

THE METABOTROPIC GLUTAMATE 5 (mGlu5Rs) AND THE ADENOSINE A_{2A} RECEPTORS (A_{2A}Rs) OPPOSITELY MODULATE CB1-INDUCED REDUCTION OF SYNAPTIC TRANSMISSION IN THE RAT STRIATUM

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The metabotropic glutamate receptors 5 (mGlu5Rs) and the adenosine A_{2A} receptors (A_{2A}Rs) are highly expressed and functionally interact in the striatum. In the same area, the cannabinoid system has been proposed to interact with both A_{2A} and mGlu5 receptors. First, the motor effects of cannabinoids have been reported to depend on physical and functional interactions between A_{2A} and CB1Rs (1). Furthermore, cannabinoids may be involved in mGlu5R-dependent depression of striatal synaptic transmission (2). The aim of the present work was to further evaluate, in electrophysiology experiments, the occurrence of functional interactions between CB1/A_{2A} and CB1/mGlu5 receptors. Extracellular field potentials (FPs) were recorded in rat corticostriatal slices. The cannabinoid R agonist WIN 55,212-2 (2-3 μM) induced a progressive decrease of the FP amplitude: 56.9±3.3 and 25.4±2% of basal at the end of treatment (t1) and after 30 min of washout (t2), N=5, P<0.05 vs basal. This effect depended on the stimulation of CB1Rs, since it was fully prevented by the CB1R antagonist AM 251 (N=3, P<0.05 vs WIN alone). Interestingly, WIN effects were also prevented by the A_{2A}R agonist CGS 21680 (100 nM, 87.3±8.9 and 63.1±15.4% of basal at t1 and t2, respectively, N=3, P<0.05 vs WIN). CGS 21680 significantly reduced WIN-induced paired-pulse inhibition (PPI), an index of reduction of pre-synaptic neurotransmitter release. The inhibitory effect of CGS21680 seemed to involve the cAMP/PKA pathway, since it was partly reproduced by the adenylyl cyclase activator forskolin. Specifically, forskolin (10 μM) prevented WIN-induced FP inhibition at t1 (91.9±3.5% of basal, N=3, P<0.05 vs WIN alone), and attenuated it at t2 (46.0±13.3% of basal, N=3, NS vs WIN alone). When applied at a lower concentration (1 μM), WIN induced a milder decrease in the FP amplitude (88.7±5.0 and 66.7±7.1% of basal at t1 and t2, respectively). This effect was markedly potentiated by the co-application of 500 μM CHPG, a selective mGlu5R agonist (39.8±10.6 and 19.94±8% of basal at t1 and t2, respectively, N=3, P<0.05 vs WIN alone in both cases). These results show that the activation of A_{2A} and mGlu5 receptors oppositely modulates CB1-induced reduction of synaptic transmission in the rat striatum. Since interacting A_{2A}Rs and mGlu5Rs play a pivotal functional role in the striatum, the involvement of CB1Rs in this cross-talk is worthy of further investigations.

(1) Ferré et al., (2006) Abstract of 36th Society for Neuroscience annual meeting.

(2) Jung et al., (2005) Mol Pharmacol. 68: 1196-1202.