Glia-Neuron GPCR Signaling as a Therapeutic Route to Axon Regeneration: cAMP-PKA Activation Elevates Excitability and Survival in Neurons

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Nerve degeneration causes devastating symptoms for millions of patients worldwide. While some peripheral nerves experience recovery, others experience chronic neuropathic pain due to sensory neuron conditions, and CNS degeneration continues to be without a cure. The role of glial cells and intercellular signaling in the process of degeneration and regeneration still leaves many questions unanswered. This study investigated whether glia-derived prostaglandin E2 (PGE2) can be used to promote axon regeneration via GPCR/cAMP signaling, and focused on determining whether neuronal health and survivability improve following treatment. Treatment with 1 uM dimethyl-PGE2 (dmPGE2) significantly reduced apoptosis in a dose-dependent manner, with the lowest Annexin-V positivity at this dose. Toxicity emerged at 100 uM. RNAScope revealed that voltage-gated sodium channels were expressed at higher levels in injured cells treated with dmPGE2 than in untreated injured cells without causing hyperexcitability. To determine the role of this signaling in vivo, scRNA-seq from a spared-nerve-injured dorsal root ganglia dataset revealed that Schwann cells upregulate cAMP- and MAPK-pathways, while a damaged Mrgprd/Gm7271 nociceptor subset downregulates cAMP-associated genes and upregulates apoptotic pathways. Together, these findings suggest that glial PGE2, through Gs-coupled receptors, elevates neuronal cAMP/PKA signaling, boosting excitability and growth, potentially rescuing low-cAMP, pro-apoptotic neuronal states. This study identifies a potential signaling pathway that can be targeted to accelerate axon regeneration, making prostaglandin E2 treatment a viable therapeutic strategy that could improve lives.

Awards Won: