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# ROLE OF THE STRIATUM IN THE MECHANISM OF SEROTONINERGIC EFFECTS ON THE COURSE OF METRAZOL CONVULSIONS IN RATS

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The effect of 5-hydroxytryptophan (5-HT) and parachlorophenylalanine (PCPA) on behavioral and electroencephalographic manifestations of metrazol convulsions during electrical stimulation and destruction of the striatum was studied in freely moving rats. The effect of the compounds on the seizures, the myoclonic spasms, and the spike-and-wave activity evoked by metrazol did not depend significantly on the functional state of the corpus striatum. Meanwhile the ability of 5-HT to ameliorate, and of PCPA to aggravate the course of the generalized convulsion and the post-convulsive state was potentiated by stimulation and abolished by destruction of the striatum. It is suggested that activation of the serotoninergic mechanisms may be responsible for the abolition of the convulsions that is observed in the case of excitation of the corpus striatum.

KEY WORDS: metrazol convulsions; serotoninergic substances; striatum.

Serotoninergic agents are known to affect the course of metrazol convulsions: the serotonin precursor 5-hydroxytryptophan (5-HT) blocks, whereas the inhibitor of serotonin synthesis parachlorophenylalanine (PCPA), on the other hand, intensifies convulsions of this sort [4-6]. As the writer showed previously [1-3], a change in the functional activity of the striatum, which has a high concentration not only of dopamine and acetylcholine, but also of serotonin, has a distinct influence on the character of metrazol convulsions.

It was therefore decided to study the effect of electrical stimulation and blocking of the striatum on the ability of 5-HT and PCPA to modify the various indices of convulsions evoked by metrazol.

## EXPERIMENTAL METHOD

Experiments were carried out on 65 albino rats of both sexes weighing 180-300 g. The pharmacological agents 5-HT (100 mg/kg) and PCPA (300 mg/kg twice at an interval of 24 h) were injected intraperitoneally 0.5 and 48 h respectively before provocation of the convulsions. In the experiments of series I the effect of serotoninergic drugs on behavioral (30 rats) and electroencephalographic manifestations (four rats) of metrazol convulsions were studied in intact animals; in series II the action of the drugs was assessed on the anticonvulsive

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TABLE 1. Effect of Serotoninergic Drugs on Some Indices of Metrazol Convulsions Before (I) and After (II) Destruction of Striatum (M ± m)

| Drug | Threshold dose (in mg/kg) of metrazol to obtain | | | | Duration of convulsion (in sec) | | Status epileptiformis (in %) | |
|---|---|---|---|---|---|---|---|---|
| | myoclonic spasms | | generalized convulsion | | | | | |
| | I | II | I | II | I | II | I | II |
| Control | 25,5±2,4 | 43,8±4,5 | 38,0±5,2 | 55,2±6,1 | 24,8±1,4 | 40,2±5,1 | — | 38 |
| 5-hydroxytryptophan | 34,4±2,5 | 57,5±6,3 | 60,2±7,8 | 77,5±5,8 | 18,6±2,1 | 45,0±3,6 | — | 50 |
| Parachlorophenylalanine | 13,0±2,4 | 26,3±4,5 | 26,8±3,2 | 47,5±7,2 | 38,8±9,8 | 20,2±2,5 | 50 | 12 |

