A2A-D2 heterodimers control glutamate release from striatal astrocytes

A. Venturini[1], C. Cervetto[1,2], M. Passalacqua[3], S. Genedani[4], A. Woods[6], G. Maura[1,2], M. Marcoli[1,2], L.F. Agnati[4,5]

[1]Department of Pharmacy, Section of Pharmacology and Toxicology, University of Genova, Viale Cembrano 4, 16148 Genova, Italy
[2]Centre of Excellence for Biomedical Research CEBR, University of Genova, Viale Benedetto XV, 5, 16132 Genova, Italy
[3]Department of Experimental Medicine, Section of Biochemistry, and Italian Institute of Biostructures and Biosystems, University of Genova, Via L.B. Alberti 2, 16132 Genova, Italy
[4]Department of Diagnostic, Clinical Medicine and Public Health, University of Modena and Reggio Emilia, via Campi 287, 41125 Modena, Italy
[5]Department of Neuroscience, Karolinska Institutet, Retzius väg 8, Stockholm, Sweden
[6]Structural Biology Unit, National Institutes of Health, National Institute of Drug Abuse-Intramural Research Program, 333 Cassell Dr., Baltimore, MD 21224, USA

Recently, there has been a growing interest in astrocytes and in the complex neuron-astrocyte network function, and the involvement of astrocytes in neurodegenerative and neuropsychiatric diseases is being increasingly recognized.
Growing evidence shows that adult striatal astrocytes express both dopamine D2 receptors and adenosine A2A receptors. Moreover, the presence of A2A-D2 heteroreceptor complexes has led to a new perspective of molecular mechanisms involved in neuropsychiatric disorders, such as schizophrenia or Parkinson's disease, providing novel drug targets.
Despite major attention to striatal A2A and D2 receptors within brain function and neuropsychiatric disorders, participation of striatal astrocytes in A2A and D2 receptor signal transmission has never been explored.

Therefore, the aim of our study was to assess the presence of D2 and A2A receptors, and their co-expression in purified astrocyte processes prepared from adult rats striatum by confocal analysis. We found that both A2A and D2 receptors were expressed on the same astrocyte processes.
Furthermore, we investigated the ability of A2A-D2 heteromers to control striatal glutamatergic transmission, by measuring the release of the gliotransmitter glutamate.
Notably, monitoring the release of a gliotransmitter from a superfused gliosomal monolayer, when superfusion removes any possibly released active substance and avoids formation of receptor biophase, allows exposure of 'nude' receptors. Thus, it can be employed as a simplified model for the pharmacological characterization of release regulating receptors as well as for the analysis of receptor-receptor interactions.
With this method, we obtained evidence of the receptor-receptor interactions: D2 receptors inhibited the 4 aminopyridine-evoked glutamate release, while activation of A2A receptors, *per se* ineffective, abolished the effect of D2 receptor activation.
The synthetic D2 peptide VLRRRRKRVN corresponding to the receptor region involved in electrostatic interaction underlying A2A-D2 receptor heteromerization abolished the ability of the A2A receptor agonist to antagonize the D2 receptor-mediated effect.

In conclusion, the findings are consistent with heteromerization of native striatal astrocytic A2A–D2 receptors being able to control striatal glutamatergic transmission, with possible consequences in neurodegenerative and neuropsychiatric disorders.