

Resistance exercise: A non-pharmacological strategy to minimize or reverse sleep deprivation-induced muscle atrophy

M. Mônico-Neto^{a,b}, H.K.M. Antunes^{b,c}, M. Dattilo^{a,b}, A. Medeiros^c, H.S. Souza^{a,b}, K.S. Lee^d, C.M. de Melo^{a,b}, S. Tufik^{a,b}, M.T. de Mello^{a,b,*}

^a Departamento de Psicobiologia, Universidade Federal de São Paulo, São Paulo, Brazil

^b Centro de Estudos em Psicobiologia e Exercício (CEPE), São Paulo, Brazil

^c Departamento de Biociências, Universidade Federal de São Paulo, Santos, Brazil

^d Departamento de Bioquímica, Universidade Federal de São Paulo, São Paulo, Brazil

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ABSTRACT

Sleep is important for maintenance of skeletal muscle health. Sleep debt can induce muscle atrophy by increasing glucocorticoids and decreasing testosterone, growth hormone and insulin-like growth factor-I. These hormonal alterations result in a highly proteolytic environment characterized by decreased protein synthesis and increased degradation. Given that sleep deprivation is increasingly prevalent in modern society, strategies to minimize or reverse its adverse effects need to be investigated. Resistance exercise has been suggested as an intervention that would benefit the muscle health. The practice of this type of exercise can increase the concentration of testosterone, growth hormone and insulin-like growth factor I and stimulate the protein synthesis through a key signaling molecule, mammalian target of rapamycin. Thus, we hypothesized that resistance exercise is an important non-pharmacological strategy to counteract deleterious effects of sleep debt on skeletal muscle.

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Background

The importance of sleep has been consolidated in several physiological aspects [1,2]. Population studies have shown that the time available for sleep has considerably decreased during last decades, especially in most industrialized countries, generating a chronic sleep debt in the population, which turned out to be an important public health problem, with large impacts on the economy [3–5]. The persistent reduction of sleep duration and/or quality can induce several adverse effects on health, increasing the risk for chronic diseases such as cardiovascular diseases, metabolic syndromes, cancer, among other [5–9].

One of the most common physiological alterations observed after sleep deprivation is hormone secretion pattern. Several studies have demonstrated that sleep deprivation results in a catabolic state because blood testosterone [10], insulin [11], insulin-like growth factor-I (IGF-I) and growth hormone (GH) [12] are reduced, whereas cortisol (in humans) [13] and corticosterone (in rats) [10] are increased under these conditions.

The muscle health is strongly influenced by hormonal secretion. Testosterone, GH and IGF-1 are known to increase the activity of protein synthesis through phosphatidylinositol-3 kinase/protein

kinase B pathway (PI3K/Akt). Thus they are anabolic hormones [16]. On the other hand, corticosterone/cortisol increases ubiquitination and proteasomal degradation pathway [17]. Thus, typical hormonal secretion patterns induced by sleep debt may decrease protein synthesis and increase protein degradation. These alterations can modify the body composition and potentially impair skeletal muscle health [14,15].

In fact, Dattilo and colleagues (2012), showed that the tibialis anterior muscle and its fibers cross-sectional area were reduced after paradoxical sleep deprivation in rats [10]. These data corroborate the findings of Nedeltcheva et al. (2010), who observed that sleep restriction in humans enhances the effects of low-calorie diet on muscle mass loss [15].

Considering that sleep debt is becoming more common in the general population [1,2,4], it seems to be extremely important to develop strategies that can minimize or even reverse harmful effects of sleep deprivation. Among many alternatives, physical exercise, especially resistance training, appears to be an interesting non-pharmacological strategy against the deleterious effects of sleep debt. Physical exercise is essential for healthy lifestyle and feasible for most of population, with only minor contraindications. Moreover, it has low cost and provides many other benefits to health. Here we discuss how physical exercise, specifically resistance exercise (RE), is important for maintenance of skeletal muscle tissue health [18] and it may overturn muscle atrophy caused by sleep debt.

* Corresponding author. Address: Francisco de Castro, 93. Vila Clementino, São Paulo, CEP 04020-050, SP, Brazil. Tel./fax: +55 11 5572 0177.

