Accepted Manuscript

Is exercise a viable therapeutic intervention to mitigate mitochondrial dysfunction and insulin resistance induced by sleep loss?

N.J. Saner, D.J. Bishop, J.D. Bartlett

PII: S1087-0792(17)30004-7

DOI: 10.1016/j.smrv.2017.01.001

Reference: YSMRV 1011

To appear in: *Sleep Medicine Reviews*

Received Date: 17 May 2016

Revised Date: 16 December 2016

Accepted Date: 10 January 2017

Please cite this article as: Saner N, Bishop D, Bartlett J, Is exercise a viable therapeutic intervention to mitigate mitochondrial dysfunction and insulin resistance induced by sleep loss?, *Sleep Medicine Reviews* (2017), doi: 10.1016/j.smrv.2017.01.001.

Is exercise a viable therapeutic intervention to mitigate mitochondrial dysfunction and insulin resistance induced by sleep loss?

Saner, NJ,[1] Bishop, DJ,[1,2] Bartlett, JD[1]

[1]Institute of Sport, Exercise and Active Living (ISEAL),
College of Sport and Exercise Science,
Victoria University,
Melbourne,
Australia.

[2]School of Medicine and Health Sciences,
Edith Cowan University,
270 Joondalup Drive,
Joondalup,
6027,
Australia

Running head: Sleep loss and exercise

Acknowledgements: The authors declare no conflict of interest and no financial support was provided in the development of this manuscript

Address for correspondence:
Jonathan D Bartlett
Institute of Sport, Exercise & Active Living (ISEAL)
College of Sport and Exercise Science
Victoria University
PO Box 14428, Melbourne, Victoria, Australia 8001
Tel: +61 3 9680 6345
Email: Jon.Bartlett@vu.edu.au

Summary

Sleep loss has emerged as a risk factor comparable to that of physical inactivity for the development of insulin resistance, impaired glucose tolerance and Type 2 Diabetes Mellitus. This is a concern as it was estimated in 2012 that approximately 70 million adults in the United States are sleeping less than 6 hours each night, and the average nightly sleep duration of a representative sample of the U.S adult population is reported to be significantly less than in previous decades. The underlying mechanisms responsible for chronic sleep loss induced insulin resistance include modifications in the regulation of hormone secretion, peripheral clock gene regulation, and the cellular signaling processes associated with regulating mitochondrial respiratory function. Emerging evidence shows these mechanisms share similar biochemical signaling pathways to those underpinning exercise-induced adaptations, which together suggest exercise might be a viable, suitable, and potent treatment alternative to alleviate sleep loss induced insulin resistance and glucose intolerance. In this theoretical review, we provide a summary of the impact of reduced sleep duration and quality on mitochondrial function and insulin resistance, before detailing the possible underlying mechanisms. Finally, we propose how and why regular exercise may be a therapeutic intervention to mitigate sleep loss induced mitochondrial dysfunction and insulin resistance.

Key Words: Clock genes, PGC-1α, AMPK, skeletal muscle

Abbreviations

AMPK - AMP-activated protein kinase
ACSM – American College of Sports Medicine
ATF2 – activating transcription factor 2
Bmal1 - Brain and muscle Arnt-like protein-1
CAMK – Calmodulin-dependent protein kinase
Clock - Circadian locomotor output cycles kaput
CREB – Cyclic-AMP response element binding protein
CS – Citrate synthase
COX-1 - Cytochrome c oxidase subunit 1
Cry 1,2 - Cryptochrome 1 and 2
GLUT4 - Glucose transporter 4
HbA1c – Glycated hemoglobin
HIIE - High-intensity interval exercise
LKB-1 – Liver kinase B1
MEF2 – myocyte enhancer factor 2
mRNA - Messenger ribonucleic acid
NAD^+ - nicotinamide adenine dinucleotide
nREM- Non-rapid eye movement sleep
NRF1/2 – Nuclear respiratory factor 1/2
OGTT – Oral glucose tolerance test
OSA - Obstructive sleep apnea
p38MAPK – p38 mitogen-activated protein kinase
PPAR – Peroxisome proliferator-activated receptor
Per 1-3 - Period 1,2 and 3
PGC-1α - Peroxisome proliferator-activated receptor γ co-activator 1α
REM – Rapid eye movement sleep
Rev-erbα – NR1D1; Nuclear receptor subfamily 1, group D, member 1
ROR-α – RAR-related orphan receptor α
SCN - Suprachiasmatic nucleus
SIRT1/3 – Sirtuin 1/3
SWS - Slow wave sleep
T2DM - Type 2 diabetes mellitus
TIB - Time in bed
Tfam – Mitochondrial transcription factor A

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) continues to rise in modern society. The World Health Organization (WHO) estimates that by the year 2025, 300 million people across the world will be diagnosed with diabetes (1). To give this additional context, T2DM was the 7^{th} leading cause of death in the United States in 2012 and costs their economy an estimated $245 billion each year (2). Typically, the onset of T2DM coincides with impaired

glucose tolerance (characterized by a fasting blood glucose level >7 mmol/L) and increased insulin resistance (reduced efficiency of insulin-stimulated glucose uptake) (3). Furthermore, the health consequences arising from diabetic complications (such as heart disease, stroke and kidney damage) add to the already extraordinary burden of this metabolic disease on health services (2).

The most common risk factors associated with the onset of insulin resistance and glucose intolerance include genetic predisposition and lifestyle factors such as diet and physical inactivity (4). However, in the last 15 years sleep has emerged as a prominent factor influencing the development of T2DM. In fact, sleep loss and reduced sleep quality are now reported to be comparable to physical inactivity (4) in terms of their relative contribution to the risk of developing T2DM. The percentage of sleep deficient people who develop insulin resistance and T2DM is difficult to determine with the available data. Nonetheless, studies investigating shift workers (a cohort often associated with insufficient sleep and reduced sleep quality (5)) indicate a significantly increased risk (40%) of developing diabetes compared to those performing day work (4). Considering the significant reduction in average nightly sleep duration compared to previous decades (6), and that it was recently estimated via self-reported measures that ~40% of the population are sleeping less than the recommended 7 hours per night (7), the role of sleep loss in contributing to the already high prevalence of T2DM is an important area for further investigation.

Potential mechanisms by which sleep loss may contribute to insulin resistance and glucose intolerance have been identified, and include modifications to the regulation of hormone secretion (8), misalignment of the molecular clock (i.e., circadian misalignment) (9), and

disruptions to cellular signaling processes (such as those involved in the insulin signaling pathway and the pathways associated with mitochondrial respiratory function) (10, 11). If sleep loss affects signaling pathways related to mitochondrial respiratory function, then this has important implications as mitochondrial dysfunction has been associated with increased insulin resistance and T2DM (12, 13). The gold standard for the assessment of mitochondrial respiratory function is the measurement of oxygen utilization in isolated mitochondria or permeabilized tissue, and indicates the ability of mitochondria to generate ATP via oxidative phosphorylation (14). Using this method, it has been reported that mitochondrial respiratory function is significantly reduced in the skeletal muscle of T2DM patients compared with obese non-diabetic subjects (13). Furthermore, this decrease in mitochondrial respiratory function was negatively associated with HbA1c results (glycated hemoglobin - a test that reflects blood glucose levels of the previous 3 months) (13). However, the effects of sleep loss on mitochondrial function are not well characterized.

