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CIRCADIAN RHYTHM OF ACTIVITY OF THE CAUDATE NUCLEUS IN CATS AND ITS SENSITIVITY TO PSYCHOTROPIC DRUGS

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Circadian changes in brain function may be reflected significantly in the action of psychotropic drugs. The specific properties of individual psychostimulants and neuroleptics largely depend on changes in activity of the basal ganglia and, in particular, of the caudate nucleus [2, 3].

It was accordingly decided to assess the character of caudate nucleus activity at different times of the 24-h period and to assess the role of this factor in the effect of the psychostimulant amphetamine and of the neuroleptic haloperidol.

EXPERIMENTAL METHOD

Altogether 96 experiments were carried out on seven cats of both sexes weighing 2-3.5 kg. Under pentobarbital anesthesia bipolar nichrome electrodes (diameter 0.2 mm) were first inserted into different parts of the caudate nucleus. One week after the operation the experiments were repeated, with the conditions of keeping and feeding standardized as much as possible. Natural illumination was used during the summer months (June to August). The level of general activity of the cats was assessed by their response to adequate test stimuli (calling by name, petting, playing) by means of a point scale [8]. To characterize stereotyped behavior the number of head movements was counted and abnormal activity of the animals was recorded cyclographically [5]. The caudate nucleus was stimulated by square pulses (frequency 2 pulses/sec, strength of current 2-20 μA, duration of stimulus 0.5 msec, of stimulation 10-15 sec). Restraint of movements arising as a result was analyzed by the method described previously [4].

In three cats (Nos. 6, 7, and 8; eight experiments) general activity and thresholds of the restraining response were determined during the 24-h period every 3 h starting at 9 a.m. In the other cases the caudate response and effect of the drugs were assessed at midday (11 a.m.-1 p.m.) and midnight (11 p.m.-1 a.m.) at intervals of 2-3 days. The drugs were injected intraperitoneally at the specified times 25-30 min before determination of the effect. The numerical results were subjected to statistical analysis by Student's t test ($P < 0.05$). After the end of the experiments and fixation of the brain, the position of the stimulating electrodes was determined in frontal sections and compared with data in the atlas [13].

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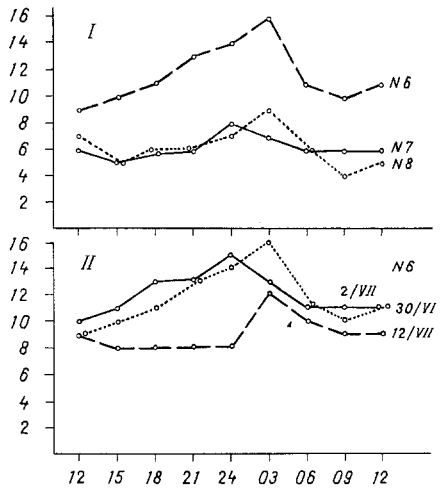

Fig. 1. Circadian rhythm of threshold of movement restraint response evoked by stimulation of caudate nucleus in different cats (I) and in the same animal (II). Abscissa, time (in h); ordinate, strength of stimulating current (in μA).

EXPERIMENTAL RESULTS

In full agreement with the general view that the cat is a nocturnal animal, higher activity was found at night (from midnight to 3 a.m.). During this time, despite complete adaptation to the experimental situation, the cats performed head turning movements and moved actively around the room more frequently than during the day. Presentation of biologically adequate test stimuli readily provoked an orienting reaction and play behavior. The average score (during successive application of three stimuli) of points characterizing the animals' general activity was 30-40% higher than the corresponding value during daylight.

An important functional characteristic of the caudate nucleus is its ability to exert a restraining influence on different kinds of behavior. This property of the nucleus is reproduced by low-frequency electrical stimulation of the nucleus as a response of restraint of spontaneous or purposive movements. Depending on the intensity of stimulation and the position of the electrodes, the response varies in strength and, in the case of response rated at 3-4 points, stopping of the movements is supplemented by a catatonic increase in muscle tone [4].

The results showed that this response differed in intensity at different times of the 24-h period. Repeated (at intervals of 3 h) determination of excitability of the nucleus round the clock showed that its functional activity is highest during the day (9 a.m. to 3 p.m.). During this period the restraint response appeared most easily of all and its thresholds were lowest and the catatonic element of the evoked response was manifested most clearly. Conversely, at night (between midnight and 3 a.m.) the thresholds of the response were highest. The acrophase of the shift occurred during this time interval both in individual animals and in the same cat in repeated experiments (Fig. 1). In the latter case, some variations of the parameters were possible, although the general trend of the shift remained the same.

The histological study of the brain showed that the source of the restraint response was mainly the ventrolateral portions of the head of the caudate nucleus. A similar time course of the variation in threshold of the caudate response was recorded, moreover, during stimulation of central parts of the head (cat No. 5).

In a low dose (0.5 mg/kg), below the threshold for provocation of stereotyped behavior, amphetamine increased the spontaneous activity, including locomotor activity, of the animals a little. The stimulating effect of the drug, in the form of more frequent movements about the chamber, an increase in the number of head movements, and a revival of the response to the test stimuli, was most marked at night. In precisely the same way, abnormal behavior was formed more easily at night (midnight to 2 a.m.) – amphetamine stereotypy – as a result of higher doses of the drug (1 mg/kg). By contrast with determinations during the daytime (noon to 1 p.m.) stereotyped behavior at night was characterized by clearer manifestations: Motor automatisms were wide in amplitude and sweeping, and were often accompanied by sniffing and licking. The number of head turnings was 20-30% greater than in the daytime (Fig. 2).

