

A Good Night's Sleep: Future Antidote to the Obesity Epidemic?

It is well established that the prevalence of obesity has been increasing over recent decades, both in the United States and the rest of the developed world. Why is this happening? Body weight is physiologically regulated, and this regulation involves a complex physiologic system encoded by an array of specific genes (1). This system involves both central and peripheral components and interacts with aspects of the environment, such as availability and composition of the diet and the need for physical exercise, to influence body weight. Although genes play a critical role in weight determination, the increased prevalence in obesity of populations over a period of decades is induced by changes in the environment in which we live rather than changes in our genetic endowment. In thinking about the environmental variables that are probably responsible for the "obesity epidemic," most of the attention has focused on the status and cost of the food supply, the composition of the food that we ingest, and our capacity for or avoidance of physical exertion. Is it possible that we have missed other environmental variables that have a capacity to modify appetite and energy balance? In this issue, Spiegel and colleagues (2) present experimental results suggesting that increasing sleep deficits (or debts), perhaps a result of our hectic lifestyles, bring about physiologic changes in the hormonal signals that promote hunger and, perhaps thereby, obesity.

To address this question, Spiegel and colleagues conducted a randomized, 2-period, 2-condition crossover clinical study in which 12 healthy men were studied after 2 days of sleep restriction or sleep extension under conditions of controlled caloric intake and physical activity. The measurements made in the period after altered sleep included the hormones leptin and ghrelin and an assessment of hunger and appetite. The findings were straightforward. Despite unchanged body weights and energy supply provided by intravenous infusion of glucose, the period of sleep curtailment was associated with reduced levels of the fat-derived hormone leptin and increased levels of the stomach-derived hormone ghrelin. Both of these changes should increase hunger. Of note, the authors' behavioral assay detected these expected effects because increased sleep debt increased a semi-quantitative measure of hunger. The correlation between the increase in appetite and the increased ratio of ghrelin to leptin was even more impressive. Thus, in this paradigm, sleep curtailment for 2 days entrains a change in 2 peripheral hormones. From our previous knowledge of the effects of these hormones, we would predict that the sleep-related changes would stimulate hunger and, possibly, weight gain.

Although the results are provocative, several key questions remain. First, it remains to be determined how closely the hormonal consequences of the authors' experimental model for sleep curtailment will predict the consequences of altered sleep that occur in the population at large. Second, although the altered levels of leptin and

ghrelin are in the right direction to stimulate hunger and their ratio correlates with hunger measurements, the relationship is an association rather than causal in nature. We need interventional studies to clarify the biological significance of the changes. Third, factors apart from leptin and ghrelin might be involved in changing appetite during sleep curtailment. For example, cortisol, which may be rising because of the stress of sleep curtailment or other unknown factors, might be the true cause of increased hunger. Finally, this study does little to clarify the potential mechanism linking sleep curtailment to changes in plasma levels and, possibly, secretion of leptin and ghrelin. An attractive possibility might be via changes in hypothalamic control of autonomic nervous system activity, including changes in the balance of cholinergic (parasympathetic) and sympathetic tone, which have been shown to influence secretion of leptin and ghrelin (3, 4).

In addition to sleep curtailment affecting appetite (and possibly body weight) via the intervention of leptin and ghrelin, it is worth considering another connection between the 2 fundamental systems controlling sleep and body weight regulation. Both systems involve neural circuits that have input from hypothalamic centers and engage neuropeptides and receptors that have critical roles in homeostasis. The best illustration involves the neuropeptide orexin, which is expressed in neurons with cell bodies in the lateral hypothalamus, an area classically known as a "feeding center" (5). Orexin was discovered as a peptide (or 1 of 2 peptides) that evoked feeding behavior in animals after injection into the brain (6). Remarkably, disruption of the orexin system is a major cause of narcolepsy in both animals and humans (7, 8). This example shows that sleep and body weight are homeostatic responses that may be controlled by intersecting and overlapping mechanisms.

Spiegel and colleagues' findings raise much food for thought (so to speak). If the findings prove to be reproducible and generalizable, and the hormonal changes of leptin and ghrelin due to sleep curtailment cause changes in food intake over time, we might add sleep duration to the environmental factors that are prevalent in our society and that contribute to weight gain and obesity. Should we design controlled studies to measure the effect of sleep-promoting interventions on appetite and body weight, just as we now prescribe reduced-calorie diets and exercise? Although recommendations to get both a better night's sleep and more exercise might superficially seem to be at odds with each other from the perspective of energy expenditure and energy balance, these simple goals may well become a part of our future approach to combating obesity.

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