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Fasting Reduces the Binding between Sugar and Protein; New Insights into Diabetic Complications

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ABSTRACT

Fasting has numerous biological, physical and mental health advantages or that as some physicians cure their patients by prescribing fasting to them. Fasting protects people from many diseases such as cancer, cardiovascular diseases, and diabetes complications. The main fasting health-promoting effects includes amplification of neurotrophic factors, activation of neuroendocrine system, the response of hormetic stress, decrement in mitochondrial oxidative stress, and autophagy promotion. This article briefly describes the molecular view of the effects of fasting on human health, according to our laboratory results, which are obtained by biophysical and biochemical methods. Based on our results, the presence of 3-β-hydroxybutyrate (BHB) as a liver produced metabolite in the fasting condition protects the body against toxicity of human serum albumin and insulin glycation products. Our results demonstrated that, BHB protects protein against sugar binding, inhibits the alteration of the protein structure and diminishes AGEs formation. By this way, BHB inhibits friend to foe transformation in proteins to protect us against diabetic complications.

Keywords: Fasting; 3-β-hydroxybutyrate; Human serum albumin; Insulin; Glycation; AGEs reduction; Promotion of autophagy

FASTING

Fasting defines as a great act of worship and voluntarily avoidance from eating, drinking and smoking for a period of time along with our spiritual connection can strengthen its weakness. Therefore, it's different from hungriness. It is one of the pillars of Islam and prescribed upon the Muslims. However, it has not made as an exclusive obligation on the Muslim but it is an age-old religious duty, for its importance and impact on the souls of humankind.

Fasting is a great blessing (virtue) as well as therapy and protects human body and mentality against diseases and improves his focus. It has become moral and spiritual development as the body must be taught to cooperate with soul, therefore fasting developed body health [1].

Fasting and Health

Fasting has numerous benefits for human health based on scientific results [1]. Ancient physicians, such as Avicenna, Paracelsus and Hippocrates cured their patients by fasting [2]. Indeed, Pythagoras required his students to undertake a 40-days fasting as an entrance requirement. According to research studies, most of chronic diseases can be improved or their severity can be reduced by fasting [3]. Researchers suggest that there are major health benefits in caloric restriction through fasting. Benefits include reduced risks of cancer [4,5], cardiovascular diseases [6], diabetes mellitus and insulin resistance [7], immune disorders and more generally, the slowing of the aging process to increase maximum life span [2]. Moreover, based on the reports by USA National Academy of Sciences, fasting can increase the stress resistance, reduce morbidity, and increase life span [8].

Neurotrophic factors increment, activation of neuroendocrine systems, mitochondrial oxidative stress decrement, reduced signals associated with aging and autophagy promotion are the mechanisms of health-promoting effects of fasting which are supported by

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experimental researches.

It is worth mentioning that, after wining of the Medical Nobel reward in 2016 by Japanese biologist, Yoshinori Ohsumi, the importance of autophagy as self-eating cellular process, in response to nutritional stress, oxidation stresses and antigen presence has been concerned significantly[9]. Literally, autophagy is recycling of cytosolic components while depending on delivery method to lysosome as degrading organelle. It has been justified into 3 pathways including chaperon mediated autophagy, micro-autophagy and macro-autophagy [10]. During starvation and diet fasting, circulating ketone bodies like beta-hydroxybutyrate, acetoacetate, and acetone are secreted from liver which not only bring energy to brain cells but also induce chaperon mediated autophagy [11]. Since via chaperon mediated autophagy, just only proteins could be degraded specifically. Hence autophagy's promotion in prevention as well as treatment of various protein folding diseases likewise Alzheimer and Type 2 Diabetes, is a new paradigm [12].

Moreover, fasting is often accompanied by increased alertness and mood enhancement, which is related to neuroendocrine activation, brain availability of serotonin, endogenous opioids, endocannabinoids and changes in neurotransmitters [13]. In addition, fasting causes mild cellular stress response, which is accompanied with increased production of neurotrophic factors [13,14] and stimulates neuronal network activity in cognitive regions of brain, enhanced synaptic plasticity and improved stress tolerance [15].

One of the most metabolic important features of fasting is ketogenesis, as a potent change in metabolic pathways and cellular processes such as stress resistance, lipolysis and autophagy [15]. So, Metabolic syndrome was reversed by fasting due to reducing of abdominal fat, inflammation and blood pressure through increased insulin sensitivity [7]. In fact, fasting decreases the level of insulin and leptin (as pro-inflammatory state inducer) and increases the level of adiponectin and ghrelin (as inflammation suppressor and insulin and leptin sensitivity booster) [15]. Fasting also is involved in glucose homeostasis and its maintenance in young healthy individuals [16].

