EDITORIAL

CYP7A1: A Liver Circadian Clock Output Mediating the Metabolic Effects of Sleep Disruption

All higher animals on this planet show some form of sleep-like behavior, but still a consensus has not been reached on what determines the evolutionary value of sleep. Recent data suggest that one important aspect might be its role in the maintenance of energy homeostasis. Over the past decades, average daily sleep times have decreased by almost 20% in Western societies, in part caused by a largely augmented demand for shift work. In parallel, metabolic disorders such as type-2 diabetes, obesity, and the metabolic syndrome have dramatically increased in prevalence. Epidemiologic data strongly suggest a causal link between both phenomena, but the difficulty of mimicking shift-work-like sleep conditions in laboratory animals and the delayed effectiveness of sleep interventions on metabolic homeostasis in humans have made it difficult to decipher the underlying mechanisms.1

In the last couple of years, a mounting body of evidence has accumulated that links disruption of our internal 24-hour timing system, the so-called circadian clock, with metabolic disruption.2 Genetically encoded circadian oscillators are found in all tissues of the body. A master pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN) is reset by light cues transmitted via melanopsin-expressing photoreceptive retinal ganglion cells and coordinates the brain and peripheral subordinate clocks and rhythms to align with external time. Rodent studies modeling shift-work conditions show that the SCN is highly resistant to alterations in the sleep–wake cycle, whereas peripheral clocks become easily perturbed, probably due to changed food-intake rhythms.3 This suggests that peripheral clocks in the metabolic tissues may link sleep-rhythm disruption with the alterations in energy metabolism observed in human shift workers. However, the molecular pathways connecting sleep loss, clock function, and metabolic deregulation have remained largely elusive so far.

In the present issue of Cellular and Molecular Gastroenterology and Hepatology, Ferrell and Chiang now show that already short-term disruption of daily sleep patterns in mice alters hepatic bile acid homeostasis and lipid metabolism, deregulating hepatic clock gene expression and the diurnal activity pattern of the clock output gene Cyp7a1, encoding a key enzyme in the conversion of cholesterol into bile acids.4

The authors used a 6-hour/5-day sleep restriction paradigm (sleep deprivation) combined with different diet conditions. Under a combined sleep deprivation/Western diet treatment, the mice started to gain weight faster than the non-sleep deprived controls, highly reminiscent of what is observed in human shift workers. This effect is accompanied by alterations in bile acid and cholesterol homeostasis. Remarkably, these changes also correlate with dampened diurnal clock and lipid metabolism gene mRNA rhythms, suggesting the existence of a sleep-clock–metabolism axis mediating the pathophysologic effects of sleep loss.

The authors further provide evidence that Cyp7a1 expression is regulated by the local clock gene machinery, showing altered promoter binding of the clock component D-site binding protein (DBP) and the clock-regulated transcription factor HNF4α. Together, these data suggest that sleep loss—via its action on hepatic tissue clock function—affects lipid homeostasis and body-weight regulation. It is tempting to speculate that in a similar way clocks in other tissues may mediate sleep effects on physiologic output.

While other systemic factors—hormones such as glucocorticoids, autonomic activity, or factors associated with altered food-intake rhythms—may still go into the equation, this study now devises a potential mechanism linking sleep and hepatic lipid metabolism. From this perspective, the peripheral clock function may become an attractive target for further research into therapeutic interventions aimed at alleviating the metabolic problems arising from prolonged sleep curtailment or shift work.

HENRIK OSTER
Medical Department I
University of Lübeck
Lübeck, Germany

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Correspondence
Address correspondence to: Henrik Oster, PhD, Medical Department I, University of Lübeck, Ratzeburger Allee 160, 23538 Lübeck, Germany. e-mail: henrik.oster@uksh.de.

Conflicts of interest
The author discloses no conflicts.