# Chapter 5
# Obesity and Chronodisruption: An Imbalance Between Energy Intake and Expenditure

**Oren Froy**

**Abstract** Obesity has become a serious public health problem and a major risk factor for the development of illnesses, such as insulin resistance and hypertension. Attempts to understand the causes of obesity and develop new therapeutic strategies have mostly focused on caloric intake and energy expenditure. Recent studies have shown that the circadian clock controls energy homeostasis by regulating circadian expression and/or activity of enzymes, hormones, and transport systems involved in metabolism. Moreover, disruption of circadian rhythms leads to obesity and metabolic disorders. Therefore, it is plausible that resetting of the circadian clock can be used as a new approach to attenuate obesity. Feeding regimens, such as restricted feeding (RF), calorie restriction (CR) and intermittent fasting (IF), provide a time cue and reset the circadian clock and lead to better health. In contrast, high-fat (HF) diet leads to disrupted circadian expression of metabolic factors and obesity. This chapter will focus on chronodisruption and feeding regimens with implications for obesity.

## Introduction: Obesity and Chronodisruption

Obesity has become a serious and growing public health problem [1]. Attempts to understand the causes of obesity and develop new therapeutic strategies have mostly focused on the imbalance between energy expenditure and caloric intake. Recent studies link energy regulation to the circadian clock at the behavioral, physiological, and molecular levels [2–5], emphasizing that the timing of food intake itself may

O. Froy, Ph.D. (✉)
The Robert H. Smith Faculty of Agriculture, Food and Environment, Nutrigenomics and Functional Foods Research Center, Institute of Biochemistry, Food Science and Nutrition, The Hebrew University of Jerusalem, P.O. Box 12, Rehovot 76100, Israel
e-mail: oren.froy@mail.huji.ac.il

M. Garaulet and J.M. Ordovás (eds.), *Chronobiology and Obesity*,
DOI 10.1007/978-1-4614-5082-5_5, 

play a significant role in weight gain [6]. The mammalian circadian clock influences nearly all aspects of physiology and behavior, including sleep–wake cycles, cardiovascular activity, endocrine system, body temperature, renal activity, physiology of the gastrointestinal tract, and hepatic metabolism [7]. Disruption of circadian coordination (chronodisruption) may be manifested by hormone imbalance, psychological and sleep disorders, cancer proneness, and reduced life span [7–11]. In contrast, robust circadian rhythms lead to well-being and increased longevity [12, 13]. This correlation reveals the prominent influence of the circadian clock on human physiology and pathophysiology. This chapter will summarize recent findings concerning the relationship between circadian rhythms, food intake, and energy expenditure with implications for obesity.

## Circadian Rhythms in Metabolism

The circadian clock regulates metabolism and energy homeostasis in peripheral tissues [5, 14]. This is achieved by mediating the expression and/or activity of certain metabolic enzymes and transport systems [15, 16] involved in cholesterol metabolism, amino acid regulation, drug and toxin metabolism, the citric acid cycle, and glycogen and glucose metabolism [5, 14, 17–20]. Moreover, lesion of rat central clock in the brain suprachiasmatic nuclei (SCN) abolishes daily variations in whole body glucose homeostasis [21], altering not only rhythms in glucose utilization rates but also endogenous hepatic glucose production. Indeed, the SCN projects to the pre-autonomic paraventricular nucleus (PVN) neurons to control hepatic glucose production [22]. Similarly, glucose uptake and the concentration of the primary cellular metabolic currency adenosine triphosphate (ATP) in the brain and peripheral tissues have been found to fluctuate around the circadian cycle [18, 22, 23].

Many hormones involved in metabolism, such as insulin [17], glucagon [24], adiponectin [25], corticosterone [26], leptin, and ghrelin [27, 28], have been shown to exhibit circadian oscillation. Leptin, an adipocyte-derived circulating hormone that acts at specific receptors in the hypothalamus to suppress appetite and increase metabolism, is extremely important in obesity. Plasma leptin levels are normally pulsatile and circadian with leptin peaking early in the non-active phase, that is during the early dark phase in diurnal animals, such as monkeys and humans [29, 30], and during the early to mid-light phase in nocturnal animals, such as rats and mice [31, 32]. Neither feeding time nor adrenalectomy affected the rhythmicity of leptin release. However, ablation of the suprachiasmatic nuclei (SCN), the location of the circadian clock in the hypothalamus, was shown to eliminate leptin circadian rhythmicity in rodents, suggesting that the central circadian clock regulates leptin expression [31]. In addition, SCN-lesioned rats, as opposed to intact animals, showed no elevation in plasma free fatty acids after intraperitoneal administration of leptin, suggesting a role for SCN in leptin function [33]. In obese subjects, leptin retains diurnal variation in release, but with lower amplitude [34]. Leptin 24-h levels were

lower in obese compared with non-obese adolescent girls, suggesting that blunted circadian variation may play a role in leptin resistance and obesity [35].

Receptors for leptin are present on SCN cells [36–38], so it is possible that leptin binds directly to SCN neurons. Thus, it seems that leptin may affect the SCN directly and/or through its effect on the arcuate nucleus (ARC), an aggregation of neurons in the mediobasal hypothalamus important in the regulation of appetite, which is then relayed to the SCN. This regulation of leptin expression by the circadian clock as well as the possible effect of leptin on the SCN places leptin as a possible bridge between energy homeostasis and circadian control. Homozygous C57BL/6 J *Clock*$^{\Delta 19}$ mice, with a truncated exon 18 and deleted exon 19 of the *Clock* gene, that have a greatly attenuated diurnal feeding rhythm, are hyperphagic and obese, and develop a metabolic syndrome of hyperleptinemia, hyperlipidemia, hepatic steatosis, and hyperglycemia [3]. Combination of the *Clock*$^{\Delta 19}$ mutation with the leptin knockout (*ob/ob*) resulted in significantly heavier mice than the *ob/ob* phenotype [39], reiterating the interrelations between leptin and the circadian clock [5, 14, 40].

