The analgesic action of morphine is known to be due to its ability to bind with opiate receptors, which are distributed heterogeneously in the spinal cord and brain [14]. Naloxone, an antagonist of the narcotic analgesics, with greater affinity for opiate receptors, displaces morphine and abolishes its analgesic action.

The results suggest that bradykinin also interacts with opiate receptors. This hypothesis is based on the fact that bradykinin had no activating action when given after morphine, evidently because the opiate receptors were already occupied by the analgesic. When application of morphine was followed by that of its specific antagonist, naloxone, the response of the neurons to bradykinin was restored.

At the level of opiate receptors of single neurons interaction thus takes place between the endogenous oligopeptide bradykinin, inducing pain, and morphine and naloxone. Confirmation that opiate receptors may be the substrate of the pain response is given by observations showing that naloxone potentiates nociceptive responses in animals [7].

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EFFECT OF AMPHETAMINE AND CAFFEINE ON BEHAVIORAL CHANGES FOLLOWING ELECTRICAL STIMULATION OF THE CAUDATE NUCLEUS IN CATS

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Low doses of amphetamine (0.1-0.5 mg/kg), not affecting the spontaneous behavior of cats, prevent the appearance of behavioral depression after repetitive low-frequency stimulation of the caudate nucleus. Activation phenomena observed after the end of stimulation are considerably potentiated, sometimes with stereotype formation. Caffeine (10-80 mg/kg), which may even activate spontaneous behavior in cats, does not prevent the development of caudate inhibition.

KEY WORDS: amphetamine; caffeine; caudate nucleus; behavioral depression; caudate depression.

Psychostimulation by drugs may depend, among other things, on changes in function of the caudate nucleus [2]. This view is based on the results of a study of caudate responses arising actually during brain

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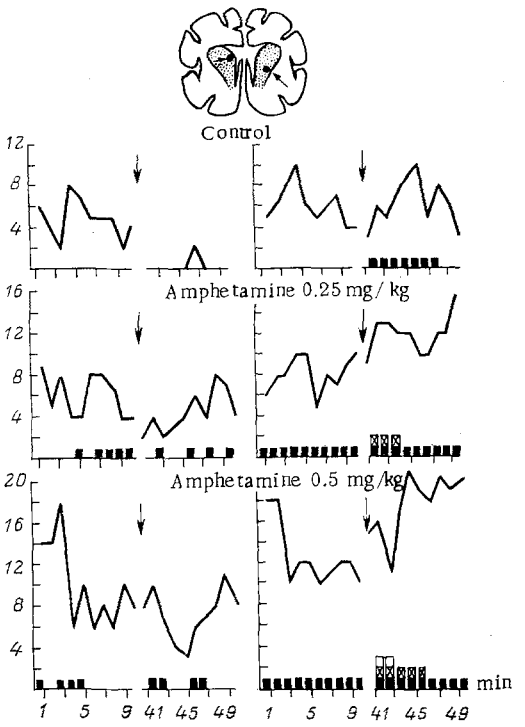

Fig. 1. Effect of amphetamine on spontaneous activity of cat and behavioral changes evoked by repeated stimulation of various zones of caudate nucleus. Arrow indicates time of stimulation of caudate nucleus (3rd stimulation, frequency 2 Hz, duration 2.5 min). Black columns denote grooming, cross-hatched columns dressage movements, unshaded columns vocalization. Left side of figure shows changes after 3rd stimulation of dorsomedial part of head of caudate nucleus, right side after stimulation of ventrolateral zone. Arrows on frontal brain sections show locations of stimulating electrodes. Abscissa, time of observation (in min); ordinate, number of head movements/min.

stimulation. However, behavioral changes induced by stimulation and persisting for a long time after its end, resemble the natural state more closely and are more appropriate for psychopharmacological purposes [5]. One such phenomenon is the so-called caudate sleep [6-9], the sensitivity of which to amphetamine and caffeine was studied in the present investigation.

