

# Out of synch: *Clock* mutation causes obesity in mice

## Previews

**The *Clock* gene encodes an essential component of the “master clock” driving circadian rhythm in the hypothalamic suprachiasmatic nucleus (SCN). New evidence that *Clock* mutant mice are hyperphagic and obese suggests a previously unrecognized link between molecular controls of circadian rhythm and energy homeostasis.**

The growing prevalence of obesity and related metabolic disorders in the United States and other industrialized nations has spurred a global research effort to better understand their underlying causes and improve existing treatment options. Key to this effort has been research into the physiology of energy homeostasis, the process whereby energy intake is matched to energy expenditure over time. Mouse models have been used extensively as tools in this effort and have led to the identification of a series of key genes. Now, a report from [Turek et al. \(2005\)](#) suggests that *Clock*, which encodes a transcription factor involved in the generation of circadian rhythms, should be added to the list. Despite only mild disruption of their locomotor activity rhythm, mutant mice expressing a dysfunctional splice variant of the *Clock* gene have a near total loss of selective nocturnal feeding, consuming close to 50% of their daily food intake during the light phase. Moreover, these mice are hyperphagic and develop obesity on a diet of regular chow, an effect that is exacerbated when placed on a high-fat diet. The resultant obesity is associated with increases in blood glucose, cholesterol, and triglyceride levels, as observed in obese humans with the metabolic syndrome.

In mammals, the “master clock” driving circadian rhythm is located in the hypothalamic suprachiasmatic nucleus (SCN). This brain area contains neurons whose firing rates vary predictably over an approximately 24 hr period and, in turn, coordinates the oscillation of “slave clocks” in other areas throughout the brain and periphery. The molecular mechanisms underlying these oscillations were originally described in *Drosophila*, but homologous genes have been identified across diverse species. After identification of the mouse *Clock* gene in 1997 ([King et al., 1997](#)), rapid progress led to a molecular model of mammalian biological clock function based on a transcrip-

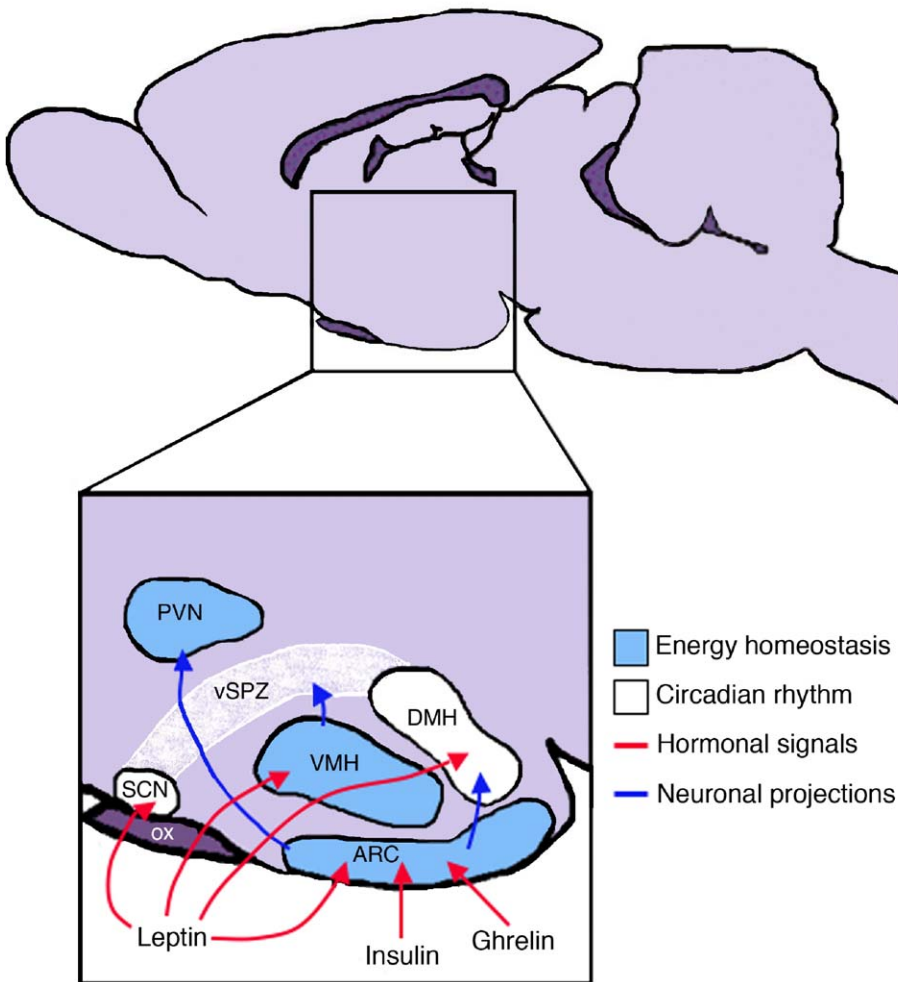
tion-translation negative feedback loop. The transcription factors CLOCK and BMAL1 heterodimerize and promote the transcription of three *period* genes (*mPer1–mPer3*) and two *cryptochrome* genes (*mCry1, mCry2*). The resulting mPER and mCRY proteins heterodimerize, translocate to the nucleus, and negatively regulate the transcription of the *mPer* and *mCry* genes by inhibiting the activity of CLOCK and BMAL1. The negative feedback cycle created by these molecular interactions takes approximately 24 hr to complete and is responsible for the endogenous circadian rhythm. Although the link between these events and changes in neuronal firing rate remains uncertain, deletion of any of these genes, or inhibition of the kinases that phosphorylate their encoded proteins, shortens or lengthens the circadian period and can lead to arrhythmicity ([Reppert and Weaver, 2002](#)).

