EFFECT OF AMPHETAMINE AND HALOPERIDOL ON STEREOTYPED BEHAVIOR IN CATS DURING ELECTRICAL STIMULATION OF THE SUBSTANTIA NIGRA

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According to data obtained by the writers previously, weak regular electrical stimulation of the substantia nigra (SN) in unrestrained cats triggers a series of stereotyped actions. Other workers consider that only contralateral rotatory movements can be produced by this method [6, 7, 11]. On the basis of the results of neurochemical investigations it must be suggested that some psychostimulants and neuroleptics have the ability to interfere with nigral control of complex forms of behavior [1, 2]. Since this is important for the understanding of their specific psychotropic action and since it requires a neurophysiological explanation, the effect of amphetamine and haloperidol on nigral stereotypy was investigated.

EXPERIMENTAL METHOD

Sixty experiments were conducted on 14 cats of both sexes weighing 2-3.5 kg, with indwelling bipolar nichrome electrodes (diameter 0.2 mm in SN, the neighboring structures of the mesencephalon, and the caudate nucleus. The parameters of stimulation were: frequency 30 Hz, square pulse duration 0.5 msec, duration of stimulation from 15 sec to 1-1.5 min. The animals' behavior was evaluated a few days later, before, during, and after stimulation of the brain, visually (the number and character of movements were taken into account), photographically, and cyclographically [5]. In another three cats the EEG was recorded by the usual method in the region of the sensomotor cortex. The test substances were injected intraperitoneally in physiological saline. After the end of the experiments and fixation of the brain, the location of the stimulating electrodes was determined in frontal sections and compared with data in the atlas [9]. The aggregated data were subjected to statistical analysis by Student's t-test ($P < 0.05$).

EXPERIMENTAL RESULTS

Weak regular stimulation of SN by a current of subthreshold strength for evoking gross motor effects, provoked stereotyped behavior in cats, in the form of monotonous head movements from side to side and up and down, sniffing and, less frequently, grooming. These actions were periodically interrupted by pauses with the gaze fixed rigidly on one point, and extremely reminiscent on the whole of the picture of amphetamine stereotypy. Electrically evoked motor automatisms were usually observed at the moment of brain stimulation, and if the stimulation was sufficiently strong and long (1-1.5 min) in duration they persisted for some time (4-5 min) after the current had stopped. As a rule the stereotypy weakened during repetitive stimulation of the nucleus and it was evoked more readily from its compact zone than from the reticular zone. With an increase in the strength of the current the sterotyped movements were replaced by contralateral rotation of the head, changing into dressage movements in a circle. After the discontinuation of nigral stimulation, desynchronization corresponding to the behavioral picture of stereotypy was recorded on the EEG. Fixed desynchronization could be interrupted 10-15 sec after discontinuation of the current by bursts of synchronized discharges, which coincided with fixation of the animal's gaze during pauses. Excitation of areas of the brain dorsally or ventrally to SN gave no clearly outlined stereotyped behavior or corresponding accompaniment on the EEG. The disturbances thus arising included compulsive motor and (or) emotional-autonomic components.

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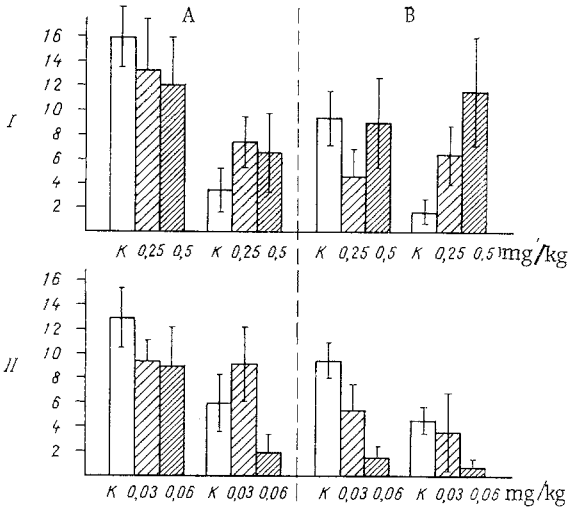

Fig. 1. Effect of amphetamine and haloperidol on intensity of stereotyped behavior due to stimulation of SN. Columns indicate stereotyped activity of animals (mean data for three cats) during first minute of brain stimulation (A) and immediately after its end (delayed stereotypy); B) following administration of amphetamine (I) and haloperidol (II). Abscissa, dose of drug (mg/kg); ordinate, number of rotations of head (per min). K) Initial stereotypy.

