RESEARCH REPORT

An exercise regimen prevents development paclitaxel induced peripheral neuropathy in a mouse model

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Abstract Peripheral neuropathy is a major, dose-limiting complication of many chemotherapeutic agents. Currently there is no effective method to prevent development of chemotherapy-induced peripheral neuropathy (CIPN). Recent studies have shown that exercise can improve regeneration of peripheral nerves but its effect in preventing peripheral neuropathy is unknown. In this study, we examined the effect of a rigorous treadmill exercise program that was started 1 week before administration of paclitaxel and continued throughout the study in a mouse model of CIPN. We showed that exercise can partially abrogate features of axonal degeneration induced by paclitaxel including reduction in epidermal nerve fiber density in the plantar hind paw and thermal hypoalgesia. Furthermore, detyrosinated tubulin that is elevated in nerves treated with paclitaxel was normal in exercised animals. This study points to a relatively simple and potentially effective therapeutic option to reduce the neurotoxic effects of chemotherapy.

Key words: exercise, neuropathy, paclitaxel

Introduction

Peripheral neuropathy is a common side effect of many chemotherapeutic drugs including paclitaxel *(Windebank and Grisold, 2008; Grisold et al., 2012; Cavaletti, 2014)*. The peripheral neuropathy caused by paclitaxel is characterized by distal hypoesthesia, paresthesia, neuropathic pain, and loss of proprioception *(Wiernik et al., 1987; Lipton et al., 1989; Forsyth et al., 1997; Dina et al., 2001; Briasoulis et al., 2002; Dougherty et al., 2004; Gracias et al., 2011; Nakahashi et al., 2014)*. Although the exact mechanism of its neurotoxicity is unknown, paclitaxel binds to beta-tubulin and stabilizes its polymerization. This leads to disruption of the mitotic spindle and arrest of cell division *(Schiff and Horwitz, 1980)*. In neurons, paclitaxel leads to an increased and altered distribution of detyrosinated tubulin, a marker for stable microtubules *(Robson and Burgoyne, 1989; Laferriere et al., 1997; Melli et al., 2006)*. How this leads to neuronal dysfunction and distal axonal degeneration is unknown although both altered transport mechanisms *(Komiya and Tashiro, 1988; Nakata and Yorifuji, 1999; Theiss and Meller, 2000)* and mitochondrial toxicity *(Flatters and Bennett, 2006; Zheng et al., 2011)* has been proposed as potential mechanisms.

There is increasing evidence to suggest that exercise decreases symptoms of acute pain in humans *(Gurevich et al., 1994; Koltyn et al., 1996; Kemppainen et al., 1998)*, has both acute *(Bagby et al., 1994; Pastva et al., 2005)* and chronic *(Kasapis and Thompson, 2005; Pitsavos et al., 2005)* anti-inflammatory effects, and is protective against both cardiovascular and neurological diseases such as dementia *(Erickson et al., 2012; Hotting and Roder, 2013)* and Parkinson's disease *(Miyai et al., 2000; Burini et al., 2006)*. Exercise reduces neuropathic pain in rodents *(Kuphal et al., 2007)* and promotes peripheral nerve regeneration *(Sabatier et al., 2008; English et al., 2009; Park and Hoke, 2014)*.

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Furthermore, exercise can prevent development of peripheral neuropathy and pain in a mouse model of pre-diabetes *(Groover et al., 2013)* and slow the disease progression in diabetic peripheral neuropathy as demonstrated by changes in epidermal innervation in a small clinical study *(Kluding et al., 2012)*. The mechanisms of exercise's influence on peripheral nerves are not only complex but also involve neurotrophic factors. Both brain-derived neurotrophic factor (BDNF) and glial cell-derived neurotrophic factor (GDNF) play a role and are upregulated in exercised muscle and nerve *(Wilhelm et al., 2012; Park and Hoke, 2014)*.

In this study, we used a mouse model of paclitaxel neuropathy to examine the potential neuroprotective effects of treadmill exercise on axonal degeneration in sensory neurons.

