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Obesity is a Ticking Bomb in the 21st Century: Can Quercetin Reverse Obesity-Induced Hippocampus Dependent Cognitive Decline?

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ABSTRACT

The prevalence of obesity in men and women is increasing in developed and developing countries around the world. Human and animal investigations indicate that obesity adversely impacts people health, predisposing them to chronic diseases such as dyslipidemia, hypertension, type 2 diabetes mellitus, cognitive dysfunction, brain ischemia, Alzheimer's disease and so on. High fat diet induces oxidative stress which may be involved in civilization neurodegenerative diseases such as mild cognitive impairment and Alzheimer's disease. In this study, we have evaluated influence of quercetin on obesity-induced cognitive decline. Thus, in the obesity-induced cognitive decline, an appropriate dose of quercetin can reduce oxidative stress resulting in an enhancement of hippocampus dependent cognition. But under a balanced condition, quercetin may force pro-oxidant effects and worsen cognition.

Key words: Obesity, Cognitive decline, Neurodegeneration, Brain ischemia, Alzheimer's disease, Quercetin, Oxidative stress.

INTRODUCTION

Obesity is described such as abnormal and/or unrestrained accumulation of body fat and is considered present when a person's weight exceeds desirable weight by 20%. Worldwide obesity levels have increased unprecedentedly over the past couple of decades [1]. Circa one-third of adults meet criteria for obesity (BMI >30), approximately 17% of women and 12% of men have severe obesity (BMI>35) in the United States [2]. Studies have shown that obesity is a risk factor for poor neurocognitive outcomes, including mild cognitive impairment, Alzheimer's disease and other forms of dementia, cardiovascular disease, metabolic syndrome, cancer and so on [3-8] and may increase multi-morbidity [9]. Current investigations have noted that severe obesity is also associated with increased risk for cognitive decline, and this risk appears to be elevated with age [10-12]. The awareness of the modern world obesity as a major health problem and an uncontrolled worldwide epidemic has to be increased in the society [6,13,14]. The epidemic of obesity is a global health problem that is expected to rise considerably in low- and middle-income countries, too. Their populations, shift from a traditional diet to more western pattern of diet and are engaging in sedentary activities [15]. As a result, the prevalence of people obesity in these countries is significant with substantial variation in levels and trends in different countries. Over the past 20 years, obesity rate increased from 15% in 1980 to 32% in 2004 among adults in the United States [16]. More than 60 million people (30%) of the United States adults aged ≥20 years are obese; the prevalence among members of minority groups is even higher [16]. In New Zealand, circa 29% of adults now are classified as obese [17]. Obesity is also increasingly prevalent among children and adolescents. Approximately, 38% and 17% of children and adolescents, respectively, in the United States are obese [18]. The prevalence of obesity is rising alarmingly among children and adolescents in the China, with an estimated 120 million now in the obese range [19]. According to the WHO global estimates in 2013 were nearly 700 million adults obese across the world [1,18].

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Obesity and overweight are widespread in women of procreative age [20-25]. In Ghana, the predominance is 37.1% [20], in the United States 35.5% [23], in the United Kingdom 33% [24], in Mexico 32.4% [21], in Brazil 16.1% [22] and in China 16% [25]. Maternal obesity can result in negative metabolic diseases for both the mother [26,27] and the offspring [26,28-30]. Obesity rise exponentially worldwide to almost epidemic ratio [6,13,14]. The World Health Organization has declared obesity as one of the top ten adverse health risk factors in the world [31]. Today worldwide, 1.5 billion population is overweight or obese [14].The recent rise in obesity rates is associated with the interaction between changes in dietary habits such as augmented consumption of foods that are either industrially processed or high in energy, lower physical activity and genes [31-33]. The evaluated complete digits of overweight and obese adults in 2005 were 937 million and 396 million, respectively [34]. If latest trends continue without any reduction in intensity and/or strength, the amount of individuals were estimated to complete 2.16 billion overweight and 1.12 billion obese persons, by 2030 [34,35]. This review will focus on obesity-induced cognitive decline and how supplementation of quercetin can improve neurocognitive outcomes.

Obesity-Related Diseases

It is well known that higher rates of obesity have been linked to higher rates of obesity-related diseases, such as some cancers, heart disease, hypertension, type 2 diabetes, respiratory diseases, stroke and neurodegenerative disorders like mild cognitive impairment,

Alzheimer's disease and different forms of cognitive decline [16,36,37]. This presents an increasing economic and social burden to individuals, families and the healthcare system [1].

