EFFECT OF PARACHLOROPHENYLALANINE AND 5-HYDROXYTRYPTOPHAN ON THE CAUDATE NUCLEUS IN CATS

É. B. Arushanyan and B. A. Tolpyshev

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Parachlorophenylalanine, an inhibitor of serotonin synthesis, raised the thresholds of the contraversive reaction, the arrest reaction, and the spindle waves accompanying it in the sensomotor cortex of unanesthetized, unrestrained cats during stimulation of the rostro-ventral zones of the caudate nucleus. The effects arising from the dorsomedial zones of the head and body of the nucleus changed in opposite directions. The serotonin precursor 5-hydroxytryptophan, on the other hand, potentiated most indices of caudate nuclear activity irrespective of the site of stimulation. The existence of serotoninergic mechanisms in the rostro-ventral zones of the nucleus antagonistic to the dopaminergic system and capable of triggering certain caudate functions is postulated.

KEY WORDS: serotonin; parachlorophenylalanine; 5-hydroxytryptophan; caudate nucleus; caudate reactions; behavior of cats.

The activity of the caudate nucleus is closely bound with various mediators (dopamine, acetylcholine, GABA). Among them, an important role may belong to serotonin. A high concentration of serotonin in the striatum has been demonstrated fluorometrically and histochemically [6, 11]. Electrical stimulation of the caudate nucleus intensifies liberation of the mediator into the cerebrospinal fluid [8], whereas local application of serotonin to the nucleus gives various behavioral effects [4].

In view of this information it was decided to study how interference with serotoninergic transmission in different ways influences the individual indices of activity of the caudate nucleus.

EXPERIMENTAL METHOD

In 46 experiments on eight adult cats of both sexes, weighing 2.2-3 kg, motor effects to stimulation of the caudate nucleus were recorded as the arrest reaction and contraversive reaction, together with their electrographic accompaniment. For this purpose, under pentobarbital anesthesia, from one to three bipolar nichrome electrodes were implanted into different zones of the caudate nucleus and steel needles were inserted into the region of the sensomotor cortex. Movements were arrested by low-frequency (2 and 10 pulses/sec) electrical stimulation of the nucleus and evaluated on a four-point scale (for details of the method, see [2]). The contraversive reaction, consisting of rotation of the head and trunk, was induced by high-frequency (30 pulses/sec) stimulation of the nucleus. The animals' behavior was recorded visually and by still and motion pictures, whereas the accompanying electrographic phenomena were recorded on a four-channel electroencephalograph.

The test substances were injected intraperitoneally. Parachlorophenylalanine (PCPA, Sandoz, Switzerland) was injected in a dose of 200 mg/kg, and observations on the animals' behavior were made 24 h later and then daily for 4-5 days. 5-Hydroxytryptophan (5-HT) was injected in increasing doses from 5 to 30 mg/kg. The effects were determined starting from 10-15 min after injection.

EXPERIMENTAL RESULTS

Effect of PCPA. Spontaneous behavior of the animals was essentially unchanged 24 h after the injection of PCPA. Changes coinciding with those described previously in the literature were observed after 48 h [9]. On the whole, some increase in locomotor activity was found. The cats became more affectionate and approach-

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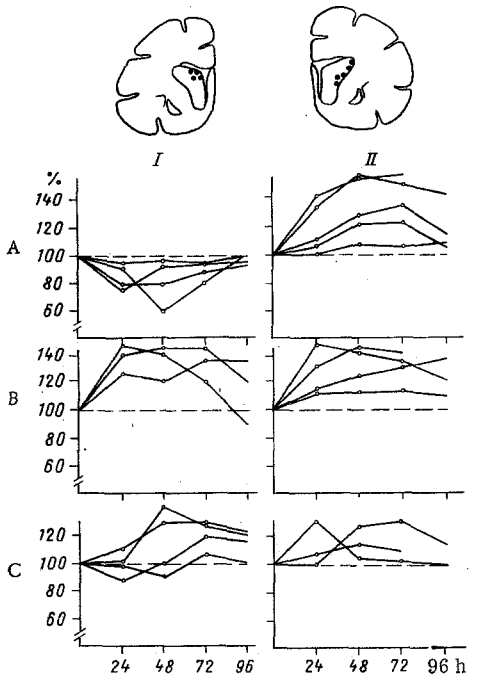

