Raizel and Tirapegui *Nutrire* (2018) 43:28
https://doi.org/10.1186/s41110-018-0087-9

Nutrire

REVIEW Open Access

Role of glutamine, as free or dipeptide form, on muscle recovery from resistance training: a review study

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Abstract

Background: Glutamine plays a key role in several essential metabolic processes and is an important modulator of the heat shock protein (HSP) response, a crucial mechanism to maintain cellular homeostasis and to promote cell resistance to injury and death. This review summarized the effects of free L-glutamine or the dipeptide L-alanyl-L-glutamine upon muscle injury and inflammation, as well as muscle recovery from resistance training.

Main body of the abstract: The 70-kDa HSP (HSP70) expression is enhanced by glutamine, via the hexosamine biosynthetic pathway, which inhibits the NF-κB pathway regenerating and recovering myofibers through the regulation of the early inflammatory response to muscle injury, which may be impaired by local and systemic inflammatory injury due to reduced intracellular levels of HSP70.

Short conclusion: Studies show that chronic oral administration of free L-glutamine or the dipeptide can attenuate the injury and inflammation induced by intense aerobic and exhaustive exercise. However, the effects on muscle recovery from resistance training are unclear.

Keywords: Glutamine, Heat shock protein, Muscle recovery

Background

Glutamine is a versatile amino acid, abundant in the plasma and skeletal muscle, accounting for most of the intramuscular free amino acid content. It is synthesized from glutamate and ammonia by the enzyme glutamine synthetase, and is stored and released predominantly by the skeletal muscle [1]. This amino acid is also synthesized by adipocytes, liver, and lung, and after its release into the bloodstream, glutamine is transported to be metabolized in several tissues [2]. As a precursor for purines and pyrimidines, glutamine enables the synthesis of DNA and RNA, for mRNA synthesis and DNA repair of nucleotide and nucleic acids [3–5]. This amino acid is also used as the main oxidative fuel to replenish intermediates of the tricarboxylic acid cycle in rapidly dividing cells [1], such as enterocytes and colonocytes [6], fibroblasts, and immune cells such as lymphocytes [7, 8], macrophages, and neutrophils [9–12]. The members of the solute carrier (SLC) 38 gene family are the principal transporters of glutamine in mammalian cells, allowing the extremely rapid cellular turnover rates of glutamine flux [13, 14] and the redox control [15].

Glutamine is the major inter-organ nitrogen transporter and regulator of acid-base balance. In the kidneys, glutamine is used by the tubular epithelial cells providing NH3 for urea synthesis and elimination of the excess acid [1, 16]. The skeletal muscle amino acid metabolism generates glutamine to detoxify the ammonia produced [17, 18]. Additionally, glutamine contributes to the intermediary metabolism [19] in the synthesis of amino sugars and proteins [20–22], promotes insulin secretion from pancreatic beta cells, and is the precursor of key molecules such as the excitatory neurotransmitter glutamate, the inhibitory neurotransmitter γ-aminobutyrate (GABA), and the antioxidant glutathione (GSH) [1, 23, 24], considered a powerful marker of the cellular redox potential [25, 26]. It has also been demonstrated that glutamine enhances the tight junction protein abundance, maintaining the integrity of the intestinal mucosal barrier and improving its function [27, 28]. Recently,

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glutamine was suggested to reduce the intestinal catabolism of amino acids, which may improve their bioavailability in the systemic circulation [29]. Notwithstanding, glutamine is also a potent inducer of the heat shock protein (HSP) response to maintain homeostasis, facilitating repair from injury and cell death [30, 31].

Despite being originally classified as a non-essential amino acid [32] in healthy individuals [33], abundant evidence suggests that glutamine is essential in specific stress situations such as severe illness, trauma, and overtraining [9, 34–38]. In hypercatabolic states, when the elevated demand exceeds the capacity to produce adequate amounts of this amino acid [39–41], the impairment of immune function may occur [37, 42]. Due to the important pleiotropic roles in metabolism and tissue homeostasis, glutamine is one of the most studied amino acids in exercise immunology [33].

