EFFECT OF STRIATECTOMY ON THE COURSE OF LEPTAZOL CONVULSIONS IN RATS

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Behavioral and EEG manifestations of leptazol convulsions were studied in freely moving rats after preliminary destruction of the striatum. Although the operation did not appreciably disturb the spike-wave activity, it interfered greatly with the provocation of myoclonic convulsions and their conversion into tonicoclonic convulsions. The threshold, duration, and severity of the fit also were increased and status epilepticus actually developed in 50% of rats. Striatectomy abolished the action of catecholaminergic drugs (apomorphine, dopa, haloperidol, chlorpromazine) on the thresholds of myoclonic spasms and convulsions. The important role of the striatum in the formation of the motor manifestations of leptazol convulsions and in the arrest of the generalized fit is emphasized.
KEY WORDS: *leptazol convulsions; striatectomy; catecholaminergic drugs.*

EXPERIMENTAL METHOD

Altogether 268 experiments were carried out on 98 noninbred albino rats of both sexes weighing 180-250 g. In 68 animals bilateral electrolytic destruction of the striatum (silver electrodes 0.2 mm thick, direct current 1.5-2.0 mA, 20-30 sec) was carried out under pentobarbital anesthesia 10-15 days before provocation of leptazol convulsions [1]. One week after this operation, recording electrodes were implanted into the cortex (occipital and parietal regions), hippocampus, and mesencephalic reticular formation of seven rats. The location of the electrodes and the destructive lesions was determined by comparing frontal brain sections with the maps in Fifkova and Maršala's atlas [4]. In every case, a three dimensional reconstruction of the brain lesions also was carried out. The results were compared with those of experiments on intact animals [1] and also on rats with injuries to the parieto-occipital regions of the cortex and the septum. After determination of the effects of leptazol the striatectomized animals were divided into four groups. The animals of each group received an intraperitoneal injection of one of the following drugs: apomorphine (5 mg/kg), L-dopa (100 mg/kg), haloperidol (3 mg/kg), and chlorpromazine (10 mg/kg). The results thus obtained were compared with those of analogous experiments on intact rats [1].

EXPERIMENTAL RESULTS AND DISCUSSION

In nearly all the rats motor hyperactivity, increased aggressiveness, and EEG-desynchronization were observed after destruction of the striatum. In most cases these phenomena disappeared 10-15 days after the operation.

As observed previously [1], in intact rats after administration of subconvulsant doses of leptazol (15-20 mg/kg) characteristic behavioral "seizures" developed, with corresponding slow negative waves and spike-wave complexes on the EEG. These continued even after striatectomy. The only difference was a decrease in the amplitude and duration of

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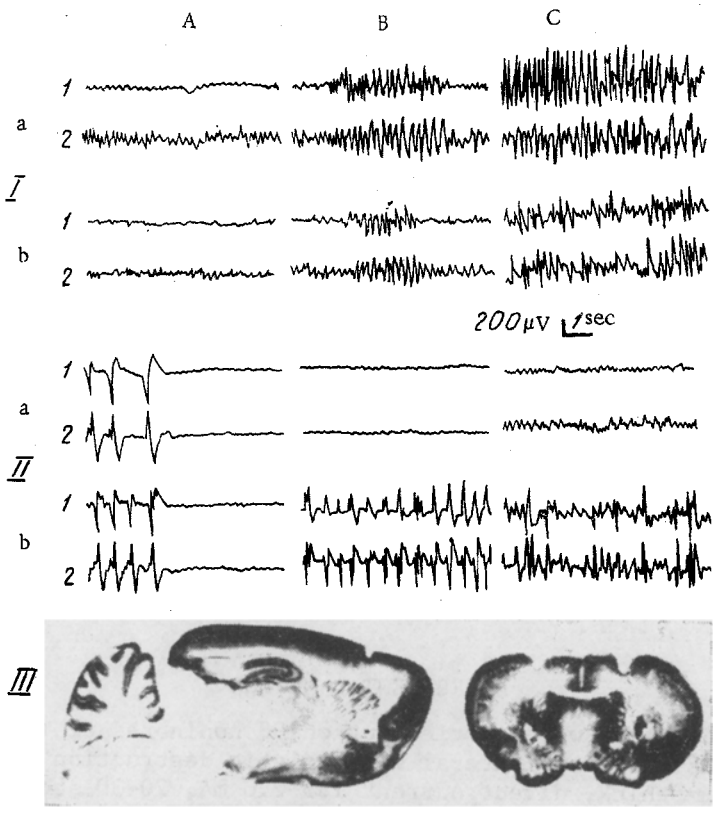

