Journal of Fasting and Health
http://jfh.mums.ac.ir
JFH

The Effects of Fasting on Physiological Status and Gene expression: An Overview

Fahimeh Afzaljavan[1,2], Alireza Pasdar[1,3]*

1. Department of Molecular Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
2. Student Research Committee, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
3. Division of Applied Medicine, Medical School, University of Aberdeen, Foresterhill, Aberdeen, AB25 2ZD, UK

ARTICLE INFO

Article type:
Review Article

Article History:
Received: 10 Aug 2015
Revised: 5 Oct 2015
Accepted: 7 Oct 2015
Published: 29 Oct 2015

Keywords:
Caloric restriction
Fasting
Gene expression

ABSTRACT

Calorie restriction through ingesting no or minimal amounts of food and caloric beverages for periods of time is called fasting. Fasting can affect body through changing in physical and metabolic adaptations, as well as mineral and hormonal status. However, psychological effects and sometimes medical complications are likely in case of inappropriate fasting. Fasting is associated with changes in expression of different genes and signaling pathways. In this brief review, physiological effects of fasting, affected pathways during fasting and potential applications of fasting are discussed.

Please cite this paper as:
Afzaljavan F, Pasdar A. The Effects of Fasting on Physiological Status and Gene expression: An Overview. J Fasting Health. 2015; 3(3):111-114.

Introduction

Fasting is defined as abstinence from eating foods and drinks (absolute), or as a type of dietary restriction through taking minimal amounts of food. There are three most commonly studied dietary restrictions including: caloric restriction (CR), alternate-day fasting or intermittent fasting (ADF) and dietary restriction (DR). Ramadan fasting is similar to ADF, both incorporate feast and fast periods however, fluid intake is forbidden during the fasting periods of Ramadan whereas it is permitted at all times under an ADF protocol (1). In many scientific studies, potential therapeutic effects of fasting as a non-pharmacological intervention on health improvement and longevity have been investigated. Studies in mammals have shown activated tissue-specific metabolic pathways in response to nutrient deprivation to reduce energy consumption and to maintain homeostasis and organism survival.

Physiological effects of fasting

Physical and metabolic processes, as well as mineral substances and hormones are affected by fasting. Some studies have also indicated psychological effects of fasting (2). Fasting can have medical applications in certain conditions such as intractable epilepsy, seizure-associated brain damage (3) and rheumatoid arthritis improvement (4), although it normally causes ketogenesis. Fasting also helps to reduce the risk of obesity, hypertension, asthma (5) and aging. In addition to the therapeutic effects of approved drugs, in some cases such as intractable epilepsy, fasting can be applied to enhance treatment efficiency and to reduce the side effects of dietary interventions for treating chronic diseases (3). All the aforementioned effects are induced by means of changes in regulation of gene expression in different pathways. Some of the observed results arising from alteration of gene expression pattern are as follows: protection against stress, enhancement of the chemotherapy effects (6), including protection of normal cells against the side effects of chemotherapy drugs (7), protection against cardiovascular (8) and endocrine diseases (9),

* *Corresponding author:* Alireza Pasdar, Department of Molecular Medicine, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran. E-mail: pasdara@mums.ac.ir

insulin sensitivity of muscle and hepatic cells (10) and body fat reduction.

Affected pathways during fasting and potential applications

In previous studies, the effects of fasting have been demonstrated through a decrease in IGF-I (11) and an increase in IGF-1 binding protein and its inhibitor, IGFBP1 (Insulin-like growth factor-binding protein1), (12) along with other endocrinological alterations inducing gene expression changes in numerous cells. Decrease in IGF-I reduces IGF-R1 downstream signaling pathway including Src/β catenin, PI3K/AKT/mTOR and GRB2/ERK pathways (Figure 1) (5). These alterations can lead to blocking of the epithelial-mesenchymal transition process and consequently, decreasing cell invasion and metastasis in cancer patients. Therefore, fasting could be regarded as an important approach to management of cancer progression by blocking cancer invasion and metastasis via epithelial-mesenchymal transition procedure and increasing the efficiency of chemotherapy in cancer patients (13).

In the brain, hippocampus neurons have an important role in learning and memory; these neurons are degenerated in Alzheimer's disease (14), stroke (15), traumatic brain injury and epilepsy (3). Brain communicates with all of the peripheral organs involved in energy metabolism, and fasting improves brain function and peripheral energy metabolism by modifying brain neurochemistry and neuronal network activity. Fasting enhances parasympathetic activity in the autonomic neurons that innervate the intestine, heart and arteries, resulting in improved intestine motility, as well as heart rate and blood pressure reduction. Oxidative stress and inflammation are also reduced throughout the body and brain, in response to fasting (5).

