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Maternal resveratrol intake during lactation attenuates hepatic triglyceride and fatty acid synthesis in adult male rat offspring

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ABSTRACT

Resveratrol (3,5,4-trihydroxystilbene) is a natural polyphenolic compound found in grapes and red wine and has been shown to exert protective effects on the liver preventing lipid accumulation induced by a high-fat diet. However, no studies have shown that the nutritional resveratrol intake by the parental generation has modified lipogenesis in an adult offspring. The aim of this study was to investigate whether maternal resveratrol intake during lactation affects lipogenesis in adult male rat offspring, and if it does, what is the molecular mechanistic basis. Six male pups born from mothers given a control diets during lactation (CC group) and six male pups born from mothers given a control diet as well as resveratrol during lactation (CR group) were fed a standard diet until sacrifice at 36 weeks. Adult male offspring from mothers given resveratrol during lactation (CR group) had lower body weight from the fourth week of lactation until adulthood, but no significant change was observed in the relative food intake. Low levels of plasma triacylglycerol were found in the CR group compared to the CC group. Histopathological analysis of the livers of adult male rat offspring revealed lipid accumulation in hepatocytes in the CC group, whereas lipid droplets were rare in the CR group. Hepatic protein levels of AMPK-phosphorylated at ser403, Sirt1, and Nampt in the CR group were upregulated significantly compared to the CC group. These results indicated the maternal resveratrol intake during lactation-induced activation of AMPK through Sirt1 upregulation. In this study, significant upregulation of the levels of precursor of sterol regulatory element binding protein-1c (SREBP-1c) and downregulation of the ratio of active-SREBP-1c/precusor-SREBP-1c were observed in the CR group compared to the CC group. These results suggested that proteolytic processing of SREBP-1c was suppressed by AMPK in the livers of the CR group. It is well known that SREBP-1c regulates the lipogenic pathway by activating genes involved in triglyceride and fatty acid synthesis. The present study showed significant downregulation of hepatic fatty acid synthase (FAS) and acetyl-CoA carboxylase (ACC) levels in the CR group. These results indicated that maternal resveratrol intake during lactation suppressed SREBP-1c cleavage and nuclear translocation and repressed SREBP-1c target gene expression such as FAS and ACC in the livers of adult male offspring. These changes attenuate hepatic triacylglycerol and fatty acid synthesis in adult male offspring.

1. Introduction

Resveratrol (3,5,4-trihydroxystilbene) is a natural polyphenolic compound found in grapes and red wine that has been shown to extend the lifespan of many organisms [1,2]. Resveratrol is well known for its biological effects, including anticancer, anti-inflammatory, and antioxidant properties [1]. Resveratrol exerts protective effects on the liver by preventing lipid accumulation induced by a high-fat diet [1–3]. Despite resveratrol's well-known health benefits, its precise mechanism of action remains controversial [4].

The biological effects of resveratrol depend on activation of Sirtuin 1 (Sirt1), a mammalian ortholog of Sir2 [5,6]. Sirt1 regulates AMP-

Abbreviations: Sirt1, Sirtuin 1; SREBPs, Sterol regulatory element binding proteins; AMPK, AMP-activated protein kinase; ACC, Acetyl-CoA carboxylase; Fas, Fatty acid synthase; Nampt, Nicotinamide phosphoribosyltransferase; LKB1, Liver kinase B1; ER, Endoplasmic reticulum

