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Sleep, circadian biology and skeletal muscle interactions: Implications for metabolic health

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ABSTRACT

There currently exists a modern epidemic of sleep loss, triggered by the changing demands of our 21st century lifestyle that embrace 'round-the-clock' remote working hours, access to energy-dense food, prolonged periods of inactivity, and on-line social activities. Disturbances to sleep patterns impart widespread and adverse effects on numerous cells, tissues, and organs. Insufficient sleep causes circadian misalignment in humans, including perturbed peripheral clocks, leading to disrupted skeletal muscle and liver metabolism, and whole-body energy homeostasis. Fragmented or insufficient sleep also perturbs the hormonal milieu, shifting it towards a catabolic state, resulting in reduced rates of skeletal muscle protein synthesis. The interaction between disrupted sleep and skeletal muscle metabolic health is complex, with the mechanisms underpinning sleep-related disturbances on this tissue often multifaceted. Strategies to promote sufficient sleep duration combined with the appropriate timing of meals and physical activity to maintain circadian rhythmicity are important to mitigate the adverse effects of inadequate sleep on whole-body and skeletal muscle metabolic health. This review summarises the complex relationship between sleep, circadian biology, and skeletal muscle, and discusses the effectiveness of several strategies to mitigate the negative effects of disturbed sleep or circadian rhythms on skeletal muscle health.

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1. Introduction

Sleep is essential for sustaining life, with humans spending approximately one third of their existence asleep [1,2]. Guidelines from the National Sleep Foundation advocate that 7–9 h of sleep each night is required for maintaining health in adults [3], but roughly one third of Americans aged 18 and over fail to meet these recommendations [4]. This modern epidemic of sleep loss coincides with the shifting demands of our 21st century lifestyle [5,6] that place a premium on 'round-the-clock' remote working hours, made possible by 24 h access to light, food, and internet-based social activities. In the face of low levels of habitual physical activity and the ease of acquiring unrestricted energy-dense snacks, normal circadian rhythms are disrupted, carrying profound implications for many physiological and metabolic processes [7]. For example, adults who fail to meet the recommended quantity of sleep have an increased risk of all-cause mortality [8], with chronic sleep insufficiency underpinning numerous negative health and performance-related outcomes [9–13]. During periods of short-term and chronic sleep restriction there are disruptions to skeletal muscle and whole-body glucose homeostasis that predispose individuals to several disease states including obesity, insulin resistance, and type 2 diabetes [14–17]. Endocrine function is also sensitive to reductions in sleep duration, provoking alterations in the concentrations of appetite hormones such as leptin and ghrelin, which influence feelings of hunger and satiety [12,15]. Additionally, the secretion of steroid hormones are affected by sleep, with higher concentrations of plasma cortisol reported in healthy adult males the evening following one night of acute sleep deprivation [18]. These alterations to the hormonal milieu induced by insufficient sleep may be a catalyst underpinning disturbances to skeletal muscle metabolism. Indeed, disturbed sleep results in decreased rates of muscle protein synthesis in healthy male adults [19] that,

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Abbreviations

ALS	autophagy lysosome system
AMPK	AMP-dependent protein kinase
BDNF	brain-derived neurotrophic factor
BMAL1	brain and muscle ant-like protein-1
CLOCK	circadian locomotor output cycles kaput
CRY	cryptochrome
DNA	deoxyribonucleic acid
EEG	electroencephalogram
ERK	extracellular signal-regulated kinase
FNDC5	fibronectin type III domain containing 5
FOX	forkhead box
FSR	fractional synthetic rate
GH	growth hormone
HIF-1α	hypoxia-inducible factor 1α
HPA	hypothalamic-pituitary-adrenal
IGF-1	insulin-like growth factor one
MPS	muscle protein synthesis
MPB	muscle protein breakdown
mTOR	mammalian target of rapamycin
NREM	non-rapid eye movement
PER	period
PGC-1α	peroxisome proliferator-activated receptor y coactivator 1α
PPARδ	proliferator-activated receptor δ
REM	rapid eye movement
SCN	suprachiasmatic nucleus
SWS	slow wave sleep
UPS	ubiquitin proteasome system

over time, may result in a loss of lean mass and concomitant reductions in muscle strength and functional outcomes [20].

To rescue some of the deleterious effects of sleep loss on health and wellbeing triggered by our modern-day lifestyle, there is a need to understand the mechanisms that underpin the perturbations to metabolic and hormonal homeostasis incurred by insufficient sleep, and their impact on skeletal muscle and other organs/tissues. Identifying these mechanisms is important to develop and implement preventative public health strategies to combat the detrimental effect of sleep loss at both the individual and population level. As the light/dark cycle is the dominant 'zeitgeber' (time giver) for the endogenous molecular clock and has a major influence on the sleep/wake cycle, an understanding of the interactions between sleep disturbances and circadian biology and how these impact on peripheral tissues is critical to develop the most efficacious interventions to tackle our modern-day sleep epidemic. This review outlines the importance of adequate sleep for human function, provides a synopsis of circadian biology, and highlights the complex interactions between sleep, circadian biology, and skeletal muscle. A discussion of several strategies to help overcome the negative effects of disturbed sleep or circadian rhythms on skeletal muscle health are also summarised.

2. Sleep architecture and the role of sleep in human function

There are two distinct stages of sleep, consisting of rapid eye movement (REM) and non-rapid eye movement sleep (NREM) [21,22]. REM sleep is characterised by episodic bursts of rapid eye movements, reductions in core and skin temperature, an irregular respiratory rate, and muscle atonia [23,24]. REM sleep, measured using electroencephalography (EEG), reveals low-amplitude, high-frequency brain waves, similar to those observed during periods of wakefulness [25]. The increased brain activity during REM sleep is associated with dreaming and has been proposed to play a critical role in memory consolidation [26]. NREM sleep is comprised of three phases: the first phase (N1) is considered a transitional stage of sleep and is characterised by the reduction of alpha brain waves and cessation of saccadic eye movements [27]. During stage two (N2), the emergence of short bursts of mixed-frequency sleep spindles and high-amplitude K-complexes are observed [27]. While these first two phases are considered 'light sleep', stage three (N3) is referred to as 'deep sleep' or slow wave sleep (SWS) due to the presence of high-amplitude, low-frequency delta brain waves [28]. Although a fourth stage of NREM sleep has been reported [29], this category has since been combined with stage three, collectively referred to as N3, mainly due to the difficulties associated with discerning the complex composite neuronal activity.

