

Chapter 19

Diet and Circadian Rhythms: Implications for Aging and Longevity



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Abstract Circadian rhythms are maintained by the interaction of external environmental cues with body's molecular clock machinery and help to optimize physiological functions by temporally coordinating them at the cellular, tissue, organ and behavioural level of an organism. Feeding-fasting pattern is one of the most important external cues that affect the robustness of the biological rhythms. Upon aging due to loss of indispensable neurons in the master clock- Suprachiasmatic nucleus (SCN), these rhythms get compromised and so does the temporal coordination thus leading to various age-related pathologies. Irregular eating-fasting patterns can also temporally disrupt the coordination between metabolism and physiology, leading to the onset of many chronic diseases and early aging. Hence, avoiding irregular feeding-fasting habits and maintaining strong rhythmic cycles following optimum amplitude and phase of rhythms can help in healthy aging and preventing diseases such as sleep disorders, cardiovascular, metabolic disorders, diabetes, obesity, breast cancer, inflammation, hypertension, neurodegeneration etc. Therefore, synchronizing the external cues and timings of signals from master clock along with time restricted eating patterns can help in sustaining a robust circadian clock. Such synchronization will help in preventing the diseases and improving their prognosis. In this chapter, we aim to discuss the role of diet in restoration of age-induced circadian dysfunction.

Keywords Circadian clock · Dietary intervention · Metabolism · Physiology · Sleep · Fasting

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19.1 Introduction

Circadian rhythms are evolutionarily conserved biological rhythms in almost all organisms ranging from archaea to mammals. Circadian (Latin: *circa* – approximately; *diēm*– day) rhythms are approximately 24 hour(h) rhythmic oscillations that regulate the physiology of an organism at molecular and behavioural level (Whitehead et al. 2009; Edgar et al. 2012). The adaptation to external environmental conditions using clock system allows an organism to predict changes and give an advantage to survival (Kondratov et al. 2006). Many diseases are associated with disruptions in the circadian clock like psychological disorders, sleep disorders, metabolic disorders, cardiovascular diseases, cancer, insomnia, fatigue, disorientation and hormonal profile shifts in night shift workers etc. (Hofman et al. 2006; Gibson et al. 2009). During aging, there is a shift in both amplitude and phases of circadian rhythm (Gibson et al. 2009; Jagota 2012).

Circadian rhythms have evolved as an adaptation to the oscillations found in the environment and to get entrained by them, notably to the day-night cycle (Jagota 2006). In the case of mammals, the main circadian rhythm regulator is SCN containing ~20,000 neurons located in the hypothalamic region. It acts as a timekeeper in controlling and synchronizing the circadian period of many physiological and behavioral functions and entraining them to 24 h light and dark cycles (Jagota et al. 2000; Jagota 2006; Takahashi et al. 2017). Three major pathways, Retino-hypothalamic tract (RHT), Geniculo-hypothalamic tract (GHT), and Retino-raphé pathway (RRP) receive the information from the environment through several cues such as photic (light) and non-photoc cues (food, sound, humidity etc.). All these pathways diverge from the retinal ganglion cells before they enter into the SCN. Among these three, RHT is a photic pathway that has a direct synaptic contact of retinal ganglionic cells with the SCN; GHT is an indirect photic pathway where the retina conveys input signals to Intergeniculate Nucleus (IGL) via a separate branch of RHT that overlaps with the RHT terminals in the SCN; RRP is the third major input pathway which participates in the non-photoc regulation of the SCN, where neuronal fibres from raphe nuclei end in the core region of the SCN (Jagota 2012). The auto-regulatory transcriptional and translational feedback loops drive the coordinated expression of genes such as (*Clock*)-circadian locomotor output cycles kaput, (*Bmal1*)-Brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1, (*Per1*)-Period1, (*Per2*)-Period2, (*Per3*)-Period3, (*Cry1*)-Cryptochrome1, (*Cry2*)-Cryptochrome2, (*Ror*)-retinoic acid-related orphan nuclear receptors, and (*Rev-Erb*)-reverse erythroblastosis virus etc. at both levels (Takahashi 2017).