## Circadian Rhythms and Body Weight

Fluctuations in body weight have been associated with changes in day length in various species, suggesting a central role for the circadian clock in regulating body weight. For example, in Siberian hamsters, modulation of body weight depends on photoperiod acting via the temporal pattern of melatonin secretion from the pineal gland, allowing the entrainment of the circadian rhythms of several biological functions [41, 42]. In studies performed on sheep, adipose tissue leptin levels were modulated by day length independently of food intake, body fatness, and gonadal activity. In addition, increasing the length of the photoperiod resulted in increased activity of the lipogenesis-promoting proteins lipoprotein lipase and malic enzyme, independent of the nutritional status [43, 44]. In humans, studies have demonstrated an increased incidence of obesity among shift workers [45–47].

In obese subjects, leptin retains diurnal variation in release, but with lower amplitude, the magnitude of change in the oscillation [34]. Leptin 24-h levels were lower in obese compared with non-obese adolescent girls, suggesting that blunted circadian variation may play a role in leptin resistance and obesity [35]. Circadian patterns of leptin concentration were distinctly different between adult women with upper-body or lower-body obesity, with a delay in peak values of leptin of approximately 3 h in women with upper-body obesity [48]. Indeed, leptin and the leptin receptor knockouts in animals or mutations in humans have been demonstrated to produce morbid, early onset obesity, hypoleptinemia, hyperphagia, hyperinsulinemia, and hyperglycemia [49, 50]. Similarly to leptin, the rhythmic expression of resistin and adiponectin, two other cytokines secreted from adipose tissue, was greatly blunted in obese (KK) and obese, diabetic (KK-A$^{y}$) mice [25]. In humans, circulating adiponectin levels exhibit both ultradian pulsatility and a diurnal variation. In the latter case, the pattern of adiponectin release is out of phase with leptin

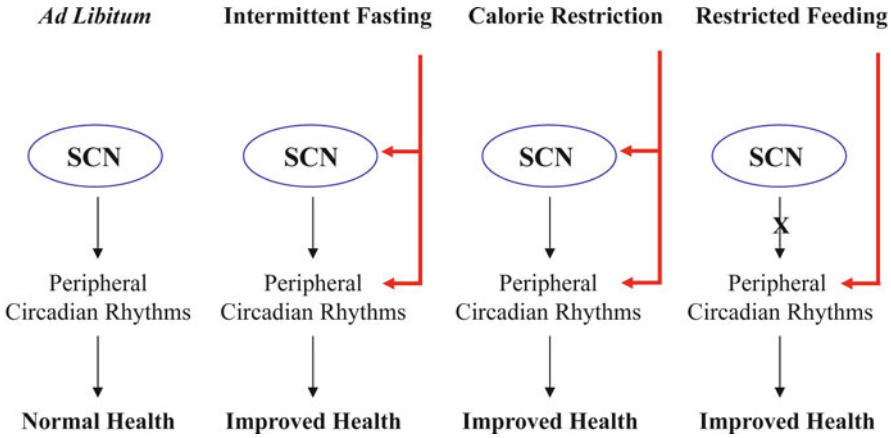


**Fig. 5.1** Effect of feeding regimens on circadian rhythms and health. *SCN* suprachiasmatic nuclei

with a significant decline at night, reaching a nadir in the early morning [51]. In obese subjects, adiponectin levels were significantly lower than lean controls, although the obese group had significantly higher average peak of secretion [52]. In rats, melatonin, a synchronizer of the SCN clock, decreased weight gain in response to high-fat diet and decreased plasma leptin levels within 3 weeks. These effects were independent of total food consumption [53]. Thus, it seems that the circadian clock plays a major role in determining body weight probably by influencing the expression and secretion of hormones. Similarly to the control of the circadian clock on metabolism, feeding is a very potent synchronizer (*zeitgeber*) for peripheral clocks (Fig. 5.1).

## Effect of Restricted Feeding (RF) on Circadian Rhythms

Limiting the time and duration of food availability with no calorie reduction is termed restricted feeding (RF) [15, 54–56]. Animals, which receive food ad libitum everyday at the same time for only a few hours, adjust to the feeding period within a few days and consume their daily food intake during that limited time [57–59]. Restricting food to a particular time of day has profound effects on the behavior and physiology of animals. 2–4 h before the meal, the animals display food anticipatory behavior, which is demonstrated by an increase in locomotor activity, body temperature, corticosterone secretion, gastrointestinal motility, and activity of digestive enzymes [54, 57, 60, 61], all are known output systems of the biological clock. RF is dominant over the SCN and drives rhythms in arrhythmic and clock mutant mice and animals with lesioned SCN, regardless of the lighting conditions [54, 62–66]. In most incidents, RF affects circadian oscillators in peripheral tissues, such as liver, kidney, heart, and pancreas, with no effect on the central pacemaker in the SCN

