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NEUROPHYSIOLOGICAL AND PHARMACOLOGICAL EVIDENCE OF SELF-REGULATION IN THE NIGROSTRIATAL SYSTEM

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Electrical stimulation of the substantia nigra in cats evokes stereotyped behavior which, as analysis has shown, is linked with potentiation of nigrostriatal dopaminergic transmission. In the course of a study of nigral stereotypy it was found that this condition can decline progressively during repeated electrical stimulation of the nucleus. This phenomenon is of fundamental importance and requires more detailed study, for it probably lies at the basis of processes determining the cardinal features of activity of the nigrostriatal system as a whole. The facts described below are evidence that the cause of the rapid decline in nigral stereotypy could be activation of presynaptic dopamine autoreceptors on nigral axons.

EXPERIMENTAL METHOD

Experiments were carried out on 14 cats of both sexes weighing 2-3.5 kg. Under pentobarbital anesthesia bipolar nichrome electrodes (diameter 0.2 mm) were inserted into the substantia nigra on both sides, and also into adjacent structures of the midbrain. The source of current was a square pulse generator. The experiments were begun 4-7 days after the operation. The cats were kept in a chamber measuring 60 × 60 × 60 cm. The animals' behavior was evaluated before, during, and after stimulation of the brain by visual, photographic, and cyclographic methods [3]. The EEG in the sensomotor cortex was recorded in two cats by the usual method. The substances for testing were injected intraperitoneally in physiological saline. After the end of the experiments the brain was fixed and the position of the electrodes determined in frontal sections and compared with coordinates of the atlas [11].

EXPERIMENTAL RESULTS

Weak unilateral stimulation of the compact part of the substantia nigra triggered a set of motor automatism in the cats, in the form of rhythmic rotations of the head from side to side and up and down, with intervals of sniffing and periodic motionlessness. During sufficiently prolonged (1-1.5 min) or stronger (by 0.5-1 V) stimulation of the nucleus this state persisted for several minutes even after the current had been switched off. This type of nigral after-stereotypy was a sufficiently specific response, for it did not arise from the extranigral formations of the midbrain or even from the reticular zone of the substantia nigra, as was shown previously it was dopaminergic in nature and, therefore, it was used as the main test object in the present investigation. A considerable external similarity between this behavioral change and amphetamine-induced stereotypy must also be emphasized.

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The expressiveness of the after-stereotypy gradually decreased during repeated stimulation of the substantia nigra on the same day of the experiment. The stronger the stimulation and the shorter the intervals between stimuli, the more rapidly the response was extinguished (Fig. 1). Usually an initial peak component was present in the nigral response, in the form of a sharp increase in the intensity of stereotypy immediately after discontinuation of the current. In most cases the peak was surprisingly standardized in time, and it lasted for the first 3 or, less frequently, 4 min. This was followed by a sudden weakening of the motor automatism and their gradual extinction. After the first or second stimulation of the brain this process continued on average for 7 ± 2 min. If the interval between stimuli was 10 min, usually only the initial short burst of activity was repeated five or six times, after which the animal developed behavioral depression: drowsiness, limitation of locomotion, and a decrease in the expressiveness of responses to afferent test stimuli.

Nigral stereotypy corresponded to desynchronization on the EEG, which was interrupted by short synchronized episodes while the animal was motionless. During extinction of stereotypy synchronization of the rhythm increased on the EEG. It gradually became monotonous in form with infrequent bursts of "sleep" spindles.

Since electrical stimulation of the substantia nigra leads to increased release of dopamine in the striatum [10, 12], the dynamics of extinction of the after-stereotypy described above can easily be explained by progressive exhaustion of dopamine reserves in the nigrostriatal pathways. At first glance this hypothesis is confirmed by the following observations. It can be regarded as proven that stereotyped behavior of animals induced by amphetamine is due to potentiation of nigrostriatal dopaminergic transmission [1]. As the present experiments showed, repeated stimulation of the substantia nigra against the background of amphetamine stereotypy leads to depression of one state by the other. In the case of first stimulation of the nucleus, motor automatisms provoked by amphetamine (0.5-1 mg/kg) initially were unchanged or their frequency increased compared with the control response. Later, 2-4 min after stopping the current, the expressiveness of stereotypy fell sharply. In individual animals repeated stimulation of the substantia nigra during this period could completely abolish the activity, or even lead to the formation of behavioral depression although, admittedly, this was easily overcome by external stimuli (Fig. 2).

The character of this interaction, as also the progressive extinction of the nigral after-stereotypy, can be attributed to exhaustion of the nigrostriatal dopamine reserves. However, the data described below are evidence more in support of the view that this phenomenon is due to the development of autoinhibition in the nigrostriatal system.

In the modern view excitation of dopaminergic neurons of the substantia nigra leads to inactivation of striatal interneurons and to disinhibition of recurrent strionigral cells, followed by limitation of hyperactivity of the whole nigro—strio—nigral loop [2]. Any conditions that lead to excessive accumulation of synaptic dopamine (repeated stimulation, addition of amphetamine, and so on) must intensify self-limitation or autoinhibition of the system as a whole. Weakening of dopaminergic transmission, on the other hand, should have the opposite effect. This is confirmed by experiments with haloperidol, which has dopamine-blocking properties [9].

