The 5-HT3 receptor antagonist granisetron lowers clonic seizure threshold in pentylenetetrazole induced seizure in mice: The involvement of nitric oxide system

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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-HT3 is completely distinct. It is a ligand-dependent cation channel highly permeable to calcium. 5-HT3 receptors are found postsynaptically in GABAergic cortical and limbic neurons beside a variety of other regions.[1] According to accumulating evidences, epileptic seizures can be induced and/or augmented by attenuation of serotonergic neurotransmission. In contrast, manipulations increasing serotonin function (like fluoxetin administration) generally suppress epileptic seizures in animals.[2] 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-HT3 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-HT3 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-HT3 and NO may be in line in a neuronal signaling pathway, presumably through calcium mediated signaling pathways increased by 5-HT3 activation.

Conclusion: The NO system involvement is described in the 5-HT3 channel/receptor for the first time. An anticonvulsive role could be presumed for 5-HT3 agonists, which could lead to further research on a new class of antiepileptic drugs.

References

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