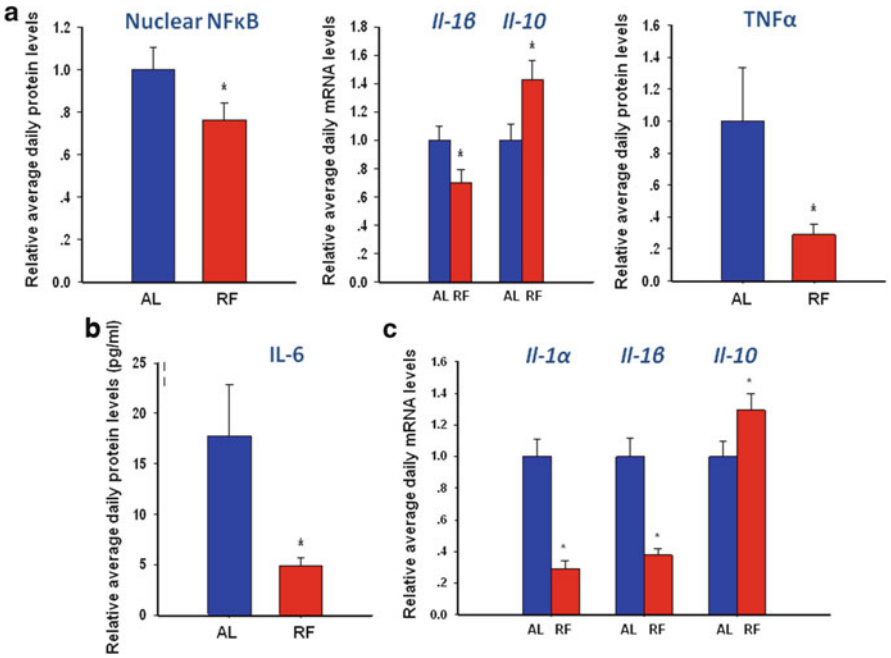


**Fig. 5.2** Reduced levels of pro-inflammatory and increased levels of anti-inflammatory markers under RF in the liver (**a**), serum (**b**) and small intestine (**c**). *Nuclear NFκB* nuclear protein fraction of nuclear factor κB (pro-inflammatory), *Il-1α* interleukin 1α mRNA (pro-inflammatory), *Il-1β* interleukin 1β mRNA (pro-inflammatory), *Il-10* interleukin 10 mRNA (anti-inflammatory), *IL-6* interleukin 6 protein (pro-inflammatory), *TNFα* tumor necrosis factor α protein (pro-inflammatory)

[15, 55, 56, 64, 65, 67, 68]. Thus, RF uncouples the SCN from the periphery, suggesting that nutritional regulation of clock oscillators in peripheral tissues may play a direct role in coordinating metabolic oscillations [69]. Many physiological activities that are normally dictated by the SCN master clock, such as detoxification by hepatic P450 activity, body temperature, locomotor activity, and heart rate, are phase-shifted by RF to the time of food availability [63, 64, 70, 71]. As soon as food availability returns to be ad libitum, the SCN clock, whose phase remains unaffected, resets the peripheral oscillators [67]. It has recently been shown that long-term day-time RF can increase the amplitude of clock gene expression, increase expression of catabolic factors, and reduce the levels of disease markers leading to better health [72] (Fig. 5.2).

Because timed feeding is dominant in resetting circadian rhythms even in animals with lesioned SCN, it has been suggested that there is a food-entrainable oscillator. However, the location of this food-entrainable oscillator (FEO) has been elusive. Lesions in brain regions involved in feeding, such as the dorsomedial hypothalamic nucleus (DMH) [73–76], the brain stem parabrachial nuclei (PBN) [74, 77], and the core and shell regions of nucleus accumbens [78, 79], revealed that these nuclei may be involved in FEO output, but they cannot fully account for the

oscillation [80]. Neither vagal signals nor leptin are critical for the entrainment [61, 81]. CLOCK [82] or BMAL1 [83] and other clock genes [84] have been shown not to be necessary for food anticipatory activity. However, it has recently been demonstrated that *Per2* mutant mice did not exhibit wheel-running food anticipation [85, 86]. Thus, how RF entrains circadian rhythms remains an extremely important topic for research.

## Effect of Calorie Restriction (CR) on Circadian Rhythms

CR refers to a dietary regimen low in calories without malnutrition. CR restricts the amount of calories derived from carbohydrates, fats, or proteins to 60–75% of ad libitum-fed animals [87]. It has been documented that calorie restriction significantly extends the life span of rodents by up to 50% [88, 89]. In addition to the increase in life span, CR also delays the occurrence of age-associated pathophysiological changes, such as cancer, diabetes, kidney disease, and cataracts [89–92]. Theories on how CR modulates aging and longevity abound, but the exact mechanism is still unknown [89]. As opposed to RF, CR entrains the clock in the SCN [93–96], indicating that calorie reduction could affect the central oscillator. CR during the daytime affects the temporal organization of the SCN clockwork and circadian outputs in mice under light/dark cycle. In addition, CR affects responses of the circadian system to light, indicating that energy metabolism modulates gating of photic inputs in mammals [97]. These findings suggest that synchronization of peripheral oscillators during CR could be achieved directly due to the temporal eating, as has been reported for RF [64, 67, 68], or by synchronizing the SCN [93–95], which, in turn, sends humoral or neuronal signals to synchronize the peripheral tissues [98, 99].

## Effect of Intermittent Fasting (IF) on Circadian Rhythms

During IF, food is available ad libitum every other day. IF-treated mice eat on the days they have access to food approximately twice as much as those having continuous access to food [100, 101]. Similarly to calorically restricted animals, IF-fed animals exhibit increased life span in comparison with the ad libitum-fed control [102] as well as improved glucose metabolism, cardio-protection, neuro-protection [100, 103–107], and increased resistance to cancer [101]. The IF-induced beneficial effects are thought to occur independently of the overall caloric intake, but the underlying mechanisms are still unknown. One suggested mechanism is stimulation of cellular stress pathways induced by the IF regimen [100, 108, 109]. Recently it has been shown that when food was introduced during the light period, mice exhibited almost arrhythmicity in clock gene expression in the liver (Fig. 5.3). Unlike daytime feeding, nighttime feeding yielded rhythms similar to those generated during ad libitum feeding [110]. The fact that IF can affect circadian rhythms differently

