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REVIEW

Age-Related Changes in Circadian Rhythm and Association with Nutrition

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Abstract

Purpose of Review Considering the increase in life expectancy, there is a time-related decline in biological functions. Age-related changes are also observed in the circadian clock which directly leads to appropriate rhythms in the endocrine and metabolic pathways required for organism homeostasis. Circadian rhythms are affected by the sleep/wake cycle, environmental changes, and nutrition. The aim of this review is to show the relationship between age-related changes in circadian rhythms of physiological and molecular processes and nutritional differences in the elderly.

Recent Findings Nutrition is an environmental factor that is particularly effective on peripheral clocks. Age-related physiological changes have an impact on nutrient intake and circadian processes.

Summary Considering the known effects of amino acid and energy intakes on peripheral and circadian clocks, it is thought that the change in circadian clocks in aging may occur due to anorexia due to physiological changes.

Keywords Circadian rhythm · Nutrition in elderly · Age-related changes

Introduction

Organs and metabolic processes change with aging physiology, and this is the basis of many diseases [1]. Aging affects all aspects of physiology and conduct. With the increase in age, the circadian system undergoes significant changes, which include behavior, temperature regulation, and hormone release. These alterations are also correlated with the progression of age-related pathological processes [2, 3].

There are major rhythms in our daily lives that we are influenced by, such as ultradian, circannual, infradian, and circadian rhythms. The rhythms that have more than one cycle per day are called ultradian rhythms. Circannual rhythms are observed approximately once a year. Rhythms lasting more than 1 day (week/month) are also called infradian rhythms [4, 5]. Circadian rhythms last approximately 1 day. The term circadian is derived from Latin ("circa" means "about" and "dies" means "day") [6]. The most important biological rhythm is the circadian rhythm, which is under the control of the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus. Circadian rhythm is regulated by internal physiological systems which are also called biological clocks and is characterized by the changes in behavior, physiology, and metabolism that can be determined on a 24-h time scale [2, 6, 7]. Circadian rhythms play a vital role in health, and long-term deterioration in this rhythm has been associated with adverse health outcomes [2, 8, 9].

Metabolic homeostasis in the organism is synchronized with circadian rhythms. This synchronization is provided by hormones that manage metabolic processes in the organism such as growth hormone, cortisol, insulin, and melatonin [10]. Circadian rhythm changes, which are also related to advancing age, are early warning signs for neurodegenerative diseases such as Alzheimer's, Parkinson, and Huntington's; moreover, these changes play an important role in the etiology of metabolic diseases, chronic inflammation, and cancer [11–16]. The relationship between energy metabolism and circadian rhythm is like the "chicken or egg" paradox. It is stated that energy metabolism is regulated by circadian rhythms, and it is emphasized that environmental factors such as diet and physical activity are also effective on

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these rhythms [10]. On the other hand, circadian rhythms are effective in energy metabolism which affects nutrition [17]. For these reasons, nutritional problems caused by aging, the decrease in nutritional diversity, the alteration of feeding intervals, malnutrition, and other physiological processes may alter circadian clocks and gene expression [5, 6].

This review aims to examine age-related changes in circadian rhythms of physiological and molecular processes and their relationships with nutritional status in aging.

Cellular Basis of Circadian Rhythms

Circadian rhythms, an adaptive mechanism with light and dark cycles on earth, regulate the cellular processes and physiological functions of organisms in a 24-h period [1]. These rhythms have been detected in different organisms, from single-celled to mammals including humans. In mammals, almost all physiological systems, such as cardiovascular, nervous, digestive, and urinary systems, show circadian control and rhythms. The main circadian clock of mammals is SCN [18].

At the cellular level, the circadian clock contains a set of genes that regulate its transcription and translation for 24 h with a series of interactive negative feedback cycles. They consist of four genes/proteins called BMAL1, CLOCK, cryptochrome (CRY), and period (PER) basically [19]. CLOCK and BMAL1 are transcription factors, and PER and CRY are targets of these transcription factors. Heterodimers of the transcription factors BMAL1 and CLOCK allow the upregulation of the expression of many target genes. Among these, the protein products of the PER and CRY genes provide a feedback mechanism for the inhibition of the transcription activity of CLOCK and BMAL1. The circadian clock not only plays an important role in cell proliferation, DNA damage and repair mechanisms, apoptosis, and cancer but also regulates the expression and/or activation of enzymes and hormones involved in metabolism [7, 14, 19, 20].