The SCN plays the role of central clock or the relay centre of information. It regulates the release of neurohormone melatonin, the messenger of time from pineal gland. Melatonin then synchronizes the peripheral clocks with the central clock (Vriend and Rieter 2014). Every mammalian cell is autonomous and has its own clock machinery constituting the peripheral clock system controlled by the SCN through both sympathetic as well as parasympathetic pathways (Kalsbeek et al.

2010). The endogenous rhythms of clock gene expression have been reported by researchers in cell culture of peripheral clocks like liver, adrenal glands, hormones like adrenocorticotrophic hormone (ACTH) and glucocorticoids (Cailotto et al. 2005; Mahoney et al. 2010).

19.2 Food as an Important Clock Regulator

Food has been reported as an important non-photic *zeitgeber* (ZT) or time giver to synchronize an organism's biological rhythms and shifting the timing of food leads to the shift in the activity of an organism (Carneiro et al. 2012). In SCN lesioned mice, food restriction has demonstrated to induce locomotor behaviours as well as temperature rhythms (Froy et al. 2010). Food timings entrain circadian clocks in different brain regions and most peripheral organs, thereby synchronizing their daily rhythms. This entrainment of peripheral clocks to mealtime is accomplished by multiple feeding-related signals, including absorbed nutrients and metabolic hormones, acting in parallel or series in a tissue-specific manner. Signals that synchronize circadian clock in the brain with feeding time are presumed to generate the circadian rhythms of food-anticipatory activity (FAA) that emerge when food is restricted to a fixed daily mealtime. Such FAA is regulated and paced by the food-entrainable oscillator (FEO) located outside the SCN (Flores et al. 2016; Chaudhari et al. 2017). Several timekeeping mechanisms involved in the FAA occurring before food intake include neuronal activation, molecular clock entrainment, hormonal cues, and metabolic regulation (Tahara et al. 2013; Challet 2019). The synchronization between food entrainable clock and central clock system is driven by a complex mechanism including humoral and enzymatic regulatory pathway (Challet 2019). β -hydroxybutyrate (β -OHB) synthesized in the liver during fasting conditions has been proposed to be a key candidate molecule in those pathways. Apart from being an energy source, β -OHB has many cellular signalling actions and participates in FAA modulation and its production is clock regulated involving *Per2* (Newman et al. 2017).

19.3 Food and Melatonin Hormone

The synthesis and release of melatonin from the pineal gland is under regulation of the SCN. The photic cues are received by the SCN clock and relayed to pineal gland through a multi-synaptic pathway. Melatonin is a "night-time hormone" in all the animals (diurnal, nocturnal and crepuscular) irrespective of their activity niche and thus called messenger of darkness (Jagota et al. 2012; 2019). Melatonin is synthesised from serotonin through N-acetylation followed by methylation reaction in the presence of arylalkylamine N-acetyltransferase (AANAT; rate limiting enzyme) and hydroxyl indole-O-methyl-transferase (HIOMT) respectively (Jagota et al. 2012).

Endogenous melatonin rhythm modulates feeding and fasting behaviour and anticipation of meal time. Melatonin cues modulate the phase and amplitudes of various hormonal rhythms including rhythms of cortisol and insulin (Challet et al. 2019). Reduced levels of melatonin has been associated with aging (Reddy and Jagota 2015). Melatonin is an important hormetin (Jagota et al. 2019), and its manipulation with dietary interventions in elderly may lead to restoration of circadian clock functions and improvement of health and wellbeing.

19.4 Circadian Dysfunction with Aging

Aging is an inevitable unidirectional natural process in the lifespan of an organism. The disruption of the endogenous nature of the molecular clock, deteriorated temporal synchronisation of the oscillators and an overall change in the physiology dampens the circadian rhythm as the organism ages (Jagota et al. 2000; Manoogiana and Panda 2017; Jagota et al. 2019). A phase advance in body temperature and melatonin secretion rhythms has been associated with aging in humans. Alterations in the daily rhythms of clock genes (Mattam and Jagota 2014), serotonin metabolism (Kalyani and Jagota 2008; 2010; Reddy and Jagota 2015), antioxidant enzymes (Manikonda and Jagota 2012), leptin (Reddy and Jagota 2014), nitric oxide (NO), and Suppressor of cytokine signaling (*Socs*) (Vinod and Jagota 2016; 2017) expression has been reported from our laboratory. Additionally, alterations in daily rhythms of Sirtuin1 (Sirt1), Nuclear factor erythroid 2-related factor 2 (Nrf2), Rev-erb α and inflammatory markers including Nfkb1, Tumor necrosis factor alpha (Tnf- α), Interleukin-6 (Il-6), Toll-like receptor 4 (Tlr4) and Toll-like receptor 9 (Tlr9) affecting circadian timing system (CTS) were observed with aging (Thummadi and Jagota 2019; Kukke-man and Jagota 2020). As endogenous rhythms dampen and deteriorate with age, the contribution by the external cues and its timing starts playing an increasingly critical role in maintaining the amplitude and phase of an organism's circadian clock (Manoogian and Panda 2017; Jagota et al. 2020).

