

# Chronobiological Effects on Obesity

Molly S. Bray · Martin E. Young

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**Abstract** The development of obesity is the consequence of a multitude of complex interactions between both genetic and environmental factors. It has been suggested that the dramatic increase in the prevalence of obesity over the past 30 years has been the result of environmental changes that have enabled the full realization of genetic susceptibility present in the population. Among the many environmental alterations that have occurred in our recent history is the ever-increasing dyssynchrony between natural cycles of light/dark and altered patterns of sleep/wake and eating behavior associated with our “24-hour” lifestyle. An extensive research literature has established clear links between increased risk for obesity and both sleep deprivation and shift work, and our understanding of the consequences of such dyssynchrony at the molecular level is beginning to emerge. Studies linking alterations in cellular circadian clocks to metabolic dysfunction point to the increasing importance of chronobiology in obesity etiology.

**Keywords** Obesity · Circadian · Molecular clock · Rhythm · Transcription · Sleep · Shift work · Gene · Chronobiological effects

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M. S. Bray (✉)  
Departments of Epidemiology and Genetics,  
University of Alabama at Birmingham,  
1530 3rd Avenue S, RPHB 230H,  
Birmingham, AL 35294, USA  
e-mail: mbray@uab.edu

M. E. Young  
Division of Cardiovascular Diseases, Department of Medicine,  
University of Alabama at Birmingham,  
703 19th Street S., ZRB 308,  
Birmingham, AL 35294, USA  
e-mail: meyoung@uab.edu

## Introduction

The dramatic rise in obesity prevalence among both adults and children is one of the most profound public health issues of our time and one that has now become a worldwide concern. Obesity is a multifactorial condition with a strong genetic basis, with body mass index (BMI) having one of the highest heritabilities (45% to 60%) of any quantitative trait [1]. Through historical accounts and paintings, there is evidence that a genetic susceptibility for severe obesity has existed throughout human history, albeit this phenotype has occurred rarely until very recently. Although a sharp increase in obesity prevalence in the United States has been documented beginning in the early 1980s, recent estimates indicate that the positive shift in the distribution of BMI may have actually begun much earlier (ie, early 20th century) [2]. Importantly, the upward trend in BMI through the 20th century, although generally gradual, has been punctuated by distinct increases following significant environmental events (e.g., subsequent to World Wars I and II), coincident with increased industrialization that resulted in dramatic alterations in lifestyle [2]. These observations suggest that environmental factors may interact with and/or exacerbate genetic susceptibility to profoundly influence obesity prevalence.

Central to the development of obesity is a basic imbalance between energy intake and energy output—one must eat to become obese, and physical activity can potentially offset the consequences of overeating. But although it is often assumed that this imbalance results from volitional food intake and/or physical activity/inactivity, we now know that a number of factors likely exert subtle effects on metabolism, behavior, and response to environmental stressors, all of which can influence obesity outcomes. In a review of the putative “nontraditional” environmental factors (i.e., not related directly to physical activity or food intake)

influencing the development of obesity that have occurred in the last 20 to 30 years, McAllister et al. [3••] include sleep debt as one of 10 key contributing components. Both experimental and observational studies of animals and human have provided evidence that sleep deprivation is strongly associated with insulin resistance, increased hunger, alterations in hormones and adipocytokines, and reduced immune response [4–8]. Sleep deprivation, sleep apnea, and shift work (a form of altered sleep and circadian behavior) are also strongly associated with increased risk for obesity, type 2 diabetes, cardiovascular disease, and cancer [9–18]. In a multivariate analysis of predictors of overweight/obesity in the Quebec Family Study, Chaput et al. [10] reported that short sleep duration (<6 h), low calcium intake, and highly disinhibited eating patterns were significantly associated with both obesity status at baseline as well as weight gain over time, after adjusting for age, gender, socioeconomic status, and other risk factors, supporting the notion that factors beyond those centered around physical activity and diet may be important determinants of long-term energy balance. For a comprehensive review of the epidemiologic and experimental evidence linking sleep alterations to obesity, see McAllister et al. [3••].