Given the high consumption of free glutamine by intestinal cells, glutamine dipeptides have been studied as an alternative for transposing the intestinal barrier and increasing the bioavailability of this amino acid to cells of the immune system. Studies in animal models from our laboratory have shown that oral supplementation with L-glutamine and L-alanine administered in its free form or as dipeptide (L-alanyl-L-glutamine), during 8 weeks, can attenuate the tissue injury, inflammation, and immune suppression induced by intense aerobic and exhaustive exercise [43–46]. Conversely, the effects of these supplements on muscle recovery from resistance training are poorly elucidated. Thus, the aim of this review was to summarize the evidence regarding the effects of free L-glutamine or the dipeptide L-alanyl-L-glutamine upon muscle injury and inflammation, as well as on muscle recovery from resistance training.

Main text

Exercise-induced stress response

In sports, high metabolic stress followed by the short recovery period makes the athlete's training routine exhaustive [47]. Muscle contractions from mechanical loading induce microtrauma in muscle fibers, resulting in the rupture of the extracellular matrix, basal lamina, and sarcolemma, in addition to the alteration of calcium homeostasis, which promotes changes in the cell membrane structure and permeability [48, 49]. Following structural damage and functional impairment of the muscle tissue, myofibrillar rupture and extravasation of intracellular proteins such as myoglobin, creatine kinase (CK), and lactate dehydrogenase (LDH), into the extracellular medium, trigger the local inflammatory response [47, 50–52]. Hence, exercise-induced stress response in the skeletal muscle is triggered by damage to protein structure and might be further increased by the secondary induced damage in addition to inflammatory processes [49].

The local inflammatory response involves muscle protein degradation systems that are orchestrated by a network of signalling pathways, activated or suppressed by hormones and cytokines [50, 53]. Protein degradation in muscle tissue is accompanied by a systemic acute phase response that may vary according to the type of exercise and its frequency, duration, and intensity [54]. Local inflammation is characterized by an increased number of infiltrating and resident immune cells, such as mast cells [55], neutrophils and T regulatory lymphocytes [56], eosinophils [57], and CD8 T lymphocytes [58] at the injury site, thereby releasing pro-inflammatory effectors. Macrophages are the predominant leucocytes observed during the regeneration phase of the stretch-injured skeletal muscle, exerting specific roles throughout the whole process. After muscle injury, tissue-resident macrophages migrate to the injured area, and part of them prevents complete monocytes' recruitment from the circulation [59]. Briefly, exercise-induced inflammatory processes include the release of cytokines and chemokines driving a rapid influx of neutrophils, followed by the differentiation of monocytes into macrophages that promote the phagocytosis of necrotic muscle debris. These cells switch then into anti-inflammatory macrophages and proliferate during the regeneration process of the damaged skeletal muscle [60].

During local inflammation occurs the synthesis and release of molecules such as monocyte chemotactic protein (MCP)-1, chemokine derived from macrophage (MDC), tumour necrosis factor (TNF)-α, interleukin (IL)-8, vascular endothelial growth factor (VEGF), leukaemia inhibitory factor (LIF), fractalkine, and urokinase plasminogen activator (uPA) [53, 61]. Most of these proteins act as chemotactic factors at the site of inflammation, promoting the initial recruitment of satellite cells, neutrophils, monocytes, and, later, lymphocytes for tissue repair [52, 62–65]. Eccentric exercise is acknowledged for the generation of a local inflammatory response in the skeletal muscle with the timing and peak of neutrophil infiltration linked to the magnitude of muscle function decrements [66, 67]. Intense exercise stimulates a well-defined systemic cytokine response, associated with the exercise-induced metabolic stress responses [68, 69]. The systemic response initiates with a rapid increase of pro-inflammatory components (IL-6, IL-8), which in turn generates an anti-inflammatory feedback by increasing the release of interleukin (IL)-10 and interleukin (IL)-1 receptor antagonist [70].

The resolution of inflammation characterizes a shift from a pro-inflammatory state to the anti-inflammatory phase, followed by repair and regeneration of injured tissues, processes markedly played by macrophages that include angiogenesis, matrix remodelling, and establishment of homeostasis [71]. This process is vital for the recovery

of injured muscle; however, continuous muscle injury triggers a chronic inflammatory response, which can aggravate the underlying lesions by degrading intact proteins, implying reduced performance and compromised health [52, 72, 73]. Systemic inflammation is associated with reduced rates of protein synthesis in addition to an enhanced protein breakdown [74]. In this regard, pro-inflammatory cytokines may account for the loss of muscle mass by activating catabolic and downregulating the anabolic pathways [75].