Material and Methods

A total of 32 6-week-old male AJ mice (15–20 g) were purchased from The Jackson Laboratory (Bar Harbor, ME, USA). The animals were housed at the Johns Hopkins animal care center in groups of five or less. They were maintained on a 12-h light/dark cycle with food and water available *ad libitum*. All procedures were conducted using protocols approved by the Johns Hopkins University Animal Care and Use Committee. After baseline tests, animals were randomly assigned to four groups of eight mice each: control without paclitaxel, exercise without paclitaxel, control with paclitaxel, and exercise with paclitaxel.

Animals in both exercise groups were placed on the treadmill a week prior to the initial drug injections to acclimatize them to the motorized treadmill environment. Treadmill exercise consisted of 50 min of continuous running at 10 m/min, with a 5-min warm up and a 5-min cool down period at 6 m/min with no incline. This was done 7 days a week, for 4 weeks. Mice in both control groups remained caged during the entirety of the experiment.

Paclitaxel was purchased from Sigma-Aldrich (St. Louis, MO, USA). The paclitaxel was diluted to 7.5 mg/ml with cremophor EL/ethanol (50/50 v/v) and stored at 4°C. Animals in the control with paclitaxel and exercise with paclitaxel groups received 3 doses of 25 mg/kg of paclitaxel via tail vein injections every other day to induce peripheral neuropathy.

At the end of 4 weeks, animals were subjected to thermal sensory testing as described previously using an IITC Life Science (Woodland Hills, CA, USA) Analgesia Meter according to the Hargreaves method *(Zhu et al., 2013)*. The next day, the animals were subjected to sensory nerve conduction studies using caudal nerve. After induction of anesthesia with isoflurane inhalation, orthodromic tail sensory nerve conduction studies were performed according to standard methods. Recording electrode was placed at the base of the tail, and the stimulating electrode was placed 5 cm distally. Sensory nerve action potential amplitude was recorded as the average of 20 stimulations, and conduction velocity was calculated using Lab Chart (AD Instruments, Colorado Springs, CO, USA).

After completion of the sensory nerve conduction studies, animals were sacrificed by decapitation while under deep anesthesia. The medial plantar footpads of the right hind limb were harvested using 2-mm punch biopsies, placed in paraformaldehyde-lysine-periodate fixative overnight and then transferred to cryoprotectant solution (30% sucrose in phosphate buffered saline). After sectioning them at 45 μm on a freezing sliding microtome, they were stained with a pan-axonal marker, anti-PGP antibody (Biogenesis, Kingston, NH, USA; catalog no. 7863-0504). Intraepidermal nerve fibers were counted in 6–10 sections for each animal and average density was calculated as previously described *(Melli et al., 2006)*. The sural nerves were also harvested and postfixed in a solution of 4% paraformaldehyde and 3% glutaraldehyde for 2 days, and transferred to Sorensen's phosphate buffer (0.1 M) for further processing. Then they were embedded in resin and polymerized at 60°C. Transverse semithin sections (1 μm) were obtained with an Ultracut E microtome (Reichert Technologies, Depew, NJ, USA) and stained with 1% toluidine blue in 1% sodium tetraborate for light microscopy. Using stereological random sampling methods, numbers of axons were counted, axon diameters, and myelin thickness were measured and g-ratios were calculated for each sample. For each sample, at least 200 myelinated axons were measured.

For Western blot analysis, homogenates of the sural nerves in tissue lysate buffer were loaded onto a 4–12% NuPAGE Bis-Tris gel and transferred onto polyvinylidene difluoride membrane (Invitrogen, Waltham, MA, USA). The membranes were probed with rabbit polyclonal anti-detyrosinated tubulin antibody (catalog no. AB3201, Millipore, Billerica, MA, USA), and detected with ECL-Plus chemiluminescence kit from Amersham (Pittsburgh, PA, USA). Equal loading was ensured by stripping the membrane with Restore PLUS Western blot stripping Buffer (catalog no. 46430, Thermo Scientific, IL, USA) and reprobing it with anti-beta actin antibody (catalog no. ab8229, Abcam, San Francisco, CA, USA). The blots were carried out in triplicates and repeated at least once to validate the findings.