It is reported that the circadian rhythm is provided not only by the SCN but also by the help of cell type-specific and autonomous oscillators found in almost all peripheral tissues. However, it should be noted that for the circadian clock to function rhythmically, the peripheral clocks including the SCN and the oscillator oscillation must work in harmony, because it is reported that the peripheral clocks affect the SCN and the SCN regulates the phases of the peripheral clocks [7, 21]. As a result, the circadian system is regulated by several environmental factors that affect the peripheral clocks and thus the SCN. Food intake, light exposure, sleep/wake cycle, and physical activity are examples of these environmental factors [18, 22•]. The sleep–wake cycle represents the dark–light cycle. In these cycles, SCN activation or inactivation can be achieved for the retina to absorb light and the rhythm of metabolism is regulated [18].

As mentioned, the oscillator released by the food intake is one of the circadian rhythms and this product constitutes the nutrient expectation activity 2–3 h before the planned feeding time. It has also been proposed that there are food-entrainable peripheral oscillators in the peripheral organs [23]. Circadian clock genes also play a role in the rhythm control of food/nutrient expectation activity. Mutations in the PER2 gene lead to a reduction in these rhythms [21]. Reports on the role of BMAL1 in the regulation of food/nutrient expectation activity are controversial. Studies have shown that downregulation of BMAL1 expression affects the formation of food/nutrient expectation activity [24, 25]; in contrast, other studies in the literature have reported no interference [26].

Age-Related Changes in Circadian Rhythms

Circadian rhythms deteriorate with increasing age due to many factors such as exposure to light and sleep patterns [27]. It has been shown in a study that SCN neurons and gene oscillations are not affected by increasing age [28]. On the other hand, intracellular connection disorder was detected in SCN of elderly individuals. In other words, even though the total number of neurons in the SCN remains the same, the number of neurons containing vasopressin, a binding factor for oscillators in the SCN, is decreasing [28, 29]. Impaired signaling with age is also observed in gamma hydroxybutyrate, an important neurotransmitter in SCN, resulting in changes in sleep patterns [30]. In response, a decrease in postsynaptic potentials occurs. This reduction in intercellular communication leads to neuronal desynchronization in SCN, which is accordingly considered a possible cause of the decrease in electrical activity in the SCN plexus and SCN outcomes [31, 32]. Decreasing electrical activity in SCN initiates a gradual effect. Reduction in both neuronal and humoral outcomes results in impaired coordination of peripheral oscillators [27]. Clock gene oscillation of peripheral clocks decreases with age. The labefaction of the intrinsic molecular clock may be the result of disruption of the temporal coordination of oscillators or a general physiological disorder associated with aging. The order of biological rhythms of an organism is determined by a combination of external factors and internal rhythms. Therefore, the timing of external factors plays an important role in the decrease of endogenous rhythms with age [2].

Sleep Patterns Changes Based on Aging

Shifts in chronotype and sleep cycles are among the most observed age-related changes in circadian rhythm. With

aging, the sleep pattern differs. Less total sleep time, less sleep activity, increased sleep latency, nighttime alertness, and excessive daytime sleepiness are observed [27, 33]. A cross-sectional study comparing the responses of older and younger adults to chronotype assessment tools found that individuals aged 60 years and older tended to go to bed earlier than adults in their 20 s and 30 s [33]. There are only a few longitudinal studies in which individual changes in age and chronotype have been observed in humans, and existing studies have found similar results to the cross-sectional study mentioned above [34–36]. In addition, nocturia and incontinence are frequently observed in elderly individuals [37]. It should also be underlined that nocturia can be observed more frequently in male elderly individuals due to prostate origin [38]. It is thought that these conditions that affect the sleep pattern may also contribute to the change of circadian rhythms in the elderly.