Intense training with continuous rest deprivation increases the release of pro-inflammatory indicators, which may induce fatigue and overtraining syndrome in athletes [53]. The effects exerted by pro-inflammatory cytokines on muscle mass are partially mediated by the induction of the transcription factor NF-κB signalling [48, 76, 77]. In a single bout of intense resistance exercise and in an acute bout of treadmill run, NF-κB activity is increased in the skeletal muscle of humans and rats, respectively [78, 79], in addition to an increase in genic expression of the interleukins IL-6, IL-8, IL-1β, and IL-15 and of TNF-α, MCP-1, LIF, and TG-β [53]. It also observed increased levels of anti-inflammatory agents, such as IL-10 and MCP-1, 24 h after eccentric exercise, in an endeavor to contain inflammation [78].

It has been proposed that cytokines (e.g. IL-10, IL-13, and IL-15) may have anabolic effects and modify the contractile function of the skeletal muscle. Cytokine secretion by the skeletal muscle involves several intracellular factors such as MCP-1, heat shock factor (HSF)-1, and histone deacetylases, besides nuclear factor of activated T cells and NF-κB [53, 61, 76, 80, 81]. The NF-κB signalling pathway acts as the central regulator of the stress-induced mechanical, oxidative, and inflammatory responses [52, 77]. However, its persistent activation, as well as increased synthesis of inflammatory molecules, may excessively recruit immune cells, consequently promoting additional tissue damage [73]. Under these conditions, protective systems such as HSP are activated against excessive inflammatory damage induced by exercise, in order to restore homeostasis and ensure cell survival [30, 31].

Physical exercise and heat shock proteins

One of the most basic mechanisms of cellular defence includes the expression of HSP to neutralize harmful agents and events, induce cell protection and tolerance to injury, and warrant maximum cell survival in the skeletal muscle [82]. HSP is a highly conserved family of stress-inducible proteins, essential for cellular homeostasis, protecting against a variety of stress stimulus [83, 84], injury, and death and modulating the early inflammatory response to muscle injury [30, 31]. These proteins are named according to the molecular weight as follows: HSP90, HSP70, HSP60, and HSP27, and the upregulation under stress conditions provides cytoprotection by re-establishing protein homeostasis against several stressors, including exercise [85]. Under normal physiological conditions, HSP acts as a chaperone protein helping the protein folding (mainly unfolded, misfolded, and partially folded new peptide chains) and translocation into the endoplasmic reticulum lumen [86]. When the body is under excessive stress, these proteins exert a protective role by lessening oxidative action of the reactive oxygen species (ROS) and a wide range of metabolic stress, including structural and functional myodamage [87, 88]. Despite the fact that exercise is a potent inductor of the HSP response [89], local and systemic inflammatory lesion leads to a reduction in intracellular HSP70 levels, which may impair tissue readjustment [30, 89, 90].

Modifications in gene expression occur to yield an increase in the content of HSP [30, 31], proteins that act as molecular chaperones, being crucial in helping the cellular remodelling processes of denatured proteins, independent of the training response [89, 91]. A reduction in pro-inflammatory cytokine release has been observed following the initiation of a heat shock response [85], and this process may be related to the binding of HSP to the heat shock element (HSE) found in the promoters of cytokine genes (e.g. IL-1β) [92, 93]. During stress, the latent monomer of heat shock factor (HSF)-1 is rapidly converted to a trimeric form active in the nucleus to bind to the promoters of HSF-responsive heat shock genes and activate their transcription [94, 95]. HSF-1 has been demonstrated to perform this function by repressing the transcription of cytokine genes, including TNF-α and IL-1β, antagonizing the acute phase response [92, 96]. Because IL-1β immediately responds to a wide diversity of pro-inflammatory insults and affects the function of many targets, it is essential to limit the potentially harmful aspects of inflammation by negatively regulating IL-1β expression [92].

HSP27 and HSP70 are considered the most robust and recognized induced chaperones; both play important cytoprotective roles acting at multiple apoptotic pathway control points to ensure that stress-induced injury does not inappropriately trigger cell death, thus disabling apoptosis [97]. The induction of HSP is characterized by low transient regulation of most cellular proteins and the expression of the 70-kDa protein family (HSP70). A 72-kDa stress-inducible Hsp72, a prominent member of the HSP70 family, is one of the largest inducible HSP isoforms interacting with other proteins in a way dependent of ATP and has been extensively studied in the mammalian skeletal muscle [31]. The Hsp72 expression is more abundant in slow-oxidative than fast-glycolytic skeletal muscle fibres, and the expression is elevated by the increased contractile activity of the muscles with exercise, as well as heat stress [98].

