COMMENTARY

Hungry for Sleep: A Role for Endocannabinoids?

Commentary on Hanlon et al. Sleep restriction enhances the daily rhythm of circulating levels of endocannabinoid 2-arachidonoylglycerol. *SLEEP* 2016;39(3):653–664.

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Inadequate sleep, both in quantity and quality, has been associated with increased body weight and risk for obesity.[1] While this link has been established convincingly in epidemiologic studies, such studies cannot determine causality or the direction of effect between sleep and weight. Indeed, both directions appear to play a role. On the one hand, e.g., an increased body mass index increases the risk for obstructive sleep apnea, and thus for disturbed sleep.[2] On the other hand, experimental sleep restriction influences processes involved in energy balance and body weight regulation.

Seminal studies under controlled laboratory conditions and controlled caloric intake have shown that experimental sleep restriction leads to decreases in the satiety hormone leptin, increases in the appetite hormone ghrelin, and increases in hunger and appetite.[3] While this may be in part due to the increased energy expenditure required by the increased time awake,[4] and thus a normal homeostatic response to a lower energy balance, this doesn't appear to be the full story. Indeed, recent experimental studies have demonstrated that restricted sleep results in overeating, thus eating in excess of the slight increase in energy expenditure, and results in weight gain.[5,6] This raises the question why people would overeat when sleep deprived.

In this issue of *SLEEP*, Hanlon and colleagues[7] provide insights into the possible involvement of food reward mechanisms to underlie increased (unhealthy) food intake following sleep restriction. Using a randomized, crossover design, in fourteen healthy non-obese study participants on a fixed diet (three identical meals per day), they investigated the influence of restricting the sleep opportunity to 4.5 h per night (4 h 11 min of actual sleep as determined by PSG) as compared to 8.5 h per night (7 h 33 min) for 3 nights on the 24-h daily profile of hourly-sampled circulating endocannabinoids. The midpoint of the sleep opportunity was kept the same for the two conditions to limit any changes in circadian phase. Sleep restriction resulted in an increase in the peak and amplitude of the 24-h daily rhythm in circulating concentrations of a key endocannabinoid, 2-arachidonoylglycerol (2-AG) and its structural analogue 2-oleoylglycerol (2-OG), without changes in the 24-h mean. Their increase was most apparent between 2:00 pm and 9:00 pm, and the timing of their peaks was significantly delayed. Serum leptin, ghrelin, and cortisol were assessed simultaneously with the endocannabinoid rhythms. While the 24-h mean didn't differ for any of the three hormones, sleep restriction reduced the amplitude of the 24-h leptin rhythm, advanced the timing of the first peak in ghrelin (close to bedtime), delayed the cortisol trough (close to bedtime) and advanced the cortisol peak (at scheduled awakening). The changes in the timing of some of these hormones could have been a direct influence of the shifted bedtime and wake time, especially for the cortisol peak, which can be acutely and transiently stimulated by awakening and morning light exposure.[8,9] Of interest, the authors found a significant increase in the ratio of the peak in ghrelin and the peak in leptin, consistent with promoting hunger and appetite. Indeed, this was in agreement with an increase in hunger, in desire to eat, and in the assessment by participants of how much they would be able to eat following sleep restriction as compared to the control condition. This was assessed using visual analogue scales before and after each of the three identical meals, after excluding the first fasted assessment in the morning. These effects of sleep restriction were observed despite a stable BMI, similar sedentary activity, and identical meals between the conditions. After 4 nights of either restricted or control sleep—thus the day after assessing the 24-h hormonal profiles under conditions of fixed caloric intake—the authors provided the subjects with two *ad lib* meals (3:00 pm and 7:30 pm) and with *ad lib* access to snacks in between those two *ad lib* meals, in order to assess the influence of sleep restriction on caloric intake. There was no significant effect of sleep restriction on the intake during the *ad lib* meals. However, during *ad lib* access to snacks, sleep restriction resulted in a trend for increased caloric intake, and for nearly twice as much fat and protein intake.

This study supports the novel insight that sleep restriction may not only lead to increased caloric intake due to changes in homeostatic regulation of energy balance, as has been shown by this group and others, but also by changes in hedonic aspects of food consumption. 2-AG is an abundant endogenous agonist of the cannabinoid CB1 receptor widely expressed in the brain, including in reward centers, and in metabolic organs, where CB1 activation stimulates food intake and lipogenesis.[10] The orexigenic effect of endocannabinoids is proposed to be linked to the reward value of food.[11] Thus, the observed increase in the peak in 2-AG following sleep restriction may be part of the mechanism by which people overeat following sleep restriction. It is also consistent with brain imaging studies that have shown that sleep restriction in humans leads to enhanced activity in brain areas associated with reward in response to food stimuli, especially unhealthy foods.[12,13] The delay in the peak of endocannabinoids and increased values late in the wake episode may result in increased food intake later in the day, which has been associated with impaired weight loss and other adverse metabolic consequences.[14–16]

In experimental animals, blocking CB1 through genetic or pharmacologic approaches leads to lean animals, primarily via decreases in caloric intake without changes in physical

activity, body temperature, or energy expenditure.[10] The question whether environmental, behavioral, or pharmacological interventions may be suitable for decreasing the signaling through the endocannabinoid system to specifically target the reward value of food and prevent overeating following inadequate sleep (or in general) is therefore of great interest considering the epidemic of obesity. However, careful considerations are required before using pharmacologic agents aimed at interfering with the endocannabinoid system. For example, while the CB1 receptor blocker rimonabant causes weight loss and has beneficial effects on the metabolic profile, it has been withdrawn from the market because of major psychiatric side effects.[17,18] As the authors recognize, future studies are also required to test whether the robust daily rhythm in endocannabinoids is caused by rhythms in environmental and behavioral factors, including the dark-light, sleep-wake, and fasting-feeding cycle, and/or by the endogenous circadian system. Uncovering and understanding the respective influence of these different factors may aid in designing novel strategies to modulate the signaling via the endocannabinoid system without the need for drug interventions. A possible role of the endogenous circadian system is suggested by the observed rise in 2-AG and 2-OG starting in the middle of the sleep episode, thus preceding the first meal, scheduled awakening, and morning light exposure. With this well-controlled experimental study, Hanlon and colleagues[7] have added compelling new evidence for an involvement of endocannabinoids and food reward mechanisms underlying excess food intake and weight gain following sleep restriction.

CITATION

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DISCLOSURE STATEMENT

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