In low doses (0.03-0.06 mg/kg), below the threshold for marked depression of spontaneous behavior and of amphetamine-induced stereotypy, haloperidol restored the decaying nigral stereotypy. Under its influence considerable initial activation of the animal after the first stimulation of the substantia nigra was weakened somewhat, but the rate of reduction in the number of motor automatisms with time was clearly retarded. However, against the background of marked weakening of stereotypy (Fig. 3) haloperidol regularly increased the frequency of stereotyped movements, both immediately and in the later stages after cessation of the current. This was manifested on the EEG as lengthening of the period of after-desynchronization, typical of nigral stereotypy.

The fact that haloperidol prevented depression of stereotyped behavior was evidence, on the one hand, that this depression is not connected with exhaustion of the nigrostriatal dopamine reserves, and on the other hand, that autoinhibition is weakened in the nigro—strio—nigral loop, on account of the dopamine-blocking effect of the drug.

Analysis of data in the literature and of our own observations indicates that the effect of haloperidol is more probably due to its depression of presynaptic dopamine receptors located on terminals of nigrostriatal axons, with consequent potentiation of dopaminergic trans-

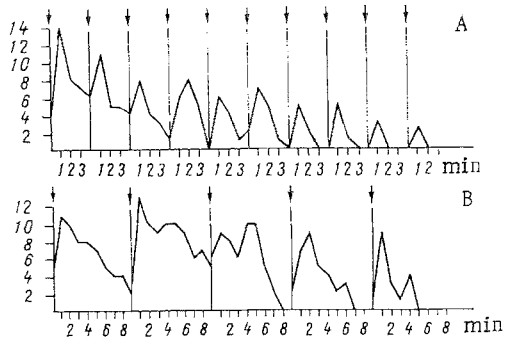

Fig. 1. Different rates of extinction of nigral after-stereotypy depending on intervals between stimulation of substantia nigra. A, B) Nigral effect to short (4 min) and longer (9 min) intervals respectively between nigral stimulation (time of stimulation shown by arrow). Here and in Figs. 2 and 3: abscissa, time (in min) after end of brain stimulation; ordinate, number of stereotyped head movements.

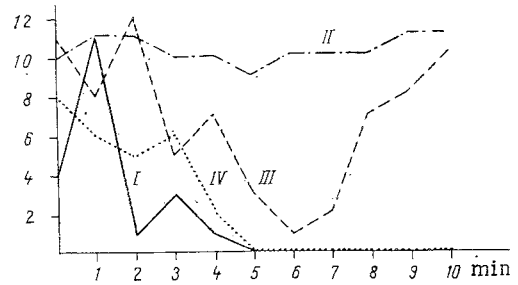

Fig. 2. Effect of repeated stimulation of substantia nigra on amphetamine-induced stereotypy. Curves reflect expressiveness of stereotyped behavior: I) nigral after-stereotypy; II) control amphetamine stereotypy (after 0.5 mg/kg amphetamine); III and IV) effects of first and second stimulation of nucleus against the background of the same dose of amphetamine.

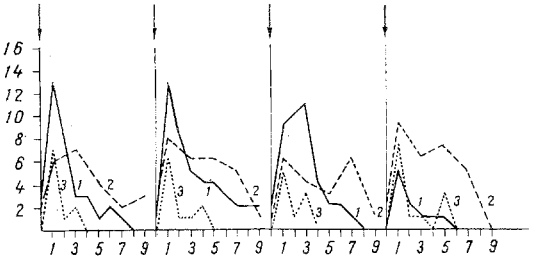

Fig. 3. Effect of small doses of haloperidol and apomorphine on extinction of after-stereotypy during repeated stimulation of substantia nigra. 1) Dynamics of nigral stereotypy during repeated stimulation of nucleus (arrow); 2) the same after preliminary injection of haloperidol (0.03 mg/kg); 3) the same against the background of apomorphine (0.05 mg/kg).

mission. According to Carlsson [5], excitation of these autoreceptors restricts the function of the neurons and prevents further release of mediators into the synaptic space. This would seem to be the only basis for explanation of the potentiation by haloperidol of dopamine synthesis in sections through the corpus striatum or in nigral axons after division of the nigrostriatal tract [6, 13].

The above hypothesis was confirmed by the results of experiments with apomorphine. According to some observations [4, 7, 8], this dopaminomimetic, in low doses, selectively excites presynaptic dopamine receptors. This results in disturbance of the synthesis of striatal dopamine *in vivo* and *in vitro*, and this action is characterized behaviorally by the development of marked sedation.

Experiments showed that a small dose of apomorphine (0.05 mg/kg) in fact had a distinct inhibitory effect on the cats; they quickly were tranquilized and began to drowse in the chamber. Against this background repeated stimulation of the substantia nigra was accompanied by the formation of weak and rapidly subsiding stereotypy. The decline spread to the early and late components of the response (Fig. 3). Progressive synchronization of electrical activity with the development of bursts of "sleep" spindles on the EEG corresponded to weakening of stereotypy. Haloperidol (0.03-0.06 mg/kg) weakened the inhibitory effect of apomorphine both on spontaneous behavior and on nigral stereotypy.

Weakening of the after-stereotypy during repeated stimulation of the substantia nigra was thus evidently due to the development of autoinhibition in the nigro–strio–nigral loop. According to the results of experiments with haloperidol and apomorphine, one reason for this may be activation of dopamine autoreceptors on nigrostriatal axon terminals with a consequent reduction in the release of synaptic dopamine. To judge from the time course of extinction of stereotypy and the character of its restoration by haloperidol, autoreceptors of this sort are not activated at once, but rather not until a short time Korf triggering of the loop. They begin to function most effectively after 2-3 min, to judge from the duration of the burst of initial poststimulation activation.

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