Sleep plays a critical role in maintaining whole-body homeostasis and preserving normal physiological and psychological function [10–12,21,26,30]. Sleep has a complex and often bi-directional relationship with many organs and tissues in the body that impact metabolic [31], immune [11], endocrine [30], musculoskeletal [20], and cognitive processes [26]. Adequate sleep facilitates complex higher cognitive processes such as memory consolidation and learning [26], whereas bouts of insufficient sleep act as a catalyst for decreased cognitive performance, manifested by increased reaction times, lapses in attention, and cognitive dysfunction [10]. An association between patterns of reduced sleep and decreased performance and function is also observed in other physiological processes [12,15,30,32]. However, the complex nature of sleep coupled with difficulties in controlling behavioural and environmental factors has made it challenging to determine the precise mechanisms that underpin declines in performance and physiological function.

3. Circadian biology: keeping time

Circadian rhythms are defined as roughly 24 h oscillations in biological and metabolic pathways, with a large number of these daily cycles dependent on endogenous molecular clocks that control a significant portion of the genome. While many of the molecular and physiological oscillations can vary in amplitude and even phase, they share a 24 h periodicity, which temporally follows the earth's rotation around its axis. Circadian rhythmicity can be observed in many physiological processes including sleep, core body temperature, glucose metabolism, heart rate, blood pressure, and hormonal and neurotransmitter secretion [33]. The circadian clock is cell autonomous and present in most human tissues/organs, with each tissue containing clocks exhibiting properties based on the sum of all the cell clocks in that tissue. The circadian clock is organised in a hierarchical manner with the hypothalamic suprachiasmatic nucleus (SCN) functioning as the 'central clock' [34,35]. Examples of SCN-directed circadian rhythms include the sleep-wake cycle, meal timing, glucose metabolism, insulin secretion, and learning and memory [33].

At the epicentre of the molecular complex that constitutes the circadian clock are the core transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle arnt-like protein-1 (BMAL1) that collectively drive the transcription of a large array of clock-controlled genes. CLOCK and BMAL1 also orchestrate the transcription of their own repressors, period (PER)

and cryptochrome (CRY), forming a self-regulated feedback loop. In humans, during the active phase of the day, which typically corresponds with daylight hours, increases in the transcription of *per* and *cry* genes results in the accumulation of the PER and CRY circadian repressors: these sequentially inhibit CLOCK-/BMAL1-driven transcription of *per*, *cry* and other clock-activated genes. While rodents express similar patterns of core clock genes in skeletal muscle, their expression is aligned with the night-time hours of the rest/active cycle [36]. The regulated degradation of PER and CRY alleviates transcriptional repression and permits CLOCK-/BMAL1-mediated transcription to proceed once again, thus underpinning the recurring and rhythmic cycles in circadian gene expression [33–35].

'Zeitgebers' are external time cues that function to align and 'fine tune' the body's endogenous clock mechanisms with the prevailing external environmental conditions. Light exposure is the dominant zeitgeber for the SCN oscillator, which then orchestrates rhythms in the peripheral organs/tissues at appropriate phases. Circadian cycles can also be reprogrammed or phase-shifted by cues from peripheral tissues/organs as they adjust to changing environmental or behavioural signals. Such fine tuning to the SCN comes from a variety of inputs including the sleep-wake cycle, food intake (both the timing of meals and meal composition), and patterns of physical activity/inactivity. In this regard, skeletal muscle is a major peripheral tissue capable of recalibrating circadian oscillations by virtue of its central role in maintaining whole-body and cellular homeostasis. Accounting for about 45% of total body mass, skeletal muscle is the major insulin sensitive tissue for postprandial glucose disposal, while exerting a major impact on core body temperature (via shivering or sweating) and driving metabolic rate via patterns of physical activity/inactivity [37]. Physical activity modulates the molecular clock in skeletal muscle, affecting both the amplitude and phase of circadian oscillations [38]. Over 2300 genes governed by circadian oscillations have been identified in skeletal muscle with crucial roles in myogenesis, transcription, and metabolism [39]. Recent attention has focussed on the timing of exercise bouts to coordinate with an individual's circadian rhythms as an efficacious strategy to maximize the health benefits of exercise [40]. Synchrony between the SCN and peripheral clocks is important, as several deleterious outcomes arise if phases of the clocks become misaligned. For example, altered sarcomere structure, mitochondrial pathologies, and impaired muscle function have been observed in skeletal muscle of rodents with circadian misalignment [41], while disturbed metabolism and peripheral insulin resistance have been reported in humans [36]. Factors that disrupt synchronicity between the SCN and peripheral clocks include insufficient sleep, perturbations to the normal timing of meals that alter individual feeding-fasting cycles, and variations to patterns of physical activity and inactivity [36,42], all of which have been exacerbated by the ongoing global pandemic [43].

