Presynaptic control of GABAergic neurotransmission by $GABA_B$ and group I mGlu heteromers in nerve endings isolated from rat cerebral cortices.

I. A. Samengo and M. Martire.
Institute of Pharmacology, School of Medicine, Catholic University of Sacred Heart, Rome, Italy.

Interaction between different transmitter receptor systems is an emerging feature of neurotransmission at central synapses (Prezeau et al., 2010). A rapidly expanding body of evidence indicates that most, if not all, G protein-coupled receptors (GPCRs) are present at the plasma membrane level as dimeric complexes with distinct pharmacological and functional properties (Fredholm et al., 2007). Hetero-dimers with properties that are not shared by their respective homomers have also been reported (Milligan, 2006). Class C GPCRs represent an interesting model for studying the role of oligomerization in receptor function (Kniazeff et al., 2011). The dimeric nature of these receptors is well-established in both transfected cells and native neurons (Pin et al., 2003). We found that, in nerve terminals isolated from the cerebral cortices of rats, co-application of the $GABA_B$ agonist, baclofen (1 μM), and of the non-selective mGlu agonist, L-CCG-I (30 μM), facilitates the basal and depolarization-evoked release of [^{3}H]GABA via a mechanism that involves mobilization of intracellular Ca^{2+} ions. The effect of L-CCG-I (30 μM) + baclofen (1 μM) was abolished by the phospholipase C inhibitor U73122 (50 μM), reduced by Xestospongin C (an IP3 receptor blocker) (0.5 μM), and blocked by 2-APB (100 μM), an IP_3 receptor antagonist. Pretreatment of the synaptosomes with the lipid-soluble Ca^{2+} chelator BAPTA-AM (30 μM) also inhibited the effects of L-CCG-I + baclofen. Subtype-selective non-competitive group I mGlu receptor antagonists, MPEP (1 μM) and CPCCOEt (30 μM), had no effect on the release enhancement produced by L-CCG-I (30 μM) + baclofen (1 μM). Exposure of synaptosomes to 3 μM CGP54626, a potent and selective $GABA_B$ receptor antagonist, completely reversed the enhancement of basal [^{3}H]GABA release produced by L-CCG-I + baclofen. The effect produced by LCCGI + baclofen was also reversed by (RS)-MCPG (30 μM), a non-selective competitive group I/group II mGlu receptor antagonist. The GABA release-enhancing effects of L-CCG-I + baclofen in our model might reflect the presence on cortical nerve endings of $GABA_B$/group I mGlu receptor heteromers with pharmacological properties distinct from those of the component receptors. Activation of these heteromeric receptors might modify the function of the $GABA_B$ receptor in such a way that it facilitates GABAergic transmission, an effect that might be useful under conditions of excessive glutamatergic activity.

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