Add-On Administration of Olanzapine to Fluoxetine Facilitates Cortical AMPA Receptor-Mediated Responses Like Ketamine and Scopolamine

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Summary and Conclusions
This study shows, in similarity to previously published results, that the combination of different atypical APDs and SSRIs facilitate NMDA receptor-mediated currents in pyramidal cells of the mPFC, an effect which may contribute to relieve both depressive symptoms and cognitive impairment in MDD.

Aims
To investigate the effects of the clinically used combination of olanzapine and fluoxetine, as well as the combination of the novel antipsychotic drug asenapine and the SSRI escitalopram on AMPA-induced currents in pyramidal cells of the rat mPFC. Aims were validated in vitro using intracellular recordings in culture. Furthermore, for comparison, we also investigated the corresponding effects of these drug combinations on NMDA-induced currents.

Methods
Animals
Male Sprague–Dawley rats were used for the electrophysiological experiments. The rats were housed under normal laboratory conditions (12:12 h with water and food available ad lib. All experiments were approved and conducted in accordance with the local Animal Ethics Committee, Stockholm North.

Preparation of brain slices
Rats were decapitated under halothane anesthesia and the brain was rapidly removed and cooled in ice-cold Ringer’s solution. The mPFC was isolated, cut into 400 µm slices using a vibratome and were kept submerged in aerated Ringer’s solution for at least one hour for recovery before experiment.

Intracellular recordings
Intracellular recordings of pyramidal cells in layer V in the mPFC. Electrodes were pulled from borosilicate capillary tubes on a horizontal electrode puller (Electrodes R) and coated with KAc (tip resistance 50-120 mΩ). Single-electrode voltage-clamp experiments were performed at a holding potential of 40 mV. The mPFC was acquired using digital analog sampling and acquisition software Clamps Plus 9.2. NMDA 10-15 µM and AMPA 2.5 µM was bath applied in the presence of tetrodotoxin (TTX, 0.5 µM to block action potentials), glycine (1 µM to enhance NMDA-induced responses) and bicuculline (3 µM to block GABA-A receptors). All drugs were diluted in Ringer’s solution and administered via bath perfusion.

Statistical analysis
Effect of the drugs on AMPA- and NMDA-induced currents compared to control response analyzed using students t-test. Statistical significance was indicated by * (p<0.05), ** (p<0.01), *** (p<0.001). Between group comparison was performed using one-way ANOVA followed by Newman–Keuls test (statistical significance indicated by *) and Dunnett’s test (statistical significance indicated by #). P<0.05 was considered significant for all tests.

Results
Addition of the antipsychotic drug olanzapine to fluoxetine at clinically relevant concentrations, which when given alone did not produce any effect on AMPA-induced currents, facilitated AMPA-induced currents in pyramidal cells of the mPFC (Fig. 1a). A similar result was obtained when the combination of the novel antipsychotic drug asenapine and the SSRI escitalopram was tested (Fig. 2). In addition, add-on of a sub-effective concentration of olanzapine to fluoxetine (Fig. 3) as well as the combination of sub-effective concentrations of asenapine and escitalopram (Fig. 4), facilitated NMDA-induced currents in pyramidal cells of the mPFC. The facilitation of NMDA-induced currents was mediated via the dopamine D1 receptor, as it was blocked by the selective D1 receptor antagonist SCH23390.

References

Materials and Methods

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