4. Skeletal muscle and sleep cross-talk

The human sleep/wake cycle can be described by the two-process model of sleep, involving the interaction of circadian rhythms and homeostatic drive [21]. While awake, levels of adenosine accumulate in the brain causing a build-up of 'sleep pressure' throughout the day. This increase in adenosine concentrations has been proposed to be responsible for the inhibition of excitatory neurons and suppression of CNS activity, which decreases wakefulness, subsequently inducing feelings of sleepiness and a desire to sleep [21]. In conjunction with the homeostatic drive, the SCN detects multiple zeitgebers from the environment that synchronise the body's internal clock and signal the release of hormones (e.g., melatonin) that facilitate the process of falling asleep. Thus, the interaction of homeostatic drive and normal circadian oscillations largely regulate the sleep/wake cycle. However, over the lifespan, there are age-related changes to sleep patterns (both architecture and duration) influenced by intrinsic and extrinsic factors that, in turn, are associated with alterations to the function of several major tissues, including skeletal muscle. For instance, the composition of sleep architecture changes with age, with infants and children obtaining longer sleep durations compared to adolescents, adults, and the elderly [44]. In older age, when regular sleep patterns are not attained, anabolic signalling pathways in skeletal muscle are down-regulated, contributing to a loss of lean mass and a predisposition to sarcopenia [45]. In this regard, peak skeletal muscle mass is attained within the first three decades of life and thereafter begins to decline with the incidence and severity of sarcopenia progressively increasing over the remaining lifespan. Muscle mass is lost in the course of healthy ageing from approximately age 30 years, a loss reaching a rate of ~1% per year after the age of 65, and associated with a corresponding 2–3 fold loss in strength [46]. The coexistence of diminished muscle mass coupled with increased fat mass, so-called 'sarcobesity', is ultimately manifested by impaired mobility and/or development of many chronic life-style-related diseases [46]. Accordingly, achieving appropriate sleep durations is important for maintaining the integrity of muscle mass across the lifespan.

At the cellular level, the maintenance of muscle tissue is regulated throughout the day by a series of cyclic metabolic processes that coordinate rates of protein synthesis and protein breakdown [47]. Such processes are influenced by habitual levels of physical activity, age, and dietary protein availability. If the rate of muscle protein synthesis is greater than the rate of protein breakdown over a sustained period (i.e., several weeks and months), there is a net increase in protein accretion and muscle hypertrophy [48]. When rates of muscle protein breakdown exceed the rate of protein synthesis for sustained periods, there is a loss of muscle mass [49]. Rates of muscle protein synthesis can be augmented by several factors including resistance-based exercise, protein intake and meal timing, the hormonal milieu, and sleep [9,19,48–51]. Exactly how protein signalling pathways interact with fragmented or insufficient sleep durations is unknown. For instance, a night of complete sleep deprivation induces a catabolic environment, possibly leading to a subsequent increase in the rate of muscle protein breakdown [52]. In contrast, there have been reports of no changes in the expression of proteolytic genes after a night of sleep deprivation [19]. These differences may be attributed to the varying timepoints (07:30 [52] vs 13:00 [19]) at which muscle biopsies were collected and differences in nutrition status (fasted [52] vs postprandial [19]). While there are direct links between sleep quality and duration, and skeletal muscle homeostasis, our understanding of how the critical nodes that control muscle bioenergetics are disrupted by disordered sleep are incomplete. How systemic inflammation in response to disturbed sleep influences muscle health and functional outcomes is an important consideration, as inflammation may contribute to muscle protein breakdown and impaired myogenesis [53]. The influence of circadian biology in these processes may also be a factor determining the magnitude of responses.

5. Circadian rhythm and skeletal muscle

The interactions between circadian rhythms, peripheral clocks, and skeletal muscle function have been reviewed previously [41,54,55]. Peripheral clocks, located in skeletal muscle tissue are predominantly regulated by BMAL1, CLOCK, PER, and CRY genes [54,55], with their expression largely regulated by the prevailing muscular environment (i.e., contractile state) and the timing of

meals [56]. Zambon et al. [56] used DNA microarrays to determine the effects of a single bout of resistance exercise on gene regulation in human muscle biopsy samples obtained six and 18 h after an acute bout of isotonic unilateral knee extensions. A comparison of gene expression profiles of the exercised and non-exercised legs revealed 704 genes were differentially regulated after 6 h, and 1479 genes at 18 h post exercise, whereas in the non-exercised 'control' leg, only 608 genes were differentially regulated at comparable time points. The bout of resistance exercise upregulated circadian clock genes (*Per2*, *Cry1*, and *Bmal1*) and circadian output genes, demonstrating that peripheral clocks are regulated independently of the SCN [56]. In support of this contention, Dyar et al. [57] report that contractile activity controls the oscillation of around 15% of skeletal muscle circadian genes independently of the core muscle clock, thereby providing direct evidence that circadian locomotor activity rhythms drive circadian rhythms of selected nuclear translocation and target gene expression.

The local 'muscular environment' appears to be sensitive to modifications to the expression of circadian clock genes, with circadian rhythms influencing rates of skeletal muscle protein synthesis [55]. Chang et al. [58] reported that circadian oscillations occur in the phosphorylation of the mammalian target of rapamycin (mTOR)/p70S6K and extracellular signal-regulated kinase (ERK) pathways in different tissue (cardiac versus skeletal muscle) and muscle fibre types (oxidative vs glycolytic). These findings suggest that the circadian oscillation in the activities of protein synthesis-related intracellular signalling pathways are tissue-specific [58]. While the precise mechanism underpinning the circadian oscillation of mTOR/p70S6K remain to be determined, the importance of activating the mTOR pathway and its downstream effector, p70S6K, and their roles in the regulation of muscle protein synthesis is well established [59]. Determining the interaction between circadian oscillations and the molecular pathways that underpin skeletal muscle protein balance is an important avenue for future research, as preservation of muscle mass is critical to maintain metabolic health and function.

6. The effects of disturbed circadian rhythms on skeletal muscle physiology

There are numerous mediators that act to disrupt the normal rhythm of the molecular clock. Insufficient or fragmented sleep is a common cause of disruption to daily biological rhythms and metabolic homeostasis, with just one night of total sleep deprivation suppressing BMAL1 expression in human peripheral leukocytes [60]. In BMAL1 global knock-out Macaque monkeys, higher nocturnal locomotion and reduced sleep are observed with physiological circadian disruption reflected by the markedly dampened and arrhythmic levels of blood hormones and disturbances to blood cortisol concentrations [61]. While suppression of BMAL1 inhibits sleep, this 'master' clock protein also plays a vital role in regulating sleep patterns [62]. Rodent models support the relationship between core clock genes and sleep/wake behaviour, with BMAL1 activity in skeletal muscle identified as a critical regulator of NREM sleep duration [62]. However, the mechanisms of how skeletal muscle BMAL1 activity influences sleep architecture in humans are not well established.

