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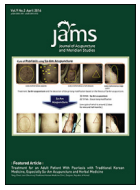

RESEARCH ARTICLE

Effect of Electroacupuncture on Inflammation in the Obese Zucker Fatty Rat Model of Metabolic Syndrome

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Abstract
Chronic inflammation is known to be associated with visceral obesity and insulin resistance and is characterized by altered levels of production of adipokines such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), IL-6, leptin, and adiponectin. Metabolic syndrome (MetS) is a major and escalating public health and clinical challenge worldwide, and patients with MetS have an increased risk of developing cardiovascular disease and type 2 diabetes mellitus. Electroacupuncture (EA) was tested as a means of decreasing inflammation in genetically obese Zucker fatty rats, which serve as a model of MetS. Repeated application of EA at the Zhongwan/Guanyuan acupoints decreased serum TNF-α, but produced no significant alterations in serum leptin, adiponectin, or IL-10. EA had no significant effect on the levels of these four adipokines in white adipose tissue. These findings are consistent with the supposition that EA inhibits proliferation and/or infiltration of macrophages into the adipose tissue of obese rats and stimulates the release of IL-10 from the decreased numbers of macrophages present in adipose tissue. Compared with the control animals, no significant change in body weight occurred. The blood glucose (BG) level over a 30-minute interval in Week 2 was relatively the same as that in Week 1, suggesting that EA treatment does not increase the likelihood of developing hyperglycemia.

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1. Introduction

Obesity and diabetes mellitus have emerged as major health issues worldwide with increasing incidence and prevalence. According to the World Health Organization Global Health Estimates, in 2014, 39% of adults aged $\geq$ 18 years were overweight (body mass index $\geq$ 25 kg/m^2), 13% were obese (body mass index $\geq$ 30 kg/m^2) [1] and 9% had diabetes [2]. The International Diabetes Federation has defined metabolic syndrome (MetS) as a cluster of risk factors such as prediabetes, diabetes, abdominal obesity, hypercholesterolemia, and hypertension that collectively increase the risk of cardiovascular diseases. The International Diabetes Federation also estimates that a quarter of the global adult population has MetS and that this is likely to be an upward trend [3].

Obesity is described as a low-grade chronic inflammatory condition characterized by adipocyte hyperplasia and hypertrophy [4], increased levels of circulating leptin [5], decreased levels of circulating adiponectin [6], and increased numbers of classically activated macrophages in the white adipose tissue which produce many proinflammatory cytokines like tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6 [4]. Obesity often coexists with other serious morbidities such as hypertension, cardiovascular disease, diabetes, and cancer [7]. Treatments that have been used to reduce obesity include physical exercise, lifestyle changes including diet, psychosocial counselling, bariatric surgery, liposuction, and acupuncture. Medications have proven to be largely ineffective, often causing serious side effects including cardiovascular disease [8].

The development of obesity has been attributed to both genetic and environmental factors. Obese Zucker fatty rats have been widely investigated and used as genetic models of obesity and MetS. These obese rats possess a single gene (fa/fa) mutation characterized by a defect in leptin receptor [9—12] and can be visually distinguished from their lean littermates by 5 weeks of age due to excessive deposition of subcutaneous [13] and visceral adipose tissue. They are characterized by hyperphagia, insulin resistance, dyslipidemia, central adiposity, and hypertension [14], all risk factors involved in MetS [12]. These rats have also previously been used to evaluate the effects of antiobesity treatment like dehydroepiandrosterone [15], agonists of peroxisome proliferator-activated receptor alpha [16,17] and gamma [16] on serum lipids, body weight, and insulin sensitivity. Although effective in regulating certain parameters in obesity, many of them also cause serious side effects [8,18,19]. Habitual exercise was also shown to increase TNF-α in the adipose tissue of obese Zucker fatty rats [20].

Based on the antiinflammatory effects of electroacupuncture (EA) [21], it has been proposed as a means to control the low-grade inflammation in the obese Zucker fatty rat model of MetS. The present study was designed to test whether repeated application of EA in obese Zucker fatty rats would lead to a change in the imbalance of proinflammatory and antiinflammatory cytokines produced by white adipose tissue. The effect of EA on body weight and levels of glucose, insulin, leptin, adiponectin, TNF-α, and IL-10 were measured. A change in the relative concentrations of IL-10 and TNF-α in blood and adipose tissue would indicate a reversal in activation state of adipose tissue macrophages, while a change in the relative concentrations of adiponectin and leptin levels would indicate an alteration in insulin resistance. Antiobesity treatments or medications should ideally not increase blood glucose (BG) levels, as otherwise, there would be a tendency towards diabetes which often coexists with obesity.

2. Materials and methods

2.1. Animals

Male obese Zucker fatty rats, 12—14 weeks of age, were obtained from a breeding colony maintained at the Taieri Animal Station and delivered to the Hercus Taieri Research Unit, University of Otago, Dunedin, New Zealand. The rats were fed standard rat chow (Specialty Feeds irradiated rat and mouse cubes, 4.8% fat, 20% protein, amino acids, vitamins and minerals, 3.34 kcal/g; Specialty Feeds, Glen Forest, Western Australia, Australia) and acclimatized to the new environment for 1 week. They were housed in individual cages with food and water *ad libitum* in a room with a 12 hour/12 hour light/dark cycle at constant temperature. Animals were deprived of food at 3:00 PM on the day prior to the experiment to ensure an overnight fast of at least 17 hours. This study was approved by the University of Otago Animal Ethics Committee.

2.2. Treatment of animals

2.2.1. Anesthesia and EA

The obese Zucker fatty rats were divided into two groups. Rats in both groups were anesthetized with halothane (1%) in 3:1 mixture of nitrous oxide:oxygen 1.2 L/min. This involved placing the nose of each animal in the nose cone of the anesthetic apparatus. BG was measured with a handheld glucometer (Accu-Chek Advantage, Roche, Roche Diagnostics NZ Ltd., Mt Wellington, Auckland, New Zealand) after needle pricking the lateral saphenous vein of one of the hind limbs at 10 minutes and 20 minutes following anesthesia. This was to confirm that at 20 minutes, BG is relatively stable and can be used as a baseline.

The obese Zucker fatty rats in Group 1 [$n = 5$; mean age (standard error) 14.6 (0.40) weeks; mean weight 528 (6.6) g] were treated with EA applied at the Zhongwan (CV12) and Guanyuan (CV4) acupoints, while obese Zucker fatty rats in Group 2 [$n = 7$; mean age 14.1 (0.40) weeks; mean weight 540 (13.0) g] were not treated with EA and served as controls. EA treatments were given on alternate weekdays giving a total of six applications of EA over 2 weeks. The acupoints were located using the acupoint detector of the EA unit. The Zhongwan acupoint is 9/14 above the pubic crest of the distance measured between the top of the xiphoid process and the pubic crest, whereas the Guanyuan acupoint is 2/14 of this distance above the pubic crest [22]. The hair at the acupoint sites was removed with electric clippers. Sterile acupuncture needles (Seirin Corporation, Shizuoka, Japan, 0.25 mm, 15 mm) were inserted into the muscle layer at the chosen acupoints to a depth of 4 mm. EA