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Review

Modulation of hepatic redox status and mitochondrial metabolism by exercise: Therapeutic strategy for liver diseases

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ABSTRACT

Liver steatosis (non-alcoholic fatty liver disease, NAFLD) is deemed as the hepatic face of the metabolic syndrome, with both physical inactivity and hypercaloric/unbalanced diet, together with increasing age playing a role as predisposing factors. Consequently, one of the most effective strategies used to counteract this scenario is physical exercise.

Given the importance of redox signaling in cellular remodeling, in which mitochondria are closely implicated along with important roles on substrate oxidation, here we briefly review the effects of both acute and chronic forms of physical exercise on the modulation of hepatic redox state, highlighting the relevance of mitochondrial metabolism and function in the induction of liver phenotypes that antagonize metabolic alterations associated with liver metabolic diseases.

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1. Introduction

Sedentary behavior is very prevalent and associated with the so-called metabolic syndrome (MetSyn). Notably, as the prevalence of MetSyn increases worldwide, so does the prevalence of liver steatosis, another trait associated with the MetSyn (Grattagliano et al., 2011, 2012).

A considerable amount of information has been collected regarding the systemic and tissue effect of physical exercise in the prevention/treatment of many pathologies, including those that do not primarily affect skeletal and cardiac muscles (Pedersen and Saltin, 2006). The liver, an active non-contractile metabolic tissue, with important xenobiotic detoxification and bioenergetic functions, has an important role in several metabolic alterations associated with pathological states. Given their key role in energy production, pH regulation, calcium and redox homeostasis, liver mitochondria are essential sensors of toxicity as mitochondrial and cellular pathologic phenotypes are most of the times associated (Begriche et al., 2006; Oliveira, 2011). In this regard, studies highlight the effects of exercise, and the underlying mechanisms involved in the induction of mitochondrial biogenesis in several tissues besides skeletal muscle, in which the liver is included (Little et al., 2011).

Oxidative stress-based etiologic theories, in which mitochondrial metabolism and (dys)function play a central role, argue that degenerative liver phenotypes are primarily due to the accumulation of oxidative

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damage to cellular components (Droge, 2002). However, and according to the hormesis concept, environmental interactions that enhance the ability of an organism to either decrease the production of reactive oxygen and nitrogen species (RONS) or up-regulate antioxidant and other cellular defenses may delay the consequences of oxidative/nitrosative damage accumulation (Ji et al., 2010). Physical exercise induces a mild RONS production increase and regulate endogenous antioxidants in many body fluids and tissues, including the liver (Jackson et al., 2010; Liu et al., 2000). With this, we hypothesize that the hormesis concept can be applied to exercise-induced gene expression of hepatic antioxidant, anti-apoptotic molecules and metabolic enzymes. In support of exercise-induced hormetic response is the fact that some pathways in mammalian cells are regulated by cellular redox environment (Droge, 2002; Ray et al., 2012). As a result of exercise-induced increased RONS production, one possible outcome is an up-regulation of defense mechanisms in the cell (Powers and Jackson, 2008). Consequently, studies provide evidence for the benefits of physical exercise and high aerobic capacity against the harmful effects of several liver pathological conditions (Tables 1–4).

The effects of acute and chronic exercise on the modulation of hepatic resilience to pathological conditions are analyzed, emphasizing how exercise modulates tissue and mitochondrial redox state, metabolism and function. The possible translation and contribution of exercise-related mechanistic adaptations into a phenotype more suitable to withstand pathological deviations including fatty liver-related diseases are discussed.

2. Acute exercise-induced hepatic oxidative stress and damage

Physical exercise increases free radical production in intact or homogenized muscle and liver tissues (Davies et al., 1982; Dillard et al., 1978). Since then, an increasing interest has been put forward regarding the mechanistic role of free radicals in tissue alterations/adaptations resulting from acute and chronic exercise (Ascensao et al., 2005, 2007, 2012a,b). Despite most studies focused on striated muscle, less attention was devoted to other tissues such as the liver. Several studies reported signs of increased oxidative damage in the liver resulting from acute exercise (Lew and Quintanilha, 1991; Venditti and Di Meo, 1996; Venditti et al., 1999, 2005) while other failed to observe these alterations (Atalay et al., 2004; Gul et al., 2002; Liu et al., 2000; Vina et al., 2000). Augmented liver RONS production and its by-products, and susceptibility to RONS-induced damage have been reported after acute exercise (Venditti and Di Meo, 1996; Venditti et al., 2005). Moreover, glutathione (GSH) and vitamin E are also decreased after acute exercise (Leeuwenburgh and Ji, 1995, 1996; Venditti et al., 2005), which is indicative of hepatic redox state alterations during and after exercise.

