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REVIEW ARTICLE

Oxidative stress and inflammation: liver responses and adaptations to acute and regular exercise

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ABSTRACT

The liver is remarkably important during exercise outcomes due to its contribution to detoxification, synthesis, and release of biomolecules, and energy supply to the exercising muscles. Recently, liver has been also shown to play an important role in redox status and inflammatory modulation during exercise. However, while several studies have described the adaptations of skeletal muscles to acute and chronic exercise, hepatic changes are still scarcely investigated. Indeed, acute intense exercise challenges the liver with increased reactive oxygen species (ROS) and inflammation onset, whereas regular training induces hepatic antioxidant and anti-inflammatory improvements. Acute and regular exercise protocols in combination with antioxidant and anti-inflammatory supplementation have been also tested to verify hepatic adaptations to exercise. Although positive results have been reported in some acute models, several studies have shown an increased exercise-related stress upon liver. A similar trend has been observed during training: while synergistic effects of training and antioxidant/anti-inflammatory supplementations have been occasionally found, others reported a blunting of relevant adaptations to exercise, following the patterns described in skeletal muscles. This review discusses current data regarding liver responses and adaptation to acute and regular exercise protocols alone or combined with antioxidant and anti-inflammatory supplementation. The understanding of the mechanisms behind these modulations is of interest for both exercise-related health and performance outcomes.

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Introduction

Historical evidence indicates that regular exercise has been long used for health-related purposes. As early as 2500 BC health control programs based on exercise training were described in China [1]. During the Greco-Roman period, first Hippocrates (460–370 BC) and then Galen (129–210 AC), recognized exercise as a healthy and prophylactic treatment against several diseases [2]. The same conclusion was reached by the philosopher Plato, who stated that "lack of activity destroys the good condition of every human being, while movement and methodical physical exercise save it and preserve it". Indeed, current evidence still support these statements, as regular exercise has been long recognized as an effective and not invasive method for health improvement through cellular, molecular, and biochemical pathways [3], which positively impacts on pulmonary, cardiovascular or liver diseases, metabolic conditions, cancer, and neuroimmunological parameters [4–9]. These benefits may be evidenced in all age groups, including children, youth, adults, and elderly [10,11], and have also been associated with reduced mortality [12,13].

Although it is difficult to determine the triggering mechanisms of each and all the aforementioned conditions and diseases, two common etiological phenomena lay behind most of them: chronic inflammatory status and accumulative oxidative damage [14,15]. Indeed, it is currently well-known that chronic low-grade inflammation and oxidative stress play a central role in the etiology of several chronic diseases [16,17]. Interestingly, regular exercise has been implicated in the modulation of both oxidative metabolism and inflammatory status in most, if not all, of the conditions mentioned above [18–20]. However, health benefits of regular

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exercise are associated with volume, intensity, and frequency. It has been shown for decades that intense exercise induces muscle microtraumas and consequently release of inflammatory cytokines into the bloodstream [21,22]. In fact, high intensity exercise may lead to tissue damage, with increased production of reactive oxygen species (ROS) and inflammatory mediators [18,19,23]. Additionally, a single and exhaustive exercise bout can induce a temporary downregulation of the immune system and studies have associated intense exercise with increased infections within two weeks after performance [24].

Nevertheless, most of the current literature addresses effects of acute and chronic exercise on skeletal muscle [25–28], despite of the fact that other tissues are also affected during physical exertion, including the gastrointestinal system. For instance, it is known that exercise induces positive effects on different gastric and intestinal diseases, such as gastroesophageal reflux, peptic ulcer irritable bowel syndrome or non-alcoholic fat liver disease (NAFLD) [29,30]. The last is a remarkable role of exercise, considering NAFLD is currently the most common liver disease in the western world [31], with 25% prevalence in Americans, and 15–35% in Europe and Middle East populations [32–34].

Although interesting studies on liver adaptations and responses to exercise have been performed during the last years, considerably less is known in comparison to skeletal muscle evidence [35,36]. Due to its central metabolic role in detoxification, synthesis and distribution of biomolecules, liver is remarkably important during exercise outcomes, including modulation of ROS and inflammatory mediators [37–39]. Therefore, the understanding of the effects of acute and regular exercise upon the liver and how this major metabolic organ adapts to these stimuli are important to broaden our knowledge concerning exercise-related health benefits.