Fig. 1. Effect of PCPA on thresholds of arrest reaction (A), on spindle waves of EEG (B), and contraversive reaction (C) induced by stimulation of caudate nucleus in certain animals. I) Changes during stimulation of dorsomedial, II) of ventrolateral zones of head and body of caudate nucleus. Location of stimulating electrodes indicated on schemes of frontal brain sections in upper part of figure. Abscissa, time of recording effect (in h) after injection of PCPA; ordinate, relative thresholds of reaction in % of initial level for each point of nucleus.

able and their appetite increased. Increased sexuality was observed in the males. The activation of behavior was accompanied by desynchronization of the EEG. These phenomena became less marked toward the 3rd-5th day after injection of the test dose of PCPA.

The effects of PCPA were studied during stimulation of nine points of the caudate nucleus. Arrest of movements caused by stimulation of the caudate nucleus [2] was changed in different directions by PCPA. Most frequently (five points) its threshold was increased, in some cases by as much as 40-50% of the initial level. The maximal effect was observed 48-72 h after injection (Fig. 1A). In three cases a tendency was observed for the threshold of the arrest reaction to be lowered 24-48 h after injection of PCPA.

Comparison of the location of the stimulating electrodes with the effect of stimulation showed that weakening of the arrest reaction took place in response to stimulation of the ventrolateral zones of the head of the caudate nucleus, whereas stimulation of the dorsal parts of the head of the nucleus, on the other hand, potentiated the arrest effect.

Arrest was usually accompanied on the EEG by so-called spindle waves. The threshold of their appearance was raised by PCPA, independently of the location of the point of stimulation (Fig. 1B). Shortening of the evoked discharges and a decrease in their amplitude also were observed (Fig. 2). The absence of correlation between the changes in the thresholds of the spindle waves and the arrest reaction during stimulation of the dorsocaudal zones of the nucleus is further evidence that the two phenomena are parallel rather than interdependent [1].

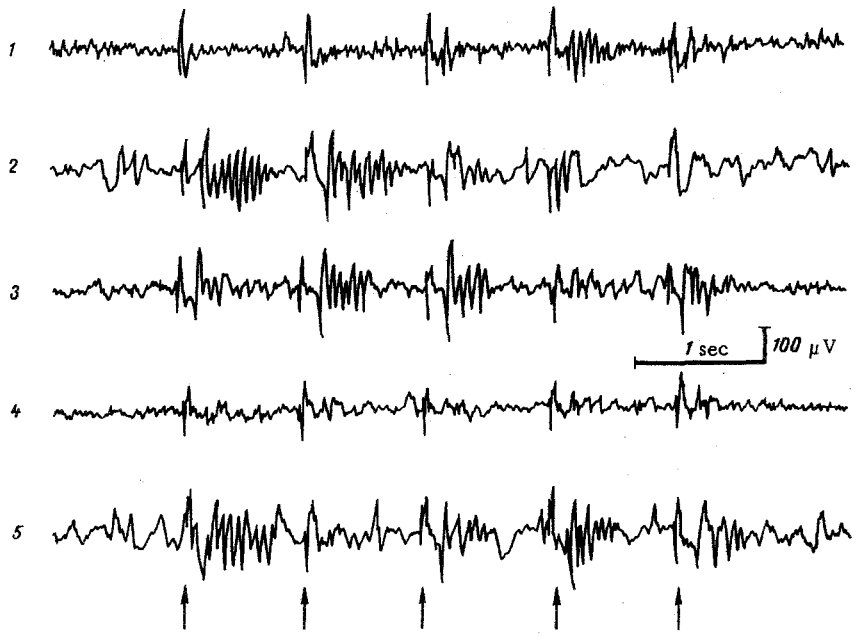

Fig. 2. Effect of 5-HT and PCPA on spindle waves in sensomotor complex during stimulation of one point of caudate nucleus in the same animal. 1 and 3) Initial picture of cortical response to stimulation of nucleus at frequency of 1 pulse/sec with voltage of 15 and 17 V respectively; 2) 20 min after injection of 5-HT, 30 mg/kg; 4) 48 h after injection of PCPA, 200 mg/kg; 5) 20 min after injection of 5-HT against this background.