Statistical Analysis

Statistical analysis was done with analysis of variance (ANOVA) with correction for multiple

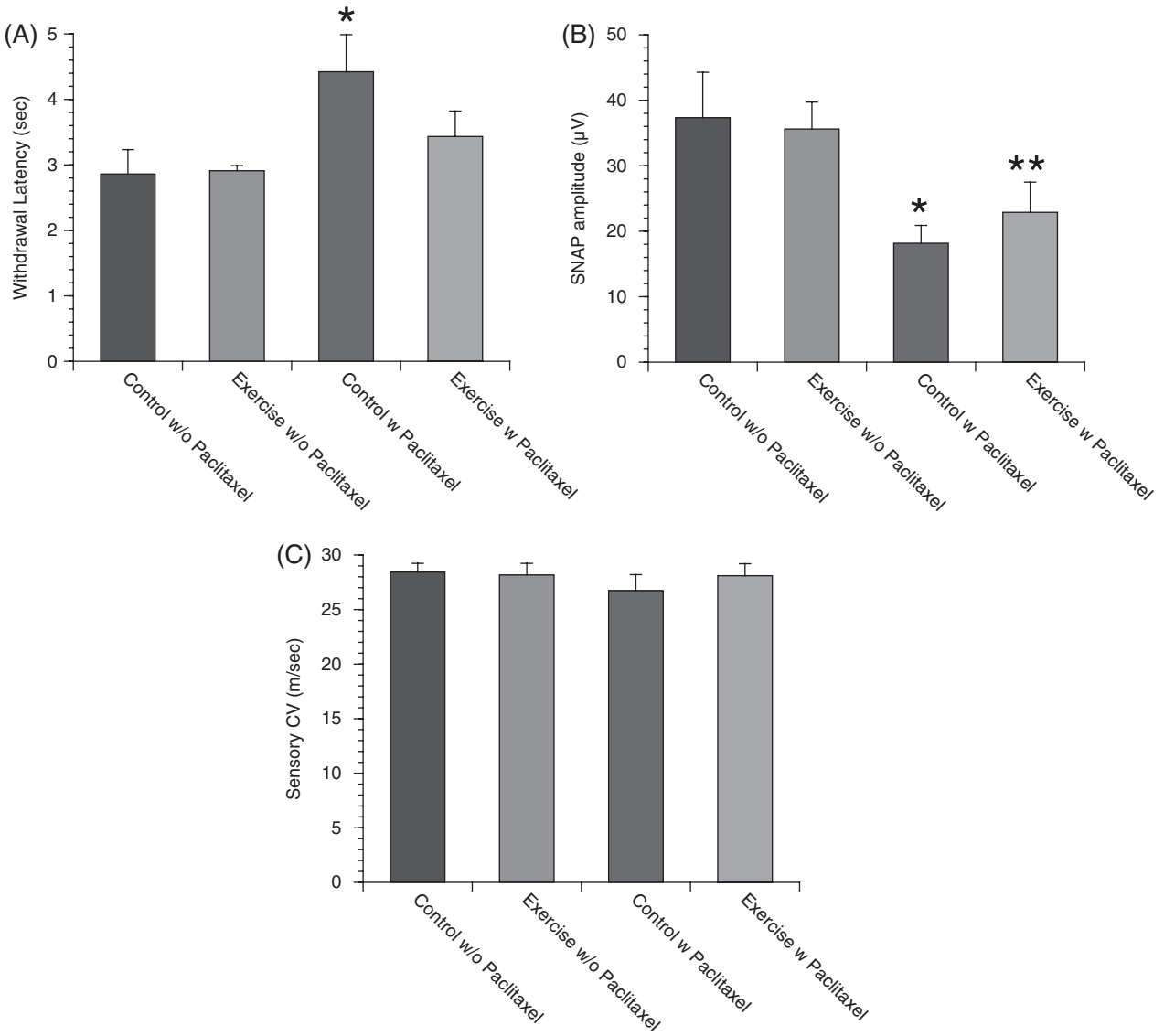

Figure 1. Effect of exercise on thermal sensation and caudal nerve sensory evoked responses. Paclitaxel induced a delay in paw withdrawal latency but this was abrogated by exercise (A). Similarly reduction in sensory nerve action potential (SNAP) amplitude by paclitaxel was partially prevented by exercise (B). There was no significant difference among the groups in sensory nerve conduction velocity (C). *Denotes $p < 0.5$ compared to other groups, **$p < 0.5$ compared to paclitaxel group without exercise. N = 8 per group. Error bars denote standard deviation (SD).

comparisons using Prism 6 software. Data are shown as mean ± standard deviation.

Results

AJ strain of mice, given 25 mg/kg of paclitaxel every other day for 3 doses, develop clear evidence of predominantly small fiber sensory polyneuropathy by 2 weeks after the last dose *(Melli et al., 2006; Zhu et al., 2013)*. As seen in Fig. 1, mice given paclitaxel developed thermal hypoalgesia that was prevented with daily exercise regimen. Furthermore, reduction in caudal nerve sensory nerve action potential (SNAP) amplitude was partially abrogated. There were no significant differences in sensory nerve conduction velocities among all four groups.

These behavioral and electrophysiological findings were supported by the histological evaluations. As seen in Fig. 2, evaluation of intraepidermal nerve fiber density in the hindpaw showed that exercise prevented the reduction in unmyelinated axon numbers caused by paclitaxel. Similarly, sural nerve morphometry showed subtle decrease in axon counts with paclitaxel, and this was abrogated by the exercise program. Although there was a trend toward a reduction in axon diameter

