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Does sex influence the effects of experimental sleep curtailment and circadian misalignment on regulation of appetite?

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Abstract

Sleep curtailment and circadian misalignment disrupt energy sensing and eating behaviors, which can contribute to weight gain and obesity-related comorbidities. Herein, we review the effects of experimental manipulations of sleep duration and circadian alignment on circulating concentrations of appetite hormones, specifically leptin and ghrelin. Further, we focus on sex differences in hormonal and behavioral responses related to food intake. The studies reviewed suggest potential sex-specific effects of sleep curtailment on key hormones involved in the gut-brain axis, presumably leading to downstream effects on neural processes involved in food seeking and consumption behaviors. However, there is insufficient evidence to declare any sex-specific effects of circadian misalignment on appetite regulation. More research is needed to elucidate the complex sex-specific relationships between sleep, circadian rhythms, energy homeostasis, and appetite regulating mechanisms. Greater knowledge of these mechanisms would aid in the development of targeted methods to mitigate risk for obesity and related metabolic diseases.

Keywords

sleep; circadian rhythms; obesity; homeostasis; appetite

INTRODUCTION

Many aspects of the modern lifestyle, including diverse work schedules, social activities and mistimed light exposure, have led to increased prevalence of short sleep duration [1, 2]. These factors also contribute to desynchrony between circadian rhythms of biological

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CONFLICT OF INTEREST

None of the authors have any conflicts to disclose.

systems and lifestyle behaviors, termed circadian misalignment (CM) [3]. Both insufficient sleep and CM have been associated with increased risk for various cardiometabolic diseases, including obesity [4, 5]. Specifically, evidence from experimental studies has demonstrated that sleep curtailment and CM alike alter eating behaviors in favor of overconsumption [6, 7], suggesting shared pathologic mechanisms related to energy homeostasis. A key factor in these homeostatic pathways is hormonal regulation of appetite. Studies have shown that sleep curtailment [8–13] and CM [14–17] influence appetite-regulating hormones. However, the directionality of findings related to the role of sleep duration on hunger and satiety signals is not consistent across studies [18, 19], and we have suggested that hormonal responses to sleep restriction, specifically, may differ between males and females [19]. Here, we evaluate recent findings from clinical trials published since our last evaluation [19] assessing the influence of sleep curtailment and CM on appetite-regulating hormones and subjective hunger, highlighting potential sex differences.

Sex-specific effects of sleep curtailment and circadian misalignment on appetite regulation

Given established associations of short sleep duration and CM with heightened risk of obesity [7, 20], several studies have been undertaken to determine causality and assess underlying mechanisms. These studies may also provide insight into a potential role of sex in changes in responses to sleep restriction and circadian misalignment.

Sleep curtailment—Despite meta-analyses reporting increased food intake following periods of acute sleep restriction [20–22], two recent studies conducted exclusively in females provide opposite findings [10, 13] (Table 1). One study was a randomized crossover trial of acute sleep restriction performed in 12 females with overweight or obesity and self-reported adequate sleep [10]. Subjective appetite, appetite-regulating hormones and food intake were measured after 2 consecutive nights of restricted sleep (5 h time in bed [TIB]) and 2 nights of sufficient sleep (9 h TIB). No differences in subjective appetite, leptin, and ghrelin concentrations were observed between restricted and habitual sleep conditions. Correspondingly, food intake was not different between conditions. A similar lack of effect of sleep restriction on food intake and leptin concentrations was observed in a separate study in which dietary behavior and physical activity were examined following 3 nights of restricted sleep (4 h TIB) and 3 nights of sufficient sleep (7 h TIB) in 16 young, healthy females [13]. Ghrelin concentrations were not assessed in that study. Thus, studies suggest that sleep restriction may have a limited impact on eating behaviors of females.

In contrast, in a study performed exclusively in young, lean males, sleep restriction was shown to influence food intake and appetite-regulating hormones [11]. In that study, appetite-regulating hormones were compared following 4 nights of restricted sleep (4.5 h TIB) and 4 nights of sufficient sleep (8.5 h TIB). Food intake was measured at a lunch and dinner buffet and from *ad libitum* access to snacks in between. Sleep restriction increased mean 24-h ghrelin concentrations as well as nocturnal and postprandial ghrelin, suggestive of increased appetite, compared to sufficient sleep. Leptin levels throughout the measurement period were not affected by the sleep intervention. Nonetheless, restricted sleep in males was associated with an increase in total caloric intake, due to an increased

intake from snacks specifically. Intakes at the two buffet meals were not different between conditions.