Exercise-related metabolic role of the liver

Exercise may be defined as a physiological stress that transitorily disrupts cellular homeostasis beyond the exercising muscles [40]. Indeed, the physiological distress imposed by exercise alters the functioning of different organs, such as cardiac muscle, stomach, brain, and liver [41,42]. In this scenario, it is worth to highlight the liver relevance to exercise, considering its central role in energy supply maintenance to exercising muscles [35]. In this scenario, acute exercise requires a supercompensation of muscle glycogen after the bout [43], while endurance-type training induces a chronic upregulation of glycogen store in the resting muscle in comparison to untrained state [44]. During exercise, rapid muscle glucose uptake is matched by the sum of increased mobilization of hepatic glycogen and gluconeogenesis, as glycogen is at its highest concentration in the liver [45].

In fact, several hepatic adaptations are expected during exercise due to the liver major metabolic roles [36]. Liver has been long recognized as a major regulator of glucose and lipid homoeostasis, with increased activities of the gluconeogenic enzymes as well as decreased lipogenic enzyme activities in response to acute exercise [45,46]. Indeed, during exercise liver glycogen reaches the bloodstream as glucose, and lactate from exercising muscles is converted into glucose in the liver, which greatly contributes to glycogen replenishment [47,48]. Hepatic cells play a central role in carbohydrate and lipid stores regulation, and thus guarantee an adequate substrate supply for vigorous exercise, besides its recycling role converting metabolites into macronutrients, amino acids into proteins, and transforming potential energy into chemical energy [36,49].

Regarding exercise, an acute bout can increase hepatic protein synthesis, while positive adaptations leading to a reduction of hepatic triglycerides occurs during or after regular performance [36]. Acute exercise does not seem to affect hepatic fat content [5]. Additionally, while bouts of moderate-intensity long-lasting exercise seem to reduce plasma triacylglycerol within 24h, shorter bouts showed no effect on its concentration after 8h [50]. Considering chronic exercise, evidence demonstrates increased expression of hepatic enzymes and overall reduction in hepatic fat levels. The augmented energy expenditure induced by exercise provokes a negative energy balance, which may be associated to hepatic mobilization of lipids to fuel substrates demands [5]. It has been reported that exercise improves serum liver enzymes and modulates hepatic lipid metabolism, favoring hepatic fatty acid oxidation, affecting very low-density lipoproteins (VLDL) secretion and reducing hypertriglyceridemia [51–53]. Indeed, 6 months of aerobic exercise training resulted in lower VLDL-apolipoprotein-B100 secretion rate in obese type 2 diabetes mellitus (T2DM) patients [54].

Hepatic adaptations to exercise should be expected considering the major role in energy maintenance played by this organ [45,55,56]. However, studies on the modulatory effect of exercise upon the redox-status and inflammatory processes in the liver are still incipient. Similarly, hepatic metabolic responses to antioxidant and anti-inflammatory intake during exercise have received even less attention, despite the common use of such supplementations by exercise practitioners and athletes [57]. Considering the ever-increasing supplementation strategies used in sports and the

aforementioned role of the liver in detoxification, it is highly relevant to unmask the effects of these compounds on hepatic metabolism.

Exercise, oxidative stress, and liver metabolism

It is currently known that intense and prolonged exercise significantly restricts visceral blood flow, which temporarily deprives oxygen supplies to tissues and thus triggers ROS overproduction [36]. Upregulation of heat shock proteins (HSP), which are transient and expected alterations also taking place in the exercising liver, seem to support this hypothesis [58,59]. Hepatic adaptations to exercise have been linked to redox status modulations triggered by exercise-related ROS production [60,61].

Despite the scarce data available on exercise-related liver redox status [35,62], intense exercise has been related to hepatic functional impairment, oxidative stress, and inflammation, among others [63–65]. In the liver, oxidative stress can reflect an unbalance between protein synthesis and the ability of the hepatocyte endoplasmic reticulum to fold and assemble proteins correctly, with an increased production of superoxide, a decrease buffering capacity, and/or a decrease activity of important antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) [66–71].

Liver plays a remarkable role in redox status, considering that 90% of the circulating glutathione (GSH) levels are produced in this organ [66,72]. In fact, hepatic GSH levels have been described to increase after exhausting exercise in both young and old animals, which reflects homeostasis disturbance by oxidative stress [73,74]. Under low GSH levels, mitochondrial function may be hampered and thus several stress-related signaling pathways are triggered, which finally results in mitochondrial injury, inflammation, and steatosis in the liver [75]. Mitochondrial ROS formation, due to increased oxygen consumption during intense exercise, is one of the main causes of liver injury [76].