HSP70 has been involved in the regulation steps of skeletal muscle plasticity [30, 31, 99, 100], apoptosis, and cell death, affecting protein refolding processes, signalling for ubiquitin degradation, and translocation of proteins [101]. Both exhaustive endurance exercise and resistance exercise with maximal eccentric repetitions have been shown to increase the level of Hsp72 expression [102]. In general, HSP70 is induced by diversified stimuli such as hypoxia, acidosis, increased muscle temperature, and ischaemia-reperfusion, most of them are by-products of resistance exercise associated with elevated levels of metabolic stress [30, 89]. Conversely, in exercise, HSP facilitates mitochondrial biogenesis, despite regulating the signalling pathways associated with apoptosis [49, 103].

HSP70 is also involved in the control of the primary response to muscle injury [30] and inhibition of the NF-κB signalling pathway by modulating the inflammatory response and attenuating pro-inflammatory cytokine release [104–106]. The chaperone equilibrium hypothesis proposes that NF-κB activation may decrease intracellular levels of HSP70, releasing extracellular HSP70 as a pro-inflammatory component, which may be linked to reduced oxidative stress in target cells. Nonetheless, when extracellular HSP70 is continuously elevated, it stimulates inflammation, oxidative stress, reduced expression of HSF-1, and possibly reduced intracellular HSP70 [91].

Stress conditions promoting instability and denaturation of proteins induce the release of HSF-1, which the activity is associated with the expression of HSP70 in the myocardium, skeletal muscle, and human leucocytes [76, 107]. Evidence suggests that the increased HSP expression on the leucocyte surface after acute intense training signals excessive stress [108]. In general, the expression of HSP70 has become a major interest of studies because of its role in modulating inflammatory immune response and cytoprotection under stress conditions in a wide diversity of experimental injury models [73, 109]. In this sense, the effect of glutamine as a potential therapeutic element has been observed. Glutamine improves HSP70 and HSP27 expression [43, 44, 110] and acts not only as a modulator of the heat shock response but also as a competent inducer of HSF-1 expression, activating its transcription [93, 111, 112].

The hexosamine biosynthetic pathway (HBP) has been shown to induce HSP70 expression, and glutamine is an essential substrate for this pathway. Its activity is enhanced by glutamine via O-glycosylation, leading to the translocation and transcriptional stimulation of key transcription factors (HSF-1 and Sp1) required for maximal HSP70 induction [113]. The expression of the HSF-1, HSP70, and HSP27 all depend on Sp1 for optimal transcriptional activity [114]. Considering the effect of glutamine on Sp1 and in the modulation of the HSP response [93, 109, 111, 115], this amino acid has been considered an important therapeutic element [33]. Hence, glutamine could be used to induce a beneficial stress response and prevent tissue damage under disturbing conditions (Fig. 1). Moreover, HSP synthesis has shown to be dependent on adequate concentrations of glutamine [93].

Roles of glutamine in response to exercise

Glutamine is endogenously synthesized from α-ketoglutarate, an intermediary metabolite of the citric acid cycle, in two steps mediated by the enzymes glutamate dehydrogenase and glutamine synthetase, that convert α-ketoglutarate into glutamate using NADPH and glutamate into glutamine using NH3, respectively [1, 22, 50]. This amino acid is essential for function and proliferation of cells that are rapidly dividing (e.g. enterocytes), as well as for the phagocytic activity of macrophages and production of GSH, which is the most potent antioxidant in the body [20, 33, 35]. The small non-protein thiol, GSH, plays a key role in maintaining the redox balance. The glutathione system (NADPH, glutathione reductase, and GSH), one of the major cellular thiol-dependent antioxidant mechanisms, participates in the synthesis and repair of DNA [116]. Accordingly, the elevation of GSH levels by dipeptides of glutamine enhances the antioxidant capacity reducing cell damage [117, 118].