Disrupted biological rhythms negatively impact several physiological processes, including muscle atrophy [55,63] and disturbances to normal mitochondrial function [64], combining to exacerbate metabolic conditions such as sarcopenia and type 2 diabetes [65]. Mitochondrial health and function are critical for skeletal muscle physiology, with over a third of the proteins in the mitochondrial proteome exhibiting circadian patterns [55,66]. Rhythmicity of the mitochondria are also observed on a functional level, with rates of muscle mitochondrial respiration exhibiting daily oscillations in both rodent [67] and human [64] skeletal muscle. When the daily oscillation of protein expression in the mitochondria is disturbed, there are reductions in the quantity of mitochondria, elevated apoptosis, and detrimental effects on exercise capacity [66]. When biological rhythms are disturbed by periods of insufficient sleep, there are marked reductions in the amplitude of the diurnal rhythm of peripheral skin temperature along with impaired mitochondrial function. In healthy young males, five nights of sleep restriction reduced glucose tolerance and decreased mitochondrial respiratory function [50]. The relationship between disturbed sleep and impaired glucose metabolism is highlighted by the sensitivity of postprandial glycaemic control to disrupted sleep/wake behaviours [68]. It appears that glucose kinetics are significantly influenced by sleep efficiency, with postprandial glycaemic control impaired in adults when delayed bedtimes were implemented and poor sleep efficiency was present [68]. Additionally, disruptions in skeletal muscle core-clock genes, lower magnitude and quantity of cycling genes, and altered patterns of oxygen consumption are observed in individuals with type 2 diabetes [64]. These findings highlight the sensitivity of the interplay between endogenous rhythms and metabolic health (Fig. 1).

7. The effect of insufficient sleep on skeletal muscle physiology

Insufficient sleep has consistently been shown to contribute to muscle atrophy [69–72] and in rodent models, restricted sleep is linked to atrophy of muscle tissue [70,71,73,74]. Reductions in muscle tissue weight and cross-sectional area of the plantaris muscle were observed in 75-day-old Wistar rats after 96 h of paradoxical sleep deprivation compared to a control group of animals with normal sleep patterns [74]. Additionally, decreases in body mass, along with reductions in tibialis anterior mass were reported after 96 h of paradoxical sleep deprivation in three-month-old Wistar rats [70]. The proposed mechanism responsible for sleep-deprivation induced muscle atrophy in rodents may be due to alterations to the local hormonal environment, with increased levels of corticosterone and reduced levels of testosterone a response to reductions in sleep [70,71,73,74] (Fig. 2). Additionally, the catabolic environment may act as a trigger for increased activity of the glucocorticoid signalling pathway which may have downstream effects on protein synthetic rates and protein degradation in skeletal muscle [75].

While sleep restriction induces muscle atrophy in rats, it is important to place such findings in context: there is a large degree of homogeneity within individual skeletal muscles from rodents, but this is not the case for humans [37]. For example, muscle atrophy induced by restricted sleep is preferentially confined to type IIa and IIb muscle fibres of the gastrocnemius when three-month-old Wistar rats were subjected to 96 h of paradoxical sleep deprivation [71]. Furthermore, oxidative muscle tissue of the soleus from rodents was resistant to sleep restricted muscle atrophy compared to glycolytic muscle tissue of the flexor digitorum longus and tibialis anterior, and mixed fibre types of the gastrocnemius in adult male Wistar rats [73]. It appears that insufficient sleep has the most marked effect on glycolytic muscle fibres, with muscles comprised of predominantly fast twitch fibres being more sensitive to sleep deprivation than slow-twitch, oxidative type I fibres.

Compared to rodent models, the relationship between sleep restriction and muscle atrophy in humans has received less investigation [19,50,76]. Population data has suggested chronic insufficient or poor-quality sleep is correlated to lower muscle mass [77], although the precise mechanisms that underpin these observations

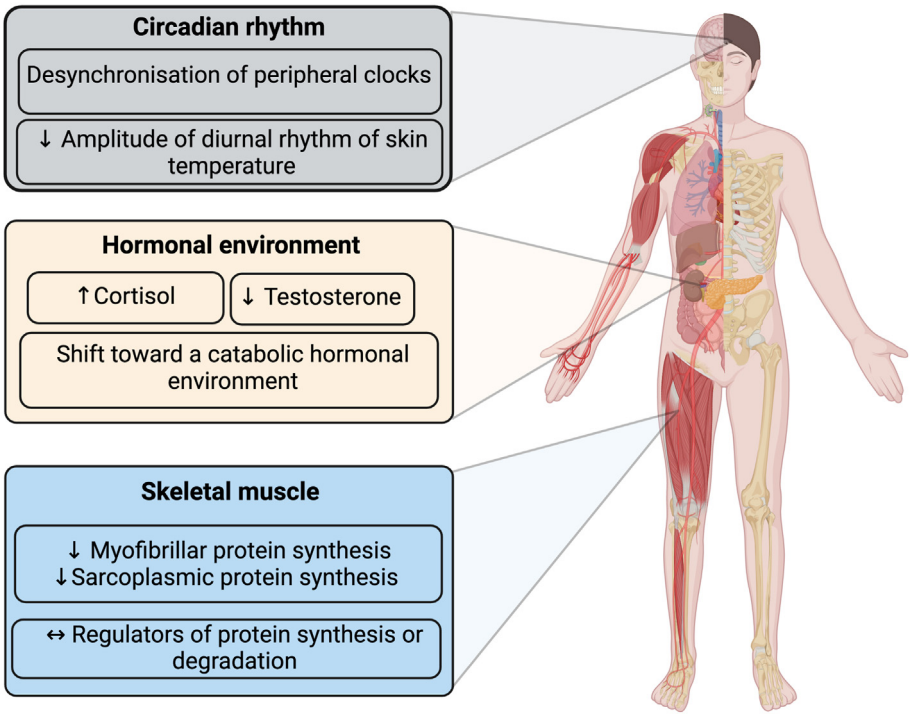

Fig. 1. Effects of insufficient sleep on the muscular environment.

