**Fasting helps nutrient sensing systems in clocking the metabolism**

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Abstract

Mankind is predisposed to metabolic syndromes (MetS) by modern lifestyle. After middle age, metabolic homeostasis consistently declines. Adverse effects of early obesity, sedentary lifestyle, and continuous ambient light conditions on metabolic homeostatic (MetH) plasticity are invariably observed. Age-related pathophysiological effects of the biochemical misalignment with a decline in tissue coordination and functioning, is a natural process, but lifestyle driven chronic circadian rhythm disruption prepones aging causing disease conditions. Molecular explanation of circadian rhythms, is a cellular gene network with transcriptional and translational feedback loops, that drives rhythmic expression of physiological processes, aligning intracellular metabolism and organismal immunometabolism. For example, absence of core clock gene, BMAL1, a cellular metabolic sensor in macrophages, intensifies pro-inflammatory responses. Just as circadian genes are implicated in rhythm regulation, nutrient sensing systems (NSS) mediate 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, sirtuins and prevents the negative effects of aging. Intermittent fasting promotes autophagy. There are several longitudinal studies on human eating patterns and shortness of sleep, but much of the mechanistic details are available from studies on model organisms including mice. There is dire need for assessing molecular underpinnings of intermittent fasting on autophagy, inflammasomes and senescence in human beings. This would provide mechanistic explanation to processes like body inflammation reduction and longevity enhancement by long-term compliance to intermittent fasting.

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

**Introduction**

Plasticity in metabolic homeostasis (MetH) varies with age in human beings. As a term, metabolic homeostasis plasticity encompasses balance of all bodily pathways, extending from downstream events (molecular or cellular) to expressions (physiology, behaviour etc.) [1]. The amount of metabolic energy that we use during our lifetime follows a bell-shaped curve. Total daily energy consumption grows exponentially from new-born to early adulthood, steadily climbs until middle age, stabilizes until 60’s, and then starts to fall in elderly persons [2]. Few predictors such as early obesity or sedentary middle age may alter the pattern of MetH plasticity [3] and chronic continuance predisposes to disease risk factor. A study by Dall and Færgeman, 2019 found a connection between cellular metabolic decline and cognitive decline experienced by older adults [4]. Moreover, lifestyle has emerged as an important trigger for metabolic disruption in recent decades, and this has been the subject of studies clarifying the molecular mechanism of age-related metabolic disruption. This review discusses aging and how some lifestyle decisions make age-related illnesses worse. Regaining circadian rhythm has been successfully achieved through fasting. Finding putative downstream pathways that need further investigation is essential for understanding the mechanics behind circadian rhythm and health. These observations emphasize how important early intervention is to preserve metabolic health.

**Aging**

Aging is characterized by a decline in physiological functions and a rise in mortality risk brought on by a loss in MetH maintenance throughout time. The link between rising body mass index and aging in humans, cannot be overemphasized. Aging-related changes in visceral fat tissue in the intra-abdominal region and myosteatosis with ectopic fat in muscles worsen sarcopenia [5], which reduces body functionalism and leads to inactivity. This causes a misalignment in mitochondrial activity at the tissue level, which raises 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 muscles are further consequences of visceral obesity. These age-related changes in body composition are usually associated with impairments in glucose tolerance and insulin sensitivity. Insulin resistance, alterations 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. Moreover, insulin resistance is linked to an increased risk of colon, liver, and pancreatic cancer. Insulin resistance and increased body mass are important risk factors for type 2 diabetes, heart attacks, 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 impacted by lifestyle factors such as eating patterns, body fat percentage, degree of physical activity, alcohol consumption and smoking behaviors [9]. According to Vajdi *et al*., 2023 the requirement 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 segregated by sex, when it comes to long-term comorbidities [11]. A study in Canada, collected nationwide data, to reaffirm incidence of at least one major chronic disease such as hypertension, COPD, diabetes, lung cancer before death, in aged people [11,12]. Lifestyle choices such as erratic eating habits, reduced physical activity, smoking, alcohol intake, and erratic sleep patterns can cause the body's metabolic pathways to become misaligned, which increases the risk of metabolic syndromes (MetS). Age-related pathophysiological effects of the biochemical misalignment include a decline in tissue coordination and functioning. These effects are progressive and irreversible. Therefore, it's critical to comprehend the relationship between metabolic processes and disease outcomes to treat age-related MetS. Endocrine functions and tissue process regulation have been linked. For instance, exercise-stimulated myokines can control the breakdown of adipose tissue, delaying inflammation and browning that obesity would otherwise exacerbate [13]. According to Fang *et al*., 2023 who have examined the processes underlying the crosstalk between adipose tissue and muscle in age-related illnesses, adipokines, myokines, and interleukin-6 (IL-6) are essential for preserving the body's metabolic equilibrium in age-related MetS [14]. In children, the socioeconomic status of family was found to be associated with comorbidity clustering of age-related disease risk variables with chronic kidney disease in healthy adult samples [15]. All things considered, age-specific risk factors for a variety of comorbidities need to be given priority in order to alleviate severe health issues, particularly non-communicable chronic illnesses, which may worsen in the elderly population.

