Involvement of NMDA and AMPA receptors in the antidepressant-like activity of antidepressant drugs in the forced swim test

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Abstract:
Background: The involvement of glutamate system (particularly the NMDA and AMPA receptors) in the mechanism of antidepressant activity was demonstrated in preclinical and clinical studies.

Methods: In the present study, we investigated the effect of NMDA and AMPA receptors’ ligands (agonists and antagonists) on the antidepressant-like activity of escitalopram, milnacipran, imipramine and reboxetine in the forced swim test in mice.

Results: Antidepressant activity (reduction in immobility time) of escitalopram and milnacipran but not of imipramine and reboxetine was antagonized by N-methyl-D-aspartate acid. CGP37849 (antagonist of the NMDA receptor) enhanced the antidepressant activity of all examined antidepressants. On the other hand, CX614 (a potentiator/positive allosteric modulator of the AMPA receptor) enhanced the antidepressant activity of imipramine and reboxetine but not of escitalopram and milnacipran in this test. NBQX (the AMPA receptor antagonist) did not influence the antidepressant activity of all tested agents.

Conclusions: The data indicate the complex interactions following the activation or blockade of the NMDA and AMPA receptors with antidepressant drugs. The general phenomenon is the enhancing effect of the NMDA receptor antagonism on the antidepressant activity. Moreover, it can be concluded that the activity of antidepressants with a serotonergic mechanism of action can be inhibited by NMDA activation, while antidepressants with a noradrenergic mechanism of action are dependent on AMPA receptor transmission.

Key words:
antidepressants, NMDA, AMPA, ligands, forced swim test, mice