Assessing the effects of dietary L-Methionine supplementation induced epigenetic alterations in type 2 diabetic rats

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Abstract

Balanced nutrition plays an important role in the maintenance of healthy life. Imbalance in any of it, results in various metabolic disorders. L-Methionine (L-Met) is one of the essential amino acids which play an important role in variety of cellular processes. Reports suggest that dietary methionine restriction as well as its supplementation both have beneficial effects in animal models. But in long run methionine restriction has prominent adverse effects on bone, immune system and can cause cardiac adverse event (via hyperhomocysteinemia). Here, we report the protective effect of L-Met (0.45% L-Met supplementation in diet) on T2DM induced hyperglycemia, dyslipidemia and other complications. Interestingly, L-Met supplementation also activates hepatic p-AMPK and its downstream signaling molecule SIRT1, mimicking anti-diabetic drug metformin, an AMPK activator. Real Time PCR, results show that L-Met supplementation prevents diabetes induced increase in expression of master regulator FOXO1, hepatic DNMT1 expression and global histone H3K36 di-methylation. Furthermore, FOXO1 regulated genes, involved in hepatic glucose metabolism and lipogenesis are also modulated by L-Met supplementation. Chromatin-immunoprecipitation assay shows that L-Met supplementation decreases the H3k36me2 abundance on FOXO1 promoter. We provide first evidence for the involvement of epigenetic alterations in preventing progression of diabetes by L-Met supplementation. The preventive effect of dietary taurine supplementation on glial alterations in retina of streptozotocin-induced diabetic rats was examined in this study. Blood glucose content, content of taurine, glutamate and -amino butyric acid (GABA) and expression of glial fibrillary acid protein (GFAP), vascular endothelial growth factor (VEGF), glutamate transporter (GLAST), glutamine synthetase (GS) and glutamate decarboxylase (GAD) in retina were determined in diabetic rats fed without or with 5% taurine in a controlled trial lasting 12 weeks, with normal rats fed without or with 5% taurine served as controls. Dietary taurine supplementation could not lower glucose concentration in blood ($P > 0.05$), but caused an elevation of taurine content and a decline in levels of glutamate and GABA in retina of diabetic rats ($P < 0.05$). The content of GABA in normal control group was not altered by taurine supplementation. With supplementation of taurine in diet, lower expression of GFAP and VEGF while higher expression of GLAST, GS and GAD in retina of diabetic rats were determinated by RT-PCR, Western-blotting and immunofluorescence ($P < 0.05$). GFAP, VEGF, GLAST, GS and GAD expressions in normal controls were not altered by taurine treatment. This may have prospective implications of using taurine to treat complications in diabetic retinopathyAmino acids are the building blocks of protein, but also play important cellular signaling roles. The mechanisms through which altered levels of many amino acids are sensed and the signals transmitted are still largely unknown. Increasing evidence is showing that these signals may influence the aging process. In this regard, methionine restriction appears to be an evolutionary conserved mechanism to delay aging and supplementation with glycine can mimic methionine restriction to extend lifespan in rodents. Tryptophan restriction may also activate specific anti-aging pathways, but it could interfere with cognitive function. With exercise the consumption of dietary branched chain amino acids (BCAAs) may be beneficial in building muscle mass, but high levels of BCAAs as well as tyrosine and phenylalanine in the bloodstream are associated with metabolic disease such as insulin resistance. Individual supplementation or restriction of several different amino acids has shown promise in the treatment of insulin resistance in rodents. Much progress regarding the effects of amino acids on longevity has been made using yeast, nematodes, and fruit flies. Clearly, much more research is needed to understand the signaling pathways activated by amino acid imbalance before efficacious and well-tolerated dietary interventions can be developed for human aging and aging-related disorders. In this review the mechanisms through which altered dietary and cellular levels of the twenty proteogenic amino acids affect aging or aging-related disorders are discussed. Metabolic chronic diseases, also named noncommunicable diseases (NCDs), are considered multifactorial pathologies, which are dramatically increased during the last decades. Noncommunicable diseases such as cardiovascular diseases, obesity, diabetes mellitus, cancers, and chronic respiratory diseases markedly increase morbidity, mortality, and socioeconomic costs. Moreover, NCDs

induce several and complex clinical manifestations that lead to a gradual deterioration of health status and quality of life of affected individuals. Multiple factors are involved in the development and progression of these diseases such as sedentary behavior, smoking, pollution, and unhealthy diet. Indeed, nutrition has a pivotal role in maintaining health, and dietary imbalances represent major determinants favoring chronic diseases through metabolic homeostasis alterations. In particular, it appears that specific nutrients and adequate nutrition are important in all periods of life, but they are essential during specific times in early life such as prenatal and postnatal phases. Indeed, epidemiologic and experimental studies report the deleterious effects of an incorrect nutrition on health status several decades later in life. During the last decade, a growing interest on the possible role of epigenetic mechanisms as link between nutritional imbalances and NCDs development has been observed. Finally, because of the pivotal role of the hormones in fat, carbohydrate, and protein metabolism regulation throughout life, it is expected that any hormonal modification of these processes can imbalance metabolism and fat storage. Therefore, a particular interest to several chemicals able to act as endocrine disruptors has been recently developed. In this review, we will provide an overview and discuss the epigenetic role of some specific nutrients and chemicals in the modulation of physiological and pathological mechanisms.

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