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Remodeling of white adipose tissue metabolism by physical training prevents insulin resistance

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ABSTRACT

Aim: This study sought to determine the role of white adipose tissue (WAT) metabolism in the prevention of insulin resistance (IR) by physical training (PT).

Main methods: Male C57BL/6 J mice were assigned into groups CHOW-SED (chow diet, sedentary; n = 15), CHOW-TR (chow diet, trained; n = 18), CAF-SED (cafeteria diet, sedentary; n = 15) and CAF-TR (cafeteria diet, trained; n = 18). PT consisted of running sessions of 60 min at 60% of maximal speed conducted five days per week for eight weeks.

Key findings: PT prevented body weight and fat mass accretion in trained groups and prevented hyperglycemia, hyperinsulinemia, glucose intolerance and IR in the CAF-TR. The CAF-SED group presented higher leptin and free fatty acid and lower adiponectin serum levels compared with other groups. Lipolytic activity (in mmol/10^6 adipose cells) stimulated by isoproterenol increased in CHOW-TR (16347 ± 3005), CAF-SED (18110 ± 3788) and CAF-TR (15837 ± 2845) compared with CHOW-SED (8377 ± 2284). The CAF-SED group reduced FAS activity compared with CHOW-SED and CHOW-TR, reduced citrate synthase activity and increased DGAT2 content compared with other groups. Both trained groups reduced G6PDH activity and increased the expression of p-AMPK (Thr172) compared with sedentary groups. CAF-SED group had lower levels of AMPK, p-AMPK (Thr172), ACC and p-ACC (Ser79) compared with other groups.

Significance: The prevention of IR by PT is mediated by adaptations in WAT metabolism by improving lipolysis, preventing an increase in enzymes responsible for fatty acid esterification and by activating enzymes that improve fat oxidation instead of fat storage.

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Introduction

The WAT participates actively in the development of IR and type 2 diabetes. The accumulation of WAT may reflect reduction in the phosphorylation of insulin receptor in adipocytes (Algenstaedt et al., 2004), decrease in the expression of insulin receptor and lower glucose uptake into adipocytes (Burén et al., 2003), reduction in PI3K activity and the expression of transporter GLUT4 in adipocytes (Hussey et al., 2011). In addition, changes in the endocrine activity of WAT are also associated with type 2 diabetes, such as reduction of adiponectin (Xita and Tsatsoulis, 2012), increase of leptin (Sutherland et al., 2008) and proinflammatory cytokines secretion (Kim et al., 2011).

Impairments in the regulation of WAT metabolic activities such as lipogenesis (triacylglycerol biosynthesis and accumulation in the intracellular lipid droplet), lipolysis (triacylglycerol hydrolysis) and fatty acid oxidation may lead to an increase in WAT mass (Savage et al., 2007; Jocken an Blaak, 2008). The dysfunction of WAT metabolism has been associated with IR and type 2 diabetes (Gaidhu et al., 2010; Arner et al., 2011). In fact, increases in lipogenesis (Berndt et al., 2007; Shankar et al., 2010), lipolysis (Samuel and Shulman, 2012) and circulating free fatty acid (FFA) levels, which may promote lipotoxicity in tissues such as skeletal muscle and liver, contribute to the development of type 2 diabetes (Savage et al., 2007; Jocken and Blaak, 2008).

PT has been extensively used for the prevention and treatment of IR and type 2 diabetes because it promotes a reduction in body weight (Marwick et al., 2009; Malin and Kirwan, 2012) and WAT mass (Nassis et al., 2005; Ross and Bradshaw, 2009), an increase in the oxidation of FFA in the skeletal muscle associated with improvement in mitochondrial function (Kelley and Sharpe, 2001) and an improvement in the secretion of adipokines associated with glycemic control and inflammatory response (Zeng et al., 2007; Sahin-Efe et al., 2012). In this

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context, adaptations in the lipid metabolism that increase FFA oxidation and reduce fat storage as induced by PT may contribute to the prevention of IR associated with obesity.

Although the effect of PT on energy metabolism and its preventive role against obesity and type 2 diabetes are well described in the literature, the relative contribution of WAT metabolism for this process needs to be better understood. Recently, we showed that PT did not change WAT gene expression pattern in chow-fed diet mice (Higa et al., 2012). In addition, chow-fed diet rats did not change mitochondrial protein expression but increased the citrate synthase enzyme activity and the expression of proteins involved in β-adrenergic signaling in WAT (Stephenson et al., 2013). On the other hand, the increase in WAT expression of some proteins was observed by others (Sutherland et al., 2009; Sakurai et al., 2010). Despite controversies, these studies were developed in trained animals fed a chow diet. However, the WAT metabolic response in trained animals exposed to hypercaloric diet, which is a typical model used to induce IR (Sampey et al., 2011), remains to be investigated.

Considering the role of WAT in the development and progression of IR and type 2 diabetes and the effect of PT to prevent the impairment of lipid metabolism and fat accumulation, the objective of this study was to determine the role of WAT metabolism in the prevention of IR by PT. We hypothesized that the prevention of IR in physically trained mice is mediated by adaptations in lipolytic and lipogenic activities of WAT that favor fat oxidation instead of fat storage.

