# The Role of 15-hydroxyprostaglandin dehydrogenase (15-PGDH) in neurodegeneration

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Prostaglandin E2 (PGE2) is a bioactive lipid that supports stem cells, and 15-hydroxyprostaglandin dehydrogenase (15-PGDH) rapidly metabolizes PGE2 by converting it to inactive 15-keto PGE2. Previous research has shown that pharmacologic inhibition of 15-PGDH prevents degradation of PGE2 and thereby potentiates hematopoietic recovery after bone marrow transplantation, as well as tissue regeneration in response to injury. Although the therapeutic efficacy of 15-PGDH inhibition has been established in peripheral organs, this has not previously been investigated in brain health. Here, we show efficacy of 15-PGDH inhibition in protecting mice from traumatic brain injury (TBI), and propose testing for similar efficacy in a preclinical model of Alzheimer's disease (AD). Wild type (WT) mice subjected to a model of poly-TBI (pTBI) that incorporates components of blast, concussive, and acceleration / deceleration injury exhibit increased levels of 15-PGDH in mouse brain, which is enriched in axonal processes. Treatment of these injured mice with intraperitoneal SW033291, a potent small molecule inhibitor of 15-PGDH (twice daily injection, 5mg/kg x 2 = 10mg/kg) for two weeks beginning 24 hours after injury, protected animals from cognitive deficits in the Morris water maze task of spatial learning and memory. These animals were also protected from pTBI-induced axon degeneration. We have also shown that 5XFAD mice, which express human amyloid precursor protein and presenilin 1 transgenes and develop a well-characterized robust phenotype of pathology and behavioral related to AD, display elevated levels of axonal 15-PGDH protein and neuronal mRNA, relative to WT. Axonal degeneration is a prominent component of AD, and thus we are extending our investigation of the role of 15-PGDH in neurodegeneration into AD by evaluating the putative therapeutic efficacy of SW033291 in 5XFAD mice.