Increasing Metabolic Substrates Improves Spreading Depolarization Recovery in a Brain Slice Model of Stroke: An Innovative Therapy for Reducing Brain Injury after Stroke

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Worldwide, stroke is the second leading cause of death and the third leading cause of disability. There is a striking lack of therapeutic interventions after the first few hours of stroke onset. Recent work has demonstrated that an event in the brain referred to as a spreading depolarization (SD) is a significant contributor to the progression of ischemic brain injury. SD is a slowly progressing wave of coordinated neuronal and glial depolarization that places an immense metabolic demand on the brain. After ischemia, repetitive SDs in vulnerable brain regions deplete neuronal sources of energy (adenosine triphosphate, ATP) resulting in further tissue death. Currently, there are no treatments that target SD specifically. In this work, the exogenous supplementation of the ATP precursors D-Ribose and adenine prior to SD was examined. D-Ribose and adenine supplementation has been shown to increase ATP concentrations in metabolically uncompromised brain tissue. SD was initiated by Potassium Chloride microinjection in a metabolically compromised brain slice model of stroke and monitored by electrophysiological recording and imaging. D-Ribose and adenine supplementation improved recovery of vulnerable brain slices after SD, likely by increasing ATP availability. These findings suggest that D-Ribose and adenine supplementation can reduce the damaging consequences of SD in vulnerable brain tissue and may pose as an innovative approach in the treatment of ischemic stroke and brain injury worldwide. By addressing the metabolic burden of SD, D-Ribose and adenine may reduce ischemic injury progression in the days following stroke onset.

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