Cytokine 119 (2019) 57–61

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

Review article

The proinflammatory effects of chronic excessive exercise

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ARTICLE INFO

Keywords:
Overtraining
Inflammation
Insulin signaling pathway
Endoplasmic reticulum stress
Hepatic fat accumulation
Pathological cardiac hypertrophy

ABSTRACT

Chronic moderate-intensity exercise is an efficient non-pharmacological strategy to prevent and treat several diseases such as type 2 diabetes mellitus, cardiovascular and chronic obstructive pulmonary diseases, cancers, and Parkinson's disease. On the other hand, improving an athlete's performance requires completing high-intensity and volume exercise sessions. When the delicate balance between high-load exercise sessions and adequate recovery periods is disrupted, excessive training (known as overtraining) can lead to performance decline. The cytokine hypothesis considers that an imbalance involving excessive exercise and inadequate recovery induces musculoskeletal trauma, increasing the production and release of proinflammatory cytokines, mainly interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and interleukin 1beta (IL-1beta), which interact with different organic systems, initiating most of the signs and symptoms linked to performance decrement. This leading article used recent data to discuss the scientific basis of Smith's cytokine theory and highlighted that the adverse effects of excessive exercise go beyond performance decline, proposing a multi-organ approach for this issue. These recent insights will allow coaches and exercise physiologists to develop strategies to avoid chronic excessive exercise-induced adverse outcomes.

1. Introduction

Physical inactivity and a sedentary lifestyle may lead to the accumulation of visceral fat mass and the development of a low-grade chronic inflammation state [1,2]. This inflammatory state is characterized by elevated serum levels of interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha), which are linked to several medical conditions such as insulin resistance, type 2 diabetes mellitus, cardiovascular and chronic obstructive pulmonary diseases, colon and breast cancers, dementia, and depression [1,3–6]. In contrast, regular moderate-intensity exercise has been extensively used as a non-pharmacological intervention strategy to prevent the previously mentioned medical conditions or to ameliorate their symptoms [1,7].

Although exercise may be considered as medicine [8], it is necessary to highlight the elite athlete paradox [1]. Generally, improved performance is achieved by completing high-intensity and volume exercise sessions. Because these high-load exercise sessions may lead to a temporary decrease in performance and acute fatigue, optimal training adaptations depend on adequate recovery periods [9]. Indeed, when this delicate balance is disrupted, excessive training (known as overtraining) can exacerbate the drop in performance. Based on the association between heavy training and skeletal muscle injury [10–13], almost two decades ago, Smith [14,15] introduced the cytokine hypothesis, which integrates most signs and symptoms related to excessive training-induced performance decrement.

Excessive exercise-induced skeletal muscle injury leads to a shift of fluid, plasma protein, and specific white blood cells (WBCs) from the circulation to injured tissue [14]. When activated, neutrophils, monocytes, and macrophages secrete more than 100 different substances, which are fundamental to the local and systemic inflammatory processes [14]. Interestingly, the coordination of these specific WBCs, as well as the amplification of various aspects of inflammation, are performed by a large family of polypeptides or proteins called cytokines [16].

Cytokines may be secreted by almost all nucleated cells and act as autocrine, endocrine, and paracrine mediators, stimulating or inhibiting their synthesis and controlling the production of other cytokines and their receptors [17,18]. Although the effects of this specific

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https://doi.org/10.1016/j.cyto.2019.02.016
Received 13 November 2018; Received in revised form 21 February 2019; Accepted 22 February 2019
Available online 15 March 2019
1043-4666/

class of proteins include cell proliferation, differentiation, migration, survival, and apoptosis, their primary function is related to immune system regulation [19].

In summary, Smith's cytokine hypothesis [14,15] considers that high-load training with insufficient recovery induces musculoskeletal trauma and enhances the production and release of IL-1beta, IL-6, and TNF-alpha. These elevated serum levels of proinflammatory cytokines interact with different organ systems, initiating most of the signs and symptoms linked to excessive training-induced performance decrement. Here, we reviewed the data regarding excessive training in human and animal models, discussed the scientific basis of Smith's theory [14,15], and connected the different effects of excessive exercise-induced cytokine release with a multiorgan approach, highlighting that this condition goes beyond performance decline.

