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Timing Is Everything: Implications for Metabolic Consequences of Sleep Restriction

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COMMENTARY

Type 2 diabetes (T2D) is a complex disease driven by a combination of genetic and environmental factors. In recent years, several lines of evidence suggest that circadian disruption and sleep loss contribute to disease pathogenesis. Epidemiologic studies indicate that shift work is associated with an increased risk of T2D (1,2). Shift work is a prime example of circadian disruption, altering the timing of light exposure, meals, activity, and sleep. In many ways, the shift workers serve as early indicators, or "canaries in a coal mine," of the long-term consequences of the circadian disruption experienced by a much broader segment of the population. A number of studies have concluded that genetic variation in melatonin receptors (notably expressed in pancreatic β-cells) is associated with impaired insulin secretion and increased risk for T2D (3,4). Similarly, genetic variation in the genes responsible for the generation of circadian rhythms has been linked to metabolic, endocrine, and behavioral changes that could push a patient toward development of T2D (5,6). This type of population study has been complimented by laboratory studies demonstrating that short duration of sleep adversely impacts glucose tolerance (7,8). More recently, laboratory studies where healthy participants were exposed to circadian misalignment using a forced desynchrony protocol provided causative evidence for a deleterious impact on diabetes risk and cardiovascular function (9,10). Sleep and circadian disruption have even been found to hinder the management of glycemic control in existing patients with T2D (11,12). The weight of these interconnections between disrupted sleep, circadian rhythms, and metabolic dysfunction has led Dr. E. Van Cauter and others to describe them as an "inseparable triad" (Fig. 1*A*).

In this issue, Leproult et al. (13) seek to break apart this triad and distinguish between the relative importance of sleep and circadian disruption. In humans, sleep normally occurs during the night as body temperature is falling and melatonin secretion is high. As described above, previous work has shown that sleep restriction alone has negative consequences, but does the timing of the sleep make a difference? To look at this under controlled conditions, healthy young adults were examined after 4 days of sleep restriction (5 h per cycle) either with nocturnal bedtimes (circadian alignment) or with diurnal bedtimes (circadian misalignment). Daily total sleep time during the intervention was nearly identical in the aligned and misaligned conditions (just under 5 h). In both groups, insulin sensitivity and disposition index (an indicator of β-cell function) significantly decreased while inflammation increased after sleep restriction. In males, at least, exposure to circadian misalignment greatly enhanced both the reduction in insulin sensitivity and disposition index and the increase in inflammation. This difference between the sexes is intriguing and will need to be explored in future studies. The authors suggest that circadian misalignment that occurs in shift work may increase diabetes risk and inflammation, independently of sleep loss (Fig. 1*B*).

The idea that circadian misalignment would increase the risk of diabetes and metabolic dysfunction fits well with clinical data and a large body of experimental evidence. For example, expression profiling has found that many of the genes involved in metabolism exhibit circadian rhythms in transcription, suggesting a close coupling between circadian rhythms and metabolism (14). Recent work indicates that these circadian clock genes provide a temporal

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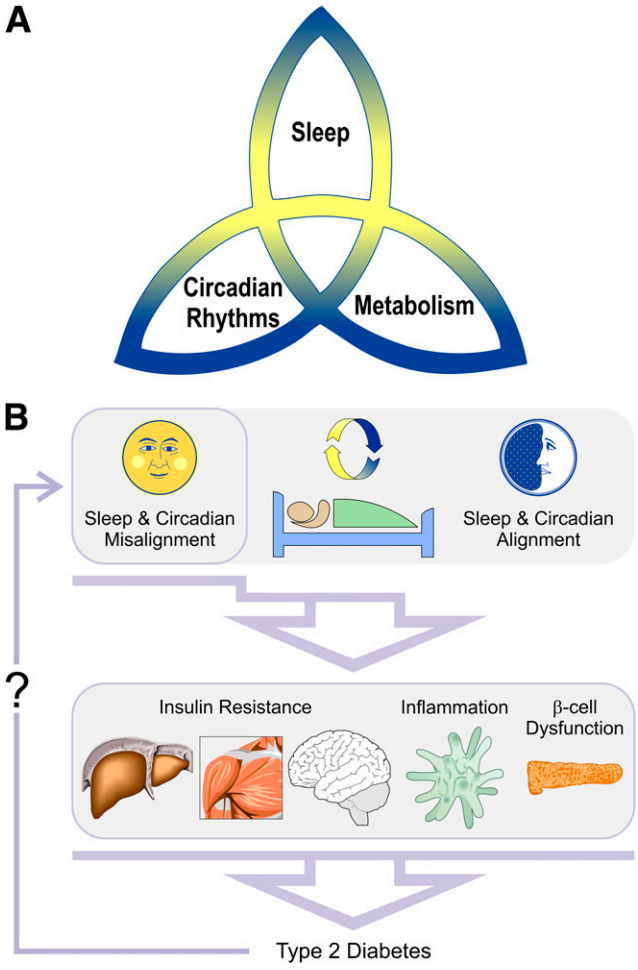

