SAMPLE 2

Protecting Vulnerable Tissue from Brain Tsunamis: Implications for Stroke

Spreading depolarization (SD) is a propagating wave of near-complete neuronal and glial depolarization that contributes to the progression of acute brain injuries. Prior work has established that SDs cause the stepwise enlargement of strokes, as the ionic challenge of SD provides a severe "second hit" to metabolically compromised tissue. We are studying approaches to limit the ionic challenge of SD, to protect vulnerable brain. The current study utilizes the clinically approved NMDA-R antagonist memantine, in studies of SD in brain slices and in an in vivo stroke model. In brain slices, memantine reduces the duration of SDs and the associated glutamate and Ca2+ loading. When slices were metabolically compromised, SDs invariably led to irreversible tissue damage, and memantine (100uM) prevented injury. This study hypothesizes that memantine will demonstrate a neuroprotective effect in a stroke model. In order to model stroke, focal ischemic damage was induced by means of photo-activation of a light-sensitive dye (Rose Bengal). The interruption of blood flow caused by the damage to endothelial cell membranes produced a reliable stroke model in vivo and was clearly visualized using laser speckle contrast imaging. Initial studies support a protective role for memantine in vivo, to protect vulnerable tissues surrounding ischemic infarcts. Low concentrations of memantine that prevent damaging consequences of SD may may prove useful in treating acute cerebral injury.