Calorie Restriction and Obesity under the Regulation of SIRT1

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ABSTRACT

Obesity is one of the most important risk factors for various chronic diseases, especially related with environmental life style and eating habits. Obesity is also a risk factor of metabolic diseases, cardiovascular diseases, diabetes, and certain cancers. Numerous studies of calorie restriction (CR) in various organisms have shown several beneficial effects of not only decreased body fat and blood pressure, decreased inflammatory markers in plasma, increased insulin sensitivity, and improved lipid profile but also improved endothelial function, decreased oxidative damage by reducing energy flux and metabolism, and decreased ectopic fat accumulation. Furthermore, CR activates SIRT1, a nutrient-sensing deacetylase, involved in metabolic regulation and longevity. Resveratrol, as a mimetic of CR, is one of well-known sirtuin activating compounds. Resveratrol is related with longer lifespan by increasing insulin sensitivity, decreasing insulin-like growth factor-1, and increasing AMP-activated protein kinase activity. Therefore, the present review focuses on CR related with obesity and also the relationship between CR and SIRT1 in metabolic mechanism levels. Furthermore, we will introduce resveratrol, as an activator of SIRT1, and the beneficial effects of resveratrol.

Key words: obesity, calorie restriction, SIRT1, longevity, resveratrol

Introduction

During the last several decades, obesity has dramatically increased worldwide. These trends have been deeply related with environmental life style changes, food product developments, and eating habit changes to the

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nutritional transition. The nutritional transition is also associated with large portion sized meals, highly energy dense foods with high fat and sugar, and low fiber of the meal.\textsuperscript{1,2} Therefore, obesity caused by these factors is a serious personal, public, and global health concern. Numerous studies have shown that adequate reduction in calorie intake is associated with prevention of chronic diseases, delay in aging process, and extension of lifespan.

One of the surprising data reported by Clive McKay, Mary Crowell, and Leonard Maynard at Cornell University in 1935 was that rodents with reduced amount of food intake lived much longer than their \textit{ad libitum} counterpart.\textsuperscript{3} It turned out that calorie restriction (CR) was responsible for health benefits. Similar results have been observed in other various species including yeast, worms, flies, spiders, rabbits, dogs, monkeys and humans. CR is defined as a reduction of energy intake in the absence of malnutrition. Several human studies have shown that CR regimen has various beneficial effects, such as (i) decreased body fat and blood pressure, (ii) decreased inflammatory markers in plasma, (iii) decreased circulating growth factors level, (iv) increased insulin sensitivity, (v) improved lipid profile, and (vi) younger appearance.\textsuperscript{4-8} The insulin sensitivity induced from CR regimen is also related with SIRT1 activation. SIRT1, an oxidized nicotinamide adenine dinucleotide (NAD\textsuperscript{+})-dependent deacetylase, was shown to promote longevity in various organisms. SIRT1 has diverse effects in metabolically important tissues, such as improved DNA stability, increased repair and defense, coordinated stress response, enhanced energy production and use, and prolonged cell survival.\textsuperscript{9,10}

Therefore, the purpose of this review is to summarize some of the literature on CR related with obesity. Then we will focus on the relationship between CR and SIRT-1 in a metabolic mechanism level. We also will try to explain CR mimetic of a resveratrol as an activator of SIRT1 and the beneficial effects of the resveratrol to health and longevity.

**Calorie Restriction (CR) and Obesity**

Numerous studies of CR in humans have presented various beneficial effects such as decreased BMI, body fat, blood pressure, insulin level, leptin level, and others against obesity-related health problems.\textsuperscript{11,12,13} In a study of CR on body composition and fat distribution for 6 months, participants (25 \( \leq \) BMI < 30) lost 10\% of BW, 24\% of fat mass, and 27\% of abdominal visceral fat.\textsuperscript{11} Furthermore, CR effects for 6 months showed that fasting glucose level and body temperature of participants (25 \( \leq \) BMI < 30) were reduced in CR group and CR with exercise groups compared with the control group.\textsuperscript{13} CR may also have alterations and beneficial effects not only on secretory profiles of adipocytes but also on several metabolic factors that are altering insulin sensitivity. Short term (3–6 weeks) CR had no effect on circulating adiponectin concentrations\textsuperscript{14,15}, whereas long term (52 weeks) CR increased the plasma adiponectin levels.\textsuperscript{16} Adiponectin is produced white adipose tissue and related to trigger insulin sensitivity by upregulating AMP activated protein kinase (AMPK) in target tissues. In addition to adipocytes, CR reduced circulating proinflammatory factors (C-reactive protein (CRP), TNF\textsubscript{a} IL-6, IL-8), in obese DM subjects.\textsuperscript{17} It is well known that increased IL-6 and CRP concentrations are predictors of development of myocardial infarction and type 2 diabetes mellitus (T2DM).\textsuperscript{5}

CR could minimize oxidative damage by reducing energy flux and metabolism, thereby influencing the aging process.\textsuperscript{9} Reduced metabolic rate by using CR may decrease oxygen consumption, which could decrease ROS formation and also decrease protein carbonylation, which is the determining factor of the amount of protein oxidation induced by ROS.\textsuperscript{18}

Based on these observations, Guarente L. suggested a hypothesis that metabolic syndrome, such as obesity, T2DM, and cardiovascular disease, and calorie restriction, such as decreasing body fat, metabolic factors and proinflammatory factors, are balanced at opposite ends of the same spectrum on the basis of diet and physical activity. Furthermore, identification of important regulators that mediate the positive effect of CR regimens could offer the hope of new treatments to improve life span.\textsuperscript{19}

**Calorie Restriction and SIRT1**

1. Sirtuins Activation by CR

Sirtuins have been known as critical regulators for expansion of life span via CR in model organisms. A role for sirtuins in mediating CR was first demonstrated in yeast (\textit{S. cerevisiae}) when dilution of glucose, the energy