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Efectos del ayuno intermitente sobre el metabolismo, la función cognitiva y el envejecimiento: una revisión de estudios en humanos y animales

Effects of intermittent fasting on metabolism, cognitive function, and aging: a review of human and animal studies

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Effects of intermittent fasting on metabolism, cognitive function, and aging: a review of human and animal studies

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Abstract

Obesity has a significant impact on society; however, there are few efficient long-term treatment strategies available. The popularity of intermittent fasting (IF) over calorie restriction has increased due to its less severe strategy of modifying only the eating pattern and not restricting the total calories ingested. Clinical studies on IF have had limitations and tended to focus only on body weight loss, thus controlled animal studies are required to establish the physiological basis of IF. The present review focuses on the effects of IF as a potential new approach to lose weight, including its effects on metabolism, cognitive function, and aging. IF has been proved to efficiently reduce body weight and insulin resistance through an improvement in lipid metabolism, inflammation, cognitive function, and neurodegeneration. Future research should include studies with experimental animals to elucidate the mechanisms involved. Long-term human studies will also be required to determine which form of IF is the most beneficial as well as its long-term effects.

Keywords: intermittent fasting, glucose, fatty acids, obesity, overweight, inflammation, rodents, weight loss

1. Introduction

The global pandemic of overweight and obesity has become a significant health problem. The increase in obesity is directly related to an increase in the consumption of processed hypercaloric food (low in nutrients and fiber, high in fat and sugar) and a decrease in physical activity[1]. Obesity is associated with severe metabolic disorders, such as insulin resistance, dyslipidemia, type 2 diabetes mellitus, and cardiovascular disease[2]. A modest loss of body weight is one of the main factors improving glucose and lipid homeostasis. Thus, the first common treatment for obesity is energy restriction. The most commonly used energy restriction approach is limiting caloric intake, without malnutrition, by 30%[3]. However, low-calorie diets maintained over time often result in poor adherence and promote physiological changes that reduce energy expenditure and thus prevent further weight loss.

Intermittent fasting (IF) has received considerable interest as an alternative approach to lose body weight and improve metabolic health. IF is a feeding pattern rather than a diet, and is defined as total food restriction or severe intake limitation during certain times of the day or week combined with *ad libitum* food intake. It can be applied alone or in combination with calorie restriction (CR)[4]. This pattern of alternating periods of fasting and feeding alleviates the circadian rhythm disturbance caused by non-stop eating throughout the day, which is often facilitated by the increased palatability of processed foods, and thus improves metabolic balance[5]. Repeated periods of mobilization and recovery of energy substrates triggered by IF favor the reduction of ectopic fat accumulation and improve insulin sensitivity[6].

Several studies have suggested that the benefits of IF increase when combined with exercise. Physical activity has been reported to act synergistically with IF mechanisms to stimulate and induce greater weight loss[7]. Moreover, these effects depend on the duration

and type of exercise, as well as the phase of IF in which it is performed[8], *i.e*. exercise during the glycogen-depleting fasting period of the IF may be the most effective combination to promote gluconeogenesis, fat oxidation and ketogenesis.

2. IF approaches

Various approaches to IF have been used as follows: (1) alternate-day fasting (ADF), which consists of alternating a normal diet one day followed by complete or severe fasting (one meal of <500 calories) the next day[9] (Fig. 1A); (2) the 5:2 fasting diet, which involves eating a normal diet five days a week and complete or severe fasting two days a week[10] (Fig. 1B); and (3) time-restricted fasting (TRF), which limits the window of food intake to 8–12 h[11–13] (Fig. 1C)