Glutamine improves the production of HSP and activates the degradation of the NF-κB p65 subunit in the nucleus, protecting against excessive inflammatory states and cell death by apoptosis [23, 119–122]. HSP72 is indicated to participate as a stress-stimulated inducer of the microbicide activity of neutrophils during moderate exercise [123]. Thus, the modulatory effect of glutamine on the heat shock response may affect neutrophil function [124]. Moreover, glutamine might decrease the synthesis of IL-8 (the major neutrophil chemoattractant) in athletes [33].

Glutamine supplementation is a strategy used in situations of intense catabolism, in which there is a decrease in the synthesis and release of glutamine by the skeletal muscle and increased uptake by other organs (kidneys and liver), such as in prolonged and intense exercises, as well as in overtraining syndrome [125, 126]. This condition may be associated with immunosuppression, in view of the lower availability of this amino acid for the immune cell metabolism [1]. The decrease in glutamine concentration mediated by exhaustive exercise is often concomitant with a decrease in the number of circulating lymphocyte and immune cell function as seen in both lymphocytes and NK cells [36] since these cells present glutaminase, the major degradation enzyme of glutamine [34, 124]. Moreover, the maintenance or increase in skeletal muscle glutamine concentration might

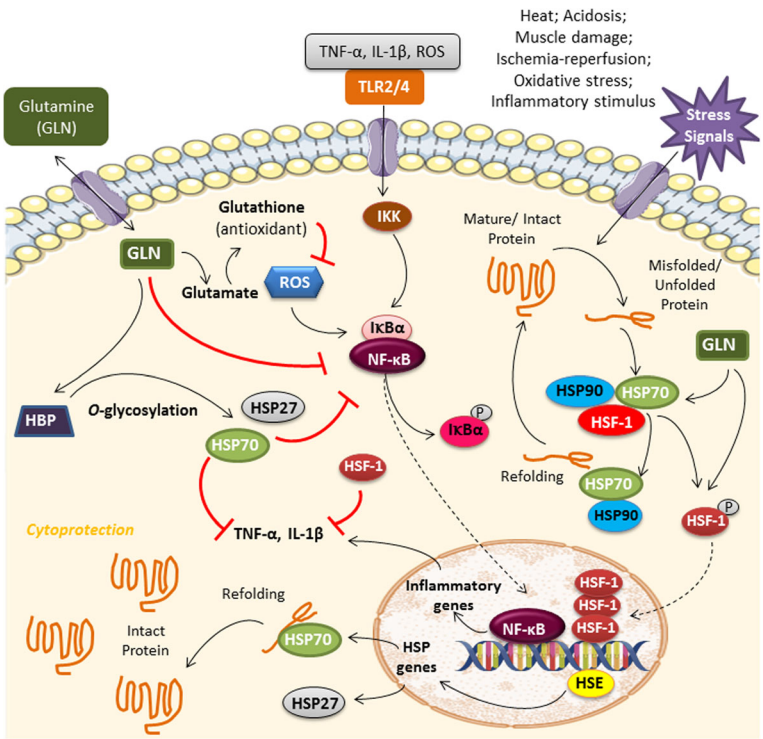

Fig. 1 Glutamine modulates the exercise-induced heat shock and inflammatory responses. The heat shock response is induced by stress signals produced during exercise. HSP70 and HSP27 are upregulated under stress conditions providing cytoprotection by remodeling misfolded and unfolded proteins and limiting damage induced by reactive oxygen species (ROS) and inflammatory stimulus. The latent heat shock factor (HSF)-1 monomer is converted to a trimeric active form in the nucleus during stress to bind to the promoters of heat shock genes and activate transcription. HSP70 also regulates the primary response to muscle lesion and inhibits the NF-κB signalling pathway by modulating the inflammatory response and attenuating pro-inflammatory cytokines release. Glutamine improves HSP70 and HSP27 expression and acts not only as a modulator of the heat shock response but also as a competent inducer of HSF-1 expression, activating its transcription. Glutamine enhances the hexosamine biosynthetic pathway (HBP), via O-glycosylation, contributing to the translocation and induction of HSF-1 transcription (→, stimulation; ⊥, inhibition; ⇢, translocation)

be fundamental for muscle protein synthesis [127–129], to prevent muscle atrophy [38, 130] and to increase glycogen synthesis [131], particularly under catabolic conditions.

