1205 ABSTRACT

Although over the years we have gained understanding of spinal cord injury (SCI) and its underlying mechanisms, the goal of creating an effective therapy to minimize tissue damage and maximize functional recovery is still unrealized. The only treatment currently available is methylprednisolone (MP), which has limited clinical efficacy. Thus, an increased emphasis should be placed on early pharmacological intervention of the secondary damage pathways initiated by disruption of blood vessels involving free radical production, inflammation, and calcium (Ca^{2+}) overload with downstream protease activation and loss of blood supply. In investigating new treatments, studies should examine mechanism of cell death, central nervous system (CNS) fiber damage, inflammation, amelioration of blood flow, and functional recovery.

Vascular and oxidative damage, inflammation, and intracellular Ca^{2+} influx are implicit in the initiation of many secondary injury pathways for cell death following SCI. By understanding the pathophysiology of SCI, we should be able to create rational therapies designed to prevent cell death, sparing greater portions of the spinal cord following injury. The goal of this project is to protect CNS cells from secondary damage using a combination of agents that can preserve tissue and promote restoration of function.

Since several pathways cause cell damage and tissue destruction, blocking only one may not be optimal. Therefore, a combination of several drugs is likely to be more neuroprotective. We intend to use the anti-oxidant and anti-inflammatory MP in combination with angiogenic promoting factors (ANG-1, VEGF) and the novel Ca^{2+} activated neutral proteinase (calpain) inhibitor, SJA6017 (SJA). We hypothesize that MP will prevent oxidative damage resulting from ischemia/reperfusion, lipid peroxidation, and monocytes phagocytosis, as well as prevent infiltration of inflammatory cells into the spinal cord. Activation of angiogenic factors will promote improved blood flow and reduce ischemic damage, and SJA will prevent over activation of calpain with the consequence of blocking downstream calpain-mediated apoptotic events. The end result of this combination therapy will be the protection of cells from secondary damage, leading to recovery of function.

Specific Aim 1: Examine the effects of MP and SJA treatments on oxidative stress and cell death following acute SCI.

Specific Aim 2: Investigate the efficacy of a combination of MP and SJA in SCI.

Specific Aim 3: Investigate the mechanisms involved in the improvement of blood flow following treatment of SCI.