Many of the aforementioned mechanisms that are potentially disrupted with sleep loss, particularly insulin signaling and mitochondrial function, share similar biochemical signaling pathways to those connected with exercise (an area of research that is comparably well studied). This suggests exercise as a potential intervention to counteract some of the negative effects associated with sleep loss. For example, single (15) and multiple (16) bouts of exercise induce a cascade of cellular signaling events that lead to improvements in mitochondrial function and insulin sensitivity (17). Exercise has long been considered the cornerstone for the treatment and prevention of T2DM, with reports that those who regularly engage in moderate physical activity (even brisk walking) have approximately a 30% lower risk of developing T2DM compared to sedentary individuals (18). However,

limited research has investigated the ability of exercise to counteract the negative effects of sleep loss on glucose tolerance and insulin resistance (19). Nevertheless, it is plausible that by increasing basal levels of exercise some of the detrimental effects associated with sleep loss might be mitigated.

The aim of this theoretical review is to draw on the available literature and propose exercise as a viable strategy to alleviate the negative effects of sleep loss. In doing so we contextualize the effect of reduced sleep duration and quality on insulin resistance, glucose tolerance, and T2DM, along with the potential underlying mechanisms, while demonstrating how and why engaging in regular exercise may act as a therapeutic intervention to mitigate sleep loss induced insulin resistance and T2DM.

Sleep loss and health

The U.S-based National Sleep Foundation recommends adults between the age of 18 and 64 sleep 7 to 9 hours each night (7). Despite this approximately 70 million Americans (30% of the population) sleep less than 6 h per night - significantly less per night than that reported in 1985 (22%), based on a large representative sample of the U.S. adult population. This reduction in sleep has been attributed to a range of lifestyle factors and work pressures, including shift work, increased work demands, changing social pressures and roles, increased travel and the consequent jet lag, sleep disorders, and stress (20). Changes in sleep habits have important consequences and have been linked to increased absenteeism, disability, industrial and motor vehicle accidents, increased alcohol consumption, risk of cardiovascular disease, and possibly increased mental health issues (21, 22).

Recent epidemiological and laboratory-based studies have also associated sleep loss with a range of chronic health concerns, particularly in relation to insulin resistance and T2DM (4, 21, 23). In humans, a 40% reduction in glucose tolerance and a 30% reduction in the acute insulin response following a glucose tolerance test (measurement of glucose and insulin levels following oral glucose administration) has been reported after 6 nights of 4 h of time in bed (TIB) per night (8). More recently, it was reported that just one night of 4 h of sleep time reduces insulin sensitivity (24-26), with many other studies consistently reporting sleep loss induced insulin resistance (10, 24-28). Thus, evidence from both epidemiological studies and intervention studies support a key role for sleep in the regulation of glucose tolerance and insulin resistance.

Sleep loss, circadian misalignment, and mitochondrial function

One proposed mechanism contributing to sleep loss induced changes in glucose tolerance and insulin resistance is circadian misalignment, a condition in which the exogenous behavioral sleep/wake schedule and feeding schedule are not aligned with endogenously generated circadian rhythms (29). These circadian rhythms include changes in hormone secretion, body temperature, heart rate, muscle tone, and substrate utilization/metabolism, which persist throughout a 24-h period under constant conditions (i.e., without environmental/exogenous time cues) (30, 31). Circadian rhythms are regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus, and the molecular clocks of peripheral tissues (such as skeletal muscle) acting synchronously as biological timekeepers. Altering the sleep/wake cycle (i.e., reduced sleep duration) may also independently alter the central and peripheral molecular clocks of human skeletal muscle (9) such that they become desynchronized with exogenous stimuli – a notion supported by rodent studies (32, 33). As

over 800 genes are regulated in a circadian manner within skeletal muscle of mice (34), sleep loss induced disruption of the molecular clocks that regulate the expression of these genes may have far-reaching effects, particularly in regard to normal cellular function and health. As such, the misalignment of both the central and peripheral clocks by exogenous stimuli has been proposed as another potential mechanism contributing to sleep loss induced insulin resistance and impaired glucose tolerance (9, 29, 35, 36).

Shift workers who undertake variable rotating day and night shifts have an increased risk of circadian misalignment (37). These workers experience reduced sleep durations, a constantly changing light/dark cycle, altered sleep/wake patterns, and mixed feeding patterns, which together can contribute to circadian misalignment (37, 38). Of significance, these changes in daily behaviors are also associated with a 40% increase in the risk of developing diabetes (4). Indeed, a longitudinal study (conducted between 1991 – 2001) of Japanese alternating shift workers concluded that, compared to day shift workers, alternating shift work was an independent risk factor for the onset of T2DM (39). Importantly, in both human and mouse models, exercise has been shown to be capable of causing a phase shift (i.e., advance or delay the circadian phase depending on the time of day that the exercise occurs) (38, 40), and has thus been suggested as a potential intervention to help realign circadian and diurnal rhythms in those with sleep issues (40). Linked to phase shifts of endogenously-regulated circadian rhythms, exercise has also been shown to cause shifts of the peripheral molecular clock in skeletal muscle (both rodent and human), thus highlighting the potential role for exercise to realign disrupted metabolic rhythms to their optimal state (38, 41).

Emerging evidence demonstrates that skeletal muscle function, and specifically that of mitochondrial respiration, also fluctuates rhythmically throughout the day. When mitochondrial respiratory function was measured in human skeletal muscle across a 24-h period, ADP-stimulated mitochondrial respiration oscillated in a "robust day/night rhythm", with a difference of approximately 20% between the highest (11 PM) and lowest (1 PM) values (42). In mice, the expression of key rate-limiting mitochondrial enzymes (i.e., pyruvate dehydrogenase and carnitine palymitoyl transferase) and ~38% of the mitochondrial proteome, which are linked to the regulation of glucose tolerance and insulin resistance, also display a diurnal rhythm (43). Similar to circadian rhythms, a diurnal rhythm follows a distinct 24-h cycle, but is synchronized to exogenous stimuli such as day and night and other factors such as the timing of meals (44). Therefore, it is possible that misalignment of these diurnal rhythms is detrimental to mitochondrial function, which would have further implications for glucose tolerance and insulin resistance.

As mitochondrial function is regulated in a diurnal manner, and sleep loss can lead to circadian misalignment, it is plausible that sleep loss may alter mitochondrial function - even if this remains to be fully elucidated in well-controlled laboratory studies. It has been reported that 120 h of sustained wakefulness (sleep loss) reduces the activity of citrate synthase (CS) (24%), malate dehydrogenase (35%), and glycerol-3-phosphate dehydrogenase (17%) in human skeletal muscle (11), collectively suggesting a decreased functional capacity of the mitochondria. More recently, 72-h of sleep deprivation was associated with reduced mitochondrial respiratory function in the hypothalamus of rats (45). Whilst these studies indicate that mitochondrial function may be directly reduced as a consequence of severe sleep loss, these initial findings have not been characterized in

models that replicate the sleep loss encountered by humans. Nonetheless, the implications are significant considering the proposed contribution of mitochondrial dysfunction to the development of insulin resistance and T2DM (12, 13). It may therefore be hypothesized that chronic sleep loss, such as that experienced by at least 30% of the American population, leads to defects in mitochondrial function and a consequent increase in the risk of developing insulin resistance and T2DM (46). Strategies to improve mitochondrial function, such as exercise (14), might be useful to combat some of the negative consequences of sleep loss.

