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REVIEW

Fasting helps nutrient sensing systems in clocking the metabolism

Neelu Jain Gupta[a,*]

[a] *Department of Zoology, Chaudhary Charan Singh University, Meerut, UP, India.*

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Abstract

Mankind is predisposed to metabolic syndromes (MetS) by its modern lifestyle. After middle age, metabolic homeostasis (MetH) consistently declines. Besides age-related pathophysiological changes, such as decline in tissue coordination and function, modifiable lifestyle factors also predispose to aging, causing disease conditions. Lifestyle choices such as erratic eating habits, reduced physical activity, smoking, alcohol intake, and erratic sleep patterns increase the risk of metabolic syndromes. These modifiable lifestyle factors operate through circadian rhythm disruption. Circadian rhythms, at the cellular level, are the gene networks with transcriptional and translational feedback loops that drive the rhythmic expression of physiological processes, aligning intracellular metabolism and organismal immunometabolism. Further, nutrient sensing systems (NSS) mediates the alignment of metabolic pathways, being central in aging control mechanisms. Recent research has shown circadian oscillations of the mammalian target of rapamycin (mTOR) complex function, as an important NSS intermediate. Autophagy stimulates NSS, including mTOR, IGF, AMPK and sirtuins, thereby preventing the negative effects of aging. The potential of intermittent fasting as a circadian health regimen and its role in promoting autophagy is highlighted in this review. It is suggested that the improvement of longevity through sustained adherence to intermittent fasting in humans, also depends on individual compliance. Therefore, global studies are needed to enhance the current understanding of the molecular underpinnings of intermittent fasting on autophagy, inflammasomes, and senescence in humans.

Keywords: Metabolic homeostasis, nutrient sensing system, intermittent fasting, mTOR, aging, lifestyle, time restricted feeding

Introduction

Plasticity in metabolic homeostasis (MetH) varies with age in humans. As a term, plasticity in metabolic homeostasis encompasses the balance of all bodily pathways, from downstream events (molecular or cellular) to expressions (physiology, behavior, *etc*.) [1]. The amount of metabolic energy we consume during our lifetime follows a bell-shaped curve. Total daily energy consumption grows exponentially from newborn to early adulthood, rises steadily until middle age, stabilizes until the 60s, and then begins to decline in the elderly [2]. Few predictors, such as early obesity or sedentary middle age, can alter the pattern of MetH plasticity [3], and chronic persistence predisposes to disease risk. A study by Dall and Færgeman, 2019 found an association between cellular metabolic decline and cognitive decline in older adults [4]. In addition, lifestyle has emerged in recent decades as an important trigger of metabolic dysregulation, and this has been the subject of studies to elucidate the molecular mechanism of age-related metabolic dysregulation. This review discusses aging and how some lifestyle choices exacerbate age-related diseases. Recovery of circadian rhythm has been successfully achieved by fasting. Identification of putative downstream pathways that require further investigation is essential to understanding the mechanisms behind circadian rhythm and health. These observations underscore the importance of early intervention to maintain metabolic health.

* Corresponding author: Neelu Jain Gupta
Mailing address: Department of Zoology, Chaudhary Charan Singh University, Meerut, UP, India.
Email address: drneelujgupta@hotmail.com
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Aging

Aging is characterized by a decline in physiological function and an increased risk of mortality due to loss of MetH maintenance over time. The relationship between increasing body mass index and human aging cannot be overemphasized. Age-related changes in visceral adipose tissue in the intra-abdominal region and myosteatosis with ectopic fat in the muscles exacerbate sarcopenia [5], which reduces physical function and leads to inactivity. This leads to an imbalance in mitochondrial activity at the tissue level, which increases the production of reactive oxygen species (ROS) and causes lipotoxicity [6-8]. Adipose tissue atrophy, insulin resistance, hyperlipidemia, and the production of pro-inflammatory cytokines from muscle are further consequences of visceral obesity. These age-related changes in body composition are usually associated with impaired glucose tolerance and insulin sensitivity. Insulin resistance, changes in body composition, and physiological reductions in growth hormone, insulin-like growth factor 1 (IGF-1), and sex hormones are examples of metabolic indicators of aging. In addition, insulin resistance is associated with an increased risk of colon, liver, and pancreatic cancer. Insulin resistance and increased body mass are important risk factors for type 2 diabetes, heart attack, and stroke.

