Effect of Cerebral Ischemia on Acute Convulsions and Chronic Epileptogenesis

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The pharmacological kindling with corazol was used as a model of chronic cerebral epileptization. In contrast to sham-operated rats or rats with unilateral occlusion of the common carotid arteries, bilateral occlusion of these vessels moderated acute seizures provoked by a single administration of the convulsant corazol and abated the enhanced cerebral seizure readiness induced by its repeated administration.

Key Words: *epileptogenesis; pharmacological kindling; enhanced cerebral seizure readiness; acute convulsions; cerebral ischemia*

Epilepsy and cerebral ischemia are the manifestations of pathological condition in the central nervous system. The problem of their interference is of great theoretical and practical interest. Our aim was to study the role of cerebral ischemia in epileptogenesis and, in particular, the effect of ischemia caused by uni- and bilateral occlusion of common carotid arteries (CCA) on acute convulsions and chronic epileptogenesis characterized by enhanced cerebral seizure readiness (pharmacological kindling).

MATERIALS AND METHODS

Experiments were carried out on 200 male Wistar rats (initial body weight 270-300 g). The animals were maintained under vivarium conditions on the standard diet. Cerebral ischemia was produced by occlusion of the left or both CCA under hexenal anesthesia (150 mg/kg intraperitoneally). The control group consisted of sham-operated rats.

In the first series of experiments we studied the effect of cerebral ischemia of various severity on acute convulsions provoked by intraperitoneal administration of corazol in the doses of 40 and 65 mg/kg. The second series related to the effect of cerebral ischemia on the development of enhanced cerebral seizure readiness elicited by diurnal intraperitoneal administration of corazol in a subconvulsive dose of 25-35 mg/kg for 30-70 days (the model of corazol-induced kindling). This intervention produced a gradual increase in cerebral seizure readiness to the action of the convulsant, which was manifested in the fact that seizures in the treated rats were elicited by subconvulsive doses of corazol, while the severity of these seizures increased during the treatment and culminated in a generalized clonic-tonic seizure. Rats with a similar corazol sensitivity were sorted out after a single administration of corazol in the minimal effective dose [2]. In both series corazol was administered one week after uni- or bilateral CCA occlusion.

The severity of corazol-produced convulsive response during kindling was evaluated daily using a scoring system in which score 1 was assigned to momentary shuddering and nodding; score 2 to discrete clonic convulsions of the whole body; score 3 to a series of clonic convulsions of the whole body or to clonus of the forelimbs; score 4 to tonic-clonic convulsions with rearing up on the hind legs ("kangaroo" posture); and, score 5 to clonic-tonic convulsions that caused the rats to fall on the side. In

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a similar way we evaluated the severity of acute convulsive response which was provoked by a single administration of corazol in the second series of experiments. In addition, in this series we determined the following parameters were: the latentcy of the first convulsive manifestations (LP_1), clonic (LP_2) and clonic-tonic (LP_3) seizures (fall on a side), seizure duration, severity of the convulsive response and lethality. The results were statistically analyzed using Student's *t* test, the precise Fisher's method, and Wilcoxon—Mann—Whitney's *U* test.

RESULTS

The severity of acute seizures induced by a single administration of corazol in a dose of 40 mg/kg was significantly lower in rats with a bilateral CCA occlusion (first series, n=10) than in rats with a unilateral CCA occlusion (p<0.02, n=10) or in the control sham-operated rats (p<0.05, n=11): the corresponding scores were 2.91±0.19, 3.90±0.31, and 3.69±0.31. Other differences were not revealed.

Pronounced differences were observed after a higher dose of corazol (65 mg/kg) (Table 1). It is noteworthy that the response of sham-operated rats to corazol in this and lower(40 mg/kg) doses also did not differ from that of rats with unilateral CCA occlusion. In rats with bilateral occlusion of CCA, LP_1 and LP_2 were significantly increased (Table 1), while LP_3 had a tendency to increase in comparison with control rats and rats with unilateral CCA occlusion: respectively, 286.50±280.55, 165.57±27.99, and 195.75±53.97 sec. At the same time, the group with bilateral CCA occlusion was characterized by a decrease in the duration of clonic seizure, the number of rats with 5-score seizures, severity of convulsive response, and lethality compared with control rats and rats with unilateral CCA occlusion.

In the second series, seizures were observed in the majority of rats with bilateral CCA occlusion in the initial phase of the development of enhanced cerebral seizure readiness in response to corazol. During the first 10 days, the 1-score seizures were developed in 30.77% sham-operated rats, in 28.57% rats with unilateral CCA occlusion, and in 66.67% (p<0.025) rats with bilateral CCA occlusion. At further stages of development of enhanced cerebral seizure readiness the severity of convulsive response was lower in rats with bilateral CCA occlusion (Fig. 1), while the clonic-tonic 5-score convulsions were developed during the first 30 days in 47.83% sham-operated rats and in 46.15% rats with unilateral CCA occlusion. There were no rats with bilateral occlusion that demonstrated 5-score convulsions in this period. In addition, the 5-score convulsions were developed in 84.6% sham-operated rats, in 69.23% rats with unilateral and 23.08% (p<0.025) rats with bilateral occlusion of CCA. There were no differences in the response of control rats and rats with unilateral CCA occlusion.

