Disrupting Rhythms: Diet-Induced Obesity Impairs Diurnal Rhythms in Metabolic Tissues

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Circadian rhythms are essential processes that coordinate the timing of basic organismal functions at the molecular, cellular, and behavioral levels. Oscillations are generated by the core molecular clock, which is composed of transcriptional activators (such as *Bmal1* and *Clock*) and repressors (such as the *Period* gene family). These activators are present in many types of central and peripheral tissues, including the liver (1) and adipose tissue (2). The oscillations of the core clock then regulate the rhythmic expression of other genes, such as those involved in insulin production (3), which in turn contributes to physiological rhythms in insulin secretion (4), as well as glucose and leptin levels (5,6). Under normal conditions, these rhythms are entrained by the 24-h cycles of light exposure and feeding behavior. However, a growing body of literature has begun to link circadian misalignment with human disease, including metabolic and cardiovascular dysfunction.

A study of polymorphisms in the *Clock* gene in humans revealed that the molecular clock may play a role in cardiovascular disease, obesity, and diabetes (7). Indeed, misalignment of environmental and endogenous rhythms, as seen in nighttime shift-workers, has revealed that this population has a higher incidence of obesity and diabetes (8). Simulated circadian misalignment mimicking shift work in humans results in disturbed metabolism as exemplified by decreased leptin, increased glucose levels and insulin resistance, as well as in physiological parameters such as blood pressure (9). Furthermore, patients already suffering from diabetes and obesity exhibit blunted rhythms of insulin secretion and glucose tolerance (10,11), highlighting the possibility that metabolic disorders and circadian rhythms are closely linked, and perturbations of one or the other may eventually lead to disease. This is substantiated by studies in transgenic animals, which have dissected some of the interactions between the circadian clockwork and metabolism. *Clock* mutant mice are known to be obese (12), and *Period* mutant mice display increased adiposity and aberrant feeding rhythms (13). Adipocyte-specific deletion of *Arntl* (*Bmal1*) results in an obese phenotype as well as a shift in the diurnal rhythm of feeding behavior (14). Although the connections between circadian rhythms and metabolic and cardiovascular disorders are clear, many of the mechanisms connecting these systems remain to be explored, and thus our understanding of the impact of metabolic diseases upon the circadian system is incomplete.

In this issue of *Diabetes*, Prasai et al. (15) describe in detail some of the mechanisms underpinning how metabolic dysfunction hampers the clockwork and physiological rhythms in cardiovascular and metabolically relevant tissues in wild-type mice (Fig. 1). In a diet-induced model of obesity, the authors demonstrate that cyclic expression of the clock genes *Bmal1* and *Per2* are blunted in adipose tissue, but unaffected in the aorta, liver, and muscle. Diurnal variations in cardiovascular physiology, such aortal constriction in response to phenylephrine, blood pressure, and heart rate, were not affected by obesity. Diurnal variation in physiological measures of metabolic homeostasis were impaired in obese animals, with the reduction of peak glucose levels in response to glucose challenge, and attenuated glucose nadir in response to insulin challenge in the evening. The authors further examined the expression of genes involved in glucose and lipid metabolism in order to elucidate second-order effects of rhythmic dysfunction. Interestingly, this revealed that rhythmic transcription of clock-associated genes such as *Rev-erbα* and *Dbp*, and metabolically relevant "output" genes such as *Pparα* and *Pepck*, were diminished in obese adipose tissue but remained largely unaffected in liver tissue.

The new report offers additional observations of tissue-specific changes in the setting of obesity where there are no reported diurnal rhythms. They find that indicators of inflammation, such as the F4–80 macrophage marker, complement C3, and tumor necrosis factor-α were upregulated in obese adipose tissue, while the vascular inflammatory marker vascular cell adhesion molecule-1 was upregulated in obese aortas. Furthermore, insulin signaling pathways were affected in obese liver but not in adipose tissue (Fig. 1).

