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Sleep disruption is related to allelic variation in the ob gene

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Recent advances make it easy to forget that investigators in the biological sciences once shunned the study of behavior. Today, students at research-intensive universities are imbued with an interdisciplinary perspective (9) that regards behavior as a higher-level expression of cellular and molecular physiology. In this issue of the American Journal of Physiology-Regulatory, Integrative, and Comparative Physiology, a paper by Laposky et al. (12a) titled "Altered Sleep Regulation in Leptin-Deficient Mice" exemplifies the natural unification of behavior and physiology. Sleep is a behavioral state that significantly alters autonomic, metabolic, and sensory-motor regulation. Sleep-dependent changes in regulatory physiology are so pronounced that behavioral states can provide an organizational structure for teaching regulatory physiology (32). The Laposky et al. (12a) paper also provides a striking example of how the interpretation of preclinical data from mice can offer mechanistic insights of potential clinical relevance. Specifically, their results have been triangulated to consider the relationship between obesity and sleep, obesity and energy expenditure, and the utility of the mouse as a tool for understanding human physiology and pathophysiology.

Obesity is a disease with many associated comorbidities (6). In the United States and United Kingdom, the number of individuals who are obese has reached epidemic proportions (1, 5). The worldwide prevalence of obesity in children indicates that obesity-related diseases and health care costs will be a problem for many years (35). The time course of the obesity epidemic has outpaced obesity research and treatment (15). A report from the United States National Task Force on the Prevention and Treatment of Obesity (19) begins by noting that as recently as 1998, the health risks of obesity were not fully appreciated. The causes of obesity are multifactorial and the variance accounted for by each putative cause remains to be quantified.

Brain regions regulating sleep overlap with areas of brain that regulate appetite (13). The ob gene is expressed by fat cells that produce leptin, and this peptide, in turn, modulates food intake (26). By unknown central mechanisms, sleep restriction and deprivation are related to leptin and insulin resistance (24, 25). Obese individuals are at risk for developing obstructive sleep apnea (OSA) (19), and OSA patients have greater serum levels of leptin (12). Total sleep deprivation decreases the diurnal rhythm of leptin (17). Recent human data indicate that sleep loss is a risk factor for developing insulin resistance and type 2 diabetes (23). Obesity is associated with short sleep duration, and short sleep duration is a risk factor for diabetes and heart disease (10). There is support for the hypothesis that OSA is part of a feed-forward metabolic syndrome, in which visceral obesity causes insulin resistance and elevates inflammatory cytokines (34). A transcription factor (Clock) has been identified in mutant mice that alters the circadian distribution of sleep and may also contribute to obesity and metabolic syndrome (33).

Consistent with previous data (7), Laposky et al. (12a) show that obese mice are sedentary. Locomotor activity contributes to the regulation of core body temperature in mice, and Laposky et al. report that obese mice have a reduced body temperature in all sleep-wake states compared with C57BL/6J (B6) mice. This too is a significant finding in view of the fact that heart rate and mean arterial pressure are significantly altered in B6 mice by reduced caloric intake and exposure to mild cold stress (36). The rodent data are in line with evidence considering fat to be an endocrine organ, from which adipocYTE-derived cytokines modulate the balance between energy intake and energy expenditure (2). Rats bred for low aerobic capacity score high on risk factors for the metabolic syndrome (37). In contrast, exercise capacity is a predictor of human mortality (18) and exercise can extend human longevity (8). Even modest decreases in weight have been shown to cause a decrease in sleep-disordered breathing (20).

Finally, the well-designed study by Laposky et al. (12a) contributes to the growing evidence that mice provide a powerful model of human disease (3, 4, 27). In 2002, the mouse genome was first published, revealing a 99% homology with the human genome (16). This remarkable homology helped promote the Trans-NIH Mouse Initiative (www.nih.gov/science/models/mouse/) and prompted the description of mice on the National Institutes of Health genome Web page, as “the most important animal model in biomedical research” (http://www.genome.gov/10005831). Years before B6 mice were used to study breathing during sleep (14, 28), obese mice were shown to be a valuable model of the altered breathing observed in obese humans (29–31). Leptin-deficient mice were discovered as a spontaneous mutation of the ob gene in B6 mice (11). Leptin-deficient mice are obese, hyperphagic, and sedentary, compared with normal B6 mice. All models have a limited domain of applicability, and the search for perfect identity between human and animal or pharmacological (14) models is a fool’s errand. Differences between a model and the system being modeled are anticipated. For example, in obese mice, the absence of leptin does not lead to upper airway collapse during sleep (21). This difference does not negate the strong genetic modulation of sleep and obesity (22). When congenic lines, such as B6 and ob mice exhibit a significant difference in phenotype, and a single difference in genotype, it is parsimonious to infer that the missing or altered gene contributes to the differences in phenotype (7). By combining a detailed phenotyping of sleep behavior, locomotion, and body temperature,

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the paper by Laposky et al. (12a) suggests that deletion of the \textit{ob} gene and/or gene product contributes to obesity and disrupts the temporal organization of sleep.

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**REFERENCES**