The disruptions induced by the challenge of an acute bout of exercise on liver metabolic and redox status, particularly at mitochondrial level, possibly results in increased resistance to deleterious insults in the long term [77]. In fact, regular exercise, such as endurance training or voluntary running, seems to favorably modulate hepatic pathways associated to a more resistant phenotype than stressed/diseased animal models [78,79]. Lately, few studies have reported the effects of exercise and the underlying mechanisms involved in mitochondrial biogenesis in the liver [80]. Regular exercise has been found to enhance hepatic antioxidant capacity, redox status and thus mitochondrial functioning [35,74]. Sun and cols [81] found elevated GSH levels in rat liver mitochondria after 4 weeks of training, which was attributed to an increased antioxidant activity. Navarro et al. [82] and Lima et al. [74] both reported that moderated exercise increases mitochondrial superoxide dismutase (MnSOD) activity and decreases mitochondrial oxidative stress markers (malondialdehyde [MDA] and proteins carbonyls) in the liver of trained rats. It seems that regular exercise may induce favorable adaptations of liver mitochondria similarly to other metabolic organs.

Oxidative stress-based etiologic theories, in which mitochondrial metabolism and (dys)function play a central role, indicate degenerative liver phenotypes as primarily factors due to the accumulation of oxidative damage to cellular components [83]. Repeated exposure to sub lethal, low-rate, and chronic stress has been proposed to induce stress resistance and survival rates due to a process named adaptation, or even, hormesis. Similarly, for sublethal, low-rate, and chronic ROS-dependent processes generated from mitochondria, it was recently proposed on a hypothetical basis the term "mitohormesis" [84–87], which can be mimetized by regular exercise practice. According to the ROS-associated hormetic theory for exercise adaptations of Radak et al. [88], exercise-related ROS production induces significant, but rather tolerable, damage which in turn modulates exercise adaptations. Since then, the discussion on the hormetic role of exercise-related ROS production has vastly increase [77,89–91], which may be also applied to the liver [92].

Antioxidants and exercise: liver effects

Due to intense exercise deleterious effects, several nutritional interventions have been studied to counteract the derived damage. In fact, antioxidant supplementation strategies to quench exercise-related ROS production have been vastly studied during the last 20 years [93,94]. While some studies found supplementation with ROS scavengers (such as antioxidant vitamins) to be unable to prevent exhaustive exercise distress both in animals and in humans models [95,96], foods containing indirect antioxidants or molecules able to induce antioxidant/detoxifying systems may suppose an alternative nutritional approach to counteract intense exercise induced stress [97].

Whereas antioxidant molecules have been used in acute exercise protocols in order to counteract the archetypal ROS overproduction, studies concerning the effects of antioxidant supplementation on liver are still incipient. Recently, Carfagna et al. [98] found that ten

days' dietary supplementation with 1% *Galdiera sulphuraria* reduced the levels of lipid hydroperoxides and protein carbonyls in liver homogenates of rats submitted to 6 h of continuous swimming, which was accompanied by increases on GSH levels and GSH/GSSG. Interestingly, increases of oxidative stress markers derived by exercise paralleled respiration unbalance, with increases on state 4 and decreases on state 3 respiration of both tissue and mitochondria homogenates of liver; *Galdiera sulphuraria* reverted these effects even though hydrogen peroxide (H_2O_2) production was not affected. Authors concluded the alga may be able to reduce ROS sources outside mitochondria, considering its peroxyl radicals' scavenger or lipid hydroperoxides metabolization activities. In this line, the exercise-related increases on GPx and glutathione reductase (GR) were not blunted.

Similarly, 4 weeks of *Rhodiola rosea* supplementation increased time to exhaustion in rats submitted to forced swimming (90 min) [70]. Exercise-related increases on superoxide and MDA production in the liver of rats were blunted by *Rhodiola rosea* supplementation, which was associated with increases on Cu/ZnSOD and MnSOD protein content in the liver [70]. On the same line, L-arginine supplementation was found to reduce MDA content in the liver of rats submitted to exhaustive treadmill running (10° slope) [69], which was associated with increases on xanthine oxidase (XO) and myeloperoxidase (MPO) activities. Korivi et al. [67] also found an antioxidant supplementation (ginsenoside-Rg1, 0.1mg/kg body weight) to attenuate SOD, GPx, and CAT reductions in liver of rats after exhaustive swimming exercise (3% body weight workload), while XO activity was decreased. The upregulation on the antioxidant enzyme activities was associated with a decrease in thiobarbituric acid reactive substances (TBARS), protein carbonyls, and nitric oxide (NO) levels after exercise in the liver of supplemented rats [67].

Contradictory results with acute exercise antioxidant supplementation have been also reported, as oral grape seed polyphenols were found to increase hepatic MDA content and NO levels in rats after a treadmill running until exhaustion, which was also associated with decreased total antioxidant levels [99]; MDA increases after exercise could be linked to the major role of liver on polyphenols' metabolism, while the rise in NO would be related to the increase in nitric oxide synthase (NOS) activity mediated by the grape seed. Finally, authors suggested grape seed may increase liver resistance to oxidative stress *per se*, which could explain the decreases on total antioxidant levels [99].

