Δ-HT<sub>1</sub> receptor mediates the dose-dependent effects of citalopram on pentylentetrazole-induced clonic seizure in mice: involvement of nitric oxide

Borna Payandemehr<sup>1</sup> (Pharm.D), Mohammad Sharifzadeh<sup>2</sup> (Ph.D), Ahmad Reza Dehpour<sup>3</sup> (Ph.D),

<sup>1</sup> Department of Pharmacology/ School of Medicine/ Tehran University of Medical Sciences, Tehran, Iran
<sup>2</sup> Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran
<sup>3</sup> Prof. Ahmad Reza Dehpour, PhD. Department of Pharmacology, School of Medicine/TUMS

Objectives and Introduction: Citalopram, a selective serotonin reuptake inhibitor (SSRI), is frequently used in the treatment of major depressive disorders. In addition to its antidepressant features, citalopram shows some anticonvulsant properties at lower doses, while higher doses, ingested in cases of suicide, have been associated with seizures. Although the exact mechanisms of these effects are not yet fully understood, Δ-HT<sub>1</sub> receptor has been recently shown to play an important role in the central effects of SSRIs. In this regard, we investigated whether these effects are mediated through modulation of Δ-HT<sub>1</sub> receptors. Then try to find the role of nitrogentic system in this phenomenon.

Methods & Materials: Male NMRI mice (20-25 gr) were used in this study. In order to measure the seizure threshold PTZ (Δ%) was infused in to the tail vein of freely moving animal with constant rate of \ mil/min. All drugs were administered (i.p) in appropriate time before inducing seizure by i.v. injection of pentylentetrazole.

Results: In our study, citalopram at lower doses (Δ and \ mg/kg, i.p.) significantly increased the seizure threshold (\ < 0.05) and at higher doses (Δ and Δ mg/kg) showed proconvulsive effects. Moreover, MCPBG (a Δ-HT<sub>1</sub> receptor agonist) at low and non-effective doses augmented while non-effective doses of tropisetron (a Δ-HT<sub>1</sub> receptor antagonist) prevented the anticonvulsant properties of low dose citalopram. Interestingly, neither Δ-HT<sub>1</sub> receptor agonist nor antagonist could alter the susceptibility of animals to convulse after higher dose of citalopram. On the other hand, Low doses of L-NAME and Y-NI alone or in combination with lower doses of Δ-HT<sub>1</sub> receptor agonist enhanced the anticonvulsive property of citalopram, while L-ARG alone or in combination with tropisetron blocked the protective effect of citalopram.

Discussion & conclusion: In summary, our findings demonstrate that Δ-HT<sub>1</sub> receptor mediates the anticonvulsant properties of low doses of citalopram, whereas it seems that the proconvulsive effect is mostly mediated through the NO pathway and can be totally blocked by NOS inhibitors. This could propose a new approach toward augmenting the efficacy of citalopram in depressive patients with epilepsy, curtailing the adverse effects of citalopram and perhaps managing the convulsions as a vicious consequence of citalopram overdose.

Keywords: Citalopram; Pentylentetrazole; Clonic seizure threshold; Mice