Sleeping and wakefulness are regulated by multiple brain regions, including the ventrolateral preoptic area (VLPO) in the anterior hypothalamus, hypocretin (orexin) neurons in the lateral hypothalamus, and locus coeruleus (LC) in the pony. VLPO contains inhibitory (galaninergic and GABAergic) neurons that are active during sleep, and lesions observed in VLPO cause deep sleep disturbance [18, 27]. Hypocretins are neuropeptides expressed in neurons that are most fueled during active awakening and silent during sleep. Activation of these neurons increases alertness. Since sleep is a strong circadian behavior, SCN is expected to regulate sleep and wakefulness in brain regions. Nonetheless, SCN rarely stimulates hypocretin neurons and directs them to the polysynaptic pathway. The nucleus of this polysynaptic pathway is the dorsomedial hypothalamus. Lesions in this region cause a decrease in circadian rhythms of sleep, alertness, nutrition, locomotor activity, and corticosteroid secretion [18].

Impaired sleep patterns and circadian rhythm changes are common in individuals with neurodegenerative disease. These changes play a role in the pathophysiology of Alzheimer's disease, Parkinson's disease, and also Huntington's disease, which is less common in elderly individuals [13]. Although the underlying pathophysiology is not clear, the hypothesis of Alzheimer's disease suggests that overproduction and accumulation of amyloid peptide B induce cascade effects that damage synapses and neurons, leading to the formation of neurofibrillary tangles containing tau protein [15]. The sleep–wake cycle was found to control the daily fluctuations of amyloid peptide B in the soluble interstitial fluid of the central nervous system. Thereby, it is concluded that the sleep–wake cycle can affect the amount of the related peptide in the soluble interstitial fluid [13, 15].

Relationship Between Nutritional Status and Circadian Processes in Elderly

Nutrition affects many physiological systems, including circadian hours. Peripheral clocks adapt to the changes in dietary plans [18, 21, 22•]. They may adapt more quickly than the liver, kidneys, lungs, or heart. Disorders in peripheral and central circadian hours cause changes in plasma glucose, triglyceride, and free fatty acid levels resembling the findings of metabolic syndrome [39]. Studies support the theory that peripheral clocks can be regulated by nutrition and that deterioration in circadian rhythms has a negative impact on health [21, 22•, 23–26].

High-fat diet, which is expressed as a Western diet, causes obesity and many metabolic changes and also affects peripheral and central circadian rhythms. Studies conducted in rats or humans were found that deterioration in circadian rhythm mainly included locomotor activity and nutritional behaviors, and decreased control rhythm expression in the circadian clock and liver control genes [24, 40]. As a result, a high-fat diet may adversely affect circadian clocks by increasing the plasma glucose levels, causing insulin resistance and many other metabolic changes [24].

Meal timing was found to have a significant effect on metabolic and physiological parameters. This finding suggests that not only the food content but also the timing of the food selection is important [41]. Nevertheless, it is not entirely clear whether there is an optimal time for food intake. Time-limited feeding was found to be effective on peripheral oscillators rather than central circadian oscillators [2]. In a study conducted in rodents, it was reported that restricted nutrition during the light phase of the day changed the expression phases of the circadian clock and clock-controlled genes in peripheral tissues, which did not affect the gene expression in the central clock (SCN). Gene expressions at the central clock were determined to be under the control of the light/dark cycle [42]. In another study, it was reported that time-restricted nutrition normalized the repetitive liver rhythms in the circadian clock gene expressions, and more importantly, metabolism and reduced obesity-related inflammation. It was also observed that metabolic outcomes improved without any reduction in food intake [43]. A pilot study in humans in which body weight reduction has been reported when obese individuals limit feeding times supports this data [44]. Contrary to these, there is also a study in the literature reporting that time-restricted nutrition does not affect circadian clocks but affects metabolic processes [45]. In this case, there is an inconsistency, and the long-term effects of time-restricted feeding are unknown.

