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THEORETICAL REVIEW

Leptin: A biomarker for sleep disorders?

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SUMMARY

Leptin, a pleiotropic protein hormone produced mainly by fat cells, regulates metabolic activity and many other physiological functions. The intrinsic circadian rhythm of blood leptin is modulated by gender, development, feeding, fasting, sleep, obesity, and endocrine disorders. Hyperleptinemia is implicated in leptin resistance. To determine the specificity and sensitivity of leptin concentrations in sleep disorders, we summarize here the alterations of leptin in four conditions in animal and human studies: short duration of sleep, sleep fragmentation, obstructive sleep apnea (OSA), and after use of continuous positive airway pressure (CPAP) to treat OSA. The presence and causes of contradictory findings are discussed. Though sustained insufficient sleep lowers fasting blood leptin and therefore probably contributes to increased appetite, obesity and OSA independently result in hyperleptinemia. Successful treatment of OSA by CPAP is predicted to decrease hyperleptinemia, making leptin an ancillary biomarker for treatment efficacy. Current controversies also call for translational studies to determine how sleep disorders regulate leptin homeostasis and how the information can be used to improve sleep treatment.

Introduction

Leptin is a 16 kDa polypeptide cytokine that is produced mainly in adipocytes. It inhibits feeding, increases sympathetic activation, modulates immune functions, influences synaptic activities, and often promotes inflammation. Many effects are mediated by the central nervous system (CNS), as leptin crosses the blood–brain barrier (BBB) by a saturable transport mechanism [1]. Leptin concentrations in blood correlate with body weight and body mass index (BMI). Hyperleptinemia in obesity is part of the intriguing phenomenon of leptin resistance. Like insulin resistance in type II diabetes, leptin resistance is a universal finding in obesity and metabolic syndrome [2]. The underlying mechanisms involve upregulation of leptin antagonists such as the soluble leptin receptor and counteracting hormones, reduced efficiency of leptin uptake by organs including the brain, desensitization of leptin signaling in target organs, and development of antagonistic cellular signaling pathways. These factors modulate the physiological response to leptin across time and condition. Partial saturation of leptin transport across the BBB is already present at physiological conditions. In obesity, the BBB becomes a rate limiting factor to reduce the efficacy of leptin in the CNS [3]. By contrast, 48 h fasting decreases blood leptin and its transport across the BBB in lean mice [4].

Sleep, circadian rhythm, and sleep disorders all affect leptin concentrations in blood. The rhythm of leptin in constant conditions differs from that in entrained conditions. There is entrainment by meals [5–7] and regulation by gender and adiposity [8,9]. In most studies, human subjects (and animals) live in an environment with feeding-fasting and wake–sleep cycles, both of which influence the concentration of leptin. Under a constant routine protocol with dim light and 38 h of wakefulness, the circadian rhythm of endogenous leptin peaks around the usual time of waking. This contrasts with the effects of sleep and fasting to lower leptin and with those of wakefulness and feeding to increase leptin. Results from this well-controlled study of six healthy human subjects indicate combined effects from the endogenous circadian pacemaker and day/night patterns on leptin concentrations [7]. While the sleep/wake schedule causes a leptin nadir upon awakening, the entrained rhythm peaks earlier (midnight) and reaches a minimum at 11:40 h, before lunch at 12:30 h. Plasma leptin is not shifted by acute sleep deprivation, but shows a rhythm shift of 5–7 h when meals are shifted 6.5 h without changing the light or sleep cycle. Furthermore, there is a 12 ± 2 h shift induced by day/night reversal (time zone shift). The results indicate meal entrainment, rather than an immediate effect of the circadian clock [5].

In patients with narcolepsy who show fragmented sleep, abnormal rapid eye movement (REM) sleep, and excessive daytime

Abbreviations: AHI, apnea–hypopnea index; BBB, blood–brain barrier; BMI, body mass index; CNS, central nervous system; CPAP, continuous positive airway pressure; EDS, excessive daytime sleepiness; OSA, obstructive sleep apnea; PAP, positive airway pressure; REM, rapid eye movement.

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sleepiness (EDS), there is a reduction of mean 24-h plasma leptin concentration and loss of the nocturnal acrophase [10]. This is not unusual since narcolepsy involves degeneration of orexin neurons and probably affects other areas of the hypothalamus involved in neuroendocrine control of feeding. Obesity and its associated leptin resistance also result in hypothalamic astrogliosis [11–13]. However, it is not yet clear whether leptin resistance plays a causal role in metabolic and neurobehavioral changes in subjects with sleep disorders.

The analysis of a relationship between leptin concentration and sleep is important since sleep disturbance contributes greatly to poor health. Sleep durations of five hours (h) or less per night are associated with a significantly increased risk of obesity [14]. Obesity is a main risk factor for obstructive sleep apnea (OSA); a recent analysis with epidemiological modeling from the Wisconsin Sleep Cohort indicates that the estimated prevalence rates increased substantially over the last two decades, from 14% to 55% among different age groups [15]. Sleep fragmentation is also a main feature of OSA and leads to EDS. Hyperleptinemia is a consequence of obesity, and it might serve a biochemical link between sleep disorders and impaired physiological functions.