Protein and Disease

Protein is a natural robot and their biological functions depend on their native structure. The loss of this structure folding induces protein misfolding that leads to inactive state of protein. Moreover, there are evidences that misfolding or conformational change of a protein induces aggregation that is a central concept in molecular pathogenesis of roughly 20 diseases. These are collectively called the conformational diseases or protein misfolding diseases or amyloidosis [17,18]. The aggregated proteins are deposited in the brain to cause diseases such as Alzheimer's or Parkinson's diseases [19] or in tissues such as heart and spleen lead to diseases like cardiac amyloidosis ("stiff heart syndrome") and splenic amyloidosis, respectively [19]. One of the prevalent agents of protein aggregation is glycation, which is described as non-enzymatic covalent binding of reducing carbohydrates to a desired protein [20]. According to our previous reports, glycation alters the proteins structure [21], induces proteins fibrillation to turn them from friend to foe as toxic for health [22,23].

Glycation and its Inhibition through Fasting

The term glycation refers to a wide variety of spontaneous covalent binding of reducing sugars and proteins which is first described by Louis-Camille Maillard to form compounds known as advanced glycation end products (AGEs) [24,25]. This process happens in the body in different conditions and is especially induced in diabetic patient because of high level of glucose in the blood. Accumulation of AGEs in various tissues has been accompanied with development of chronic diabetes [26] which brings about tissue and organ deterioration in other pathological conditions like chronic inflammatory disease [27], neurodegenerative disorders such as Parkinson's disease [28], amyotrophic lateral sclerosis [29], Alzheimer's disease [30], atherosclerosis [31] and also physiological aging [32]. Prevention of the aforementioned diseases seems to be possible by AGEs decreasing via using inhibitors as therapeutic agents.

Ketone bodies are water soluble metabolites which are produced through metabolism of fatty acids in the liver when glucose is not readily available, especially during fasting. These compounds includes three components as 3-β-hydroxybutyrate, acetone and acetoacetate.

The two main ketone bodies are 3-β-hydroxybutyrate and acetoacetate, while acetone is the third, and least abundant

[33]. The metabolism of fatty acids increases during fasting and enhances the concentration of 3-β-hydroxybutyrate in the serum [34,35]. It is reported that 3-β-Hydroxybutyrate is a beneficial compound because it causes reduction of Alzheimer's and Parkinson diseases [36], inhibits the apoptosis of cell [37], and adipocyte lipolysis [38], causes neuroprotection, and reduces lipid peroxidation [39]. We have investigated the effect of 3-β-hydroxybutyrate, as a metabolite, on human serum albumin (HSA) and insulin glycation in physiological like condition in our laboratory. HSA as an abundant, important and multifunction protein was incubated with glucose in the presence and absence of 3-β-hydroxybutyrate (BHB) for 5 weeks. We studied the albumin structural alterations using biophysical and biochemical methods such as differential scanning calorimetry (DSC), circular dichroism (CD) and fluorescence techniques. Accordingly, the structural change of protein, which is incubated with glucose in the presence of BHB, was less than the structural change of protein which is incubated in the absence of BHB. In the case of insulin, the BHB inhibitory effect was monitored in treated insulin with glucose via measuring of some alteration in fluorescent activities like: fluorescent AGEs, BSA intrinsic and extrinsic emission, the specific binding of thioflavin T (ThT) , and finally, using circular dichroism (CD) spectrophotometer.

The results showed 3-β-hydroxybutyrate reduced AGEs formation during glycation processes (data not shown) [40, 41]. Therefore, BHB protects protein against sugar binding, inhibits the consequent alteration of the protein structure and diminishes AGEs formation. These results indicate that BHB as a fasting enhanced metabolite, directly involved in decreasing diabetic complications at molecular insight [40, 41]. Fasting in addition to be a great act of worship as one of the pillars of Islam for an entire month every year, has many health benefits for humans through prevention or lessening diseases in which BHB may act as an important contributor according to our observations.

There is a good relationship between religion and science [42]. There are notable advices about natural medicine, food consumption and general physical wellness in religions, since this kind of diets has proved by scientific researches and become a part of culture of developed world [43].

Believers have decreed fasting not only as worship and to piety gain but also for its benefits on the health. Today in non-Muslim country defined a new term as "Intermittent fasting" to reducing blood glucose and insulin levels [44]. Finally, Humans can discover the benefits of worship accompanying action through scientific and technological advances.

CONCLUSIONS

The binding of sugar to biomacromolecules especially proteins is the root of many diseases because of structural and functional changes of biomacromoleculs and induced toxic compounds formation (AGEs). According to our published results, BHB (produced by the liver and increased during fasting), diminishes AGEs as the toxic agents. The diabetic complications are the initiators of many diseases such as Alzheimer's, Parkinson, and Atherosclerosis and so on. Hence, fasting gives us physical, mental and spiritual health.

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