The action of amphetamine was studied in doses causing different changes in spontaneous behavior of cats. The small dose (0.25 mg/kg) caused some briskness of locomotion, and with an increase in dose (0.5 mg/kg) elements of amphetamine stereotypy appeared, in the form of short-range head movements of surveying type. In most animals, starting with a dose of 1 mg/kg of the psychostimulant, the stereotypy which developed was relatively strong.

In a low dose amphetamine facilitated the formation of nigral motor automatisms if they were weakly expressed in the initial state. The developing behavioral picture resembled a clear electrically or drug-induced stereotypy. Triggering also was facilitated, and the delayed, poststimulation stereotypy was prolonged. With an increase in the dose of the drug to 0.5 mg/kg, the latter increased to a particularly pronounced degree (Fig. 1). Responses from the compact zone of the nucleus were more distinctly strengthened and those from the reticular zone were much weaker. Strengthening of nigral stereotypy was accompanied by characteristic EEG changes in the form of progressive desynchronization of brain electrical activity. In the poststimulation period, short synchronized episodes corresponded to pauses with a fixed gaze (Fig. 2).

If the initial stereotypy was well marked, the small dose of amphetamine (0.25 mg/kg) often gave an inhibitory effect: a decrease in the number of rotations of the head, a less detailed behavioral picture of stereotypy on account of disappearance of the sniffing actions. Against this background, doubling the dose of the drug restored the poststimulation stereotyped behavior some way toward normal, and with a further increase in the dose it assumed the form of a clear amphetamine stereotypy, with a stable time course. On the whole, the evoked responses were modulated less strongly than the delayed responses.

Thresholds of contralateral rotatory movements arising in response to stronger stimulation of SN showed different changes under the influence of 0.25 mg/kg amphetamine and they had a tendency to diminish after its administration in a dose of 0.5 mg/kg.

The drug had a facilitatory effect on extranigral responses. Doses below and at the stereotype-inducing level (0.5 and 1 mg/kg) lowered the thresholds of compulsive limb movements and the motor restlessness during stimulation of the base of the brain and the region of the medial lemniscus and medial geniculate body became more marked. In two cats, stimu-