Regarding training, the deleterious effects of antioxidant intake on exercise remains uncertain in both skeletal muscle and liver tissues [100]. Part of the controversy relies on the highly variable uptake of these compounds from different tissues, non-specific cellular compartmentalization and complex dosage dependent on pro-oxidant/anti-oxidant properties that are unclear on *in vivo* models [101]. Thus, intake of antioxidant compounds may be either positive or harmful [97,102–105].

Antioxidant supplementation has been shown to improve liver metabolism during exercise. For instance, it has been suggested that quercetin supplementation combined with chronic swimming at moderate intensity (60min 5days/week, 4weeks) exercise exerts a protective effect in diabetes by attenuating hyperglycemia-mediated oxidative stress in hepatic tissue of rats [105]. In this case, both exercise training and antioxidant treatment acted synergically to diminish diabetes-associated oxidative stress in the liver. Similarly, a recent study showed that broccoli extract-enriched diet increased GR, CAT and glutathione S transferase (GST) activities in rat liver after intense exercise on a treadmill with 7° slope, which was associated to decreases in cholesterol oxidation products [97]. In addition, a combination of a diet containing 2% *Jussara Açaí* pulp and exercise training on a treadmill improved the hepatic oxidative status of mice and attenuated hepatic steatosis [106]. Similarly, a positive association between caffeine and a moderate-intensity swimming exercise protocol (3% body weight workload) has been demonstrated in the liver of middle-aged rats [107]. In this study, the experimental protocol resulted in an increased ratio of reduced/oxidized glutathione (GSH/GSSG), leading to the conclusion that exercise training combined with caffeine supplementation may induce positive adaptations in the hepatic redox status [107].

Considering exercise performance, swimming training combined with grass carp protein or peptide supplementation prolonged time to exhaustion in mice when compared to control animals, although high peptide dose presented better results [108]. Authors partially attribute this fatigue-preventing effect to a 7- to 10-fold increase on liver glycogen storage afforded by high dosage of protein and peptide, respectively. These results were associated with increased SOD, CAT, and GPx activities in serum of supplemented animals, which could be also related to increased performance considering the role of ROS on fatigue [108].

In another study, eight weeks of chronic treadmill running combined with creatine did not affect MDA and GSH levels in rats, while GPx and CAT enzyme activities were increased [109]. Interestingly, a decreased SOD activity, which was partially explained by an inhibitory effect of increased H_2O_2 levels, was reported [110].

Authors hypothesized that creatine could have directly neutralized ROS independently of antioxidant enzyme activities as previously reported by Sestili et al. [111]. Contrarily, Yoon and Park [112] found that five weeks of treadmill running combined with soy isoflavones supplementation increased SOD activity and CAT activities, which was associated to decreased TBARS levels on the liver of training rats, despite unchanged GPx levels.

Consistently with the concept of mitohormesis, it has been demonstrated that exercise-induced oxidative stress ameliorates insulin resistance and causes an adaptive response promoting endogenous antioxidant improvements [94]. As such, antioxidant intake may preclude health-promoting effects of regular exercise [94], such as redox-related adaptations in the liver [37]. Indeed, vitamin E, one of the most routinely consumed dietary antioxidants worldwide, has been shown to inhibit liver redox-related adaptations to exercise training [113]. In this study, rats submitted to chronic swimming presented decreased levels of relevant antioxidant- and mitohormetic-related transcription factors in the liver, such as nuclear factor erythroid 2–related factor 2 (NRF-2) and peroxisome proliferator-activated receptor gamma coactivator *1*-alpha (PGC-1α), respectively. Authors also found protein carbonyls and hydroperoxides production to be unchanged in trained and supplemented animals, although antioxidant defenses were lower. It was concluded that vitamin E may decrease exercise-related mitochondrial biogenesis, thus hampering important training adaptations. Similarly, we have also reported that caffeine supplementation exerts antioxidant effects in the liver of trained rats (swimming with 5% body weight workload), which dumped the expected TBARS increases derived from exercise training [37]. Likewise, SOD CAT, and GPx activities were unaffected by training and caffeine combined, suggesting that caffeine blunted exercise-related adaptations in the liver, similarly to evidence described in skeletal muscle of healthy young men [94]. Please revise Table 1 for detailed information about these studies.

Exercise, inflammation, and the liver

It has been long known that acute, high-intensity or unaccustomed exercise triggers several inflammatory-related pathways in skeletal muscle [114–116]. Post-exercise humoral and local changes resemble acute-phase responses to tissue trauma/inflammation, including proinflammatory cytokine production, mobilization, and migration into the muscle to mediate leukocyte infiltration [117]. These are key mechanisms to the onset of local inflammation and vasodilatation [118].