Mechanistic pathways connecting sleep loss, misalignment of circadian rhythms, and the potential benefits of exercise

At a molecular level, circadian rhythms are controlled by a number of genes - collectively known as Clock genes. A transcriptional:translational feedback loop, which includes the core Clock genes *Bmal1, Clock* and *Ror-α* (often referred to as the activators of the feedback loop), and *Per 1-3, Cry 1/2* and *Rev-erb-α* (considered the repressors of the feedback loop), together coordinate circadian rhythmicity and metabolism at a cellular level via their ability to regulate the transcriptional activity of a host of other genes (clock controlled genes – CCGs) (see (47) for review). Of significant note, the mRNA expression in human skeletal muscle of two of these clock genes (*Bmal1* and *Cry1*) is decreased following a night of sleep loss (9).

Central to metabolic health and circadian regulation is the energy sensor, *AMP-activated protein kinase* (*AMPK*). AMPK is activated upon changes in the AMP:ATP ratio, is important in the regulation of mitochondrial biogenesis, and interacts closely with clock genes.

Activation of AMPK causes the phosphorylation and destabilization of *Cry1*, leading to de-repression of the BMAL1:CLOCK complex (48). Moreover, Rev-erb-α (a regulator of the clock gene transcriptional feedback loop and mitochondrial biogenesis) (49) regulates AMPK (50) via LKB1 - a protein responsible for upstream regulation of AMPK. It has also been suggested that clock genes within skeletal muscle (i.e., *Per1*, *Cry2*) are regulated by AMPKγ3 (51) - an AMPK isoform specific to skeletal muscle and essential for the regulation of glucose tolerance and insulin sensitivity (52). Exercise also activates and phosphorylates AMPK (15), which subsequently plays a role in GLUT4 (glucose transporter 4) mediated skeletal muscle glucose uptake (53). Furthermore, muscle-specific *Bmal1* knockout mice have decreased skeletal muscle glucose uptake through decreased GLUT4 translocation (36), which may be due to reduced expression of *Tbc1d1* - a Rab-GTPase member involved in the GLUT4 translocation process and a potential target of the CLOCK:BMAL1 complex (54). Together, this suggests exercise-induced AMPK activation might help counteract impairments in insulin resistance and glucose tolerance that may be associated with abnormalities in clock gene expression.

Downstream of AMPK is the transcriptional co-activator peroxisome proliferator-activated receptor γ (PGC-1α) (55), which is also upregulated in response to exercise (15). PGC-1α is often referred to as the 'master regulator' of mitochondrial biogenesis, due to its role in the transcriptional co-activation of a number of transcription factors (NRF 1/2, Tfam and PPARs) involved in the regulation of mitochondrial respiratory function and content (16). Importantly, PGC-1α also regulates the expression of, and is in itself regulated by interactions with, members of the clock gene family (as demonstrated in a number of rodent studies) (35, 56, 57). For example, PGC-1α knockout mice models demonstrate

reduced clock gene expression, while *Bmal1 knockout mice models* and mice with a mutated CLOCK protein (truncated CLOCK$^{\Delta 19}$ protein) display reduced PGC-1α protein content (35, 56, 57). Decreases in PGC-1α protein content may contribute to the reductions in mitochondrial content and respiration that are observed in *Bmal1* knockout mice and CLOCK$^{\Delta 19}$ mutant mice (35, 57). These same clock gene mutant mice have also been shown to have reduced insulin sensitivity, and the early development of T2DM (47, 58-60), which may be explained in part by the close association between mitochondrial dysfunction and the development of insulin resistance and T2DM (12, 13, 46, 61). These findings suggest that reductions in the protein content and expression of clock genes and PGC-1α may help to explain the reported effects of sleep loss on insulin sensitivity and T2DM. Importantly, both single and multiple bouts of exercise increase PGC-1α expression (15, 62) and mitochondrial function (63, 64), with subsequent improvements in insulin sensitivity (17). Thus, there is emerging evidence suggesting exercise might be a viable strategy to counteract the effects of sleep loss on clock gene expression, PGC-1α expression, reduced mitochondrial function, and subsequently increased insulin resistance.

While the role of PGC-1α as a key metabolic regulator is well established, it is also important to note its role may be determined by factors such as tissue specificity and its level of expression (65, 66). Hepatic overexpression of PGC-1α in mice induces hepatic insulin resistance, potentially via increased stimulation of gluconeogenesis, leading to hyperglycemia (66). However, increased expression of PGC-1α within physiological levels (as seen with exercise), improves mitochondrial content, GLUT4 expression, and insulin sensitivity in skeletal muscle (65).

Another key regulator of mitochondrial function, which can also be classified as a clock-controlled gene, is SIRT3 (a member of the sirtuin family) (67). SIRT3 is a mitochondrial protein that controls the acetylation levels of key functional oxidative metabolism and fatty acid oxidation proteins (i.e., long-chain acyl dehydrogenase), and thus can influence the overall respiratory function of the mitochondria (67). Knockout of SIRT3 in mice causes a reduction in the expression of mitochondria related genes that are induced by PGC-1α (68). Using liver-specific *Bmal1* knockout mice, it was reported that mitochondrial respiration in the liver could be influenced in a circadian manner via clock gene dependent regulation of nicotinamide adenine dinucleotide (NAD^+ - a mitochondrial co-enzyme), which in turn controls the deacetylase activity of SIRT3 (67). Another member of the sirtuin family, SIRT1 – a regulator of insulin sensitivity in mouse skeletal muscle, also appears to be activated by CLOCK and BMAL1, with mutation and knockout of these clock proteins, respectively, leading to the induction of insulin resistance (69). This indicates the dysregulation of clock genes, suggested to occur in response to sleep loss (9), may also lead to increased insulin resistance via a reduced content of SIRT proteins.

Of note, and similar to both AMPK and PGC-1α, it has been shown that SIRT1 and SIRT3 can be upregulated by exercise in the skeletal muscle of both animals (70, 71) and humans (72). Elevated SIRT1 activity has been shown to be important in the subsequent deacetylation and induction of PGC-1α transcriptional activity (73). Together, this demonstrates that both clock genes and exercise influence many regulators of mitochondrial biogenesis. This might help to explain why there is a diurnal rhythm to mitochondrial function and enzyme activity, why these may be affected by sleep loss, and equally why exercise may play a role in

mitigating sleep loss induced insulin resistance. The connection between clock genes, AMPK, PGC-1α, SIRT1 and SIRT3 is summarized in Figure 1.

INSERT FIGURE 1 HERE

Exercise increases mitochondrial signaling and clock gene expression

Exercise induced increases in the activation of AMPK, the protein content of PGC-1α, and activity of SIRT1 and SIRT3, are important signaling events that coordinate the expression of mitochondria-related genes (leading to increased mitochondrial content and function) as well as improvements in insulin sensitivity (74, 75). Among the genes that PGC-1α increases the expression of, are the mitochondrial enzymes that have been reported to have diminished activity following sleep loss in humans. For example, CS activity (a key enzyme of the citric acid cycle and a marker of mitochondrial content) is significantly reduced in human skeletal muscle following 120 h of sustained wakefulness (11). Importantly, skeletal muscle CS mRNA and PGC-1α mRNA is increased following a single bout of high-intensity interval exercise (HIIE), with subsequent increases in CS activity and PGC-1α content (16). Moreover, activity of the same complexes in the electron transport system that are reduced following sleep deprivation in rats (45) can be improved via exercise training (76). Therefore, exercise can promote increased activity and content of mitochondrial enzymes that are reduced following sleep loss and which may lead to insulin resistance and T2DM.