Although acute forms of exercise, particularly long-term and exhaustive, may result in negative consequences for the hepatic tissue, no clear reference exists in literature indicating massive structural and/or functional hepatic impairment. Despite the physiological meaning of exercise-induced oxidative damage is not yet definitely established, hormesis-based interpretation of these effects appears to be promising in the context of cellular adaptation to second-hit stimuli and favorable remodeling.

3. Alterations of liver mitochondrial bioenergetics and redox state induced by acute exercise

Although not as much energy-dependent as muscles, the liver is a highly metabolic tissue, with mitochondria having a very important role in cell physiology. Oxidative phosphorylation is based in a series of redox reactions, with electron transfer through the mitochondrial respiratory chain being coupled to the build-up of a proton motive force (Δp) across the inner mitochondrial membrane (Fig. 1a). During this process, electrons can univalently reduce oxygen in distinct sites of the respiratory chain. This process leads to superoxide anion generation and downstream reactions can form other reactive oxygen species (ROS), including hydrogen peroxide. Also, mitochondria can be sources of reactive nitrogen species (RNS) through a specific mitochondrial isoform of nitric oxide (NO) synthase (Tatoyan and Giulivi, 1998). Both endogenous and exogenous NO contribute to regulate mitochondrial metabolism through several mechanisms (Giulivi, 1998), including by reversible inhibition of cytochrome *c* oxidase (Sarti et al., 2012). Despite its physiological role, NO can react with superoxide anion and originate peroxynitrite, a very reactive RNS (Sarkela et al., 2001). Therefore, mitochondria are not only important RONS sources, responsible for the regulation of several redox-dependent transcription factors (Ray et al., 2012), but are also the primary targets of their own uncontrolled RONS production.

As opposed to the traditional idea of oxidative stress as an unbalance between oxidant production and antioxidant activity, a more audacious theory proposed the concept of redox compartmentalization, in which specific redox environments interact in cells both under normal and stressed conditions (Jones and Go, 2010). This idea proposes that in the absence of global oxidative stress causing macromolecular damage,

Table 1
Effects of acute exercise bouts on liver tissue oxidative stress, damage and antioxidant markers.

Exercise protocol	Alteration(s)	Reference
42 min treadmill running	↑ %GSSG	Lew and Quintanilha (1991)
5 and/or 8 h exhaustive swimming	↑ MDA, HP, carbonyls, GR ↓ GSH, Ca, = Vit E, GPx	Venditti and Di Meo (1996), Venditti et al. (1999, 2005)
5 h swimming in hyperthyroid rats	↑ MDA, carbonyls, in vitro susceptibility to ROS ↓ Vit E, = GPx, GR	Venditti et al. (2005)
Exhaustive running (young and old rats)	= DCF oxidation, MDA, carbonyls, GR ↓ GPx	Bejma et al. (2000)
Exhaustive running	= TGSH, GSH, GSSG, GR, GST, GCS, GPx, CAT, conjugated dienes, HSP60, G6PDH, carbonyls, Vit E, CoQ, oxo8dG ↑ GPx, MDA, TGSH, 4-HNE, Vit C, GSSG ↓ GSH, GSH/GSSG, TGSH, GGT, GS, cysteine, cystin	Atalay et al. (2000, 2004), Gul et al. (2002), Leeuwenburgh and Ji (1996), Liu et al. (2000), Oksala et al. (2006), Sen et al. (1997), Vina et al. (2000)
15 × 30 s sprint bouts	= SOD, GPx, MDA	Kayatekin et al. (2002)
~200 min exhaustive swimming	↓ GSH, GSSG, GSH/GSSG, TGSH, CS, GGT = GPx, GR, GCS, GST, GGT, SOD ↑ MDA, GPx	Leeuwenburgh and Ji (1995, 1998)

↑—increase, ↓—decrease, =—unaltered, 4-HNE—4-hydroxynonenal protein adducts, Ca—antioxidant capacity, CAT—catalase, CoQ—coenzyme Q, CS—citrate synthase, DCF—dichlorofluorescein, G6PDH—glucose-6-phosphate dehydrogenase, GCS—γ-glutamylcystein synthetase, GGT—γ-glutamyltranspeptidase, GPx—glutathione peroxidase, GR—glutathione reductase, GS—glutamine synthetase, GSH—glutathione, GSSG—glutathione disulfide, GST—glutathione-S-transferase, HP—hydroperoxides, HSP—heat shock proteins, MDA—malondialdehyde, oxo8dG—8-hydroxy-2′-deoxyguanosine, ROS—reactive oxygen species, SOD—superoxide dismutase, TGSH—total glutathione, Vit C—vitamin C, Vit E—vitamin E.