To date, only a few studies have reported the effects of acute exercise upon inflammatory pathways in the liver. Huang et al. [64] found exhaustive exercise to induce significant hepatic inflammation through inflammatory cell infiltration in rats, and acute exercise induces cytokine/cytokine receptor signaling in the liver, with upregulation of chemokine ligands, IL-11 receptor, and IL-1 in rodent models. For instance, IL-11 belongs to the IL-6-type family of cytokines that triggers Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway and the upregulation of suppressor of cytokine signaling (SOCS)-3 [119], which are, together with nuclear factor kappa B (NF-kB), among the most relevant signaling pathways in liver inflammation [120]. Interestingly, we have also found IL-6 and IL-1β to be increased in liver homogenate after an acute bout of exercise in rats through NF-kB activation [38].

On the opposite, regular exercise has been considered a powerful anti-inflammatory tool when performed at controlled intensities [11,121]. For instance, regular exercise is associated with reduced inflammatory cytokines, adipokines, and other injury-related markers in the liver [122–125]. The exercise training anti-inflammatory hypothesis has been increasingly investigated during the last decade [126]. It seems moderate-to-high intensity training induces anti-inflammatory pathways through several mechanisms, including the suppression of pro-inflammatory cytokines [127], endothelium anti-inflammatory status improvement [128], and down-regulation of toll-like receptors (TLRs) expression [11]. The anti-inflammatory effects of exercise are not only mediated by visceral fat reduction, but also through an anti-inflammatory cascade induction after each exercise bout [129,130]. This is partially due to the fact that some anti-inflammatory mediators, such as the cytokines IL-4, IL-10, and IL-13, which are released during exercise [131], also modulate miogenesis [132,133]. As such, regular exercise increases muscle mass (or blunts atrophy) partially due to a modulation on the inflammatory/anti-inflammatory balance required by skeletal muscle growth [134].

In this sense, a major crosstalk between liver and skeletal muscle occurs during exercise in order to orchestrate inflammatory modulation. For instance, muscle contraction-derived IL-6 triggers production of several cytokines and anti-inflammatory signaling pathways [135], and is considered a key mediator of exercise acute effects [126,136]. On the opposite, during chronic inflammation IL-6 activates monocytes and macrophages via TNF-α stimulation, while muscle contraction triggers IL-6 activation independently to

Table 1. Exercise-related modulation of liver redox status.

Study	Exercise type	Drug/diet	Model	Exercise Exercise + treatment	Gender
Huang et al., 2008	Acute/treadmill 10° slope, 30 m/min until exhaustion	Diets with 2% L-arginine for 30 days	Sprague–Dawley rats	↑XO, MPO, MDA ———— ↓XO, MDA	M
Huang et al., 2009	Acute/swimming 90 min swimming	125 mg/day of *Rhodiola rosea* extracts for 4 weeks	Wistar rats	↑Superoxide, MDA ————- ↓Superoxide, MDA ↑Cu/Zn-SOD, CAT	M
Ren et al., 2011	Chronic/swimming 25 min/day, 4 weeks	Grass carp protein diet – 5 mg/g/day, 4 weeks	National Institutes of Health Mice	Control ———— ↑SOD, CAT, GPx	M
Korivi et al., 2012	Acute/swimming 3% body weight load swimming until exhaustion	0.1 mg/kg for 10 weeks of *Panax ginseng* extracts.	Sprague–Dawley rats	↑MDA, PC, XO, NO ↓GSH, SOD, CAT, GPx ———— All changes reverted	M
Araújo et al., 2013	Chronic/treadmill 26 m/min – 40 min/day, 5 days/week, 8 weeks	Diet with creatine 2%/day for 8 weeks	Wistar Rats	↑H_2O_2, GPx ———— ↑H_2O_2, GPx ↓SOD ↑CAT	M
Belviranli et al., 2013	Acute/treadmill 30 m/min – until exhaustion	Grape seed extract 100 mg/kg/day for 6 weeks	Sprague–Dawley rats	↑MDA, NO, XO ———— ↑MDA, NO ↓AOA, XO	M
De Castro et al., 2014	Chronic/treadmill 16 m/min – 1 h/day, 5 days/week, 12 weeks	*Açaí* fruit pulp 3.25 g/kg/day for 12 weeks	ApoE$^{-/-}$ Mice	↓Lipid droplets ———— ↓Lipid droplets	M
Cechella et al., 2014	Chronic/swimming 3% of body weight, 20 min/day, 4 weeks	Caffeine 30 mg/kg – 5 days/week, for 4 weeks	Wistar Rats	↑GSH ———— ↑GSH	M
Barcelos et al., 2014a	Chronic/swimming 5% of body weight – 50 min/day – 5 days/week, 4 weeks	Caffeine 6 mg/Kg/day for 4 weeks	Wistar Rats	↑SOD, GPx, MDA ———— All changes reverted	M
Yoon & Park 2014	Chronic/treadmill 20 m/min – 30 min/day, 5 days/week	Isoflavone-rich soy 0.5% diet – 5 day/week for 5 weeks	Sprague–Dawley rats	↑MDA ↓CAT, SOD ———— All changes reverted	M
Venditti et al., 2014	Chronic/swimming 90 min – 5 days/week, 10 weeks	Vitamin E 700 mg/Kg/day for 10 weeks	Wistar rats	↓Hydroperoxides, PC ↑NRF-1, NRF-2, PGC-1, GPx ———— All changes reverted	M
Carfagna et al., 2015	Acute/swimming 6 h swimming	Diet with *Galdieria sulphuraria* 1% diet for 10 days	Wistar rats	↑HPS, PC, ↓GSH ———— All changes reverted	M
Chis et al., 2016	Chronic/swimming 60 min/day – 5 days/week, 4 weeks	Quercetin 20 mg/Kg/day for 4 weeks	Diabetic Wistar rats	↑MDA, PC ↓SOD, CAT, GSH ———— ↑SOD, CAT, GSH	M
Cardenia et al., 2016	Acute/treadmill 7° slope and speed risen up to 24 m/min	Broccoli extract-enriched die BE for 45 days (2.5 mg of supplement/g of diet)	Wistar rats	↓ CAT, ↑COPs ———— ↑GST, GR and CAT ↑COPs	F