Today obesity and obesity-induced disorders are the main focus of healthcare providers and healthcare policy due to its sustained increase in prevalence over the last decade [38]. A consistent body of evidence now demonstrates that being overweight or obese in childhood and adolescence has health consequences and leads to increased morbidity and premature mortality in adulthood [39]. Relative to normal weight, both obesity grades 2 and 3 were associated with significantly higher all-cause mortality [40]. As obesity and dementia rates reach epidemic proportions, an even greater interest in the effects of nutrition on the brain have become evident. The basis for the inter-relationships between chronic obesity and cognitive decline and others diseases lay at a basic intracellular level that is oxidative stress [38]. Augmented oxidative stress, which is attributed to an excessive production of reactive oxygen species and/or impaired antioxidant defense machinery in body, seems responsible for the abnormal gain of weight in obese subjects [38]. Preventing obesity and obesity-induced disorders are the optimal long-term population strategy [37] and must be a government's priority. There are many approaches which could be taken to facilitate this, however it is important not to forget those who are currently obese. The costs of obesity and its consequences are staggering for any society, crippling for countries in development [1]. Many different therapeutic approaches in obesity and obesity-induced cognitive decline have been investigated including exercise, diet [37], behavioral therapy, and medication. None have been found to be effective enough as sole tool in this health problem. In order to improve the quality of the health care and to minimize the cost, it is important to investigate and standardize prevention and/or treatment and to adapt them to social and cultural aspects. Today, nutrition research has moved on from the traditional concepts of avoiding nutrient deficiencies and basic nutritional adequacy to the new concept of positive and/or optimal nutrition [37]. Many traditional food products including vegetables, fruits, flaxseed, barley, oat, whole grains, and milk have been found to contain component with potential health benefits. Nowadays, functional foods can be used in the prevention and amelioration of several chronic diseases, such as the obesity-related disorders [37,41].

Obesity-Related Cognitive Decline and Treatment by Quercetin

The paper by Xia et al. [8] deals with the nature of the problem population obesity along with their own proposal in the treatment of obesity-induced disorders dangerous to health such as cognitive decline. Above study addresses the new therapeutic options in the treatment of obesity-induced cognitive decline with special emphasis on emerging knowledge of its genetics [8]. This timely study is a 2-side discussion paper which serves to define the dangerous relationship between obesity, cognitive decline, genes [37] and quercetin. The authors investigate the diverse effects of quercetin under different diets. Quercetin (3,3′,4′,5,7-pentahydroxyflavone) an important flavonoid found in apples, citrus fruits, red onion, berries, tea, and red wine is one of the most common flavonoids in the human diet. Because quercetin is plentiful in plant-based products in the diet, it is important to determine whether quercetin can reduce human health challenges such as obesity and obesity-induced cognitive decline. Hence, they have characterized the effects of quercetin in an appropriate animal model of diet-induced obesity and associated cognitive decline. Their rodent model mimics most of the problems associated with human obesity. Quercetin is a potent antioxidant and exhibits some vital medicinal properties. In fact, growing body of evidence shows that flavonoids regulate the activities of metabolizing enzymes, modulate gene expression, nuclear receptors, and subcellular signaling pathways, and repair injured DNA by oxidative stress [42-45]. Free radicals, which can damage cell membranes and DNA through a process known as oxidative stress, are blamed for many of the diseases associated with obesity.

