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Exercise-mediated improvements in painful neuropathy associated with prediabetes in mice

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ABSTRACT

Recent research suggests that exercise can be effective in reducing pain in animals and humans with neuropathic pain. To investigate mechanisms in which exercise may improve hyperalgesia associated with prediabetes, C57Bl/6 mice were fed either standard chow or a high-fat diet for 12 weeks and were provided access to running wheels (exercised) or without access (sedentary). The high-fat diet induced a number of prediabetic symptoms, including increased weight, blood glucose, and insulin levels. Exercise reduced but did not restore these metabolic abnormalities to normal levels. In addition, mice fed a high-fat diet developed significant cutaneous and visceral hyperalgesia, similar to mice that develop neuropathy associated with diabetes. Finally, a high-fat diet significantly modulated neurotrophin protein expression in peripheral tissues and altered the composition of epidermal innervation. Over time, mice that exercised normalized with regards to their behavioral hypersensitivity, neurotrophin levels, and epidermal innervation. These results confirm that elevated hypersensitivity and associated neuropathic changes can be induced by a high-fat diet and exercise may alleviate these neuropathic symptoms. These findings suggest that exercise intervention could significantly improve aspects of neuropathy and pain associated with obesity and diabetes. Additionally, this work could potentially help clinicians determine those patients who will develop painful versus insensate neuropathy using intraepidermal nerve fiber quantification.

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1. Introduction

Diabetic neuropathy (DN) occurs in up to 60-70% of diabetes patients. Distal symmetric DN is the most common neuropathy associated with diabetes and may present with either positive (pain, burning, or tingling) or negative symptoms (numbness or altered proprioception) [45]. Neuropathy symptoms can precede diagnosis of diabetes and may develop in the initial stages of glucose dysregulation, or prediabetes [14,40], with prediabetes being defined as impaired fasting glucose and/or impaired glucose tolerance [3]. Although neuropathy associated with prediabetes is usually less severe than neuropathy in overt diabetic patients [51], it is still a devastating complication of the disease. Unfortunately, painful symptoms are the predominant feature in prediabetes patients. Current treatment options for patients with painful diabetic neuropathy (PDN) are rarely effective and less than 30% of patients achieve satisfactory pain relief [4].

Recent studies have demonstrated that cutaneous nerve growth factor (NGF) is increased in hind paw skin of rodent models of type 1 and type 2 diabetes [9,15]. It has been suggested that increased NGF may play a significant role in the development of PDN. Additionally, NGF is known to be critical in the development and maintenance of chronic pain, especially inflammatory pain [30,43]. In fact, cutaneous injections of NGF result in thermal and mechanical hyperalgesia in both animals and humans [33]. Besides NGF, additional neurotrophins that play a role in pain sensation include brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF). Like NGF, BDNF is believed to play a role in the development and maintenance of pain states, as BDNF is upregulated in the dorsal root ganglion (DRG) in inflammatory conditions and in models of neuropathic pain [32]. Furthermore, delivery of antibodies against BDNF reduced pain related behaviors in rat [60] and mouse [59]. Although NGF and BDNF are important for the development and maintenance of pain, GDNF is believed to play an antinociceptive role. Previous studies have shown that administration of exogenous GDNF results in analgesia in various models of neuropathic pain [1,6].

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Exercise training has long been suggested to reduce pain and improve functional outcomes [29,53]. In fact, a recent study demonstrated that aerobic and strength training had positive effects on diabetic peripheral neuropathy patients, improving pain and other neuropathic symptoms [28]. Furthermore, studies have shown that exercise increases neurotrophin expression [25,35,36] and increased neurotrophins can promote neuronal healing [5,17,23]. Additionally, these exercise-induced neurotrophin alterations are associated with analgesia [50]. Previous studies have begun to investigate potential therapeutic roles of neurotrophins in diabetic neuropathy using type 1 and type 2 models [2,9,22]. In the current study, we investigated how a high-fat diet alters metabolic and neural features normally associated with DN, as well as how exercise modulates these neuropathy phenotypes. We demonstrate that a high-fat diet induces mechanical allodynia and visceral hyperalgesia, and that exercise reverses these behavioral changes. The exercise-induced modulation of behavior was associated with normalization of neurotrophin levels and epidermal fiber density.