Despite our increased understanding of mitochondrial signaling, and models of sleep disruption and circadian misalignment, there are a number of additional exercise-induced signaling pathways associated with improved mitochondrial function that have yet to be

investigated in response to sleep loss. In humans muscle contraction leads to the activation of kinases such as calmodulin-dependent protein kinase (CAMK) and p38 mitogen activated protein kinase (p38MAPK) (in addition to AMPK), via changes in calcium and reactive oxygen species, respectively, which converge on myocyte enhancer factor 2 (MEF-2), activating transcription factor 2 (ATF2) and cyclic-AMP response element binding protein (CREB), and exert their influence on enhancing PGC-1α promoter activity (77). In addition, Perry et al. (16) demonstrated that exercise training modulates mitochondrial fission and fusion proteins important for regulating mitochondrial integrity and turnover. Moreover, we have recently reported in human skeletal muscle that single (15) and multiple (62) bouts of exercise increase phosphorylation and protein levels of the tumor suppressor protein, p53. Ablation of p53 content in mice results in reduced mitochondrial respiration, lowered PGC-1α content and decreased exercise capacity (78), whilst p53 has also been shown to regulate insulin resistance (79). Collectively, these pathways represent varying avenues for future research in the context of sleep loss, exercise, mitochondrial function and insulin resistance.

The detrimental mitochondrial characteristics previously demonstrated in clock gene knockout mice can also be somewhat ameliorated by exercise (57). Following an 8-week exercise training program, mice with mutated CLOCK$^{\Delta 19}$ proteins were able to restore PGC-1α protein content to that of trained wild-type mice (57). This was accompanied by similar increases in COX-I activity (another marker of mitochondrial content (80)). Moreover, a single bout of resistance exercise is associated with increased expression of *Per2*, *Cry1* and *Bmal1* in human skeletal muscle, compared with resting muscle (41). Together, these associations between clock controlled genes, PGC-1α, and mitochondrial dysfunction (35,

56) provide a theoretical mechanism by which exercise-induced contractile activity may play a role in ameliorating sleep loss induced disruptions of clock genes following a night of sleep loss (9) and hence mitigate consequent impairments in mitochondrial function and insulin sensitivity. That said, future research should focus on uncovering the specific relationships and underpinning mechanisms between sleep loss, changes in skeletal muscle mitochondrial function, and exercise. A schematic overview summarizing the hypothesized connection between sleep, exercise and insulin resistance is shown in Figure 2.

INSERT FIGURE 2 HERE

The role of sleep on muscle mass and insulin resistance

As skeletal muscle is the major site for glucose disposal, it is conceivable that maintenance of muscle mass and function is also important for maintaining glucose tolerance and insulin sensitivity. In this context, it has been reported that sleep loss can lead to a decrease in muscle mass – likely due to an increased catabolic and reduced anabolic hormone profile (81-83). Moreover, while on a calorie restricted diet, curtailing sleep opportunities to 5.5 h a night for 14 consecutive nights increased the fraction of muscle mass lost compared to participants who had an 8.5 h sleep opportunity each night (84). Together, this marks another possible convergence point at which sleep *and* exercise may interact.

While inconclusive thus far, evidence from animal models used to investigate muscle atrophy and sarcopenia (a progressive loss of muscle mass, quality and function, associated with aging (85)) point towards the disruption of clock genes as a contributing mechanism. For example, *Bmal1* knockout mice display features associated with advanced aging and

sarcopenia, including significantly reduced strength and altered myofilament structure (35, 86). This suggests that the molecular clock is necessary for the maintenance of skeletal muscle function and phenotype. Another mechanism thought important in the regulation of muscle mass is inflammation. Indeed, lifestyle factors such as sedentary behaviors and sleep loss, as well as obesity and T2DM, induce dramatic increases in pro-inflammatory signaling (87), which may also be implicated in muscle atrophy (88).

Strategies that can regulate the molecular clock, such as resistance-based exercise interventions, have also been shown to increase muscle mass and to protect against sarcopenia (89). Furthermore, exercise has been shown to have anti-inflammatory properties (90), providing a potential additional mechanism to counteract sleep loss induced muscle loss. Importantly, it has been shown in rats that resistance exercise training performed prior to sleep loss attenuates muscle atrophy (82), providing preliminary evidence of the role contractile activity can play in protecting against sleep loss induced muscle mass loss. Whether it also helps reduce the development of insulin resistance, by maintaining skeletal muscle functionality, remains to be determined. Nonetheless, considering the increased prevalence of sarcopenia in T2DM patients (91, 92), this appears an important area of emerging research.

Sleep quality, insulin sensitivity and exercise

In addition to sleep loss, sleep quality may also be a critical factor influencing the regulation of insulin sensitivity (93). It was recently reported that, like sleep loss, reduced sleep quality is associated with a similar increase in the risk of T2DM as physical inactivity (~40%) (4). Additionally, patients with sleep disorders, such as obstructive sleep apnea (OSA), in which

sleep quality is significantly reduced, have an increased risk of insulin resistance (4). Sleep quality can be determined via polysomnography, which analyzes multiple physiological parameters relevant to sleep. Specifically, the time spent in different stages of sleep can be quantified (i.e., non-rapid eye movement (nREM, stages 1-3) and rapid eye movement (REM)) (94). A reduction in the time spent in slow wave sleep (SWS, nREM stage 3) (i.e., restorative sleep) is also associated with increased insulin resistance (93, 95). Indeed, when SWS is disturbed, but the overall time spent asleep is not reduced, there are increases in insulin resistance of between 20-25%. However, a night of REM sleep disturbance did not produce similar reductions in insulin sensitivity, suggesting that SWS rather than REM sleep may play a role in the regulation of insulin sensitivity (95). In considering there were no associations between sleep stages and fasting insulin resistance following 1 night of restricted sleep (25), when taken together, this suggests more research is warranted to determine the role of REM and SWS on the regulation of glucose tolerance and insulin resistance.

Given that sleep quality is an important determinant of glucose tolerance and insulin sensitivity (23, 93), improving sleep quality by means of regular engagement in exercise could also prove beneficial in the treatment and prevention of insulin resistance and T2DM. There are a number of strategies for improving sleep quality (e.g., sleep hygiene practices such as caffeine restriction and reducing the use of electronic devices prior to bed). However, engaging in physical activity and exercise (both acutely and chronically), as alternative or complementary approaches, may be beneficial (96, 97). In a comparison of older adults who were assigned to either a moderate-intensity exercise program or a health education control program over a 12-month period, an exercise program was shown to

improve aspects of sleep quality (98). Indeed, decreases in nREM stage 1 sleep (considered a transitional state from wake to sleep), increases in nREM stage 2 sleep (considered more stable sleep than stage 1) and reduced sleep disturbances (as assessed via polysomnography) were reported, which coincided with improved self-reported parameters of sleep quality following the exercise program. Moreover, exercise is currently prescribed, and has been shown to be effective in improving sleep quality, for a variety of clinical sleep disorders, including insomnia and obstructive sleep apnea, in which sleep quality is typically reduced (99, 100). However, further research is required to determine whether, in addition to metabolic function, exercise-induced improvements in sleep quality (regardless of duration) can help to maintain glucose tolerance and insulin resistance.

Conclusion

To date, sleep *and* exercise in the context of human health have remained relatively independent lines of research. However, with the emergence of sleep loss as a significant risk factor for the development of insulin resistance and T2DM, engagement in exercise to mitigate these risks may offer an alternative solution. Indeed, this review presents and uncovers a framework and mechanistic underpinning of how exercise can be of significant benefit to counteract the mechanisms by which sleep loss might increase the risk of impaired mitochondrial function and the subsequent development of insulin resistance and T2DM.