### The Molecular Circadian Clock

Although the relationship between altered sleep/wake behavior and many common metabolic diseases has been solidly established, the molecular mechanism linking the two is only beginning to be elucidated. Organisms on Earth evolved within the environmental context of a 24-hour day, and most organisms examined to date have developed intrinsic mechanisms to optimize their physiology to the 24-hour daily cycle of light and dark. Chronobiology refers to this natural phenomenon of rhythmicity in bodily function coincident with light/dark cycles. For example, rhythms in heart rate, blood pressure, core body temperature, and cortisol have been observed across multiple mammalian species. These rhythms are controlled in large part by circadian clocks, intrinsically maintained molecular transcriptional mechanisms that serve to condition the organism to changes in its environment [19, 20].

Early studies of rhythmic behavior in rats established the existence of the suprachiasmatic nucleus (SCN), located within the hypothalamus, as a central neural regulator of adrenal rhythmicity [21]. Complete ablation of the SCN in neonatal rats was later shown to abolish circadian rhythms in spontaneous locomotor activity, drinking, and estrous cycling, establishing the SCN as the primary center of gross circadian regulation [22]. The SCN is entrainable by light and serves to synchronize physiologic function to the natural daily cycles of light and dark [23]. At the heart of the molecular circadian clock are two genes, *Clock* (circadian locomotor output circuits kaput) and *Bmal1* (brain-muscle arnt-like 1), which

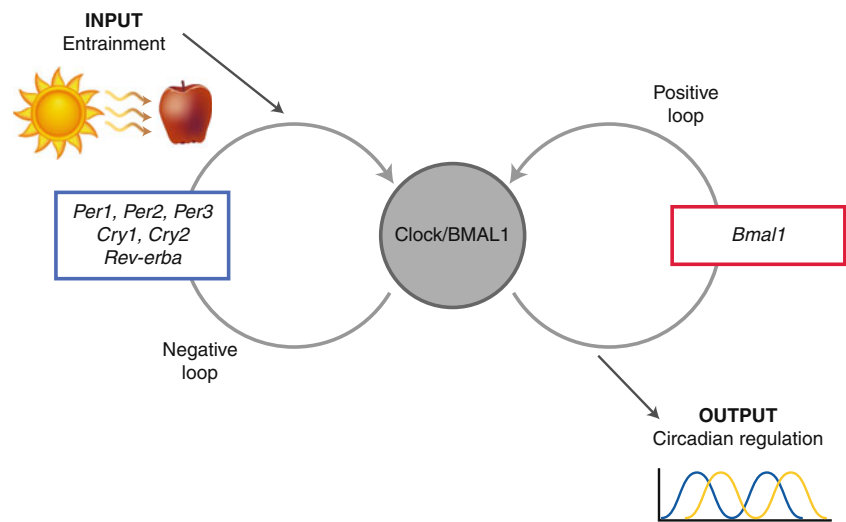
dimerize to form the core of a dual-feedback loop system that comprises the primary circadian clock machinery [24, 25]. Together, the CLOCK:BMAL1 dimer facilitates the transcription of the *period* (*per1*, *per2*, and *per3*), *cryptochrome* (*cry1* and *cry2*), and *rev-erb  $\alpha$*  (*rev-erba*) genes, the primary components of the negative feedback loops. BMAL1 regulates the transcription of both the *Clock* and *Bmal1* genes to form the positive feedback loop within the molecular circadian clock [26–28]. The basic circadian clock structure is depicted in Fig. 1. We now know that the mammalian circadian clock is composed of an expanding list of core proteins that generate a series of feedback loops, resulting in rhythmic expression of clock components as well as downstream target genes [29]. These discoveries have been a major breakthrough in our understanding of the molecular basis of cellular circadian function.

Of equal importance to the establishment of the SCN as a central “master regulator” of circadian physiology was the discovery that an intact, cell-autonomous and self-sustained circadian clock mechanism is expressed in almost every mammalian cell type examined to date [30]. Both peripheral and central circadian clocks act in concert to maintain behavioral and biological rhythms linked to the 24-hour light-dark cycle and both are essential to health. Cellular clocks have been shown to regulate metabolic and physiologic processes at the whole body, organ, and cellular level, including sleep-wake cycles, locomotor activity, body temperature, hormone secretion, metabolism, and innate immune responses. The rhythmicity imposed by these clocks confers biological advantage by anticipating both environmental and internal changes, so that cells (and organisms) can efficiently program their physiologic tasks and prepare for them [31]. Clocks are reset or entrained on a daily basis by zeitgebers, environmental cues such as light, food, noise, and/or neurohumoral factors that are likely specific to each target tissue and provide information about the external time [28, 32, 33].