1.1. Cytokines and serum

Considering that elevated systemic levels of IL-1beta, IL-6, and TNF-alpha are the critical factors in Smith's theory [14,15], some studies concerning excessive training have evaluated these parameters in humans [9,20,21] and rodents [22–26]. Halson and coworkers [9] observed that endurance-trained cyclists showed a decrease in performance in maximal cycle ergometer, time trial, and intermittent tests after a 2-week intensified training period. However, the authors did not verify significant changes in plasma concentrations of IL-6 and TNF-alpha during the same period. Main et al. [20] monitored elite rowers over an 8-week training period and verified significant associations between IL-6 and TNF-alpha using the Perceived Stress Scale (PSS). Because the authors did not report any performance parameter, it is not possible to reinforce Smith's cytokine hypothesis [14,15].

Regarding the investigations involving rodents as an experimental model [22–26], two of them [23,24] tested Wistar rats primarily using the same excessive running protocol [27]. Dong and coworkers [23] verified increased plasma levels of IL-1beta, IL-6, and TNF-alpha 36 h after the last session of training. To examine data reproducibility, Gholamnezhad et al. [24] submitted two groups of rats to the same excessive training protocol. Whereas the first group displayed an increase in only IL-6, the second group saw an increase in both IL-6 and TNF-alpha 24 h after the last session of the excessive running protocol. Interestingly, after a 2-week total recovery period, these cytokines did not decrease significantly [24].

Finally, Pereira and coworkers [25,26] observed an increase in the serum levels of IL-1beta, IL-6, and TNF-alpha in response to different excessive running protocols based on downhill, uphill, and no inclination running. Interestingly, these proinflammatory cytokines returned to basal levels after two weeks of total recovery [28]. Although further experiments with humans are necessary to elucidate the relationship between cytokines and excessive training, the findings with rodents [22–26] reinforce the idea that an imbalance between overload and recovery induces an increase in IL-1beta, IL-6, and TNF-alpha in serum right after the overtraining period [14,15].

However, after two weeks of recovery, the proinflammatory status in serum returned to normal levels without any performance improvement [29]. This critical fact weakens the cytokine hypothesis proposed by Smith [14] since without elevated systemic proinflammatory cytokines, other mechanisms may be contributing to the impairment of physical performance. Throughout this article, we will review the excessive training effects on the main organs that could interfere in this condition.

1.2. Cytokines and skeletal muscle

Experimental data demonstrating the levels of proinflammatory cytokines IL-1beta, IL-6, and TNF-alpha in skeletal muscle samples during excessive training are minimal [25,26,29,30]. Using Hohl's excessive training protocol [27], Xiao and coworkers [30] showed that the gene expression of IL-1beta and TNF-alpha did not change in Wistar rat gastrocnemius muscle, whereas IL-6 increased 36 h after the last session of this protocol and decreased after a 1-week total recovery period. As highlighted in other studies using this same protocol [22–24], Xiao's group [30] did not report performance parameters, the primary adverse outcome related to excessive training according to Smith's theory [14,15,31].

In response to the excessive downhill running protocol, our research group observed an increase in the intramuscular protein levels of IL-1beta, IL-6, and TNF-alpha regardless of the predominant skeletal muscle fiber type [25,29]. In contrast, the other excessive running protocols (i.e., uphill and without inclination) led to a particular increase of these proinflammatory cytokines, which emphasize the predominating muscle contraction type in the different degrees of treadmill inclination [29]. Independent of the treadmill inclination type, all excessive protocols induced micro injuries with polymorph nuclear infiltration and modulated glucocorticoid and androgen receptor protein content/activation [29]. Altogether, these findings suggest an inflammatory status in mice skeletal muscle after excessive training [25,29,30].

