ACID-SENSING ION CHANNEL 1A IS REQUIRED FOR MGLUR-DEPENDENT LONG-TERM DEPRESSION AND IS INVOLVED IN AB-INDUCED SYNAPTIC TOXICITY IN THE RODENT HIPPOCAMPUS

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Acid-sensing ion channels (ASICs), members of the degenerin/epithelial Na+ channel superfamily, are widely distributed in the mammalian nervous system. ASIC1a are highly permeable to Ca2+ and their activation has a crucial importance in numerous physiological and pathological processes, including synaptic plasticity, learning and memory (Huang et al., 2015). To further understand the role of ASIC1a in neurotransmission, we investigated metabotropic glutamate (mGlu) receptor-dependent long-term depression (LTD) in the hippocampus. We found that a functional crosstalk between ASIC1a and group I mGlu receptors occurs in mGlu receptor-dependent LTD in adult animals. In fact, the ASIC1a selective blocker psalmotoxin-1 (PcTx1) reduced the magnitude of mGlu receptor-dependent LTD induced by application of the group I mGlu receptor agonist (S)-3,5-Dihydroxyphenylglycine (DHPG). Notably, PcTx1 was able to prevent the increase in GluA1 S845 phosphorylation at the post-synaptic membrane AMPA following group I mGlu receptors activation (Mango et al., 2017).

Growing experimental evidence has indicated that the accumulation of soluble amyloid beta (Aβ) is associated with, and probably induces, profound neuronal and synaptic changes in brain regions critical for memory and cognition. Accordingly it has been shown that Aβ oligomers induce early synaptic loss in several non-clinical models of Alzheimer's disease (AD) (Selkoe et al., 2016). Excessive Aβ levels can disrupt excitatory synaptic transmission and plasticity, and this can be due to dysregulation of both AMPA and NMDA glutamate receptors in the brain. We also present data suggesting that pharmacological blockade of ASIC1a is able to rescue the Aβ-dependent alteration of mGlu receptor-dependent LTD.

These findings suggest a novel function of ASIC1a channels in the regulation of specific forms of synaptic plasticity. Therefore ASIC1a may represent a novel target for the development of drugs to prevent and/ or treat memory loss in AD and related cognitive impairments.

References

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