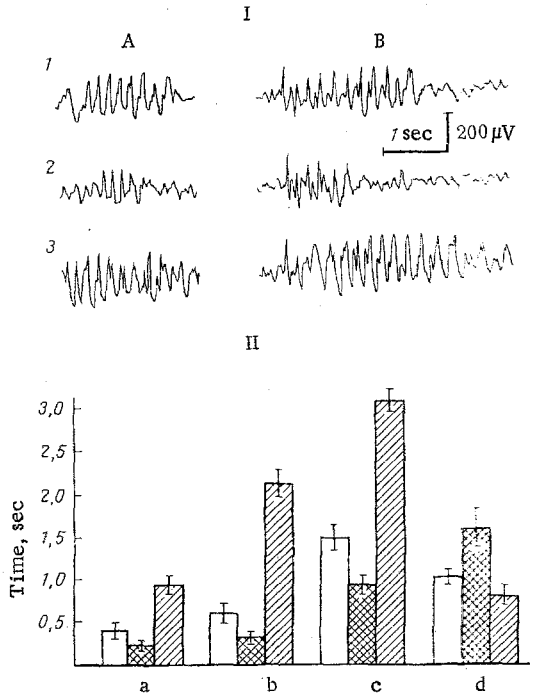


Fig. 1. Effect of 5-HT and PCPA on cortical responses evoked by single stimulation of striatum after subconvulsant doses of metrazol. I) Character of spontaneous changes (A) and changes evoked (B) by caudate stimuli on EEG in sensomotor cortex of same rat under normal conditions (1) and after administration of 5-HT (2) and PCPA (3); II) combined changes in duration of cortical responses on EEG to striatal stimulation (40 μA, 0.1 msec) in a rat before (a) and after administration of increasing doses of metrazol (10, 20, and 30 mg/kg in b, c, and d, respectively); unshaded column – control, columns with cross-hatching and oblique shading – after 5-HT and PCPA, respectively. Ordinate, time (in sec).

effect of electrical stimulation of the striatum. The methods of obtaining convulsions and of stimulating the brain were described in detail previously [1, 2]. In series III the effect of 5-HT and PCPA was studied on the course of the convulsions in 23 striatectomized rats. For this purpose, 2 weeks before the experiments bilateral electrolytic destruction of the striatum was carried out (silver electrodes, dc of 2 mA, duration 20-30 sec). After the end of the experiments the location and volume of the lesions in the corpus striatum were determined in every case.

## EXPERIMENTAL RESULTS

Interference with the activity of the serotoninergic systems of the brain clearly modified the course of the preconvulsive period, the generalized fit, and the postconvulsive state evoked by metrazol (Fig. 1).

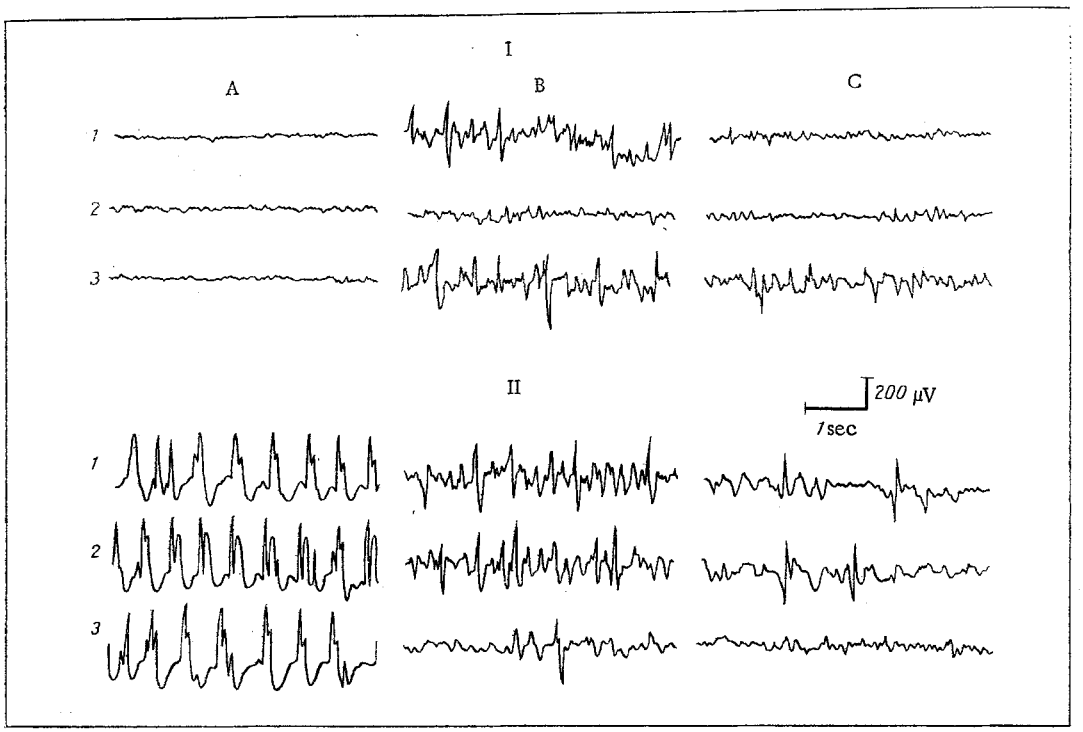


Fig. 2. Action of drugs modifying serotoninergic transmission on dynamics of EEG during postconvulsive period in intact (I) and striatectomized (II) rat. A, B, and C) EEG of occipital cortex 5 sec and 5 and 50 min, respectively after end of convulsion; 1) control, 2) after 5-HT, 3) after PCPA.

