EFFECT OF CATECHOLAMINERGIC DRUGS ON EPILEPTOGENIC PROPERTIES OF THE CAUDATE NUCLEUS

R. M. Avakyan and É. B. Arushanyan

UDC 615.217.22.015.4:612.826.1

Drugs stimulating catecholaminergic transmission (dopa, apomorphine, amphetamine, and their combination with disulfiram) weakened the epileptogenic properties of the caudate nucleus in freely moving rats. Under the influence of these drugs the cortical electroencephalographic response to single stimulation of the nucleus was shortened in animals receiving subconvulsant doses of leptazol and the intensity of the spike-wave rhythm bound with repeated caudate stimuli was reduced. Conversely, inhibitors of catecholaminergic transmission (chlorpromazine, haloperidol, α-methyltyrosine, and disulfiram) potentiated the epileptogenic effects of the caudate nucleus.

KEY WORDS: *caudate nucleus; catecholaminergic mechanisms; leptazol convulsions.*

The caudate nucleus has been shown [3, 4, 6] to stimulate the formation of a state of readiness for convulsions. This is expressed, in particular, as an increase in various indices of preconvulsant action of leptazol. This may be taken as evidence of the participation of the caudate nucleus in the formation of the attack of petit mal.

To clarify the neurochemical mechanisms of this participation the effect of substances potentiating and weakening central catecholaminergic transmission on the ability of the caudate nucleus to potentiate behavioral and electroencephalographic manifestations of leptazol activation was studied.

EXPERIMENTAL METHOD

Experiments were carried out on 15 male albino rats weighing 200-300 g. Under pentobarbital anesthesia monopolar recording electrodes for taking the EEG were inserted into the sensomotor cortex and contralateral caudate nucleus. In addition, bipolar electrodes for stimulation (single or repetitive square pulses, 1-3/sec, 0.1 msec, 5-35 μA, duration 10 sec) were inserted into the rostral pole of the ipsilateral caudate nucleus. A few days after the operation the EEG and behavioral responses to intraperitoneal injection of gradually increasing doses of leptazol (10-40 mg/kg) with and without stimulation of the caudate nucleus were investigated in the freely moving rats. An interval of 24 h was allowed after the control determinations and the animal was then given an intraperitoneal injection of one of the drugs, and during the period of its action the relations between caudate and leptazol effects were studied in the same order. The drugs were given in the following doses (in mg/kg): apomorphine and amphetamine, each 5; D,L-dopa 200, haloperidol 3, chlorpromazine 10, disulfiram 300, and a-methyltyrosine 100 [1]. From 3 to 6 experiments were carried out on each animal.

Department of Pharmacology, Medical Institute, Chita. (Presented by Academician of the Academy of Medical Sciences of the USSR V. V. Zakusov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 80, No. 8, pp. 66-69, August, 1975. Original article submitted November 15, 1974.

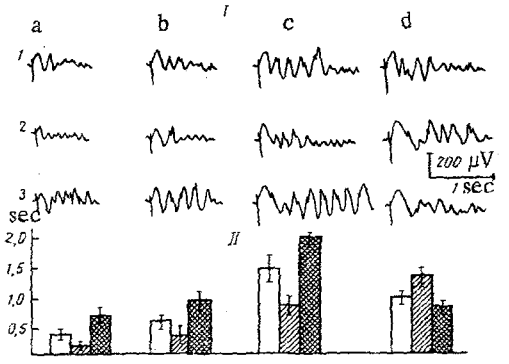

Fig. 1

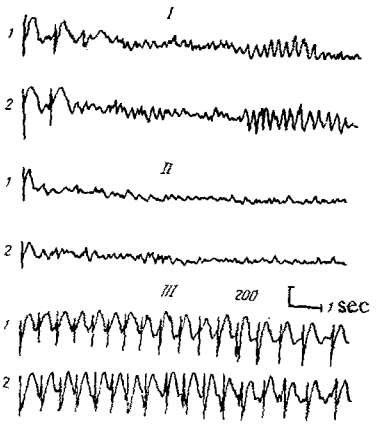

Fig. 2

Fig. 1. Effect of apomorphine and haloperidol on cortical responses evoked by single stimulation of caudate nucleus together with subconvulsant doses of leptazol: 1) evolution of caudate responses in one animal receiving different treatments. 1) Control; 2) injection of apomorphine (5 mg/kg); 3) injection of haloperidol (3 mg/kg). a) initial response; b, c, d) after injection of 10, 20, and 30 mg/kg leptazol respectively. II) Dynamics of duration of caudate responses evoked by threshold strength of current for behavioral changes. Mean values of duration of response for same rat (in sec): unshaded column — control; obliquely shaded column — after apomorphine; cross-hatched column — after haloperidol. Each group of columns corresponds to above-mentioned stages (a, b, c, d) of leptazol poisoning (M ± m).

Fig. 2. Effect of apomorphine and haloperidol on after-responses triggered by repetitive stimulation of caudate nucleus. I) Control; II) injection of apomorphine; III) injection of haloperidol. Recordings from: 1) sensomotor cortex; 2) corpus striatum. Effect detected against the background of leptazol (20 mg/kg).

