

# The 5-HT<sub>3</sub> receptor antagonist granisetron lowers clonic seizure threshold in pentylenetetrazole induced seizure in mice: The involvement of nitric oxide system

<sup>1,2</sup>Taha Gholipour, <sup>2</sup>Ali Mojtahed, <sup>2</sup>Ahmad Reza Dehpour

<sup>1</sup>Iranian Center of Neurological Research and <sup>2</sup>Basic Medical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran.

**Background and Objective:** There are at least 7 classes of receptors known for serotonin (also well known as 5-hydroxy tryptamine: 5-HT); among them 5-HT<sub>3</sub> is completely distinct. It is a ligand-dependent cation channel highly permeable to calcium. 5-HT<sub>3</sub> receptors are found postsynaptically in GABAergic cortical and limbic neurons beside a variety of other regions.<sup>1</sup> According to accumulating evidences, epileptic seizures can be induced and/or augmented by attenuation of serotonergic neurotransmission. In contrast, manipulations increasing serotonin function (like fluoxetine administration) generally suppress epileptic seizures in animals.<sup>2</sup> Nitric oxide (NO) is a small membrane-diffusing molecule synthesized by nitric oxide synthase (NOS). NO is found to be a modulator of seizure susceptibility with either anticonvulsant or proconvulsant effects in different seizure paradigms. We evaluated the effect of the 5-HT<sub>3</sub> antagonist granisetron on clonic seizure induced by pentylenetetrazole (PTZ) and the potential connection with the NO system.

**Methods:** PTZ (1%) was infused at a constant rate through tail vein catheter of male Swiss mice and halted when clonus followed by falling was observed. Minimal dose of PTZ (mg/kg of mice weight) needed to induce clonic seizure was measured as an index of seizure threshold. The interaction of granisetron effects with NO was examined using NOS inhibitor, N(G)-nitro-L-arginine methyl ester (L-NAME) and NOS substrate L-arginine.

**Results and Discussion:** L-NAME could increase seizure threshold in its effective dose (100mg/kg,  $p < 0.01$ ). On the other hand, L-arginine showed a proconvulsive effect in doses higher than 100 mg/kg ( $p < 0.01$ ). Mice pretreated with granisetron had lower threshold than controls (31.37 versus 36.95 mg/kg,  $p < 0.01$ ) which could be reversed by effective doses of L-NAME (up to baseline). Co-administration of subeffective doses of granisetron and L-arginine (3 and 75 mg/kg, respectively) demonstrated a synergistic effect ( $p < 0.05$ ).

Our results confirm the proconvulsant role of NO. The 5-HT<sub>3</sub> receptor antagonist granisetron also showed a proconvulsant effect in this model, probably as a consequence of decreased excitation of GABAergic inhibitory neurons. The interaction of L-NAME and L-arginine with granisetron suggest that 5-HT<sub>3</sub> and NO may be in line in a neuronal signaling pathway, presumably through calcium mediated signaling pathways increased by 5-HT<sub>3</sub> activation.

**Conclusion:** The NO system involvement is described in the 5-HT<sub>3</sub> channel/receptor for the first time. An anticonvulsive role could be presumed for 5-HT<sub>3</sub> agonists, which could lead to further research on a new class of antiepileptic drugs.

## References

1. Benarroch EE. Basic neurosciences with clinical applications. 1<sup>st</sup> ed. Philadelphia: Butterworth Heinemann (Elsevier), 2006: 829-35.
2. Richman A, Heinrichs SC. Seizure prophylaxis in an animal model of epilepsy by dietary fluoxetine supplementation. *Epilepsy Res* 2007 Jan 8; [Epub ahead of print]

# This paper was awarded the Tadokoro Prize, Best Poster Presentation, 1<sup>st</sup> Prize