Effect of Myo-Inositol on Convulsions Induced by Pentylenetetrazole and Kainic Acid in Rats

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We studied the effect of myo-inositol on pentylenetetrazole and kainic acid-induced seizures in rats. Myo-inositol significantly reduced seizure activity.

Key Words: *epilepsy; myo-inositol; kainic acid; pentylenetetrazole*

Plants of the *Ranunculaceae* family (*Aquilegia vulgaris*, *Aquilegia viridis*) are actively used in Chinese and Tibetan popular medicine as antiepileptic and soporific drugs. We previously showed that water extract from *Aquilegia vulgaris* (*Ranunculaceae* family) completely inhibited binding of ^{3}H-muscimol (GABA-A receptor agonist) and stimulated binding of ^{3}H-flunitrazepam (specific ligand of GABA-A receptor benzodiazepine site) [12]. The binding of neuroligands to GABA-A receptors is affected by fraction of low-molecular-weight (<2 kDa) substances in the extract, which is also characterized by antiepileptic effects on convulsions induced by acoustic stimulation in Krushinskii—Molodkina rats [12]. Gas chromatography and mass spectrometry revealed two active compounds in this fraction: oleamide and myo-inositol [11]. We showed ^{3}H-muscimol binding to GABA-A receptors in rat brain *in vitro* is inhibited by myo-inositol [11]. CNS is characterized by high content of myo-inositol and capacity to its production [3]. Myo-inositol is not only a precursor for the synthesis of inositol lipids, but also a physiologically important osmolyte [3]. Oral treatment with myo-inositol was effective in some neurological diseases [1,2, 4,6-9], but antiepileptic activity of this lipid was never reported.

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In order to find out whether myo-inositol can mediate the antiepileptic effects of the low-molecular-weight fraction from *Aquilegia vulgaris*, we studied the effect of myo-inositol on seizures induced by pentylenetetrazole (PTZ) and kainic acid (KA).

MATERIALS AND METHODS

Tests with PTZ and KA are used for evaluating the efficiency of antiepileptic agents.

Experiments with PTZ were carried out on rats divided into 2 groups. Group 1 animals (n=10) were intraperitoneally injected with myo-inositol (20 mg/kg), group 2 rats (n=10) with the same volume of saline. After 30 min animals of both groups were injected with PTZ (60 mg/kg), after which each rat was placed into an individual box and its behavior was observed for 1 h. The intensity of convulsions was scored using a modified Racine's scale (0: complete absence of motor convulsions; 1: stupor, closed eyes, seizures (ears, whiskers), sniffing, facial clonus; 2: nodding because of a stronger facial clonus; 3: clonus of bilateral forelimbs without rearing; 4: bilateral forelimbs clonus with rearing; 5: falling on the side (without rearing), loss of setup reflex, paralleled by generalized clonic convulsions; 6: rearing and falling on the side, paralleled by general clonic convulsions) [10]. A total of 6 experimental series were carried out. The percentage of animals without convulsions (0 points) was evaluated for each group.

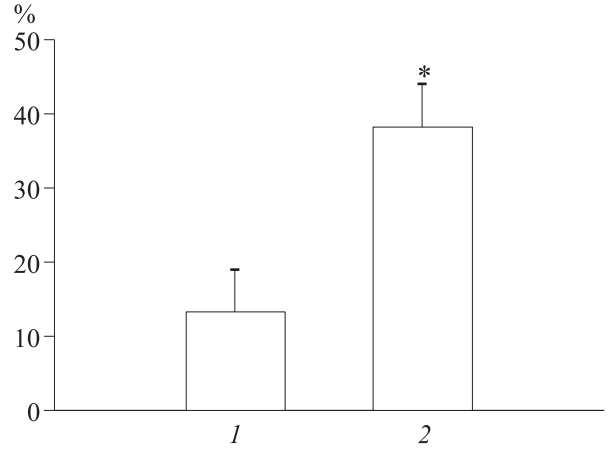

Fig. 1. Effect of myo-inositol on the percent of animals exhibiting no seizure activity after PTZ injection. Here and in Figs. 2, 3: *1*) control group (saline); *2*) animals injected with myo-inositol. **p*=0.014 compared to the control (saline).