2. Materials and methods

2.1. Animals and diet

Seven-week-old male C57Bl/6 mice were purchased from Charles River (Wilmington, MA) and maintained on a 12:12 hour light/dark cycle in the research support facility at the University of Kansas Medical Center. All mice were given ad libitum access to food and water and were fed either a standard diet (8604; Harlan Teklad, Madison, WI; 14% kcals from fat, 32% protein, and 54% carbohydrate) or a high-fat diet (07011; Harlan Teklad; 54% kcals from lard and corn oil fat, 21% protein, and 24% carbohydrate). All animals were fed the standard diet through all baseline tests. After baseline tests, the animals were separated according to diet. All animal use was in accordance with NIH guidelines and conformed to the principles specified in a protocol approved by the University of Kansas Medical Center Institutional Animal Care and Use Committee.

2.2. Energy intake

Daily food intake was measured by monitoring the weight of the remaining food after an initial food bolus. New food boluses were given every 3-4 days. Energy intake was calculated by:

$$\text{Intake per day} = \frac{(\text{initial weight of food}/\text{final weight of food})}{\#\text{ of days between feedings}}$$

Standard diet energy was calculated by multiplying the intake per day by 3.0 kcal/g, while high-fat diet energy was calculated by multiplying intake per day by 4.9 kcal/g. The combined mean energy intake from each mouse was used to calculate the group means.

2.3. Voluntary exercise

Following baseline testing, animals were separated into either sedentary controls or exercise groups. Exercise animals were housed individually in cages designed to hold stainless-steel running wheels (Mini Mitter; Bend, OR) and given free access to run 24/7. VitalView (Mini Mitter) software measured total wheel revolutions for each mouse during the course of the study. Sedentary animals were housed 1 to 2 per cage at the suggestion of the veterinarians in the animal facility. Mice were started on diet and running wheels simultaneously following baseline behavior testing. Treatment groups are identified throughout the study as: standard diet sedentary (Std-Sed), standard diet exercise (Std-Ex), high-fat diet sedentary (HF-Sed), and high-fat diet exercise (HF-Ex).

2.4. Blood chemistry

Animal weight, blood glucose (glucose diagnostic reagents; Sigma, St. Louis, MO), and serum insulin (mouse insulin ELISA; Alpco, Salem, NH) were measured biweekly. Hemoglobin A1c levels (A1CNow+; Bayer, Sunnyvale, CA) were measured at 0, 6, and 12 weeks following high-fat diet and exercise initiation. All mice were fasted 3 hours prior to blood collection for all blood chemistry panels, with the exception of the glucose tolerance test.

After 12 weeks, an intraperitoneal glucose tolerance test (IPGTT) was performed after a 6 hour fast. Animals were given an intraperitoneal (IP) injection of glucose at 2 g glucose/kg body weight. Blood glucose levels were measured via tail clip immediately before glucose injection and 15, 30, 60, and 120 minutes thereafter.

2.5. Behavior testing

Behavior testing to assess signs of diabetic neuropathy was carried out at baseline and biweekly time points. For all behavioral tests, animals were allowed to acclimate to the testing equipment in two separate sessions prior to the initial testing day. Before each behavior test, animals were allowed to acclimate to the behavior testing room for 30 minutes followed by a 30-minute acclimation to the testing equipment.

2.6. Mechanical sensitivity

Mice were placed in individual clear plastic cages on a wire mesh table 55 cm above the table. von Frey monofilaments (0.07-4.0 g) were applied perpendicularly to the plantar surface of the hind paw until the filament bent. Testing began with the 0.6 g filament. If the animals withdrew their paw, it was counted as a positive withdrawal and the next lowest filament was applied. If the animal did not respond, the next larger filament was applied. Filaments were applied until there was an initial change in response followed by 4 additional filament applications. The 50% withdrawal threshold was calculated using the formula from the up-down method previously described [8].

2.7. Thermal sensitivity

Mice were placed in individual clear plastic cages on a Hargreaves's apparatus and a 4.0 V radiant heat source was applied twice to each hind paw for a total of four tests. Time elapsed for each animal to withdraw the hind paw was counted as withdrawal latency (seconds). Latencies from 4 applications were used to calculate the mean latency per animal and mean latencies were combined to calculate group means.

2.8. Visceral sensitivity

At 12 weeks, electrode implantation and colorectal distension (CRD) were performed as described previously [11]. The electromyographic (EMG) activity of the abdominal musculature was amplified, filtered, and recorded with Spike 2 software (Cambridge Electronic Design, Cambridge, UK) during each applied pressure: 15, 30, 45, 60, and 75 mmHg, in triplicate for 20 seconds with a 4-minute rest period in between. CRD responses were quantified by measuring the area under the curve for the entire distension period divided by the duration of the distension and expressed as a percent of baseline activity (10 seconds prior to distension).

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