19.5 Circadian Rhythms, Metabolism and Homeostasis with Aging

The circadian clock controls energy metabolism and maintains homeostasis in peripheral tissues through the controlled expression of various metabolic hormones like leptin, ghrelin, secretin etc. involved in different metabolic pathways. This helps in maintaining the normal physiological functions and healthy aging (Green et al. 2008; Froy 2009). The circadian clock is itself under metabolic regulation and the disturbances induced by a nutrient imbalance results in circadian dysfunction (Chaix et al. 2014). Many hormones such as insulin, glucagon adiponectin, corticosterone,

and ghrelin have been found to show circadian expression and oscillation (Ando et al. 2005; Yang et al. 2006). The temporal regulation of insulin which shows a peak in its production at 1700 h and a nadir at 0400 h is achieved by both the patterns of feeding-fasting and SCN signalling (Sadacca et al. 2011; Vieira et al. 2015). Leptin, a well-known appetite repressor also shows circadian rhythmicity in its expression. The removal of the SCN abolishes the rhythmicity of its secretion in rodents leading to uncontrolled feeding behaviour, obesity, pathologies, and early aging effects suggesting the role of the clock system in aging, metabolism and maintaining homeostasis (Kalra et al. 2003). The receptors for leptin and ghrelin have been demonstrated in SCN (Yi et al. 2006; Zigman, et al. 2006) thus, establishing a direct link between the main circadian clock (SCN) and metabolism (Prosser et al. 2003). Metabolism is also influenced by the microbiome which makes an important component of the gastrointestinal tract (GIT). The microbiome shows rhythmic oscillations in its composition as per the requirement in GIT for proper metabolism. Erratic feeding patterns can dampen the taxonomic diversity and disrupt the oscillating rhythm of the microbiome, contributing to metabolic disorders like intestinal dysbiosis, obesity, and early aging (Voigt et al. 2016). Forced feeding-fasting patterns achieved by different strategies like intermittent fasting (IF), periodic fasting (PF), and calorie restriction (CR) have been shown to restore some of these oscillations to normal and achieve healthy aging (Zarrinpar et al. 2014).

19.6 Chrononutrition: Timing of Food as a Therapeutic Intervention

Due to demanding work pressure and changing food habits, unhealthy and unscheduled meals including junk food have now become a part of our lifestyle. Such unscheduled meals with unhealthy amounts of sugar, salts, caffeine, processed meat, fats and an inadequate intake of fruits, green leafy vegetables, cereals etc. are the major risk factors for developing age-related pathologies and accelerate the aging process (Micha et al. 2017). Patterns of feeding and fasting can potentially contribute to the development of chronic pathologies and thus have an influential impact on human health and onset of diseases (Zarrinpar et al. 2014). Although clock oscillators in our body can recuperate from mild alteration in our daily feeding times, chronic imbalanced and unscheduled feeding behaviour results in untimed cues, circadian dysfunction and disease pathologies later in life with unhealthy aging (Asher and Sassone-Corsi 2015; Lopez-Minguez et al. 2019). Thus, the temporal attributes of food and its role in health and disease are as vital as the qualitative and quantitative nutritional aspects (Gupta et al. 2017; Kant et al. 2018).

