POTENTIAL OF MEDIUM TO LONG-TERM FASTING TO TRIGGER AN AUTOIMMUNE RESPONSE THROUGH HYPERAGGRESSIVE AUTOPHAGY

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Abstract

Intermittent fasting is a lifestyle intervention that is increasingly gaining traction among the general population. An enhancement in the rate of autophagy is one of the fundamental results of intermittent fasting. Autophagy is a principal intracellular strategy for the maintenance of cellular, somatic, and systemic homeostasis. Gene-based and pharmacological therapeutic modalities which serve to dysregulate autophagy stimulate or exacerbate various diseases in a multiplicity of studies. Consistently, mutations in autophagy-related genetic processes may cause severe human pathologies. We review research and experimental models in order to establish a linkage between autophagy dysfunction to the pathogenesis of some major human disorders, particularly autoimmune disease.

Keywords: *Caloric deficit, macroautophagy, aggrephagy, autosis, ribophagy, peroxiphagy, mitophagy, lipolysis*

INTRODUCTION

The process of delivering unneeded cytoplasmic remnants to lysosomes in the cells of the body for degradation is termed as autophagy[1-3]. Autophagy is the systematic process responsible for delivering unnecessary cytoplasmic remnants to lysosomes for degradation, and it plays a critical role in maintaining the body's cellular quality control mechanisms. This intricate process plays a pivotal role in molecular regulation.

Autophagy is broadly categorized into different types, each facilitating the degradation of cytoplasmic components within lysosomes through distinct pathways. These processes, collectively referred to as "autophagy" due to their nature of cellular "self-eating," encompass chaperone-mediated autophagy (CMA), microautophagy, and macroautophagy. Chaperone- mediated autophagy (CMA) operates by directly translocating specific proteins containing the KFERQ pentapeptide sequence across the lysosomal membrane.[3,4] In contrast, microautophagy involves a different approach, where the lysosomal membrane undergoes invagination and pinching off, ultimately enabling the sequestration and removal of cytoplasmic components. It's worth noting that the precise molecular mechanisms driving this process still hold many mysteries. Macroautophagy follows a distinct route by giving rise to a new organelle, known as the autophagosome.[4] This organelle serves as a pivotal intermediary that enables the efficient delivery of a wide array of diverse cargo molecules to the lysosome for subsequent degradation, contributing significantly to the overall protoplasmic quality management.[3]

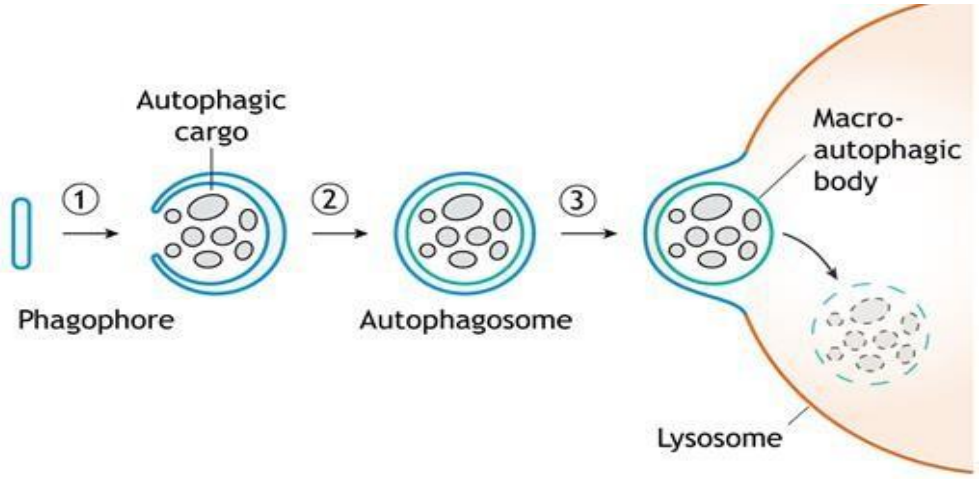

Fig 1[3,4]: A schematic diagram of macroautophagy showing its various stages – 1. Formation of the double-membraned phagophore. 2. Formation of autophagosome as the phagophore forms a complete vesicle 3. Merger of autophagosome with the lysosome.