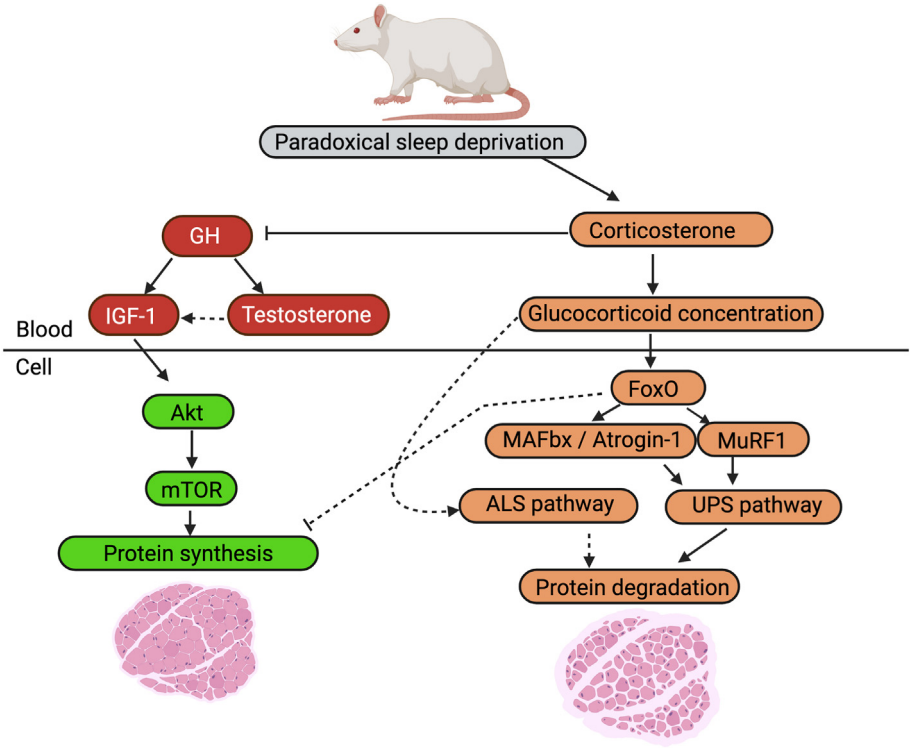

Fig. 2. Potential mechanisms that affect rates of skeletal muscle protein turnover after paradoxical sleep deprivation in rodents. Elevated levels of corticosterone in response to paradoxical sleep deprivation can cause stimulation of the forkhead box O (FoxO) family, MAFbx1, and muscle RING finger protein (MuRF1) which can amplify the activity of the ubiquitin proteasome system (UPS) and autophagy lysosome system (ALS) protein degradation pathways [75]. Additionally, the elevation of catabolic hormones may down-regulate the phosphorylation of proteins involved in the Akt-mTOR pathway [70], inhibiting rate of protein synthesis. GH: Growth hormone, IGF-1: Insulin-like growth factor one, mTOR: Mammalian target of rapamycin.

are not well understood. To date, studies reveal that acute and chronic (one to five nights) bouts of insufficient sleep negatively affect rates of muscle protein synthesis in healthy adults [19,69,76]. Saner et al. [76] found reduced sleep (4 h sleep opportunity each night) over five nights impaired myofibrillar protein synthesis in the vastus lateralis (fractional synthetic rate (FSR): 1.24 ± 0.21% d^{-1}) in healthy male adults compared to an 8 h sleep opportunity (FSR: 1.53 ± 0.09% d^{-1}). Additionally, Lamon et al. [19] reported one

night of total sleep deprivation was sufficient to decrease muscle protein synthesis in the vastus lateralis by 18% (FSR: 0.059 ± 0.014%·h^{-1}) compared to a night of normal sleep (FSR: 0.072 ± 0.015%·h^{-1}). This reduction in FSR after sleep deprivation is of a similar magnitude to the decreases in muscle protein synthesis observed after short-term energy restriction [78].

7.1. The interplay between sleep, circadian rhythms, the hormonal environment, and skeletal muscle

The endocrine system and sleep have an intricate bi-directional relationship [79], with sleep affecting the secretion of hormones and in turn, sleep being affected by their secretion. Hormones commonly reported when assessing the interaction between sleep and muscle tissue include cortisol, testosterone, insulin-like growth factor 1 (IGF-1) and growth hormone (GH) [19,69,80], all of which are subject to diurnal rhythms. However, there are marked differences in the hormonal profiles between males and females, without consideration of the normal hormonal fluctuations encountered during the menstrual cycle [81]. Cortisol is secreted by the adrenal glands in a pulsatile cycle, with the highest concentrations typically measured in the early morning upon waking, and declining throughout the afternoon and evening [79]. In contrast, low concentrations of testosterone are observed in the late evening, followed by a rise shortly after the onset of sleep, reaching their highest levels during the early morning in healthy adult males [82]. In addition, GH, secreted by the pituitary gland, occurs during SWS, with the majority (~80%) of the total 24-h GH release occurring during the first 90 min of sleep [83]. Sleep is a critical regulator of these endocrine secretions, with each hormone showing regular oscillations in their expression and often being sensitive to disrupted or fragmented sleep, altering their patterns of expression [79].