Blomstrand and Essen-Gustavsson [132] observed significant reductions in *vastus lateralis* muscle glutamine concentrations of male subjects 2 h following 40 leg press repetitions at 80% of their maximum, indicating glutamine homeostasis disturbance following eccentric exercise, as already demonstrated in the literature [133].

A study with L-glutamine supplementation (0.3 g kg^{-1} day^{-1} + 0.3 g kg^{-1} day^{-1} maltodextrin), following eccentric exercise, has found attenuated strength loss, shorter strength recovery, and muscle soreness at 24, 48, and 72 h postexercise in the quadriceps muscle of healthy participants [67]. An enhancement of protein synthesis and attenuation of catabolic responses induced by heavy resistance training, which were related to increased muscular hypertrophy and reduced exercise-induced immunosuppression, have additionally been observed after glutamine supplementation [134]. It has been suggested that the effects of glutamine are mixed, and studies fail to demonstrate positive benefits on buffering capacity, time to exhaustion, protein balance, and other ergogenic effects regarding muscle recovery from exercise [135]. While a study showed that glutamine supplementation inhibits total body proteolysis by increasing leucine flux [136], other did not find any effect of glutamine on protein degradation markers [137].

Although glutamine supplementation in exercise has shown benefits, the effectiveness of oral administration has been questioned because approximately 50% of glutamine is metabolized by cells of the intestinal mucosa and liver before the peripheral circulation and skeletal muscle are achieved [138]. Hence, the bioavailability of this amino acid to cells of the immune system may be compromised [45]. Nonetheless, the alternative for transposing the intestinal barrier has been the utilization of glutamine dipeptides [2], such as L-alanyl-L-glutamine (DIP), due to the higher stability during heat sterilization and storage and higher solubility compared to free glutamine [139]. Lima et al. [140] reported high stability of alanine and glutamine together, possibly via an improvement in intestinal ion transporters,

which may be responsible for the lower fatigue feelings in soccer players [141].

A previous study carried out for us investigated the acute and chronic effects of oral supplementation with DIP on glutamine concentrations in plasma and tissues. Rogero et al. [142] demonstrated that acutely, DIP supplementation increased plasma glutamine concentration, and chronically, DIP administration promoted increased glutamine stores in the muscle and hepatic tissues of healthy rats. In 2006 [45], it was demonstrated that chronic DIP supplementation increased glutamine concentrations in the gastrocnemius and soleus muscles immediately after an exhaustion test, compared to chronic glutamine supplementation. In the long-term exercise, oral supplementation with DIP or L-glutamine associated with L-alanine, both in the free form, represents an efficient alternative for the supply of glutamine and glutamate to the organism, promoting higher muscular and hepatic stocks of glutathione and influencing the cellular redox state [46].

The efficacy of DIP is due to the intestinal transporter (PepT)-1, which facilitates a wide absorption of dipeptides and tripeptides, behaving as a facilitated diffusion peptide transporter. The mechanism underlying the clearance of dipeptides is suggested to be exerted by hydrolysis through the membrane-bound peptide hydrolases [143]. DIP also warrants the supply of more glutamine molecules in the osmolality required for physiological fluids [43, 144]. Hence, the combination of glutamine and alanine allows the enhancement of electrolyte and fluid absorption compared to glutamine alone, and this effect is likely due to the specific ion transporters, increasing the absorption rate in intestinal epithelia [140]. Recently, the dipeptide L-alanylglutamine was suggested to inhibit signalling proteins that trigger protein degradation following an acute bout of resistance exercise [145].

In a study that evaluated rehydration with DIP in a sports drink during an hour of endurance exercise at submaximal intensity, the authors observed an increase in the reaction time of athletes to visual stimuli [146]. The intake of DIP during a moderate intensity run was also investigated, and the results indicated a significant improvement in performance during a subsequent exhaustion test. The authors of both studies attributed the results to an improvement in the intestinal absorption of fluids and electrolytes and possibly increased skeletal muscle uptake causing greater neuromuscular performance, besides a possible gluconeogenic effect of alanine, sparing muscle glycogen, and retarding fatigue [144, 146]. Although glutamine is a major gluconeogenic substrate, mainly in the kidney, alanine also contributes donating carbon for gluconeogenesis, being essentially confined to the liver [147].