Materials and methods

Animals

Ten-week-old male C57BL/6J mice were assigned to four groups: CHOW-SED (chow diet, sedentary; n = 15), CHOW-TR (chow diet, trained; n = 18), CAF-SED (cafeteria diet, sedentary; n = 15) and CAF-TR (cafeteria diet, trained; n = 18). The standard chow diet contained 4% of kilocalories from fat, 55% from carbohydrate and 22% from proteins (Nuvilab®, Paraná, Brazil). The cafeteria diet was modified from Estadella et al. (2004) and contained 18.8% of kilocalories from fat, 55% from carbohydrate and 14.8% from proteins. Animals were maintained under the same housing conditions (12-h light/12-h dark cycle, temperature 22 ± 2 °C) with free access to tap water and food *ad libitum*. All procedures were performed in accordance with the guidelines of the Brazilian College for Animal Experimentation and were approved by the Ethics Committee of the School of Physical Education and Sport of University of Sao Paulo (#13/2010).

Physical training

CHOW-TR and CAF-TR animals were submitted to PT as described by Ferreira et al. (2007). Animals were trained during the dark cycle (*i.e.*, during their active period) on a motorized treadmill for 1 h/day at 60% of maximal velocity achieved in the running capacity test, five times per week for eight weeks. PT intensity was progressively increased and adjusted after the running capacity test done in the fourth week. PT and diet were started simultaneously. To minimize the influence of the treadmill stress, sedentary mice were placed on the treadmill for 5 min twice weekly at 0.3 km/h during the experimental protocol.

Body weight composition

Body weight was measured weekly at the same time of day using a digital balance (Gehaka, Model BK4001, Brazil). Body weight gain was calculated as the difference between body weight measured at the beginning and at the end of the PT protocol.

Food intake

The 24-h food intake was determined weekly throughout the study in mice that were housed at four animals per cage.

Running capacity test

Running capacity was assessed before, in the fourth and eighth weeks of PT using a progressive test without inclination on a treadmill as described by Ferreira et al. (2007). The initial speed was 0.4 km/h and the speed was increased by 0.2 km/h every three minutes until exhaustion of the animal, which was characterized by the impossibility of maintaining the standard rate. The test variable was quantified as the maximum execution time (min).

Resting blood pressure and heart rate measurements

Tail-cuff blood pressure (BP) and heart rate (HR), estimated from the pulse rate, were determined after eight weeks of PT *via* the use of a computerized tail-cuff system (BP 2000 Visitech Systems). BP and HR values for each animal were determined by averaging 20 measurements obtained during their dark cycle.

Glucose tolerance test (GTT) and insulin tolerance test (ITT)

GTT and ITT were performed after the 8-week PT protocol. Both experiments were performed in awake animals at 08:00 a.m. and after a 12-h fast. The glucose load (2 g/kg body weight) was injected as a bolus intraperitoneally, and the blood glucose levels were determined in caudal blood sampled at 0, 15, 30, 60, 90 and 120 min after glucose infusion. The glucose concentration was determined using a glucometer (AccuChek Advantage Roche Diagnostics®).

After 72 h of GTT test, a similar procedure was performed for ITT. The insulin load (0.75 U/kg body weight) was injected as a bolus intraperitoneally, and the blood glucose levels were determined in caudal blood samples collected at 0, 5, 10, 15, 20, 25 and 30 min after injection. The values obtained between 5 and 30 min were used to calculate the rate constant for the disappearance of plasma glucose (kITT) according to the method proposed by Bonora et al. (1989).

Tissue and blood collection

Forty-eight hours after the end of the last training session, the animals were killed with an intraperitoneal injection of pentobarbital sodium (4 mg/100 g body weight). The Lee index was determined based on the naso-anal length and body weight measurements ($\sqrt[3]{\text{body weight}}$/naso-anal length) (Bernardis and Patterson, 1968). Subcutaneous (inguinal) and visceral (periepididymal and retroperitoneal) fat pads, organs and skeletal muscle were harvested, weighed and stored at −80 °C. The adiposity index was calculated as 100× (sum of fat pad weights)/(body weight) (Taylor and Phillips, 1996). The cava venous blood was collected and centrifuged at 4 °C (10.000 g for 10 min) and serum was stored at −80 °C.

Serum analysis

Insulin, leptin and adiponectin were quantified using mouse-specific radioimmunoassay (RIA) kits (Merck Millipore Corp., St. Charles, MO). The insulin detection sensitivity was 0.02 ng/mL, the within-run variation was less than 5.8%, and the interassay CV was less than 10%. Assays were performed in duplicate using a sample volume of 50 μL. The leptin detection sensitivity was 0.2 ng/mL, the within-run variation was less than 4.6% and the interassay CV was less than 10%. Assays were performed in duplicate with a sample volume of 50 μL. Adiponectin detection sensitivity was 1 ng/ml, the within-run variation was less than 4.5% and the interassay CV was less than 10%. Assays were performed in

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