E-mail address: tmello@demello.net.br (M.T. de Mello).

Hypothetical profile of protein synthesis and degradation in sleep debt

The muscle mass is mainly regulated by the balance between protein synthesis and degradation. Higher activity of synthetic pathways over degradation pathways results in muscle fiber hypertrophy, and the opposite situation results in muscle atrophy [19]. Protein synthesis requires the activation of translation factors (eukaryotic initiation, elongation and release limiting factors – eIFs, eEFs and eRFs, respectively), which occurs through a cascade of reactions [20]. The PI3K/Akt pathway, which can be stimulated by IGF-1, is one of the important signaling cascades in protein synthesis. It inhibits protein kinase glycogen-3 (GSK-3 β) and activates the mammalian target of rapamycin (mTOR) [16]. The mTOR signaling pathway has a wide range of functions, which culminate in hormonal, nutritional, mechanical, hypoxic and cellular stress signals including the regulation of protein synthesis, cell proliferation, apoptosis and autophagy [21]. Two subsequent downstream proteins of mTOR are p70 ribosomal protein S6 kinase (p70S6K) and eukaryotic translation initiation factor 4-E binding protein 1 (4EBP1). These molecules regulate ribosomal biogenesis and eukaryotic translation initiation factor 4E (eIF4E), respectively. Thus, mTOR is a critical regulator of protein synthesis and cell growth [22].

Testosterone is an anabolic signal molecule, which acts on cell structures stimulating cell growth. In addition to the regulation of gene expression and activation of satellite cell, testosterone also indirectly stimulates mTOR activity by inhibiting REDD1 (regulated in development and DNA damage responses 1), which negatively regulates mTOR [23]. Moreover, testosterone can inhibit the expression of myostatin, a potent inhibitor of muscle growth [24,25]. Another hormone capable of enhancing the protein synthesis pathways is GH. Binding of GH to its membrane-bound receptor initiates Janus kinase 2 (JAK2) signaling. JAK2 has several downstream substrates that signal a variety of cellular functions. Of particular importance, GH-induced JAK2 signaling activates PI3K and, thereby, the previously mentioned Akt/mTOR protein synthesis pathway [26].

Unlike anabolic signal, the cortisol (in human) and corticosterone (in rats) activate the major protein degradation pathway, the ubiquitin–proteasome system, inhibit IGF-1 production in muscle [27,28] and enhance the transcription of REED1, resulting in reduced mTOR activity and its targets [29]. The ubiquitin–proteasome system plays an important role for the degradation of long-lived myofibrillar proteins in skeletal muscle. Two important E3 ubiquitin ligases, atrogin-1 (or MAFbx) and muscle RING-finger protein-1 (MuRF-1) [17,30], are regulated by forkhead transcription factor (FoxO) family members and target myofibrillar proteins for degradation [31].

Considering that 85% of muscle proteins are composed of myofibrillar proteins, conditions that alter the balance between synthesis and degradation of myofibrillar proteins may contribute to muscle hypertrophy or atrophy. Thus, hormonal responses to sleep debt can lead to muscle atrophy by altering the balance of protein synthesis/degradation [10].

Resistance exercise and modulation of protein synthesis

RE is one of the popular physical activity that improves musculoskeletal health [32,33]. The physiological adaptations to RE indicate that mechanical loading, hormonal and metabolic changes, and diverse intracellular events contribute to increased strength and muscle protein synthesis [33,34].

The possible mechanisms of how RE modulates muscle mass seem to be related to the IGF-I [35], which activates the PI3K/Akt/mTOR pathway and induces the protein synthesis, resulting

in muscle growth [34]. Moreover, the mechanical deformation of muscle fibers (contraction and/or stretching), that is an acute effect of RE, is capable to activate the Akt/mTOR pathway, regardless of hormonal changes and immune/inflammatory responses [36].

