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CORTICAL AND SUBCORTICAL GENE-EXPRESSION IMAGING BY DIFFERENT N-METHYL-D-ASPARTATE RECEPTOR (NMDA-R) ANTAGONISTS AT GLUTAMMATERGIC SYNAPSES: IMPLICATIONS FOR DOPAMINE-GLUTAMATE INTERPLAY IN PSYCHOSES

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Introduction: According to the NMDA-R hypofunction hypothesis of psychosis, the administration of certain antagonists at NMDA-R, such as ketamine, may exacerbate psychotic symptoms in humans and provide a preclinical model of psychosis. Both ketamine and antipsychotic drugs induce molecular changes in genes of the post-synaptic density (PSD), involved in glutamate signaling and dopamine-glutamate interplay.
Memantine, an antagonist/partial agonist at NMDA-Rs with procognitive properties, has been proposed as an adjunctive treatment for schizophrenia.
Aims: We tested the hypothesis that memantine and propsychotic NMDA-Rs antagonists (ketamine and MK-801) may elicit divergent molecular changes at glutamatergic synapses.
Methods: Sprague-Dawley rats were treated by:
1) vehicle;
2) MK-801 0.8mg/kg;
3) memantine 5mg/kg;
4) ketamine 25mg/kg;
5) ketamine 50mg/kg.
We compared, by in situ hybridization histochemistry, the expression of PSD genes in cortical and striatal brain regions.
Results: Homer1a expression was significantly induced by ketamine 25mg/kg and reduced by MK-801 in striatum and cortex. Arc expression was significantly induced by ketamine and memantine in the cortex and by MK-801 in nucleus accumbens. Homer1b/c expression was significantly decreased by ketamine compared to vehicle in motor cortex and dorsolateral striatum. PSD-95 expression was significantly decreased by MK-801 compared to vehicle in all striatal regions and by ketamine in dorsomedial striatum.
Conclusions: These results demonstrate that NMDA-Rs antagonists with different pharmacological properties trigger different molecular changes at glutamatergic synapses. These results are consistent with the different clinical profiles of these compounds and with the observation that NMDA-R blockade is not necessarily associated to psychosis exacerbation.

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