Pharmacological profiles of presynaptic, release-regulating mGlu2-preferring and mGlu3-preferring autoreceptors and their functional role in demyelinating disease

T. Bonfiglio[1], G. Olivero[1], M. Vergassola[1], C. Cervetto[1], M. Grilli [1], C. Usai[2], M. Marchi[1,3] and . Pittaluga[1,3]
[1]Department of Pharmacy, DiFAR, Pharmacology and Toxicology Section, viale Cembrano 4, Genoa, Italy.
[2]Institute of Biophysics, National Research Council, via De Marini 6, 16149, Genoa, Italy.
[3]Center of Excellence for Biomedical Research, University of Genoa, Viale Benedetto XV, Genoa, Italy.

AIMS
Presynaptic, release-regulating metabotropic glutamate 2 and 3 (mGlu2/3) autoreceptors exist in central nervous system (CNS). They represent suitable targets for therapeutic approaches to central diseases that are typified by hyperglutamatergicity. The availability of specific ligands able to differentiate between mGlu2 and mGlu3 subunits allows to further characterize these autoreceptors. This study aims at investigating the pharmacological profile of mGlu2/3 receptors in selected CNS regions and at evaluating their functions in mice suffering from experimental autoimmune encephalomyelitis (EAE).
METHOD
The comparative analysis of presynaptic mGlu2/3 autoreceptors was performed by analyzing the effect of selective mGlu2/3 receptor agonist(s) and antagonist(s) on the release of [^{3}H]-D-aspartate from cortical and spinal cord synaptosomes in superfusion. Experiments were also carried out to analyze mGlu2/3 autoreceptor-mediated releasing functions in EAE animals and whether *in vivo* LY379268 administration can restore impaired glutamate release in these mice.
RESULTS
Western blot analysis and confocal microscopy confirmed the presence of presynaptic mGlu2/3 receptor proteins. Cortical synaptosomes possess LY541850-sensitive, NAAG-insensitive autoreceptors having low affinity for LY379268, while LY541850-insensitive, NAAG-sensitive autoreceptors with high affinity for LY379268 exist in spinal cord terminals. In EAE mice, mGlu2/3 autoreceptors lost completely their inhibitory activity in cortical, but not in spinal cord synaptosomes. *In vivo* LY379268 (1-0.01 mg kg^{-1}) administration restored glutamate exocytosis capability in spinal cord but not in cortical terminals.
CONCLUSIONS
We propose the existence of mGlu2-preferring and mGlu3-preferring autoreceptors in mouse cortex and spinal cord, respectively. The mGlu3-preferring autoreceptors could represent a target for new pharmacological approach for demyelinating diseases.