19.6.1 Food, Energy Metabolism, Circadian Dysfunction, and Aging

Various mitochondrial rate-limiting enzymes are rhythmically expressed (Neufeld-Cohen et al. 2016). In circadian mutant mice, enforced feeding-fasting patterns can reinstate rhythmic expression of some of metabolites, such as Acylcarnitine carrier protein and Acyl CoA Dehydrogenase (Manoogian and Panda 2016; Neufeld-Cohen et al. 2016). Mice with a deleted exon-19 of the *Clock* gene shows an altered feeding rhythm, over-eating, obesity and other metabolic syndromes like high blood leptin, lipids and glucose levels (Turek et al. 2005). Such mutant (*Clock*^{Δ19}) mice also showed a decrease in the expression of hypothalamic peptides like ghrelin and orexin, which are important for energy balance (Turek et al. 2005). *Per2* mutations abolished rhythmicity for glucocorticoids, feeding patterns and caused obesity (Yang et al. 2009).

Aging leads to significant disruption in adipogenesis by affecting circadian components, *Bmal1*, *Rev-erba* causing multiple pathologies like obesity, cardiovascular diseases and decline in longevity (Duez et al. 2008). Peroxisome proliferator-activated receptor α (PPAR α) is important for transcriptional activation of *Bmal1* and genes responsible for the metabolism of lipids and glucose (Lefebvre et al. 2006; Lamia et al. 2008). Impairment of PPAR α leads to defective fatty acid oxidative pathways, enhanced inflammatory response, oxidative stress and renal fibrosis and impaired energy metabolism (Adnan 2007). Adenosine 5'-monophosphate-activated protein kinase (AMPK), an energy sensor of cells integrates the circadian clock with metabolism by regulating the response to feeding and modulating NAD⁺ levels and SIRT1 activity (Hardie et al. 2006; Canto et al. 2009). Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α), a transcriptional co-activator of *Bmal1* and *Rev-erba* also regulates energy metabolism. Disrupted expressions of AMPK and PGC-1 α leads to abnormal daily diurnal rhythms, body temperature energy imbalance, metabolic disorders, multiple pathologies and early aging (Grimaldi et al. 2007). Another important protein found to display a link between metabolism and the circadian clock of mammals is SIRT1. The influence of nutrient state and the circadian clock on insulin sensitivity is via SIRT1 (Bass and Takahashi 2010). It is an NAD⁺ dependent histone deacetylase that plays an important role in extending the life span in yeast, *Caenorhabditis elegans*, *Drosophila* and mice (Mair et al. 2008; Canto et al. 2009). SIRT1 can interact with CLOCK directly and deacetylate BMAL1 and PER2 in cultured fibroblasts (Asher et al. 2008; Nakahata et al. 2008). The information on the food, circadian clock, and metabolic factors discussed here has been compiled as a schematic diagram in Fig. 19.1.

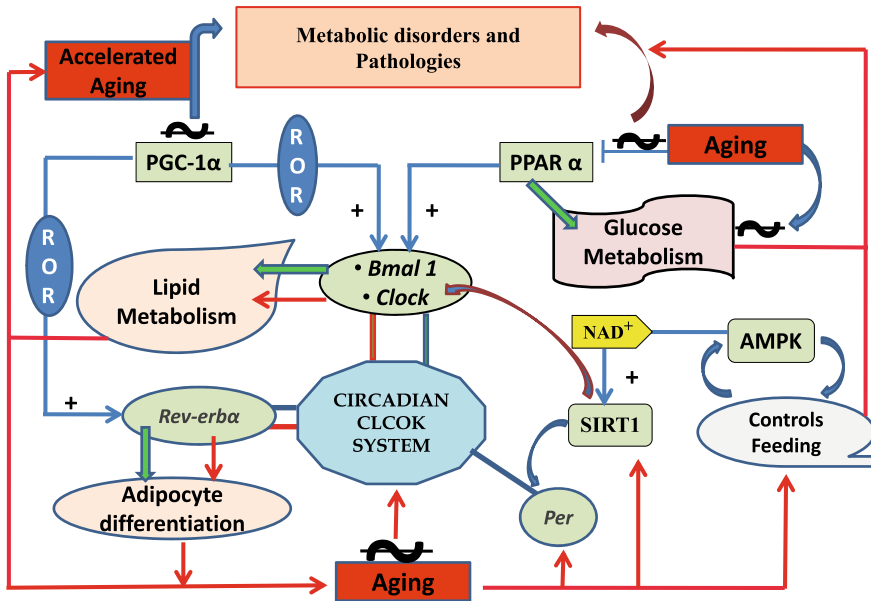



Fig 19.1 Simplified schematic representation of the link between circadian clock, metabolism and aging. Aging leads to significant disruption in glucose and lipid metabolism by affecting circadian components like *Bmal1*, *Clock*, *Rev-erba* etc. and metabolic components like Peroxisome proliferator-activated receptor α (*PPAR* α) and Peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PGC-1* α). Also, feeding and fasting cycle, controlled by Adenosine 5'-monophosphate-activated protein kinase (*AMPK*), with the involvement of NAD^+ , and *SIRT1* gets desynchronised upon aging. This age induced desynchronization between clock and metabolism leads energy imbalance, metabolic disorders and accelerated aging.  = Abolition of rhythms; (+) = Induces the expression