Autophagosomes are specialized structures which exhibit the capacity to envelop extensive portions of the cellular cytoplasm, individual organelles, protein aggregates, and even invading pathogens. Autophagosomes are double-membraned vesicles formed when endoplasmic reticulum or membranes created *de novo*[5, 6] starting as phagophores, wrap around to sequester degradation- worthy intracellular substrates.[1, 4] When autophagosomes undergo fusion events with endosomal compartments, they result in the formation of amphisomes.[4, 5] These transitional structures represent an intermediate step before their eventual fusion with lysosomes. Within the lysosomal environment, the cargo enclosed within these autophagosomes meets its ultimate fate, undergoing breakdown, while the resulting metabolites undergo recycling back into the cellular cytoplasm. The continued presence of these substrates, including p62/SQSTM1, ferritin, and damaged mitochondria[7] in the cytosol, is recognized by the body's internal mechanisms to be deleterious,[8] which makes autophagy an inexpungible multistage pathway.[9] It aids in maintaining cellular homeostasis,[10, 11] helping cells to acclimatize to nutritional scarcity.

Fasting implies not consuming any calorie-containing food[12] for a certain duration,[13-15] although drinking water is customarily sanctioned. Sometimes, fruit juice coupled with extracts of various leaves is also permitted. The variations in fasting include short-term fasting, intermittent fasting and prolonged fasting.[12] Although there is no consensus over definitions, short-term fasting is typically a few hours in length, intermittent fasting is usually considered to be between 18 hours to three to four days, and prolonged fasting is abstinence which may extend from four days to a week or more. All these types of fasting have been investigated with regards to their role in enhancing physiological markers.[16-21] It has been shown that within twelve hours of fasting, our human growth hormone levels increase. This increase of HGH levels is good for brain function and for the immune system. It is said to improve sleep quality, enhance sexual health, ramp up the fat burning, and keep the body young. Fasting is at times called our "natural inner physician." One of the crucial health-related signs that has been seen to accompany intermittent and long-term fasting is autophagy.[21, 22]

Literature Review

The PRISMA format was followed to search and evaluate the literature about fasting, autophagy, and the role of autophagy in disease, specifically autoimmune disease. The primary search engines used were Google Scholar, PubMed and MedlinePlus and the primary databases searched were MEDLINE and Scopus. The keywords used in search queries were autophagy, taken with autoimmunity, autoimmune disease, inflammation, protein aggregation, mutations, autosis, fasting and caloric deficit.

Background

Autophagy has become a prominent area of research in recent years. The 2016 Nobel Prize in Physiology for Medicine was awarded to Yoshinori Ohsumi for his discovery of mechanisms of autophagy.[a] The catabolic process has been implicated in many positive processes and diseases in the human body. Recent studies have highlighted the role of autophagy in the regulation of certain molecules, like cytokines, that play a crucial role in inflammatory and immune response of the human body. Variations or mutations in genes involved in the autophagic pathways are potential contributors to the misregulation of immune responses and increasing susceptibility to autoimmune conditions. Our interest lies in unraveling the specific molecular mechanisms through which autophagy influences immune responses and contributes to the pathogenesis of autoimmune disorders.

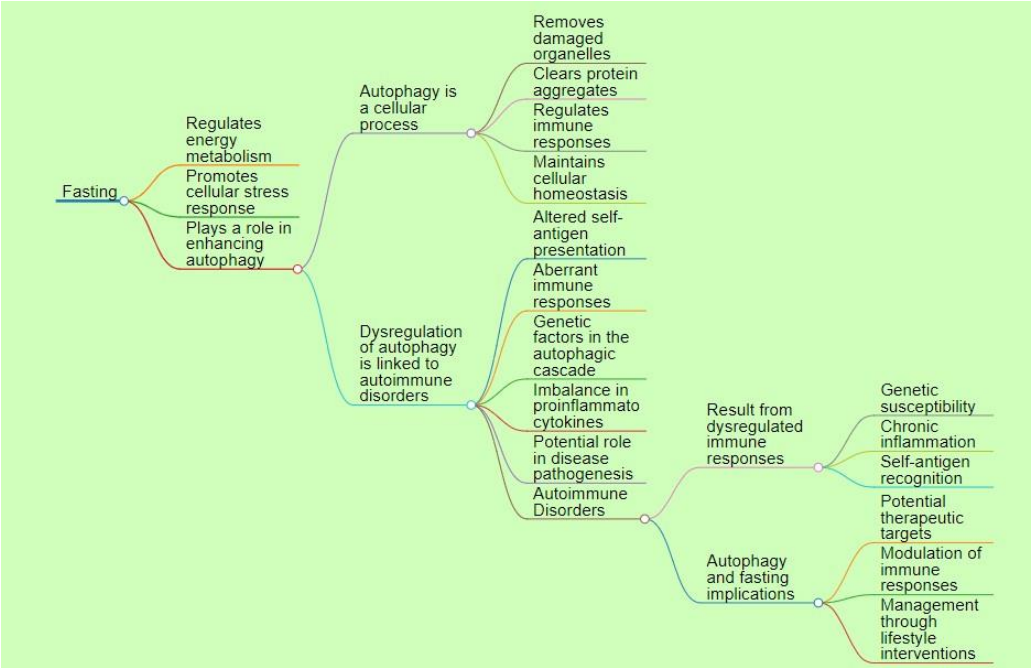

Fig 2: A concept map for intermittent fasting, autophagy, and autoimmune disorders, and how each of them is linked to one another.