In 2010, Hoffman et al. [148] found that the dipeptide L-alanyl-L-glutamine administration provided a beneficial ergogenic effect by increasing time to exhaustion following a mild hydration stress, and the effects were linked to an enhanced fluid and electrolyte absorption. In 2012, Hoffman et al. [149] demonstrated that rehydration with the dipeptide contributes in maintaining basketball skill performance and visual reaction time. The authors also suggested an enhanced intestinal fluid and electrolyte uptake, thus preserving the neural commands for fine motor control during physical activities. Investigations with animal model induced to intense and exhaustive aerobic exercise protocols or, in situations of high catabolism, such as sepsis, show that chronic supplementation with DIP or with glutamine and alanine in their free forms is efficient for the supply of glutamine to the body, which can attenuate biomarkers of injury and inflammation after periods of intense training, as well as attenuate the inflammatory response induced by long-term exercise [142].

In 2016 [150], we evaluated the effect of glutamine and alanine supplementation in their free forms or as DIP in rats subjected to intense resistance exercise and compared with the effects of free alanine. It was found that animals supplemented with L-glutamine presented increased glutamine concentration in plasma and muscle tissues, in addition to a reduction in the GSSG/GSH ratio, TBARS, and CK rates. The contents of HSF-1 and HSP-27 were elevated in all supplemented groups. The authors concluded that supplementations with L-glutamine and L-alanine either in free form or as DIP improved the GLN-GSH axis and promoted cytoprotective effects against oxidative stress caused by resistance exercise [150]. In a study that also used an intense resistance exercise protocol during 8 weeks, we showed that plasma and muscle glutamine levels were restored in trained rats receiving supplements containing glutamine in both forms. Additionally, there was an increase in HSP70 content in the skeletal muscle and peripheral blood mononuclear cells, concomitant with reduced activation of NF-κB and decreased concentration of cytokines [151].

Unlike skeletal muscle, leucocytes are largely dependent of the glutamine synthetized and released into the blood by the skeletal muscle, to satisfy their metabolic requirements [5, 152]. Raizel et al. also found muscle protection, shown by reduced plasma levels of CK, LDH, TNF-α, and IL-1β, in addition to the increased concentration of IL-6, IL-10, and MCP-1. Thus, oral supplementation with L-glutamine (administered with L-alanine or as DIP) has been shown to induce HSP70-mediated cytoprotective effects in response to muscle injury and inflammation [151]. In addition to these results, our group has recently demonstrated that the form of glutamine administration (free along L-alanine or as L-alanyl-L-glutamine) is an important

factor determining improvement or impairment of central fatigue parameters in rats submitted to 8 weeks of heavy resistance training [153].

Conclusions

Although studies are contradictory regarding the effect of free glutamine supplementation on muscle injury and inflammation, due to the high intestinal and hepatic metabolism with consequently decreased availability of consuming organs and cells of the immune system, current evidence indicate that oral supplementation with free L-glutamine or the dipeptide provides an effective alternative for increasing plasma and muscle glutamine concentrations. Thus, cytoprotective systems, such as the heat shock response, and the body antioxidant system appear to be preserved and effectively activated in response to muscle injury and inflammation induced by intense resistance training.

Studies show that chronic oral administration of free L-glutamine or the dipeptide can attenuate the injury and inflammation induced by intense aerobic and exhaustive exercise. However, the effects on muscle recovery from resistance training are unclear.

Abbreviations

CK: Creatine kinase; DIP: L-alanyl-L-glutamine; GABA: γ-Aminobutyrate; GSH: Glutathione; HSE: Heat shock element; HSF: Heat shock factor; HSP: Heat shock proteins; HSP70: 70-kDa protein family; IL: Interleukin; LDH: Lactate dehydrogenase; LIF: Leukaemia inhibitory factor; MCP: Monocyte chemotactic protein; MDC: Chemokine derived from macrophage; PepT: Intestinal transporter; ROS: Reactive oxygen species; SLC: Solute carrier; TNF: Tumour necrosis factor; uPA: Fractalkine and urokinase plasminogen activator; VEGF: Vascular endothelial growth factor

Acknowledgements

Not applicable

Funding

Not applicable

Availability of data and materials

Not applicable

Authors' contributions

RR and JT were responsible for all the steps of the review. The figure was drawn by RR. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

Publisher's Note

Received: 23 August 2018 Accepted: 7 November 2018
Published online: 05 December 2018

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