Metabolism Clinical and Experimental xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com

Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes

Sirimon Reutrakul [a,*], Eve Van Cauter [b]

[a] Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Illinois at Chicago, Chicago, IL, USA
[b] The Section of Adult and Pediatric Endocrinology, Diabetes and Metabolism and Sleep, Metabolism and Health Center, Department of Medicine, The University of Chicago, Chicago, IL, USA

ARTICLE INFO

Article history:
Received 24 August 2017
Received in revised form 18 February 2018
Accepted 27 February 2018
Available online xxxx

Keywords:
Sleep restriction
Sleep fragmentation
Sleep extension
Glucose metabolism
Energy intake
Insulin resistance
Type 2 diabetes
Obesity

ABSTRACT

A large body of epidemiologic evidence has linked insufficient sleep duration and quality to the risk of obesity, insulin resistance and type 2 diabetes. To address putative causal mechanisms, this review focuses on laboratory interventions involving several nights of experimental sleep restriction, fragmentation or extension and examining metabolically relevant outcomes. Sleep restriction has been consistently shown to increase hunger, appetite and food intake, with the increase in caloric intake in excess of the energy requirements of extended wakefulness. Findings regarding decreases in hormones promoting satiety or increases in hormones promoting hunger have been less consistent, possibly because of confounding effects of changes in adiposity when energy intake was not controlled and sampling protocols that did not cover the entire 24-h cycle. Imaging studies revealed alterations in neuronal activity of brain regions involved in food reward. An adverse impact of experimental sleep restriction on insulin resistance, leading to reduced glucose tolerance and increased diabetes risk, has been well-documented. There is limited evidence indicating that sleep fragmentation without reduction in sleep duration also results in a reduction in insulin sensitivity. The adverse metabolic outcomes of sleep disturbances appear to involve multiple mechanistic pathways acting in concert. Emerging evidence supports the benefits of behavioral, but not pharmacological, sleep extension on appetite and glucose metabolism. Further research should focus on the feasibility and efficacy of strategies to optimize sleep duration and quality on obesity and diabetes risk in at-risk populations as well as those with established diseases. Further work is needed to identify mechanistic pathways.

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* Corresponding author at: Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, University of Illinois at Chicago, 835 S. Wolcott St, Suite 625E, Chicago, IL, USA.
E-mail address: sreutrak10800@gmail.com (S. Reutrakul).

https://doi.org/10.1016/j.metabol.2018.02.010
0026-0495/

1. Introduction

Approximately one third of human's lifetime is spent sleeping. Sleep is a state of energy restoration and replenishment. In modern society, bedtime is often curtailed to meet increasing personal and social demands. In the United States, self-reported sleep duration has declined over the last 2–3 decades [1]. The epidemics of obesity and diabetes developed simultaneously. Evidence from large cross sectional and longitudinal epidemiologic studies, discussed elsewhere in detail in other articles in this series, demonstrated that insufficient sleep is a risk factor for obesity and diabetes [2,3]. Moreover, poor sleep quality has been linked to similar detrimental effects [3]. To elucidate potential causal mechanisms, this review will focus on the findings from laboratory studies involving the impact of experimental sleep manipulations, including sleep restriction, fragmentation and sleep extension on the control of energy balance and/or glucose metabolism.

2. Sleep Restriction and Obesity Risk

Outcome measures in laboratory studies addressing the impact of sleep restriction on obesity risk have included assessments of circulating levels of appetite-regulating hormones, self-reports of hunger and appetite, objectively assessed food intake, energy expenditure, weight changes and neuronal activity in specific brain regions. Fig. 1 illustrates our current understanding of pathways linking sleep restriction to obesity risk.