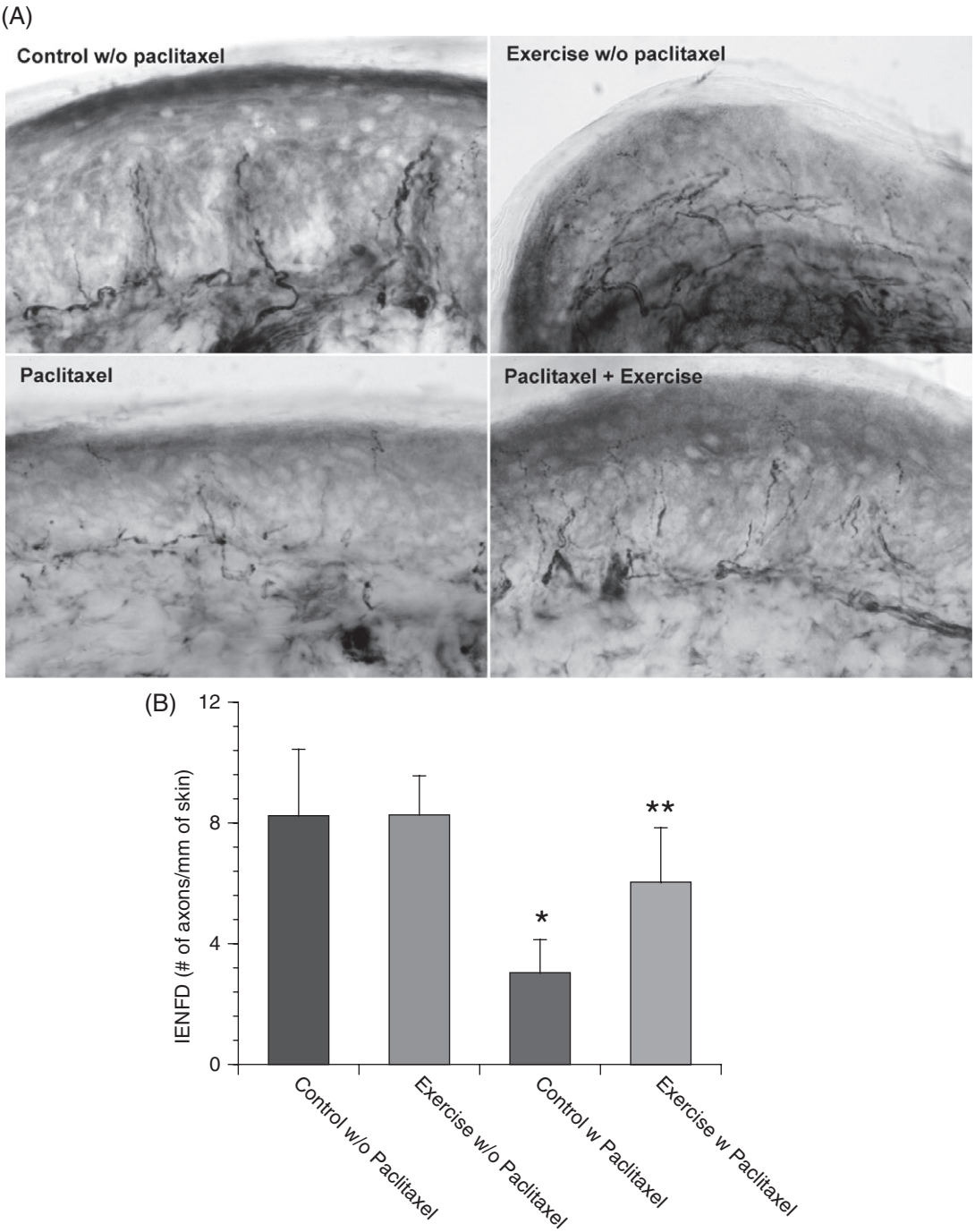

Figure 2. Effect of exercise on paclitaxel induced reduction on intraepidermal nerve fiber density. Representative images are shown in (A) and quantitation is shown in (B). *Denotes $p < 0.5$ compared to controls, **$p < 0.5$ compared to paclitaxel group without exercise. N = 8 per group. Error bars denote standard deviation (SD).

and reduced g-ratio in paclitaxel treated no exercise group, these parameters were not statistically different among all four groups (Fig. 3).

As seen in Fig. 4, sural nerves of paclitaxel treated mice had increased levels of detyrosinated tubulin, but exercise animals did not have the same increase in detyrosinated tubulin.

Discussion

There has been a growing interest in the pleiotrophic effects of exercise on the nervous system. Previous pre-clinical animal studies and controlled trials in patients have shown that exercise has beneficial effects in some of the neurodegenerative