### Circadian Clocks and Obesity

In terms of obesity susceptibility, studies of the seasonal variability in adiposity that occurs in many mammalian species serve to illustrate that fluctuations in body weight associated with changes in the light/dark cycle occur naturally, independent of the societal and behavioral constraints present in humans, suggesting a global role for the circadian clock in regulating body weight. Molecular circadian clocks may provide the critical mechanistic link between epidemiologic observations associating altered daily rhythms resulting from shift work and sleep disturbances to alterations in adiposity and body weight. One of the first lines of evidence that disruptions in cellular clock function may lead to obesity was provided by Turek et al. [34] who described the

**Fig. 1** Basic structure of the cellular circadian clock



metabolic phenotype of the *Clock*<sup>Δ19</sup> mutant animals. *Clock*<sup>Δ19</sup> mutant mice, in which circadian clock function is disturbed via a dominant-negative mutation that eliminates the transactivation domain of the CLOCK protein, are significantly heavier, have altered patterns of feeding, and are hyperphagic. In addition, these animals have 24-hour hyperlipidemia, hyperglycemia, and hyperleptinemia, and display altered diurnal patterns of physical activity, expending a greater proportion of daily energy during times when the animals are normally sleeping [34]. Interestingly, global disruption of *Bmal1* results in a markedly lean phenotype, with decreased subcutaneous adipose and muscle tissue mass, defective glucose homeostasis, and reduced life span [35–37]. These observations provide evidence that global clock disturbances at the molecular level can lead to altered adiposity and metabolic disorders. Among the putative mechanisms linking the circadian clock to obesity, alterations in adipogenesis, satiety signaling, and energy metabolism have all been associated with circadian regulation.

### Adipogenesis

One potential mechanism linking molecular clock disruption to increased adiposity/disturbed metabolism is the regulation of adipogenesis, which appears to be due at least in part to the adipocyte circadian clock. Within adipose tissue, 650 genes have been identified via microarray analysis that are robustly expressed in a rhythmic manner across multiple (epididymal, inguinal, and brown) types of adipose tissues, including core circadian clock genes [38]. Among the rhythmic genes expressed in adipose are peroxisome proliferator-activated receptor-γ (*Pparg*) and CCAAT/enhancer binding protein-β (*Cebpb*), two important initiators of adipocyte differentiation, suggesting a putative time dependency of fat cell formation. Shimba et al. [37] reported that BMAL1, a core clock component, is also a potent initiator of adipogenesis. Fibroblasts

from *Bmal1* knockout animals failed to differentiate in vitro, and this failure was reversed via adenovirus-mediated transfer of intact *Bmal1*. In these experiments, genes related to lipogenesis were stimulated in a BMAL1-dependent manner, and overexpression of BMAL1 in 3T3-L1 adipocytes increased lipid synthesis activity [37]. More recently, these investigators have shown that the inability to form adipose tissue in *Bmal1*<sup>-/-</sup> mice leads to ectopic lipid formation in liver and skeletal muscle, along with elevated plasma triglycerides, free fatty acids, and cholesterol, providing a direct link between clock-regulated adipogenesis and the development of metabolic syndrome [39]. In addition to *Bmal1*, another core clock gene, *Rev-erba*, has been shown to act as a key repressor of anti-adipogenic genes, and to act downstream of other differentiation factors, including *Pparg* and *Cebpa* [40]. *Noc* (*noc*), a circadian-regulated protein associated with resistance to diet-induced obesity and altered adiposity, has also been demonstrated to bind to *Pparg* and markedly enhance *Pparg* transcriptional activity [41, 42]. Together, these observations suggest a potential time-of-day dependency for adipocyte formation, with circadian clock genes either directly or indirectly regulating this process.