Figure 1—*A*: A number of recent studies indicate a close, interconnected relationship between sleep, circadian rhythms, and metabolism—or the "inseparable triad." *B*: Disruption of sleep and circadian rhythms are gaining greater appreciation as risk factors for T2D. These disruptions promote global insulin resistance, inflammation, and loss of pancreatic β-cell function. Leproult et al. (13) suggest that sleep loss and circadian disruption independently contribute to metabolic abnormalities associated with T2D. Could the inseparable triad be broken apart? The study raises a number of important questions about the underlying mechanisms, including the role of specific organ systems (liver, skeletal muscle, or central nervous system), in quickly developed insulin resistance. Identification of the mechanistic link between circadian disruption and impaired β-cell secretory function, growth, and survival also seems to be a research priority. Finally, we need to understand whether T2D per se contributes to sleep and circadian disruption, and thus promotes a viscous cycle of metabolic abnormalities and sleep/wake disturbances in patients with T2D.

patterning for mitochondrial oxidative metabolism (15). Genetic disruption of the core molecular clock can produce metabolic dysfunction (16). Importantly, the targeted disruption of the molecular clock in the pancreas directly results in defective β-cell function and hyperglycemia (17). Even environmental perturbations of the circadian timing impair insulin sensitivity and promote obesity (18). For example, we have shown that exposing rats to constant light disrupts islet circadian clock function as well as diminishes glucose-stimulated insulin secretion due to a decrease in insulin secretory pulse mass (19,20). This body of preclinical data clearly links circadian disruption with metabolic syndrome and T2D.

The hypothesis that the circadian misalignment works independently of sleep loss will be much more controversial. The circadian system has reciprocal neural connections to the brain regions that regulate arousal and sleep. Through these connections, the suprachiasmatic nucleus can convey temporal information to the diffuse network of sleep- and arousal-promoting structures of the brain and body. Under normal conditions, peak circadian drive of arousal in humans is thought to occur in the afternoon to counteract the growing fatigue as the homeostatic drive to sleep increases. Interestingly, this communication appears to be bidirectional, as "sleep centers" communicate information related to sleep state back to the suprachiasmatic nucleus as well (21). Thus, the sleep and circadian control system are closely intertwined and can be difficult or even impossible to disentangle. A long line of experimental evidence indicates that surgical or genetic manipulations that interfere with the circadian system will alter the timing of sleep. But there is also evidence that mistimed sleep can disrupt the circadian timing system. For example, recent work has shown that many of the rhythms in transcription measured in the human blood, including those in core circadian clock genes, are damped when sleep is mistimed (22,23). Thus, disentangling the relative contributions of sleep and circadian disruption is a topic that is not yet settled and the debate will continue on.

From our perspective, this new work from Leproult et al. (13) is the latest of a series of important studies from this laboratory and others that indicate that disrupting the sleep/wake cycle is a risk factor for T2D. As for metabolic parameters, mistimed sleep lacks the same restorative benefits of sleeping at an appropriate phase of the circadian cycle. With so many people in our society living and working in temporally disrupted environments, the study by Leproult et al. suggests that greater attention should be placed on the timing and not just the duration of our sleep.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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