Atypical Antipsychotics Regulate NMDA Receptor expression via GSK3beta/beta-catenin and GSK3beta/CREB1 Pathways in the Striatum of Young Rats

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Antipsychotic drugs were developed to treat schizophrenia in adults; however, they have been widely and increasingly used (mostly 'off label') for short-term control of various mental disorders in children/adolescents, without solid scientific and medical evidence to support that use. Although N-methyl-D-aspartate (NMDA) receptors are involved in the pathophysiology of various mental disorders, antipsychotics mainly bind with dopamine D2-like and serotonin 5-HT2 receptors to exert their therapeutic effects, but do not directly bind with NMDA receptors. Therefore, this study investigated effects of three antipsychotics commonly used in children/adolescents, aripiprazole, olanzapine and risperidone, on modulating NMDA receptors, as well as GSK3beta-CREB1 and beta-catenin signalling in the striatum of juvenile rats. Male juvenile rats were orally treated with aripiprazole (1 mg/kg), olanzapine (1 mg/kg), risperidone (0.3 mg/kg), or vehicle (3 times/day) from postnatal day 23 for 3 weeks. The levels of GSK3beta, beta-catenin, CREB1 and NMDA receptor NR1 and NR2A subunits were measured in the striatum by Western Blots. All of three antipsychotics upregulated significantly the protein levels of NMDA NR1 subunit, while aripiprazole and olanzapine also increased NMDA NR2A levels. Correlated with this upregulated NMDA NR1 expression, all of the three antipsychotics elevated significantly p-GSK3beta, the ratio of p-GSK3beta/GSK3beta, and ratio of p-beta-catenin/beta-catenin. Aripiprazole and risperidone also elevated the ratio of p-CREB1/CREB1. These results suggest that antipsychotics upregulate NMDA receptors in the striatum of juvenile rats, probably via GSK3beta-CREB1 and beta-catenin signalling, which may contribute to the therapeutic efficacy of antipsychotics in children and adolescents.