



A potential mechanism for the ameliorative effect of thymoquinone on pentylenetetrazole-induced kindling and cognitive impairments in mice.

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Abstract:

Cognitive dysfunction is commonly observed in epileptic patients. Pentylentetrazole (PTZ) kindling is a well established animal model which simulates clinical epilepsy. This study evaluated the potential role of glutamate, oxidative stress and nitric oxide (NO) overproduction in pentylenetetrazole (PTZ)-induced kindling and associated cognitive impairments in mice and effect of thymoquinone on these parameters. Repeated treatment of mice with a subconvulsive dose of PTZ (35 mg/kg i.p.) once every alternate-day for 12 injections induced kindling. PTZ-kindled mice showed learning and memory impairments as assessed by acquisition and probe trials of Morris water maze and step-through latency of passive avoidance tests. Concurrently, the brain glutamate, malondialdehyde and nitrite levels were increased while the brain intracellular reduced glutathione level and glutathione peroxidase activity were decreased in PTZ-kindled mice. Also, the brain inducible but not neuronal NO synthase mRNA and protein expressions were increased in PTZ-kindled mice. Treatment of mice with thymoquinone (5, 10 and 20 mg/kg i.p.) along with alternate-day subconvulsive dose of PTZ produced dose-dependent protection against PTZ-induced kindling and learning and memory impairments. Moreover, treatment of mice with thymoquinone (20 mg/kg) inhibited the biochemical alterations induced by PTZ in the brain except the elevation of brain glutamate level. The associated increase in brain inducible NO synthase mRNA and protein expressions were also inhibited. These results suggest that glutamate, and subsequent oxidative stress and NO overproduction, via inducible NO synthase, play an important role in the pathophysiology of PTZ-induced kindling and cognitive impairments in mice. Thymoquinone dose-dependently protects against PTZ-induced kindling and cognitive impairments. Inhibition of PTZ-induced brain oxidative stress and NO overproduction, via increase the expression and activity of inducible NO synthase, may play an important role in thymoquinone action.

Keywords:

Cognitive impairments Kindling Pentylenetetrazole Thymoquinone

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