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RESEARCH ARTICLE

Differential Effect of Electroacupuncture on Inflammatory Adipokines in Two Rat Models of Obesity

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Abstract
Chronic inflammation is known to be associated with visceral obesity and insulin resistance which are characterized by altered levels of production of pro- and anti-inflammatory adipokines. The dysregulation of the production of inflammatory adipokines and their functions in obese individuals leads to a state of chronic low-grade inflammation and may promote obesity-linked metabolic disorders and cardiovascular diseases such as insulin resistance, metabolic syndrome, and atherosclerosis. Electroacupuncture (EA) was tested to see if there was a difference in its effect on pro- and anti-inflammatory adipokine levels in the blood serum and the white adipose tissue of obese Zucker fatty rats and high-fat diet-induced obese Long Evans rats. In the two rat models of obesity, on Day 12 of treatment, repeated applications of EA were seen to have had a significant differential effect for serum tumor necrosis factor-α, adiponectin, the adiponectin:leptin ratio, and blood glucose. For the adipose tissue, there was a differential effect for adiponectin that was on the borderline of significance. To explore these changes further and how they might affect insulin resistance would require a modification to the research design to use larger group sizes for the two models or to give a greater number of EA treatments.

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1. Introduction

Obesity is a major public health concern and is associated with an increased risk of chronic diseases including type 2 diabetes, cardiovascular disease, cancer, decreased health-related quality of life and overall life expectancy, and increased health care costs [1]. It results from a complex interplay of many genetic and environmental factors.

Several studies have shown that the detrimental influence of abdominal obesity on metabolic processes is mediated by the intra-abdominal fat depot [2,3]. The visceral fat depot correlated with glucose intolerance in the presence of hyperinsulinemia during an oral glucose tolerance test, suggesting an insulin-resistant state in human obesity [4]. Insulin resistance and hyperinsulinemia are often associated with obesity, and the ability of obesity to engender insulin resistance is the major basis for the association of obesity with type 2 diabetes mellitus.

The accumulation of fat mass during the development of obesity is characterized by adipocyte hyperplasia and hypertrophy. The prevalence of hypertrophied adipocytes in adipose tissue results in a reduction in blood flow with subsequent hypoxia and macrophage infiltration, and increased production of proinflammatory adipokines [3—7]. Many of the proinflammatory cytokines are secreted by the adipocytes, whereas others are predominantly derived from adipose tissue-infiltrated macrophages. The dysregulation of pro- and anti-inflammatory adipokine production and their functions in obese individuals leads to a state of chronic low-grade inflammation and may promote obesity-linked metabolic disorders and cardiovascular diseases such as insulin resistance, metabolic syndrome, and atherosclerosis [8]. Obesity-associated inflammation may impair insulin action systemically through increasing free fatty acids (FFA) or proinflammatory adipokines [e.g., leptin, tumor necrosis factor-α (TNF-α)] in circulation as both are able to target insulin receptor substrate proteins and modify the metabolic and mitotic effects of insulin leading to insulin resistance [9—13].

This paper examines whether the effect of electroacupuncture (EA) is different in two rat models of obesity by comparing the levels of pro- and anti-inflammatory adipokines in the two models with and without EA treatment. The two models used were the obese Zucker fatty rats and diet-induced obese Long Evans rats. Obesity develops in the former as a result of a genetic mutation in the leptin receptor, while in the latter it develops as a result of high dietary fat intake. The obese Zucker fatty rat has been used as a model of metabolic syndrome and develops hyperphagia, dyslipidemia, hyperleptinemia, hyperinsulinemia, central adiposity, hypertension, insulin resistance, and diabetes [14,15], all being risk factors involved in metabolic syndrome [16]. Homeostasis model assessment of insulin resistance was significantly greater for obese Zucker fatty rats than lean Zucker fatty rats [17]. Obesity induced in Long Evans rats by a high-fat diet (HFD) was reported to be associated with hyperleptinemia and insulin resistance [18,19]. Li et al [20] have shown that HFD-induced obese Long Evans rats at 25 weeks of age had significantly higher fasting plasma total cholesterol, triglyceride, insulin, leptin, and adiponectin levels when compared with lean animals of that age. Fasting plasma glucose was not significantly different to the lean animals. In oral glucose tolerance test at 21 weeks of age, both glucose and insulin levels were significantly higher after overnight fasting and at every time point after the oral glucose challenge in the diet-induced obese rats indicating impaired insulin sensitivity. There is increasing clinical evidence for the effectiveness of acupuncture as a treatment of insulin resistance [21], and possible changes in the circulating levels of pro- and anti-inflammatory adipokines by EA intervention could lead to a decrease in insulin resistance by affecting insulin sensitivity.

2. Materials and methods

2.1. Animals

Male Zucker *fa/fa* rats 12—14 weeks of age and male Long Evans rats at 3 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 obese Zucker 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), housed in individual cages and acclimatized to the new environment for 1 week. The just-weaned Long Evans rats were fed with a HFD (Specialty Feeds SF 03-020, 23% fat, 20% protein, 42% sucrose, amino acids, vitamins and minerals, 4.78 kcal/g; Specialty Feeds) for 9 weeks immediately following delivery and group housed (5 rats/cage). All the rats were given free access to food and water in a room with 12-hour/12-hour light/dark cycle at a constant temperature. The HFD-fed Long Evans rats were weighed on the day immediately prior to the start of the study and those with a weight equal to or greater than the mean weight plus two standard deviations of normal rat chow-fed male Long Evans rats of the same age were selected for the study and placed in individual cages. These rats were designated as obese Long Evans rats. All 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

This involved lightly anesthetizing the animals with 1% halothane in a 3:1 mixture of nitrous oxide:oxygen 1.2 L/min. Blood glucose (BG) was measured with a hand-held 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. The obese Zucker rats in Group 1 ($n = 5$) were treated with EA applied at the *Zhongwan* (conception vessel; CV12) and *Guanyuan* (CV4) acupoints on alternate weekdays (Monday/Wednesday/Friday) over 2 weeks giving a total of six applications of EA; those in Group 2 ($n = 7$) were not treated with EA and served as controls [22]. Similarly the obese Long Evans rats in Group 3 ($n = 7$) were