19.7 Various Dietary Interventions: Circadian Clock, Aging and Longevity

Dietary intervention is an ancient practice and various researchers using experimental models from invertebrates (*C. elegans*) to mammals (rat/mice) have demonstrated mean life-span extension by using different strategies of dietary interventions (Di Francesco et al. 2018). Such strategies (Table 19.1) achieved either by fasting for a certain period or reducing the calorie intake are discussed below.

19.7.1 Restricted Feeding (RF)

Restricting food to a particular time of the day while still ensuring nutritional adequacy is called restricted feeding (RF) (Froy et al. 2010). RF controls the FAA,

Table 19.1 Various dietary interventions in therapeutic strategies towards circadian dysfunction and aging

Restricted feeding (RF)	
Hepatic P450 levels, body temperature, locomotor activity, and heart rate (↑)	Hara et al. 2001, Hirao et al. 2006
Corticosterone secretion, gastrointestinal motility and activity of digestive enzymes	Stephan 2002
Core clock apparatus of liver, kidney, heart, and pancreas, life span (↑)	Damiola et al. 2000, Hara et al. 2001, Stokkan et al. 2001, Schibler et al. 2003, Hirota et al. 2004
Expression of c-myc & p53 (↓) and increases lifespan (↑)	Wu et al. 2004
Obesity (↓) & aging in rat (↓)	Sherman et al. 2012, Chaix et al. 2014
Caloric restriction (CR)	
Life span in <i>C. elegans</i> , <i>Drosophila</i> , rodents, and monkeys (↑)	Mair and Dillin 2008
Phosphorylation of CREB, and aging	Ripperger et al. 2006
Clock, memory & aging	Etcheberry et al. 2006
Life span in the clinical trials (↑)	Mattson et al. 2017
Oxidative stress, aging, mitochondrial function, and inflammation (↓)	Lopez-Lluch et al. 2019
Arterial hypertension (↓)	An et al. 2020
Intermittent fasting (IF)	
Life span as compared to food given ad libitum (↑)	Goodrick et al. 1990, Mattson et al. 2005
Glucose metabolism (↑), cardio-protection, Aging, neuro-protection (↑)	Anson et al. 2003, Contestabile et al. 2004; Mattson and Wan 2005
Resistance to aging & cancer (↑)	Descamps et al. 2005, Mattson and Wan 2005
Cardiovascular diseases (↓)	Varady et al. 2007
Aging and Cognitive performance (↑)	Singh et al. 2012
Abdominal fat and blood pressure in humans (↓)	Harvie et al. 2011
Visceral fat, and insulin resistance (↓)	Barnosky et al. 2014
Inflammatory diseases (↓)	Johnson et al. 2007

which includes corticosterone secretion, gastrointestinal motility and activity of digestive enzymes before meals (Stephan et al. 2002). RF is dominant over the SCN and able to drive the rhythms in clock mutant rodents and animals with lesioned SCN regardless of photic cues (Hara et al. 2001; Stephan 2002). But in some cases, RF only affects the clock system in peripheral tissues such as the heart, kidney, pancreas and liver, causing their uncoupling from the SCN, followed by metabolic disorders, pathologies and early aging (Schibler et al. 2003; Hirota et al. 2004). This suggests the nutritional regulation of clock oscillators in peripheral tissues and its involvement in metabolic disorders and aging (Lin et al. 2008). Damiola et al. 2000

demonstrated when the food availability is made normal, the SCN, whose phase remains unaffected, resets the peripheral oscillators and synchronization of physiology. *Per2* mutant mice do not show wheel-running food anticipation (Mistlberger 2006). In one of the interesting studies, the survival time of mice inoculated with osteosarcoma was prolonged under RF (Wu et al. 2004). RF has been found to modify the expression of genes responsible for carcinogenesis and tumor progression such as *c-myc* and *p53* (Filipski et al. 2005) but whether RF affects life span in a real sense or not is still not clear.