The critical next step is to perform well controlled experiments that reveal the specific mechanisms by which sleep loss contributes to the development of insulin resistance and reductions in glucose tolerance. Such findings will allow for more targeted interventions

aimed at improving human health, whether that is obtaining more and a better quality of sleep and/or increasing basal levels of exercise. Furthermore, this research may help to inform which exercise modalities might be best to counteract the detrimental effects of sleep loss. To this end, it is particularly important for future research to elucidate whether an emphasis should be placed on improving sleep duration and quality, or whether it would be more time efficient (in the context of improving human health) to focus attention on increasing habitual exercise in the face of reduced sleep, so as to counteract the detrimental impact of sleep loss.

Practice Points

- Reduced sleep duration and quality is associated with an increased risk for the development of insulin resistance and T2DM.
- Sleep loss leads to disruptions in circadian rhythm and the expression of skeletal muscle clock genes, which negatively influences mitochondrial content and function.
- Mitochondrial dysfunction is associated with the development of insulin resistance and T2DM, suggesting a possible relationship between sleep loss, changes in mitochondrial function, and the development of insulin resistance.
- Exercise induces a cascade of signaling events associated with mitochondrial biogenesis, and may thus alleviate sleep loss induced mitochondrial dysfunction, insulin resistance and impaired glucose tolerance.
- Exercise may improve sleep quality, which could improve insulin sensitivity and reduce the risk of development of T2DM.

Research Agenda

- To uncover the relationships and underpinning mechanisms associated with sleep loss, skeletal muscle mitochondrial function, and insulin sensitivity.
- The role of exercise (single bouts and chronic exercise training) in mitigating sleep loss induced reductions in whole-body metabolic health and skeletal muscle function remains to be determined.
- To investigate how sleep *and* exercise influence the synchronicity between central and peripheral clocks and the subsequent effects on metabolic health.
- Further research is needed to determine the most time efficient approach to improve insulin sensitivity and glucose tolerance in the context of sleep *and* exercise.

References:

1. World Health Organization. Life in the 21st Century - a Vision for All. Geneva, Switzerland: 1998.
2. Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and its Burden in the United States. Atlanta, GA: US Department of Health and Human Services, 2014 2014. Report No.
3. National Collaborating Centre for Chronic Conditions. Type 2 diabetes: national clinical guideline for management in primary and secondary care (update) London2008.
* 4. Anothaisintawee T, Reutrakul S, Van Cauter E, Thakkinstian A. Sleep disturbances compared to traditional risk factors for diabetes development: Systematic review and meta-analysis. Sleep Med Rev. 2015;30:11-24.
5. Akerstedt T. Shift work and disturbed sleep/wakefulness. Occup Med (Lond). 2003;53(2):89-94.
6. Ford ES, Cunningham TJ, Croft JB. Trends in Self-Reported Sleep Duration among US Adults from 1985 to 2012. Sleep. 2015;38(5):829-32.
7. National Sleep Foundation. International bedroom poll 2013 [cited 2016 13 January]. Available from: https://sleepfoundation.org/sites/default/files/RPT495a.pdf.
* 8. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. Lancet. 1999;354(9188):1435-9.
* 9. Cedernaes J, Osler ME, Voisin S, Broman JE, Vogel H, Dickson SL, et al. Acute sleep loss induces tissue-specific epigenetic and transcriptional alterations to circadian clock genes in men. J Clin Endocrinol Metab. 2015:JC20152284.
10. Broussard JL, Ehrmann DA, Van Cauter E, Tasali E, Brady MJ. Impaired insulin signaling in human adipocytes after experimental sleep restriction: a randomized, crossover study. Ann Intern Med. 2012;157(8):549-57.
11. Vondra K, Brodan V, Bass A, Kuhn E, Teisinger J, Andel M, et al. Effects of Sleep-Deprivation on the Activity of Selected Metabolic Enzymes in Skeletal-Muscle. European Journal of Applied Physiology and Occupational Physiology. 1981;47(1):41-6.
12. Lowell BB, Shulman GI. Mitochondrial dysfunction and type 2 diabetes. Science. 2005;307(5708):384-7.
* 13. Mogensen M, Sahlin K, Fernstrom M, Glintborg D, Vind BF, Beck-Nielsen H, et al. Mitochondrial respiration is decreased in skeletal muscle of patients with type 2 diabetes. Diabetes. 2007;56(6):1592-9.
14. Bishop DJ, Granata C, Eynon N. Can we optimise the exercise training prescription to maximise improvements in mitochondria function and content? Biochim Biophys Acta. 2014;1840(4):1266-75.
15. Bartlett JD, Hwa Joo C, Jeong TS, Louhelainen J, Cochran AJ, Gibala MJ, et al. Matched work high-intensity interval and continuous running induce similar increases in PGC-1alpha mRNA, AMPK, p38, and p53 phosphorylation in human skeletal muscle. J Appl Physiol (1985). 2012;112(7):1135-43.
16. Perry CGR, Lally J, Holloway GP, Heigenhauser GJF, Bonen A, Spriet LL. Repeated transient mRNA bursts precede increases in transcriptional and mitochondrial proteins during training in human skeletal muscle. Journal of Physiology-London. 2010;588(23):4795-810.
17. Meex RC, Schrauwen-Hinderling VB, Moonen-Kornips E, Schaart G, Mensink M, Phielix E, et al. Restoration of muscle mitochondrial function and metabolic flexibility in type

2 diabetes by exercise training is paralleled by increased myocellular fat storage and improved insulin sensitivity. Diabetes. 2010;59(3):572-9.
18. Jeon CY, Lokken RP, Hu FB, van Dam RM. Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. Diabetes Care. 2007;30(3):744-52.
19. VanHelder T, Symons JD, Radomski MW. Effects of sleep deprivation and exercise on glucose tolerance. Aviat Space Environ Med. 1993;64(6):487-92.
20. Sleep Health Foundation. Common Reasons Why People Don't Get Enough Sleep 2011 [Available from: http://www.sleephealthfoundation.org.au/files/pdfs/Common-Causes-Inadequate-Sleep.pdf.
21. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. J Clin Sleep Med. 2007;3(5):519-28.
22. Perlis ML, Grandner MA, Chakravorty S, Bernert RA, Brown GK, Thase ME. Suicide and sleep: Is it a bad thing to be awake when reason sleeps? Sleep Med Rev. 2016;29:101-7.
23. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care. 2010;33(2):414-20.
24. Donga E, van Dijk M, van Dijk JG, Biermasz NR, Lammers GJ, van Kralingen KW, et al. A single night of partial sleep deprivation induces insulin resistance in multiple metabolic pathways in healthy subjects. J Clin Endocrinol Metab. 2010;95(6):2963-8.
25. Cedernaes J, Lampola L, Axelsson EK, Liethof L, Hassanzadeh S, Yeganeh A, et al. A single night of partial sleep loss impairs fasting insulin sensitivity but does not affect cephalic phase insulin release in young men. J Sleep Res. 2015.
26. van den Berg R, Mook-Kanamori DO, Donga E, van Dijk M, van Dijk JG, Lammers GJ, et al. A single night of sleep curtailment increases plasma acylcarnitines: Novel insights in the relationship between sleep and insulin resistance. Arch Biochem Biophys. 2016;589:145-51.
27. Rao MN, Neylan TC, Grunfeld C, Mulligan K, Schambelan M, Schwarz JM. Subchronic sleep restriction causes tissue-specific insulin resistance. J Clin Endocrinol Metab. 2015;100(4):1664-71.
28. Robertson MD, Russell-Jones D, Umpleby AM, Dijk DJ. Effects of three weeks of mild sleep restriction implemented in the home environment on multiple metabolic and endocrine markers in healthy young men. Metabolism. 2013;62(2):204-11.
29. Leproult R, Holmback U, Van Cauter E. Circadian misalignment augments markers of insulin resistance and inflammation, independently of sleep loss. Diabetes. 2014;63(6):1860-9.
30. Colten H, R., Altevogt, B.M., . Sleep Disorders and Sleep Deprivation: An Unmet Public Health Problem2006.
31. Dunlap JC, Loros, J.J., DeCoursey, P.J.,. Chronobiology: Biological timekeeping. Sunderland, MA, US: Sinauer Associates Chronobiology; 2004.
32. Yamazaki S, Numano R, Abe M, Hida A, Takahashi R, Ueda M, et al. Resetting central and peripheral circadian oscillators in transgenic rats. Science. 2000;288(5466):682-5.
33. Antle MC, Mistlberger RE. Circadian clock resetting by sleep deprivation without exercise in the Syrian hamster. J Neurosci. 2000;20(24):9326-32.
34. McCarthy JJ, Andrews JL, McDearmon EL, Campbell KS, Barber BK, Miller BH, et al. Identification of the circadian transcriptome in adult mouse skeletal muscle. Physiol Genomics. 2007;31(1):86-95.