Aging and metabolic syndromes

Potentially modifiable risk factors that confound with age-related comorbidities can be grouped into 1) lifestyle, 2) metabolic, and 3) socioeconomic factors. Aging and insulin resistance are directly influenced by lifestyle factors such as dietary habits, body fat percentage, level of physical activity, alcohol consumption, and smoking behavior [9]. According to Vajdi *et al*., the need for Iranian individuals to maintain a healthy lifestyle is correlated with normoglycemia and normal triglyceride levels [10]. Age and lifestyle factors, as important age determinants, can be separated by sex when it comes to long-term comorbidities [11]. A study in Canada, collected nationwide data to confirm the incidence of at least one major chronic disease such as hypertension, COPD, diabetes, lung cancer before death, in older people [11, 12]. Lifestyle choices such as irregular eating habits, reduced physical activity, smoking, alcohol consumption, and irregular sleep patterns can cause the body's metabolic pathways to become misaligned, increasing the risk of metabolic syndrome (MetS). Age-related pathophysiological effects of biochemical imbalance include a decline in tissue coordination and function. These effects are progressive and irreversible. Therefore, it's critical to understand the relationship between metabolic processes and disease outcomes to treat age-related MetS. Endocrine functions and the regulation of tissue processes have been linked. For instance, exercise-stimulated myokines can control the breakdown of adipose tissue, delaying inflammation and browning that would otherwise be exacerbated by obesity [13]. According to Fang *et al*., who investigated the processes underlying the crosstalk between adipose tissue and muscle in age-related diseases, adipokines, myokines, and interleukin-6 (IL-6) are essential for maintaining the body's metabolic equilibrium in age-related MetS [14]. In children, family socioeconomic status was found to be associated with comorbidity clustering of age-related disease risk variables with chronic kidney disease in healthy adult samples [15]. Taken together, age-specific risk factors for a variety of comorbidities need to be prioritized to alleviate severe health problems, particularly non-communicable chronic diseases that may worsen in the elderly population.

Aging, circadian dysregulation and metabolic syndromes

Sleep patterns change with age. Worldwide, wake delay is considered an obvious indicator of aging. The number of non-REM bouts, deeper or slow-wave sleep stages decreases in adults in their 50s [16]. Heart, kidney, and liver disease predispose to inadequate sleep duration and quality. Digitalization exacerbates this by exposing people to more blue light emitting devices. Overuse of mobile devices is a major concern. Human melatonin levels, secreted by the pineal gland in the brain and a biomarker of sleep, can be directly measured to determine sleep duration and quality. Its levels rise and peak in the evening and fall in the morning in healthy individuals. Circadian physiology is dysregulated by melatonin suppression and vice versa. Elevated melatonin levels are associated with the antioxidant and restorative benefits of sleep, including improved brain function and metabolite clearance. The suprachiasmatic nucleus (SCN), a major pacemaker in the hypothalamus and the main synchronizer of the circadian mechanism, regulates the release of melatonin by the pineal gland. Light-dark cycles control circadian functions through melatonin feedback on the SCN. By detecting ambient light, the SCN improves the brain's temporal program. It also controls body temperature, eating habits, sleep/wake cycles, neuroendocrine, autonomic, and other metabolic processes. According to Saper *et al*. and Zisapel, the SCN functions as a multistep processor that responds to environmental inputs and synchronizes with clock signals to regulate daily rhythms of physiological and behavioral activity [17, 18]. Many impairments in downstream autonomic outputs, regardless of age or comorbidity, are often related to altered circadian timing resulting from unstable signaling between circadian function and metabolic nuclei in the brain [19, 20].

Age-related neuroanatomical changes and aging of other organs involved in maintaining circadian rhythms can be interpreted as a disruption of the underlying clock gene machinery. The transcriptional and translational feedback loops that drive the expression of clock-controlled genes are these cellular gene networks, referred to as cell autonomous clocks [21, 22]. Daily waveforms with measurable characteristics such as amplitude and period are known

