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Circadian rhythms, nutrition and implications for longevity in urban environments

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Presently, about 12% of the population is 65 years or older and by the year 2030 that figure is expected to reach 21%. In order to promote the well-being of the elderly and to reduce the costs associated with health care demands, increased longevity should be accompanied by ageing attenuation. Energy restriction, which limits the amount of energy consumed to 60–70% of the daily intake, and intermittent fasting, which allows the food to be available *ad libitum* every other day, extend the life span of mammals and prevent or delay the onset of major age-related diseases, such as cancer, diabetes and cataracts. Recently, we have shown that well-being can be achieved by resetting of the circadian clock and induction of robust catabolic circadian rhythms *via* timed feeding. In addition, the clock mechanism regulates metabolism and major metabolic proteins are key factors in the core clock mechanism. Therefore, it is necessary to increase our understanding of circadian regulation over metabolism and longevity and to design new therapies based on this regulation. This review will explore the present data in the field of circadian rhythms, ageing and metabolism.

Clock: Life span: Feeding: Nutrition: Metabolism: Circadian rhythms

Circadian rhythms

Mammals have developed an endogenous circadian clock located in the brain suprachiasmatic nuclei (SCN) of the anterior hypothalamus that responds to the environmental light–dark cycle (Fig. 1). Light is absorbed through the retina and this information is transmitted to the SCN, which in turn relays the information *via* neuronal connections or circulating humoral factors to peripheral clocks, such as the liver, heart and lungs, regulating cellular and physiological functions[1–3]. The clock mechanism in both SCN neurons and peripheral tissues consists of CLOCK and BMAL1 (brain-muscle-Arnt-like 1) proteins that heterodimerise and bind to E-box sequences to mediate transcription of tissue-specific genes, including *Period*s (*Per1*, *Per2*, *Per3*) and *Cryptochrome*s (*Cry1*, *Cry2*). PER and CRY constitute part of the negative feedback loop, which inhibits CLOCK:BMAL1-mediated transcription[1,4].

Chronodisruption and ageing

Disruption of the coordination between the endogenous clock and the environment leads to symptoms of fatigue, disorientation and insomnia. Night-shift workers have disrupted circadian rhythms and they exhibit metabolic disorders, hormone imbalance[5], psychological and sleep disorders[6], and increased incidence of cancer and malignant growth[5]. Longevity in hamsters is decreased with disruption of rhythmicity and is increased in older animals given fetal SCN implants that restore high-amplitude rhythms[7]. Even chronic reversal of the external light–dark cycle at weekly intervals results in a significant decrease in the survival time of cardiomyopathic hamsters[8].

It has been shown that circadian rhythms change with normal ageing, including a shift in the phase and decrease in amplitude[9,10]. Deficiency of the CLOCK protein significantly affects longevity, as the average

Abbreviations: BMAL1, brain-muscle-Arnt-like 1; CRY, cryptochromes; CR, calorie restriction; IF, intermittent fasting; PER, Periods; SCN, suprachiasmatic nuclei; RF, restricted feeding.

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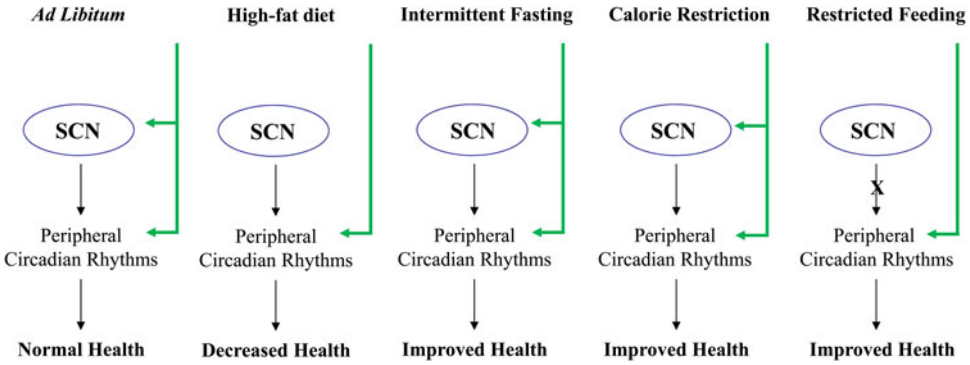

Fig. 1. (Colour online) Effect of feeding diet regimens on circadian rhythms and health. SCN, suprachiasmatic nuclei.

lifespan of *Clock*$^{-/-}$ mice was reduced by 15% compared with wild-type mice, while maximum life span was reduced by more than 20%. CLOCK deficiency also resulted in the development of cataracts and dermatitis, two age-specific pathologies[11,12], at a much higher rate than in wild-type mice[13]. In addition, *Bmal1*$^{-/-}$ knockout mice have reduced life span and they display various symptoms of premature ageing, including cataracts and organ shrinkage[14]. *Per1,2*$^{-/-}$ mice are morphologically indistinguishable from wild-type animals at birth, but as early as 12–14 months of age they start to develop features of premature ageing, such as a faster decline in fertility, loss of soft tissues and kyphosis[15,16].

