Sleep and muscle recovery: Endocrinological and molecular basis for a new and promising hypothesis

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ABSTRACT

Sleep is essential for the cellular, organic and systemic functions of an organism, with its absence being potentially harmful to health and changing feeding behavior, glucose regulation, blood pressure, cognitive processes and some hormonal axes. Among the hormonal changes, there is an increase in cortisol (humans) and corticosterone (rats) secretion, and a reduction in testosterone and Insulin-like Growth Factor 1, favoring the establishment of a highly proteolytic environment. Consequently, we hypothesized that sleep debt decreases the activity of protein synthesis pathways and increases the activity of degradation pathways, favoring the loss of muscle mass and thus hindering muscle recovery after damage induced by exercise, injuries and certain conditions associated with muscle atrophy, such as sarcopenia and cachexia.

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Background

Several pieces of evidence point to sleep as an important regulator of numerous biological aspects, maintaining vital physiological functions, homeostasis, learning and memory, by promoting the development of the central nervous system and physical recovery [1,2].

However, in recent years, a reduction in the duration of sleep time is becoming evident in the populations of industrialized countries, motivating a search for a better understanding of the potential health hazards arising from sleep debt. Studies involving both animals and humans have shown that sleep deprivation/restriction results in impairments in many aspects, such as cognitive [3], immunological [4], metabolic [5,6] and hormonal [6–10] functions.

From a metabolic point of view, almost all studies performed in humans suggest that sleep debit favors an increase in body mass [11,12], mainly due to increased hunger and appetite [13]. In contrast, opposing results have been found in mice, where a marked increase in metabolism can be observed for up to 21 days, causing a reduction in body mass in response to protocols that employ total deprivation of paradoxical sleep and its maintenance in the protocols of sleep restriction (shorter sleep per night) [14].

Among the hormonal changes, it is worth noting that major axes are negatively affected, including the hypothalamic–pituitary–adrenal axis [9,15] and hypothalamic–pituitary–gonadal axis [9]. In humans, total sleep deprivation is associated with two distinct outcomes: increases in the secretion of catabolic hormones, such as cortisol [16–18], and changes in the pattern of rhythmic secretion of anabolic hormones, such as testosterone [19]. Furthermore, sleep restriction also seems to be associated with increased levels of cortisol, as described by Spiegel et al. [6]. It should also be noted that significant reductions in testosterone are observed in apneic individuals, who, despite completing seemingly adequate periods of sleep, have clearly impaired sleep quality due to multiple awakenings throughout the night [20].

The animal experiments performed by our group demonstrate that, in rats, paradoxical sleep deprivation results in increases in corticosterone concentrations and reductions in testosterone after just 24 h, and that these concentrations remain altered for up to 96 h [9]. Moreover, other evidence indicates that concentrations of Insulin-like Growth Factor 1 (IGF-1), a hormone with anabolic properties that is secreted predominantly by the liver in response to growth hormone, are rapidly reduced under conditions of sleep deprivation [10].

Hormonal changes resulting from sleep deprivation/restriction and its impact on skeletal muscle metabolism

Considering the physiological properties that the hormones testosterone, IGF-1 and cortisol/corticosterone have on the body, a potentially catabolic and proteolytic environment may be present in sleep debt conditions. Although this condition appears to be associated with increased body mass in humans, the mechanisms responsible for this association need to be better understood,

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considering that individuals deprived of sleep for 72 h showed higher urinary excretion of urea, suggesting greater muscle proteolysis [21]. A second piece of evidence that raises questions about this issue is the interesting finding reported by Nedeltcheva et al. [22], in which a 14-day calorie restricted diet caused similar reductions in body mass in people who slept either 5.5 or 8.5 h (sleep restriction versus normal sleep, respectively). However, under the conditions of sleep restriction, the decrease in fat mass was 55% lower and, interestingly, the loss of muscle mass was 60% higher. This suggests that a peculiar pattern of hormone secretion may promote different effects in modulating body composition, and that skeletal muscle can potentially be impaired.

Considering the large number of deleterious effects observed under conditions of sleep debt, many researchers have aimed to better understand the molecular mechanisms involved in these situations. Thus, it is pertinent to further consider the impact of sleep deprivation/restriction on the expression of intramuscular proteins that are directly involved in maintaining muscle mass.

Given that body mass is maintained on the basis of an energy balance, i.e., when energy consumption equals caloric expenditure, maintenance of muscle mass reflects a balance between the relative rates of protein synthesis and degradation, with the predominance of synthesis favoring muscle hypertrophy (protein accretion), while the prevalence of degradation instead results in muscle atrophy and a loss of protein content. Moreover, the maintenance of skeletal muscle is tightly regulated by hormonal and nutritional factors that, in turn, modulate the dynamic balance between anabolic (hypertrophy) and catabolic (atrophy) reactions, thereby determining muscle protein content [23].

The theoretical foundation, pioneered by our group, for the relationship between hormonal patterns resulting from sleep deprivation/restriction and reductions in protein synthesis and/or increased proteolysis, as mediated by the expression of proteins involved in the hypertrophy and atrophy pathways, is extremely strong, plausible and promising. Therefore, the impact of sleep deprivation/restriction on muscle metabolism observed in humans [22] can, in part, be explained by this model. Concerning rats, although there are no reports in the literature regarding the direct impact of sleep deprivation/restriction on skeletal muscle, it is pertinent to consider that the reduction in body mass [14] is accompanied by muscle atrophy.

