PHARMACOLOGICAL CHARACTERIZATION OF PRESYNAPTIC RELEASE-REGULATING mGLU2-PREFERRING AND mGLU3-PREFERRING AUTORECEPTORS IN MOUSE CNS

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Presynaptic, release-regulating metabotropic glutamate 2 and 3 (mGlu2/3) autoreceptors exist in the central nervous system (CNS). They represent suitable targets for therapeutic approaches to central diseases characterized by hyperglutamatergicity. The availability of specific ligands able to differentiate between mGlu2 and mGlu3 subunits allows to further characterize these autoreceptors. We performed a comparative analysis of presynaptic mGlu2/3 autoreceptors in cortical and spinal cord nerve terminals by analyzing the effect of the following selective compounds on the release of [3H]-D-aspartate from synaptosomes in superfusion : LY379268, a broad spectrum agonist of mGlu2/3 receptors; NAAG, a selective mGlu3 agonist; LY541850, a selective mGlu2 receptor agonist with mGlu3 receptor antagonist activity; LY566332, a positive allosteric modulator of the mGlu2 receptor subtype and LY2389575, a selective mGlu3 negative allosteric modulator. Concomitantly, we approached the pharmacological characterization of these autoreceptors by investigating whether and to what extent incubation of these nerve terminals with selective antibodies raised against the outer sequences of the mGlu2 or the mGlu3 receptor proteins could affect the LY379268-mediated inhibition of glutamate exocytosis.

Cortical nerve endings possess LY541850-sensitive, NAAG-insensitive autoreceptors having low affinity for LY379268. These receptors are also sensitive to LY566332, but slightly, although significantly, to LY2389575. Differently, spinal cord terminals are endowed with LY541850-insensitive, NAAG-sensitive autoreceptors with high affinity for LY379268. These receptors are LY566332-insensitive and LY2389575-sensitive.

Incubation of cortical synaptosomes with the anti-mGlu2 antibody prevents the LY379268-induced inhibition of glutamate exocytosis, that is only in part reduced by the anti-mGlu3 antibody, while the anti-mGlu3, but not anti-mGlu2, antibody abolishes the LY379268-mediated reduction of glutamate exocytosis from spinal cord nerve terminals. Western blot and confocal microscopy analysis are largely consistent with these functional observations.

In conclusion, 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 to central disorders, like demyelinating diseases.