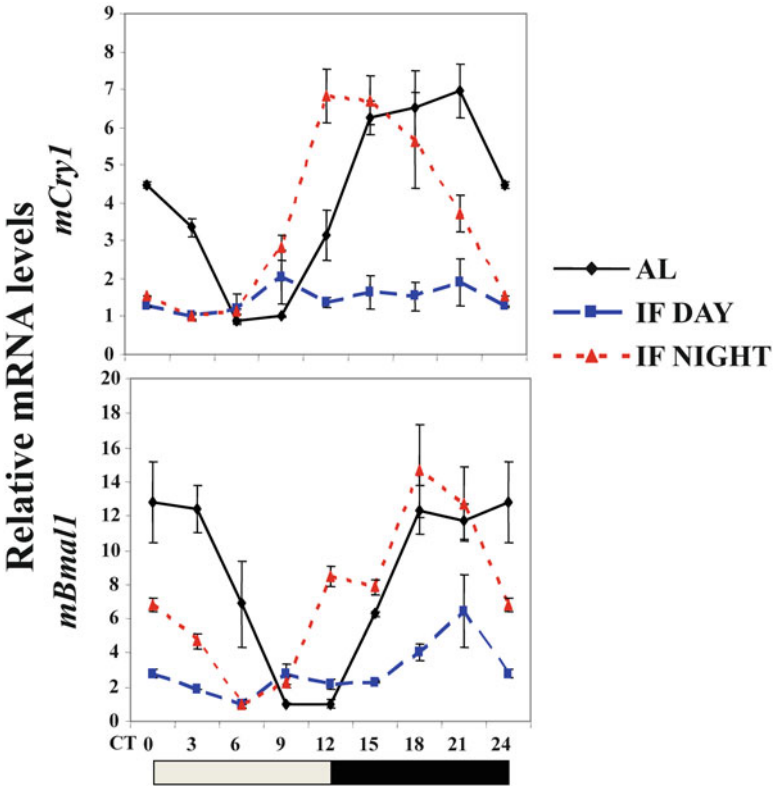


**Fig. 5.3** Day-time IF abolishes circadian rhythms. mRNA expression levels of two mouse clock genes *mCry1* and *Bmal1* in the liver during ad libitum (AL) and day and night intermittent fasting (IF). The *gray* and *black bars* designate the subjective day (formerly the light period) and dark cycles, respectively. CT0 and CT12 represent the circadian times at which the lights would have been turned on and off, respectively, had the animals remained in light–dark. *CT* circadian time

depending on the timing of food availability suggests that this regimen affects the SCN clock, similarly to CR. SCN resetting by IF and CR could be involved in the health benefits conferred by these regimens [99].

## Effect of High-Fat Diet on Circadian Rhythms

Few studies show that a high-fat diet leads to minimal effects on the rhythmic expression of clock genes in visceral adipose tissue and liver [111]. However, recent studies have shown that introduction of a high-fat diet to animals leads to rapid changes in both the period of locomotor activity in constant darkness and to increased food intake during the normal rest period under light–dark conditions [112]. These

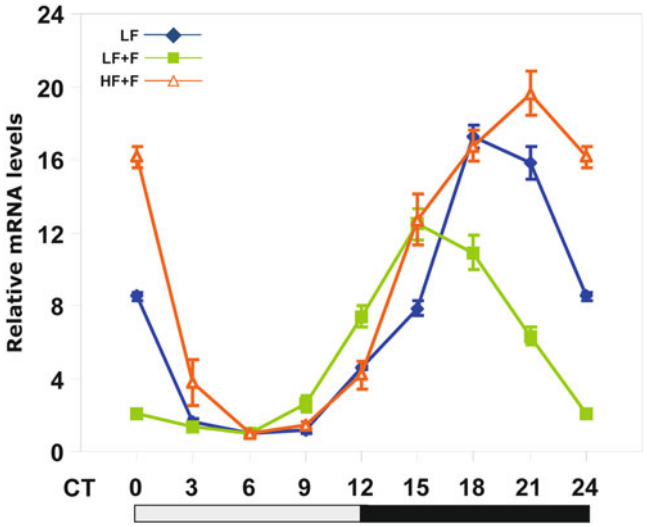


**Fig. 5.4** Fasting induces phase advances while high-fat diet causes phase delays. mRNA expression levels of the clock gene *Bmal1* in the liver after fasting or high-fat diet. The *gray* and *black bars* designate the subjective day (formerly the light period) and dark cycles, respectively. CT0 and CT12 represent the circadian times at which the lights would have been turned on and off, respectively, had the animals remained in light–dark. *CT* circadian time, *LF* low-fat diet, *LF + F* low-fat diet + fasting, *HF + F* high-fat diet + fasting

changes in behavioral rhythmicity correlated with disrupted clock gene expression within hypothalamus, liver, and adipose tissue, as well as with altered cycling of hormones and nuclear hormone receptors involved in fuel utilization, such as leptin, thyroid stimulating hormone (TSH), and testosterone in mice, rats, and humans [112–117]. Furthermore, a high-fat diet modulates carbohydrate metabolism by amplifying circadian variation in glucose tolerance and insulin sensitivity [118].

In addition to the disruption of clock gene expression, high-fat diet induced a phase delay in clock and clock-controlled genes [116, 117] (Fig. 5.4). Recently, AMPK has been found to phosphorylate Ser-389 of CKIε, resulting in increased CKIε activity and degradation of PER2. PER2 degradation leads to a phase advance in the circadian expression pattern of clock genes in wild-type mice [119]. As the levels of AMPK decline under HF diet [116, 117], it is plausible that the changes seen in the expression phase of genes under HF diet are mediated by changes in AMPK levels. In addition to its effect on gene expression, high-fat feeding led to impaired adjustment to local time by light resetting, including slower rate of re-entrainment of behavioral and body temperature rhythms after "jet-lag" tests (6 h advanced light–dark cycle) and reduced phase-advance responses to light. These results correlated with reduction in c-FOS and phosphoERK expression in the SCN in response to light-induced phase shifts [120].

## Summary Points

- Western lifestyle leads to high food consumption, inactivity during the active period, enhanced activity in the rest period, and shortened sleep period.
- Disrupted biological rhythms might lead to attenuated circadian feeding rhythms, disrupted metabolism, cancer proneness, and reduced life expectancy.
- Feeding time has the ability to reset bodily rhythms.
- Resetting the biological clock by food or feeding time may lead to better functionality of physiological systems, preventing metabolic disorders, promoting well-being, and extending life span.