* 35. Andrews JL, Zhang X, McCarthy JJ, McDearmon EL, Hornberger TA, Russell B, et al. CLOCK and BMAL1 regulate MyoD and are necessary for maintenance of skeletal muscle phenotype and function. Proc Natl Acad Sci U S A. 2010;107(44):19090-5.
* 36. Dyar KA, Ciciliot S, Wright LE, Bienso RS, Tagliazucchi GM, Patel VR, et al. Muscle insulin sensitivity and glucose metabolism are controlled by the intrinsic muscle clock. Mol Metab. 2014;3(1):29-41.
37. Nagano M, Adachi A, Nakahama K, Nakamura T, Tamada M, Meyer-Bernstein E, et al. An abrupt shift in the day/night cycle causes desynchrony in the mammalian circadian center. J Neurosci. 2003;23(14):6141-51.
* 38. Wolff G, Esser KA. Scheduled exercise phase shifts the circadian clock in skeletal muscle. Med Sci Sports Exerc. 2012;44(9):1663-70.
39. Suwazono Y, Sakata K, Okubo Y, Harada H, Oishi M, Kobayashi E, et al. Long-term longitudinal study on the relationship between alternating shift work and the onset of diabetes mellitus in male Japanese workers. J Occup Environ Med. 2006;48(5):455-61.
40. Richardson CE, Gradisar M, Short MA, Lang C. Can Exercise Regulate the Circadian System of Adolescents? Novel Implications for the Treatment of Delayed Sleep-Wake Phase Disorder. Sleep Medicine Reviews. 2016.
* 41. Zambon AC, McDearmon EL, Salomonis N, Vranizan KM, Johansen KL, Adey D, et al. Time- and exercise-dependent gene regulation in human skeletal muscle. Genome Biol. 2003;4(10):R61.
42. van Moorsel D, Hansen J, Havekes B, Scheer FAJL, Jörgensen JA, Hoeks J, et al. Demonstration of a day-night rhythm in human skeletal muscle oxidative capacity. Molecular Metabolism. 2016;5(8):635-45.
43. Neufeld-Cohen A, Robles MS, Aviram R, Manella G, Adamovich Y, Ladeuix B, et al. Circadian control of oscillations in mitochondrial rate-limiting enzymes and nutrient utilization by PERIOD proteins. Proc Natl Acad Sci U S A. 2016;113(12):E1673-82.
44. Scheer FA. Fundamentals of the Circadian System. 2011. In: Basics of Sleep Guide [Internet]. Sleep Research Society.
45. Andreazza AC, Andersen ML, Alvarenga TA, de-Oliveira MR, Armani F, Ruiz FS, et al. Impairment of the mitochondrial electron transport chain due to sleep deprivation in mice. J Psychiatr Res. 2010;44(12):775-80.
46. Koliaki C, Roden M. Alterations of Mitochondrial Function and Insulin Sensitivity in Human Obesity and Diabetes Mellitus. Annu Rev Nutr. 2016.
* 47. Harfmann BD, Schroder EA, Esser KA. Circadian Rhythms, the Molecular Clock, and Skeletal Muscle. J Biol Rhythms. 2015;30(2):84-94.
48. Lamia KA, Sachdeva UM, DiTacchio L, Williams EC, Alvarez JG, Egan DF, et al. AMPK Regulates the Circadian Clock by Cryptochrome Phosphorylation and Degradation. Science. 2009;326(5951):437-40.
49. Woldt E, Sebti Y, Solt LA, Duhem C, Lancel S, Eeckhoute J, et al. Rev-erb-alpha modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy. Nat Med. 2013;19(8):1039-46.
50. Duez H, Staels B. Rev-erb-alpha: an integrator of circadian rhythms and metabolism. J Appl Physiol (1985). 2009;107(6):1972-80.
51. Vieira E, Nilsson EC, Nerstedt A, Ormestad M, Long YC, Garcia-Roves PM, et al. Relationship between AMPK and the transcriptional balance of clock-related genes in skeletal muscle. Am J Physiol Endocrinol Metab. 2008;295(5):E1032-7.