COPs: Cholesterol oxidation products; GST: Glutathione-S-transferase; GR: glutathione reductase; GPx: glutathione peroxidase; CAT: catalase; XO: xanthine oxidase; MPO: myeloperoxidase activities and in lipid peroxidation end-product (MDA: malondialdehyde; PC: protein carbonyl; GSH: reduced glutathione; HPS: Lipid hydroperoxides; AOA: antioxidant activity; NFR: Nuclear respiratory factor; PGC-1: Peroxisome proliferator-activated receptor gamma coactivator 1).

previous responses from TNF-α, suggesting a possible metabolic role of this cytokine [136,137]. As such, IL-6 plasma levels are exponentially elevated during and after exercise [138–141] reaching out to various tissues, including the liver [140,142,143]. In the liver, IL-6 modulates hepatocyte homeostasis and mitogen activities, and exerts a vital role in the acute phase response as well [144].

Different studies have addressed the effects of exercise training on liver-related metabolic diseases/conditions. In this scenario, treadmill training was able to decrease hepatic TNF-α levels in mice with high-fat diet and high-fructose water, which was corroborated by decreased fibrosis markers [145]. Exercise training was also shown to reduce IL-1β, IL-6, and transforming growth factor β (TGB-β) of high-fat feed rats, which was

associated to improvements on the insulin sensitive index (in sedentary normal diet as well) [146]. Surprisingly, it has been reported that 10-weeks of voluntary wheel running (VWR) did not protect against increases in the hepatic expression of TNF-α, IL-6, and IL-1β induced by LPS administration in ∼22-month-old C57BL/6J mice [147]. Contrarily, other authors have found that 10-weeks of VWR attenuate the inflammatory response to LPS within the liver of mice [131]. Exercised mice also show an increase of the hepatic chemokine CXCL-1 which attracts neutrophils and is involved in inflammation and wound healing; muscle-derived IL-6 seems to be triggered by this response [140].

An interesting condition regarding liver injury and exercise training is NAFLD, which is characterized by fat accumulation as triglycerides in the liver, and is associated to long periods of physical inactivity [148]. This is a progressive liver disease ranging from simple steatosis (triglyceride storage ∼5% by weight), to non-alcoholic steatohepatitis (NASH), fibrosis, and cirrhosis in the absence of excess alcohol consumption (<20 g/day) [149]. Considering its etiology, inflammation and ROS overproduction are among the main factors leading to NFALD [150]. Moreover, recent studies indicate that alterations of the innate immunity may be linked to NAFLD, which is consistent with the fact that liver is a major immune organ [31]. Food restriction and exercise training are known to prevent and improve NAFLD-related outcomes [151]. Although the efficacy of these lifestyle modifications in the treatment of liver fibrosis remains unclear, weight management treatments, which include energy restriction and exercise training, are broadly prescribed [152,153]. Indeed, a recent meta-analysis by Orci et al. [154] found that exercise reduced intrahepatic lipid content, blood levels of alanine and aspartate transaminases, and body mass index (BMI), while peripheral insulin sensitivity was increased in individuals with NAFLD. Comparison among exercise modalities indicated that aerobic training associates to more profound reduction in intrahepatic lipid content when compared to resistance training [154]. Contrarily, a systematic review by Hashida et al. [6] has found no differences between the two exercise modalities regarding changes on BMI, serum levels of ALT or intrahepatic lipids, concluding that both may improve NAFLD equally, despite the clear difference on maximal oxygen uptake and METs during exercise [6]. Golabi et al. [155] also found that exercise was able to reduce intrahepatic triglyceride content regardless the training modality. Therefore, exercise has been considered an effective non-pharmacological intervention to NAFLD individuals [156].