## References

1. Wyatt SB, Winters KP, Dubbert PM (2006) Overweight and obesity: prevalence, consequences, and causes of a growing public health problem. Am J Med Sci 331:166–174
2. Oishi K, Shirai H, Ishida N (2005) CLOCK is involved in the circadian transactivation of peroxisome-proliferator-activated receptor alpha (PPARalpha) in mice. Biochem J 386:575–581
3. Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, Laposky A, Losee-Olson S, Easton A, Jensen DR, Eckel RH, Takahashi JS, Bass J (2005) Obesity and metabolic syndrome in circadian *Clock* mutant mice. Science 308:1043–1045
4. Marcheva B, Ramsey KM, Buhr ED, Kobayashi Y, Su H, Ko CH, Ivanova G, Omura C, Mo S, Vitaterna MH, Lopez JP, Philipson LH, Bradfield CA, Crosby SD, JeBailey L, Wang X, Takahashi JS, Bass J (2010) Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. Nature 466:627–631
5. Froy O (2010) Metabolism and circadian rhythms—implications for obesity. Endocr Rev 31:1–24
6. Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW (2009) Circadian timing of food intake contributes to weight gain. Obesity (Silver Spring) 17:2100–2102
7. Reppert SM, Weaver DR (2002) Coordination of circadian timing in mammals. Nature 418:935–941
8. Penev PD, Kolker DE, Zee PC, Turek FW (1998) Chronic circadian desynchronization decreases the survival of animals with cardiomyopathic heart disease. Am J Physiol 275:H2334–H2337
9. Fu L, Pelicano H, Liu J, Huang P, Lee C (2002) The circadian gene *Period2* plays an important role in tumor suppression and DNA damage response *in vivo*. Cell 111:41–50
10. Filipski E, King VM, Li X, Granda TG, Mormont MC, Claustrat B, Hastings MH, Levi F (2003) Disruption of circadian coordination accelerates malignant growth in mice. Pathol Biol 51:216–219
11. Davis S, Mirick DK (2006) Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle. Cancer Causes Control 17:539–545
12. Hurd MW, Ralph MR (1998) The significance of circadian organization for longevity in the golden hamster. J Biol Rhythms 13:430–436
13. Karasek M (2004) Melatonin, human aging, and age-related diseases. Exp Gerontol 39:1723–1729
14. Garaulet M, Madrid JA (2010) Chronobiological aspects of nutrition, metabolic syndrome and obesity. Adv Drug Deliv Rev 62:967–978
15. Hirota T, Fukada Y (2004) Resetting mechanism of central and peripheral circadian clocks in mammals. Zoolog Sci 21:359–368

16. Kohsaka A, Bass J (2007) A sense of time: how molecular clocks organize metabolism. Trends Endocrinol Metab 18:4–11
17. La Fleur SE, Kalsbeek A, Wortel J, Buijs RM (1999) A suprachiasmatic nucleus generated rhythm in basal glucose concentrations. J Neuroendocrinol 11:643–652
18. La Fleur SE (2003) Daily rhythms in glucose metabolism: suprachiasmatic nucleus output to peripheral tissue. J Neuroendocrinol 15:315–322
19. Davidson AJ, Castanon-Cervantes O, Stephan FK (2004) Daily oscillations in liver function: diurnal vs circadian rhythmicity. Liver Int 24:179–186
20. Ramsey KM, Marcheva B, Kohsaka A, Bass J (2007) The clockwork of metabolism. Annu Rev Nutr 27:219–240
21. Cailotto C, La Fleur SE, Van Heijningen C, Wortel J, Kalsbeek A, Feenstra M, Pevet P, Buijs RM (2005) The suprachiasmatic nucleus controls the daily variation of plasma glucose via the autonomic output to the liver: are the clock genes involved? Eur J Neurosci 22:2531–2540
22. Kalsbeek A, Ruiter M, La Fleur SE, Cailotto C, Kreier F, Buijs RM (2006) The hypothalamic clock and its control of glucose homeostasis. Prog Brain Res 153:283–307
23. Yamazaki S, Ishida Y, Inouye S (1994) Circadian rhythms of adenosine triphosphate contents in the suprachiasmatic nucleus, anterior hypothalamic area and caudate putamen of the rat—negative correlation with electrical activity. Brain Res 664:237–240
24. Ruiter M, La Fleur SE, van Heijningen C, van der Vliet J, Kalsbeek A, Buijs RM (2003) The daily rhythm in plasma glucagon concentrations in the rat is modulated by the biological clock and by feeding behavior. Diabetes 52:1709–1715
25. Ando H, Yanagihara H, Hayashi Y, Obi Y, Tsuruoka S, Takamura T, Kaneko S, Fujimura A (2005) Rhythmic messenger ribonucleic acid expression of clock genes and adipocytokines in mouse visceral adipose tissue. Endocrinology 146:5631–5636
26. De Boer SF, Van der Gugten J (1987) Daily variations in plasma noradrenaline, adrenaline and corticosterone concentrations in rats. Physiol Behav 40:323–328
27. Ahima RS, Prabakaran D, Flier JS (1998) Postnatal leptin surge and regulation of circadian rhythm of leptin by feeding. Implications for energy homeostasis and neuroendocrine function. J Clin Invest 101:1020–1027
28. Bodosi B, Gardi J, Hajdu I, Szentirmai E, Obal F Jr, Krueger JM (2004) Rhythms of ghrelin, leptin, and sleep in rats: effects of the normal diurnal cycle, restricted feeding, and sleep deprivation. Am J Physiol Regul Integr Comp Physiol 287:R1071–R1079
29. Kalra SP, Bagnasco M, Otukonyong EE, Dube MG, Kalra PS (2003) Rhythmic, reciprocal ghrelin and leptin signaling: new insight in the development of obesity. Regul Pept 111:1–11
30. Downs JL, Urbanski HF (2006) Aging-related sex-dependent loss of the circulating leptin 24-h rhythm in the rhesus monkey. J Endocrinol 190:117–127
31. Kalsbeek A, Fliers E, Romijn JA, La Fleur SE, Wortel J, Bakker O, Endert E, Buijs RM (2001) The suprachiasmatic nucleus generates the diurnal changes in plasma leptin levels. Endocrinology 142:2677–2685
32. Sukumaran S, Almon RR, DuBois DC, Jusko WJ (2010) Circadian rhythms in gene expression: Relationship to physiology, disease, drug disposition and drug action. Adv Drug Deliv Rev 62:904–917
33. Shen J, Tanida M, Niijima A, Nagai K (2007) In vivo effects of leptin on autonomic nerve activity and lipolysis in rats. Neurosci Lett 416:193–197
34. Licinio J (1998) Longitudinally sampled human plasma leptin and cortisol concentrations are inversely correlated. J Clin Endocrinol Metab 83:1042
35. Heptulla R, Smitten A, Teague B, Tamborlane WV, Ma YZ, Caprio S (2001) Temporal patterns of circulating leptin levels in lean and obese adolescents: relationships to insulin, growth hormone, and free fatty acids rhythmicity. J Clin Endocrinol Metab 86:90–96
36. Guan XM, Hess JF, Yu H, Hey PJ, van der Ploeg LH (1997) Differential expression of mRNA for leptin receptor isoforms in the rat brain. Mol Cell Endocrinol 133:1–7
37. Yi CX, van der Vliet J, Dai J, Yin G, Ru L, Buijs RM (2006) Ventromedial arcuate nucleus communicates peripheral metabolic information to the suprachiasmatic nucleus. Endocrinology 147:283–294

