Voluntary Exercise Modulates Macrophage Polarization Following Sciatic Nerve Injury and Improves Functional Recovery in Mice

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Introduction

Peripheral nerve injury is associated with trauma and is often amenable to surgery. Functional recovery remains a challenging clinical problem that often leads to significant morbidity. Therapies that augment surgical repair may be beneficial in functional outcomes. Macrophages are responsible for the breakdown of debris following injury as well as promotion of regenerative signals. Macrophage polarization is the process by which macrophages take on phenotypically distinct functions based on the local environment and signaling cues. Exercise has been shown to drive macrophage polarization from a pro-inflammatory M1 phenotype towards an anti-inflammatory M2 phenotype in numerous tissues, but remains uninvestigated in the peripheral nervous system.

Methods

The purpose of our study was to identify how exercise affects macrophage polarization, motor and sensory function, and neuroregeneration following sciatic nerve crush. Male and female C57BL/6 mice underwent sciatic nerve crush injury and were then given access to running wheels (exercised) or not given access to running wheels (sedentary) for 4 weeks. Analysis included behavioral assessments, anatomical studies, and in vitro studies.

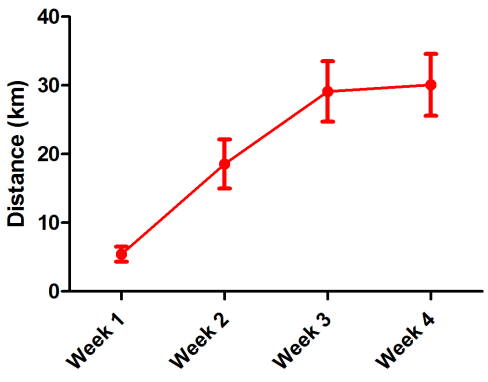
Funding Sources

Neurosurgery Research and Education Foundation Research Fellowship and AAANS/CNS Section on Pain Research Fellowship Grant

Results

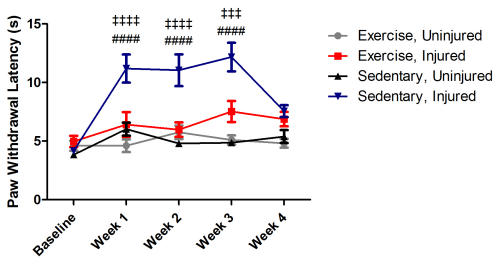
Exercised mice ran an average of 2.9 km per night. Injured exercised mice were protected from the development of thermal hyperalgesia. Exercised mice had fewer paw slips on beam walk testing compared to sedentary mice. No differences were measured in mechanical sensitivity or motor coordination and balance. Motor nerve conduction velocities from injured exercised animals were significantly higher than injured sedentary animals suggesting improved nerve recovery with exercise. Injured sciatic nerves from exercised mice demonstrated increased M2 macrophages compared to sciatic nerves from injured sedentary mice. The behavioral changes and altered macrophage polarization correlated with increased epidermal nerve fiber density, improved myelination, and increased in vitro neurite outgrowth from injured exercised animals.

Running Distance



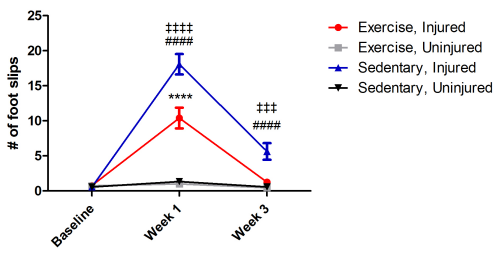
Mice ran an average of 2.9 km/day.

Hargreaves Thermal Testing



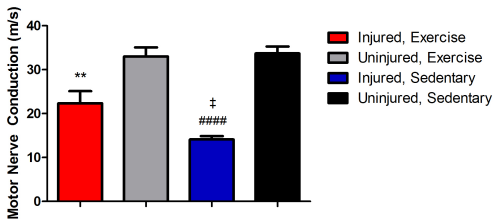
Exercised mice are protected from the development of thermal insensitivity following sciatic nerve injury.

Beam Walk



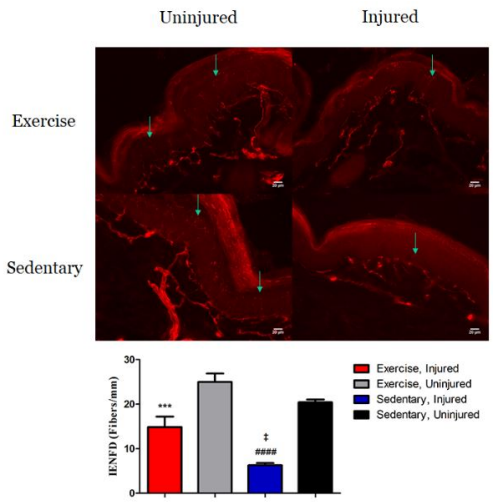
The injured hindpaw of exercised mice have fewer foot slips compared to the injured hindpaw of sedentary mice.

Motor Nerve Conduction Velocity



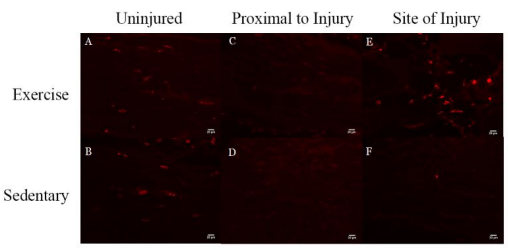
Exercise is able to partially rescue the reduced motor nerve conduction velocity following sciatic nerve injury.

Intraepidermal Nerve Fiber Density



Exercise is able to partially rescue intraepidermal nerve fiber loss following sciatic nerve injury.

M2 Macrophage Localization in the Sciatic Nerve



Following injury, anti-inflammatory M2 macrophages are found at the site of injury following exericse for 4 weeks.

Conclusions

Exercise alters macrophage polarization towards an anti-inflammatory phenotype which improves repair and recovery of the injured peripheral nerve.