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

Martire Alberto, Tebano Maria Teresa, Domenici Maria Rosaria, Popoli Patrizia.

Department of Therapeutic Research and Medicines Evaluation, Istituto Superiore di Sanità, Roma (Italy).

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.