The neurons of dentate gyrus, which serve as receiver of inputs from the entorhinal cortex neurons (EC) show increased activity as a result of fasting which can in turn, increase the production of brain-derived neurotrophic factor

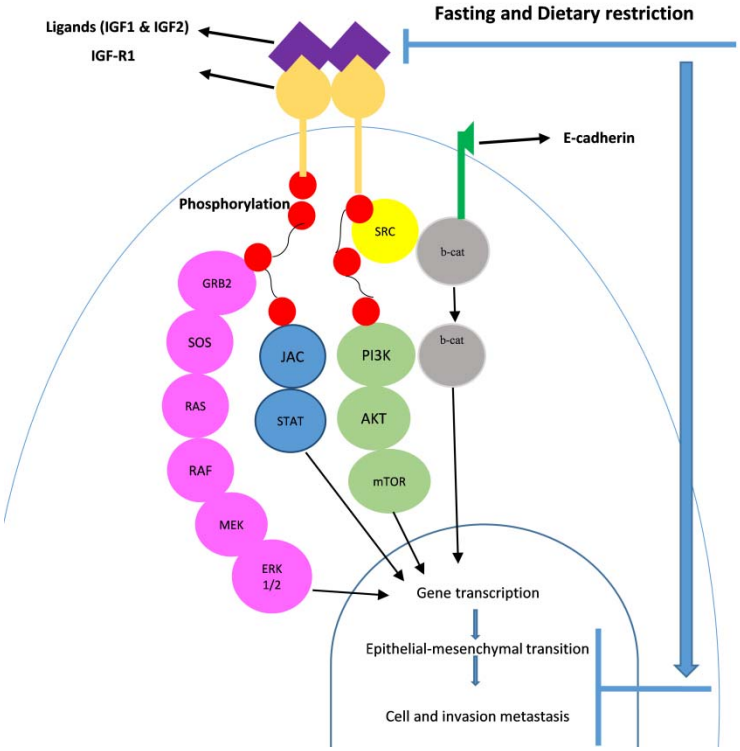

Figure 1. Effect of fasting and dietary restriction on IGF-R1 signaling pathway in cancer cells (adapted and summarised from Ref. 13)
Legend: GRB2: Growth factor receptor-bound protein 2; SOS: Son of Sevenless; ERK: extracellular signal-regulated kinases; JAK: Janus kinase; STAT: Signal Transducer and Activator of Transcription; PI3K: Phosphoinositide 3-kinase; mTOR: mammalian target of rapamycin; b- cat: beta catenin

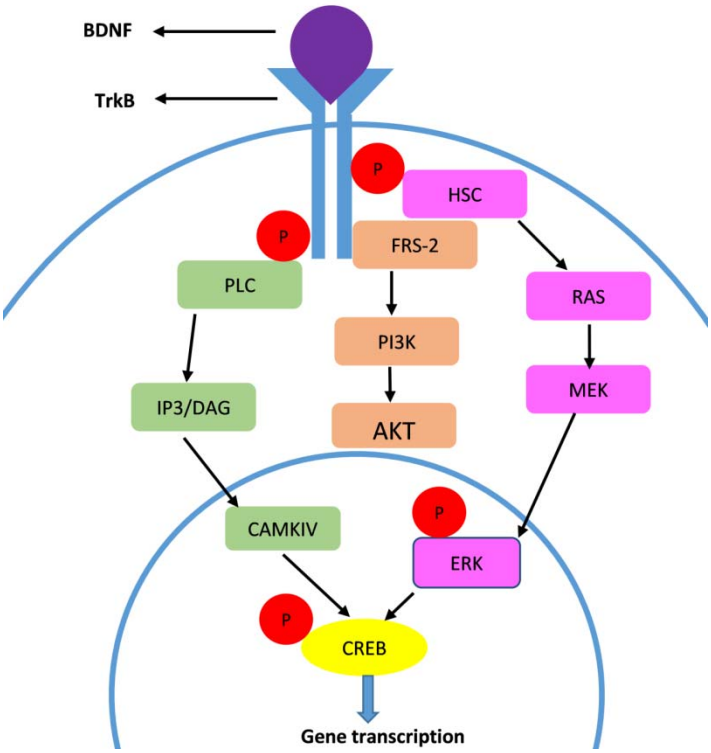

Figure 2. BDNF signaling pathway in the brain in response to fasting (adapted and summarised from Ref. (19))
PLC: Phospholipase C; TrkB: Tropomyosin receptor kinase B; IP3: Inositol triphosphate; DAG: Diacylglycerol; CREB: cAMP response element-binding protein; FRS-2: fibroblast growth factor receptor substrate 2; CAMK: Ca2+/calmodulin-dependent kinase

(BDNF). BDNF causes changes in synaptic structure and function, which is believed to affect memory enhancement and learning function. BDNF signaling in the brain (Figure 2) may also mediate behavioral and metabolic responses to dietary energy restriction and exercise, including regulation of appetite, activity levels, peripheral glucose metabolism and autonomic control of the cardiovascular and gastrointestinal systems (16). Association of *BDNF* gene with schizophrenia has also been reported in some studies (17). Furthermore, animal studies have suggested involvement of this gene in the angiogenesis pathway. In response to fasting in male Wistar rats after induction of MI, an increased expression of the *BDNF* gene has been demonstrated, which leads to an increase in expression of vascular endothelial growth factor in the cardiac muscle, where it increases angiogenesis and decreases apoptosis (18).

