Up-regulation of the P2Y2 receptor by cytokines in neuronal cells

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Alzheimer's Disease (AD) is characterized by inflammation and neurodegeneration in the brain due to the presence of extracellular amyloid beta (Aβ) plaques and neurofibrillary tangles. Microglial and astrocyte cells associated with these plaques and tangles have been shown to release cytokines in AD patients, which have a proinflammatory effect on the brain. The P2Y2 receptor (P2Y2R) is a receptor protein that is up-regulated in response to damage or stress in a variety of tissues, including blood vessels and salivary gland epithelium. Recently, our laboratory has shown that activation of the P2Y2R enhances α-secretase-dependent amyloid precursor protein (APP) processing. APP is proteolytically processed by β- and γ-secretases to release neurodegenerative Aβ. Alternatively, APP can be cleaved within the Aβ domain by α-secretase releasing the non-amyloidogenic product, sAPPα, which has been shown to have neuroprotective properties.

Primary neurons have low P2Y2R expression, however, it has been demonstrated that cytokines up-regulate P2Y2R in smooth muscle cells. Therefore, this study will explore if cytokines up-regulate P2Y2R expression in primary rat neurons and in SH-SY5Y human neuroblastoma cells. Primary rat neurons and SH-SY5Y human neuroblastoma cells were plated on glass cover slips 24 or 48 hours with individual treatment, or a combination of, human interleukin-1β (IL1-β), tumor necrosis factor α (TNF α), and interferon γ (IF γ). P2Y2R activity was measured by increases in intracellular calcium concentration ([Ca2+]i) in response to the P2Y2R agonist UTP. Results support the hypothesis that P2Y2R is up-regulated by cytokines in neuronal cells. Furthermore, real-time PCR results indicate a two-fold increase in P2Y2R mRNA after cytokine treatment. Therefore, activation of the up-regulated P2Y2R in stressed neurons generates a neuroprotective (sAPPα) rather than neurodegenerative (Aβ) peptide. These results could have a substantial impact on the understanding and treatment of neurological disorders such as AD.