Interestingly, a 2-week total recovery period after these excessive protocols increased and normalized the intramuscular levels of anti-inflammatory and proinflammatory cytokines, respectively, but without a concomitant reestablishment of performance [28]. These findings also did not support Smith's theory [14,15], which considers elevated proinflammatory cytokines to be the main factor responsible for excessive exercise-induced performance decrement.

In the health context, high skeletal muscle levels of IL-6 and TNF-alpha are related to insulin resistance [1], atrophy, and endoplasmic reticulum (ER) stress activation [32]. After downhill running excessive training, mice skeletal muscles displayed insulin signaling pathway impairment, hypertrophy inhibition, and ER stress activation [33–35]. Also, the other two excessive protocols impaired insulin signal transduction and activated ER stress in a fiber-type-specific manner [33,36]. In summary, excessive training induces many dysfunctions in skeletal muscle that could be triggered by cytokines. However, there is no evidence that intramuscular proinflammatory cytokines have a direct impact on performance reduction.

1.3. Cytokines and the central nervous system

High peripheral inflammatory stimuli-induced hypothalamic levels of IL-1beta, IL-6, and TNF-alpha are linked to food intake restriction [37–39]. Corroborating this concept, Romanatto et al. [40] verified that a single hypothalamic intracerebroventricular (ICV) injection of TNF-alpha reduced food intake and favored catabolism. Interestingly, a growing amount of evidence considers body weight and food intake reductions as classic symptoms of chronic excessive training [14,15,27,31,41,42]. Therefore, Smith [14,15] hypothesized that proinflammatory cytokines play an essential role in excessive training-induced appetite inhibition.

Indeed, downhill running excessive training led to low body weight gain and food intake [26]. To clarify the molecular mechanisms responsible for these alterations, Pereira and coworkers [26] observed upregulation of the hypothalamic levels of IL-1beta, stress-activated protein kinase/c-Jun NH2-terminal kinase (SAPK-JNK) phosphorylation, suppressor of cytokine signaling 3 (SOCS3), and TNF-alpha. Interestingly, after a 2-week total recovery period, hypothalamic inflammation in mice was reversed and body weight and food intake normalized [26]. Altogether, these data partially reinforce Smith's hypothesis [14,15], demonstrating a relationship between excessive training, cytokines, hypothalamic inflammation, and appetite inhibition.

Based on the crosstalk between inflammation and ER stress [32], Pinto et al. [43] verified hypothalamic ER stress activation after downhill running excessive training, while the other protocols

presented an attenuated response. Remarkably, after a 2-week total recovery period, the groups saw a partial increase in ER stress proteins but without hypothalamic inflammation [44], which may be characterized as a physiological condition related to an adaptation mechanism [32].

These data reinforce the idea that proinflammatory cytokines could act as an initial stimulus to induce some maladaptations in the central nervous system right after an excessive training period. However, when a recovery period was provided, the inflammation and ER stress were normalized, characterizing a physiological adaptation condition without simultaneous reestablishment of physical performance.

1.4. Cytokines and liver

According to the cytokine hypothesis [14,15], excessive training-induced appetite inhibition requires the maintenance of adequate blood glucose levels for specific organs such as the brain. The liver balances the uptake and storage of glucose via glycogenesis as well as the release of glucose via glycogenolysis and gluconeogenesis to maintain glycemic homeostasis [45]. Interestingly, Zisman and coworkers [46] verified that glucose is partially shifted to the liver in rodents with skeletal muscle deletion of glucose transporter 4 (GLUT4). Also, Kotani et al. [47] observed that the liver assumes a pivotal role in maintaining glucose homeostasis in both adipose tissue and skeletal muscle GLUT4 in knockout mice. These studies reinforce the idea that the liver probably acts as a regulatory organ when there is some disturbance in skeletal muscle to capture glucose via the GLUT4 mechanism.

As Pereira and coworkers [33] verified that the impairment of the insulin signaling pathway in skeletal muscle after downhill running excessive training occurred without significant alterations in the insulin tolerance test (ITT), our research group hypothesized that the liver could be acting as a compensatory organ for glucose homeostasis. Indeed, Da Rocha and coworkers [48] observed that this excessive exercise model improved some proteins linked to the hepatic insulin signaling pathway, inducing hepatic glycogen accumulation.