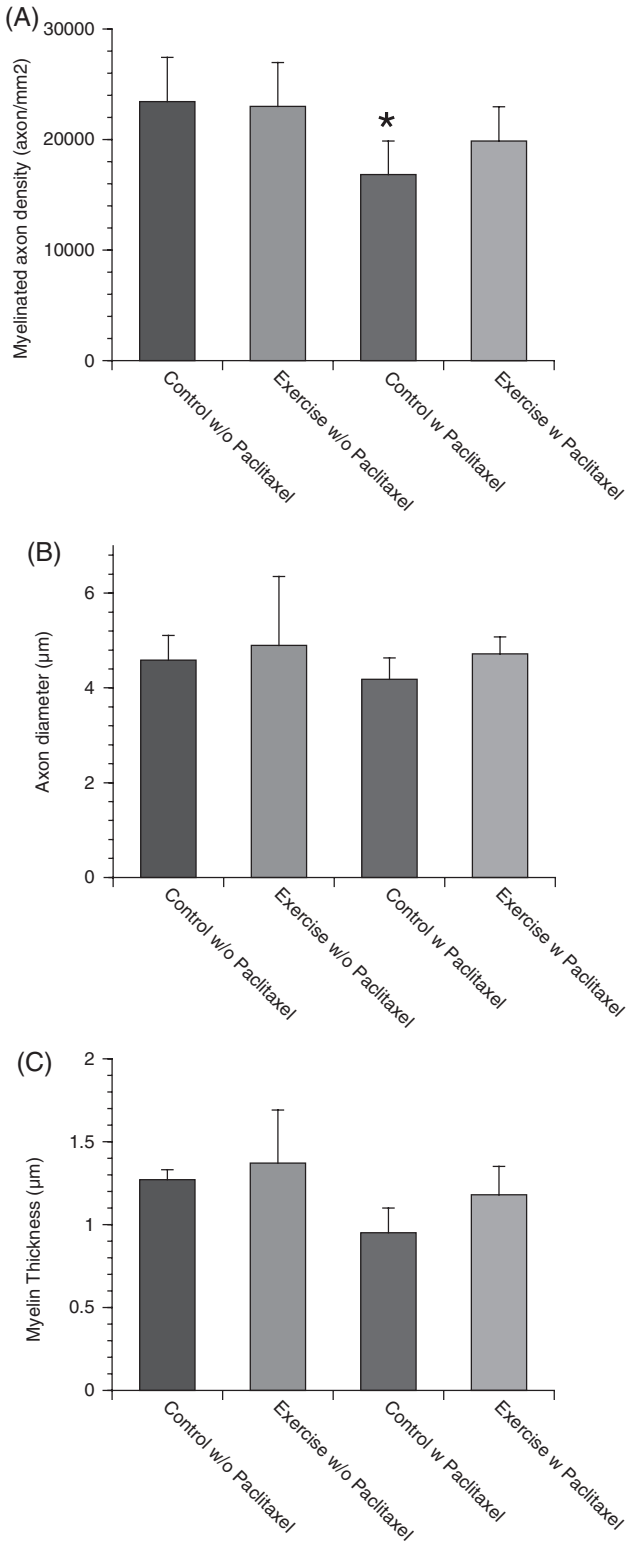

Figure 3. Effect of exercise on nerve morphometry in sural nerve. Paclitaxel reduced the number of myelinated axons in the sural nerve and this was partially prevented by exercise (A). There was no statistically significant difference among groups in axon diameter or g-ratio (B and C). *Denotes $p < 0.5$ compared to controls. N = 8 per group. Error bars denote standard deviation (SD).