Potential Effects of Fasting on the Human Body

Contemporary medical research has provided substantial evidence affirming the effectiveness of intermittent fasting in mitigating symptoms of obesity. This dietary approach not only diminishes the likelihood of developing metabolic diseases and age-related health conditions but also enhances various health markers in both individuals with chronic diseases and those in good health. Intermittent fasting exhibits a diverse array of health-promoting effects rooted in the intricate mechanisms operating through multiple pathways. It has also been shown to raise serum HDL and triglyceride levels, thereby optimizing the lipid profile.[16, 23] Further, it has been proven to promote fat tissue thermogenesis as well as metabolic homeostasis,[12,24] thereby improving metabolic pace and efficiency. It has been demonstrated to help reduce blood glucose in diabetics.[25] Fasting depletes glycogen stores from the body and glucose from the blood.[26] As a result, triglycerides amassed in adipose tissues are metabolized for sustaining the body and provide for its energy needs.[15,27]

This is called lipolysis. Free fatty acids that are produced from lipolysis are converted into ketone bodies, and they are used by tissues – particularly brain tissues[28]– that need them for energy. This is a part of the activation of a liver-brain-adipose neural axis.[29] Ketone bodies are currently believed to have a curative impact in many lifestyle and non-communicable diseases.[30] Glycerol formed in lipolysis is converted to glucose, as a part of gluconeogenesis.[31] This glucose is used by other tissues – particularly muscles, where it is converted to Adenosine Triphosphate (ATP), for energy.[32] Such reduction of adipose tissue in the body can help with obesity.

Fasting also has an impact on protein catabolism,[12, 15] which also takes place through gluconeogenesis.[15] Gluconeogenesis causes production of glucose from glucogenic amino acids which metabolize in body tissues such as muscular tissue.[33] Elevated glycogen levels within cells can impede glucose uptake by tissues, resulting in increased blood glucose concentrations. Intermittent fasting effectively boosts glucose uptake by organ tissues while also enhancing the capacity to store glucose in the form of glycogen.

During fasting periods, the liver adeptly manages blood glucose levels through the regulation of metabolic pathways. This includes the elevation of gluconeogenesis (GNG) and the upregulation of two crucial regulatory enzymes, phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6- phosphatase (G6Pase). These enzymes work in tandem to regenerate glucose and sustain stable blood glucose levels. Similarly, ketone bodies are formed from amino acids called ketogenic amino acids.[34] A study has concluded that fasting causes a marked reduction in the quantity of essential amino acids in body.[12, 35]

When someone begins fasting, they often encounter tension-type headaches.[36] These headaches typically result from hypoglycemia, dehydration, and caffeine withdrawal.[12, 36-38] Fasting has demonstrated the ability to decrease testosterone levels in young men, potentially leading to depression.[39, 40] Researchers have also investigated fasting's influence on autophagy, and some studies suggest that intermittent fasting significantly upregulates autophagy.[41-44]

Factors that Link Fasting to Autophagy

Fasting is a condition when the cells are starved of nourishment. In such a situation, the intracellular turnover rate of proteins and organelles increases.[45] The cell needs energy to survive, and it attains that by consuming its constituents while also regenerating them.[46] It disassembles its constituent organelles, especially those which are in a ramshackle state and need to be replaced, through the process of autophagy, thereby not only getting the energy to survive, but also refurbishing itself. The maintenance of a balance between incoming nutrition and energy expenditure is called energy homeostasis, and autophagy is the lynchpin of cellular energy homeostasis during caloric deficit or starvation.[47]

Autophagy and its Positive Effects on the Body

Autophagy involves the recycling of damaged cellular components. The word "autophagy," derived from the Greek words "auto," meaning self, and "phagy," meaning eating denotes a process which is crucial for maintaining cellular health and is often considered a way of cellular "self- cleansing."