Anti-inflammatory drugs and exercise: liver effects

Animal models are widely used to study molecular mechanisms modulated by exercise [35]. Although data concerning effects of anti-inflammatory supplementation on exercise-related inflammatory pathways in the liver are scarce, the existing literature indicates similar results to those observed in skeletal muscle. In fact, it has been found that quercetin reduces liver content of IL-6 and TNF-α in mice after an intense treadmill running with 5° slope [157]. Another study demonstrated that freshwater clam extract supplementation improved endurance time to exhaustion in treadmill running (10° slope) and reduced muscle damage induced by an acute bout of exhaustive exercise in rats, attenuating exercise-induced inflammatory response and liver injury markers, such as CK, LDH, AST, ALT, and TNF-α, which indicates a potent hepatic anti-inflammatory effect [158]. However, anti-inflammatory drugs intake should be taken cautiously considering hepatic metabolism. The detoxification role of liver is mainly performed by cytochrome P450 (CYP) enzymes, which are abundantly present in this organ in comparison to other tissues [159]. CYPs are responsible for almost 80% of all phase I metabolism reactions, and have also been described to participate on the metabolism of broadly known anti-inflammatory drugs, such as the non-steroidal anti-inflammatory drugs (NSAIDs) [160].

Traditional NSAIDS, such as diclofenac, ibuprofen, and naproxen, inhibit cyclooxygenases enzymes (COX) and their effects are still partially unknown and controversial [161–163]. NSAIDs are responsible for 70 million prescriptions per year, while 30 billion purchases are annually made without prescription [164–166]. In sport scenarios, NSAIDs intake has been frequently reported during the last decade [167,168]. Excessive NSAID consumption by professional athletes made this medication class one of the most utilized in sports field [169] in different modalities [170].

In sports, the role of COX-1 and COX-2 inhibition on muscle damage has been recently studied due to NSAIDs effects upon inflammation and pain sensitization. As previously mentioned, NSAIDs anti-inflammatory mechanism is based on the inhibition of COXs, selectively or not. The consequence is a decrease on cytokines secretion by macrophages at the injury site, which reduces the inflammatory response and related pain sensitization [171]. However, studies regarding the regulation of COX-2 expression after muscle damage are still incipient and controversial. While some report upregulation [172–174] others have not found COX-2 expression to be altered after muscle injury in humans [175,176].

Table 2. Exercise-related modulation of liver inflammatory status.

Study	Exercise type	Drug/diet	Model	Exercise Exercise + Treatment	Gender
Huang et al., 2013b	Acute/treadmill 10° slope, 30 m/min, until exhaustion	Freshwater clam extract 20 mg/kg for 7 days	Wistar–Kyoto rats	↑CPK, LDH, AST, ALT, lactate, TNF-α ↓Glucose, IL-10 ———— All changes reverted	M
Barcelos et al., 2014b	Chronic/swimming 5% of body weight – 50 min/day – 5 days/ week, 4 weeks	Caffeine 6 mg/Kg/day for 4 weeks	Wistar rats	↓MPO ———— ↓MPO, AChE	M
Cechella et al., 2014	Chronic/swimming 3% of body weight, 20 min/day, 4 weeks	Caffeine 30 mg/kg – 5 days/week, for 4 weeks.	Wistar rats	No changes ———— ↓IL-1β, INF-ɤ, TNF-α ↑GSH/GSSG	M
Barcelos et al., 2016	Acute/treadmill −16° slope – 16 m/min, 90 min	Diclofenac 10 mg/Kg/day for 7 days	Wistar rats	↑TLR4, MyD88, TRIF, NFκB ↑IL-6, TNF-α, iNOS ———— ↓TLR4, MyD88, TRIF, NFκB IL-6, TNF-α	M
Knudsen et al., 2016	Chronic/wheel 20 km/week, 16 weeks	High-fat diet for 16 weeks	C57BL6 mice	↑IL-6, PEPCK, G6Pase, PDK ———— All changes reverted	M
Tang et al., 2016	Acute/treadmill 5° slope 28m/min, 90 min/day, 1 week	Quercetin 100 mg/Kg/day during 5 weeks	BALB/C mice	↑AST, ALT, MDA, ROS ↓GSH ↑IL-6, TNF-α ↓IRE1, PI3K ↑PERK, NFκB, ATF6, JNK ———— All changes reverted	M