The authors conclude that the impact of loss of circadian rhythms in obesity is particularly obvious in adipose tissue, and that the inflammation observed in this tissue may indicate shared mechanisms between these two processes. Prasai et al. also suggest that cardiovascular tissues may be more resilient to clock dysfunction in the setting of obesity, and that these tissues may need a prolonged exposure to clock disruption before displaying impaired rhythms. The difference between adipose and liver tissue in their loss of clock rhythms and observed insulin resistance hints that there may be divergent mechanisms at work in the pathogenesis of metabolic dysfunction. Phenomena such as the coincidence of inflammation with *clock* gene dysfunction in adipose tissue from obese mice remain enigmatic. They also raise questions about the mechanism underlying the divergence of impairment in fat and liver clocks, and the contributions of

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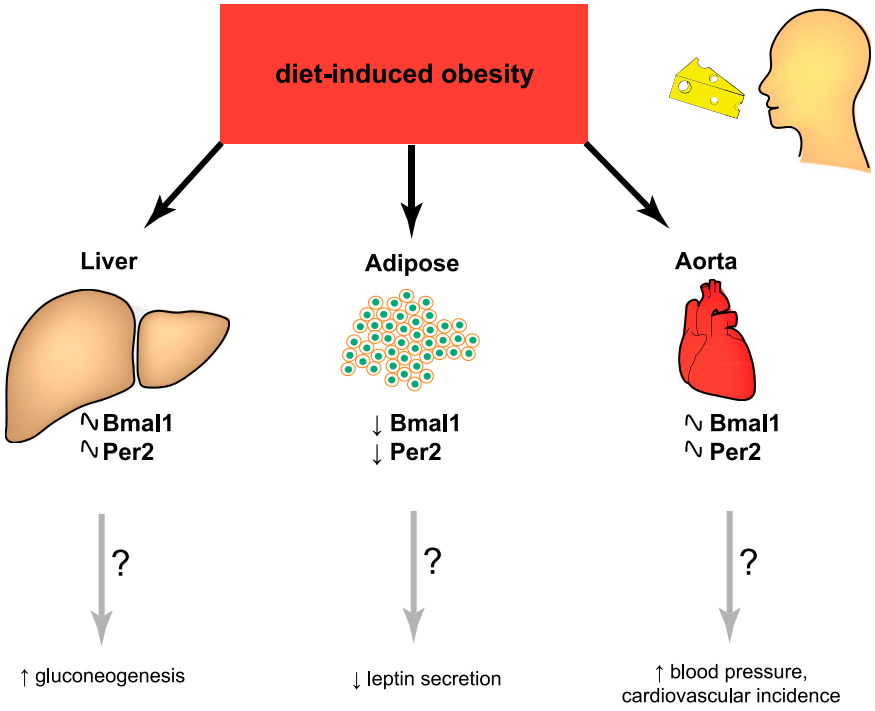

FIG. 1. Obesity is known to induce physiological changes in measures of gluconeogenesis, leptin secretion, and blood pressure and to elevate risk of cardiac incidence. In this issue, Prasai et al. (15) examine how diet-induced obesity interferes with the circadian clockwork in the liver, adipose, and cardiovascular tissues. Despite demonstrating the blunting of diurnal rhythms in the expression of *clock* genes and downstream effectors in adipose tissue, the broad mechanisms of how the circadian clockwork results in the dysfunction exemplified in metabolic syndrome remains a mystery.

tissue-specific clock dysfunction to the pathology of diet-induced obesity and other metabolic syndromes.

Nevertheless, by examining alterations of physiological rhythms in the setting of obesity, the authors' findings highlight new and important avenues of investigation concerning the interactions among health, disease, and the circadian system: What are the long-term consequences of disruption in rhythms in metabolic tissues? Does the restoration of rhythms reverse or mitigate the effects of obesity or diabetes? Can diurnal rhythm–based interventions work in human populations that are at risk for metabolic syndrome?

As obesity levels rise in developed nations and the growing demands of life in global society—shift work, long-distance travel, and social jet-lag (16)—exert pressures on the maintenance of regular diurnal rhythms, the dysregulation of metabolism and the disruption of rhythms are becoming a burden for health care systems. Elucidating the many ways in which metabolic dysfunction may impair the clock, and how disruption of the clock may make the body more susceptible to disease must be important targets for future research.

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