as circadian rhythms. These elements of the daily pattern of clock-driven gene expression have been thoroughly examined practically in every animal model organism, including mice and cyanobacteria. Core clock proteins in mice, including BMAL1, CLOCK, NPAS2, PER1, PER2, CRY1, CRY2, and REV-ERBs, bind to over a thousand locations in the mouse genome [23], and thousands of transcripts oscillate daily, indicating a possible role for circadian rhythms in most bodily processes [24]. In the current decade, there has been interest in the role that clock genes play in both immunometabolism and intracellular metabolism. For instance, BMAL1, a core clock transcription factor, targets macrophage inflammatory response while also interacting with other physiological processes. BMAL1 regulates glucose flux via glycolysis and the Krebs cycle, and its impact on succinate levels influences the synthesis of IL-1β. BMAL1 influences the levels of PKM2, a glycolytic enzyme that triggers STAT3, which in turn controls the expression of IL-1β mRNA. The pro-inflammatory cytokine IL-1β levels indicate that macrophages have undergone a particular metabolic reprogramming. According to Timmons *et al*., BMAL1 functions as a cellular metabolic sensor in macrophages [25]. In the absence of BMAL1, the cell undergoes enhanced cytoplasmic glycolysis and mitochondrial respiration, which intensifies pro-inflammatory responses [24-26]. These findings have chronotherapeutic implications.

Besides carbohydrate metabolism, circadian rhythms are involved in the temporal consolidation of protein homeostasis (proteostasis). The latter is a highly controlled process involving proper protein folding, transport, and degradation and is managed by chaperones. The oscillations of the mammalian target of rapamycin (mTOR) complex have been used by Stangherlin and colleagues to explain circadian cell physiology [27]. Notably, MetH involves several different food absorption pathways (Figure 1), one of which is mTOR-mediated. According to Boutouja *et al*., targeted mTOR activity inhibition is a viable molecular target to reduce comorbidities and may slow the aging process [28]. mTOR regulates cellular metabolism by activating signaling cascades in response to nutrient availability, thereby modulating cellular functions such as proliferation, secretion, and autophagy.

Aging and nutrient-sensing systems

Nutrient sensing by the mammalian target of rapamycin complex 1 (mTORC1) is a critical determinant of cellular and organismal aging. Among the four nutrient-sensing systems (NSS), mTORC1 plays a crucial role. The other three are IGF, AMP-activated protein kinase (AMPK) and sirtuins. The gastrointestinal tract lining's chemosensory secretory epithelial cells or NSS, are crucial for nutrient absorption [29]. Fasting is a subtle example of how energetic cell sensors that are essential to a cell's MetH function [30]. According to Zhang, the liver maintains blood glucose levels during fasting, hence regulating metabolic pathways, including gluconeogenesis [31]. However, MetS may result from an imbalance between cellular energy demand and nutrient availability. This directly highlights the need to understand the rhythmic mechanisms by which cells determine nutrient availability and energy demand [32].

Members of the sirtuin family are significant nutrient-sensing molecules that play a role in the regulation of the circadian clock by the liver (peripheral circadian clock) and the brain (central circadian clock). Nicotinamide phosphoribosyltransferase (NAMPT) is one of the circadian genes whose transcription is driven by the core clock transcriptional machinery controlled by CLOCK and BMAL1. This transcriptional process results in oscillating levels of NAD^+ in the SCN and ventromedial hypothalamus, which depend on NAD^+-dependent SIRT1 activity in the brain for circadian function. SIRT1, SIRT3, and SIRT6 play a role in metabolic control and circadian transcription