In rodents, chronic sleep deprivation markedly affects the expression of a several hormones, with prolactin, leptin, GH, and IGF-1 suppressed by paradoxical sleep deprivation [84]. Additionally, the pulsatile nature of GH appears to be shunted by sleep deprivation, with the high-amplitude pulses which normally occur during the first episode of SWS not observed when sleep is disrupted [85]. In contrast, catabolic 'stress' hormones such as corticosterone are elevated in response to paradoxical sleep deprivation [70,71]. In response to sleep deprivation, there may be an emergence of a potential 'anabolic resistant' phenotype, as observed in elderly humans, causing a decrease in the rate of muscle protein synthesis even in the presence of adequate amino acid availability [71,86]. It has also been suggested that the elevation of catabolic hormones down-regulates the phosphorylation of proteins involved in the Akt-mTOR pathway [71], further inhibiting rates of protein synthesis. This pattern of a sleep-restricted catabolic hormonal environment is thought to be similar in humans.

Disrupted sleep phases lead to shorter periods of REM sleep, which may induce increases in cortisol levels due to disruption of the hypothalamic-pituitary-adrenal (HPA) axis [13]. As a result of increased HPA activity, corticotropin-releasing hormone is secreted from the hypothalamus causing a downstream effect on both the anterior pituitary gland and subsequently, the adrenal glands, resulting in elevated levels of cortisol released [87], promoting a more catabolic environment. One night of complete sleep deprivation was sufficient to elevate plasma cortisol levels by 21% in healthy adult male and females [19]. Additionally, plasma cortisol was reported to be elevated by 37% the evening after acute partial sleep restriction and by 45% after complete sleep deprivation [18]. Considering the role of cortisol and glucocorticoids in stimulating muscle protein degradation pathways such as the ubiquitin proteasome system (UPS) and the autophagy lysosome system (ALS) [88], insufficient sleep is likely to be a catalyst for a catabolic and proteolytic muscular environment, potentially promoting anabolic resistance in humans.

Anabolic hormones such as testosterone, GH, and IGF-1 are regulators of muscle tissue growth and repair through their effect on rates of muscle protein synthesis [89]. However, during periods of insufficient sleep, anabolic hormone concentrations in healthy adult males decrease [90]. For example, Lamon et al. [19] observed a 24% decrease in testosterone concentration following a single night of sleep restriction in a cohort of healthy young adult males and females. Although the study was not powered to detect between-sex differences, male participants encountered greater declines in testosterone during periods of sleep deprivation compared to females. In contrast, there were no observable changes in total testosterone, but a higher ratio of cortisol:testosterone after 48 h of sleep deprivation followed by a 12-h sleep in a group of healthy males [69]. However, both studies reported a similar pattern of perturbed testosterone secretion across the day [19,69]. It is important to acknowledge the physiological differences in hormonal profiles between males and females [91] as findings and recommendations from research are likely to be sex-specific. Therefore, further investigation into sex-specific differences in hormonal changes, as well as how they interact with sleep and the muscular environment is warranted [92]. Moreover, accounting for the variation in hormone concentrations during the menstrual cycle may be prudent, as hormonal fluctuations with varying stages of the menstrual cycle have been observed and how these changes interact with sleep are largely unknown.

8. Mitigating the effects of insufficient sleep

Considering the detrimental effects of sleep deprivation on skeletal muscle, several strategies to attenuate muscle tissue atrophy induced by insufficient sleep have been proposed [50,71,72,74]. In rodent models, high-intensity resistance-based exercise or leucine supplementation may provide a protective mechanism against sleep-restricted muscle atrophy by stimulating muscle protein synthesis via the Akt/mTORC1/p70S6K signalling pathway. An overview of strategies used to mitigate the detrimental effects of insufficient sleep on muscle protein synthesis in rodents are displayed in Fig. 3.

To date, the precise mechanisms responsible for insufficient sleep-related muscle atrophy in humans are not well defined [19,50,76]. This limited information presents a challenge when attempting to recommend efficacious preventative strategies. Saner et al. [50,76] implemented a high-intensity interval exercise cycling protocol during a five-night sleep restriction intervention (4 h sleep opportunity each night) which mitigated the adverse effect of reduced sleep on myofibrillar and sarcoplasmic protein synthesis in a group of healthy male adults (Fig. 4). The results of these studies highlight the possible protective nature of exercise on preserving rates of muscle protein synthesis in the face of disturbed sleep. Further exploration of alternate modalities of exercise warrant investigation as metabolic responses to exercise are mode specific. For example, resistance exercise has been shown to stimulate myofibrillar protein synthesis to a greater extent than high intensity aerobic-based exercise [93].

The ability to preserve rates of muscle protein synthesis and promote skeletal muscle health has broad appeal to a variety of sleep-restricted populations. Identifying appropriate and effective preventative exercise interventions for sleep-restricted individuals is an important next step. While HIIE appears to promote or maintain rates of muscle protein synthesis during periods of reduced sleep [50], exploring additional modalities of exercise and their efficacy in wider populations is prudent. Establishing the