Other studies have included both males and females [9, 12]. One study was conducted in 14 young, healthy adults (11 males; 3 females), to assess the effects of sleep restriction on food intake and hedonic and hormonal regulators of ingestive behavior [12]. This randomized crossover inpatient study tested each participant under 2 conditions: 4 nights of sufficient sleep (8.5 h TIB) or restricted sleep (4.5 h TIB), resembling previous protocols. Appetite-regulating hormones were assessed under controlled feeding conditions, which were followed by an *ad libitum* late afternoon meal and dinner, with free access to a snack bar in between. Food intake from those meals and snacks was measured. Mean 24-h leptin concentration was not different between the 2 sleep conditions, but the amplitude of its variation was blunted under sleep restricted conditions compared to sufficient sleep. Ghrelin concentrations were not affected by sleep restriction. However, feelings of hunger and desire to eat were reportedly higher during restricted compared to sufficient sleep. Food intake at the 2 meal buffets did not differ between conditions, but intakes from snacks were higher after sleep restriction compared to sufficient sleep. The authors did not report whether combined intakes from meals and snacks were different between conditions. These data, from a male-dominated sample, align with those conducted exclusively in males reporting increased intake from snacks [11]. However, exclusion of sex-stratification in data analyses, likely due to the imbalanced number of males and females, precludes definitive conclusions related to sex-specific effects.

A similar randomized crossover study, consisting of young, healthy adults (8 males; 8 females) assessed the effects of sleep restriction on energy balance [9]. The study included a 3-d baseline period (9 h TIB) followed by two 5-d conditions of restricted sleep (5 h TIB) or sufficient sleep (9 h TIB). Appetite-regulating hormones were assessed under *ad libitum* feeding conditions and food intake was measured. Mean 24-h leptin levels increased and mean 24-h ghrelin levels decreased from baseline during restricted sleep, but differences in these hormones were not observed between conditions. Correspondingly, subjective hunger levels decreased during both sleep conditions and were not different between restricted and sufficient sleep. When data were examined by sex, hunger decreased in both conditions in males whereas it did not change in females. This contradicts changes in weight: males gained weight during both sleep conditions whereas females only gained weight during the restricted sleep condition. Appetite hormone concentrations were not analyzed separately by sex.

In summary, two sleep restriction studies conducted exclusively in females report no effect on leptin [10, 13] and ghrelin [10] concentrations. Food intake at a buffet meal was similarly unaffected. Meanwhile, one study in males reported increased ghrelin, but no difference in leptin, associated with higher intake of snacks as a result of sleep restriction [11]. These findings align with our prior evaluation of the literature in this field, concluding that hormonal regulation of appetite as a result of sleep restriction may differ by sex [19]. Furthermore, in studies with a mix of males and females, changes in leptin and ghrelin concentrations are not different between restricted and sufficient sleep conditions [9, 12] and a meta-analysis of clinical intervention studies failed to show any effects of sleep restriction

on leptin and ghrelin, nor any sex differences [20]. Moreover, whereas energy intake in the most recent studies reviewed here was not affected by sleep restriction in females [10, 13], one study has reported increased intakes in males [11]. Differences in measurement type for food intake, whether buffet meals or total daily intake, may further contribute to the disparate findings related to this outcome.

It is important to keep in mind that increases in energy intake are of concern if (1) they represent unhealthy dietary patterns, and (2) are unmatched by an equivalent increase in energy expenditure to maintain energy balance. In this regard, studies of sleep curtailment have observed a small but significant increase in energy expenditure relative to adequate sleep [23–25] that is well below the increase in energy intake observed in the literature [21, 22]. However, sex differences in the impact of sleep restriction on energy expenditure have not been examined and could potentially contribute to differences in weight outcomes observed between men and women.

Circadian misalignment—Similar to sleep restriction, CM is a lifestyle pattern linked to adverse health outcomes [5]. Circadian misalignment can result from discordance between lifestyle behaviors and the 24-h light/dark cycle, which causes desynchrony between central and peripheral rhythms. Such disruption of the circadian cycle can lead to downstream effects on metabolic and endocrine function [5]. Interestingly, sex differences in circadian rhythms are well known, with females displaying a shorter circadian period than males [26] and earlier circadian phase timing at same age [27]. These observations may contribute to sex-specific differences in the effects of CM on appetite regulating hormones [14] and adiposity [28]. A small number of clinical interventions have examined the effect of CM on appetitive behavior and energy balance regulation in males and females.

