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Impact of physical exercise on visceral adipose tissue fatty acid profile and inflammation in response to a high-fat diet regimen

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ABSTRACT

Purpose: Studies associate specific fatty-acids (FA) with the pathophysiology of inflammation. We aimed to analyze the impact of exercise on adipose tissue FA profile in response to a high-fat diet (HFD) and to ascertain whether these exercise-induced changes in specific FA have repercussions on obesity-related inflammation.
Methods: Sprague-Dawley rats were assigned into sedentary, voluntary physical-activity (VPA) and endurance training (ET) groups fed a standard (S, 35kcal% fat) or high-fat (71kcal% fat) diets. VPA-animals had unrestricted access to wheel-running. After 9-wks, ET-animals engaged a running protocol for 8-wks, while maintained dietary treatments. The FA content in epididymal white-adipose tissue (eWAT) triglycerides was analyzed by gas-chromatography and the expression of inflammatory markers was determined using RT-qPCR, Western and slot blotting.
Results: Eight-wks of ET reversed obesity-related anatomical features. HFD increased plasma tumor necrosis factor (TNF)-α content and eWAT monocyte chemoattractant protein (MCP)-1 protein expression. HFD decreased eWAT content of saturated FA and monounsaturated FA, while increased linoleic acid and prostaglandin E2 (PGE2) levels in eWAT. VPA decreased visceral adiposity, adipocyte size and MCP-1 in HFD-fed animals. The VPA and ET interventions diminished palmitoleic acid and increased linoleic acid in HFD-fed groups. Moreover, both interventions increased PGE2 levels in standard diet-fed groups and decreased in HFD. ET increased eWAT fatty acid desaturase 1 (FADS1) and elongase 5 (ELOVL5) protein content in both diet types. ET reduced eWAT inflammatory markers (TNF-α, IL-6), macrophage recruitment (MCP-1 and F4/80) and increased IL-10/TNF-α ratio in plasma and in eWAT in both diet types.
Conclusions: Exercise induced FA-specific changes independently of dietary FA composition, but only ET attenuated the inflammatory response in VAT of HFD-fed rats. Moreover, the exercise-induced FA changes did not correlate with the inflammatory response in VAT of rats submitted to HFD.

1. Introduction

Fatty acids (FA) are energy-rich molecules that play important physiological roles in several organs, including white adipose tissue (WAT) (Vaughan et al., 2015; Oliveira et al., 2015). In humans, the most abundant FA esterified to triglycerides are oleic (C18:1*n*9), palmitic (C16:0) and linoleic (C18:2*n*6) that account for over 85% of FA in WAT triglycerides (Hodson et al., 2008). Some FA have been suggested to be involved as direct regulators in inflammation (Vaughan et al., 2015; Oliveira et al., 2015), a complex and tightly regulated biological process that is triggered by obesity (Vieira et al., 2009; Kawanishi et al., 2015). Obesity is the result of a positive energy intake with low levels of physical activity, interacting or not with genetic factors, which explain at least in part the excess of visceral adiposity accumulation observed in large proportions worldwide (Bray and Bellanger, 2006). Obesity-associated inflammation is locally observed

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Table 1
Fatty acid composition of standard and high-fat diets.

	Standard diet (g/L)				HFD (g/L)			
	Safflower	Olive oil	Corn oil	Total	Safflower	Olive oil	Corn oil	Total
C18:2*n*6	78	7	60	145	78	7	120	205
C18:1*n*9	12.2	77	26.5	115.7	12.2	77	53	142.2
C16:0	6.9	10.5	10.8	28.2	6.9	10.5	21.6	39
C18:0	2.9	3	2.1	8	2.9	3	4.2	10.1
C18:3*n*3	–	0.6	0.6	1.2	–	0.6	1.2	1.8
C16:1*n*7	–	1.0	–	1.0	–	1.0		1.0

The standard and high-fat diets were purchased to Diets Inc., catalog #710027 and 7120131. The two diets differed in the amount of corn oil each other, 40 g of was added to obtain high-fat diet. Standard diet contain 12%, 39 and 49% of saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids, respectively. The high-fat diet contain 12%, 35% and 51% of saturated fatty acids, monounsaturated fatty acids and polyunsaturated fatty acids, respectively.