38. Zigman JM, Jones JE, Lee CE, Saper CB, Elmquist JK (2006) Expression of ghrelin receptor mRNA in the rat and the mouse brain. J Comp Neurol 494:528–548
39. Oishi K, Ohkura N, Wakabayashi M, Shirai H, Sato K, Matsuda J, Atsumi G, Ishida N (2006) CLOCK is involved in obesity-induced disordered fibrinolysis in ob/ob mice by regulating PAI-1 gene expression. J Thromb Haemost 4:1774–1780
40. Green CB, Takahashi JS, Bass J (2008) The meter of metabolism. Cell 134:728–742
41. Gorman MR (2003) Differential effects of multiple short day lengths on body weights of gonadectomized siberian hamsters. Physiol Biochem Zool 76:398–405
42. Morgan PJ, Ross AW, Mercer JG, Barrett P (2003) Photoperiodic programming of body weight through the neuroendocrine hypothalamus. J Endocrinol 177:27–34
43. Bocquier F, Bonnet M, Faulconnier Y, Guerre-Millo M, Martin P, Chilliard Y (1998) Effects of photoperiod and feeding level on perirenal adipose tissue metabolic activity and leptin synthesis in the ovariectomized ewe. Reprod Nutr Dev 38:489–498
44. Faulconnier Y, Bonnet M, Bocquier F, Leroux C, Chilliard Y (2001) Effects of photoperiod and feeding level on adipose tissue and muscle lipoprotein lipase activity and mRNA level in dry non-pregnant sheep. Br J Nutr 85:299–306
45. Di Lorenzo L, De Pergola G, Zocchetti C, L'Abbate N, Basso A, Pannacciulli N, Cignarelli M, Giorgino R, Soleo L (2003) Effect of shift work on body mass index: results of a study performed in 319 glucose-tolerant men working in a Southern Italian industry. Int J Obes Relat Metab Disord 27:1353–1358
46. Karlsson B, Knutsson A, Lindahl B (2001) Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. Occup Environ Med 58:747–752
47. Karlsson BH, Knutsson AK, Lindahl BO, Alfredsson LS (2003) Metabolic disturbances in male workers with rotating three-shift work. Results of the WOLF study. Int Arch Occup Environ Health 76:424–430
48. Perfetto F, Tarquini R, Cornelissen G, Mello G, Tempestini A, Gaudiano P, Mancuso F, Halberg F (2004) Circadian phase difference of leptin in android versus gynoid obesity. Peptides 25:1297–1306
49. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM (1994) Positional cloning of the mouse obese gene and its human homologue. Nature 372:425–432
50. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S (1997) Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 387:903–908
51. Gavrila A, Peng CK, Chan JL, Mietus JE, Goldberger AL, Mantzoros CS (2003) Diurnal and ultradian dynamics of serum adiponectin in healthy men: comparison with leptin, circulating soluble leptin receptor, and cortisol patterns. J Clin Endocrinol Metab 88:2838–2843
52. Yildiz BO, Suchard MA, Wong ML, McCann SM, Licinio J (2004) Alterations in the dynamics of circulating ghrelin, adiponectin, and leptin in human obesity. Proc Natl Acad Sci U S A 101:10434–10439
53. Puchalski SS, Green JN, Rasmussen DD (2003) Melatonin effect on rat body weight regulation in response to high-fat diet at middle age. Endocrine 21:163–167
54. Stephan FK (2002) The "other" circadian system: food as a *Zeitgeber*. J Biol Rhythms 17:284–292
55. Cassone VM, Stephan FK (2002) Central and peripheral regulation of feeding and nutrition by the mammalian circadian clock: implications for nutrition during manned space flight. Nutrition 18:814–819
56. Schibler U, Ripperger J, Brown SA (2003) Peripheral circadian oscillators in mammals: time and food. J Biol Rhythms 18:250–260
57. Honma KI, Honma S, Hiroshige T (1983) Critical role of food amount for prefeeding corticosterone peak in rats. Am J Physiol 245:R339–R344