Regarding gluconeogenesis, high levels of forkhead box O1 (Foxo1) phosphorylation were found after all excessive training protocols, culminating in a lack of significant alterations during the pyruvate tolerance test (PTT). These data did not support the proposed relationship between excessive training, cytokines, and hepatic gluconeogenic activation [14,15]. In respect to hepatic inflammation and excessive training, Lira et al. [49] did not observe significant differences for IL-6, IL-10, and TNF-alpha after an 11-week excessive running protocol [27]. Reinforcing these data, the hepatic contents of IL-6, IL-15, TNF-alpha, and SOCS3 were not altered in response to our different excessive exercise protocols [48].

On the other hand, downhill running excessive training increased the hepatic content of IL-10 as well as the phosphorylation of IκB kinase alpha and beta (IKKalpha/beta), and SAPK/JNK. Finally, this protocol activated the 70-kDa ribosomal protein S6 kinase 1 (S6K1) [48], a downstream target of the mammalian target of the rapamycin complex 1 (mTORC1) [50]. Based on the overactivation of protein kinase B (Akt)/mTORC1 pathway leading to hepatic lipogenesis via regulation of the action of sterol regulatory element binding protein-1 (SREBP-1) [51], we demonstrated activation of the mTOR signaling pathway and SREBP-1 content, which culminate in hepatic fat accumulation after downhill running excessive training [52].

1.5. Cytokines and heart

Proinflammatory status may be linked to the development of pathologic cardiac hypertrophy [53]. This pathophysiological condition may lead to heart failure and is accompanied by reactivation of fetal genes, upregulation of apoptosis and fibrosis, as well as downregulation of the mTOR signaling pathway [53,54]. On the other hand, regular moderate-intensity exercise-induced physiological cardiac hypertrophy enhances cardiac function [53].

Recently, our research group [55] verified an elevation in the protein levels of IL-6 and beta-myosin heavy chain gene expression, a reduction in 5′ AMP-activated protein kinase (AMPK) activation, and in mTOR and ribosomal protein S6 protein (rpS6) contents, as well as signs of fibrosis in the left ventricle of mice after the excessive downhill running protocol. Altogether, these data suggest excessive eccentric training can induce molecular signs of pathological cardiac hypertrophy, contributing to physical performance impairment [53]. Also, all excessive protocols increased left ventricle glycogen content [56], which probably contribute to glucose homeostasis due to skeletal muscle insulin signaling impairment.

Data regarding excessive training and cardiac response are scarce. Indeed, there are only speculative linkages between proinflammatory cytokines induced by this model and cardiac impairment. Although some evidence suggests that excessive training can modulate signaling pathways involved in pathological cardiac hypertrophy [55], more studies investigating this relationship should be performed.

2. Conclusions

According to Smith [14,15], excessive training induces an onset of traumas in skeletal muscle and connective and bone tissue. These traumas lead to the release of proinflammatory cytokines that affect the central nervous system, sympathetic nervous system, hypothalamic gonadal hypothalamic axis, and liver [14,15]. Data from our research group did not support the central role of proinflammatory cytokines as the only factor responsible for excessive exercise-induced performance decrement. Also, we highlighted that the effects of excessive exercise-induced cytokine release go beyond performance decline, leading to pathological conditions in skeletal muscle, the hypothalamus, liver, and heart, which suggests a multi-organ model (Fig. 1).

3. Future perspectives

Although our studies did not support the idea of proinflammatory cytokines being the only factor responsible for impaired physical performance, there is one molecule of Smith's hypothesis present in all parts of the multi-organ model: IL-6. Recently, we demonstrated that global knockout of IL-6 attenuated the endoplasmic reticulum stress in skeletal muscle induced by exhaustive exercise [57]. Future studies should investigate the direct role of this cytokine in the metabolism in excessive training conditions. Furthermore, another exciting and unexplored mechanism that can directly influence proinflammatory cytokine release and physical performance reduction is the toll-like receptor 4 (TLR4) pathway. Briefly, the activation of TLR4 by lipopolysaccharides stimulates nuclear factor kappa beta (NF-kB), which enhances the production of IL-6, IL-1beta, and TNF-alpha [58,59].