in the expanded VAT (Lumeng et al., 2007), but then becomes systemic through the release of several pro-inflammatory mediators, including interleukin (IL)-6 and tumor necrosis factor (TNF)-α, among others (Lumeng et al., 2007; Lopategi et al., 2016). Therefore, this inflammatory state triggers the secretion of macrophage chemoattractant protein (MCP)-1 by macrophages, which can either sustain a macrophage-like phenotype in undifferentiated precursor cells or diminish the ability of adipocytes to further expand and store lipids, thus supporting a deleterious "vicious cycle" (Lumeng et al., 2007; Lopategi et al., 2016). Some recent studies reported that specific FA, such as saturated fatty acids (SFA) (Choi et al., 2014; Tousoulis et al., 2010), monounsaturated fatty acids (Esser et al., 2015) and *n*6-polyunsaturated fatty acids (PUFA) (Johnson and Fritsche, 2012) are involved in the pathophysiology of inflammation during obesity (Vaughan et al., 2015; Oliveira et al., 2015; Chan et al., 2015; Finucane et al., 2015). In fact, a fat diet rich in SFA likely enhance circulating biomarkers of (pro) inflammation in health individuals (Tousoulis et al., 2010), and *in vitro* studies showed that macrophages exposed to SFA increased pro-inflammatory gene expression and cytokine secretion, such as TNF-α and IL-6, and the chemokine CXCL1/KC (Choi et al., 2014). A MUFA-enriched high-fat diet (HFD) reverted inflammation-mediated insulin resistance and adipose tissue dysfunction when compared with SFA-fed mice (Finucane et al., 2015). On the other hand, MUFA intake induced an upregulation of several pro-inflammatory genes in obese individuals (Esser et al., 2015), possibly because the unsaturated double bond of MUFA turns these FA more susceptible to oxidation, and therefore to the activation of a pro-inflammatory stress response (Calder, 2006). Moreover, the various oxidized forms of linoleic acid (C18:2*n*6) contribute to stimulate inflammation (Johnson and Fritsche, 2012), mainly due to its role as a precursor of arachidonic acid-mediated eicosanoid biosynthesis and in the reduction of the synthesis of anti-inflammatory eicosanoids from eicosapentaenoic acid and docosahexaenoic acid (Fritsche, 2015).

Physical exercise has been well recognized as a strategy to prevent visceral adiposity accumulation, improve inflammatory process as well as lipid metabolism, such as fatty acid profile (Vieira et al., 2009; Kawanishi et al., 2015; Gollisch et al., 2009; Jenkins et al., 2012). In fact, studies demonstrated that endurance training (ET) induced FA profile-specific changes in WAT triglycerides by increasing the percentage of long chain and PUFA (Petridou et al., 2005; Wirth et al., 1980; Thorling and Overvad, 1994). Moreover, ET decreased MUFA in humans (Danner et al., 1984; Sutherland and Woodhouse, 1981) and in rodents (Wirth et al., 1980; Bailey et al., 1993); however the findings are not consistent (Thorling and Overvad, 1994; Rocquelin and Juaneda, 1981). The anti-inflammatory impact of regular physical exercise are well documented (Kawanishi et al., 2015; Gollisch et al., 2009; Jenkins et al., 2012) and rely on several modulatory effects, such as decreased expression of pro-inflammatory cytokines (TNF-α and IL-6) and macrophage recruitment and infiltration (Gollisch et al., 2009; Kawanishi et al., 2010) independently of body weight reduction (Vieira et al., 2009)). In addition, an increased IL-10 expression was also observed in response to ET (Jenkins et al., 2012; Lira et al., 2010; Lira et al., 2009), strengthening the anti-inflammatory effects of physical exercise. However, to our best knowledge, the role of physical exercise as a modulator of FA profile-specific changes on VAT and concomitantly on the inflammatory response associated to obesity has never been clarified. Therefore, in the present study we aimed to analyze the impact of two distinct physical exercise regimens (voluntary physical activity – VPA and endurance training – ET) on VAT fatty acids profile in response to a high-fat diet (HFD) and to ascertain whether these exercise-induced changes in specific FA have significant repercussions on the inflammatory response.

2. Material and methods

2.1. Animal care and dietary treatments

The study was approved by local Institutional Ethics Committee and followed the guidelines for the care and use of laboratory animals in research advised by the Federation of European Laboratory Animal Science Association (FELASA) and Portuguese Act 129/92. Male Sprague-Dawley rats (6 wks old) were purchased from Charles River (L'Arbresle, France) and housed (2 rats per cage) in a controlled environment (12-h light/dark cycle), constant temperature (21–22 °C) and humidity (50–60%) with free access to water and food (provided in a liquid state). Rats with initial body weight 233.9 ± 2.6 g were fed a nutritionally adequate isoenergetic standard (35Kcal% fat, 47Kcal% carbohydrates, and 18Kcal% protein) or a high-fat (HFD, 71Kcal% fat, 11Kcal% carbohydrates, and 18Kcal% protein)-liquid diets purchased from Dyets Inc. (catalog no. 710027 and 712031, respectively) over 17 weeks. The two diets differed in the amount of corn oil in each other, 40 g packed separately and then mixed into the diet to obtain HFD (for a detailed description of diets see Table 1). The standard diet was given to all animals as an adaptation to the liquid feeding during the first week. Afterwards, animals were divided into four groups (n = 7-8/group): standard-diet sedentary (SS), standard-diet voluntary physical activity (SVPA), high-fat diet sedentary (HS) and high-fat diet voluntary physical activity (HVPA). After 9-weeks of the beginning of the protocol, half of SS and HS animals were divided into standard-diet endurance training (SET) and high-fat diet endurance training (HET) groups. Energy intake (kilocalories) and body weight (g) were recorded daily and weekly, respectively, during the 17 weeks of the experiment.

2.2. Physical exercise protocols

2.2.1. Voluntary physical activity

Animals from SVPA and HVPA groups were individually housed in cages equipped with 365-mm (diameter) running wheel coupled to turn counter (type 304 stainless steel). The wheel revolutions were recorded daily from a digital counter between 08.00 and 10.00 h.