EXPERIMENTAL RESULTS

Subconvulsant doses of leptazol caused synchronization of the EEG in the form of bursts of slow negative waves and spike-wave complexes. The rats stayed frozen on the spot and developed myoclonic spasms. Single caudate stimuli increased the amplitude and duration of potentials of this type and also facilitated the appearance of their behavioral correlates. In agreement with previous observations [1], dopa, apomorphine, and amphetamine, whether alone or in conjunction with disulfiram, an inhibitor of noradrenalin synthesis, reduced the intensity of spontaneous leptazol EEG synchronization. At the same time, the caudate effects were definitely weakened. This was shown by a decrease in the amplitude and duration of the first wave of the evoked response, and by the less frequent development of accessory waves. The total duration of the caudate response was shorter ($P < 0.05$) against the background of 20 mg/kg leptazol than in the control (Fig. 1). Dopa had a stronger action than apomorphine. Whereas the original duration of the evoked response was 1485 ± 165 msec, in conjunction with dopa it was only 462 ± 87 msec, and for apomorphine 825 ± 181 msec. Changes in this direction took place only within a strictly limited range of doses of the convulsant. The nearer to the convulsant doses they were, the more strongly the EEG

response began to exceed the control response in magnitude. The test drugs had a similar action on the effects arising in the course of repetitive (1-3 pulses/sec) stimulation of the caudate nucleus.

Repetitive caudate stimuli, after preceding subconvulsant doses of leptazol, also left as aftereffects either hypersynchronous waves (often in the form of a series of spike-wave complexes) or a generalized convulsion, directly depending on the stage of poisoning. The substances tested raised the threshold of onset of these after-responses: the hypersynchronous rhythm was induced only by higher doses of leptazol, and the long periods of freezing of the animal on the spot which corresponded to this rhythm became less clear (Fig. 2). Although the threshold of appearance of generalized convulsions rose a little, the duration of the fit increased steadily and it followed a much more severe course than in the control (Fig. 3), often ending in death of the animal.

It must be emphasized that, despite the lengthening of the electroencephalographic manifestation of the fit, the paroxysmal discharges were lower in amplitude.

Stimulation of catecholaminergic transmission thus weakens only those indices of the epileptogenic properties of the caudate nucleus that relate to the effects of low doses of leptazol, that behaviorally and electrographically are similar to the manifestations of petit mal.

Conversely, neuroleptics (chlorpromazine and haloperidol), like inhibitors of catecholamine synthesis (disulfiram and α-methyltyrosine), irrespective of the special features of their own intracellular action, facilitated synchronization of the EEG when small doses of leptazol were given and, in a few cases, lowered the threshold of myoclonic spasms [1].

Meanwhile disturbance of aminergic transmission increased the intensity of the caudate effects. After previous administration of leptazol in a dose of 20 mg/kg the prolongation of discharges evoked by single stimulation of the nucleus was particularly marked (Fig. 1). With respect to this effect haloperidol and α-methyltyrosine acted more strongly than chlorpromazine and disulfiram. As the convulsant dose of leptazol (30 mg/kg) was approached, the caudate response, by contrast, weakened and returned to the control level. If the nucleus was stimulated at above-threshold strength, the limitation of the response took place sooner (with a dose of 20 mg/kg leptazol). A similar pattern was found in the case of repetitive brain stimulation.

All the inhibitory compounds also facilitated generation of after-discharges triggered by repetitive caudate stimuli. If they were combined with leptazol in a dose of 20 mg/kg, stimulation of the caudate nucleus easily provoked a stable spike-wave rhythm and corresponding behavioral manifestations (Fig. 2). It is noteworthy that hypersynchronous potentials as a rule were not transformed into an attack of clonicotonic convulsions such as usually occurred in such cases. If, however, with an increase in the dose of leptazol, a generalized fit ensued, it was shorter than in the control, its course was less severe and, except in the experiments with disulfiram, it did not lead to death of the animals.

Consequently, inhibition of central catecholaminergic transmission, by contrast with the action of stimulants, facilitates the influence of the caudate nucleus on some parameters of the preconvulsant effect of leptazol.

These facts can be explained by interference of both types of drugs with the function of both dopaminergic and noradrenergic brain synapses. Potentiation of the dopaminergic nigro-striatal restraining mechanisms [2, 5] weakens the synchronizing influences of the corpus striatum on neocortical electrical activity. The same result is observed during excitation of the noradrenergic components of the desynchronizing system of the brain stem. Blockade of catecholaminergic synapses leads to the opposite result, followed by potentiation of the epileptogenic effects of the caudate nucleus. It is important to note that to modulate preconvulsant effects all that is

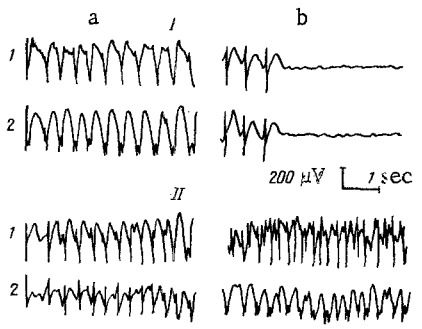

Fig. 3. Changes in character of convulsion evoked by caudate stimuli under the influence of dopa. I) Spike-wave rhythm triggered in late stages of leptazol poisoning (40 mg/kg); II) the same, after preceding injection of dopa (200 mg/kg). Spike-wave rhythm transformed into severe attack of clonico-tonic convulsions: a) immediately after end of repetitive stimulation of caudate nucleus; b) 12 sec later. Explanation of 1 and 2 the same as in Fig. 2.

necessary is to interfere with the operation of the dopaminergic mechanisms alone (as when apomorphine and haloperidol or a combination of amphetamine or dopa with disulfiram is used). This encourages the search for drugs suitable for the treatment of petit mal among dopaminomimetic compounds.

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