19.7.2 Intermittent Fasting (IF)

IF is a cyclic pattern of eating and fasting, one of the regimen of IF is alternate day fasting (ADF), where food is available *ad-libitum* every alternate day (Froy et al. 2010). Two more variations of IF include: Periodic Fasting (PF) which lasts for 2 or more days followed by the next cycle after 6–7 days (Longo et al. 2016; Vargas et al. 2020) and Time restricted feeding (TRF), where food is taken in a specific time window of 8 h or less (Mattson et al. 2017). Recently, IF has gained popularity due to its various beneficial effects on health (De Cabo et al. 2019). Animals on IF exhibit increased life span, improved glucose metabolism, cardio physiology, neuro-protection and resistance towards cancer (Descamps et al. 2005; Mattson et al. 2005; Varady et al. 2007). *Rev-erb α* , an important component of the circadian clock, also regulates the expression of genes involved in metabolism and inflammation. It was observed that there is an average 11 fold increase in its levels at the end of the 4th week during 30-days of IF (Mindikoglu et al. 2020). RF schedules elicit a phase shift in molecular and metabolic machinery components of peripheral clocks. Likewise, imposed periods of extended daily fasting, independent of dietary composition and calorie intake have significant metabolic and lifespan benefits (Mitchell et al. 2018).

19.7.3 Time-Restricted Feeding (TRF)

A feeding regime like Time-restricted feeding (TRF) has shown beneficial effects in animals and is believed to compensate and consolidate the circadian rhythms (Chaix et al. 2014; De Cabo and Mattson 2019). Flies on TRF showed a sustained nocturnal sleep which is about double the total sleep duration of the flies with food *ad libitum* (Gill et al. 2015). Nocturnal rodents given TRF with food *ad libitum* during the light phase (normally their rest period) show altered expression of clock genes and clock-controlled genes (CCGs) in the peripheral tissues without affecting SCN (Damiola et al. 2000; Stokkan et al. 2001). A differential adaptation to the novel feeding regimens has been observed in peripheral clocks where Kidneys, lungs, or heart adapts to changes slower than the liver. TRF of normal diets improves energy metabolism in humans in short-term studies and contributes to a healthy life span

even though calories are not restricted (Sutton et al. 2018; Jamshed et al. 2019). High-fat diets (HFD), representing the western diet model, has been reported to cause circadian dysfunction by disrupting the feeding-fasting rhythms and gene expression rhythms (Hatori and Panda 2015; Potter et al. 2016). A very recent report has shown that an extended HFD and night restricted feeding (NtRF) regimen on senescence-accelerated mouse strain, SAMP8 ameliorates age-related phenotypes. The positive impact of HFD has been manifested till metabolic perturbations kicked in. So, the HFD and chrono-nutritional feeding in combination can be an effective anti-aging strategy (Oike et al. 2020) ensuring a healthy life span.

19.7.4 Caloric Restriction (CR)

CR has almost similar beneficial effects on health as that mediated through IF and leads to circadian clock plasticity by chromatin remodelling (Nakahata et al. 2007). CR can induce expression of brain-derived neurotrophic factor (BDNF) in the hippocampus, phosphorylation of cAMP response element-binding protein (CREB), dendritic spine density and transcription of BDNF (Whitmore et al. 2000; Eide et al. 2001; Etchegaray et al. 2006). CR not only reduces the risk of age-associated circadian dysfunction and disorders but also significantly impedes aging and enhances longevity (Taormina et al. 2014). When *Drosophila* was subjected to caloric restriction, expression of several clock genes showed increase in amplitude (Katewa et al. 2015). CR affects significantly the expression of several genes in both central clock-SCN and the peripheral clocklike the liver (Patel et al. 2016). The importance of meal timing by studies on α -MUPA mice have shown that reduced calories alone were not able to sustain rhythms unless feeding was spontaneously timed at night, or the day through a RF protocol. Further, to investigate the involvement of the circadian clock in impacting the metabolic activity and life span via CR, core clock gene knockouts were used (*Bmall* in mice and *Per* and *Timeless (Tim)* in *Drosophila*); circadian clock disruption along with multiple metabolic disorders and increased life span was noted in such experiments (Patel et al. 2016; Katewa et al. 2015). In mammals, CR mediates decline in blood IGF-1 level and the effect was compromised in mice deficient for BMAL1, an important circadian transcriptional factor. With CR, the diurnal activity and sleep pattern dampens in fruit flies as seen in humans with night sleep pattern. An overall diagrammatic representation of effects of different feeding regimens on aging and longevity has been summarised as Fig. 19.2.

