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Peripheral Nerve Suicide Transport Generates a Reproducible SCI

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Abstract

Unlike many organs in the body, the brain and spinal cord are unable to promote regeneration. The brain has a limited capacity for adaptive plasticity, but lacks functional replacement of injured, diseased or damaged neural parenchyma. Novel approaches to treat CNS lesions are required, as current therapies are solely palliative and do not generate repair. Essentially all clinical breakthroughs come from pre-clinical research where the fundamental principal for scientific advancement is experimental reproducibility. We describe a simple and reproducible pre-clinical model of spinal cord injury that can provide a platform to develop strategies to promote neural repair and regeneration.

Keywords: Plasticity; CNS lesions; Spinal cord injury; Fickle-P; Suicide transport

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Current therapies are inadequate in current animal models of spinal cord injury (SCI) [1-7]. A common objective is to mimic clinical SCI by generating a chaotic wound through cord laminectomy followed by controlled impact [2]. Not only is the surgery slow and challenging, but variations can generate a spectrum of wounds, and small sample sizes fail the limits of the 'fickle-P' [5]. Not surprisingly, many results have proven irreproducible and fail to enter clinical trials [7]. In short, the impact trauma model is inadequate.

Spinal cord research could benefit from insights on experimental design gained through years of invertebrate genetics, where virtually all genes involved in mammalian neural development were first identified. The *Drosophila* embryo at mid-neurogenesis is 4 mm, much less than the width of a mouse spinal cord. Thousands can be harvested daily and quickly genotyped using fluorescent markers, and unlike the mouse model dozens of nerve cords can be dissected in one surgery session. The historical success of *Drosophila* reflects a tool kit that includes short gestation time, large sample sizes and absolute reproducibility. Combining this with genetic analysis has allowed experimenters to focus on a single variable at a time. Each of these factors is missing in pre-clinical vertebrate SCI models. The theme common to all major advances in biological sciences, from bacteriophage and *Drosophila* genetics to molecular biology and genomics, is 'keep it simple'. This theme is missing in pre-clinical SCI models and that has hindered progress. The experimental approach of simplicity and reproducibility is desperately needed in SCI research [8,9].

Retrograde transport of a neurotoxin, a process termed "suicide transport" may present a more useful approach to generate a reproducible spinal cord injury [9]. We examined suicide transport to generate SCI in mice using the sciatic nerve (Sn) for toxin delivery, in order to target motor neurons. We focused on delivery of an inhibitor of phosphoinositide 3'-kinase (PI3'K), a key intracellular effector of cell survival. Wortmannin binds the catalytic domain of PI3'K, blocks PI3K activity at very low concentrations (IC50=5 nM), and it has a very short half-life which we considered an advantage for focal targeted MN destruction [8].

We accessed the SN at mid-thigh and injected 100 ng wortmannin; the surgery is quick, survival is 100% and >80% of test animals developed an ipsilateral hind leg motor deficit while sham controls had no visible phenotype. We used a simple water exit test to assess motor function of control and injured animals. Wild type mice exited without hesitation (2.1 ± 0.8 sec, mean ± S.D, 8 mice n=71 trials), while mice treated with wortmannin had a significant delay (38.6 ± 21, 15 mice n=253 trials, $p<0.001$), a phenotype that persisted through 6 months. At 14 days post wortmannin, histology revealed a reduction of choline acetyltransferase positive motor neurons in the ipsilateral lumbar

spinal cord, relative to the contralateral cord. We also detected an ipsilateral gliotic response including astrocyte activation and microglial recruitment. These findings indicate that Sn delivery of wortmannin induces a site specific CNS motor neuron injury, and also show that water avoidance was a consistent and reliable test for measuring the functional consequences.

The Sn has historically been used for neuropathic pain and peripheral nerve regeneration studies [6]. Sn injury models generate distinct phenotypes after nerve compression, severance and transection. In our model the sham surgery generated a mild phenotype, consistent with transient peripheral neuropathy including reversal of axonal transport [1].

Motor neurons in the spinal cord survive peripheral transection [10] due to tropic support from Schwann cells in the proximal nerve and from re-innervated muscle after chronic injury [4]. We did not observe motor deficits after delivery of a Wnt pathway inhibitor, demonstrating that loss of MN in our model was wortmannin specific and likely represents suicide transport. We thus suggest that Sn suicide transport represents a valid experimental SCI model that is suitable for genetically tractable small mammals (rodents) and can be scaled for statistically significant sample sizes.

The reproducibility of the injury provides a strong platform on which strategies to promote neural repair and regeneration can be explored in a meaningful way. Ideally such studies would focus on individual and specific aspects of the traumatic SCI wound, such as immune suppression, cell replacement, neural plasticity and path-finding, and remyelination [3].

Conflict of Interest

The authors declare no conflict of interests.

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