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

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**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),
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-1 (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-1 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.
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