Intermittent fasting can lead to a temporary upward trend in the rate of autophagy. Apart from that, regular physical activity,[48] adequate sleep[49] and staying hydrated, especially during fasting,[50, 51] can also promote autophagy. Intake of foods like resveratrol,[52] spermidine,[53] green tea epigallocatechin-3-gallate[54] has also been shown to promote autophagy. THC has been shown to induce autophagy in melanoma cells leading them to show anti-tumor behavior.[55] Food sources containing resveratrol, a polyphenol, include grapes, peanuts, raspberries, mulberries, and red wine.[56, 57] Nutritional sources of spermidine, a polyamine, include fresh green pepper, wheat germ, broccoli, mushrooms, and soybean.[58,59] Spermidine is also produced through cellular biosynthesis and by certain colonic microbiota.[60] Partly for the reason that it promotes autophagy, spermidine is thought to be an anti-aging panacea.[58, 61]

Autophagy was traditionally regarded as a non-specific process for breaking down proteins in bulk. However, recent research has unequivocally demonstrated that it can also operate with a high degree of selectivity. Selective autophagy hinges on the presence of specific cargo-recognizing autophagy receptors and adaptor proteins, which act as connectors between the cargo and the core autophagic machinery. Different types of selective autophagy are given distinct names to characterize their specific cargo. These include "aggrephagy" for clearing aberrant protein aggregates and disease-related inclusions, "mitophagy" for targeting mitochondria, "pexophagy" for peroxisomes, and "xenophagy" for invasive pathogens. The primary function of selective autophagy is presumed to be quality control, which means it must possess the ability to differentiate between its target, such as misfolded proteins or dysfunctional mitochondria, and their normally functioning counterparts. The precise signals involved in recognizing specific cargo for autophagy remain largely unknown.

Aggrephagy implies the selective removal of protein aggregates via macroautophagy.[62] Therefore, one of the crucial advantages that autophagy provides the body with is the disposal of harmful protein aggregates.[63] This process is specifically prominent in case of neurological health since it consumes toxic protein aggregates implicated in neurodegenerative diseases like Alzheimer's and Parkinson's.[64] Autophagy has also been claimed to get rid of dangerous exogenous entities, including bacteria, viruses, and fungi, that find their way into the body, through a process known as xenophagy ("xeno" means "foreign")[65-69] Xenophagy has been seen as a potential opportunity in the field of cancer therapeutics.[66] Mitophagy is another form of selective autophagy where damaged mitochondria are done away with through macroautophagic mechanisms.[65]

Pexophagy is a kind of selective autophagy which is directed towards peroxisomes and maintains homeostasis of peroxisomes.[70] Selective degradation of ribosomes is termed ribophagy, and it involves selective disposal of most preribosomes and mature ribosomes when the cell is undergoing stress conditions like caloric deficit during fasting.[71-73] It helps in maintaining homeostasis of ribosomes. Other types of selective autophagy are nucleophagy (nucleus as autophagic cargo), reticulophagy (endoplasmic reticulum as autophagic cargo), lipophagy (lipids as autophagic cargo), lysophagy (lysosomal membrane as autophagic cargo), secretophagy (Atg15 protein as autophagic cargo) and others.[4]

Enhanced autophagy has been linked to improved insulin sensitivity, which is important for metabolic health.[74] Autophagy is thought to have a role in suppressing the formation of tumors by eliminating damaged cells and preventing the accumulation of mutations.[75]

Autophagy is involved in maintaining cardiac function and protecting heart health during a case of ischemia-reperfusion injury, which is defined as the paradoxical aggravation of cellular dysfunction and death, after reinstatement of blood flow to formerly ischemic cardiac tissue.[76, 77] Autophagy is involved in the turnover of cellular components in muscle cells, contributing to upkeep of muscle health and maintenance.[78, 79]

Risks Associated with Autophagy

While autophagy can lead to obvious benefits, it may have its own list of adverse effects. Research has demonstrated that the endurance of cancer cells against anticancer drugs can enhance through an increase in rate of autophagy.[80] Autophagy can support the survival of established tumors by providing nutrients during stress conditions.[81,82] Autophagy can also enable cancer growth and metastasis by fostering the incursion capacity and relocation of cancer cells.[83] Having also been termed as a process that is beneficial in the realm of neoplasia, it is rightly termed as a double-edged sword with regards to cancer.[82, 84, 85]

While autophagy has been shown to curb inflammation by causing the degradation of protein aggregates, damaged cell organelles and pathogens that stimulate inflammation,[86] it has also been shown to promote inflammation under certain circumstances.[87,88] In certain neurodegenerative diseases like Alzheimer's, Parkinson's, Huntington's disease, amyotrophic lateral sclerosis and the suchlike, impaired autophagy may contribute to the accumulation of toxic protein aggregates leading to aggravation of these diseases.[89, 90] Whereas autophagy plays a characteristic, fundamental, and deep-seated role in human body's immunity,[91, 92] imbalanced autophagy may impair the immune response, potentially leading to increased susceptibility to certain infections.[93]