### Food Anticipatory Behavior and Satiety Signaling

Among the strongest entraining influences for circadian clocks in peripheral tissues is the timing of feeding [43, 44]; whether and how circadian clocks in turn regulate feeding initiation and satiety signaling has been the subject of some controversial findings. Food-anticipatory rhythms (i.e., the anticipation of food availability when food is restricted or presented at certain times of the day) persist following complete SCN ablation, suggesting that the central circadian regulator of food intake and food entrainment lies outside the SCN [45]. Fuller et al. [46] reported that food-anticipatory rhythms, which are absent in *Bmal1*<sup>-/-</sup>

mice, can be rescued with cell-specific restoration of *Bmal1* expression in the dorsomedial hypothalamus (DMH). Nevertheless, Moriya et al. [47•] reported that, although clock genes are expressed in DMH cells and exhibit a daily rhythm of expression that is set by mealtime and persists during food deprivation, food-entrained rhythms of behavior, temperature, and clock gene expression in brainstem and forebrain areas are unaffected by DMH ablation. More recently, it has been suggested that because lesions of specific hypothalamic, corticolimbic, and brainstem structures do not eliminate all food anticipatory rhythms, circadian regulation of food-anticipatory behavior is likely controlled by a distributed, interconnected system of oscillators entrained by fluctuations in different humoral signals [48, 49]. Hypoglycemia preceding feeding anticipation may be one means of central regulation of food anticipatory behavior, since control of rhythmicity in glucose metabolism by the SCN has been well established [50–52].

Multiple complex and redundant pathways influence feeding behavior and include components arising from both the hypothalamus and peripheral tissues. Leptin, an adipocyte-specific cytokine and central regulator of both appetite and energy balance, exhibits striking circadian patterns in both gene expression and protein secretion, with peaks in leptin expression occurring during the sleep phase [53, 54]. Ghrelin, a powerful initiator of feeding behavior arising from the gastrointestinal tract, exhibits a reciprocal rhythmic expression pattern to that of leptin, and it has been suggested that preservation of the temporal relationships between these two factors may be critical in maintenance of energy balance [55]. Ablation of the SCN in animals completely eliminates the diurnal pattern of plasma leptin levels but neither timing of feeding nor adrenalectomy affect the rhythmicity of leptin release, suggesting some level of regulation by the central circadian clock [54, 56]. Peripheral clocks or some other peripheral mechanism rather than the central clock may play a more important role in regulating feeding behavior [55, 56]. Leptin receptors are expressed in areas of the brain that also express additional factors influencing both feeding behavior and energy metabolism, including neuropeptide Y (*Npy*), agouti-related protein (*Agrp*), proopiomelanocortin (*Pomc*), cocaine and amphetamine-related transcript (*Cart*), orexin (*Ox*), ghrelin (*Ghrl*), and others [57–59]. *Clock*<sup>Δ19</sup> mutant mice exhibit altered food intake patterns, and rhythmic expression of *Cart*, *Ox*, and *Ghrl* is greatly attenuated in these animals [34].

### Energy Homeostasis and Metabolism

The maintenance of energy balance is influenced by a complex metabolic system involving multiple cell types (e.g., enterocytes, hepatocytes, adipocytes, myocytes, etc.) performing discrete and overlapping functions, including

absorption, digestion, and substrate utilization, synthesis, and turnover. A substantial body of research has decisively established a link between both central and peripheral circadian clocks and metabolism [60, 61]. Hoogerwerf et al. [62, 63] report that circadian clock genes are robustly expressed throughout the gastrointestinal tract and that timed feeding can dramatically shift intestinal clocks, suggesting a putative role for the gastrointestinal circadian clock in regulating motility, cell proliferation, and migration. The capacity for both lipolysis and lipogenesis varies throughout the 24-hour day, and such capacity can be altered via manipulations of the light/dark cycle and period length [64, 65]. We and others have demonstrated rhythmic patterns in lipid metabolism in multiple tissues, such that factors that promote lipid utilization are highest upon waking, and factors that promote lipid storage are highest immediately prior to sleeping [66•, 67]. These observations suggest that energy balance may be critically dependent upon synchronization of macronutrient intake to metabolic rhythms.

