

Review of Metabolomic Effects of Glycemic Index on Neuroplasticity, Systemic Inflammation and Epigenetic Contributors to Longevity in Man and Animals

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ABSTRACT

The recent update on the traditional food pyramid emphasizes a greater reliance on wholesome, nutritious foods, placing refined sugars and highly processed foodstuffs further down in the pyramid in attempt to decrease the prevalence of obesity and its pathophysiologic sequelae, and improve human health outcomes. Overconsumption of refined carbohydrates has been linked to systemic inflammation including neuroinflammation in the CNS, and the pathophysiologic sequela of systemic inflammation is a common observation in obesity and T2DM, where it contributes to the stigmata of the comorbidities linked to the disorder. Multiple factors contribute to the systemic inflammation, including elements of lifestyle, dietary macronutrient, micronutrient, and caloric intake, genetic predisposition, and the magnitude of the excess body fat accretion, particularly excess central adiposity. The interaction between epigenetic metabolic factors and the above contributors remain unclear but appear to include the quantity, type and glycemic index of the carbohydrates consumed. Carbohydrates with a high glycemic index contribute to greater excursions in glycemic and insulinogenic parameters, increase the generation of reactive oxygen species (ROS) and have been reported to contribute to neuronal dysregulation, neurologic demise, and epigenetically mediated senescence and cognitive decline in man and animals.

Keywords

T2sDM, Obesity, Nutrition, Therapeutics, Aging, Epigenetics, Lifestyle, Epidemiology, Metabolism, Glycated hemoglobin, Wound healing.

Introduction

In the recently posted 2025–2030 Dietary Guidelines for Americans (DGAs) developed jointly by the US Dept of Agriculture and the Division of Health and Human Services (DHHS), emphasis has been placed on consumption of wholesome, nutrient-dense foods while strictly limiting ultra-processed items, added sugars, and refined carbohydrates [1]. Hereditary, environmental and familial factors are established primary contributors to body composition [2]. While the quality and quantity of an individual's dietary intake are clear and uncontested contributors to healthy aging, the biochemical mechanisms through which the nutrient-

induced epigenetic interactions on longevity and senescence remain complex, unclear and incompletely defined. The typical dietary composition consumed by populations throughout many of the industrialized nations has undergone gradual changes with the advent of improvements in industrial technology and food processing maneuvers over the past century, including what often appear to be less healthy adjustments in the macronutrient and micronutrient composition of commercially prepared food selections. The fresh, wholesome farm-to-table foods of past generations are being replaced by manufactured foods that contain greater quantities of additives, including preservatives, simple sugars and salt that are typically not present in wholesome food selections [3]. From a food safety perspective, the commercialized global food supply is considered safer overall than in past generations despite the addition of various additives during their manufacture that are intended to help to preserve the foodstuffs

and thus extend their viable shelf life. This shift in the food supply has resulted in a greater reliance of artificially sweetened, manufactured, and calorically dense foods often lacking adequate fiber content than were commonplace with our ancestors, including the consumption high fructose syrup sweetened enriched foods and beverages now at an historic high [4]. Additionally, the prevalence of obesity and overweight conditions, along with their major comorbidities including T2DM are approaching epidemic proportions throughout much of Western civilization, where more than a third of the population continues to remain at risk [5]. Thus, the combination of dietary changes and familial predispositions to contribute to unhealthy metabolic and pathophysiologic attributes of emerging lifestyles poses a challenge to health and longevity of the affected global populations.

