Neuronal hyperexcitability mediated by GqPCR-mediated signaling in astrocytes

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Astrocytes maintain extracellular milieu, provide nutrients and release signaling molecules to regulate neuronal excitability. Dysfunction or augmentation of astrocytic roles is implicated in neuronal hyperexcitablity found in many neurological disease, such as epilepsy and Alzheimer's disease. In disease, astrocytes generally become reactive and reactive astrocytes show more Ca^{2+} signals with increase in Gq-protein coupled receptors (GqPCRs). To investigate the role of augmented GqPCR-mediated Ca^{2+} signals in neuronal excitability, we engineered mice whose astrocytes specifically overexpress P2Y1 receptor, one of major GqPCRs in astrocytes in adult brain, (astrocyte P2Y1OE). Using dual color Ca^{2+} imaging of neurons and astrocytes by two different colors of genetically encoded Ca^{2+} indicators, we found that astrocytes showed robust Ca^{2+} signals in response to neuronal stimuli and neurons showed enhanced dendritic responses in P2Y1OE, both of which depend on P2Y1 receptor signaling. Extracellular glutamate increased by neuronal stimuli was also enhanced in P2Y1OE. Astrocyte P2Y1OE mice show higher susceptibility to pilocarpine-induced status epilepticus. Overall data suggest that astrocytic Ca^{2+} signals mediated by GqPCR lead to neuronal hyperexicitability through enhancement of glutamatergic signaling.