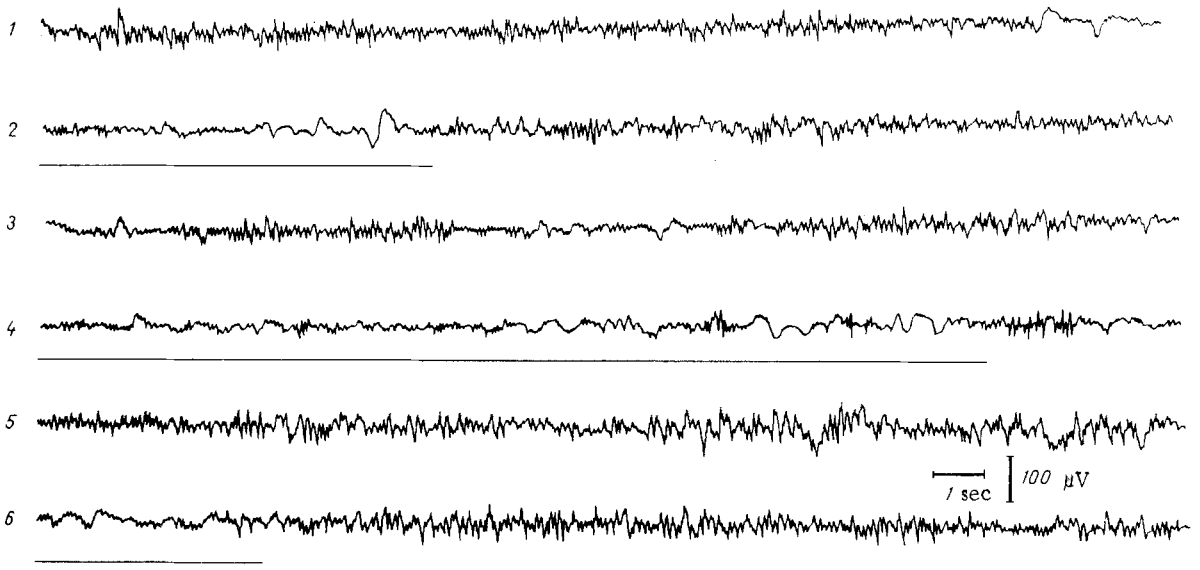

Fig. 2. Effect of amphetamine and haloperiodol on EEG changes after stopping stimulation of SN. 1) Initial EEG; 2) immediately after stimulation of SN (30 Hz, 1 min); 3, 5) effect of amphetamine (0.5 mg/kg) and haloperidol (0.06 mg/kg), respectively; 4, 6) poststimulation nigral stereotypy after administration of the same substances. Horizontal line represents period of delayed desynchronization. Results on different experimental days obtained with cat No. 22.

lation of the lateral supranigral zone regularly inhibited an already developed amphetamine stereotypy.

Since drug-induced stereotypy has been shown to be closely dependent on changes in the normal relations between SN and the caudate nucleus [3] it was interesting to determine the effect of amphetamine on these relationships. The writers observed previously that nigral stereotypy is accompanied by weakening of the arresting function of the caudate nucleus. In response to its stimulation, against the background of stereotyped activity the thresholds of the arrest reaction increased, and this was reflected in the cutting short of spontaneous and goal-directed locomotion. If the weak nigral stereotypy was potentiated by amphetamine (0.25-0.5 mg/kg), under those conditions the arrest of movements was disturbed more sharply. The shift and duration of the threshold increased. Meanwhile stimulation of extranigral points did not appreciably change the caudate effects, and amphetamine added nothing to this result (Fig. 3).

The neuroleptic haloperidol was injected in low doses (0.03-0.125 mg/kg) not giving rise to gross disturbances in the cats' spontaneous behavior. However, after injection of the drug in a dose of 0.03 mg/kg weakening of nigral stereotypy was observed. Delayed poststimulation motor automatisms were particularly highly sensitive, and in some experiments they were completely abolished by haloperidol. The evoked response actually at the moment of brain stimulation proved to be more resistant (Fig. 1). In some cases the weak evoked stereotypy increased somewhat under the influence of low doses of the neuroleptic but weakened with an increase in the dose. Behavioral changes during stimulation of the reticular zone of the nucleus were inhibited sooner and more strongly than from the compact zone. When visible restlessness developed in the animals under the influence of the drug (0.5 mg/kg), stereotyped behavior disappeared completely. On the whole it can be stated that the disturbance of nigral stereotypy by haloperidol followed the same sequence and occurred with the use of the same doses of the drug as with weak amphetamine stereotypy.

Limitation of the stereotyped actions was accompanied by typical EEG changes. Haloperidol (0.03-0.06 mg/kg) shortened the duration of after-desynchronization, corresponding to the clear motor automatisms. By contrast, periods of a synchronized rhythm during the animal's pauses were formed sooner and lasted longer. With an increase in dose of the neuroleptic the EEG began to be dominated by monotonous synchronization (Fig. 2). It appeared before the behavioral picture of stereotypy had disappeared.

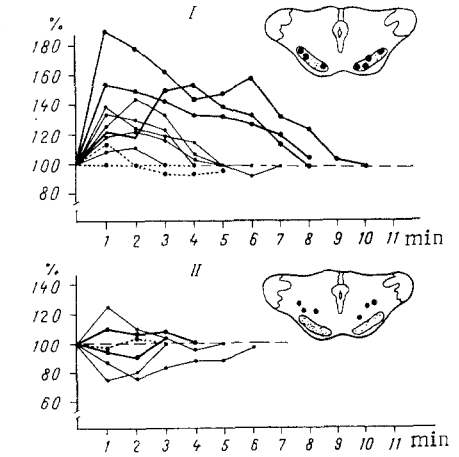

Fig. 3. Changes in thresholds of caudate arrest reactions after stimulation of SN (I) and of extranigral points (II) under the influence of amphetamine and haloperidol. Abscissa, time (in min); ordinate, changes in shift of threshold of movement arrest reaction evoked by stimulation of caudate nucleus (2 Hz, 15 sec) in individual animals (in % of initial level). Thin line reflects results of control determinations, bold line shows effect of amphetamine, and dotted line action of haloperidol. Location of electrodes indicated in diagrams of midbrain.