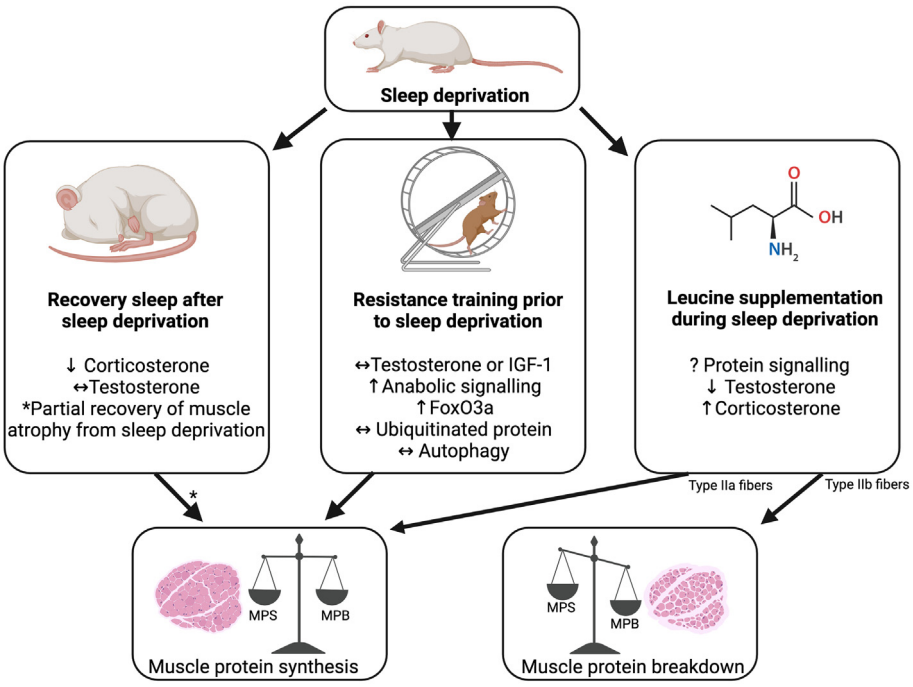

Fig. 3. Effects of sleep deprivation on muscle protein turnover in rodents and potential strategies to mitigate these effects. In rodents, high-intensity resistance training can mitigate the catabolic effects of sleep restriction on skeletal muscle and promote a more 'anabolic environment' with increases in insulin-like growth factor (IGF-1) and testosterone [73]. Such increases in anabolic hormones result in similar levels as observed in rodents who obtain normal sleep patterns. Supplementing rodents with leucine (1.35 g/kg of body mass *per* day) provides a protective effect on type IIb muscle fibre atrophy during 96 h of paradoxical sleep deprivation [70]. However, intermediary (i.e., type IIa) fibres atrophied even with leucine supplementation [70]. MPS: Muscle protein synthesis, MPB: Muscle protein breakdown, Fox03a: Forkhead box O3 a.

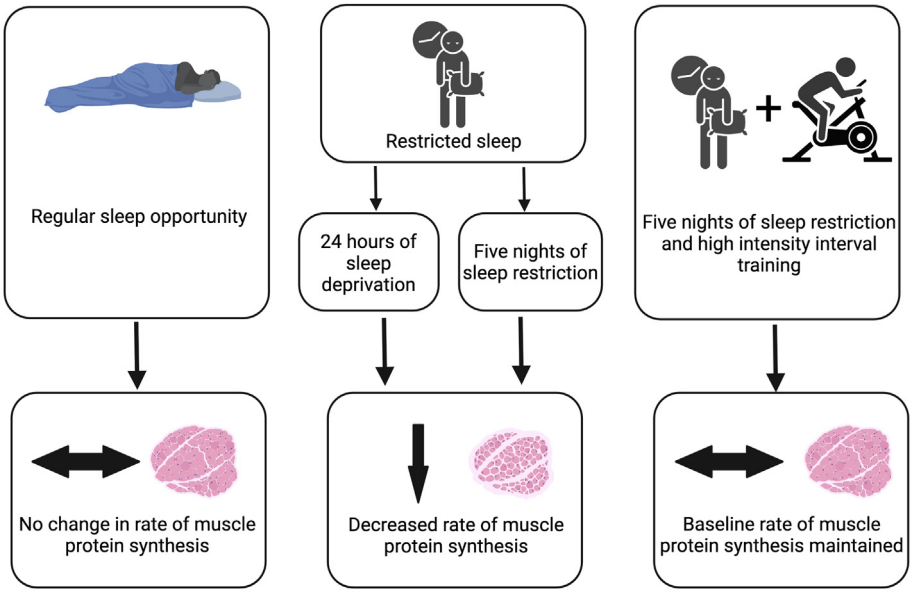

Fig. 4. Overview of the effects of sleep restriction on rates of skeletal muscle protein synthesis. Reduced sleep durations lower the rate of myofibrillar and sarcoplasmic protein synthesis in the vastus lateralis of healthy adults [50,76]. Implementing high intensity interval training during periods of sleep restriction result in a preservation of the rates of muscle protein synthesis.

optimal mode, frequency, duration, and intensity of exercise may allow for the development of specific exercise guidelines and recommendations to help mitigate the detrimental effects of restricted sleep on human skeletal muscle. Additionally, developing and promoting efficacious sleep enhancement strategies in synergy with evidence-based exercise guidelines may aid in reducing the host of detrimental effects of insufficient sleep on skeletal muscle and metabolic health.

9. Exercise as an intervention to improve sleep and realign circadian rhythms

Exercise has a positive effect on sleep-wake behaviours and circadian rhythms [94,95]. Regular exercise increases sleep duration and improves SWS, while also reducing sleep onset latency, REM sleep, and wake after sleep onset [96]. However, there are several factors to consider when interpreting these findings,

including the exercise prescription (mode, duration, timing, and intensity), and individual characteristics such as age, sex, and fitness level [96]. These factors highlight the complex interactive nature between physiological and psychological pathways that influence sleep [97], making it difficult to determine the precise mechanisms that underpin improved sleep after exercise.

There are three independent, but related hypotheses that attempt to explain the beneficial effects of exercise on sleep: the thermoregulatory hypothesis, the energy conservation hypothesis, and the body restoration hypotheses [96]. The thermogenic hypothesis proposes that sleep onset coincides with reductions in basal metabolic rate and core body temperature, induced by systemic vasodilation and the accompanying peripheral heat loss [96]. The energy conservation and body restoration hypotheses purport that the greater daily exercise-induced energy expenditure may be a catalyst for increased SWS and total sleep time. As exercise is a significant catalyst for increased energy turn-over and overall daily energy expenditure, it is thought that the increased exercise-induced energy deficit may be a driving force underlying improved sleep patterns.

Recently, it has been suggested that exercise-induced peripheral factors may be a potential mechanism for improved sleep after exercise [98]. For instance, elevated levels of brain-derived neurotrophic factor (BDNF) have been linked with increased slow wave activity during sleep in rodent models [99]. The BDNF-induced improvements in sleep architecture are purportedly underpinned by increases in the synaptic strength of corticortical connections as a response to the elevated brain BDNF [98]. In humans, aerobic exercise elevates peripheral BDNF levels in the blood [98]. However, increased brain BDNF is likely a result of fibronectin type III domain containing 5 (FNDC5) protein activity, which is cleaved and secreted from skeletal muscle during exercise as the myokine irisin [100]. Another mechanism for increased brain BDNF concentrations is through the exercise induced stimulation of the peroxisome proliferator-activated receptor *y* coactivator 1α (PGC-1α)/FNDC5 pathway [101]. Indeed, studies in rodents demonstrate a PGC-1α/FNDC5/BDNF pathway that is activated in the hippocampus by endurance exercise [100].