2.1. Sleep Restriction and Appetite Regulating Hormones

The first laboratory studies exploring the impact of insufficient sleep on obesity risk focused on changes in leptin levels in healthy lean individuals submitted to experimental sleep restriction. Leptin is a peptide hormone secreted from white adipose tissue and is a signal of positive energy balance, promoting satiety [4]. Circulating leptin concentrations show a rapid decline or increase in response to acute caloric shortage or surplus, respectively. Therefore, changes in leptin levels following sleep restriction can only be interpreted if caloric intake was rigorously controlled and weight remained stable. Leptin levels undergo a large and consistent diurnal variation, with maximal levels during the nighttime. Thus, an accurate evaluation of the impact of sleep duration on leptin concentrations requires sampling across the 24-h cycle. The first studies linking insufficient sleep with a dysregulation of human leptin were published in 2003 [5,6]. Both indicated that leptin levels and amplitude of diurnal variation were reduced following sleep loss. In 2004, Spiegel et al. reported the impact of sleep restriction on leptin levels in two separate studies, using different experimental designs [7,8]. In one study, the 24-h leptin profile was assessed under three sleep conditions (three nights of 8-h bedtime, six nights with 4-h bedtime and seven nights with 12-h bedtime) in 11 healthy lean men, under controlled diet and activity conditions [7]. Despite no changes in weight, mean, maximal levels and rhythm amplitude of leptin decreased by 19%, 26% and 20%, respectively, after sleep restriction compared to sleep extension. The 24-h profile measured during the 8-h bedtime condition was intermediate between the other two conditions, with the difference between 8-h bedtime and 4-h bedtime being most apparent during the nighttime (top panel of Fig. 2). The authors suggested that sleep restriction may alter the ability of leptin to accurately signal energy balance, or that the decrease in leptin could represent a normal adaptation in response to the increased caloric need of extended wakefulness [7]. Consistent findings were obtained in a randomized crossover study in 12 young lean men with two days of sleep restriction and two days of sleep extension [4-h and 10-h time in bed (TIB)], while controlling caloric intake under the form of a constant glucose infusion and stable low levels of physical activity [8]. Mean leptin levels decreased by 18%, with simultaneous increase in hunger and appetite, especially for caloric dense foods. This early evidence suggested that sleep curtailment may be a risk for weight gain and obesity. Subsequent studies examined the impact of various degrees of sleep restriction on leptin levels, often measured only in the morning, under variable dietary conditions (weight maintenance, ad libitum or weight reducing) in lean, overweight or obese men and women. Not surprisingly, the findings were mixed, with elevations, instead of reductions, in leptin levels observed in some studies [9–12], no significant changes in others [13–16] and variable changes across the period of sleep restriction [17]. An

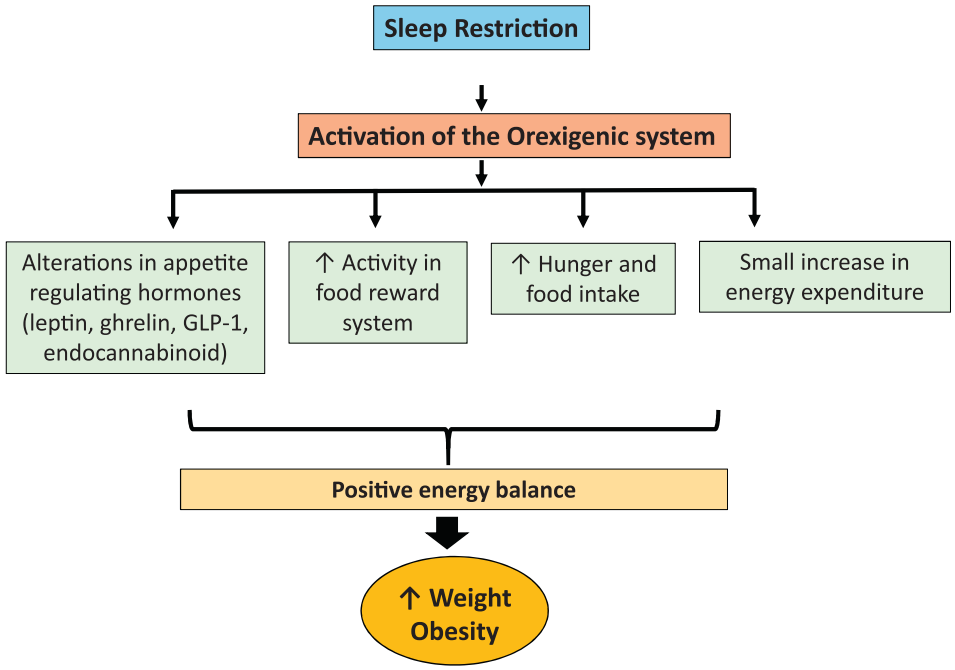

Fig. 1. Putative pathways linking insufficient sleep and obesity risk.
(Adapted from Reutrakul S, Van Cauter E. Interactions between sleep, circadian function, and glucose metabolism: implications for risk and severity of diabetes. Ann N Y Acad Sci. 2014;1311:151–73, with permission).

Please cite this article as: Reutrakul S, Van Cauter E, Sleep influences on obesity, insulin resistance, and risk of type 2 diabetes, Metabolism Clinical and Experimental (2018), https://doi.org/10.1016/j.metabol.2018.02.010