Regulation of striatopallidal GABA neurotransmission by striatal A2A, D2 and mGlu5 receptor interactions: implications in Parkinson's disease.

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G-protein coupled receptors can function not only as monomers but also as oligomers transducing different integrated intracellular signals (1-4). In particular heterodimers formed by A2A adenosine receptor (A2AR) and D2 dopamine receptor (D2R) are present on GABAergic striatopallidal neurons, where they show antagonistic interactions leading to reduced D2R signaling. In rat striatopallidal GABA neurons, mGlu5 receptor (mGlu5R) showed a similar localization of A2AR and D2R long with indications about the existence of a A2AR/D2R/mGlu5R heterotrimer. Thus, the A2AR/D2R/mGlu5R complex might be relevant to striatal function.

In the present study, the *in vivo* characterization of the functional role of individual striatal A2AR, D2R and mGlu5R possibly along with the A2AR/D2R/mGlu5R heterotrimer, in regulating rat basal ganglia activity has been performed by using dual-probe microdialysis in freely moving rats. Specifically, intrastriatal perfusion with the D2R agonist quinpirole (10 μM, 60 min) induced a significant decrease on ipsilateral pallidal GABA and glutamate levels ($p < 0.01$ vs. control, n = 6-7), while intrastriatal CGS21680 (A2AR agonist; 1 μM, 60 min) was ineffective either on pallidal GABA and glutamate levels or the quinpirole-induced effects. Intrastriatal perfusion with the mGlu5R agonist CHPG (600 μM, 60 min), by itself ineffective on pallidal and glutamate levels, partially but significantly ($p< 0.05$ from the quinpirole group, n = 5-7) counteracted the effects of quinpirole. When combined with GS21680 (1 μM, 60 min), CHPG (600 μM, 60 min), fully counteracted the quinpirole (10 μM, 60 min)-induced reduction of ipsilateral pallidal GABA and glutamate levels. These effects were fully counteracted by local perfusion with the mGlu5R antagonist MPEP (300 μM) or the A2AR antagonist ZM 241385 (100 nM). Based on previous studies, it is possible to hypothesize that this interaction can be realized, within a heterotrimer where A2ARs and mGlu5Rs, when stimulated, synergize for their inhibitory effect on D2Rs signaling. Thus the current findings suggest the possible usefulness of using not only A2A antagonists but also mGlu5R antagonists and their combinations in the treatment of Parkinson's disease to increase inhibitory D2 signalling in the postulated A2AR/D2R/mGlu5R heterotrimer on striatopallidal GABA neurons (5).