Restriction of the total energy of the diet is used to examine food expectation activity. Energy restriction is known to

have multiple metabolic benefits. It has been suggested that it significantly retards aging and reduces the risk of age-related diseases, and it is effective in prolonging life expectancy [46]. Energy restriction has a significant effect on the expression of BMAL1, PER1, and PER2 genes, especially in the liver. Energy restriction was also reported to significantly affect the expression of several clock genes in SCN. That is, the energy constraint affects both central and peripheral clocks. In mammals, energy restriction mediates a decrease in plasma IGF-1 levels. This decrease affects BMAL1, a circadian transcriptional factor [47•, 48]. Although there is no conscious energy restriction in elderly individuals, it is concluded that the declines in energy intake due to chewing and deglutition with the decreased taste and smell sensations problems may also affect the circadian clock. After all, further research is needed to determine the optimal duration of nutrition and the effectiveness of time-restricted feeding, which is a factor in circadian rhythm in humans.

Feeding and fasting cycles cause many changes such as nutrient intake. Macro- and micronutrient concentrations in plasma and tissues change and hormone secretions are differentiated. The secretions of insulin, glucagon, growth hormone, and cortisol hormones involved in metabolism show the circadian rhythm [49]. Feeding causes an increase in plasma glucose, followed by insulin release from the pancreas. Insulin affects many tissues and organs, especially the liver and brain. It has been hypothesized that insulin is an effective factor in peripheral clocks. Insulin stimulates hepatocytes that affect the expression of the PER1, PER2, and DEC1 genes. Studies on cell level show that insulin injection changes the liver clock phase. This effect of insulin is tissue specific [50]. Yet, the circadian rhythm, which deteriorates due to aging, changes in insulin and contr-regulator hormone levels. BMAL1 affects pancreatic islet cells and plays a role in insulin production and secretion. The decrease in BMAL1 function with aging leads to impaired plasma glucose homeostasis. The degradation of CRY and PER peptides also contributes to this disorder [51].

Dietary protein has also been shown to affect circadian clocks. It has been found that the total amino acid level or some specific amino acids may affect the clock. For example, phosphorylation of the circadian clock transcription factor BMAL1 is performed by S6 kinase. This S6 kinase enzyme is a sub-target of mTORC1, and mTORC1 activity is regulated in the presence of growth factors including insulin and amino acid. Therefore, the rhythms mentioned in mTORC1 activity may be a result of amino acid concentrations [47•, 52, 53]. In a rat study in which the effect of amino acids on circadian rhythm was evaluated, an amino acid mixture containing all amino acids except asparagine and glutamine was infused into the jugular vein. As a result of the study, it was determined that the peak time of PER2 expression in the SCN and liver changed [54•]. It is thought that protein-energy malnutrition, which is frequently observed in elderly individuals, may contribute to changes in circadian clock function by decreasing amino acid levels.

