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EDITORIAL

Waking Up to the Importance of Sleep and Circadian Rhythms for Metabolic Health: The Need for In-Depth Phenotyping

Commentary on Arble et al. Impact of sleep and circadian disruption on energy balance and diabetes: a summary of workshop discussions. SLEEP 2015;38:1849–1860.

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On February 19th and 20th, NIDDK held a workshop on the impact of sleep and circadian disruption on energy balance and diabetes. The meeting was chaired by Drs. Allan Pack and Eve Van Cauter. A summary[1] of the workshop has been written by the Junior Investigators who attended the meeting through support by the Sleep Research Society and the scientists invited by NIDDK. It should be noted that the summary is not an extensive review of the literature in this area but solely an overview of the workshop. This commentary summarizes potential areas of future research that were highlighted and discussed at the workshop.

The goals of the workshop were to (1) bring together experts in the fields of circadian regulation, sleep and glucose/lipid metabolism; (2) review the current state of knowledge linking circadian rhythms/sleep and energy metabolism in human and non-human models; and with this background, (3) determine the appropriate methodologies and studies needed to elucidate the mechanisms that mediate the effects of sleep and/or circadian disruption on human obesity and diabetes. Overall, it was considered that identification of mechanisms and intermediate endpoints of sleep and circadian disruption would contribute to the design of future clinical trials aimed at establishing whether modulating sleep and circadian rhythms can effectively contribute to the treatment of obesity and diabetes.

The impressive and sophisticated science presented at the workshop illustrated the many advances made in the field of circadian biology, particularly within the context of metabolism. Mechanistic, molecular, genetic, and epigenetic studies in animal models demonstrate that disruptions in circadian rhythms and/or the molecular components of central and peripheral clock proteins profoundly influence body weight as well as glucose and lipid metabolism. In humans, epidemiological studies have shown that decreased sleep duration is associated with increased weight and impaired glucose tolerance. Small clinical studies also reveal that sleep deprivation as well as circadian misalignment are associated with insulin resistance and impaired glucose tolerance. However, the mechanisms mediating the differential effects of the circadian clock, the sleep-wake cycle and the timing of feeding on metabolism have not been identified and the translation of these findings has only been applied to humans in limited approaches. To determine if and how modulation of sleep/circadian rhythms and timing of feeding can be used to attenuate, and perhaps treat, the growing epidemic of obesity and type 2 diabetes (T2D), it is essential to move the field forward and identify the mechanisms linking sleep and circadian rhythms to metabolism in humans. This goal could be facilitated by collaborations between basic and clinical scientists to translate the findings from animal models to humans.

To date, the paradigm taken for most human studies has involved inducing sleep deprivation or circadian misalignments in normal healthy populations to elucidate effects on metabolism. Convincing evidence is still lacking, however, with regards to whether amelioration of sleep deprivation or circadian misalignment restores or improves glucose tolerance and/or energy balance in populations with impairments. For example, the potential beneficial metabolic effects of increasing sleep duration, aligning feeding with chronotype, or treating obstructive sleep apnea with continuous positive airway pressure (CPAP) therapy have not been investigated at an in-depth metabolic level. Shifting the focus of human studies towards specified populations with known environmentally (or genetically) induced alterations in sleep or circadian rhythms may contribute to elucidating the mechanisms mediating the effects of disrupted sleep and circadian misalignment on glucose and lipid metabolism. Populations of interest could include: individuals with chronic jet lag, night shift workers, short sleepers, individuals with fragmented sleep, and individuals with known sleep or clock gene mutations. On the metabolic side, improved phenotyping and identification of subgroups of individuals with metabolic disease would decrease variation of measured outcomes, improve responsivity to interventions, as well as contribute to our understanding of mechanism. Examples of populations stratified by metabolic responses could include: metabolically fit and unfit obese individuals, obese individuals with varying levels of body adiposity or differential distribution of fat (visceral vs. subcutaneous), pre-diabetes or early stage diabetes with intact b-cell function, persons with mature onset diabetes of the young (MODY), patients with type 1 diabetes with and without hypoglycemic unawareness, or individuals with and without diabetic neuropathy.