**Aging, Circadian Dysregulation and Metabolic Syndromes**

Sleep pattern changes with age. Worldwide, wake time preponement is seen as an obvious indicator of aging. The number of non-REM bouts, deeper or slow wave stages of sleep, decreases in adults in their 50s [16]. Heart, kidney, and liver disorders are predisposed by inadequate sleep duration and quality. Digitalization makes this worse by exposing people to more blue-light emitting devices. Overuse of mobile devices is one of the most significant issues. Human melatonin level, which is secreted by the pineal gland in the brain and is a biomarker of sleep, can be measured directly to determine the length and quality of sleep. Its level in healthy persons rise and peak in the evening and fall in the morning. Circadian physiology is dysregulated by melatonin suppression and vice versa. Elevated melatonin levels are associated with 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 pineal gland's release of melatonin. Light-dark cycles control circadian functions because of melatonin feedback on the SCN. By detecting ambient light, the SCN improves the brain's temporal program. It also controls the body temperature, eating habit, sleep/wake cycle, neuroendocrine, autonomic, and other metabolic processes. According to Saper *et al*., 2005 and Zisapel, 2018 SCN functions as a multistage processor that responds to environmental inputs and synchronizes with clock signals to regulate daily rhythms of physiological and behavioral activity [17,18]. Many detriments in downstream autonomic nervous outputs, irrespective of age consequence or comorbid condition, often relate to altered circadian timing disorders, resulting from instable signalling between circadian function and metabolic nuclei in the brain [19,20].

Age-related neuroanatomical changes and aging in other organs involved in maintaining circadian rhythms, can be interpreted by disruption in underlying clock gene machinery. The transcriptional and translational feedback loops that drive the expression of clock-controlled genes are these cellular gene networks, which are referred to as cell autonomous clocks [21,22]. Daily waveforms with measurable characteristics like amplitude and period are known as circadian rhythms. These elements of the daily pattern of clock-controlled genes 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 the flow of glucose via glycolysis and the Krebs cycle , and its impact on succinate level 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*., 2021 BMAL1 functions as a cellular metabolic sensor in macrophages [25]. When BMAL1 is lacking, the cell undergoes enhanced cytoplasmic glycolysis and mitochondrial respiration, which intensifies pro-inflammatory responses [24-26]. These findings have chrono-therapeutic implications.

Besides carbohydrate metabolism circadian rhythms are involved in temporal consolidation of protein homeostasis (proteostasis). The latter is a highly controlled process that involves 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, one of which is mTOR mediated. According to Boutouja *et al*., 2019 targeted mTOR activity inhibition is a viable molecular target to reduce comorbidities and may slow down the aging process [28]. mTOR regulates cellular metabolism by activating signalling cascades in response to nutrient availability, modulating cellular functions like proliferation, secretion, and autophagy.

**Aging and Nutrient-Sensing Systems**

Nutrient sensing by mammalian target of rapamycin complex 1 (mTORC1) is a critical determinant of cellular and organismal aging. Of the four nutrient-sensing systems (NSS), mTORC1 has 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 nutritional absorption [29]. Fasting is a subtle example of how energetic cell sensors, which are essential to a cell's MetH, function [30]. According to Zhang, 2019 the liver maintains blood glucose levels during fasting, hence regulating metabolic pathways, including gluconeogenesis [31]. However, MetS can arise from an imbalance between cellular energy demand and nutrient availability. This directly highlights the need of understanding 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 through the liver (peripheral circadian clock) and brain (central circadian clock,). Nicotinamide phosphoribosyltransferase (NAMPT) is one of the circadian genes whose transcription is driven by the core clock transcriptional machinery, which is controlled by CLOCK and BMAL1. This transcription process causes oscillating levels of NAD+. SCN and ventromedial hypothalamus depends on NAD+-dependent SIRT1 activity in the brain for circadian function. SIRT1, SIRT3, and SIRT6 play a role in metabolic control and circadian transcription in the liver [33].

AMPK is next to sirtuins acting as an energy sensor inside the cell. It is triggered when the body's energy reserves are depleted, and it 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 the activation of AMPK, demonstrating the interconnectivity of these pathways [35].