58. Grasl-Kraupp B, Bursch W, Ruttkay-Nedecky B, Wagner A, Lauer B, Schulte-Hermann R (1994) Food restriction eliminates preneoplastic cells through apoptosis and antagonizes carcinogenesis in rat liver. Proc Natl Acad Sci U S A 91:9995–9999
59. Froy O, Chapnik N, Miskin R (2006) Long-lived alphaMUPA transgenic mice exhibit pronounced circadian rhythms. Am J Physiol Endocrinol Metab 291:E1017–E1024
60. Saito M, Murakami E, Suda M (1976) Circadian rhythms in disaccharidases of rat small intestine and its relation to food intake. Biochim Biophys Acta 421:177–179
61. Comperatore CA, Stephan FK (1987) Entrainment of duodenal activity to periodic feeding. J Biol Rhythms 2:227–242
62. Stephan FK, Swann JM, Sisk CL (1979) Anticipation of 24-hr feeding schedules in rats with lesions of the suprachiasmatic nucleus. Behav Neural Biol 25:346–363
63. Mistlberger RE (1994) Circadian food-anticipatory activity: formal models and physiological mechanisms. Neurosci Biobehav Rev 18:171–195
64. Hara R, Wan K, Wakamatsu H, Aida R, Moriya T, Akiyama M, Shibata S (2001) Restricted feeding entrains liver clock without participation of the suprachiasmatic nucleus. Genes Cells 6:269–278
65. Oishi K, Miyazaki K, Ishida N (2002) Functional CLOCK is not involved in the entrainment of peripheral clocks to the restricted feeding: entrainable expression of *mPer2* and *Bmal1* mRNAs in the heart of *Clock* mutant mice on Jcl:ICR background. Biochem Biophys Res Commun 298:198–202
66. Horikawa K, Minami Y, Iijima M, Akiyama M, Shibata S (2005) Rapid damping of food-entrained circadian rhythm of clock gene expression in clock-defective peripheral tissues under fasting conditions. Neuroscience 134:335–343
67. Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U (2000) Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. Genes Dev 14:2950–2961
68. Stokkan KA, Yamazaki S, Tei H, Sakaki Y, Menaker M (2001) Entrainment of the circadian clock in the liver by feeding. Science 291:490–493
69. Lin JD, Liu C, Li S (2008) Integration of energy metabolism and the mammalian clock. Cell Cycle 7:453–457
70. Boulamery-Velly A, Simon N, Vidal J, Mouchet J, Bruguerolle B (2005) Effects of three-hour restricted food access during the light period on circadian rhythms of temperature, locomotor activity, and heart rate in rats. Chronobiol Int 22:489–498
71. Hirao J, Arakawa S, Watanabe K, Ito K, Furukawa T (2006) Effects of restricted feeding on daily fluctuations of hepatic functions including p450 monooxygenase activities in rats. J Biol Chem 281:3165–3171
72. Sherman H, Frumin I, Gutman R, Chapnik N, Lorentz A, Meylan J, le Coutre J, Froy O (2011) Long-term restricted feeding alters circadian expression and reduces the level of inflammatory and disease markers. J Cell Mol Med 15:2745–2759
73. Mieda M, Williams SC, Richardson JA, Tanaka K, Yanagisawa M (2006) The dorsomedial hypothalamic nucleus as a putative food-entrainable circadian pacemaker. Proc Natl Acad Sci U S A 103:12150–12155
74. Gooley JJ, Schomer A, Saper CB (2006) The dorsomedial hypothalamic nucleus is critical for the expression of food-entrainable circadian rhythms. Nat Neurosci 9:398–407
75. Landry GJ, Simon MM, Webb IC, Mistlberger RE (2006) Persistence of a behavioral food-anticipatory circadian rhythm following dorsomedial hypothalamic ablation in rats. Am J Physiol Regul Integr Comp Physiol 290:R1527–R1534
76. Landry GJ, Yamakawa GR, Webb IC, Mear RJ, Mistlberger RE (2007) The dorsomedial hypothalamic nucleus is not necessary for the expression of circadian food-anticipatory activity in rats. J Biol Rhythms 22:467–478
77. Davidson AJ, Cappendijk SL, Stephan FK (2000) Feeding-entrained circadian rhythms are attenuated by lesions of the parabrachial region in rats. Am J Physiol Regul Integr Comp Physiol 278:R1296–R1304

78. Mistlberger RE, Mumby DG (1992) The limbic system and food-anticipatory circadian rhythms in the rat: ablation and dopamine blocking studies. Behav Brain Res 47:159–168
79. Mendoza J, Angeles-Castellanos M, Escobar C (2005) Differential role of the accumbens Shell and Core subterritories in food-entrained rhythms of rats. Behav Brain Res 158:133–142
80. Davidson AJ (2006) Search for the feeding-entrainable circadian oscillator: a complex proposition. Am J Physiol Regul Integr Comp Physiol 290:R1524–R1526
81. Mistlberger RE, Marchant EG (1999) Enhanced food-anticipatory circadian rhythms in the genetically obese Zucker rat. Physiol Behav 66:329–335
82. Pitts S, Perone E, Silver R (2003) Food-entrained circadian rhythms are sustained in arrhythmic *Clk*/*Clk* mutant mice. Am J Physiol Regul Integr Comp Physiol 285:R57–R67
83. Pendergast JS, Nakamura W, Friday RC, Hatanaka F, Takumi T, Yamazaki S (2009) Robust food anticipatory activity in BMAL1-deficient mice. PLoS One 4:e4860
84. Storch KF, Weitz CJ (2009) Daily rhythms of food-anticipatory behavioral activity do not require the known circadian clock. Proc Natl Acad Sci U S A 106:6808–6813
85. Feillet CA, Ripperger JA, Magnone MC, Dulloo A, Albrecht U, Challet E (2006) Lack of food anticipation in *Per2* mutant mice. Curr Biol 16:2016–2022
86. Mistlberger RE (2006) Circadian rhythms: perturbing a food-entrained clock. Curr Biol 16:R968–R969
87. Masoro EJ, Shimokawa I, Higami Y, McMahan CA, Yu BP (1995) Temporal pattern food intake not a factor in the retardation of aging processes by dietary restriction. J Gerontol A Biol Sci Med Sci 50A:B48–B53
88. Koubova J, Guarente L (2003) How does calorie restriction work? Genes Dev 17:313–321
89. Masoro EJ (2005) Overview of caloric restriction and ageing. Mech Ageing Dev 126:913–922
90. Weindruch R, Sohal RS (1997) Seminars in medicine of the Beth Israel Deaconess Medical Center. Caloric intake and aging. N Eng J Med 337:986–994
91. Roth GS, Lane MA, Ingram DK, Mattison JA, Elahi D, Tobin JD, Muller D, Metter EJ (2002) Biomarkers of caloric restriction may predict longevity in humans. Science 297:811
92. Roth GS, Mattison JA, Ottinger MA, Chachich ME, Lane MA, Ingram DK (2004) Aging in rhesus monkeys: relevance to human health interventions. Science 305:1423–1426
93. Challet E, Caldelas I, Graff C, Pevet P (2003) Synchronization of the molecular clockwork by light- and food-related cues in mammals. Biol Chem 384:711–719
94. Challet E, Solberg LC, Turek FW (1998) Entrainment in calorie-restricted mice: conflicting zeitgebers and free-running conditions. Am J Physiol 274:R1751–R1761
95. Mendoza J, Graff C, Dardente H, Pevet P, Challet E (2005) Feeding cues alter clock gene oscillations and photic responses in the suprachiasmatic nuclei of mice exposed to a light/dark cycle. J Neurosci 25:1514–1522
96. Resuehr D, Olcese J (2005) Caloric restriction and melatonin substitution: effects on murine circadian parameters. Brain Res 1048:146–152
97. Mendoza J, Drevet K, Pevet P, Challet E (2008) Daily meal timing is not necessary for resetting the main circadian clock by calorie restriction. J Neuroendocrinol 20(2):251–260
98. Froy O, Chapnik N, Miskin R (2008) Relationship between calorie restriction and the biological clock: lessons from long-lived transgenic mice. Rejuvenation Res 11:467–471
99. Froy O, Miskin R (2010) Effect of feeding regimens on circadian rhythms: implications for aging and longevity. Aging (Albany N Y) 2:7–27
100. Anson RM, Guo Z, de Cabo R, Iyun T, Rios M, Hagepanos A, Ingram DK, Lane MA, Mattson MP (2003) Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proc Natl Acad Sci U S A 100:6216–6220
101. Descamps O, Riondel J, Ducros V, Roussel AM (2005) Mitochondrial production of reactive oxygen species and incidence of age-associated lymphoma in OF1 mice: effect of alternate-day fasting. Mech Ageing Dev 126:1185–1191