Exercise and the molecular clock have an intricate, bi-directional relationship interconnected by numerous signalling pathways. As such, exercise can be used as an effective 'time cue' for realigning circadian rhythms in skeletal muscle [102]. This is an important consideration, because when the molecular clock is disrupted in muscle, metabolic dysfunction and muscle atrophy are exacerbated [55]. There are several potential mediators linking exercise and circadian rhythms, with the AMP-activated protein kinase (AMPK), PGC-1α, and hypoxia-inducible factor 1α (HIF-1α) all playing regulatory roles in the molecular clock response to exercise [102]. Increased metabolic and cellular energy requirements induced by exercise are potent activators of AMPK, which in turn, affect core molecular clock gene expression by reducing the stability of PER and CRY proteins [95]. The increased AMPK activity and subsequent CRY1 instability enhance proliferator-activated receptor δ (PPARδ) regulation of lipid metabolism and energy uncoupling in skeletal muscle [95,103], thus maintaining cellular energy homeostasis.

The transcriptional coactivator PGC1-α regulates several exercise-associated aspects of muscle function including mitochondrial biogenesis and muscle plasticity (i.e., fibre type transitions), mediating many of the beneficial effects of exercise on human health, while also suppressing a broad range of inflammatory responses. During exercise in both humans and rodents, there is a rapid increase in PGC-1α mRNA expression followed by induction of elevated PGC-1α protein expression throughout recovery and for the subsequent 24 h post-exercise [104]. The expression of *PGC-1α* exhibits a strong diurnal rhythm in skeletal muscle, with PGC-1α inducing the expression of several core clock genes, particularly *Bmal1*, *Clock*, *Per2* and *Rev-erbα*, in a cell-autonomous manner. The induction of these clock genes is partly mediated through its coactivation of orphan nuclear receptor RORα, with the PGC-1α/ROR and Rev-erbα/HDAC transcriptional complexes playing an antagonistic role in the transcriptional regulation of *Bmal1* expression. The physiological role of PGC-1α in normal clock function is supported by the finding of significant impairments of diurnal rhythms of locomotor activity, body temperature and metabolic rate in *PGC-1α null* mice [105]. PGC-1α also plays a role in the exercise-induced increase in HIF-1α expression, which influences the molecular clock via binding with core clock promoters. Taken collectively, these findings strongly implicate the PGC-1 family of coactivators as a nodal point in integrating energy metabolism and the body clock, and reinforce the notion of exercise as a potent 'time cue' to recalibrate circadian rhythms [95,102]. For recent reviews on the relationship between circadian biology and exercise, the reader is referred to Wolff and Esser [102] and Mansingh and Handschin [95].

10. Conclusions

This review highlights the complex relationship between sleep, circadian biology, and skeletal muscle health. At a population level, significant proportions of society experience insufficient sleep and are at increased risk of numerous metabolic and musculoskeletal conditions. Fragmented or insufficient sleep disrupts daily biological rhythms and can cause a cascade of detrimental effects to numerous cells, tissues, and organs, resulting in impaired metabolic and physiological functions. Both acute and chronic sleep restriction have a negative influence on muscle health and function. At the cellular level, inadequate sleep disrupts metabolic function and biological rhythms. Skeletal muscle metabolism is disrupted by poor sleep, with reduced rates of protein synthesis in response to the perturbations in the hormonal environment. The disruption to skeletal muscle metabolism and the hormonal milieu is likely responsible for the atrophic effect on muscle tissue associated with insufficient sleep. However, research in this area is in its infancy, and precisely how circadian clocks interact with these physiological processes is unclear. The ability to mitigate the negative effects of insufficient sleep may have numerous benefits in both regulating and maintaining metabolic health and physical performance.

Investigating the mechanisms that underpin the relationship between sleep, circadian rhythms, and skeletal muscle is warranted and expanding current findings to divergent population groups is important. Determining and quantifying the existence of between-sex responses to sleep deprivation is critical, as embracing such differences will allow for personalised recommendations for improved sleep strategies. Exploring if responses are similar in exercise-trained versus sedentary populations is also needed. Evaluating the utility of various exercise interventions to maintain skeletal muscle metabolism during periods of reduced sleep is prudent. Examining the role of circadian phenotypes ('owls versus larks') and their influence on the interactions between the molecular clock, muscle metabolism, and sleep is also an area of potential future research and may help to identify the extent to which individual endogenous rhythms need to be accounted for when designing and implementing sleep interventions.

Practice points

1. Disrupted sleep/wake patterns negatively impact skeletal muscle clocks, with reduced rates of protein synthesis observed following acute periods of sleep restriction.
2. Inadequate sleep durations can misalign peripheral muscle clocks from the central oscillator and perturb daily biological rhythms, with deleterious effects on muscle physiology and metabolic health.
3. Exercise may attenuate some of the negative effects of reduced sleep patterns on rates of muscle protein synthesis.

Research agenda

1. Investigating the effect of chronic sleep disruption on muscle metabolism, as well as population specific responses (e.g., sex, age) would lead to a greater understanding of the relationship between sleep and whole-body metabolic health
2. A greater understanding of the mechanisms associated with sleep, circadian rhythms, and skeletal muscle health is prudent when developing interventions aimed at mitigating the detrimental effects of insufficient sleep.
3. Establishing the efficacy of various exercise strategies (i.e., timing and mode) after periods of disrupted sleep would allow for effective interventions to be designed and implemented to maintain skeletal muscle and whole-body metabolic health.

Declaration of competing interest

No authors have a conflict of interest with the publication of this manuscript.

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