There are also signaling pathways by which glutamate, BDNF, insulin and glucagon-like peptide improve neuronal bioenergetics and protect the neurons against neurodegenerative diseases and traumatic injuries (5). All these findings demonstrate the protective role of fasting against development of devastating disorders and also long-term maintenance of individuals' good health status.

Summary

According to different studies, the type of nourishment and diet play a key role in health and protection against diseases. With regard to the existing data, caloric restriction and limitation of food intake induce physiological effects and lead to a change in different signaling pathways such as IGF-I, Src/β catenin, PI3K/AKT/mTOR, GRB2/ERK and BDNF. This instigates increased stress resistance, better protection against chronic diseases such as cardiovascular and endocrine diseases, cancers and enhancing chemotherapy results as well as alleviating its side-effects.

Given the fact that fasting is considered as a method of caloric restriction and dieting without any serious side-effects, it can enhance normal physiological status and help with improving the overall well-being.

References

1. Trepanowski JF, Bloomer RJ. The impact of religious fasting on human health. Nutr J. 2010; 9(1):57.
2. Fazel M. Medical implications of controlled fasting. J R Soc Med. 1998; 91(5):260-3.
3. Hartman AL, Rubenstein JE, Kossoff EH. Intermittent fasting: a "new" historical strategy for controlling seizures? Epilepsy Res. 2013; 104(3):275-9.
4. Muller H, de Toledo FW, Resch KL. Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systematic review. Scand J Rheumatol. 2001; 30(1):1-10.
5. Longo VD, Mattson MP. Fasting: molecular mechanisms and clinical applications. Cell Metab. 2014; 19(2):181-92.
6. Lee C, Raffaghello L, Longo VD. Starvation, detoxification, and multidrug resistance in cancer therapy. Drug Resist Updat. 2012; 15(1-2):114-22.
7. Raffaghello L, Lee C, Safdie FM, Wei M, Madia F, Bianchi G, et al. Starvation-dependent differential stress resistance protects normal but not cancer cells against high-dose chemotherapy. Proc Natl Acad Sci U S A. 2008; 105(24):8215-20.
8. Wan R, Ahmet I, Brown M, Cheng A, Kamimura N, Talan M, et al. Cardioprotective effect of intermittent fasting is associated with an elevation of adiponectin levels in rats. J Nutr Biochem. 2010; 21(5):413-7.
9. Tikoo K, Tripathi DN, Kabra DG, Sharma V, Gaikwad AB. Intermittent fasting prevents the progression of type I diabetic nephropathy in rats and changes the expression of Sir2 and p53. FEBS Lett. 2007; 581(5):1071-8.
10. Halberg N, Henriksen M, Söderhamn N, Stallknecht B, Ploug T, Schjerling P, et al. Effect of intermittent fasting and refeeding on insulin action in healthy men. J Appl Physiol. 2005; 99(6):2128-36.
11. Fontana L, Partridge L, Longo VD. Extending healthy life span--from yeast to humans. Science. 2010; 328(5976):321-6.
12. Thissen JP, Ketelslegers JM, Underwood LE. Nutritional regulation of the insulin-like growth factors. Endocr Rev. 1994; 15(1):80-101.
13. Al Moustafa AE. Fasting inhibits human cancer progression via the epithelial-mesenchymal transition process: Important evidence unraveled. Clin Cancer Invest J. 2012; 1(4):181-3.
14. Halagappa VK, Guo Z, Pearson M, Matsuoka Y, Cutler RG, LaFerla FM, et al. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's disease. Neurobiol Dis. 2007; 26(1):212-20.
15. Arumugam TV, Phillips TM, Cheng A, Morrell CH, Mattson MP, Wan R. Age and energy intake interact to modify cell stress pathways and stroke outcome. Ann Neurol. 2010; 67(1):41-52.
16. Rothman SM, Griffioen KJ, Wan R, Mattson MP. Brain-derived neurotrophic factor as a regulator of systemic and brain energy metabolism and cardiovascular health. Ann N Y Acad Sci. 2012; 1264(1):49-63.
17. Neves-Pereira M, Cheung JK, Pasdar A, Zhang F, Breen G, Yates P, et al. BDNF gene is a risk factor for schizophrenia in a Scottish population. Mol Psychiatry. 2005; 10(2):208-12.
18. Katare RG, Kakinuma Y, Arikawa M, Yamasaki F, Sato T. Chronic intermittent fasting improves the survival following large myocardial ischemia by activation of BDNF/VEGF/PI3K signaling pathway. J Mol Cell Cardiol. 2009; 46(3):405-12.
19. Mahan AL, Ressler KJ. Fear conditioning, synaptic plasticity and the amygdala: implications for posttraumatic stress disorder. Trends Neurosci. 2012; 35(1):24-35.