Role of Striatal A_{2A}, D_2 and $mGlu_5$ Receptor Interactions in the Modulation of Glutamate Levels from Rat Striatal Nerve Terminals

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In the central nervous system the oligomerization of neurotransmitter/neuromodulator receptors generates functional entities with biochemical features that are different from those of the individual components of the heteromer (Fuxe et al., 2008). It has been reported that adenosine A_{2A} ($A_{2A}R$), D_2 receptor (D_2R) and metabotropic glutamate type 5 ($mGlu_5R$) receptors colocalize in striatopallidal efferent neurons (Cabello et al., 2009), where they interact both physically and functionally (Cabello et al., 2009; Ciruela et al., 2011). Specifically, the co-stimulation of both $A_{2A}R$ and $mGlu_5R$ produces a modulation of D_2R agonist binding that is significantly stronger than the reduction induced by stimulation of either receptor alone (Popoli et al., 2001). Taken together, these initial results suggested the existence of a striatal $A_{2A}R/D_2R/mGlu_5R$ oligomer, which has been also supported by co-immunoprecipitation experiments (Cabello et al., 2009).

Striatal glutamatergic nerve terminals possessed $A_{2A}R$, D_2R and $mGluR_5$, suggesting a presynaptic functional interaction between these receptors or the putative $A_{2A}R/D_2R/mGlu_5R$ oligomer. In the attempt to investigate the functional relevance of this interaction, in the present study we evaluated the effects of the $A_{2A}R$ agonist CGS21680, the $mGluR_5$ agonist CHPG and the D_2R agonist quinpirole, alone or in combination on K^+-evoked glutamate levels from rat striatal nerve terminals.

The $A_{2A}R$ agonist, CGS21680 (10 and 30 nM) and the $mGluR_5$ agonist CHPG (300-600 μM) by themselves facilitated K^+-evoked glutamate levels from striatal nerve terminals. On the contrary, the D_2R agonist quinpirole (10-100 nM) significantly decreased K^+-evoked glutamate levels from striatal nerve terminals. Either CGS21680 or CHPG, at concentrations by themselves ineffective (1 nM and 100 μM, respectively), partially counteracted the quinpirole-induced reduction of K^+-evoked glutamate levels from rat striatal nerve terminals. Interestingly, the co-stimulation of both $A_{2A}R$ and $mGlu_5R$ produces a modulation of quinpirole-induced reduction of K^+-evoked glutamate levels that is stronger than the reduction induced by stimulation of each receptor alone.

These results provide evidence that an interaction between $A_{2A}R$, D_2R and $mGluR_5$ and/or the putative $A_{2A}R/D_2R/mGlu_5R$ heterotrimer modulate glutamate release from rat striatal nerve terminals. As dopamine, adenosine and glutamate regulate striatal output nuclei involved in the control of motor behaviour, the $A_{2A}R/D_2R/mGlu_5R$ complex might be relevant to striatal function both under normal and pathological conditions, like Parkinson's disease.

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