It has been reported that old mice are approximately 20 times less sensitive to the synchronising effect of light compared with young animals[17]. When the SCN becomes less sensitive, the endogenous period (τ) becomes extremely important. A positive link between τ close to 24 h and survival has been previously suggested[7,18]. According to this suggestion, τ longer or shorter than 24 h necessitates a daily synchronisation to external time cues (i.e. light–dark cycles) with a physiological cost proportional to the deviation. This cost might affect survival. We have recently shown that a long-lived transgenic mouse has a τ of 24 h at a young and old age compared with its short-lived genetic background whose τ is 23·5 h at young age and 25 h at old age[19].

Circadian rhythms in metabolism

Obesity has become a serious and growing public health problem[20]. Attempts to understand the causes of obesity and develop new therapeutic strategies have mostly focused on the imbalance between energy expenditure and energy intake. However, studies in the last decade link energy regulation to the circadian clock at the behavioural, physiological and molecular levels[21–24], emphasising that the timing of food intake itself may play a significant role in weight gain[25]. Obesity, which is characterised by the excess of fat accumulation in white adipose tissue, has been related to irregular sleep–wake schedules, high snacking frequency or social jet lag known to disrupt the circadian clock[26].

The circadian clock regulates metabolism and energy homeostasis in peripheral tissues[24,27,28]. This is achieved by mediating the expression and/or activity of certain metabolic enzymes and transport systems[29,30] involved in cholesterol metabolism, amino acid regulation, drug and toxin metabolism, the citric acid cycle, and glycogen and glucose metabolism[24,27,31–34]. Moreover, lesions of rat central clock in the SCN abolishes diurnal variations in whole body glucose homeostasis[35], altering not only rhythms in glucose utilisation rates but also endogenous hepatic glucose production. Indeed, the SCN projects to the pre-autonomic paraventricular nucleus neurons to control hepatic glucose production[36]. Similarly, glucose uptake and the concentration of the primary cellular metabolic currency ATP in the brain and peripheral tissues have been found to fluctuate around the circadian cycle[32,36,37]. In addition, many hormones involved in metabolism, such as insulin [31], glucagon[38], adiponectin[39], corticosterone[40], leptin and ghrelin[41,42], have been shown to exhibit circadian oscillation.

However, the most compelling connection between the circadian clock and metabolism is achieved by genetic knockout or mutated clock genes. Homozygous *Clock* mutant mice have a greatly attenuated diurnal feeding rhythm, are hyperphagic and obese, and develop a metabolic syndrome of hyperleptinaemia, hyperlipidaemias, hepatic steatosis and hyperglycaemia[22]. Combination of this mutation with the leptin knockout (*ob*/*ob*) resulted in significantly heavier mice than the *ob*/*ob* phenotype[43], emphasising the inter-relations between leptin and the circadian clock[24,27,44]. In addition, *Bmal1*$^{-/-}$ knockout mice, similarly to *Clock* mutant mice, exhibit suppressed diurnal variations in glucose and TAG as well as abolished gluconeogenesis[45].

Moreover, several key metabolic factors have been shown to participate in the core clock mechanism. REV-ERBα, the negative regulator of *Bmal1*[46], is induced during normal adipogenesis[47]. The positive regulators of *Bmal1* expression, retinoid-related orphan receptor α and PPARα, regulate lipid metabolism[48,49]. In turn, CLOCK:BMAL1 heterodimer regulates the

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expression of *Rev-erbα*, *Pparα* and *Rora* (retinoid-related orphan receptor α)[21,46,48–51]. PPARγ co-activator-1α, a PPARγ transcriptional co-activator that regulates energy metabolism, stimulates the expression of the clock genes, *Bmal1* and *Rev-erbα*, through co-activation of the retinoid-related orphan receptors; mice lacking PPARγ co-activator-1α show abnormal diurnal rhythms of activity, body temperature and metabolic rate[52]. AMP-activated protein kinase, a sensitive sensor of low energy and nutrient state in the cell, leads to the degradation of PER and CRY proteins[53,54]. Degradation of the negative feedback loop leads to a phase advance in the circadian expression pattern of clock genes in mice[55,56]. Mammalian target of rapamycin, which functions as a sensor of cellular nutrient and energy levels, is regulated by light in the SCN[57]. One of the key factors in the mammalian target of rapamycin pathway, protein 70 S6 kinase 1, rhythmically phosphorylates BMAL1 allowing it to both associate with the translational machinery and stimulate circadian oscillations of protein synthesis[58]. SIRT1, a key factor involved in metabolism and life span, interacts directly with CLOCK and deacetylates BMAL1 and PER2[59–61].