Xia's and colleagues [8] discus various mechanisms by which a high fat diet can alter the brain and cognition [37]. The balance of evidence from their paper indicates that high fat dietary pattern predisposes to obesity and damages the brain and cognition. To the best of our knowledge, this is the first research to document the relationship between a high fat diet, oxidative stress, gene dysregulation and cognition changes in a more detailed way and one of the first to hold the view that quercetin can enhance memory. Their report was to determine the protective and detrimental effects of quercetin on hippocampus dependent learning and memory in mice fed with either normal or high-fat diets. The authors demonstrated that the supplement of quercetin can improve cognition in only high-fat diet group, but not in the normal diet group. The authors give the reason of their findings that quercetin may act as pro-oxidant agent in normal situation, but quercetin acts as anti-oxidant agent in high oxidative stress condition. The authors proposed that the beneficial effect of quercetin was on the cellular effects by the interactions with specific proteins involved in intracellular signaling such as improving of Pi3k/Akt signaling followed the augmentation of BDNF expression [46]. One of the major defense systems against oxidative stress-related injury is the Nrf2 system. Nrf2 is a transcription factor present in inactive forms in the cell. Once activated, Nrf2 translocates to the nucleus and activates the antioxidant response machinery. This, in turn, gives rise to enzymes and proteins, such as HO-1, which reduce the cellular oxidative stress. This suggests that the activation of Nrf2 system by quercetin can protect hippocampus dependent function. Their data show that the genes such as Creb, Bdnf, Pi3k, Camk II, Nrf2 and Akt, originally identified as a pathogen sensor and a proposed regulator of the cognitive function response against oxidative stress, are down regulated in the hippocampus of obese individuals. One most important point in quercetin action is probably related to the integration of signals from different molecules with similar biological functions. It is very likely that each of these factors plays a role in diet-induced obesity and/or obesity-induced cognitive decline.

However, long-term effects of obesity on the brain need to be further examined. The aspect of the diverse effects of quercetin, depending on food categories, may look controversial at a fist glance [46]. The appearance of controversy may arise in part because studies of different doses of quercetin (low and high) in different diets (normal and high fat) are completely new.

Quercetin high dose intervention results in large effects on down regulated genes involved in learning and memory. Xia and colleagues [8] presented strong evidences to support beneficial effects of quercetin on obesity-induced cognitive decline. However, given the unexplained heterogeneity these findings must be interpreted cautiously. Strengths of their study include the assessment of markers of oxidative stress in serum and hippocampus at baseline and after the intervention, measurement food intake, blood glucose, serum lipids, body weight, learning and memory and gene dysfunction. Currently some research in experimental models of Alzheimer's disease [47,48], brain ischemia [49] and aged animals [50] support the beneficial effect of quercetin on cognitive decline.

Conclusions

The paucity of literature on treatment of obesity-induce cognitive decline in humans points out the need for much additional research on obesity and obesity linked diseases [8,37].

However, further studies considering gene-gene and gene-environment-oxidative stress interaction should be conducted to investigate the association [37]. Further research is also required to analyze how quercetin influences down regulated genes as driving mechanisms for the clustering of obesity-associated cognitive decline. Additionally, more research is needed to determine optimum for the quercetin's positive action. We hope that the present paper will stimulate further research in this topic and brings to attention the data that would provide a better understanding of the management of obesity-induced cognitive decline. Xia's and colleagues [8] findings have important public health implications concerning the control by quercetin of the cognitive decline associated with obesity epidemic [37] and supporting idea of clinical trials of this relatively safe natural compound. A better understanding of the mechanisms linking severe obesity to adverse neurological outcomes is much needed [37]. In conclusion, the present results indicate that quercetin has protective and detrimental effects on cognition depending on the diet. Thus, careful consideration must be given to the evaluation of the redox status of the organism and the in vivo concentration of quercetin when utilizing dietary quercetin to improve animal and human cognition. Changes in nutritional status and lifestyle may decrease permanent damage to cognition health [37]; thus, prevention of obesity should be the goal by taking antioxidants rather than pharmaceutical treatment. Additionally, quercetin treatment prevents cognitive dysfunction provoked by chronic stress induced in rats, which may render quercetin as an effective agent for the treatment of stress-related disorders [51]. The protective action of quercetin on cognitive decline may be connected with both reducing the plasma corticosterone level and its pro-oxidant activity [51]. More research is required to support quercetin use as a lead particle in its free form in acute therapies, requiring new pharmacological formula and/or structural modification to limit its pro-oxidant effect. This fact would limit an acute treatment by quercetin in spite of its hopeful protective property in vivo and in vitro. Adjustment of the molecule by changing the harmful hydroxyl groups of the catechol moiety can reduce the generation of quinones and could be the first key step to increase its protective activity over the toxic one [52]. Activation of Nrf2, increasing its displacement to the

nucleus and facilitating the formation of proteins against oxidation and pro-survival is especially important. Increasing glutathione level is a key factor in the restoration of the redox system in intracellular space [52]. Activation of transcription factor such as NF-kB and/or molecules for survival, like sirtuins, and kinase inhibition as well as influence on intracellular signaling seem factors of the complex pro-survival feature of quercetin [51].

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