mGLU1 RECEPTOR AND $GABA_B$ RECEPTOR HETERODIMERIZATION IN CORTICAL NERVE TERMINALS

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Introduction: $GABA_B$ receptors ($GABA_B$) mediate slow and fast inhibitory transmission in the central nervous system. mGlu type 1 receptor (mGlu1) mediates glutamate signalling. Thought to be preferentially located postsynaptically receptor, mGlu1 receptors was shown also to exist presynaptically. Based on previous studies, we focussed on mGlu1 and $GABA_B$ receptors in order to unveil a functional interaction between them in the central nervous system.

Material and methods: We used cortical synaptosomes in superfusion to evaluate the exocytosis of glutamate and GABA and the effects of the concomitant activation of both receptors on these events. In addition, we performed neurochemical studies and confocal analysis to support the functional observations.

Results: The results showed an impressive colocalization of the mGlu1 and the $GABA_B$ receptors in the GABAergic synaptosomes. The 12 mM KCl-evoked [^{3}H]GABA exocytosis was inhibited by the $GABA_B$ agonist, (±) baclofen in a CGP 53423-sensitive manner. The mGlu1/5 agonist failed to affect the KCl-induced [^{3}H]GABA overflow, while LY 367385, an orthosteric mGlu1 antagonist, significantly amplified the (±) baclofen-mediated inhibition of [^{3}H]GABA exocytosis in a PKC-dependent fashion. A large colocalization of mGlu1 protein and $GABA_B$ subunits also emerged in cortical glutamatergic synaptosomes. Again, LY 367385, inactive on its own, reinforced the (±) baclofen-induced inhibition of the 12 mM KCl-evoked glutamate overflow. Then we moved to the $Grm1^{crv/crv44}$ mice, which bear a spontaneous mutation of the Grm1 gene leading to the functional inactivation of the mGlu1 receptors. Here, the (±) baclofen-induced inhibition of [^{3}H]GABA exocytosis from cortical synaptosomes was more pronounced than that observed in controls. Consistently, an increased expression of the $GABA_{B2}$ subunits was observed in these mice.

Conclusion: Our findings suggest an unusual cross talk linking mGlu1 and $GABA_B$ receptors in cortical nerve endings which depends on PKC-dependent intra-terminal pathway and could have a great impact in neuronal process and in pathological condition.