102. Goodrick CL, Ingram DK, Reynolds MA, Freeman JR, Cider N (1990) Effects of intermittent feeding upon body weight and lifespan in inbred mice: interaction of genotype and age. Mech Ageing Dev 55:69–87
103. Contestabile A, Ciani E (2004) Dietary restriction differentially protects from neurodegeneration in animal models of excitotoxicity. Brain Res 1002:162–166
104. Mattson MP (2005) Energy intake, meal frequency, and health: a neurobiological perspective. Annu Rev Nutr 25:237–260
105. Sharma S, Kaur G (2005) Neuroprotective potential of dietary restriction against kainate-induced excitotoxicity in adult male Wistar rats. Brain Res Bull 67:482–491
106. Ahmet I, Wan R, Mattson MP, Lakatta EG, Talan M (2005) Cardioprotection by intermittent fasting in rats. Circulation 112:3115–3121
107. Mager DE, Wan R, Brown M, Cheng A, Wareski P, Abernethy DR, Mattson MP (2006) Caloric restriction and intermittent fasting alter spectral measures of heart rate and blood pressure variability in rats. FASEB J 20:631–637
108. Mattson MP, Duan W, Wan R, Guo Z (2004) Prophylactic activation of neuroprotective stress response pathways by dietary and behavioral manipulations. NeuroRx 1:111–116
109. Mattson MP (2008) Dietary factors, hormesis and health. Ageing Res Rev 7:43–48
110. Froy O, Chapnik N, Miskin R (2009) Effect of intermittent fasting on circadian rhythms in mice depends on feeding time. Mech Ageing Dev 130:154–160
111. Yanagihara H, Ando H, Hayashi Y, Obi Y, Fujimura A (2006) High-fat feeding exerts minimal effects on rhythmic mRNA expression of clock genes in mouse peripheral tissues. Chronobiol Int 23:905–914
112. Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, Kobayashi Y, Turek FW, Bass J (2007) High-fat diet disrupts behavioral and molecular circadian rhythms in mice. Cell Metab 6:414–421
113. Havel PJ, Townsend R, Chaump L, Teff K (1999) High-fat meals reduce 24-h circulating leptin concentrations in women. Diabetes 48:334–341
114. Cha MC, Chou CJ, Boozer CN (2000) High-fat diet feeding reduces the diurnal variation of plasma leptin concentration in rats. Metabolism 49:503–507
115. Cano P, Jimenez-Ortega V, Larrad A, Reyes Toso CF, Cardinali DP, Esquifino AI (2008) Effect of a high-fat diet on 24-h pattern of circulating levels of prolactin, luteinizing hormone, testosterone, corticosterone, thyroid-stimulating hormone and glucose, and pineal melatonin content, in rats. Endocrine 33:118–125
116. Barnea M, Madar Z, Froy O (2009) High-fat diet delays and fasting advances the circadian expression of adiponectin signaling components in mouse liver. Endocrinology 150:161–168
117. Barnea M, Madar Z, Froy O (2010) High-fat diet followed by fasting disrupts circadian expression of adiponectin signaling pathway in muscle and adipose tissue. Obesity (Silver Spring) 18:230–238
118. Rudic RD, McNamara P, Curtis AM, Boston RC, Panda S, Hogenesch JB, Fitzgerald GA (2004) BMAL1 and CLOCK, two essential components of the circadian clock, are involved in glucose homeostasis. PLoS Biol 2:e377
119. Um JH, Yang S, Yamazaki S, Kang H, Viollet B, Foretz M, Chung JH (2007) Activation of 5'-AMP-activated kinase with diabetes drug metformin induces casein kinase Iepsilon (CKIepsilon)-dependent degradation of clock protein mPER2. J Biol Chem 282:20794–20798
120. Mendoza J, Pevet P, Challet E (2008) High-fat feeding alters the clock synchronization to light. J Physiol 586:5901–5910