In a recent paper, Yi et al. established carbohydrate quality as an indicator of glycemic index as a contributor to epigenetic markers of aging in a cross-sectional clinical study [6]. The authors quantified established DNA markers linked to aspects of longevity over a broad range of diets extending from those with a high fiber to carbohydrate ratio to those presenting with a 20+ year history of consuming diets with a lower fiber to carbohydrate ratio [6]. In those studies, the authors obtained their DNA analysis in a large cohort of patients after following them for 20 to 30 years, and correlated their findings with recent analysis of dietary preferences based on an elaborate dietary recall information survey obtained during interviews during their most recent month. Individuals who reported caloric extremes in their dietary preferences and practices including dietary history were excluded from their study. Their results demonstrated that epigenetic markers were inversely related to the CHO to fiber ratio and to total carbohydrate ingestion, thereby establishing an association between dietary carbohydrate type and epigenetic markers of longevity. Moreover, these observations further suggested that both nutritional and environmental factors being implicated in the epigenetic expression of aging and antiaging traits. Among those contributory factors, the discovery of sirtuins, as silent information transfer factors may play a central role [7-10]. Specifically, Sirtuin-1(Sirt-1) has been reported to be calorically sensitive to nutritionally mediated transcriptional factors that are implicated in the epigenetic regulation of mitochondrial apoptosis, immune functions, appetite, diabetogenic expression, glucose homeostasis, hormonal regulation, and numerous other aspects of human health, longevity and energy metabolism [7,11,12]. Indeed, Sirt 1, an NAD(+) dependent histone deacetylase protein, has been proposed as the defective entity in the progression of various chronic diseases including insulin resistance and systemic inflammation, common hallmarks of obesity and T2DM and has often been referred to as the 'antiaging' factor [10,11]. In addition, as reviewed by Martins, the down regulation of sirtuins reduces hepatic biochemical detoxification processes, thereby further contributing to major organ dysfunction syndromes that threaten healthful longevity [8]. Thus, the nutritional regulation of Sirt 1 activation and function is deemed an essential intermediate in maintaining glucose and insulin homeostasis, immune regulation, the expression of genomic mRNA transcription factors and their

physiological contributions to health, disease and longevity in man and animals [8] Thus, Sirt 1 would seem to fulfill the biological criterion as a silent but essential nutritionally modulated anti-aging factor [7,11].

In animal studies with a congenic rodent model highly predisposed to early-onset obesity, Tulp et al. recently reported that an isoenergetic, high carbohydrate vs. a high glycemic index isoenergetic diet, consisting of a high carbohydrate, high glycemic index sucrose-laden diet vs a lower glycemic index cornstarch diet of the same caloric density resulted in significantly decreased brain mass in the obese phenotype when compared to similarly fed lean littermates of the same strain [13-16]. In addition, decreases in total brain protein and DNA content were also noted, consistent with an interaction between the obese phenotype and the carbohydrate source contained in the diet. When the effects of cornstarch vs sucrose were measured, it was observed that the higher glycemic index [sucrose-laden] diet was associated with yet further decrements in net mass, brain protein and DNA content [3,13,14]. In contrast to the human studies, in the rodent study the carbohydrate to fiber ratio remained constant throughout in both the higher- and lower glycemic index rodent diets, suggesting the important contributions of both the epigenetic factors that resulted in the obese phenotype, in addition to the glycemic index of the prevailing diet were predominating factors in the neurosenescence and brain shrinkage observed. As in most humans, hyperinsulinemia is a landmark feature of the obese phenotype in this strain and became further exaggerated when fed the sucrose-laden diet in this and other studies [3,15,17,18] Chronic inflammation is a hallmark of obesity and insulin resistance, and while markers of inflammation were not directly measured in the recent studies, the pathophysiologic stigmata common to chronic hyperinsulinemia were present, including the presence of atheromatous lesions in the obese phenotype [19].

While acute inflammation is an essential component of normal physiological defense mechanisms, prolonged or excessive inflammation can contribute to pathophysiologic features of disease. Chronic systemic inflammation of obesity has been linked to neuroinflammation and apoptosis, with often serious consequences [19-24]. In addition, dysregulation of Sirt 1 has been demonstrated to be associated with the type and quality of carbohydrate consumption consumed and the ratio of carbohydrate to dietary fiber in recent large scale clinical studies [6]. In those studies, the carbohydrate to fiber ratio was found to be critical in determining the magnitude of inflammatory damage, with the highest carbohydrate/lowest fiber ratio the most injurious [5]. In contrast, while in the recent rodent studies the ratio of carbohydrate to fiber remained constant throughout the study, thus eliminating the macronutrient to fiber ratio as a variable. In those studies, both the absolute content and the glycemic index of the carbohydrate were contributory to brain senescence, and the higher glycemic index ration further impeded retention of brain protein and DNA content [3,6,20-28]. Chronic systemic low grade inflammation contributes to metabolic and cardiovascular disorders, deemed