PEPCK: Phosphoenolpyruvate carboxykinase; G6Pase: hepatic glucose-6-phosphatase; PDK: pyruvate dehydrogenase kinase; TLR: toll-like receptor; MyD88: myeloid differentiation primary response gene 88; TRIF: TIR domain containing adaptor inducing interferon; NF-κB: nuclear factor kappa B; IL: interleukin; iNOS: Inducible nitric oxide synthase; TNF-α: tumor necrosis factor-α; INF-ɤ: interferon-ɤ; CPK: creatine phosphokinase; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ROS: Reactive oxygen species; JNK: Jun N-terminal kinase; ATF6: activating transcription factor 6; PERK: anti-p-protein kinase RNA-activated like ER kinase; PI3K: phosphoinositide 3-kinase; IRE1: inositol-requiring enzyme 1.

Surprisingly, and despite the aforementioned remarkable metabolic roles of liver during exercise and drug detoxification [36] and the ever increasing NSAIDs intake by athletes, little is known considering these drugs effects on the hepatic tissue. It has been shown that treadmill training attenuates some adverse effects of *in vitro* salicylate on liver mitochondrial toxicity in rats [177]. In this study, authors found that liver mitochondria isolated from the exercise group presented increased tolerance to salicylate effects, which was partially mediated through sirtuin-3 (SIRT-3) increase and caspase 8 decrease, whereas no changes in caspase 3 were detected. Exercise training also decreased basal mitochondrial states 3 and 4 respiration, while membrane potential remained unchanged and mitochondrial permeability transition pore induction (MPTP) were unaffected. Authors concluded exercise training did not alter basal liver mitochondria function, although some adverse effects of salicylate were attenuated.

On the opposite, a study by Santos-Alves et al. [39] found exercise to prevent diclofenac-induced decreases in membrane potential, increased state 4 respiration and MPTP susceptibly in treadmill trained or VWR rats. Additionally, both exercised groups presented increases on complex IV oxidative phosphorylation (OXPHOS) subunit, SIRT-3 and B-cell lymphoma 2 (Bcl-2), which was associated with decreased caspase 9 activity. Authors concluded that exercise may be considered a valid non-pharmacological strategy to be applied in subjects with toxicity risk factors for several clinically used drugs, such as diclofenac. However, although interesting, these studies have not access the effects of NSAIDs and exercise on hepatic inflammatory pathways.

Recently, we have conducted studies concerning the effects of anti-inflammatory drugs on hepatic metabolism [107,178]. We found moderate-intensity swimming training (3% body weight workload) combined with caffeine supplementation to reduce pro-inflammatory cytokines with concomitant increases of IL-10 levels in middle-aged rats, which was also associated to enhanced hepatic redox status [107]. In another study, swimming training (5% body weight workload) positively modulated plasma acetylcholinesterase and MPO activities in young rats supplemented with caffeine,

which was associated to positive hepatic adaptations [178]. More recently, a study from our group reported that diclofenac pretreatment attenuated the liver pro-inflammatory response associated with acute eccentric exercise (−16° slope) through a down-regulation of both the myeloid differentiation primary-response protein 88 (MyD88)- and TIR domain-containing adaptor inducing interferon (TRIF)-dependent pathways, which was associated with an activation of TLR4-NFκB signaling pathway [38]. Table 2 depicts the studies' details.

Concluding remarks

This review summarizes the effects of acute and regular exercise upon liver redox status and inflammatory pathways. The hepatic responses to both modalities of exercise seem to be similar to those described in skeletal muscle: while acute protocols challenge the liver, regular exercise induces health-related hepatic adaptations. Indeed, studies have found acute exercise to induce liver injury, which is partially associated to increased production of ROS and inflammatory mediators. On the other hand, regular exercise increases hepatic antioxidant defenses and redox status through mithormetic and hormetic mechanisms driven by training stimuli. Considering that, an ever-increasing number of studies regarding antioxidant and anti-inflammatory strategies combined with exercise have been carried out to understand the redox- and inflammation-related hepatic mechanisms behind exercise outcomes. Currently, antioxidant intake combined with exercise has been more widely studied, although recent interest upon NSAIDs consumption has grown due to a dramatic increase in athletes' intake of these drugs lately. In any case, more research is needed to clarify the mechanisms by which exercise training induces liver adaptations, alone of combined with the intake of antioxidant and anti-inflammatory compounds.

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Disclosure statement

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