

Public Abstract
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Role of P2Y₂ Nucleotide Receptors in Reactive Astrogliosis
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ABSTRACT

Astrocytes, a type of cell in the brain, become activated in response to brain injury that increases their rates of migration and growth, responses that are collectively termed reactive astrogliosis. Although there are indications that reactive astrocytes can protect undamaged tissue and limit secondary injury, excessive or chronic accumulation of astrocytes can produce inflammation and prevent regeneration of neurons within the damaged area. Therefore, a greater understanding of the mechanisms involved in reactive astrogliosis should provide new ways to prevent irreversible brain damage in neurological disorders. Damage to brain cells causes the release of cellular nucleotides, such as ATP and UTP, whereupon they activate a cell surface receptor called the P2Y₂ nucleotide receptor (P2Y₂R) that mediates responses associated with reactive astrogliosis. Results in this study with primary rat astrocytes indicate that P2Y₂R activation increases cell migration. UTP-induced astrocyte migration was inhibited by silencing of P2Y₂R expression with P2Y₂R siRNA, providing direct evidence that the P2Y₂R is involved. UTP also increased the expression in astrocytes of integrins called $\alpha_v\beta_{3/5}$ that are known to bind the P2Y₂R to modulate its function. Anti- α_v integrin antibodies prevented UTP-stimulated astrocyte migration, suggesting that P2Y₂R/ α_v interaction is required for this effect. P2Y₂R-mediated astrocyte migration required the activation of intracellular kinases including the PI3-K/Akt and MEK/ERK signaling pathways, responses that also were inhibited by anti- α_v integrin antibody. These results suggest that P2Y₂Rs and their associated signaling pathways may be important factors regulating inflammation in brain disorders.