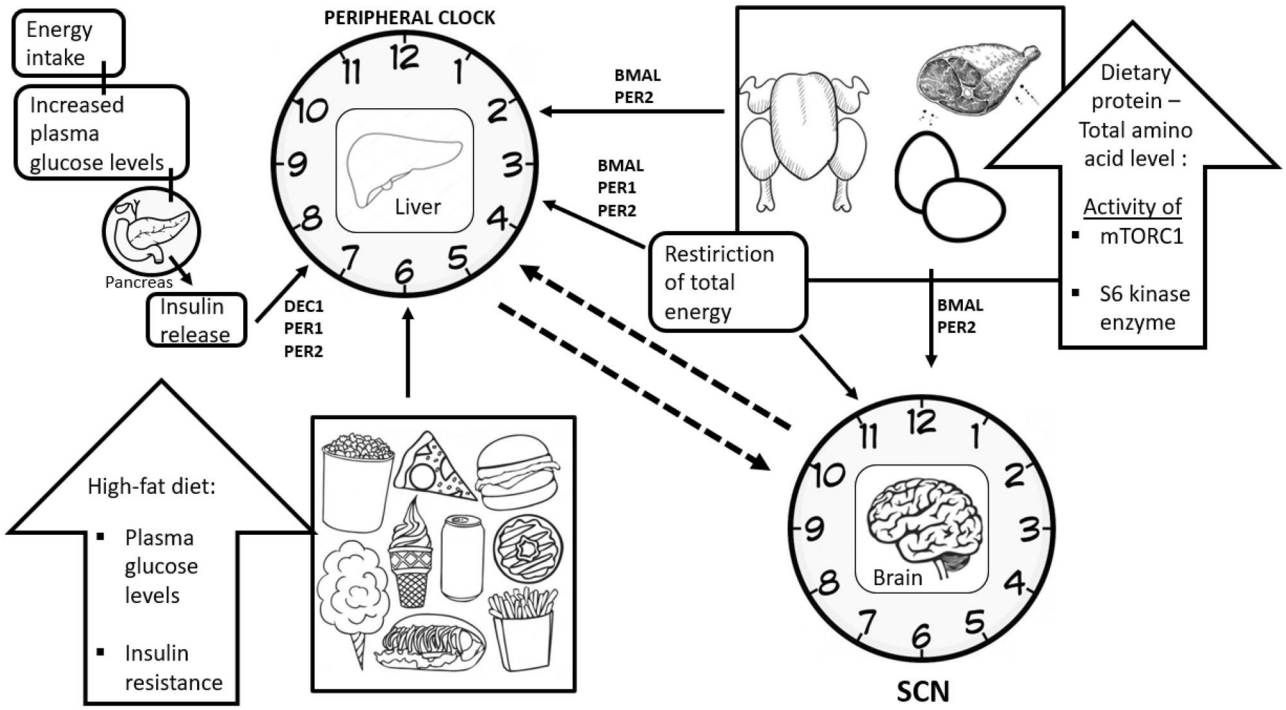


Fig. 1 Relationship between nutrition and peripheral and central circadian clocks

Recently, the efficacy of microbiota during the circadian clocks has been of interest [55]. The circadian clock in intestinal epithelial cells is responsible for glucocorticoid production, and endocrine control is provided from the pituitary-adrenal axis [56]. The circadian clock of intestinal epithelial cells is severely disrupted by the change of microbiota, which leads to changes in corticosteroid levels and consequent metabolic disorders [57]. The control herein is mediated by natural immune receptors TLRs and NOD2, which are expressed in intestinal epithelial cells and are under the circadian clock regulation. Therefore, changes in the microbiota composition induced by different feeding patterns regulate the circadian clock in the intestine in different ways [55, 58]. Microbiota contributes to homeostasis by determining the proper function of the intestinal clock. It should be noted that the decrease in food intake and diversity in elderly individuals may be a cause of the observed decrease in intestinal microbiota diversity, which may affect the circadian clock. All relationships are summarized in Fig. 1.

Conclusion and Recommendations

As a result, circadian rhythms, including central and peripheral clocks, are integral parts of human physiology. The irregular lifestyle (irregular meal hours, increase or decrease in daily energy intake and sleep irregularity, inappropriate light exposure, jetlag, and shift work) associated with modern society contributes to circadian rhythm disruption. Biological rhythms naturally decrease with age, which may contribute to the emergence of various age-related diseases. Physiological changes and sleep problems caused by aging may adversely affect biological rhythms. Decreases in the release of neurotransmitters affected by advancing age led to neuronal desynchronization, resulting in disruption in circadian rhythms.

Nutrition is an environmental factor that is particularly effective on peripheral clocks. Peripheral clocks provide the circadian expression of specific genes involved in various physiological functions in each of their respective tissues and play an integrative and unique role. Differences in nutritional patterns and timing can also affect circadian hours by changing hormone releases. It is stated that nutrients, especially amino acids, change gene expression in circadian hours. The energy restriction also contributes to this decline by changing the central and peripheral clockwork. It is thought that anorexia, which is encountered due to physiological changes, especially in old age, may affect circadian hours by causing a decrease in energy intake.

Disorders in circadian rhythms affect many physiological processes and increase the risk for non-communicable chronic diseases such as metabolic syndrome, diabetes, cardiovascular diseases, and cancer. It is thought to be promising to provide circadian rhythm regulation in preventing diseases that increase with the incidence of increasing age in humans. However, more research is needed to clarify the regulation processes by identifying the nutritional pathways of circadian clocks.

Author Contribution Şerife Akpinar: research, writing—original draft, visualization, writing review and editing; Nilüfer Acar Tek: supervision, writing review and editing.

Declarations

Conflict of Interest The authors do not have any potential conflicts of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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