Unlike amphetamine, haloperiodol more frequently raised the thresholds of contralateral rotations of the head and stepping movements in the case of strong stimulation of SN. Extranigral responses also were weakened by the neuroleptic, but in higher doses than nigral stereotypy. Under the influence of 0.5-1 mg/kg of the drug the formation of emotionally expressive components of the behavioral response was impaired but without any significant change in its autonomic accompaniment.

Whereas amphetamine potentiated, haloperidol clearly limited inhibition of the arresting function of the caudate nucleus of nigral origin. Against the background of the neuroleptic thresholds of the caudate arrest reaction remained on average at their previous level. This action correlated with weakening of the nigral stereotypy even by small doses of the drug (Fig. 3).

The ability of SN to modify spontaneous behavior of cats observed in these experiments is thus modulated in a directly opposite manner by low doses of amphetamine and haloperidol. We know that electrical stimulation of the nucleus leads to the release of dopamine in the corpus striatum [8, 10]. Meanwhile amphetamine increases, whereas heloperidol, on the contrary, weakens dopaminergic transmission [1, 2]. Accordingly the results of the present experiments can be interpreted primarily as the result of a change in nigro-striatal relations. This is shown directly by the results of a study of the arresting mechanisms of the caudate nucleus, nigral disturbance of which is potentiated by amphetamine and abolished by haloperidol. The data obtained by the present writers for the first time in experimental neurophysiology thus confirm the neurochemically based view of amphetamine stereotypy as a behavioral phenomenon due to an increase in activity of SN and functional insufficiency of the caudate nucleus [3]. They can also be regarded as evidence in support of dependence of the specific action of neuroleptics on changes in nigro-striatal dopaminergic transmission.

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EFFECT OF CLONIDINE AND NALOXONE ON HEMODYNAMIC REACTIONS IN DECEREBRATE CATS

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Activation of central α-adrenoreceptors by clonidine is accompanied by changes in functions of the cardiovascular system — hypotension, bradycardia, facilitation of the baroreceptor reflex [11, 15], and by modulation of the mechanisms of regulation of the muscular system — facilitation of the flexor reflex, stimulation of central generators of locomotion or of scratching movements [3, 10].

Considering data on the connection between the hypotensive and certain other effects of clonidine and activation of the endogenous opiate system [8, 9], the investigation described below was carried out to study interaction between the effects of clonidine and naloxone, which blocks opiate receptors, on the mechanism of central somato-autonomic stress, which is one of the components leading to development of adaptive hemodynamic reactions to physical exertion [2].

EXPERIMENTAL METHOD

Experiments were carried out on unanesthetized decerebrate cats. During preparation of the animals for the experiments, under ether anesthesia the carotid artery and jugular vein were catheterized and a bipolar electrode was applied to the central end of the divided nerve to the gastrocnemius muscle. Miniature sensors of an ultrasonic Doppler flowmeter were applied to the ascending arch of the aorta and the common iliac artery, and the dorsal surface of the two upper segments of the spinal cord was exposed. After intercollicular decerebration, by means of a comb electrode and EN-57 electrocoagulation apparatus flaxedil was injected into the animal (3-5 mg/kg, intravenously) and it was artificially ventilated. To facilitate evocation of the scratch reflex, a solution of D-tubocurarine was applied to the exposed surface of the spinal cord [7].

The scratch reflex was evoked by mechanical stimulation of the concha auriculae [5, 6], which was accompanied by the appearance of bursting activity in the nerve to the gastrocnemius muscle. The signal from the nerve was led to a type EMT-12B universal amplifier (Sweden), after which it underwent full-wave rectification and smoothing by means of an active RC integrator. The arterial blood pressure (BP) was measured with an EMT-34 electromanometer. All parameters were recorded on the N 338-6N instrument.

Clonidine (Boehringer Ingelheim) was tested in a dose of 30 μg/kg, naloxone (Endo Laboratories) in a dose of 0.12-0.15 mg/kg. The drugs were diluted with physiological saline.

The results were subjected to statistical analysis by Student's t-test for paired comparison.

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