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Research Report

Effect of exercise on neurogenic inflammation in spinal cord of Type 1 diabetic rats

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ABSTRACT

Neuropathy is a long-standing and hard to treat complication of diabetes that interferes almost 25–30% of diabetic patients and impacts the quality of life of the patients. Unforeseen side effects, dependency and addiction made the existing medical treatments comparatively ineffective. A number of studies indicate that moderate physical activity provides health-related advantages. However, existing data do not confirm whether regular physical activity would reduce the amount of inflammation in the nervous system of the subjects with Type 1 diabetes. This study reveals the significance of exercise to alleviate inflammation in the spinal cord of the nervous system and preserve sensory nerve function in animals with Type 1 diabetes after 6 weeks of exercise paradigm. Streptozotocin-diabetic animals were placed in motorized running wheels for sixty minutes per day, for five days a week for 6 weeks starting at one week after diabetes. Emerging evidence suggests that the increases in inflammatory mediators play an important role in the development of sensory neuropathy. This study shows that moderate exercise can reduce the release of a number of proinflammatory cytokines in the dorsal horn (DH) of spinal cord, subsequently delaying the development of neuropathy along with an increase in the anti-inflammatory mediator IL10 in the DH. In general, this study indicates that exercise may provide an alternative to the treatment for sensory neuropathy in Type 1 diabetic subjects via reducing the use of medication and providing an easier way to manage neuropathy.

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1. Introduction

Diabetes mellitus is the most common cause of neuropathy in the United States. Fifty percent of diabetic patients suffer from sensory neuropathy, which contributes an adverse effect on quality of life of the patients (Van Acker et al., 2009). Disappointingly, existing pharmacological interventions are relatively unsuccessful with partial efficacy and complication by side effects (Barbano et al., 2003). Prevailing evidence suggests that increases in inflammatory mediators in the peripheral and central nervous system play a key role in the progress of sensory neuropathy which is induced by damage to peripheral nerve (Gonzalez-Clemente et al., 2005; Herder et al., 2009; King, 2008).

Uceyler and colleagues showed differences in the cytokine expression profile levels in painful and painless patient populations. They evaluated both pro- and anti-inflammatory cytokines in a number of neuropathic pain conditions, including diabetic neuropathy and chronic inflammatory demyelinating neuropathy (Uceyler et al., 2007). The patients with painful neuropathy had 2-fold greater levels of TNF-α and IL-2 compared to controls and painless neuropathy patients. The cytokine profile of the painless patients' samples showed statistically higher circulating levels of the anti-inflammatory cytokine, IL-10, twofold higher compared to controls. The elevated level of serum TNFα in Type 1 diabetes patients suggests that TNFα may play a pathogenic role in the development of diabetic neuropathy (Gonzalez-Clemente et al., 2005; Kaul et al., 2010). These findings are exciting as previous studies have found diabetic rodents with decreased DRG TNF-α levels demonstrate hypoalgesia (Saleh et al., 2011) whereas diabetic rats with increased DRG TNF-α levels display hyperalgesia (Yamakawa et al., 2011). Studies on patients with Type 2 diabetes with or without polyneuropathy exhibit a different immune profile and specific neuropathic deficits, suggesting that inflammation is associated with diabetic neuropathic impairments involving certain immune mediators (Empl et al., 2001). Previously, we have shown that the inflammatory mediators in the dorsal root ganglia are altered with the development of pain in Type 2 model of diabetes (Galloway and Chattopadhyay, 2013). In recent studies, we and others have demonstrated the effects of physical exercise

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on pain perception (Rossi et al., 2011; Yoon et al., 2015), not many have shown the effects of moderate exercise on the levels of inflammation in DH of diabetic animals with peripheral neuropathy. Hyperglycemia can cause vascular dysfunctions by multiple phases including activation of protein kinase C (PKC) and p38 mitogen-activated protein kinase, which may induced the release of proinflammatory cytokines, leading to changes in cell viability. This study also examines the possibility whether exercise can modify these stress associated markers, thereby altering the sensory nerve function. Moreover, exercise training is a non-pharmacological and noninvasive treatment method. This study explores the effect of exercise on the release of anti-inflammatory mediators in the dorsal horn of spinal cord of the Type 1 diabetic animals. This study offers an alternative way to evade systemic side effects of the treatment eventually leading to a novel therapeutic approach for this debilitating complication of diabetes.

2. Results

2.1. Exercise altered levels of inflammatory mediators in the spinal cord of exercise group

Diabetic exercised animals showed a decrease in IL1β in the spinal cord dorsal horn compared to diabetic sedentary group. There were no significant difference between the diabetic exercise and control exercised animals after 6 weeks of exercise. Western Blot analysis of diabetic sedentary animals showed an increase in proinflammatory cytokine IL1β in the DH compared to control sedentary group (Fig. 1a), whereas the diabetic exercise group showed a decrease in IL1β after 6 weeks of exercise. Exercise also exhibited a significant increase in the anti-inflammatory cytokine IL10 in the DH (Fig. 1b) of the diabetic exercise group compared to the diabetic sedentary group, which suggests that exercise may play a role in interleukins levels of the diabetic animals.