Identification of the mechanisms mediating the effects of sleep and circadian disruption on metabolism and energy balance will also require a more in-depth metabolic phenotyping than has been conducted to date. For example, systemic

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glucose and lipid metabolism can be investigated by the use of stable isotopes which can reveal rates of gluconeogenesis, glucose disposal, muscle and hepatic-specific insulin resistance, triglyceride synthesis and metabolism, as well as protein flux. In addition, epigenetic, metabolomics and proteomic analysis of adipose and muscle tissue would provide information on potential mechanistic pathways influenced by sleep/circadian disruption. Ultimately, the additional insights gained by using these techniques and methodologies could reveal sites of defects as well as potential clues for the development of therapeutics.

In addition to peripheral metabolic measurements, measurement of peripheral or central nervous system responses to sleep or circadian disruptions may also be critical. Changes in cardiovascular autonomic activity were identified in some of the first human studies demonstrating the link between sleep deprivation and impaired glucose tolerance. Furthermore, increased sympathetic activation is an important component in the pathophysiology of obstructive sleep apnea. While it is known that the autonomic nervous system is the primary neural pathway between the suprachiasmatic nucleus (SCN) and peripheral tissues, the role of the autonomic nervous system (ANS) as a mediator of the effects of circadian misalignment and sleep disruption has not been thoroughly investigated.

Individual differences in central nervous system responses reflected by alterations in brain metabolism, as monitored through imaging (such as fMRI, PET, or MRS) could also be explored. While some studies have examined individual susceptibility to sleep deprivation at the behavioral and cortical levels, other factors may play a role in modulating interactions between nutrients and sleep/circadian disruptions. Low blood sugar as occurs in patients with type 1 diabetes can elicit altered brain fuel utilization and astrocyte storage of glycogen. Individuals with type 1 diabetes also have increased sleep efficiency compared to healthy control subjects, illustrating the bidirectional nature of the pathways mediating the effects of sleep and circadian disruptions and metabolism. Levels of circulating nutrients, low or high, may influence circadian alignment and sleep quality or duration. Studies conducted in rodents suggest that hypocaloric and high fat diets can cause phase shifting in both the peripheral and central clocks which ultimately may influence how nutrients are metabolized. Thus, alterations in circulating peripheral factors may be the initiating signals for changes in circadian alignment, which then in turn could elicit changes in feeding and subsequent circadian-mediated changes in metabolism. Teasing out the relative influence of afferent signals to the brain from the effects of efferent signals from the brain and the interactions among food, sleep and circadian disruption on metabolism will require well-designed and complex experimental designs.

The high incidence of OSA in patients with T2D suggests significant comorbidity between the two diseases. While only a small percentage of obese individuals actually develop overt T2D, OSA and obesity share many common pathophysiological mechanisms, including increases in free fatty acids, inflammatory cytokines, and sympathetic nervous system activity, which all contribute to insulin resistance. It remains unclear if treating OSA could either improve glycemia and/or decrease diabetes medication usage. There are numerous small studies which report lack of effects of CPAP on glycemia but these are typically underpowered, of insufficient duration, and have poor phenotyping of the populations being tested. Before conducting a large multisite clinical trial, it will be critical to identify the population that is most likely to be responsive to CPAP. Three clinical factors need to be considered when deciding on the most receptive population to OSA treatment for improvements in glycemia and/or dyslipidemia: the severity of the OSA, the stage of diabetes and the magnitude and perhaps the location of the adiposity. Both OSA and T2D are often present for long periods of time prior to clinical diagnosis. While early intervention to lower blood glucose in persons with pre-diabetes has been found to be effective in delaying the onset of diabetes, the effects of early OSA treatment are unknown. Persons with pre-diabetes and intact b-cell function that have OSA may be the most receptive population to OSA treatment. It will also be important to consider that even in this population; responsivity to treatment may also depend on the degree of adiposity.

Given the considerations discussed above, we propose the following recommendations for future human research studies in the area of sleep and circadian disruptions on metabolism:

1. Increase the depth of the metabolic and physiological phenotyping of the populations under investigation
2. Move the focus of investigations from healthy control groups to populations with identified sleep disorders, circadian misalignments, or defined metabolic differences.
3. Recognize the bi-directionality of the relationship between sleep/circadian disruptions and metabolism and try to tease apart the individual components of the signals from and to the brain.
4. Increase collaborations among basic and clinical scientists from the fields of sleep, circadian biology, and metabolic research.

This is an exciting time in the fields of sleep and circadian biology, and NIDDK looks forward to taking part in the advances that will be made by this community in promoting the health of the nation.

CITATION

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

REFERENCE

1. Arble DM, Bass J, Behn CD et al. Impact of sleep and circadian disruption on energy balance and diabetes: a summary of workshop discussions. Sleep 2015;38:1849–60.