To explore the possible impact of CM on concentrations of appetite hormones, our lab conducted an inpatient crossover study with 4 males and 2 females [15]. Each participant was tested under 4 combinations of meal and sleep timing: normal sleep/normal meals, normal sleep/late meals, late sleep/normal meals and late sleep/late meals, each separated by a 4-wk washout period. Meals were consumed either 1 h or 4.5 h after awakening in normal and delayed conditions, respectively. Sleep was also delayed by 3.5 h in the late, relative to the normal, sleep condition. Overnight ghrelin concentrations were significantly affected by sleep timing, meal timing, and sleep × meal timing interaction, with lower ghrelin in the evening hours and higher postprandial ghrelin due to combination of normal sleep and meals, consistent with healthy circadian rhythms in this hormone. Overnight leptin concentrations were also affected by meal timing, with higher values observed in normal meal conditions. Moreover, under *ad libitum* feeding conditions, there was a significant effect of meal timing on fat intake, while sleep × mealtime interactions were only significant for monounsaturated fat intake. Intake was highest when a snack was consumed close to bedtime in normal sleep conditions [15]. Although far from definitive, results from this pilot study suggest that CM induced by delaying meals may influence appetite regulation.

In a study of more severe CM, 14 healthy young adults (8 males; 6 females) were evaluated during 2 different conditions: circadian alignment, which consisted of 8 days of 8 h nighttime sleep opportunity, and CM, which consisted of 3 days of 8 h nighttime sleep

opportunity, followed by a 12 h shift in the wake/sleep behavioral cycle for 5 days, with sleep occurring during the day and wake at night [14]. Each study phase was performed in random order under controlled feeding conditions. In females, CM decreased wake and 24-h leptin levels and increased wake ghrelin levels relative to circadian alignment. In males, on the other hand, CM increased both wake and sleep leptin levels but not ghrelin concentrations relative to the aligned condition. Higher cravings for energy-dense and savory foods were also reported in the CM condition [14]. These results would suggest greater hedonic susceptibility to overeating in misaligned conditions in males, whereas females would experience greater homeostatic drive to eat. This study strictly controlled food intake and did not include a period of *ad libitum* consumption, therefore information on self-selected energy intake is not available.

To enhance ecological validity of findings from these tightly-controlled trials, appetitive behaviors have been compared between day and night workers [17]. Female nurses working either day (0800–1600 h) or night (1600–2400 h and 1600–0800 h) shifts were enrolled in a study to assess the metabolic effects of CM. Leptin concentrations were higher in night workers compared to day workers. It is notable that body weight of the participants was not reported in that study. However, based on those findings, one would expect higher weight in night vs day nurses, given leptin's role as an adiposity signal [29].

Due to insufficient studies that include males and females and perform sex-specific analyses, we cannot conclude that CM plays a differential role in hormonal regulation of appetite between males and females. Only one study examined subjective hunger, and appetite hormone concentrations in adults separately by sex [14]. That study found increases in waking ghrelin concentrations and decreases in 24-h leptin profiles in females, while males had no change in waking ghrelin and increased 24-h leptin profiles. Correspondingly, subjective fullness ratings were decreased in females but not in males due to CM, while males had increased cravings for energy-dense foods, which were not observed in females [14]. These findings suggest differences in appetite-regulating pathways between males and females that warrant further study.

It is interesting to note that the different results observed between males and females in response to CM suggest increased hunger from higher ghrelin concentrations with decreased fullness ratings in females, while in males, increased hunger from subjective, but not objective, measures were observed [14]. These findings in part align with prior findings from sleep restriction interventions by our group: females had reductions in glucagon-like peptide 1 concentrations, a satiety-promoting hormone, and males had increases in ghrelin, a hormone involved in triggering food consumption, following 3 nights of 4 h TIB vs 9 h TIB [8]. At the time, we had suggested different regulatory mechanisms implicated in food intake control between males and females following sleep restriction. This effect may similarly be at play for CM. Indeed, observed differences in eating behavior, with males consuming more energy-dense foods may be due to a sex-specific activation ratio of hedonic to homeostatic signals, respectively. Future studies should evaluate eating frequency and duration to determine whether effects on perception of fullness translate to differences in eating behaviors.