To address the question of whether altering the timing of ingestion of specific types of macronutrients to specific times of day would differentially impact energy balance, we conducted a series of experiments in which we compared animals fed either a high-fat meal upon waking combined with a low-fat meal prior to sleeping or a low-fat meal upon waking combined with a high-fat meal prior to sleeping [68]. Two striking findings resulted from these experiments. First, animals fed either high-fat or low-fat food (but not mixed combinations of these foods) only during the normal 12-hour waking period (lights off for these nocturnal animals) did not differ in body weight, body fat, or any metabolic parameter measured; this is in stark contrast to ad libitum feeding in which animals fed high-fat diets were heavier, fatter, and showed significantly poorer metabolic profiles compared with animals fed low-fat diets [68]. These observations suggest that uniform diets ingested during appropriate times of the day do not promote obesity.

The second important observation from these studies was that animals fed daily “meals” of mixed composition only during the normal 12-hour waking period (eg, a waking high-fat meal combined with a low-fat meal prior to sleeping or vice versa), simulating human patterns of eating, demonstrated significant differences in body weight, body fat, and glucose tolerance, with a high-fat waking meal combined with a low-fat meal later in the waking period associated with significantly better metabolic outcomes [68]. Interestingly, the high-fat waking meal seemed to promote metabolic flexibility (ie, appropriate switching from fat to carbohydrate metabolism in response to the food being eaten throughout the day), whereas a low-fat, high-carbohydrate waking meal was associated with rapid initiation of carbohydrate metabolism that persisted throughout



the waking period, even when the animals were eating the high-fat meal. Although these studies need to be replicated in humans, they suggest that coordination of food intake with natural fluctuations in substrate metabolism may play an essential role in energy balance. The studies described above support the importance of eating a daily breakfast and limiting caloric density at the end of the waking period. Certainly, a dietary regimen based on timing of food intake rather than restriction of food intake may ultimately be a more tolerable approach for losing or maintaining body weight.

### Which Came First?

Although substantial evidence suggests that disruptions in circadian clocks and/or dyssynchrony with the diurnal rhythms of light and dark can lead to obesity and related comorbidities, some studies suggest that obesity itself can disrupt circadian clocks. Obesity is associated with altered sleep patterns and obstructive sleep apnea, and because circadian rhythms in sleep-wakefulness are controlled primarily by the SCN, obesity-associated sleep disturbances have the potential to disrupt central circadian rhythms [69]. Numerous studies have demonstrated that obesity induced through high-fat feeding in animals is associated with altered rhythms in both core circadian clock genes as well as clock-regulated genes [38, 70, 71]. Studies in humans have reported lower amplitude of peak leptin release and delayed phase of peak plasma leptin levels in obese versus lean subjects [54, 72, 73]. Nevertheless, Ando et al. [74•] have recently reported that *ob/ob* mice, which completely lack a functional leptin gene and ultimately develop obesity via hyperphagia and altered basal metabolism, demonstrate altered expression of circadian clock genes in peripheral tissues as early as 3 weeks of age and prior to the development of overt obesity, suggesting that altered regulation of leptin rhythmicity may be a critical component of circadian clocks disturbances associated with obesity [74•].

### Conclusions

A substantial and growing body of research has established clear links between the development of obesity and altered circadian behavior and function. At the epidemiologic level, circadian disturbances resulting from shift work and/or sleep manipulation have consistently been associated with increased risk for obesity and related comorbidities. As we expand our knowledge of cellular circadian clocks at the molecular level and begin to unravel the ways in which cellular circadian clocks coordinate metabolism and energy balance, a mechanistic understanding of these epidemiologic associations is

emerging. The burden of obesity is a worldwide concern, and it is certain that we must find new ways to tackle this problem. We live in a 24-hour environment, where we can literally eat, work, shop, play, exercise, and perform any number of tasks 24 h a day, 7 days a week. Devices such as smart phones and related technology keep us continually connected to global events, and it is not surprising that average sleep duration continues to decrease [75]. There is evidence that daily behavioral patterns of eating and sleeping that are dyssynchronous with natural cycles increase risk for the development of metabolic disease; as such, this is an important area to target for intervention. New insight into how patterns of eating and physical activity behavior may be optimized to improve concordance between fluctuations in metabolism and these behaviors may lead to more efficacious strategies for weight loss and weight maintenance.

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