After injection of 5-HT the behavior and EEG of the intact animals showed no significant change. The compound blocked the generation of metrazol seizures and the corresponding slow negative waves (SNW) and spike-and-wave complexes. After 5-HT the manifestation of both the myoclonic spasms and the generalized convulsion was greatly impaired. However, the threshold of the latter rose by a greater degree than the threshold of the myoclonic spasms (Table 1). Stimulation of serotoninergic transmission lowered the intensity and shortened (by shortening the tonic and clonic phases) the duration of the convulsion and also improved the course of the postconvulsive period: It reduced by 3-4 times the duration of the postconvulsive myoclonic spasms and the EEG returned to normal faster than in the control (Fig. 2, I).

PCPA evoked motor hyperactivity, aggressiveness, and desynchronization of the EEG in the rats. PCPA appreciably facilitated the onset of seizures, SNW, and spike-and-wave complexes and also distinctly increased their duration (Fig. 1, I, A). PCPA lowered the threshold of the myoclonic spasms by a greater degree than the threshold of the convulsion. By contrast with 5-HT, it caused no significant change in the duration of the convulsion and appreciably aggravated the course of the postconvulsive period (Table 1, Fig. 2, 1).

As was shown earlier [2], stimulation of the caudate nucleus in rats by single electric pulses facilitated the onset of metrazol seizures, SNW, and spike-and-wave complexes and increased their duration. 5-HT inhibited but PCPA potentiated this property of the striatum. The action of the drugs was exhibited most clearly when preceded by administration of metrazol (20 mg/kg). For example, in intact animals under these conditions the caudate stimulus evoked paroxysmal after discharges with a duration of 1522 ± 251 msec in the sensomotor cortex, but in rats receiving 5-HT or PCPA their duration was 812 ± 182 and 3110 ± 242 msec respectively (Fig. 1, II). As the dose of metrazol approached the convulsant level, the ability of the striatum to provoke seizures and a spike-and-wave rhythm became much weaker. Single stimuli, it will be noted, were applied at a time of absence of "spontaneous" metrazol paroxysmal waves (with an interval of 5-10 sec).

A previous investigation [2] showed that repeated caudate stimuli (1-3 pulses/sec), directly depending on the stage of metrazol poisoning, preserved either the hypersynchronous SNW and spike-and-wave complexes accompanied by torpor and tremor of the rat's head, or a generalized convulsion. 5-HT raised the threshold and reduced the duration and severity of these responses. PCPA had a directly opposite action on the effects of repetitive stimulation. In fact, whereas after PCPA a certain pool of neurons triggered a regular spike-and-wave rhythm and convulsion after the injection of 10-15 and 20-25 mg/kg metrazol, respectively, if 5-HT was

was given these doses were almost doubled. PCPA also appreciably lengthened the duration of convulsions provoked by striatal stimulation and increased their severity compared with the control.

After destruction of the striatum in intact animals the severity and duration of the seizures, the SNW, and spike-and-wave activity were reduced, the thresholds of the myoclonic spasms and the generalized convulsion were almost doubled, the duration of the convulsion was increased, and, finally, in 50% of rats status epileptiformis was produced (Table 1). After striatectomy the effect of the serotoninergic drugs on metrazol seizures, myoclonic spasms, and their EEG manifestations still remained. 5-HT increased the threshold of the myoclonic spasms already raised as the result of injury to the caudate nucleus, whereas PCPA had the opposite action (Table 1). Meanwhile, the operation modified the character of the effect of these drugs on the generalized convulsion and on the postconvulsive state. 5-HT did not exhibit its protective effect on the course of the convulsion and of the postconvulsive state in the striatectomized animals (Fig. 2, II), although as in the control, it raised the threshold of the convulsion. PCPA after striatectomy caused no change in the threshold of the convulsion in the rats and had an action opposite to that exhibited by it normally: The duration of the convulsion was reduced, the number of striatectomized rats developing status epileptoformis was reduced by almost two thirds (Table 1), the duration of the postconvulsive myoclonic spasms was shortened, and normalization of the EEG took place more rapidly (Fig. 2, II).

These results indicate that the striatum plays an important role in the action of serotoninergic drugs on the generalized convulsion and the postconvulsive state. Meanwhile, the effect of these drugs on the dynamics of the preconvulsive manifestations is probably determined by different mechanisms. The reason may be certain functional peculiarities of the corpus striatum. Analysis of data in the literature shows that the strengthening of serotoninergic transmission facilitates the triggering of striatal effects. Meanwhile, it has clearly been demonstrated that the corpus striatum can abolish the paroxysmal process, reduce the duration of the convulsions, and prevent the onset of repeated fits [3].

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