Purinergic System Perturbations in Schizophrenia

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Keywords: Adenosine; Schizophrenia; Anterior Cingulate Cortex; Transcript Expression

Published: 22 May 2024

Background: Schizophrenia is a devastating neuropsychiatric disorder characterized by hallucinations, delusions, and disordered thought processes. Dysregulation of the glutamate and dopamine neurotransmitter systems are implicated in the pathophysiology of schizophrenia. The adenosine system is an important neuroregulatory system in the brain that modulates glutamate and dopamine signaling via adenosine receptors; however, the gene expression of the high affinity adenosine A1 and A2A receptors (A1R and A2AR) is not well characterized in neurons in frontal cortical brain regions implicated in this disorder.

Methods: In the present study, we analyzed A1R and A2AR mRNA expression via qPCR in enriched populations of pyramidal neurons, isolated from postmortem anterior cingulate cortex (ACC) tissue from schizophrenia (n=20) and age and sex-matched non-psychiatrically ill control (n=20) subjects, using laser capture microdissection.

Results: A2AR mRNA expression was significantly increased in schizophrenia subjects who were off antipsychotic medication (ANCOVA: $F(1,12)=6.444$, $p=0.026$), suggesting that A2AR expression may be normalized by chronic antipsychotic treatment. A1R expression was significantly increased in female schizophrenia subjects compared to female control subjects ($t(13)=-4.008$, $p=0.001$). A1R expression was also significantly decreased in female controls compared to male control subjects ($t(17)=2.137$, $p=0.047$). We also identified a significant positive association between dementia severity and A2AR mRNA expression (Spearman's $r=0.424$, $p=0.009$).

Conclusion: Overall, these results provide novel insights into the pyramidal neuron specific expression of adenosine receptors in the ACC in schizophrenia and suggest that changes in receptor mRNA expression may be sex-dependent and associated with dementia in these subjects.

Funding Acknowledgement

National Institute of Mental Health (MH107487); American Foundation of Suicide Prevention (YIG-1-139-20)

