A2A-D2 HETERODIMERS ON STRIATAL ASTROCYTES

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The interaction between adenosine A2A and dopamine D2 receptors at the striatal neuronal plasma membrane is a well-established phenomenon and has opened up new perspectives on the molecular mechanisms involved in the pathophysiology of neuropsychiatric disorders such as Parkinson's disease or schizophrenia. However it has barely been investigated in astrocytes, although involvement of astrocytes in neuropsychiatric disease vulnerability is increasingly recognized. Here, we investigate A2A-D2 receptor integrative processes at the plasma membrane level of striatal astrocyte processes prepared from adult rat striatum. The effects of A2A and D2 receptor activation/blockade, the A2A-D2 receptor-receptor interaction and interference by receptor peptides or homocysteine were studied on glutamate release from the processes.

We here report that A2A and D2 receptors were co-expressed on the processes, and A2A-D2 receptor-receptor interaction controlled glutamate release from the processes. The synthetic peptide VLRRRRKRVN, corresponding to the D2 receptor region involved in electrostatic interaction underlying A2A-D2 heterodimerization, abolished the ability of the A2A receptor agonist to antagonize the D2 receptor-mediated effect. The complexity of the integrative action of A2A-D2 receptor-receptor interaction is suggested by the effect of intracytoplasmic homocysteine, which inhibited D2-mediated effect on glutamate release (i.e., homocysteine allosteric action on D2), without interfering with the A2A-mediated antagonism of the D2 effect (i.e., maintained A2A-D2 receptor-receptor interaction).

In conclusion, our findings indicate the crucial integrative role of A2A-D2 molecular circuits at the plasma membrane level of striatal astrocyte processes. The fact that homocysteine reduced D2-mediated inhibition of glutamate release could provide new insights into striatal astrocyte-neuron intercellular communications. In fact, hyperhomocysteinemia has been repeatedly reported in Parkinson’s patients, especially during L-dopa treatment, and hypothesized to play a role in tardive side effects of L-dopa.

As striatal astrocytes are increasingly recognized to be involved in the pathophysiology of Parkinson’s disease, these findings may shed light on the pathogenic mechanisms of the disease and contribute to the development of new drugs for its treatment.

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