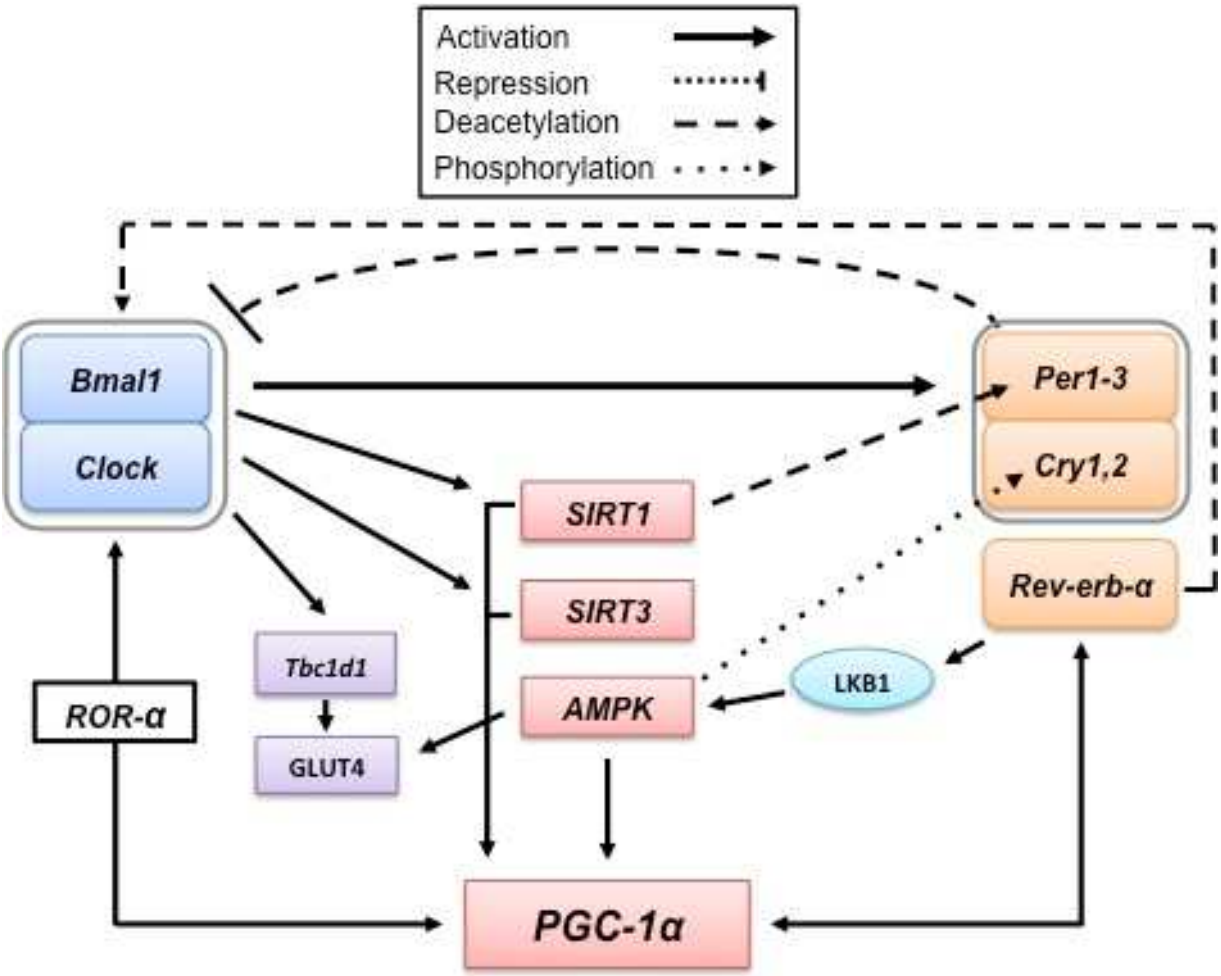
52. Barnes BR, Marklund S, Steiler TL, Walter M, Hjalm G, Amarger V, et al. The 5'-AMP-activated protein kinase gamma3 isoform has a key role in carbohydrate and lipid metabolism in glycolytic skeletal muscle. J Biol Chem. 2004;279(37):38441-7.
53. Hayashi T, Hirshman MF, Kurth EJ, Winder WW, Goodyear LJ. Evidence for 5' AMP-activated protein kinase mediation of the effect of muscle contraction on glucose transport. Diabetes. 1998;47(8):1369-73.
54. Kumaki Y, Ukai-Tadenuma M, Uno KD, Nishio J, Masumoto KH, Nagano M, et al. Analysis and synthesis of high-amplitude Cis-elements in the mammalian circadian clock. Proc Natl Acad Sci U S A. 2008;105(39):14946-51.
55. Jager S, Handschin C, St-Pierre J, Spiegelman BM. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. Proc Natl Acad Sci U S A. 2007;104(29):12017-22.
56. Liu C, Li S, Liu T, Borjigin J, Lin JD. Transcriptional coactivator PGC-1alpha integrates the mammalian clock and energy metabolism. Nature. 2007;447(7143):477-81.
* 57. Pastore S, Hood DA. Endurance training ameliorates the metabolic and performance characteristics of circadian Clock mutant mice. J Appl Physiol (1985). 2013;114(8):1076-84.
58. Lefta M, Wolff G, Esser KA. Circadian rhythms, the molecular clock, and skeletal muscle. Curr Top Dev Biol. 2011;96:231-71.
59. Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, et al. Obesity and metabolic syndrome in circadian Clock mutant mice. Science. 2005;308(5724):1043-5.
60. Rudic RD, McNamara P, Curtis AM, Boston RC, Panda S, Hogenesch JB, et al. BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. PLoS Biol. 2004;2(11):e377.
61. Montgomery MK, Turner N. Mitochondrial dysfunction and insulin resistance: an update. Endocr Connect. 2015;4(1):R1-R15.
62. Edge J, Mundel T, Pilegaard H, Hawke E, Leikis M, Lopez-Villalobos N, et al. Ammonium Chloride Ingestion Attenuates Exercise-Induced mRNA Levels in Human Muscle. PLoS One. 2015;10(12):e0141317.
63. Granata C, Oliveira RS, Little JP, Renner K, Bishop DJ. Training intensity modulates changes in PGC-1alpha and p53 protein content and mitochondrial respiration, but not markers of mitochondrial content in human skeletal muscle. FASEB J. 2016;30(2):959-70.
64. Bishop DJ, Thomas C, Moore-Morris T, Tonkonogi M, Sahlin K, Mercier J. Sodium bicarbonate ingestion prior to training improves mitochondrial adaptations in rats. Am J Physiol Endocrinol Metab. 2010;299(2):E225-33.
65. Benton CR, Wright DC, Bonen A. PGC-1alpha-mediated regulation of gene expression and metabolism: implications for nutrition and exercise prescriptions. Appl Physiol Nutr Metab. 2008;33(5):843-62.
66. Liang H, Balas B, Tantiwong P, Dube J, Goodpaster BH, O'Doherty RM, et al. Whole body overexpression of PGC-1alpha has opposite effects on hepatic and muscle insulin sensitivity. Am J Physiol Endocrinol Metab. 2009;296(4):E945-54.
67. Peek CB, Affinati AH, Ramsey KM, Kuo HY, Yu W, Sena LA, et al. Circadian clock NAD+ cycle drives mitochondrial oxidative metabolism in mice. Science. 2013;342(6158):1243417.
68. Kong X, Wang R, Xue Y, Liu X, Zhang H, Chen Y, et al. Sirtuin 3, a new target of PGC-1alpha, plays an important role in the suppression of ROS and mitochondrial biogenesis. PLoS One. 2010;5(7):e11707.
69. Liu J, Zhou B, Yan M, Huang R, Wang Y, He Z, et al. CLOCK and BMAL1 Regulate Muscle Insulin Sensitivity via SIRT1 in Male Mice. Endocrinology. 2016;157(6):2259-69.

