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Title: 4-Aminopyridine provides rapid and sustained improvements in a model of thoracic spinal cord injury

Abstract:

Spinal cord injuries (SCI) result in life-long disability and yet, effective treatment options for acute SCI injury remain limited. We now provide a new means of targeting multiple acute sequelae of SCI, by applying the potassium channel blocker 4-aminopyridine (4AP). 4AP has long been of interest as a means of providing transient symptomatic relief in chronic SCI and other chronic neurological conditions due to its ability to improve conduction in demyelinated axons and to enhance synaptic efficacy. Consequently, 4AP has been used to provide symptomatic relief for patients with multiple sclerosis or chronic SCI. However, the benefits observed with 4AP treatment in chronic conditions are transient, and are lost once treatment is discontinued. Using a rat, thoracic contusion SCI model, we now demonstrate that acute treatment of SCI with 4AP causes significant improvements in multiple injury parameters and across variable parameters - most importantly, that these improvements are durable and do not require continued treatment with 4AP. Gait analysis using BBB scoring and video assisted Catwalk revealed rapid improvements in motor function of 4AP-treated animals over saline-treated controls as early as four days after start of treatment. In addition, 4AP treated animals recovered bladder function sooner than untreated animals. 4AP treatment also decreased lesion size, cell death and glial scarring and increased numbers of oligodendrocytes. Remarkably, all of these outcomes were achieved when treatment was initiated 24 hours post-injury, and persist when treatment is discontinued at 2-weeks post injury. Our studies thus provide a previously unrecognized utility of 4AP as a treatment of acute traumatic injury to the spinal cord. As 4AP is FDA approved for the treatment of multiple sclerosis, and has been shown to be safe in patient populations in over 30 years of clinical studies, 4AP appears to represent an excellent candidate for consideration as a novel therapy in the setting of acute SCI.