injection of haloperidol.

after microinjection of inactivated TT and implantation of the cannulas for intracerebral injection. The control for intracerebral injections of GABA consisted of an iso-osmotic solution of NaCl of the same pH, which had no effect on the course of the stereotypy syndrome. The control for intraperitoneal injection of haloperidol was injection of corresponding solvents, which did not alter the animals' behavior.

EXPERIMENTAL RESULTS

Symptoms of stereotypy appeared in the rats usually 12-18 h after injection of TT into the rostral part of both CN. They appeared periodically as repeated paroxysms of stereotyped behavior, or as continuous stereotyped manifestations sometimes going on for several hours. The syndrome consisted of a set of regularly repeated movements, including walking, running, tapping with the forelimbs, searching movements of the head with intensive sniffing of the interior of the cage, biting and licking the floor, and masticatory movements.

The stereotypy is known to be based on enhanced activity of neostriatal dopaminergic mechanisms. This activity is depressed by neuroleptics, which block dopamine receptors [13]. Accordingly the effects of haloperidol (a blocker of dopamine receptors and an antagonist of stereotypy) were investigated in the syndrome of stereotypy described above.

In the animals with stereotypy haloperidol had an inhibitory action on the syndrome, and the effect depended on dose. In a dose of 1.0 mg/kg haloperidol caused a decrease in the frequency of the stereotyped complexes and a decrease in the intensity of individual stereotyped manifestations in most animals. Complete suppression of the syndrome and the development of mild catalepsy in all the animals investigated were observed after haloperidol in a dose of 2.5 mg/kg (Fig. 1). Restoration of the stereotypy after injection of haloperidol in doses of 1.0 and 2.5 mg/kg was observed after 1.2-1.8 and 2-3.1 h respectively. Stereotyped behavior was restored as a gradual increase in the frequency of individual stereotyped manifestations and an increase in their intensity.

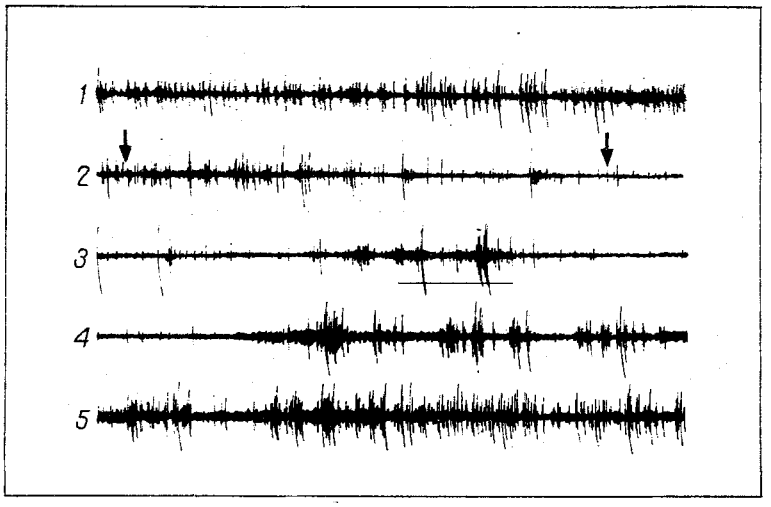

Fig. 2. Effect of microinjection of GABA into CN on stereotypy induced in rats by microinjection of TT. Stereotypy before (1) and during (2) injection of GABA (beginning and end of microinjections indicated by arrows): gradual decrease in stereotyped manifestations observed during the course of injection. Complete absence of stereotypy at 2nd-7th (3) minute after cessation of injection of GABA; continuous line indicates grooming. Restoration of stereotypy at 10th-15th (4) and 20th-25th (5) minutes after injection of GABA.

Disinhibition of the dopaminergic system in CN can thus be regarded as the essential pathogenetic component of the stereotypy syndrome described above.

On the basis of evidence of the presynaptic action of TT [4] and, in particular, of the blocking of GABA secretion from nerve endings [10, 11] and data showing increased liberation of dopamine in response to injection of picrotoxin and bicuculline, antagonists of the postsynaptic action of GABA, into CN in cats immobilized with galanthamine [5], it was postulated that hyperactivation of dopaminergic mechanisms in CN arises as a result of disturbance of inhibitory GABA-ergic mechanisms under the influence of TT.