EXPERIMENTAL METHOD

Altogether 156 experiments were carried out on 37 cats of both sexes weighing 2.2-3.2 kg. As a preliminary measure, under pentobarbital anesthesia monopolar nichrome electrodes (0.1 mm in diameter) were inserted into different parts of the caudate nucleus and neighboring brain structures. Spontaneous behavior of the cats and the character of their response to test stimuli (calling by name, introduction of an indifferent object into the chamber, waving the hand, stroking, and so on) were assessed visually. Stable behavioral changes were produced by prolonged (2.5 min) repeated (4-5 times every 10-15 min) low-frequency (2 Hz) stimulation of the brain. Amphetamine (in doses of 0.1, 0.25, and 0.5 mg/kg) and caffeine (in doses of 10, 20, 40, and 80 mg/kg) were injected intraperitoneally. Experiments on one animal were carried out not more often than once every 3 days. The results of the main experiments were compared with those of various control determinations (prolonged recording of spontaneous behavior, assessment of evoked responses in a given animal, effects of psychostimulants alone, effect of injection of physiological saline on spontaneous and evoked behavior).

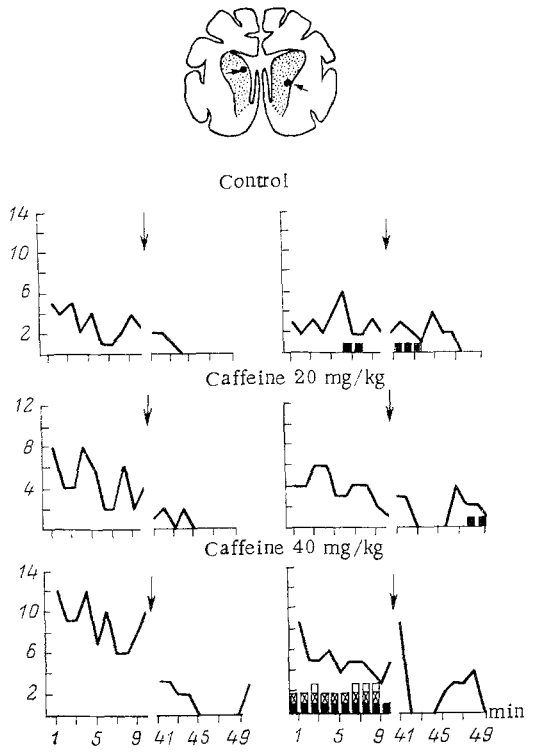

Fig. 2. Changes in caudate depression under the influence of increasing doses of caffeine. Legend as in Fig. 1.

After the end of the experiments the location of the electrode was verified in a series of frontal brain sections against coordinates taken from a stereotaxic atlas [10].

EXPERIMENTAL RESULTS

During repeated stimulation of the caudate nucleus in cats so-called caudate depression developed. The animals lay on the floor, closed their eyes, and responded apathetically to test stimuli: calling, waving, stroking, introduction of an object into the chamber. This state lasted on average 6-8 min after the end of stimulation and, in most cases (73%), it was well marked as early as after the 3rd stimulation. It was evoked most easily from the dorsal and dorsomedial zones of the head of the caudate nucleus. Stimulation of the ventral zones of the nucleus frequently provoked the opposite effect: caudate activation, which was followed by depression. Manifestations of activation were rhythmic turning of the head and a series of grooming movements. Caudate activation was a less stable phenomenon and was more characteristic of the first stage of the experiments. With an increase in the number of stimulations, the intensity of the activation phenomena diminished.

In a low dose (0.1 mg/kg), not changing the animals' spontaneous behavior, amphetamine influenced the course of the evoked responses. It facilitated the formation of caudate activation and, conversely, inhibited the appearance of caudate depression, for the production of which a larger number of stimulations of the nucleus (on average one or two more) was required. Under these circumstances the cats began to respond in a more lively and organized manner to external stimuli. Even a weak stimulus such as calling, to which adaptation quickly developed, provoked the animals to raise their head and open their eyes. With an increase in the dose of the drug to 0.25 mg/kg caudate depression could not be obtained even in response to stimulation of the dorsomedial zones of the nucleus. Caudate activation did not just increase, but its pattern changed: the head turning became more swinging in character, wider in amplitude, and mainly toward the stimulated nucleus. The grooming also became more distinctive and paroxysmal in character. Stubbornly, persistently, and chaotically the animals licked the tail, anus, side, and so on.