While enhanced autophagy is associated with improved insulin sensitivity,[74] dysregulated autophagy may contribute to insulin resistance in certain metabolic disorders.[94] In certain cardiac conditions, maladaptive autophagic responses may contribute to cardiac dysfunction and poorer prognosis and outcomes in cardiac myopathies.[95, 96] The relationship between autophagy and longevity is complex.[97, 98] While some studies suggest that enhanced autophagy may promote longevity,[99] excessive autophagy or impaired autophagic function has also been associated with aging-related diseases.[97, 100] Additionally, dysregulation of autophagy has been linked to autoimmune diseases, where excessive or insufficient autophagy may contribute to chronic inflammation and immune system dysfunction.[101-103]

Autophagy and Autoimmune Disease

Autophagy is involved in the regulation of immune responses by influencing the presentation of antigens to immune cells.[91] It plays a role in the processing and presentation of self-antigens by major histocompatibility complex (MHC) molecules,[104] a process essential for immune tolerance.[105] Dysfunctional autophagy may lead to aberrant presentation of self-antigens,[101,106] triggering an autoimmune response.[101, 102] If someone fasts for two to three days, the rate of autophagy increases to multiple times its natural value, which may lead to the process getting out of control. If autophagy fails to properly clear or process self-antigens, or goes berserk, it may cause immune cells to recognize these antigens as foreign, leading to the activation of autoreactive T cells.[91,93,103]

Compromised autophagy can lead to the release of pro-inflammatory cytokines, contributing to chronic inflammation,[73,86,88] a hallmark of and the trigger of many autoimmune diseases. Genetic variations in autophagy-related genes have been linked to susceptibility to certain autoimmune diseases. For example, polymorphisms in genes involved in the autophagic process have been identified in individuals with autoimmune conditions[107] like systemic lupus erythematosus (SLE),[108] rheumatoid arthritis (RA),[109] and Crohn's disease.[110]

Autophagy plays a role in the differentiation and function of immune cells, including T cells and B cells.[111, 112] Dysregulated autophagy can impact the balance between different subsets of immune cells,[111, 113, 114] influencing the immune response. Autophagy is involved in the clearance of immune complexes, which can form when antibodies bind to antigens.[91] Impaired autophagy may result in the accumulation of immune complexes, contributing to tissue damage and inflammation.[97, 115, 116] Toxic protein aggregates left by impaired autophagy may interact with DNA and cause mutations in the genes,[117] leading to an autoimmune response.[118]

Discussion and Outcomes

Autophagy is activated in response to cellular stress, such as oxidative stress and endoplasmic reticulum stress.[119,120] In autoimmune diseases, chronic stress conditions may lead to dysregulated autophagy and contribute to further immune system dysfunction,[121] including autosis, which is a non-necrotic, non-apoptotic, autophagy-related cell death.[122,123] Given the role of autophagy in autoimmune diseases, it has been considered as a potential therapeutic target.124 Modulating autophagic activity[125] may be explored as a strategy to regulate immune responses and attenuate the progression of autoimmune disorders.

The Importance of Fasting-Autophagy-Autoimmune Disease Entente in Medical Education

Medical education is getting decidedly modernized, with the introduction of avant-garde techniques of instruction delivery. In line with this, there must be certain shifts in medical school curriculum as well.[126-129] The study of fasting-autophagy-autoimmune disease entente provides valuable insights into cellular health and cellular disease mechanisms. Currently, we believe that the teaching of this critical node in medical curricula often receives limited attention, and there exists a convincing case for enhancing the time allocated to this topic. With autoimmune diseases affecting millions of humans worldwide, medical educators and professionals must grasp the multifaceted relationship between fasting, autophagy, and immune responses. Providing in-depth analysis of this module will aid in empowering future practitioners of medicine in better understanding the nuances and the underlying mechanisms of autoimmune disorders and come up with innovative therapeutic strategies.

Conclusion

In an era when medicine is progressing in leaps and bounds,[130-132] it can be noted that the relationship between autophagy and autoimmune diseases is an active area of research. The mechanisms involved therein must continue to be elucidated to further understand the relationship between autophagy and autoimmune disease. While the heterogeneity of autoimmune diseases and the intricacy of autophagy regulation make it challenging to draw a sweeping conclusion, it may be said that out-of-control autophagy may trigger autoimmune disease. Further research is needed to better understand the specific contributions of autophagy to various autoimmune conditions and to identify possible pharmacological interventions. Insights into the molecular processes involving autophagy provide a foundation for developing targeted therapies aimed at modulating autophagic activity to manage or treat these conditions.

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