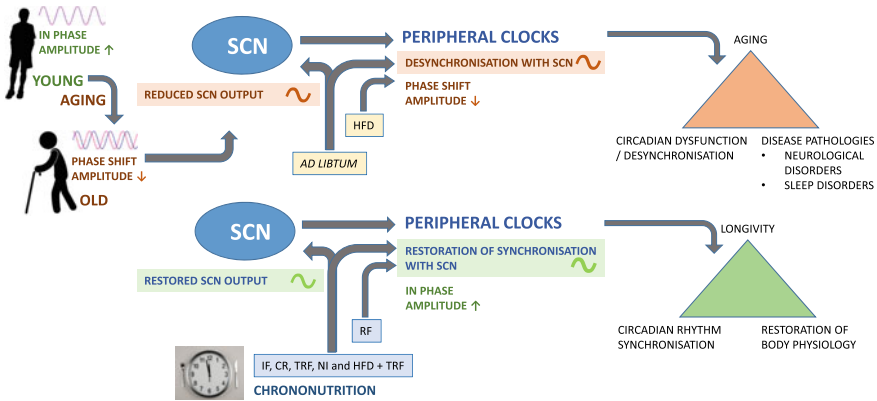


Fig 19.2 A diagrammatic representation of the effect of feeding regimens on aging and longevity through resetting of central and peripheral clock system. Intermittent fasting, caloric restriction, time restricted feeding, and high fat diet with TRF helps in resetting the circadian rhythms in both peripheral and the central clock systems but RF resets the rhythms only in the peripheral clocks

19.8 Nutritional Epigenetic: Aging and Clock

The nutritional modulation of the circadian clock has been reported to be linked with the epigenetic regulation of various clock genes. The modifications by sirtuins, a class III NAD⁺ dependent diet-sensitive histone deacetylase enzymes, are of vital importance to genome stability. *Sirt1* is believed to be a key epigenetic regulator protecting the mammals from events and consequences that ultimately lead to aging (Hudec et al. 2020). Higher *Silent information regulator 2* (*Sir2*; mammalian *Sirt1* equivalent) expression has been reported to extend the lifespan in *Drosophila melanogaster* and *Sirt1* knock-outs die young owing to developmental defects. Single nucleotide polymorphism (SNPs) gene variants for core clock genes have been implicated in age related disorders and individual dietary response in humans. Among the epigenetic mechanisms that control circadian rhythms, microRNAs are the least studied ones compared to SNPs and such studies can be a key to novel chrono-therapeutic interventions (Mico et al. 2016).

19.9 Conclusion

Dietary interventions are promising and easy-to-adapt strategies for the modulation and prevention of circadian dysfunction and senescence in humans of different ages. Recently, adjustment of caloric intake using different strategies like IF, PF and TRF have emerged as potential strategies towards treatment of metabolic syndromes like cardiovascular diseases, cancer and possibly neurodegenerative diseases etc. and helping in the synchronization of the circadian clock system. RF entrains peripheral

clocks suggesting their role via temporal food consumption, whereas, CR and IF appears to synchronize the central pacemaker in the SCN, suggesting their role by involving low calories intake in the entrainment of the central clock system. A direct relationship between feeding time and onset of chronic diseases such as obesity, breast cancer and inflammatory and metabolic disorders, neurological and sleep disorders explains that metabolic state is linked to sensitization in different parts of the brain, especially the hypothalamus and hippocampus, to maintain the coordination between the neuroendocrine system, metabolism, and energy balance. The CTS, thus influences and resets a wide variety of output systems like cellular and physiological systems to perform in a more synchronized manner hence maintaining the robust circadian rhythms using dietary interventions can ensure better tissue and body homeostasis and mediating aging attenuation and promoting longevity.

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Compliance with Ethical Standards

Conflict of Interest All authors declare they have no conflict of interest.

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