2.2. Exercise reduced macrophage activation markers in the DH of diabetic exercise group

Diabetic sedentary animals showed an increase in macrophage activation in the DH by immunohistochemistry of CD11b (Fig. 2a) as well as by western blot of CD68 (Fig. 2b), whereas the diabetic exercise group showed a decrease in the activated macrophage expression after 6 weeks of exercise. This correlates with decrease in pro-inflammatory cytokines in the diabetic exercise group 6 weeks after exercise.

2.3. Exercise modified a number of stress related markers in the DH of diabetic exercise group

Diabetic sedentary animals showed increased levels of stress related kinase p38 MAPK in the DH by immunohistochemistry. Six weeks of moderate exercise demonstrated a decrease in the activation of the stress-related MAP kinase p38 in the diabetic exercise group (Fig. 3a). Phosphorylation of protein kinase C (PKC) was also decreased significantly ($>50\%$) in the DH of diabetic exercised group compared to the diabetic sedentary group 6 weeks after exercise (Fig. 3b). These changes in exercised animals may play a role in changing the inflammatory mediators in the DH of these diabetic animals.

2.4. Exercise preserved the sensory nerve amplitude in the diabetic exercise group

Measurement of the evoked sensory nerve action potential revealed a marked decrease in amplitude in diabetic rats compared to the exercised control group (Con-Ex 24.03 ± 0.7 μV, Dia-Sed 12.4 ± 0.4 μV $P < 0.001$). The sensory nerve amplitude was significantly protected in

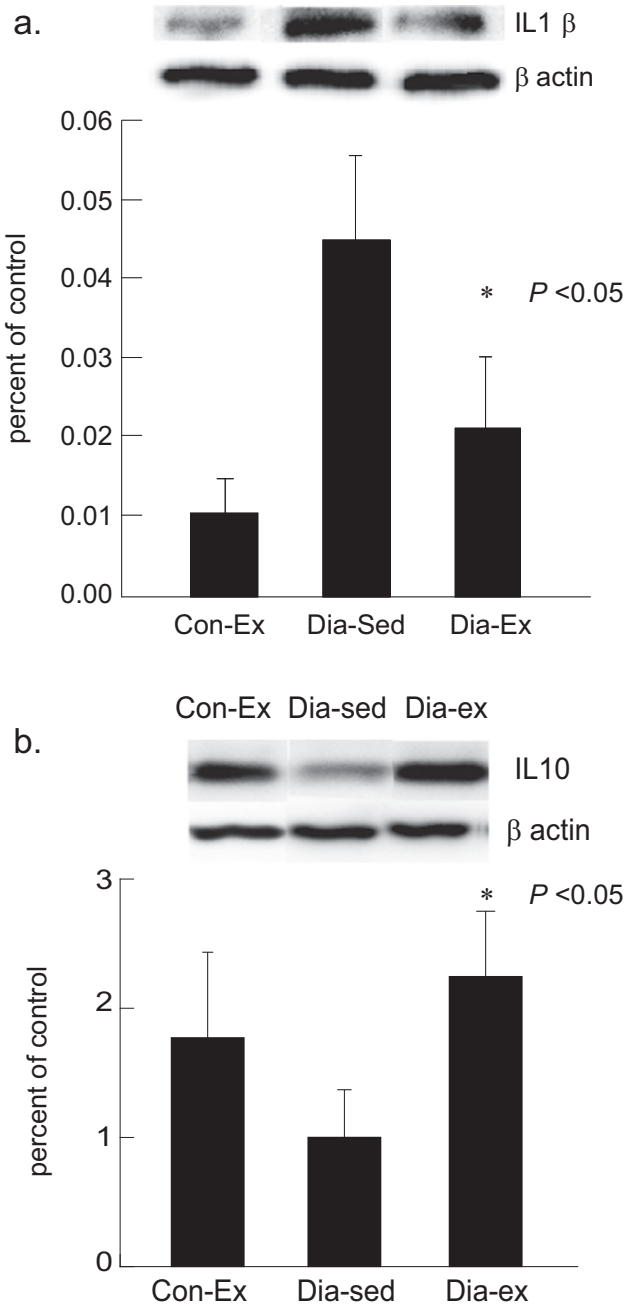

Fig. 1. Exercise decreased IL1β expression in DH of diabetic animals after 6 weeks of exercise. (a) Western Blot analysis of diabetic sedentary animals showed an increase in proinflammatory cytokine IL1β in the DH compared to control sedentary group, whereas the diabetic exercise group showed a decrease in IL1β after 6 weeks of exercise. (b) A significant increase in the anti-inflammatory cytokine IL10 in the DH of the diabetic exercise group was revealed compared to the diabetic sedentary group. Representative Western blots of DH are showing random selection of independent samples from each group.

animals with diabetic-exercise group (16.8 ± 1.2 μV; $P < 0.05$ compared to diabetic sedentary, ANOVA). While the sensory nerve amplitude of the control exercised group was significantly different from the diabetic exercised group ($P < 0.01$), but it is clear that exercise can preserve some extent of sensory nerve function (Fig. 4).

2.5. Exercise modulated CGRP levels in the DH of diabetic exercise group

Diabetic sensory neuropathy was characterized by neuropeptide content in sensory nerve terminals of primary afferents in the

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