Figure 1

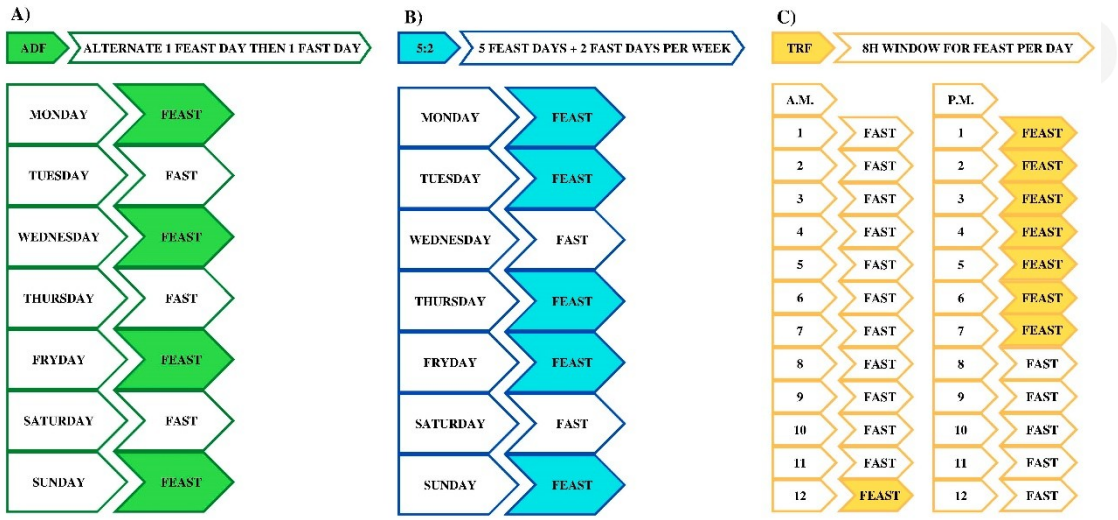

Figure 1. IF approaches. (A) Schematic representation of an example of alternate-day fasting (ADF) during a week, based on feast days (Monday, Wednesday, Friday, and Sunday) and fast days (Tuesday, Thursday, and Saturday). **(B)** Schematic representation of an example 5:2 diet during a week, based on

feast days (Monday, Tuesday, Thursday, Friday, and Sunday) and fast days (Wednesday and Saturday). **(C)** Schematic representation of an example of time-restricted fasting (TRF) during a day, based on feast from 00:00 to 19:00 h and fast from 20:00 to 11:00 h.

Most rodent studies that use IF protocols employ a 24-h total fast every other day. However, the sustainability of this model is questionable in humans, as it is the most extreme intervention. In contrast, TRF with a diurnal feeding window may be one of the most easily adaptable options in humans.

3. IF in humans

IF in humans produces mild-to-moderate weight loss (3–8% loss from baseline) that is comparable to that achieved using traditional diets (daily CR) over short periods of time[14,15]. While ADF and the 5:2 diet decrease body weight more than the TRF diet, no studies have directly compared different IF strategies[16,17]. Clinical studies have shown that participants do not fully compensate for the lack of food consumed during the fasting period, which often results in an energy deficit that would explain the weight loss[17]. Some studies have reported that IF reduces blood pressure, low-density lipoprotein (LDL), cholesterol, and triglyceride levels, and improve insulin resistance, while other studies have reported no significant improvement in these parameters[18].

This disparity between results may be explained by the fact that the impact of IF depends on many factors, such as age, sex, and nutritional and health status of the individual, as well as the protocol used, its duration, and adherence to the food intake schedule. Furthermore, most studies on IF in humans have been short-term and it is unclear whether the effects seen were due to calorie reduction or the feeding pattern. Further studies are needed, particularly animal studies, as they allow the precise monitoring of food intake

and analysis of many other parameters that may led to a better understanding of the physiological mechanisms underlying IF (Table 1).

Similarities	**Differences**
Increased insulin sensitivity ([1,2])	Prominent weight loss is not always seen in humans ([3,4])
Improved glucose tolerance ([2,5])	Alterations of HDL cholesterol levels are not very clear in humans ([3,6,7])
Reduced fat mass ([3,8])	Pro-inflammatory cytokine levels are not consistent in humans ([4,9,10])
Decreased CVD risk (decreased LDL levels and increased LDL particle size) ([6,8])	BDNF expression is increased in mice but unchanged in humans ([11,12])
Decreased leptin and increased adiponectin levels ([13,14])	
Decreased oxidative damage in brain ([15,16])	

Table 1. Summary table with the main similarities and differences between humans and rodents in response to IF.

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4. Mechanisms of action of IF

Although human studies on IF often result in reduced calorie intake, weight loss is not the main driver of the health benefits, as shown by multiple animal studies. Rodent studies have shown that fasting for a limited number of hours per day is more relevant at the metabolic level than the composition of the diet itself[19]. This is because IF allows switching between two sources of energy substrate: glucose and lipids. The mobilization of stored lipids during fasting periods promotes the synthesis of ketone bodies, which act as an alternative source of acetyl-CoA for tissues[20]. However, ketone bodies are not just used as fuel and may also influence health and aging status by regulating the expression and activity of several proteins and molecules[21,22]. These include peroxisome proliferator–activated receptor γ coactivator 1α, fibroblast growth factor 21, nicotinamide adenine dinucleotide, polymerase 1, ADP ribosyl cyclase, and brain-derived neurotrophic factor (BDNF), which has implications for brain health and psychiatric and neurodegenerative

disorders[23]. The decrease in glucose and ketone bodies levels inhibits multiple anabolic pathways and stimulates catabolic autophagy to eliminate damaged proteins and organelles and improve mitochondrial function[24]. It was recently reported that the beneficial effects on health and longevity in mice are more pronounced when the fasting period also matches the diurnal inactive phase, underlining the influence of the circadian cycle on IF[15].