Effect of restricted feeding on circadian rhythms

Limiting the time and duration of food availability with no energy reduction is termed restricted feeding (RF)[3,29,62,63]. Animals which receive food *ad libitum* every day at the same time for only a few hours, adjust to the feeding period and consume their daily food intake during that limited time[64–66]. Restricting food to a particular time of day has profound effects on the behaviour and physiology of animals. Two to four hours before the meal, the animals display food anticipatory behaviour, which is demonstrated by an increase in locomotor activity, body temperature, corticosterone secretion, gastrointestinal motility and activity of digestive enzymes[62,64,67,68], all are known output systems of the circadian 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[62,69–73]. In most incidents, RF affects circadian oscillators in peripheral tissues, with no effect on the central pacemaker in the SCN[3,29,63,71,72,74,75]. Thus, RF uncouples the SCN from the periphery[76]. We have shown that long-term daytime 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[77] (Fig. 1). RF diet regimen resembles the month of Ramadan, as Muslims abstain from eating and drinking during the activity period. The average low levels of cholesterol and TAG found during RF are in agreement with those found during Ramadan[78,79]. Aksungar *et al.*[80] demonstrated that Ramadan fasting has some positive effects on the inflammatory state and on risk factors for CVD, such as C reactive protein and homocysteine.

Effect of energy restriction on circadian rhythms

Calorie restriction (CR) refers to a dietary regimen low in energy without malnutrition. CR restricts the amount of energy to 60–75% of *ad libitum*-fed animals[81]. It has been documented that CR significantly extends the life span of rodents by up to 50%[82,83]. In addition to the increase in life span, CR also delays the occurrence of age-related diseases, such as cancer, diabetes and cataracts[83–86]. Theories on how CR modulates ageing and longevity abound, but the exact mechanism is still unknown[83]. The reduction of energy intake, and, as a result, in oxidative stress, is considered the critical beneficial factor in the CR diet regimen[83]. It has been argued that in mice, the oxidative stress theory can account for age-related diseases, such as cancer, but not for longevity *per se*[87].

As opposed to RF, CR entrains the clock in the SCN[88–91], indicating that energy reduction could affect the central oscillator. CR during the daytime affects the temporal organisation of the SCN clockwork and circadian outputs in mice under light–dark cycle. In addition, CR affects photic responses of the circadian system, indicating that energy metabolism modulates gating of photic inputs in mammals[92]. These findings suggest that synchronisation of peripheral oscillators during CR could be achieved directly due to the temporal eating, as has been reported for RF[71,74,75], or by synchronising the SCN[88–90], which entrains the peripheral tissues[93,94] (Fig. 1).

Effect of intermittent fasting on circadian rhythms

Intermittent fasting (IF) allows food to be available *ad libitum* every other day. Similarly to energetically restricted animals, IF-fed animals exhibit increased life span as well as improved cardio- and neuro-protection and increased resistance to cancer[95]. One suggested mechanism for its beneficial effects is the stimulation of cellular stress pathways induced by the IF diet regimen[95,96]. IF alters circadian rhythms depending on the time of food introduction (Fig. 1). When food was introduced during the light period, mice exhibited almost arrhythmicity in clock gene expression in the liver. Unlike daytime feeding, night-time feeding yielded rhythms similar to those generated during *ad libitum* feeding[97].

Effect of high-fat diet on circadian rhythms

Several studies have shown that a high-fat diet leads to disruptions in locomotor activity in total darkness and to elevated food intake during the rest phase under light–dark conditions[98]. These changes were also manifested by disrupted clock gene expression in the hypothalamus, liver and adipose tissue as well as altered cycling of hormones in mice, rats and human subjects[56,98–102]. In addition, a high-fat diet induced a phase delay in clock and clock-controlled genes[56,102]

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(Fig. 1). Combining high-fat diet with RF led to a leaner phenotype although the energy intake was the same as mice fed a low-fat diet[103]. Altogether, these studies demonstrate the importance of timing of feeding over its content.

Effect of breakfast on circadian metabolism

Breakfast has previously been demonstrated to be of major importance for the 24-h regulation of glucose[104]. Indeed, skipping breakfast has been shown to be associated with weight gain and other adverse health outcomes, including insulin resistance and increased risk for developing type 2 diabetes. In contrast, consumption of a high-energy breakfast and a low-energy dinner resulted in a significant reduction of all-day postprandial glycaemia and body weight[105–107]. The importance of breakfast has recently been demonstrated in type 2 diabetic patient who skipped breakfast and had increased postprandial hyperglycaemia after both lunch and dinner in association with impaired insulin response[108].

Conclusions

Disruptions in clock genes and/or circadian rhythms promote ageing and shorten life span, whereas appropriate resetting of circadian rhythms leads to well-being and increased longevity. Life span extension has been a goal of research for several decades. CR, IF and RF reset circadian rhythms and promote better health (Fig. 1). In addition, breakfast consumption has been shown to affect all-day metabolism. Therefore, it is necessary to increase our understanding of circadian regulation over metabolism and longevity and to design new therapies based on this regulation.

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Conflicts of Interest

None.

Authorship

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