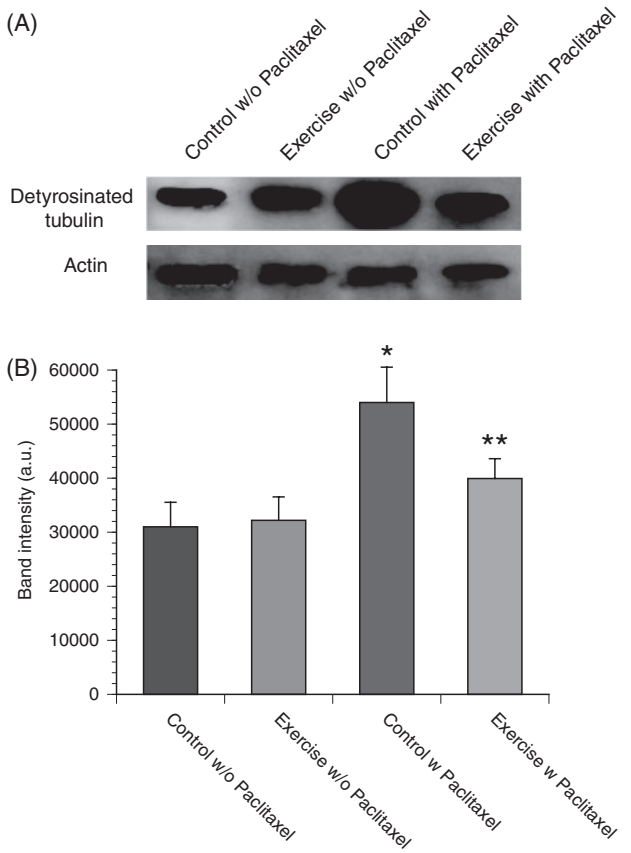

Figure 4. Effect of paclitaxel and exercise on detyrosinated tubulin in sural nerve samples. Representative image of a Western blot is shown in (A) and quantitation is shown in (B). *Denotes $p < 0.5$ compared to controls, **$p < 0.5$ compared to paclitaxel group without exercise. N = 3 per group. Error bars denote standard deviation (SD).