4.1. Effects of IF on metabolic health

Rodent studies have shown that IF reduces body weight and body fat and improves glucose homeostasis. Furthermore, these effects are even more pronounced in rodents exposed to obesogenic diets[25]. The decrease in adiposity has been shown to be due to a decrease in adipocyte size and storage of fuel as triglycerides, LDL, and cholesterol, as well as an increase in the transport of lipoproteins, such as high-density lipoprotein[26]. In addition to reducing the percentage body fat, IF promotes the browning of white adipose tissue, mitochondrial biogenesis, and increases oxygen consumption rate in mice[27].

IF may substantially alter the composition of the gut microbiome, with a significant induction of acetate and lactate metabolites produced by the microbiome, as the gut microbiota exhibits diurnal oscillations, which are influenced by feeding rhythms in mice and humans[27].

Several studies have suggested that stress induced during the fasting phase of IF causes an immune response that repairs cells and induces positive metabolic changes in glucose and lipid pathways, reduces leptin, and increases adiponectin production and levels. Other prominent effects of IF include decreased blood glucose levels due to a protective effect on pancreatic β-cells and enhanced insulin secretion, as well as decreased inflammation due to low levels of interleukin 6 and tumor necrosis factor-α (TNF-α)[7].

4.2. Effects of IF on cognitive function

IF may enhance cognition in mice and humans, specifically in terms of associative and working memory. IF decreases neuroinflammation that occurs during the impairment of spatial learning and memory[23]. Reduced inflammation improves several memory-associated conditions, such as Alzheimer's disease[28]. In animal models, IF improved memory and learning while increasing BDNF levels[29]. This BDNF's increased stimulated neuroplasticity, neuroprotective protein synthesis, and the activation of antioxidant and DNA repairing enzymes[30]. IF can upregulate BDNF via activation of brain-intrinsic glutamate receptors or peripheral signals that activate the transcription factors cAMP response element-binding protein and nuclear factor kappa-B[13].

4.3. Effects of IF in aging

De Cabo *et al.* reported an 80% increase in the average life span of young adult rats maintained under an IF regimen and proposed an inverse relationship between reduced adiposity and life expectancy[23]. However, this effect may be influenced by sex, diet, age, and genetic factors[14].

IF reduces inflammation in the brain. Neuroinflammation plays an important role in neurodegeneration and neurodegenerative diseases. Inflammation and microglia activation are common in the brain and the periphery during aging. In addition, IF reduces circulating levels of leukocytes and proinflammatory cytokines, such as TNF-α and interleukins[14,31].

The nine "hallmarks of aging" include mitochondrial dysfunction, loss of proteostasis, cellular senescence, altered intercellular communication, stem cell exhaustion, deregulated nutrient-sensing, epigenetic alterations, genomic instability, and telomere

shortening[14]. These are all altered by IF, which induces physiological changes that may inhibit aging[32].

5. Study limitations

The main limitation of the IF studies is that there are few human studies reported and most of them combine IF with CR[33]. In addition, although in most animal studies IF involves many hours of fasting to facilitate the analysis of this pattern on food intake, perhaps the most appropriate IF approach in humans would be to achieve a daily fast of about 12 hours. Otherwise, lipolysis and feelings of hunger may be excessively increased.

6. Conclusions and future perspective

Several studies have highlighted IF as a promising approach to reduce body weight and improve insulin sensitivity. The main mechanisms involved include alterations to lipid metabolism, specifically affecting adipose tissue, and reduced inflammation. IF may also have profound effects on cognitive function and neurodegenerative processes associated with aging. Further studies using experimental animals are required to elucidate the mechanisms by which IF modifies these parameters.

Despite the popularity of IF over the past years, most human studies have been short-term (4–12 weeks). Thus, more long-term studies are needed to expand our knowledge of IF and determine how long the benefits of IF persist and which long-term effects implies. Future studies are required to demonstrate the benefits of IF in patients with obesity-associated diseases, such as diabetes, since IF has been shown to improve insulin sensitivity both in mice and human studies, regardless of the body weight loss. Moreover, additional IF approaches should be studied to include and compare gender, age, ethnicity, clinical, and individual differences, and obtain safe and homogeneous outcomes.

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