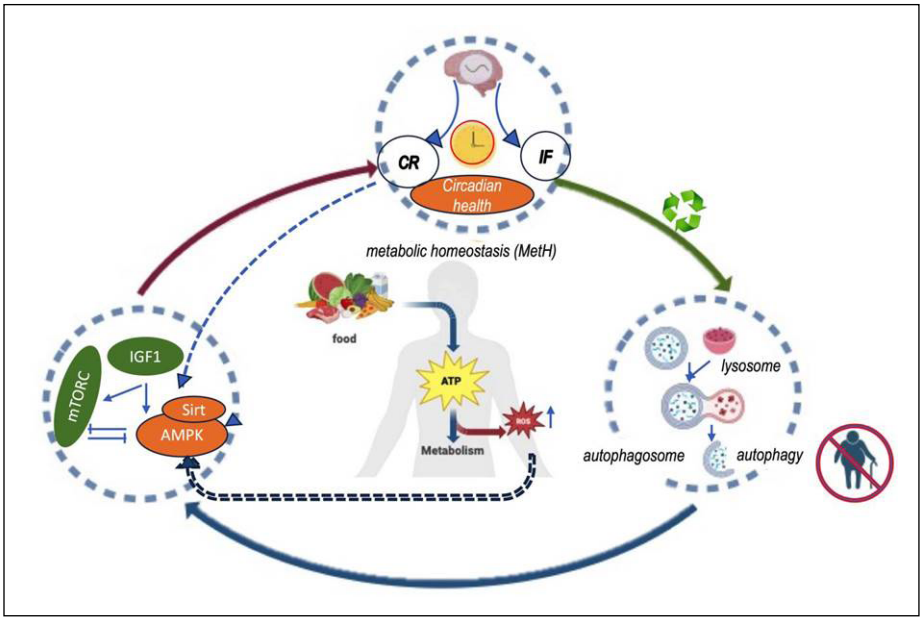

Figure 1. Metabolic homeostasis (MetH) and role of metabolic communication in healthy aging: Circadian regimens like intermittent fasting (IF) and caloric restriction (CR) restore circadian health, by stimulating autophagy. The latter crosstalk's with nutrient-sensing signaling. Autophagy via autophagosome, recycles the breakdown products of cell and improves cellular metabolism through nutrient sensing system, *i.e.* AMPK, insulin/IGF and mTORC signaling.

in the liver [33].

AMPK is next to sirtuins acting as an energy sensor in the cell. It is triggered when the body's energy reserves are depleted and either speeds up the breakdown of proteins or conserves ATP by blocking certain biosynthetic processes. By controlling the stimulation of food intake and synchronizing circadian rhythms of metabolism, AMPK regulates MetH. By controlling non-metabolic processes such as the cell cycle and neuronal membrane excitability, AMPK also keeps cellular ATP levels stable [34]. The interaction between AMPK and sirtuins vary depending on the tissue. SIRT6 regulates MetH in skeletal muscle through activation of AMPK, demonstrating the interconnectivity of these pathways [35].

The activity of insulin-like growth factor 1(IGF-1) is comparable to that of insulin in humans, according to research on the metabolism of amino acids, fats, and carbohydrates. Insulin and IGF-1 work in tandem to regulate MetH. Eating causes a rise in insulin level in blood, which raises free IGF-1. The liver secretes IGF-1 and the pancreatic islets secrete insulin. IGF-1 supports normal cell growth and development in healthy individuals. Although the structures of IGF-1 and insulin are similar, both low and high serum concentrations of IGF-1 increase the risk of developing insulin resistance, even in those without a history of growth hormone-related disorders [36]. Experiments in mice have suggested that the similar function of IGF-1 and insulin is mediated by decrease in plasma glucose levels and inhibition of gluconeogenesis in the liver. Decrease in IGF-1 and insulin signaling can delay aging and increase lifespan in mammals [37, 38]. Secretion of growth hormone, and consequently IGF-1, declines over time until only low levels can be detected in individuals aged ≥ 60 years [39]. This is further supported by the role of IGF-1 in the regulation of the growth hormone axis, which controls somatic growth and metabolic homeostasis [40]. Declining IGF-1 levels during aging may contribute to brain senescence in mammals [41]. Serum IGF-1 increases adult neurogenesis, sustains neuronal health through a variety of fundamental homeostatic mechanisms, participates in brain angiogenesis, contributes to brain β-amyloid clearance and affects learning and memory. Overall, diminished trophic input resulting from decreasing serum IGF-1 levels during aging likely contributes to brain senescence, but its role in humans remains to be explored.

The relationship between insulin signaling and IGF-1 is referred to as the "insulin and IGF-1 signaling" (IIS) pathway. The somatotrophic axis in mammals consists of growth hormone, which is produced by the anterior pituitary gland, and its secondary mediator, IGF-1, which is produced in response to growth hormone by a variety of cell types, most notably hepatocytes. As previously mentioned, both IGF-1 and insulin use the same intracellular signaling mechanism in response to glucose levels in the body. Interestingly, the most advanced aging control system is the IIS pathway. The FOXO family of transcription factors and the mTOR complexes are also associated with aging and have evolved through evolution, as shown by studies in *C. elegans* models [42].

The age-controlling role of IIS is channeled through multiple processes in mTORC1-regulated pathways, which consummate into a coordinated pro-longevity effect [43]. mTORC1 actively promotes mitochondrial biogenesis and metabolism through PPARγ co-activator 1α (PGC-1α) and the transcription factor, and even promotes HIF-1 to activate glycolytic flux, which downregulates mitochondrial oxygen consumption and reduces reactive oxygen species (ROS) [44]. In addition, SIRT1 can deacetylate and activate PGC-1α [45]. PGC-1α orchestrates a complex metabolic response that includes mitochondriogenesis, enhanced antioxidant defenses, and improved fatty acid oxidation [46]. Moreover, SIRT1 and AMPK can engage in a positive feedback loop, linking both low-energy state sensors into a unified response [47].

