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EFFECTS OF CHRONIC ORAL TREATMENT WITH ARIPIPRAZOLE ON EXPRESSION OF NMDA RECEPTOR SUBUNITS AND BINDING SITES IN RAT BRAIN

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Introduction: The glutamatergic theory of schizophrenia proposes a dysfunction of ionotropic N-Methyl-D-aspartate (NMDA)-receptors (NR). Several therapeutic strategies address NR function and effects of antipsychotic agents on NR expression have been described.

Objectives: The partial dopaminergic and serotonergic agonist aripiprazole (APZ) was able to counteract behavioural effects of NR antagonists, but effects of APZ on NR expression have not been investigated.

Aims: To evaluate effects of APZ on NR mRNA and protein expression

Methods: We treated Sprague-Dawley rats for 4 weeks or 4 months with APZ in daily oral doses of 10 and 40 mg per kg body weight. Expression of the NR subunits NR1, NR2A, NR2B, NR2C and NR2D was assessed by semiquantitative radioactive in situ-hybridization, and in parallel receptor binding using ^{3}H-MK-801 receptor autoradiography.

Results: Increased expression levels of NR1 (4 weeks), NR2A (4 weeks), NR2C (4 weeks and 4 months) and NR2D (4 months) were observed in several hippocampal and cortical brain regions. The parallel reduced expression of NR2B mRNAs (4 months) resulted in a relative increase of the NR2A/NR2B ratio. Marked differences between specific brain regions, the doses and time points of assessment became obvious. On the receptor level, increased MK-801-binding was found after 4 weeks in the 40 mg-group and after 4 months in the 10 mg-group.

Conclusions: The effects of APZ converge in enhanced NMDA-receptor expression and a shift of subunit-composition towards adult-type receptors. Our results confirm regulatory connections between dopaminergic, serotonergic and glutamatergic neurotransmission with relevance for cognitive and negative symptoms of schizophrenia.

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