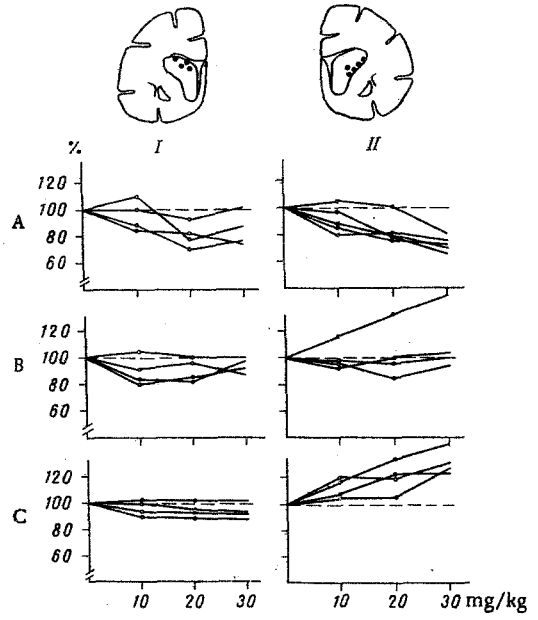

Fig. 3. Effect of increasing doses of 5-HT on thresholds of test reactions during stimulation of caudate nucleus in individual animals. Abscissa, doses of 5-HT, mg/kg; ordinate, time of recording effect. Remainder of legend as in Fig. 1.

High-frequency stimulation of the caudate nucleus most frequently evoked rotation of the head and trunk of the cats in the contralateral direction – a contraversive reaction. After injection of PCPA, its threshold was raised in most cases (Fig. 1C). Injection of PCPA also disturbed circular stepping movements, whereas stable isolated rotary movements of the head were more resistant. In two cases an ipsiversive reaction was observed, and this was unaffected in one animal but weakened in another by PCPA.

Effect of 5-HT. In a small dose (10 mg/kg) 5-HT in most cases did not significantly change the cats' behavior. Only occasionally was moderate sedation observed. After injection of 20 mg/kg of the compound spontaneous locomotion was distinctly weakened. Changes in the animals' emotional state, in the form of alertness and fear, appeared at the same time. All these changes developed against the background of increased tone of the parasympathetic system: miosis, salivation, diarrhea, and bradycardia. With an increase in the dose (up to 30 mg/kg) these phenomena were intensified and were sometimes accompanied by choreiform hyperkineses of the limbs and a fine tremor of the head.

The effect of 5-HT on the caudate reactions was studied during electrical stimulation of nine points of the caudate nucleus. Arrest of movements on the whole changed uniformly, with a decrease in the threshold of the responses. The same effect was observed during stimulation of both dorsal and ventral zones of the head or body of the nucleus. The only difference was perhaps that the responses from the dorsal zone were more distinctly weakened after injection of 20 mg/kg of the compound, and with an increase in the dose, there was a tendency, conversely, for the change to diminish (Fig. 3A).

After injection of 5-HT the background EEG showed moderate synchronization with infrequent spontaneous spindles. Against this background, single caudate stimuli more easily provoked bursts of spindle waves. The threshold of their appearance was as a rule lowered, although in one case it was raised (Figs. 2 and 3B).

The contraversive reaction showed little change under the influence of 5-HT in the case of stimulation of the dorsal zone of the nucleus. The thresholds of responses evoked from the ventrolateral regions of the head were raised (Fig. 3C). Ipsilateral rotations, on the other hand, were inhibited by 5-HT.

If 5-HT was injected after PCPA, the effects of the latter on the arrest reaction, spindle waves, and rotatory movements evoked by stimulation of definite points of the nucleus were suppressed. Nevertheless, the action of the two preparations was not always clearly in opposite directions. It is interesting to note that after injection of PCPA the serotonin precursor evoked more marked synchronization of the EEG. In response to a single caudate stimulus slow activity appeared, and at times this masked or deformed the spindle waves (Fig. 2B).