Recently, VanderVeen and coworkers [60] reviewed the emerging evidence linking cancer-induced chronic inflammation to the dysfunctional regulation of mitochondrial dynamics, mitophagy, and biogenesis in cachectic muscle. On the other hand, moderate-intensity exercise increases extracellular non-esterified fatty acids, activating TLR4 response [61] and mitochondrial biogenesis [62]. Based on these findings [60–62], we can speculate that excessive exercise over activates the production and release of proinflammatory cytokines induced by TLR4, dysregulating mitochondrial dynamics, mitophagy, and biogenesis as well as contributing to a decline in physical performance. This theory should be addressed in future studies.

Funding

This study received financial support from São Paulo Research Foundation (FAPESP; process numbers 2010/08239-4, 2011/02652-0, 2012/23258-0, 2013/19985-7, 2013/20591-3, 2013/22737-5, 2014/

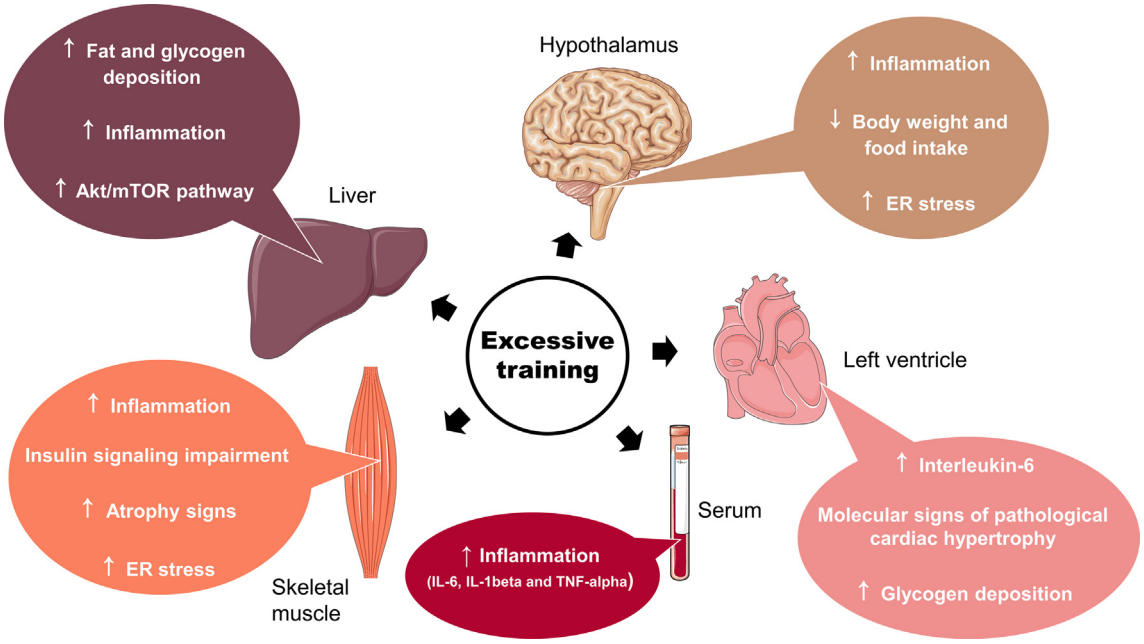

Fig. 1. Schematic figure summarizing the proinflammatory effects of excessive exercise in multiple tissues.

25459-9, 2015/08013-0, 2017/09038-1, 2017/12765-2 and 2017/19869-8), the National Council for Scientific and Technological Development (CNPq; process number 309339/2016-2), and the Coordination for the Improvement of Higher Education Personnel (CAPES; finance code 001).

Conflict of interest

The authors declare that they have no conflict of interest.

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