to be brought about via actions of inflammatory cytokines and reactive oxygen species (ROS) including IL-6 and others and inflammatory cytokines that are linked to chemoattractant proteins including inflammatory MCP-1 [28-30]. The inflammatory state has been reported to damage DNA including its repair mechanisms, thereby preventing cellular regeneration and further cellular replication or restoration. Accordingly, it has been associated with premature cellular decline of neuronal and other tissues, increased mortality and morbidity resulting from the comorbidities cited above. Adipose tissue based M1 and M2 macrophages infiltrate fatty tissue depots, with the visceral depots posing the greatest risk [13,22]. The M1 macrophages are considered proinflammatory, while M2 macrophages contribute protective functions including a balancing neutralization of the inflammatory actions [29,30]. During inflammatory responses, tissue macrophages are activated by various noxious stimuli, including microbial products, damaged cells, or other immuneoreactive cells, and which factors contribute to the progression of macrophages into pro-inflammatory M1 phenotypes. When active, they release IL-6, IL-12, TNF- α and other inflammatory substances which contribute to a spectrum of pathophysiologic processes. In contrast, endogenous M2 macrophage pathways reduce ROS and obesity related inflammation and improve cardiovascular and other pathologic processes. Antioxidants and phytochemical compounds commonly found in fresh, wholesome foods help to quench inflammatory ROS and thus contribute to the protective, M2 Macrophage support and other hormonal and metabolic actions and thus enhance natural longevity [28-34].

Summary

In conclusion, the onset of parameters of cognitive decline often become apparent in aging, but the metabolic and nutritional factors which initiate the processes remain largely unclear. Several recent studies cited have now associated obesity and insulin resistance to brain senescence in humans and in aging congenic obese rats. Several studies that support a link between chronic hyperinsulinemia, epigenetic expression of obesity, brain shrinkage and decreased brain protein and cellular deoxyribose nucleic acid (DNA) content in a congenic rodent model of early onset obesity were reviewed. Aging congenic obese LA/Ntvl/-cp rats developed early onset, epigenetically induced obesity and hyperinsulinemia soon after weaning regardless of diet, resulting in pathophysiologic stigmata that persisted thereafter throughout their lifespan, and which became further aggravated when fed a sucrose laden, high glycemic index diet. Groups of lean and obese rats were fed nutritionally complete isoenergetic diets continuing cornstarch (ST) or sucrose (SUC) from weaning until 10.5 months of age. Longevity of obese << lean in both sexes. Obese rats were found to exhibit decreased brain mass associated with insulin resistance, and accompanied with proportionate decreases in brain lipid, protein and DNA content in the obese but not the lean phenotype. In addition, the decreases in brain mass, protein and DNA composition were of greater magnitude when fed the sucrose-laden vs isoenergetic cornstarch diets in both lean and obese phenotypes. These observations are suggestive of an

increased potential for a contribution of the metabolic sequelae of insulin resistance as a pathophysiologic factor in the progression of neurosenescence, brain shrinkage and cognitive decline in the aging obese, hyperinsulinemic rat, analogous to clinical observations which may occur in dementia and Alzheimer's disease in humans. Thus, nutritionally complex carbohydrate, consumed in moderation has been found to promote a healthy contribution to metabolomic profiles and longevity and, while consumption of high glycemic index diets contributes to insulin resistance and multiple pathophysiologic sequelae including variable magnitude of cognitive decline in man and animals [35]. Malnutrition from an early age is a well-established contributor to impaired neurologic and decreased cognitive development in man and animals, implicating both the macronutrient to fiber ratio and the macronutrient and micronutrient distribution as critical factors in degerming metabolic and pathophysiologic aspects of health and longevity, while the recent clinical observations that implicate dietary sweetness cited above support the same phenomena in animal and human studies.

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