Extracellular ATP attenuates gamma oscillations by inhibiting excitatory synaptic input on parvalbumin positive interneurons by activating P2X4 receptors

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Abstract

Background and Purpose: P2X4 receptors (P2X4R) are ligand gated cation channels that are activated by extracellular adenosine 5'-triphosphate (ATP) released by neurons and glia. The receptors are widely expressed in the brain and have fractional calcium currents comparable to NMDA receptors. Although P2X4Rs were described to modulate synaptic transmission and plasticity, their involvement in shaping neuronal network activity remains to be elucidated. Exp. Approach: We investigated the effects of P2X receptors on network and synaptic level using local field potential electrophysiology, whole cell patch clamp recordings and calcium imaging in fast spiking parvalbumin positive interneurons (PVINs) in rat and mice hippocampal slices. The stable ATP analogue ATPγS, selective antagonists and P2X4R knockout mice were used. Key results: The P2XR agonist ATPγS reversibly decreased the power of gamma oscillations. This inhibition could be antagonized by the selective P2X4R antagonist PSB-12062 and was not observed in P2X4-/- mice. The phasic excitatory inputs of CA3 PVINs were one of the main regulators of the gamma power. Associational fibre compound excitatory postsynaptic currents (cEPSCs) in CA3 PVINs were inhibited by P2X4R activation. This effect was reversible, dependent on intracellular calcium and dynamin-dependent internalization of AMPA receptors. Conclusions and Implications: The results indicate that P2X4Rs are an important source of dendritic calcium in CA3 PVINs, thereby regulating excitatory synaptic inputs onto the cells and the state of gamma oscillations in the hippocampus. P2X4Rs represent an effective target to modulate hippocampal network activity in pathophysiological conditions such as Alzheimer's disease and schizophrenia.

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