Regular article

日本食品化学学会誌、Vol. 30(2), 68-81(2023)
Japanese Journal of Food Chemistry and Safety (JJFCS)

Alkyl resorcinol protects against obesity-related metabolic disorder with mitochondrial activation by PGC-1α deacetylation

(Received January 5, 2023)
(Accepted March 9, 2023)

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Abstract

The deacetylation of peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α) by the activation of mammalian sirtuins (SIRTs) promotes mitochondrial function and metabolic homeostasis. We previously demonstrated that alkylresorcinols (ARs) from rye wheat raised the Vmax of recombinant SIRT1 for NAD+ and extended the lifespan of the fruit fly *Drosophila melanogaster*. Olivetol (1,3-Dihydroxy-5-pentylbenzene), the smallest alkyl chain AR from lichen, also raised the Vmax of recombinant SIRT1. We hypothesized that the specific deacetylation of PGC-1α would: (*i*) be enhanced by increasing the rate of the enzyme-catalyzed reaction of SIRT1, and (*ii*) affect mitochondrial function and obesity-related metabolic disorders. We investigated the effect of ARs on obesity in mice fed a high-fat diet and in humans. The weight of the olivetol-high-fat diet (HFD) mice was significantly suppressed compared to the control-HFD group. The human subjects' BMI was significantly lower in both the first and second halves of the 40-day test period compared to the placebo group. Compared to the control-HFD data, the amount of acetylated PGC-1α in the skeletal muscle of the olivetol-HFD mice was significantly decreased and the number of mitochondria in their brown adipose tissue (BAT) was significantly increased. In a supplementary experiment, the median lifespan of *Drosophila melanogaster* fed the olivetol-HFD was significantly extended by up to 113% in males and 109% in females versus that in the *D. melanogaster* fed a normal diet. The AR effects were thus associated with an induction of genes for lipid metabolism and were largely explained by PGC-1α deacetylation.

Keywords : sirtuin, olivetol, alkylresorcinol, obesity, PGC-1α

I Introduction

Sirtuin, a protein with a core domain that is highly conserved in evolution from bacteria to mammals, is a nicotine adenine dinucleotide (NAD)-dependent deacetylase[1]. SIRT1 (homolog of the sirtuin 2 (sir2) in yeast) regulates peroxisome proliferator-activated receptor gamma (PPARγ) coactivator-1alpha (PGC-1α) in skeletal muscle cells[2]. It has also been reported that the browning of white adipose tissue (WAT) is promoted by SIRT1-dependent deacetylation[3]. Functions of SIRT1 metabolic regulation in each major tissue of the mammalian have been described[4]. SIRT1 and PGC-1α form a stable complex, and SIRT1 regulates the activity and acetylation status of PGC-1α[5]. PGC-1α was the first molecule identified as a cofactor for the nuclear hormone receptor PPARγ, which is required for adaptive thermogenic reactions to low temperatures[6]. Oxidative phosphorylation and mitochondrial biogenesis by resveratrol (Res) were largely explained by

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