THE RELEASE OF ENDOCANNABINOIDS IN THE CA1 HIPPOCAMPAL AREA IS MODULATED BY MGLU1 RECEPTORS: A PATCH CLAMP STUDY

Baccini Gilda, Landucci Elisa, Moroni Flavio, Pellegrini-Giampietro Domenico & Mannaioni Guido

Dipartimento di Farmacologia Preclinica e Clinica, Università di Firenze, Viale Pieraccini 6, 50139 Firenze

Activation of CB1 cannabinoid receptor produces a reduction of GABA(A)-mediated synaptic transmission in the CA1 area through a presynaptic mechanism (1). This effect has been shown to be triggered by group I metabotropic glutamate (mGlu) receptors activation at CA1 pyramidal cells (2). Moreover, it has been recently demonstrated a CB1-dependent tonic inhibition of GABA release at cholecystokinin-positive basket cell to pyramidal cell synapses in the CA1 region of the rat hippocampus (3). Therefore, in order to investigate the possible interplay through which mGlu group 1 receptors and CB1 receptors modulate GABAergic neurotransmission in the hippocampus, whole-cell voltage-clamp recordings were performed on CA1 pyramidal neurons in rat hippocampal slices. The mGlu1 selective antagonists LY367385 (100-300 µM) and 3-MATIDA (300 µM) dose dependently and persistently increased the frequency and the amplitude of pharmacologically isolated spontaneous inhibitory post synaptic currents (sIPSCs). Conversely, the selective mGlu5 antagonist MPEP did not modify neither the sIPSCs frequency nor the amplitude. Interestingly, the mGlu1 antagonists mediated effect on GABAergic transmission was present only when a KCl-based internal solution filled the postsynaptic cell, while it was partially abolished when a CsCl-based internal solution was used. This suggests a possible mGlu1 interaction with the endocannabinoid retrograde transmission system in the postsynaptic cell. To test this hypothesis, we co-applied LY367385 with the selective CB1 receptor agonists WIN 55,212-2 (30 µM) or CP55,940 (10 µM) and observed that the mGlu1-antagonist mediated effect was reverted. Finally, mGlu1/endocannabinoid-mediated modulation of inhibitory GABAergic neurotransmission has been shown to control CA1 pyramidal cell death in an *in vitro* model of ischemia (Landucci et al., this meeting). Therefore, our data suggest the existence of an mGlu1-mediated glutamatergic tone which is important in regulating inhibitory GABAergic transmission through a presynaptic CB1 receptor activation at CA1 pyramidal cells.

1) Hoffman & Lupica, J. Neurosci, 20: 2470, 2000
2) Chevaleyre & Castillo, Neuron, 38: 461, 2003
3) Neu et al., J. Physiol., 578, 233, 2006