The experiments showed that recovery of the GABA-ergic inhibition disturbed by microinjection of GABA into CN (the region of injection of TT) led to suppression of the stereotypy. Immediately after injection of GABA the animals' runs and walks became less pronounced, their regularity was considerably disturbed, and their frequency reduced. At the same time the animals ceased to tap with their forelimbs; the searching movements of the head, biting, licking, and sniffing around the cage were reduced next. A few minutes after the beginning of injection of GABA the animals exhibited only a few paroxysms of masticatory movements, and these also soon disappeared. The duration of this effect of GABA, i.e., inhibition of the stereotypy, varied from 10-15 to 30-35 min, and it was inversely proportional to the intensity of the syndrome. It was noted that in some animals the grooming behavior could take place after the stereotypy had completely disappeared as a result of microinjections of GABA (Fig. 2). Restoration of the stereotyped behavior was paroxysmal in character. The stereotyped manifestations appearing in the course of individual paroxysms very soon reached their original level. Bursts of masticatory movements appeared initially and these were soon joined by intensive sniffing, licking, and biting and searching movements of the head. The locomotor components of the stereotyped behavior described above were restored next.

Disturbance of the GABA-ergic inhibitory mechanisms in CN can thus be regarded as an essential condition for the development of stereotypy. It leads to secondary disinhibition of the dopaminergic apparatus and to increased secretion of dopamine. This conclusion is supported by the results of the writers' latest experiments which show that bilateral injection of penicillin and picrotoxin, which likewise cause a disturbance of GABA-ergic inhibition [8, 9], into the heads of both CN also leads to the appearance of stereotypy.

LITERATURE CITED

1. G. N. Kryzhanovskii, Zh. Nevropatol. Psikhiat., No. 11, 1730 (1976).
2. G. N. Kryzhanovskii, Tetanus [in Russian], Moscow (1966).
3. G. N. Kryzhanovskii and M. N. Aliev, Byull. Éksp. Biol. Med., No. 4, 397 (1976).
4. Yu. S. Sverdlov, Neirofiziologiya, No. 1, 25 (1969).
5. G. Bartholini and H. Stadler, in: Chemical Tools in Catecholamine Research, edited by O. Almgren et al., Vol. 2, Amsterdam (1975), p. 235.
6. V. B. Brooks, D. R. Curtis, and J. C. Eccles, J. Physiol. (London), 135, 655 (1957).
7. D. R. Curtis and W. C. De Groat, Brain Res., 10, 208 (1968).
8. D. R. Curtis, A. W. Duggan, D. Felix, et al., Brain Res., 32, 69 (1971).
9. D. R. Curtis, C. J. A. Game, G. A. R. Johnston, et al., Brain Res., 43, 242 (1972).
10. D. R. Curtis, D. Felix, C. J. A. Game, et al., Brain Res., 51, 358 (1973).
11. J. Davies and P. Togroach, Br. J. Pharmacol., 59, 4890 (1977).
12. E. Fifkova and J. Marsala, in: Electrophysiological Methods in Biological Research, edited by J. Bures, M. Petran, and J. Zachar, Prague (1967), p. 653.
13. R. Fog, Acta Neurol. Scand., 48, Suppl., 1 (1972).
14. I. Munkvad, H. Pakkenberg, and A. Randrup, Brain Behav. Evol., 1, 89 (1968).

CHANGES IN POSTSYNAPTIC EXCITATION PROCESSES IN THE PRESENCE OF THE SOVIET BENZODIAZEPINE DERIVATIVE PHENAZEPAM

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The new psychotropic drug phenazepam inhibits spike discharges of neurons composing the visceral ganglion of the garden snail *Helix aspersa* and depresses excitatory postsynaptic potentials arising in response to application of acetylcholine to the membrane of the isolated neuron. The parameters of the electrically excitable membrane remain basically unchanged. It is suggested that one possible mechanism of the manifestation of the pharmacological action of the drug may be depression of postsynaptic excitation of the cholinergic receptor membrane.

KEY WORDS: phenazepam; excitatory postsynaptic potential; postsynaptic inhibition of excitation; acetylcholine.

Investigations of the biological activity of 1,4-benzodiazepine-2-bases (BD) have yielded an extensive literature on the subject [9]. Changes in the level and metabolism of catecholamines and acetylcholine (ACh) have been demonstrated in different parts of the brain [5, 6, 8]. Correlation has also been observed between the pharmacological activity of BD and their ability to bind with the glycine receptor [10].

On the basis of these results suggestions were put forward regarding the possible mechanism of action of BD [5, 8, 10]. The arguments supporting these hypotheses were later subjected to critical analysis, and new explanations of the various manifestations of the biological activity of compounds of this series were proposed [2, 3, 7]. In particular, it is suggested [3] that certain effects of diazepam are mediated through the γ-aminobutyric acid (GABA) system. On the basis of these data and also of the structural similarity between ACh and GABA and the possibility of competitive interaction between them for the muscarinic cholinergic receptor [4], it is natural to suggest that BD may influence excitation processes induced by ACh.

The object of this investigation was to test this hypothesis.

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