Fig. 1. EEG picture of preconvulsive state (I) and postconvulsive period (II) in intact (a) and striatectomized (b) rats. In I: A) original activity, B and C) after injection of 20 and 40 mg/kg leptazol respectively. In II: A) immediately after end of fit, B) 5 sec, C) 60 min after fit. Recordings from: 1) occipital cortex, 2) hippocampus. III) Sagittal and frontal sections through rat brain showing location of destruction in striatum.

the paroxysmal waves and their predominance in the hippocampus (Fig. 1, I). However, despite the continued generation of paroxysmal rhythms after destruction of the striatum, the production of motor disturbances in these rats was much more difficult. The threshold dose of leptazol for the formation of myoclonic spasms in these animals was almost twice as high as in the intact animals (42±3.7 and 22.5±3.5 mg/kg respectively). Usually before development of myoclonic spasms, striatal hyperactivity and aggressiveness were discontinued and fairly prolonged "seizures" (5-10 sec, compared with 1-3 sec in the intact animals) appeared; these were accompanied on the EEG by polymorphic paroxysmal activity consisting of pointed and slow waves and spike-wave complexes.

A very characteristic feature of the striatectomized rats was impairment of the generalization of myoclonic convulsions into an extended tonicoclonic fit. As a rule, a series of strong spasms was observed. With the appearance of these spasms, the intensity of the slow waves decreased.

Destruction of the corpus striatum led not only to a definite increase in the threshold of the fit (Fig. 2A), but also to a change in its character. Compared with the control, the tonic phase of the fit was very greatly shortened whereas the clonic phase was substantially lengthened (Fig. 2B). On the whole, the total duration of the convulsions was greater in the striatectomized than in the intact rats (50.2±4.5 and 31±3.9 sec respectively). The morphology and the frequency—amplitude parameters of the paroxysmal waves accompanying the fit were indistinguishable from those found normally. After the operation 35% of the rats had extremely severe fits: The animal jumped high into the air, and this was followed by