Pathways involved in protein synthesis and degradation, and its possible modulation in response to sleep deprivation/restriction

IGF-1-mediated signaling is a central element in the stimulation of muscle protein synthesis, best characterizing muscle growth and relating to adaptive processes in skeletal muscle [24]. In muscle, the binding of IGF-1 to its receptor promotes the activation of phosphatidylinositol 3-kinase (PI3K) and Akt, which induces muscle hypertrophy. This is primarily mediated by stimulation of protein translation via regulation of glycogen synthase kinase-3β (GSK-3β) and mammalian Target of Rapamycin (mTOR) [25], resulting in increased p70S6 kinase activity, a determinant of cell size and ribosome biogenesis.

The mTOR pathway is a master positive regulator of protein synthesis, integrating signals from growth factors, nutrients, hypoxia, and cellular stress, and stimulating the binding of eIF4G to eIF4E to promote cap-dependent translation initiation [26]. Moreover, phosphorylation and activation by mTOR of p70S6 kinase is an important determinant of cell and skeletal muscle size [27–29].

Testosterone mediates its anabolic properties by binding to cytoplasmic androgen receptors, which migrate to the nucleus and bind specific regulatory (promoter) sequences, thereby increasing transcription and stimulating protein synthesis. In addition, testosterone can also indirectly promote transcription and protein synthesis by inhibiting the activity of Regulated in Development and DNA damage responses 1 (REDD1), a protein that blocks the activity of mTOR [30].

Some evidence indicates that testosterone is capable of inhibiting myostatin, a member of the TGF-beta superfamily that inhibits skeletal muscle growth [31] by inhibiting satellite cell proliferation and differentiation, a critical step in muscle recovery and growth. This results in a downregulation of the myogenic regulatory factors, MyoD and myogenin [32–34].

Elevated levels of cortisol/corticosterone, may modulate muscle protein metabolism because glucocorticoid-induced muscle atrophy is associated with both increased catabolism [35] and reduced synthesis [36] of muscle proteins, which further potentiate the muscular atrophy. The ubiquitin–proteosome pathway has been linked to much of the increase in muscle protein catabolism that occurs during atrophy [37,38]. In this pathway, ubiquitin ligases mark proteins for degradation by covalent modification with poly-ubiquitin chains [39]. Two muscle-specific E3 ubiquitin ligases, muscle atrophy F-box (MAFbx; also called atrogin-1) and Muscle RING-Finger-1 (MRF1), play important roles in muscle atrophy. Another mechanism for the actions of these glucocorticoids is through up-regulation of REDD1 [40], thereby inhibiting mTOR and p70s6 kinase and reducing protein synthesis.

Integrating these results suggests that sleep deprivation/restriction results in reductions in IGF-1 and testosterone concentrations, which may be able to decrease the activity of the IGF-1/PI3K/Akt and mTOR pathways, also diminishing the signal inhibition for myostatin expression, thereby promoting protein degradation. The increase in glucocorticoid levels up-regulates REDD1, activates the ubiquitin–proteosome system and up-regulates myostatin expression, which further reduces the rates of protein synthesis by increasing protein degradation and promoting muscle atrophy.

Can the process of muscle recovery be damaged by sleep deprivation/restriction?

Sleep, and the lack thereof, should be stressed as contributing an important role in the process of muscle recovery after certain kinds of damage, whether induced by exercise or injury. It is well established that muscle has highly plastic properties and is capable of recovering from several types of damage. However, significant molecular changes are required to allow damaged cells to recover or be replaced by new cells, involving steps that depend on the proliferation, fusion and differentiation of satellite cells [41]. These
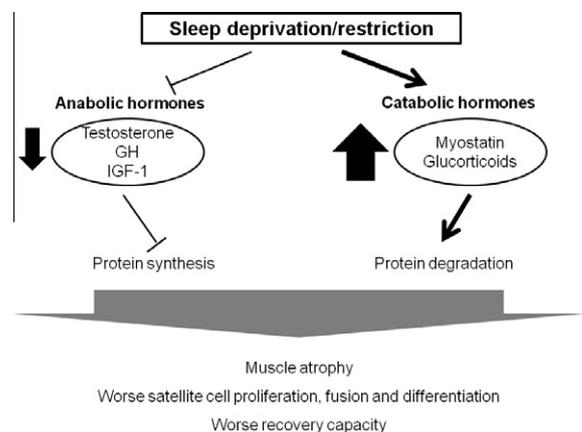

Fig. 1. Schematic representation of the effects of sleep debt on skeletal muscle metabolism.

processes must be accompanied by a concomitant signal of muscle hypertrophy because the cells need to increase in volume until the muscle fibers reach their ideal size. Such growth is dependent on the activation of the aforementioned syntheses pathways and inhibition of protein degradation pathways. It is noteworthy that these issues are relevant to the clinical condition of sarcopenia, characterized by decreased protein synthesis signaling and increased apoptosis, which occurs in the elderly population and in the setting of certain diseases, such as cachexia.

Thus, we hypothesize that sleep debt damages muscle physiology and impairs muscle recovery because of increased stimulation of protein degradation, which is detrimental to protein synthesis and promotes muscular atrophy. Muscle recovery would potentially be compromised because this process is strongly regulated by the previously discussed anabolic and catabolic hormones, which are strongly influenced by sleep (as detailed in Fig. 1). By expanding our knowledge of these issues, a new field of research can be established to investigate various strategies for minimizing the deleterious effects arising from a lack of sleep.

Conflict of interest

None declared.

Acknowledgements

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