Insulin-like growth factor I (IGF-1) activity is comparable to insulin in humans, according to research on the metabolism of amino acids, fats, and carbohydrates. Insulin and IGF-I work in tandem to regulate MetH. Eating causes a rise in insulin level in blood, which raises free IGF-I. The liver secretes IGF-I, and the pancreatic islets secrete insulin. IGF-1 aids in normal cell growth and development in healthy persons. Although the structures of IGF-I and insulin are similar, both low and high serum concentrations of IGF-I increase the risk of developing insulin resistance, even in those without a history of growth hormone-related illnesses [36]. Experiments on mice have suggested that the similar functioning of IGF-1 and insulin is mediated by decrease in plasma glucose levels and inhibition of gluconeogenesis in liver. Decrease in IGF-1 and insulin signalling can delay aging and increase lifespan in mammals [37,38]. Secretion of growth hormone, and consequently that of 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-I 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-I levels during aging likely contributes to brain senescence, but its role in humans is not yet explored.

The relationship between insulin signalling and IGF-1 is referred to as the "insulin and IGF-1 signalling" (IIS) pathway. The somatotrophic axis in mammals is composed of the growth hormone, which is produced by the anterior pituitary, 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, in reaction to the body's glucose levels, both IGF-1 and insulin use the same intracellular signalling mechanism. Interestingly, the most advanced aging-controlling system is the IIS pathway. The transcription factors FOXO family and mTOR complexes, which are also linked to aging and have evolved through evolution, as shown by studies from C. elegans [42] to knocked out mice models.

Age controlling role of IIS is channelised 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 [44] to activate glycolytic flux that downregulates mitochondrial oxygen consumption, reducing reactive oxygen species (ROS). In addition, SIRT1 can deacetylate and activate the PGC-1α [45]. PGC-1α orchestrates a complex metabolic response that includes mitochondriogenesis, enhanced anti-oxidant defenses, and improved fatty acid oxidation [46]. Moreover, SIRT1 and AMPK can engage in a positive feedback loop, thus connecting both sensors of low-energy states into a unified response [47].

In conditions favouring individual’s growth, mTORC1 promotes mRNA translation and protein synthesis, acting as a determinant of proteastasis [48]. During aging, there is reduction in mRNA translation affecting 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 function as significant aging accelerators in the body and are mediated by the IIS or mTORC1 pathway. Recent years have seen the emergence of autophagy being viewed 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. Aging-related cellular dysfunction is encouraged by a decrease in autophagic degradation capacity [50]. The activation of autophagy enhances the breakdown of aged cellular components by inhibiting mTORC1. Disease mitigation for non-communicable chronic illnesses such as cancer, diabetes, cardiovascular disease, and neurodegenerative illnesses is a diverse relationship between autophagy and these conditions [51]. There is increasing evidence that mTORC1 has a central role in this process, and that inhibition of mTORC1 can preserve, and perhaps even rejuvenate stem cell. The complexity of the mTOR network presents a hurdle in defining the mechanistic details of how mTOR influences longevity and health span.

Erlangga and colleagues, 2023 have shown molecular signatures of prolonged intermittent fasting on autophagy, inflammasomes and senescence in healthy young males to suggest 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 blood of 25 healthy young males who performed 17–19 h/day fasting for 30 days. Gene expression of autophagy genes (ATG5, ULK1, and BECN1), inflammasomes (NLRP3, IL-1 β, ASC, and TNF- α), and senescence (p16INK4A, p21, and P53) marker expression levels 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 nutrient sensing systems**

Voluntary abstention from food and drink throughout intervals of time known as "intermittent fasting". With its age-old significance as a societal observation in many countries initial experiments on mice [53] showed the relevance of intermittent fasting in MetH. Pan globe longitudinal studies on eating patterns and shortness of sleep, revealed circadian disruption in digitised societies [54-56]. Rise in comorbidities due to circadian disruptions highlighted the significance of fasting. Landsberg, 2006 showed that fasting suppresses the sympathetic nervous system [57], although Naïmi, 2010 and Wijngaarden, 2014 both highlighted the role of energetic cell sensors in translating the cell's energy situation into distinct metabolic programs during fasting [58,59].

Most fasting processes are targeted to induce autophagy. and invigorates metabolic efficiency by inducing NSS. Time restricted feeding (TRF) is a daily fasting regime, that limits the length of feeding to a specific period of the day, after which there is a period of fasting, the compliance to which, lessen the burden of MetS [60,61]. TRF improves cardiometabolic health and delays aging [62-65]. The improvement of insulin sensitivity as a consequence of TRF has molecular underpinnings in the alignment of molecular circadian clocks with the daily behaviour and physiological re-adjustments such as energy intake through feeding, activity-rest, sleeping etc. Basically, TRF synchronizes daily rhythm of organs, also known as the peripheral circadian clock. The feeding restriction modulates daily rhythm of peripheral clock and clock-controlled genes in peripheral organs viz. liver, adipose tissue, and muscle to align with core clock of SCN. Specifically, restricted feeding 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].

Most fasting regimens differentially yet effectively delay aging. TRF render health outcomes by inhibiting a series of hallmarks of senescence and aging at organismal and cellular level. Experimental studies suggest potential effect of TRF through aligning nutrient sensing, promoting proteostasis and sustaining stem cell function.

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