As mentioned previously, Akt phosphorylates and activates mTOR during muscle overload [36,16]. However, other studies have shown that mechanical deformation can activate mTOR in a PI3K/Akt independent manner [37,38]. Studies with Akt knock-out animals showed increased mTOR activity during mechanical stimulation [37,39,40]. Mechanical stimuli increase phospholipase D, which results in phosphatidylcholine hydrolysis and produces phosphatidic acid (PA) and choline. PA phosphorylates mTOR in FRB (FKBP Rapamycin binding) domain and activates p70S6K, increasing protein synthesis [38]. These large protein interactions possibly occur in the sarcomere through a giant structural protein of sarcomere, the titin, which transmits the information from contractile machinery to the nucleus, affecting gene expression. The titin is located in Z-disk and extends through M-band that contains a serine/threonine kinase domain involved with sarcomere contraction and stretching [41–43].

In addition to the acute effect described above, long term RE can evoke chronic anabolic hormonal response by increasing GH, IGF-I and testosterone release [44–48], which activate the PI3K/Akt/mTOR pathway and stimulates the synthesis of myofibrillar proteins. Also, phosphorylation of FoxO decreases the activity of ubiquitin–proteasome system and muscle proteolysis [41,49]. IGF-I also contributes to muscle growth by stimulating satellite cell proliferation and differentiation [20].

Can resistance training minimize or reverse the muscle atrophy process stimulated by sleep debt?

The resistance exercise is beneficial for prevention and treatment of various health disorders: it improves blood glucose levels, insulin sensitivity [50,51], bone mass [54] and mental health [56]. It prevents from prehypertension state or stage 1 hypertension [52] and metabolic syndrome [53]. RE can also reduce pain and disability in rheumatic diseases [55]. This type of physical exercise is widely practiced around the world, has low cost to the general population and is an important tool for health promotion. Thus, we believe that the muscle and endocrine responses generated by resistance exercise can minimize or even nullify the deleterious effects of sleep debt on skeletal muscle.

Under normal conditions, RE-induced muscular adaptations are an integrated sequence of events. Acute responses, such as hormonal, mechanical and metabolic changes, result in modifications of protein turnover, which can result in chronic adaptation (increased cross-sectional area of muscle fibers) in long-term [57]. As described above, peripheral and intracellular signals (mechanical and hormonal stimuli) converge into these adaptations, and mTOR serves as the master regulator of effectors involved in protein synthesis [16] (detailed in Fig. 1).

Conversely, we speculate that sleep debt-induced muscle atrophy follows the same pathway of RE, but in the opposite direction. That is, the hormonal pattern induced by sleep debt is a potential suppressor of mTOR activity, and resistance exercise provides a potential non-pharmacological intervention for skeletal muscle volume maintenance (as detailed in Fig. 2).

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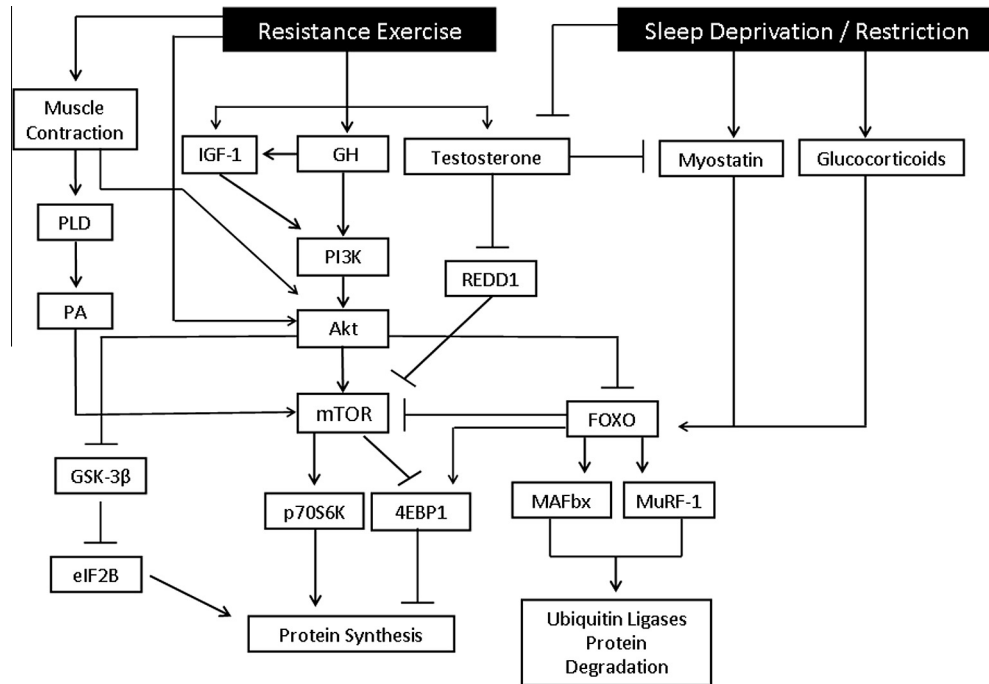


