Physical exercise mitigates neuropathic changes in an animal model for Charcot-Marie-Tooth disease 1X

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Highlights

- Physical Exercise improves the clinical outcome in a mouse model for CMT1X (Cx32def).
- Peripheral nerve inflammation is modulated upon physical exercise.
- Axonal damage is mitigated by physical exercise.
- Restricted exercise has an additional myelin-preserving effect with an elevation expression of *Bdnf* mRNA in peripheral nerves.

Abstract

Inherited neuropathies of the Charcot-Marie-Tooth (CMT) type 1 are still untreatable diseases of the peripheral nervous system. We have previously shown that macrophages substantially amplify neuropathic changes in various mouse models of CMT1 subforms and that targeting innate immune cells substantially ameliorates disease outcome. However, up to date, specific approaches targeting macrophages pharmacologically might entail side effects. Here, we investigate whether physical exercise dampens peripheral nerve inflammation in a model for an X-linked dominant form of CMT1 (CMT1X) and whether this improves neuropathological and clinical outcome subsequently. We found a moderate, but significant decline in the number of macrophages and an altered macrophage activation upon voluntary wheel running. These observations were accompanied by an improved clinical outcome and axonal preservation. Most interestingly, exercise restriction by ~40% accelerated amelioration of clinical outcome and further improved nerve structure by increasing myelin thickness compared to the unrestricted running group. This myelin-preserving effect of limited exercise was accompanied by an elevated expression of brain-derived neurotrophic factor (BDNF) in peripheral nerves, while the expression of other trophic factors like neuregulin-1, glial cell line-derived neurotrophic factor (GDNF) or insulin-like growth factor 1 (IGF-1) were not influenced by any mode of exercise. We demonstrate for the first time that exercise dampens inflammation and improves nerve structure in a mouse model for CMT1, likely leading to improved clinical outcome. Reducing the amount of exercise does not automatically decrease treatment efficacy, reflecting the need of optimally designed exercise studies to achieve safe and effective treatment options for CMT1 patients.