We know of only one study that has assessed the impact of CM on 24-h energy expenditure, measured using whole-room indirect calorimetry in healthy men and women [30]. Misalignment, induced via simulated night shift work, resulted in small reductions in 24-h energy expenditure relative to baseline. Differences between males and females were not examined in this study. However, Qian et al have reported that females experience an increase in postprandial energy expenditure and lipid oxidation from CM whereas males do not [14]. More research is necessary to determine the influence of CM on energy expenditure and substrate oxidation in males and females.

Directions for future research to improve understanding of the role of sex in SR and CM in appetite regulation

The effects of sleep and circadian rhythms on appetite regulation and differences between males and females must be further explored if we are to understand how sleep affects metabolic signaling related to hunger and satiety. Results of the studies reviewed here indicate that sleep curtailment and CM impact concentrations of appetite regulating hormones, presumably influencing downstream signaling on neural processes involved in food seeking and consumption behaviors. We further note that effects on appetite regulation and subsequent eating behavior(s) may differ by sex. However, data on sex-specific effects are limited, particularly for CM. Therefore, more research focusing on the impact of sleep restriction and CM on circulating concentrations of appetite hormones is necessary to understand behavioral effects associated with these metabolic signaling cascades. Sex-specific regulation of appetite hormones is suspected but is largely unexplored. The central mechanisms associated with homeostatic and hedonic feeding have not been studied extensively in humans, and the effects of CM and sleep curtailment on hedonic and homeostatic regulation of energy balance remain unclear. Effects on these physiological markers should be further investigated to determine whether different mechanistic pathways influence obesity risk in males and females. These measures should be accompanied by more sophisticated and comprehensive estimations of food intake, namely 24-h dietary intake profiles that include information on number and timing of eating occasions, along with measures of additional appetite-regulating hormones beyond leptin and ghrelin, such as glucagon-like peptide 1 and peptide YY.

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Table 1.

Impact of sleep restriction and circadian misalignment on energy intake, ghrelin, and leptin concentrations relative to sufficient sleep and circadian alignment.

Study	Subjects	Sleep	Energy intake	Leptin	Ghrelin
Sleep Restriction					
Hart et al.[10]	12 females, overweight to obese	5 h TIB; 9 h TIB (2 nights)	Not different	Not different (fasting)	Not different (fasting)
Tajiri et al.[13]	16 females, normal weight	4 h TIB; 7 h TIB (3 nights)	Not different	Not different (fasting)	(Not measured)
Markwald et al.[9]	8 males and 8 females, normal weight	5 h TIB; 9 h TIB (5 nights)	Increased by ~ 182 kcal/d	Not different (24-h)	Not different (24-h)
Hanlon et al.[12]	11 males and 3 females, normal weight	4.5 h TIB; 8.5 h TIB (4 nights)	Increased by 101 kcal; significant increase from snacks (381 kcal) but not meals	Blunted amplitude (24-h)	Not different (24-h)
Broussard et al.[11]	19 males, normal weight	4.5 h TIB; 8.5 h TIB (4 nights)	Increased by 340 kcal	Not different (24-h)	Increased mean (24-h) levels
Circadian Misalignment					
St-Onge et al.[15]	6 males and females, overweight to obese	Normal sleep (0000–0800) vs late sleep (0330–1130); normal meals vs late meals (3.5 h delay)	Increased energy intake during normal sleep × late meal condition	Higher overnight concentrations in normal meal conditions	Lower overnight and higher postprandial concentrations in normal sleep × normal meal condition
Qian et al.[14]	14 males and females, normal weight to overweight	CM (12 h shifted behavioral cycle) vs circadian alignment	Controlled; increased craving for energy dense and savory foods in men and reduced fullness in women	Increased wake and sleep concentrations in men and decreased wake and 24-h concentrations in women during CM	No changes in men and increased waking concentrations in women during CM
Cakan et al.[17]	60 females, weight not reported	Whole night (1600–0800 h), half-night (1600–2400 h), or day (0800–1600 h) shift workers	(Not measured); all groups consumed foods rich in carbohydrates and sugar	Higher in women working whole or half-night shift (single sample)	(Not measured)