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EFFECT OF REPEATED TREATMENT WITH SSR504734, A SELECTIVE GLYCINE TRANSPORTER TYPE 1 INHIBITOR, ON SEIZURE THRESHOLDS AND AMINO ACID LEVELS IN BRAIN STRUCTURES OF MICE

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Glycine transporter type 1 (GlyT1) is involved in regulation of both excitatory glutamatergic and inhibitory glycinergic neurotransmission by controlling the reuptake of glycine. By changing extracellular glycine concentrations, GlyT1 inhibitors can influence the excitation/inhibition balance and thereby affect seizure susceptibility. The aim of the study was to investigate the effect of a 2-week treatment with SSR504734, a selective GlyT1 inhibitor, on seizure thresholds in three seizure tests in mice: the 6 Hz-inducted psychomotor seizure test, maximal electroshock seizure test (MEST) and intravenous (i.v) pentylenetetrazole (PTZ) infusion test in adult male CD-1 mice. In addition, the changes in the amino acid levels in different brain structures were analyzed using the HPLC-ESI-MS technique. We found that SSR504734 (30 mg/kg) significantly increased the threshold for the tonic hindlimb extension in the MEST but it was ineffective in the 6 Hz and i.v. PTZ-induced seizure thresholds tests. Analysis of amino acids content in brain structures showed significant increase in glycine concentration in the brainstem and increase in serine concentration in the cerebral cortex. The obtained results suggest that inhibition of GlyT1 can suppress tonic seizures.

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CEREBELLAR TRANSCRANIAL DIRECT CURRENT STIMULATION (TDCS) AND PITOLISANT PREVENTED BEHAVIORAL AND NEUROINFLAMMATORY DISTURBANCES IN PENTYLENETETRAZOL (PTZ)-KIDNLING

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The work aimed to investigate behavioral manifestations in PTZ-kindled rats under combined treatment with the histamine H3 receptor inverse agonist pitolisant and mTOR blocker rapamycin. Kindling was produced in Wistar male rats by administering three weeks of pentylenetetrazole (PTZ, 35.0 mg/kg, i.p.). tDCS of the cerebellum (500 mcA, anode, 5.0 min) and pitolisant (Selleck, 5.0 mg/kg) were treated for ten days in fully kindled rats. Behavior was investigated in the open field test. Immunohistological data – Ki67, collagen IV type, and CD34 in brain slices was quantified using the object colocalization module available in the HALO software (Indica Labs, USA). The number of crossed central squares of the kindled animals in the open field was 4.1 times less than in control rats ($P<0.01$). Under conditions of combined treatment with tDCS and pitolizant, the reduction of central squares crossing was 18.5% ($P>0.05$), while differences remained after separate drug administration. The density of Ki67, collagen IV type, and CD34 in cortical slices of kindled rats was higher by 1.75-3.5 times ($P<0.01$) than in the sham-stimulated control and reduced by 1.5-2.3 times after combined treatment ($P<0.01$). A conclusion was made that the developed treatment effectively controls neuroinflammation, which underlays chronic brain epileptization.

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