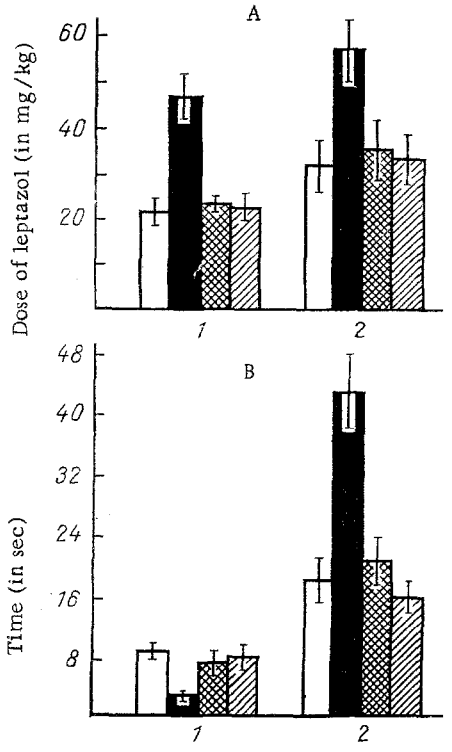

Fig. 2

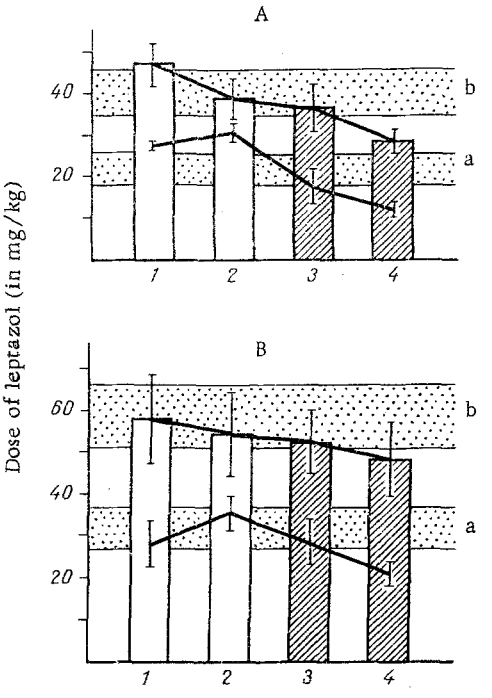

Fig. 3

Fig. 2. Effect of striatectomy on various indices of leptazol convulsions. A) Thresholds of myoclonic spasms (1) and fit (2) induced by leptazol. B) Duration of tonic (1) and clonic (2) phases of fit. Unshaded columns represent intact, black columns striatectomized rats; cross-hatched and obliquely shaded columns represent animals with destruction of septum and parieto-occipital cortex respectively.

Fig. 3. Effect of catecholaminergic drugs on thresholds of myoclonic spasms (A) and fit (B) after destruction of striatum. 1) Apomorphine; 2) L-dopa; 3) haloperidol; 4) chlorpromazine. a) Region of scatter of threshold doses of leptazol in intact rats; b) in striatectomized rats.

tonic extension of the hind limbs (the forelimbs were pressed tightly against the trunk). The tonic convulsions were replaced by flaccid, chaotic twitching of the limbs for 20-90 sec. If no anticonvulsant was used, the fit usually terminated in death.

Destruction of the striatum greatly reduced the duration of postconvulsive depression (to 8-10 sec from the normal 20-60 sec) and in most cases bursts of spikes and pointed waves appeared on the EEG 4-6 sec after the end of the fit (Fig. 1, II), with no behavioral manifestations. In half of the experimental rats status epilepticus developed, and in the other half the duration of the postconvulsive myoclonic spasms was sharply increased (to 2-3 h compared with 10-20 min in the control).

Analysis of the histological material showed that the changes described above depend not on the localization, but on the volume of the striatal lesion. The above effects were typical of rats with bilateral destruction of 7-15% of the volume of the structure (Fig. 1, III). With larger lesions (about 30-40%) myoclonic spasms and fits were more difficult still to produce, and status epilepticus and death of the rats were observed in 100% of cases. With small lesions (up to 3-4% of the volume of the striatum) only an increase in the duration of the fit was observed. Destructive lesions of the septum and parieto-occipital cortex had no significant effect on the course of the leptazol convulsions (Fig. 2).

The results are evidence of the role of the striatum, on the one hand, in the formation of the motor manifestations of leptazol convulsions and their conversion into a generalized fit and, on the other hand, in the cutting short of the fit. This was confirmed also by the results of pharmacological tests using substances inhibiting (dopaminomimetics) and potentiating (neuroleptics) functional activity of the striatum. Injury to the striatum abolished the effect of dapaminomimetics (apomorphine and dopa) and dopaminolytics (haloperidol and chlorpromazine) on the threshold of the myoclonic spasms and generalized convulsions. The exception was chlorpromazine (Fig. 3A). The drugs tested (except chlorpromazine) had no appreciable effect on the threshold of the fit in intact rats [1]. After striatectomy, the threshold was increased, and was unchanged even by chlorpromazine (Fig. 3B). Whereas before the operation status epilepticus was provoked only by apomorphine and dopa, after striatectomy chlorpromazine and haloperidol were actually more effective in this respect.

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