Here, we review the conflicting literature about leptin and sleep within the last decade (2002–2012) in each of four areas: short sleep duration, sleep fragmentation, OSA, and the use of continuous positive airway pressure (CPAP) for treatment of OSA. The results, including reduction, elevation, or lack of change of leptin, show the complexity of the leptin system that can be influenced by biological behavior and efficacy of treatment. Taking into consideration circadian rhythm changes, adiposity, and the rigor of control of experimental conditions, the most consistent conclusion is that effective treatment of OSA reduces hyperleptinemia. This makes leptin a biomarker for treatment efficacy.

Effects of short sleep duration on leptin in human studies (Table 1)

Human studies showing decreased leptin in short sleepers

Overnight polysomnography (PSG) is the gold standard for evaluation of sleep duration and quality. By use of PSG, the Wisconsin Sleep Cohort showed that subjects sleeping 5 h had fasting blood leptin concentrations 15.5% lower than those sleeping 8 h [16]. The significant correlation between sleep duration and leptin was independent of BMI, age, sex, or the presence/extent of sleep-disordered breathing. This appears counterintuitive, especially that short sleepers in this study tended to have a higher BMI (usually associated with higher leptin), making the reduction of leptin concentrations even more significant. Blood sampling time, in relation to sleep–wake cycle and nycthemeral effects on blood leptin concentrations, therefore, might provide a feasible explanation (Fig. 2).

Prolonged sleep loss decreases the circadian amplitude of leptin, as shown in 10 healthy men after 88 consecutive hours of sustained sleeplessness [17]. Multiple consecutive nights of shortened sleep also decreases leptin concentrations. After a week of nightly sleep restriction to 4 h, the maximal blood leptin concentrations were 26% lower in 11 healthy men. This occurred without change in caloric intake, physical activity, body weight, or BMI. Both daytime and nighttime leptin concentrations decreased, as did the amplitude of the diurnal variation. The acrophase of the circadian rhythm was also advanced; i.e., the time it took for the usual increase of blood leptin from a low in the early morning to the nocturnal peak was decreased by about 1.5 h [18].

Human studies showing unchanged leptin in short sleepers

The effect of habitual short sleep duration (less than 6.5 h by actigraphy worn at home) on leptin concentrations was tested in 80

Table 1
Effects of sleep duration on blood leptin concentrations in human studies.

Study	Sleep duration	Leptin level	Experiment type	Population sampled	Method to measure sleep
Benedict 2012 [20]	24 h no sleep	No change	Prospective with crossover design	14 men, 22.6 ± 0.8 y old, BMI 23.9 ± 0.5 kg/m^2	Laboratory environment
Charles 2011 [24]	<5 h or >8 h vs 5–7 h	↑	Cross sectional	443 police	Questionnaire
Klingenberg 2012 [23]	4 h × 3 nights	No change	Prospective with crossover design	21 teenagers (15–19 y old), BMI < 25 kg/m^2	Laboratory environment
Knutson 2011 [19]	6.5 h of sleep at home	No change; blood drawn 8–10 am	Prospective	80 habitual short sleepers, BMI 38.2 kg/m^2	Actigraphy
Mullington 2003 [17]	88 h sleep loss	↓Circadian amplitude	Time series	10 healthy men	Sleep lab environment
Nedeltcheva 2009 [29]	5.5 h vs 8.5 h × 14 nights with overeating	No difference	Prospective	11 people; overeating dominates the effect, 39 ± 5 y old, BMI 26.5 ± 1.5 kg/m^2	EEG and EMG for sleep staging
Omisade 2010 [28]	4 h × 5 nights	↑Morning leptin 0.2 ng/ml (7.7%)	Prospective	136 people, 18–25 y old (21.6 ± 2.23), BMI 18.3–51.9 kg/m^2 (24.47 ± 8.09)	Laboratory environment
Reynolds 2012 [25]	4 h × 5 nights	↑0.5 ng/ml (13.7%)	Prospective	14 men, 27 y old, BMI 23.5 kg/m^2	Laboratory environment
Schmid 2008 [21]	4.5 or 0 h vs 7 h	No change	Prospective	10 healthy men, BMI 23.8 kg/m^2, 1 night	PSG
Schmid 2009 [22]	4.5 h × 2 nights	No change	Prospective with crossover design	15 healthy young adults (age 27.1 ± 1.3), BMI 22.9 kg/m^2	accelerometry
Simpson 2010 [27]	3 h	↑33%	Prospective	15 young women	Laboratory environment
Spiegel 2004 [18]	4 h vs 12 h for 6 d	↓ 26%	Prospective	11 healthy men (22 ± 1 y old), BMI 23.4 kg/m^2	PSG
Taheri 2004 [16]	5 h vs 8 h	↓ 15.5%	Prospective cohort	1017 people from Wisconsin Sleep Cohort, BMI 29.7 kg/m^2	PSG in combination with questionnaires and sleep diary
Van Leeuwen 2010 [26]	4 h × 5 nights	↑0.35 ng/ml (163.3 ± 42.4% at 5th day of sleep restriction, 123.1 ± 7.0% at 2nd night of recovery sleep)	Prospective	23 men, 23.1 ± 2.5 y old, BMI 23.2 kg/m^2	Laboratory environment