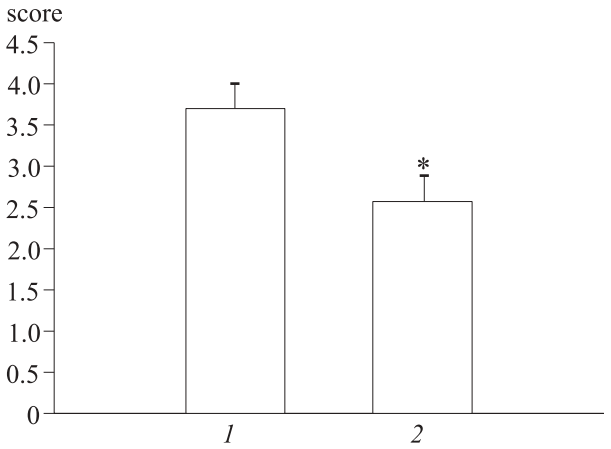

Fig. 2. Dynamics of seizure activity induced by injection of PTZ (*a*) or KA in rats (*b*). **p*=0.0145 compared to the control group.

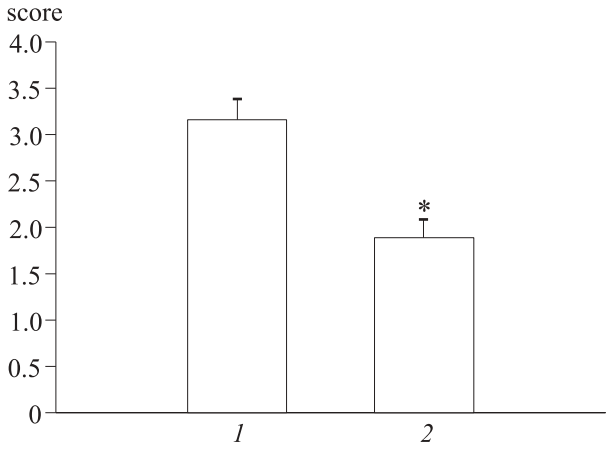

Fig. 3. Dynamics of seizure activity in rats induced by injection of KA. **p*=0.0001 compared to the control group.

Experiments with KA were also carried out in 2 groups of rats. Group 1 (n=10) animals were intraperitoneally injected with myo-inositol (20 mg/kg), group 2 rats (n=10) with the same volume of saline. After 30 min all rats were injected with KA (10 mg/kg) [5]. Each animal was then placed into an individual box and its behavior was observed during 4 h. Convulsions were scored using Racine's scale. Six experiments were carried out. Animals, in whom KA induced no convulsions were registered. The efficiency of myo-inositol was evaluated by unifactorial analysis of variables. The data were evaluated using the Student and Mann—Whitney tests.

RESULTS

The effects of myo-inositol or saline on animals treated with PTZ were significant ($F_{1,10}$=9.35, p=0.012). The number of animals exhibiting no epileptic activity (convulsions) was significantly higher in the group treated with myo-inositol than in the control group (p=0.014; Fig. 1).

Hence, myo-inositol significantly reduced seizure activity induced by PTZ in comparison with the control (saline injection) according to Mann-Whitney test (W=2910.5, p=0.0145; Fig. 2).

In animal injected with KA, the effects of saline and myo-inositol on the percent of animals exhibiting no seizure activity were negligible ($F_{1,10}$= 1.71, p=0.221). The percent of animals without seizures in the group treated with myo-inositol virtually did not differ from the control. The effect of myo-inositol in rats treated by KA manifested in a significant decrease in the intensity of seizures (Mann—Whitney test: W=4037.0, p=0.0001; Fig. 3).

These results suggest that myo-inositol demonstrates antiepileptic properties in seizure activity caused by chemical convulsants. In seizures provoked by PTZ , myo-inositol decreases the percent of animals exhibiting no seizures and total severity of convulsions. In seizures caused by KA, myo-inositol decreases the intensity of seizures. PTZ and KA have different targets in the CNS, and therefore the effects of myo-inositol are different. Our findings indicate antiepileptic effects of myo-inositol.

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