Fig. 1. mTOR: mammalian target of rapamycin, GH: growth hormone, IGF-I: insulin-like growth factor I, eIF2B: eukaryotic initiation factor-2B, PI3K: phosphatidylinositol-3, Akt: protein kinase B, 4EBP1: eukaryotic translation initiation factor 4-E binding protein 1, p70S6K: p70 ribosomal protein S6 kinase, REDD1: regulated in development and DNA damage responses 1, atrogin-1/MAFbx: ubiquitin ligase *atrogin1*/muscle atrophy F-box, FoxO: forkhead transcription factor, MuRF-1: muscle RING-finger protein-1, PLD: phospholipase D, PA: phosphatidic acid, GSK-3β: protein kinase glycogen-3. ↓ activation; ⊥ inhibition.

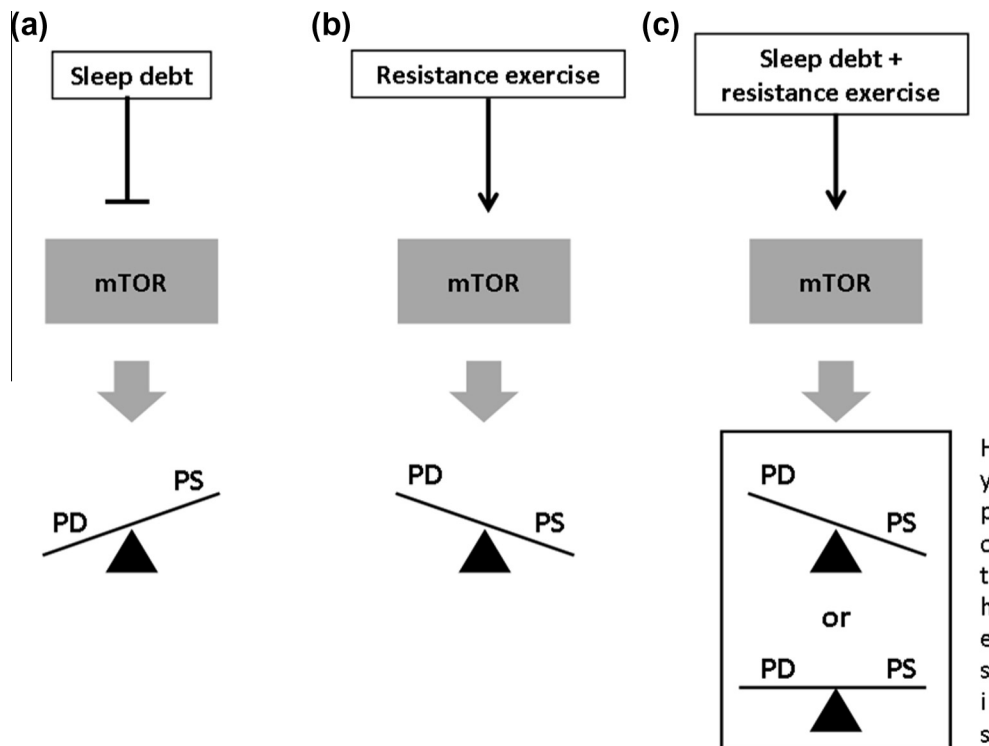


Fig. 2. PD: protein degradation, PS: protein synthesis. (a) Debt sleep promotes catabolic environment leading higher protein degradation than protein synthesis. (b) The resistance exercise leading greater protein synthesis than degradation. (c) The hypothesis study: resistance exercise can minimize or reverse the protein degradation generated by sleep debt, keeping skeletal muscle tissue volume.

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Conflict of interest

None.

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