A Novel Treatment for Stroke, Traumatic Brain Injury, Alzheimer's, and other Neurodegenerative Disease: Sildenafil Promotes Axonal Outgrowth in the CSPG Inhibitory Environment through Modulation of miRNA Levels

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Axons form communication highways in the body that control fundamental neurological functions as movement. However, injury to matured axons results in devastating consequences to victims, such as paralysis, due to limited regeneration of axons in the adult central nervous system. Currently, there is no treatment to facilitate regeneration of adult axonal highways. One of major inhibitory components that block axon regeneration is a family of molecules called chondroitin sulphate proteoglycans. This project has, for the first time, demonstrated that Sildenafil, the active ingredient of the drug Viagra®, robustly promoted axonal growth and confounded the inhibitory effect of CSPGs. Moreover, immunocytochemistry analysis demonstrated endogenous presence of Ago2, a vital aspect of miRNA biogenesis, while silencing of Ago2 by siRNA eliminated Sildenafil's promotional ability. A miRNA PCR array provided strong evidence that Sildenafil regulates axonal outgrowth through modulation of axonal miRNA profiles. Meanwhile, a Taqman PCR assay quantified and ranked the most significant miRNA's, whose targets were found using MetaCoreTM software. Finally, this investigation identified miR-29c-3p and its validated targeted Integrin β1/FAK pathway as the means in which Sildenafil promotes axonal outgrowth. Collectively, Sildenafil is able to promote axonal outgrowth in the CSPG inhibitory environment with strong evidence showing that it is through modulation of expression levels of miRNAs, especially that of miR-29c-3p, that targets the Integrin β1/FAK pathway. This exciting discovery has great therapeutic potential for patients of stroke, traumatic brain injury, spinal cord injury, multiple sclerosis, Parkinson's and other neurodegenerative disease to restore neurological function.

Awards Won:

Second Award of $2,000