

Activation of Enteric Glia Contributes to Enteric Neuron Death in Inflammation

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Abstract

Enteric glia (EG), a type of peripheral astroglia, surround enteric neurons and are critical for the maintenance of enteric circuits. Loss of glial maintenance is thought to lead to neuron death and gut dysfunction during inflammation (Aube et al 2006). However, this theory is at odds with data showing that astroglial activation drives neuron death during neuroinflammation (Mayo et al 2014) and our data showing that enteric neuron death is driven by activation of neuronal P2X7 purine receptors (P2X7Rs) (Gulbransen et al 2012). We hypothesized that EG activation promotes neuronal death via P2X7R pathways. We activated EG *in situ* with P2Y1 receptor (P2Y1R) agonists, measured glial ATP release with biosensors and neuronal survival with immunohistochemistry. Glial activity was monitored using Ca²⁺ imaging and glial ATP release pathways involving connexin-43 (Cx43) hemichannels were modulated by altering nitric oxide (NO) levels with drugs or selectively ablated in EG using inducible Cx43 null mice. P2Y1R agonists primarily activated EG in the myenteric plexus. Glial activation drove ATP release through Cx43 channels and reduced neuron density by 23%. Inhibition or ablation of glial Cx43 prevented P2X7R-driven neuron death *in situ* and *in vivo* ($p < 0.01$). Cx43-dependent glial ATP release was potentiated by NO ($p < 0.05$) and Cx43 inhibition protected against NO-mediated neuron death ($p < 0.05$). Our data demonstrate a novel pathogenic role of enteric glia in enteric neuron loss during colitis. Direct glial activation is sufficient to cause enteric neuron loss in a Cx43 and NO dependent manner. This research was supported by NIH/PHS K12 HD065879.