Thus, a different dynamics of the development of enhanced cerebral seizure readiness was revealed in the control sham-operated rats and in the rats with uni- and bilateral CCA occlusion. During the first kindling days, the convulsions appeared in larger (by 2 - 2.3 times) number of rats with bilateral CCA occlusion than in other rats. In addition, in rats with bilateral CCA occlusion the severity of convulsive response during the development of kindling (days 16-44) was smaller, the 5-score clonic-tonic convulsions appeared later (by the 15th day), and the number of rats with such convulsions was smaller by 3-3.7 times than in the other groups.

These data show that unilateral occlusion of CCA has no profound effect on the initiation and manifestation of convulsions induced by a single administration of convulsive dose of corazol. Severity, latency, and duration of convulsions in these rats were the same as in control sham-operated rats. Bilateral occlusion of the CCA markedly moderated the convulsive process: the latencies of the first convulsive manifestations, clonic and clonic-tonic seizures were prolonged, while the severity of the convulsive response and lethality was decreased.

The rats with bilateral CCA occlusion demonstrated abatement of severity of convulsions under

TABLE 1. Effect of Cerebral Ischemia of Various Severity on Acute Epileptic Seizure ($M\pm m$)

Animal group	LP_1, sec	LP_2, sec	Duration of clonic convulsions, sec	Number of rats with 5-score convulsions, %	Number of died rats, %	Severity of convulsions, score
Control (n=18)	48.61±2.80	53.20±2.98	28.75±2.48	77.78	66.67	4.78±0.06
CCA occlusion:						
unilateral (n=9)	41.71±1.39*	48.67±3.71	24.67±5.00	88.89	55.55	4.89±0.11
bilateral (n=18)	55.20±2.52**	96.45±19.97**	16.00±2.09*	11.11**	11.11**	3.61±0.26****

Note. *p<0.05, **p<0.001, compared with control; *p<0.05, **p<0.001, compared with rats with a with unilateral occlusion of CCA.

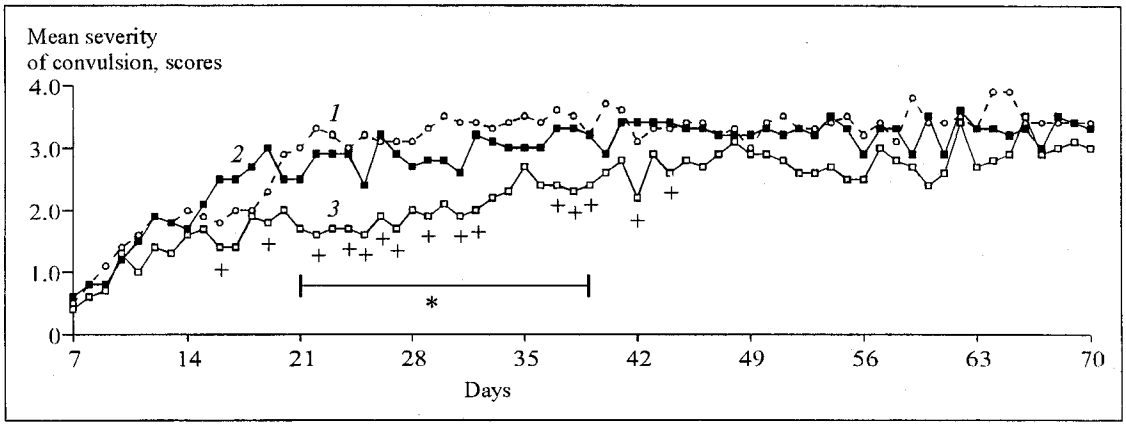

Fig. 1. Severity of convulsive response in the rats resulting from kindling induced by diurnal administration of the subconvulsive corazol doses. *1*) Control (sham-operated) rats; rats with (*2*) uni- and (*3*) bilateral occlusion of the common carotid arteries. *$p<0.05$ compared with (*1*), +$p<0.05$ compared with (*2*).

corazol-induced kindling, mostly in its middle and final stages. An increase in the number of rats reacting with 1-score convulsions during the first 10 days of kindling may be related to their individual specific reactivity to repeated affect of corazol. The lower severity of convulsions developing during kindling in rats with bilateral CCA occlusion indicates that respective plastic changes induced by daily administration of corazol were insignificant. It agrees with the data on a single administration of corazol which produced smaller convulsive effect under bilateral CCA occlusion. It is not clear why the convulsive effect of corazol was smaller in rats with severe cerebral ischemia. It should be remembered that bilateral CCA occlusion is highly lethal for rats, so the experiments with corazol were conducted on the survived rats which were sufficiently resistant to cerebral ischemia. Presumably, these rats have an enhanced level of antiepileptic protection, i.e., an effective antiepileptic system [3]. There is evidence that the hypoxia-resistant animals are also resistant to convulsants [1]. It should be also taken into account that ischemia leads to a drastic increase in the cerebral content of adenosine [5], a compound participating in the inhibitory processes [8,9]. Severe ischemia results in degeneration and death of glutamatergic neurons in the cortex and hippocampus [6,7], i.e., in the brain subdivisions responsible for cerebral epileptogenesis. Therefore, in this case epileptogenesis is also moderated. It agrees with our findings [4] that damage to hippocampus retards the development of enhanced cerebral seizure readiness during corazol-induced kindling.

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