70. Suwa M, Nakano H, Radak Z, Kumagai S. Endurance exercise increases the SIRT1 and peroxisome proliferator-activated receptor gamma coactivator-1alpha protein expressions in rat skeletal muscle. Metabolism. 2008;57(7):986-98.
71. Palacios OM, Carmona JJ, Michan S, Chen KY, Manabe Y, Ward JL, 3rd, et al. Diet and exercise signals regulate SIRT3 and activate AMPK and PGC-1alpha in skeletal muscle. Aging (Albany NY). 2009;1(9):771-83.
72. Gurd BJ, Perry CG, Heigenhauser GJ, Spriet LL, Bonen A. High-intensity interval training increases SIRT1 activity in human skeletal muscle. Appl Physiol Nutr Metab. 2010;35(3):350-7.
73. Gurd BJ. Deacetylation of PGC-1alpha by SIRT1: importance for skeletal muscle function and exercise-induced mitochondrial biogenesis. Appl Physiol Nutr Metab. 2011;36(5):589-97.
74. Leick L, Fentz J, Bienso RS, Knudsen JG, Jeppesen J, Kiens B, et al. PGC-1{alpha} is required for AICAR-induced expression of GLUT4 and mitochondrial proteins in mouse skeletal muscle. Am J Physiol Endocrinol Metab. 2010;299(3):E456-65.
75. Puigserver P, Wu Z, Park CW, Graves R, Wright M, Spiegelman BM. A cold-inducible coactivator of nuclear receptors linked to adaptive thermogenesis. Cell. 1998;92(6):829-39.
76. Granata C, Oliveira RS, Little JP, Renner K, Bishop DJ. Mitochondrial adaptations to high-volume exercise training are rapidly reversed after a reduction in training volume in human skeletal muscle. FASEB J. 2016;30(10):3413-23.
77. Egan B, Carson BP, Garcia-Roves PM, Chibalin AV, Sarsfield FM, Barron N, et al. Exercise intensity-dependent regulation of peroxisome proliferator-activated receptor coactivator-1 mRNA abundance is associated with differential activation of upstream signalling kinases in human skeletal muscle. J Physiol. 2010;588(Pt 10):1779-90.
78. Saleem A, Adhihetty PJ, Hood DA. Role of p53 in mitochondrial biogenesis and apoptosis in skeletal muscle. Physiol Genomics. 2009;37(1):58-66.
79. Kung CP, Murphy ME. The role of the p53 tumor suppressor in metabolism and diabetes. J Endocrinol. 2016.
80. Larsen S, Nielsen J, Hansen CN, Nielsen LB, Wibrand F, Stride N, et al. Biomarkers of mitochondrial content in skeletal muscle of healthy young human subjects. J Physiol. 2012;590(14):3349-60.
81. Dattilo M, Antunes HK, Medeiros A, Monico-Neto M, Souza Hde S, Lee KS, et al. Paradoxical sleep deprivation induces muscle atrophy. Muscle Nerve. 2012;45(3):431-3.
82. Monico-Neto M, Antunes HK, Lee KS, Phillips SM, Giampa SQ, Souza Hde S, et al. Resistance training minimizes catabolic effects induced by sleep deprivation in rats. Appl Physiol Nutr Metab. 2015;40(11):1143-50.
83. Bell LN, Kilkus JM, Booth JN, 3rd, Bromley LE, Imperial JG, Penev PD. Effects of sleep restriction on the human plasma metabolome. Physiol Behav. 2013;122:25-31.
84. Nedeltcheva AV, Kilkus JM, Imperial J, Schoeller DA, Penev PD. Insufficient sleep undermines dietary efforts to reduce adiposity. Ann Intern Med. 2010;153(7):435-41.
85. Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Front Physiol. 2012;3:260.
86. Schroder EA, Harfmann BD, Zhang X, Srikuea R, England JH, Hodge BA, et al. Intrinsic muscle clock is necessary for musculoskeletal health. J Physiol. 2015;593(24):5387-404.
87. Mullington JM, Simpson NS, Meier-Ewert HK, Haack M. Sleep loss and inflammation. Best Pract Res Clin Endocrinol Metab. 2010;24(5):775-84.

88. Haddad F, Zaldivar F, Cooper DM, Adams GR. IL-6-induced skeletal muscle atrophy. J Appl Physiol (1985). 2005;98(3):911-7.
89. Taylor AH, Cable NT, Faulkner G, Hillsdon M, Narici M, Van Der Bij AK. Physical activity and older adults: a review of health benefits and the effectiveness of interventions. J Sports Sci. 2004;22(8):703-25.
90. Mathur N, Pedersen BK. Exercise as a mean to control low-grade systemic inflammation. Mediators Inflamm. 2008;2008:109502.
91. Kim TN, Park MS, Lim KI, Choi HY, Yang SJ, Yoo HJ, et al. Relationships between sarcopenic obesity and insulin resistance, inflammation, and vitamin D status: the Korean Sarcopenic Obesity Study. Clin Endocrinol (Oxf). 2013;78(4):525-32.
92. Lim S, Kim JH, Yoon JW, Kang SM, Choi SH, Park YJ, et al. Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). Diabetes Care. 2010;33(7):1652-4.
93. Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. Proc Natl Acad Sci U S A. 2008;105(3):1044-9.
94. Moser D, Anderer P, Gruber G, Parapatics S, Loretz E, Boeck M, et al. Sleep classification according to AASM and Rechtschaffen & Kales: effects on sleep scoring parameters. Sleep. 2009;32(2):139-49.
* 95. Herzog N, Jauch-Chara K, Hyzy F, Richter A, Friedrich A, Benedict C, et al. Selective slow wave sleep but not rapid eye movement sleep suppression impairs morning glucose tolerance in healthy men. Psychoneuroendocrinology. 2013;38(10):2075-82.
96. Kredlow MA, Capozzoli MC, Hearon BA, Calkins AW, Otto MW. The effects of physical activity on sleep: a meta-analytic review. J Behav Med. 2015;38(3):427-49.
97. Yang PY, Ho KH, Chen HC, Chien MY. Exercise training improves sleep quality in middle-aged and older adults with sleep problems: a systematic review. J Physiother. 2012;58(3):157-63.
98. King AC, Oman RF, Brassington GS, Bliwise DL, Haskell WL. Moderate-intensity exercise and self-rated quality of sleep in older adults. A randomized controlled trial. JAMA. 1997;277(1):32-7.
99. Kubitz KA, Landers DM, Petruzzello SJ, Han M. The effects of acute and chronic exercise on sleep. A meta-analytic review. Sports Med. 1996;21(4):277-91.
100. Baron KG, Reid KJ, Zee PC. Exercise to improve sleep in insomnia: exploration of the bidirectional effects. J Clin Sleep Med. 2013;9(8):819-24.

Figure 1. Interplay between peripheral molecular clock genes, AMPK, SIRT1, SIRT3 and PGC-1α. BMAL1 and CLOCK activate *Per1-3* and *Cry1,2*. PER1-3 and CRY1,2 transcriptionally repress the action of *Bmal1* and *Clock*. AMPK phosphorylates CRY1,2 leading to less repression of *Bmal1* and *Clock*, whilst PGC-1α transcriptionally regulates and is itself regulated by Rev-erb-α. Rev-erb-α also represses the effects of BMAL1. PGC-1α regulates *Clock* through a ROR-α dependent pathway and is regulated also by the CLOCK:BMAL1 complex. CLOCK:BMAL1 can activate both SIRT1 and SIRT3 whereby SIRT1 deacetylates Per2, whilst SIRT1 and SIRT3 upregulates transcription of PGC-1α. Furthermore, BMAL1:CLOCK directly exerts its influence on Tbc1d1 which is required for GLUT4 translocation. AMPK also regulates GLUT4 translocation to the plasma membrane. Rev-erb-α activates AMPK via LKB-1, which directly upregulates transcription of PGC-1α.

Figure 2. One of the main proposed models, based on current literature, of the impact of sleep loss with or without exercise on mitochondrial signaling, mitochondrial biogenesis, and insulin sensitivity. Reduced sleep duration disrupts circadian rhythm and alters molecular clock gene expression, which subsequently impacts on mitochondrial signaling events associated with mitochondrial biogenesis and results in a reduction in insulin sensitivity. Conversely, exercise activates the mitochondrial signaling events associated with mitochondrial biogenesis and, therefore, may be a viable strategy to mitigate sleep loss induced reductions in insulin sensitivity. Furthermore, exercise may induce a phase shift and thus a 'resyncing' of the peripheral clock. While reduced sleep quality also induces reductions in insulin sensitivity, exercise induced improvements in sleep quality may mitigate these responses.


Activation
Repression
Deacetylation
Phosphorylation
Bmal1
Clock
Per1-3
Cry1,2
SIRT1
SIRT3
AMPK
Rev-erb-α
LKB1
Tbc1d1
GLUT4
ROR-α
PGC-1α