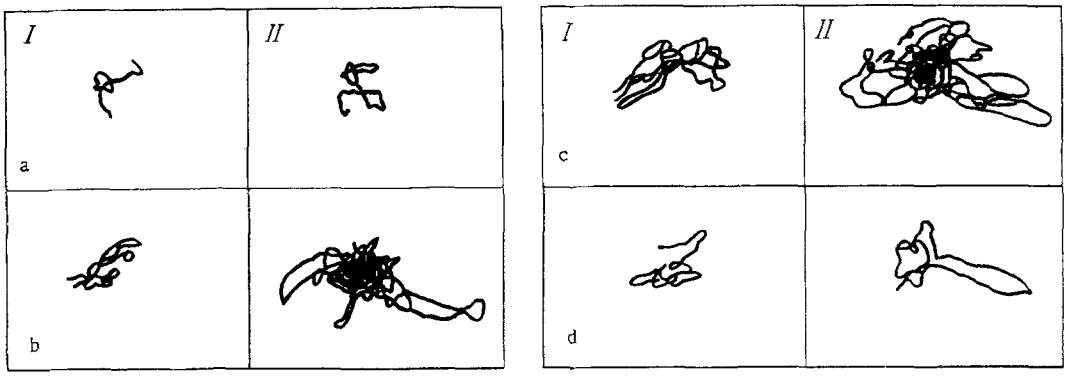

Fig. 2. Cyclographic characteristics of amphetamine stereotypy in cat No. 9 at different times of day and night. a) Initial activity; b, c) after administration of amphetamine in doses of 0.5 and 1 mg/kg respectively; d) abolition of stereotypy by haloperidol (0.5 mg/kg). I) Day (noon-1 p.m.); II) night (midnight-1 a.m.).

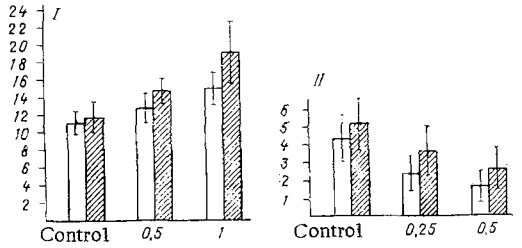

Fig. 3. Effect of amphetamine (I) and haloperidol (II) on thresholds of caudate restraint response at different times of day and night. Unshaded columns – data of daytime experiments (11 a.m.-1 p.m.), shaded columns – data of experiments at night (11 p.m.-1 a.m.). Mean results of six experiments on one animal (cat No. 6) shown. Abscissa, dose of drug (in mg/kg); ordinate, strength of stimulating current (in μA).

Haloperidol (0.25-0.5 mg/kg) inhibited the cats' spontaneous activity more strongly by day than by night. Even after the smaller dose of the neuroleptic the animals were quietened, they took up a certain position in the chamber, and began to doze. Responses to afferent stimuli were abolished more easily. By day the ability of haloperidol to block stereotyped behavior evoked by large doses of amphetamine was manifested more clearly.

The drugs tested changed the parameters of activity of the caudate nucleus in different directions depending on circadian variations in its activity. In a substereotype dose amphetamine raised ($P > 0.05$) the thresholds of the restraint response by day relative to the control level (injection of physiological saline). At night, however, this effect was much stronger, and even during a small number of observations on the same animal, it was statistically significant. With an increase in the dose of amphetamine and as the stereotype developed, the restraining properties of the nucleus were disturbed even more sharply, and also more clearly at night. For the case represented in Fig. 3 (cat No. 6), whereas at night the response thresholds rose from 14.3± 1.3 to 18.8 ± 3.3 μA, by day they were at lower levels (from 12.7 ± 1.4 to 14.8 ± 1.8 μA).

By contrast with amphetamine, haloperidol potentiated the restraining function of the caudate nucleus and lowered the thresholds of the restraint response. Even in a dose of 0.25 mg/kg the neuroleptic led to a more significant lowering of the response threshold in the daytime and had a weaker effect on this parameter at night. These same tendencies were maintained when the dose of the drug was increased (Fig. 3).

The results are evidence of the existence of circadian fluctuations in activity of the caudate nucleus, which are distinctly reflected in the effectiveness of psychotropic drugs tested. Weakening of the restraining function

of the nucleus which we found at night in cats can be explained by elevation of the general level of wakefulness of the animals on account of limitation of activity of the inactivation system of the brain, of which the caudate nucleus is part. The primary cause of the caudate deficiency may be strengthening of nigro-striatal dopaminergic control [6]. Evidence of this is given by the increase in the dopamine concentration in the striatum of certain species of nocturnal animals (rats, guinea pigs) or an increase in the number of dopamine receptors during the dark period of the day [11, 12].

Under these conditions stereotyped behavior and limitation of the caudate restraint response were marked after injection of amphetamine, stimulating the release and accumulation of dopamine in nigrostriatal pathways [1]. Conversely, the action of haloperidol, a blocker of dopamine receptors, is manifested less strongly during activation of dopaminergic transmission at night, in agreement with the results of experiments in which other effects of the neuroleptic (sedation, catalepsy) were estimated in rodents [7, 9, 14]. Meanwhile circadian variations in sensitivity to haloperidol may also be due to the pharmacokinetic properties of the drug [10]. Whatever the interpretation of the results, it is clearly essential to take account of circadian fluctuations in the activity of psychotropic drugs when they are prescribed.

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