That the obese phenotype of *Clock* mutant mice arises from loss of circadian rhythm is an important possibility. This hypothesis is compatible with the tight coupling between the circadian clock and patterns of feeding and physical activity. Master clock-controlled rhythms have also been demonstrated for blood glucose, glucose tolerance, and plasma leptin levels ([la Fleur, 2003](#)), and it seems likely that other metabolism-related functions are also subject to regulation by the SCN or peripheral clocks. It is therefore possible that loss of circadian patterning of these parameters accounts for the obesity of *Clock*-deficient mice. Nevertheless, several observations argue against this explanation. First, disruption of the preferentially nocturnal feeding pattern in normal rodents does not result in obesity; when animals are maintained on a schedule requiring them to ingest food only during their inactive phase or at varying times throughout the entire 24 hr period, they maintain normal food intake and body weight (e.g., [Rao and Sharma, 1980](#)). Indeed, such obser-

vations are taken as evidence of a robust energy homeostasis control system capable of adapting to imposed changes in circadian patterns of food availability. Second, obesity is not reported in any of several other mouse models of impaired circadian rhythm resulting from mutation of other clock genes (e.g., *Bmal1, mPer 2*), nor do SCN lesions cause obesity, despite having a pronounced effect on diurnal feeding patterns ([Strubbe et al., 1987](#)).

Recent progress in our understanding of energy homeostasis may provide alternative hypotheses about how the *Clock* mutation causes obesity. Adiposity-related hormones such as leptin and insulin are secreted (by adipose tissue and the endocrine pancreas, respectively) in proportion to body fat mass, cross the blood-brain barrier, bind to their neuronal receptors, and interact with diverse neuronal systems that influence food intake and autonomic function. When adipose mass is decreased (e.g., by a calorically restricted diet), afferent input from leptin and insulin signals decreases, reducing the activity of “catabolic” brain circuits and releasing inhibition on “anabolic” circuits, resulting in increased food intake, decreased energy expenditure, and recovery of lost weight. Accordingly, obesity can result from defective secretion of or neuronal responsiveness to adiposity-related hormones, from impaired signaling via catabolic neurocircuits, or from overactivity of anabolic pathways ([Schwartz and Niswender, 2004](#)).

In this context, several possibilities can be forwarded in an effort to explain the obesity of *Clock* mutant mice. Because these animals remain hyperphagic despite elevated plasma leptin levels, the hypothesis that leptin resistance contributes to the underlying disorder may be considered. The SCN itself expresses leptin receptors ([Hakansson et al., 1998](#)), so it is conceivable that this structure normally senses and responds



**Figure 1.** Hypothalamic neurocircuitry involved in circadian rhythms and energy homeostasis. The suprachiasmatic nucleus (SCN) serves as the “master clock,” generating diurnal rhythms of behavior and metabolism. Output from the SCN (shown in white) is conveyed to other brain areas via the ventral subparaventricular zone (vSPZ) to the dorsomedial nucleus (DMH). Afferent input involved in energy homeostasis is supplied by hormones such as leptin, insulin, and ghrelin. The arcuate nucleus (ARC) integrates this input and relays it to “downstream” areas including the paraventricular nucleus (PVN), lateral hypothalamic area (not shown), and DMH. Leptin can also act directly on the SCN, DMH, and ventromedial hypothalamic nucleus (VMN). In addition to the SCN, the *Clock* gene is expressed at high levels in the ARC.

to changes of body fat mass via a mechanism requiring intact *CLOCK* signaling. The activity of essential integrators of SCN output—the dorsomedial nucleus and subparaventricular zone of the hypothalamus—are also likely to be disrupted in *Clock* mutants (Saper et al., 2005), and this in turn could affect tonic activity and/or leptin sensitivity of key neurocircuits involved in energy homeostasis. Finally, the *Clock* gene is expressed in several leptin-sensitive hypo-

thalamic nuclei outside of the SCN (Shieh, 2003), including the arcuate nucleus, which plays a central role in sensing input from multiple hormone- and nutrient-related signals that influence energy balance (Figure 1). If the loss of *CLOCK* function affects the activity of one or more of these neuronal subsets, the defense of an elevated body weight could be the result. Delineating the specific mechanisms whereby *Clock* mutation causes hyperphagia and obesity is thus a formidable challenge that may ulti-

mately depend upon tissue-specific (or even cell-specific) gene-deletion strategies.

Turek et al. (2005) novel findings establish a previously unrecognized link between circadian rhythms and energy homeostasis and, in so doing, raise fundamental questions about how biological clock proteins influence neuronal systems controlling food intake and autonomic function. An improved understanding of the pathogenesis of obesity and its increasing prevalence will undoubtedly benefit from insights into these questions.

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