Under conditions that favor an individual's growth, mTORC1 promotes mRNA translation and protein synthesis, acting as a determinant of proteastasis [48]. During aging, there is a reduction in mRNA translation, affecting the endogenous protein repair machinery, which is appended by protein aggregation and ROS generated in various metabolic pathways [49].

Aging, mammalian target of rapamycin and autophagy

Numerous trophic and anabolic pathways in the body act as significant accelerators of aging and are mediated by the IIS or mTORC1 pathway. In recent years, autophagy has emerged as a critical mTORC1-regulated mechanism that prevents the negative effects of aging. Dead organelles and damaged cell cycle intermediates are removed from the cytoplasm by autophagy. Age-related cellular dysfunction is encouraged by a decrease in autophagic degradation capacity [50]. Activation of autophagy enhances the breakdown of aged cellular components by inhibiting mTORC1. Disease mitigation in non-communicable chronic diseases such as cancer, diabetes, cardiovascular disease, and neurodegenerative diseases is a diverse relationship between autophagy and these conditions [51]. There is increasing evidence that mTORC1 plays a central role in this process and that inhibition of mTORC1 can preserve and perhaps even rejuvenate stem cells. The complexity of the mTOR network presents a hurdle in defining the mechanistic details of how mTOR influences longevity and health span.

Erlangga have shown molecular signatures of prolonged intermittent fasting on autophagy, inflammasomes and senescence in healthy young men to suggest a mechanistic explanation to enhance longevity by long-term compliance to intermittent fasting, which induces autophagy and reduces body inflammation [52]. Autophagy and senescence-related genes were measured in the blood of 25 healthy young men who fasted 17–19 h/day for 30 days. Gene expression levels of autophagy genes (ATG5, ULK1, and BECN1), inflammasomes (NLRP3, IL-1 β, ASC, and TNF- α), and senescence markers ($p16^{INK4A}$, p21, and p53) were measured to suggest that prolonged

intermittent fasting affects the activities of autophagy, inflammasomes, and senescence in a time-dependent manner.

Fasting invigorates metabolic efficiency by inducing NSS

Voluntary abstention from food and drink throughout intervals of time is known as "intermittent fasting". With its age-old significance as a social observation in many countries, initial experiments in mice showed the relevance of intermittent fasting in MetH [53]. Worldwide longitudinal studies on eating habits and sleep deprivation revealed circadian disruption in digitized societies [54-56]. The increase in comorbidities due to circadian disruption highlighted the significance of fasting. Landsberg showed that fasting suppresses the sympathetic nervous system [57], while Naïmi and Wijngaarden both highlighted the role of energetic cell sensors in translating the energy state of the cell into distinct metabolic programs during fasting [58, 59].

Most fasting regimens are designed to induce autophagy and increase metabolic efficiency by inducing NSS. Time-restricted feeding (TRF) is a daily fasting regimen that limits the duration of feeding to a specific period of the day followed by a period of fasting, compliance with which reduces the burden of MetS [60, 61]. TRF improves cardiometabolic health and delays aging [62-65]. The improvement in insulin sensitivity resulting from TRF has a molecular basis in the alignment of molecular circadian clocks with daily behaviors and physiological readjustments such as energy intake from food, activity, rest, sleep, *etc*. Basically, TRF synchronizes the daily rhythm of organs, also known as the peripheral circadian clock. Food restriction modulates the daily rhythm of the peripheral clock and clock-controlled genes in peripheral organs viz. liver, adipose tissue, and muscle to align with the core clock of the SCN. In particular, food restriction plays an essential role in modulating the peripheral circadian clock in the liver [66]. In mice, TRF can also activate the fasting-sensitive protein kinase AMPK by increasing AMP levels [67].

Conclusions

Most intermittent fasting regimens improve circadian health, although compliance with regulated eating and sleeping schedules is key. Imperatively, these are differentially but effectively implicated in delaying aging. It is suggested that the role of circadian health outcomes in inhibiting a number of hallmarks of senescence and aging at the organismal and cellular levels cannot be underestimated. In the current scenario, animal experiments clearly suggest the potential effects of TRF by modulating nutrient sensing, promoting proteostasis, and maintaining stem cell function. Therefore, future research provides avenues for pan-global studies to elucidate the molecular basis of intermittent fasting on autophagy, inflammasomes, and senescence in humans.

Declarations

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