diseases such as Parkinson's disease *(Tillerson et al., 2003; Lamotte et al., 2015)* and Alzheimer's disease *(Lazarov et al., 2005; Barnard et al., 2014)*. Furthermore, exercise may play a role in cognitive decline associated with normal aging *(Behrman and Ebmeier, 2014; Kelly et al., 2014; Kirk-Sanchez and McGough, 2014)*. Exercise's role in ameliorating the effects of diabetic neuropathy has been studied in both animal models *(Groover et al., 2013; Jin et al., 2015)* and in a small-scale clinical trial *(Kluding et al., 2012)*. However, the effects of exercise as prevention strategy for chemotherapy-induced peripheral neuropathy have not been evaluated. In this study, we show that a rigorous exercise program that starts before the onset of administration of chemotherapy drug, paclitaxel, and continues throughout the study can partially prevent development of peripheral neuropathy.

We used the epidermal nerve fiber density measurement as the primary end-point because the evaluation of epidermal unmyelinated sensory fibers can be done in an objective and blinded manner and does

not rely on vagaries of various sensory or electrophysiological testing that involves direct contact with the animals. The impact of exercise on this primary end-point was clear-cut, demonstrating a robust neuroprotective effect. However, the exercise program did not prevent all distal sensory axon degeneration. In fact, this partial neuroprotection was evident in other data including the sural nerve morphometry and electrophysiology. Perhaps this is not completely unexpected. Although exercise is likely to have an effect on multiple pathways, none of them may completely interfere with the specific mechanisms that underlie paclitaxel's neurotoxicity.

One potential mechanism where we observed an effect is the role of exercise on detyrosinated tubulin levels in sural nerves induced by paclitaxel (Fig. 4). Paclitaxel has been shown to interfere with axonal transport mechanisms, presumably by increasing the stability of tubulin polymers as demonstrated by increase in detyrosinated tubulin *(Cavaletti et al., 1997; Theiss and Meller, 2000; Gornstein and Schwarz, 2014)*. In our study, we found that paclitaxel treated animals had normal levels of detyrosinated tubulin when they were placed on the exercise program suggesting that perhaps through unknown molecular pathways, exercise is interfering with paclitaxel's ability to alter microtubule dynamics in long axons. Further studies are needed to evaluate the impact of exercise on axonal transport mechanisms and specifically how it could be altering the effects of paclitaxel on microtubule dynamics.

Although not specifically examined in this study, our previous findings have shown that exercise induces an upregulation of various neurotrophic factors in large muscle groups, in serum and even in peripheral nerves in animals with experimental nerve transection *(Park and Hoke, 2014)*. These included GDNF, BDNF, and insulin-like growth factor-1 (IGF-1). It is possible that one or more of these upregulated neurotrophic factors or potentially others may underlie the partial neuroprotection observed with exercise. Another potential source of neurotrophic factors is the repeated activation of motor neurons, which respond to exercise by upregulating expression of BDNF *(Wilhelm et al., 2012)*. It is possible that this upregulated BDNF in motor axons may help protect the unmyelinated sensory axons against the toxicity of paclitaxel. However, these observations need to be supported by examining the effect of exercise in mice where upregulation of these neurotrophic factors in exercised muscles or in neurons is prevented.

Regardless of its mechanism of action, our observations in this study point to a relatively simple and potentially effective therapeutic option to reduce the neurotoxic effects of chemotherapy if confirmed in human trials. A potential shortcoming of our study is the relatively mild and acute form of chemotherapy induced neuropathy model we used and the small number of animals studied. Other drug dosing schemes with repeated chronic administration of paclitaxel may mimic the human disease better *(Carozzi et al., 2010)* and the effect of exercise may need to be validated in such models. Furthermore, future studies are required to elucidate the exact molecular mechanisms that may underlie the pleiotrophic effects of exercise on the peripheral nervous system.

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