The results are evidence that interference with serotoninergic transmission by means of an inhibitor of synthesis of the mediator or its precursor has an appreciable effect on certain functions of the caudate nucleus. Consequently, the mechanism of these functions and also the pharmacodynamics of certain neurotropic drugs acting on the caudate nucleus must be closely bound with serotonin metabolism. Meanwhile, as the results of these investigations show, the role of this transmitter in the nucleus has by no means been unequivocally solved. The conclusion of Cools [4, 5], that topographically demarcated zones are dependent primarily on the state of serotoninergic transmission, must evidently be accepted. According to the facts described above, these zones are concentrated in the rostroventral parts of the nucleus, and serotonin evidently plays the role of activator of several functions of the caudate nucleus. Disturbance of serotoninergic mechanisms against the background of PCPA weakens the restraining properties of the nucleus and interferes with the manifestation of the EEG accompaniment, in the form of spindle waves, whereas 5-HT acts in the opposite way. Serotonin thus behaves like an antagonist of the other important mediator of the nucleus – dopamine. In fact, a disturbance of dopaminergic transmission lowers the thresholds of the arrest reaction and of the caudate spindle waves in the cortex [3]. This fact confirms the concept of reciprocal relations between the two transmitters in the maintenance of striatal functions [7].

Meanwhile the possibility cannot be ruled out that secondary changes take place in the activity of the caudate nucleus because of modulation of extracaudate serotoninergic processes by the substances tested, or that they intervene directly in the activity of dopaminergic terminals [10].

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EFFECT OF ETHIMIZOLE ON CHANGES IN BRAIN METABOLISM CAUSED BY OVERSTIMULATION

E. V. Moreva and V. V. Bul'on

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During overstimulation (electrical stimulation for 3 h) of rats considerable changes are observed in their brain metabolism. These changes are manifested as exhaustion of the noradrenalin reserves and disturbance of energy metabolism, leading to a fall in the creatine phosphate level. Preliminary (before electrical stimulation) administration of ethimizole prevented the noradrenalin and creatine phosphate deficiencies in the brain tissue of the overstimulated animals.

KEY WORDS: prolonged electrical stimulation of the brain; energy metabolism; noradrenalin; ethimizole.

Analysis of reflex dystrophies of the internal organs has shown that the development of tissue injuries is connected with a disturbance of the regulatory influences of the CNS. This is shown by the protective action of neurotropic drugs blocking cholinergic and adrenergic systems in the CNS and by the sharp decrease in the concentration of mediators – acetylcholine and, in particular, noradrenalin (NA) – in the brain tissue [1, 9, 10].

The invariable participation of the CNS in the transmission of noxious impulses during stimulation of reflexogenic zones was the motivation for the present investigation to determine whether metabolic changes take place under these circumstances in the brain tissue and whether they can be regulated by neurotropic drugs such as are used for the treatment of experimental neurodystrophies.

For this purpose, some indices of energy metabolism of the brain were studied and the NA concentration determined. The neurotropic drug used was ethimizole, an alkylamide of imidazoledicarboxylic acid with a marked central action on the energy metabolism of the CNS. The writers showed previously that ethimizole, 20 min after injection into normal animals, increases glycolysis, oxidative phosphorylation, and the creatine phosphate (CP) concentration, but reduces the inorganic phosphorus content [2, 5, 11].

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 180-200 g. For overstimulation, leading to the development of neurogenic dystrophies, the animals were stimulated electrically for 3 h through needle electrodes implanted into the muscles of the forelimbs [3]. Ethimizole was injected intraperitoneally in a dose of 25 mg/kg 20 min before electrical stimulation began. Immediately after the end of stimulation the rats were killed by immersion in liquid oxygen, the brain was removed, and the content of NA [6], pyruvic acid [16], lactate [13], glycogen [17], CP [14], and inorganic phosphorus [15] was determined in the cerebral hemispheres. Intact animals served as the control.

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