Repeated stimulation of the ventral zones of the nucleus against the background of action of the drugs led to circular dressage movements around the chamber, mainly toward the stimulated nucleus (on average three or four tours of the chamber in a 10-min interval).

These phenomena progressed even more after injection of 0.5 mg/kg amphetamine. Activation changes, especially in response to stimulation of the ventrolateral zones of the nucleus, resembled stereotyped behavior, just as when neurotoxic doses of the drug were used (Fig. 1).

Meanwhile, with a 5-7-fold increase in the number of stimuli applied to the dorsomedial zones of the caudate nucleus the animals showed short periods (not exceeding 20 sec) of depression. These appeared more frequently during the first minutes after the end of stimulation. The cats stopped all their motor activity, froze on the spot, and gazed fixedly at one point.

Caffeine, starting with a dose of 20-40 mg/kg, appreciably activated the animals' spontaneous behavior and, in particular, their motor activity. The cats moved about the chamber actively, tried to escape from it, and turned their head. Meanwhile caudal depression, by contrast with the effects of amphetamine, was no less stable than before. Admittedly, in its characteristics it differed appreciably from that observed in the control. It was rather shorter in duration, and even when most clearly expressed, it did not exceed 5 min. The animals continued to hold their head high, but their eyes remained half closed and their ears stuck out prominently.

Activation phenomena were potentiated by caffeine. The number of turning movements of the head increased, but the movements themselves were of low amplitude, rapid, and took place in fits and starts. Grooming was of the same character as in the control (Fig. 2).

An increase in the dose of caffeine to 80 mg/kg led to marked excitation of the animals. Their behavior became extremely chaotic in character: turning the head, moving across the chamber in all possible directions, grooming of fragmentary type with licking of different parts of the body, licking all over, and tapping with the forelimbs. The excitation also had a well defined autonomic and emotional overtone, with mydriasis, tachypnea, piloerection, and crying. The animals were highly excited and alert and responded to external stimulation by alarm. Despite the manifest spontaneous activity, caudate depression continued to arise after this dose of the drug, although it was superficial in character. Its duration was reduced to 2-4 min, and it occurred typically in the first few minutes after the end of stimulation. Under the influence of caudate stimulation the emotional state also became rather more normal. The animals began to respond adequately to the test stimuli (calling, stroking, waving).

The results thus showed that amphetamine, even in low doses (0.1-0.25 mg/kg), inhibited the development of caudate depression and at the same time potentiated behavioral activation, even to the extent of formation of a definite stereotype in the cats' behavior. Caffeine, on the other hand, although it considerably activated the animals' spontaneous behavior, was much weaker than amphetamine in its action on caudate responses. Even after a large dose of caffeine (80 mg/kg) caudate depression still continued to develop, although it was short in duration.

On the basis of the similarity of the external and electroencephalographic manifestations some workers have identified caudate depression with sleep, and they number the caudate nucleus itself among the hypnogenic structures of the brain [7-9]. In that case caffeine, as an analeptic, ought to suppress caudate effects in the same way as amphetamine. However, this does not take place, and this raises doubts about the hypnogenic nature of caudate depression. Moreover, the structure of the behavioral change evidently includes elements of a predisposition to sleep, and through its action on this, caffeine may shorten the caudate response. From this point of view the depressant effect of the drugs on caudate effects may determine different aspects of drug psychostimulation.

Meanwhile the results of the study of the action of caffeine suggest that caudate depression is largely due to a disturbance in the motor sphere, evidently on account of relations between the nucleus and other structures of the extrapyramidal system [1]. These relations are probably resistant to the action of caffeine which, unlike amphetamine, does not possess antiparkinsonism properties [3, 4].

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