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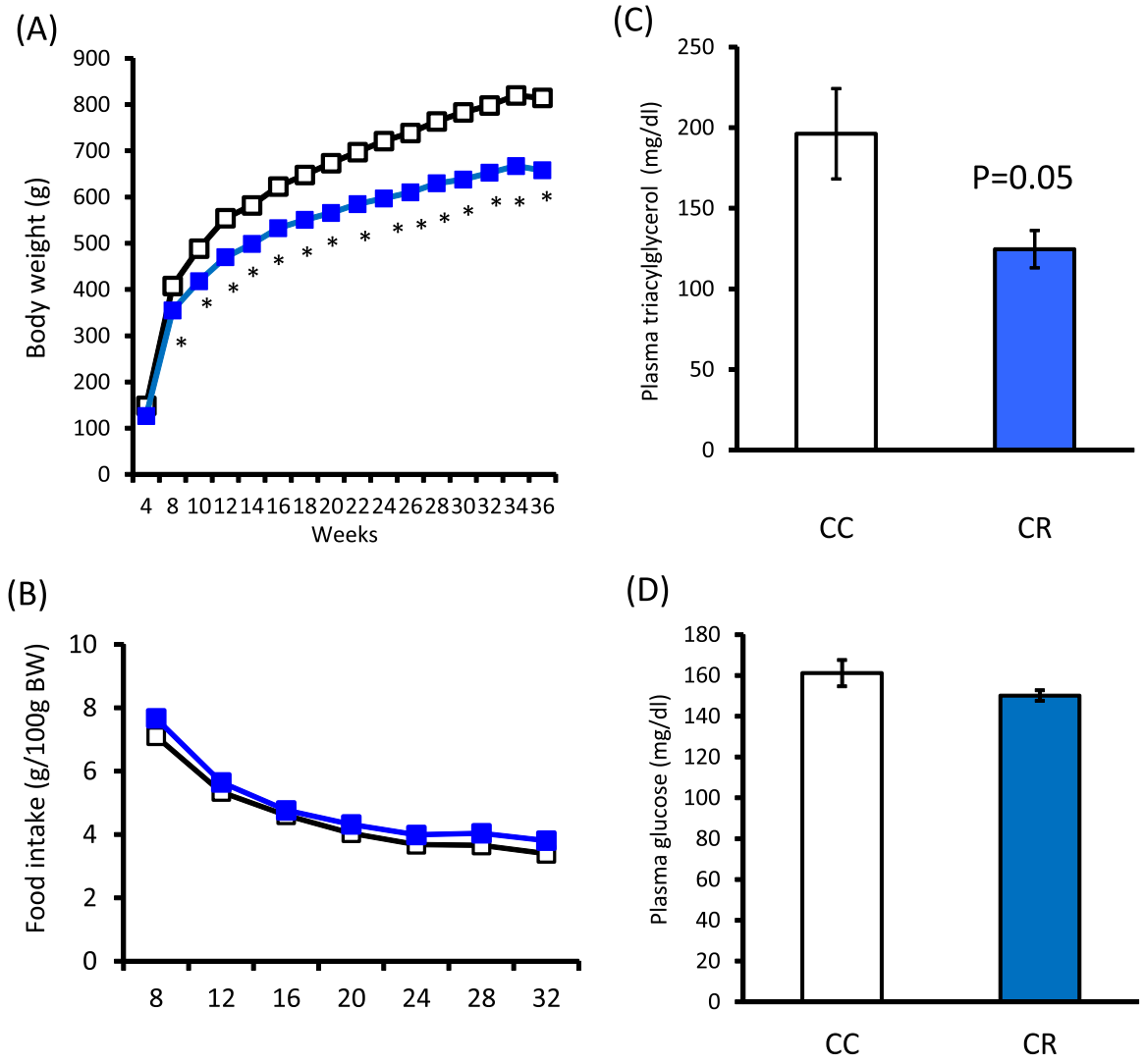

Fig. 1. Body weight and relative food intake. (A) Body weight of rats whose mothers were fed with a control diet (open square) (CC group) or control diet+administration of resveratrol diet (blue square) (CR group) during lactation. (B) The relative food intake (g/100 g body weight) from 8 weeks to 32 weeks. (C) Plasma triacylglycerol concentration (mg/dL) of rats in each group. (D) Plasma glucose concentration (mg/dL) of rats in each group. n=6 in each group. *$p < 0.05$.

activated protein kinase (AMPK) through deacetylation and activation of LKB1 [7]. A previous report has shown that polyphenols, including resveratrol, increased phosphorylation of AMPK and its downstream target, acetyl-CoA carboxylase (ACC) in HepG2 hepatocytes [8]. AMPK activation by polyphenols can explain their beneficial effects on hepatic lipid accumulation, hyperlipidemia, and atherogenesis in type 1 diabetic LDL receptor deficient mice [8].

Sterol regulatory element binding proteins (SREBPs) are key lipid synthesis transcription factors [9,10]. SREBP-1c regulates the lipogenic pathway by activating genes involved in fatty acid and triglyceride synthesis. SREBP-1c is synthesized as a precursor protein that is inserted into the endoplasmic reticulum (ER) membrane. The precursor of SREBP migrates from the ER to the Golgi and undergoes sequential proteolytic processing to release the transcriptionally active N-terminal domain. The active nuclear form of SREBP-1c is translocated into the nucleus; it binds to the sterol regulatory element and activates the transcription of SREBP-responsive genes. The dysregulation of SREBP-1c has been implicated in the pathogenesis of hepatic steatosis, dyslipidemia, and type 2 diabetes [11,12]. AMPK and AMPK activators such as polyphenols phosphorylate inhibit SREBP-1c proteolytic process, nuclear translocation, and gene expression of target lipogenic enzymes activity and it ultimately suppresses hepatocyte lipogenesis [13]. SREBP-1c regulates the lipogenic pathway by activating genes involved in fatty acid and triglyceride synthesis. Fatty acid synthase (FAS) play an essential role in *de novo* lipogenesis by converting the acetyl-CoA into palmitate that subsequently is esterified into triglycerides in the liver. ACC, the rate-limiting enzyme that catalyzes the carboxylation of acetyl-CoA to form malonyl-CoA, is the pivotal enzyme in the biosynthesis of long-chain fatty acids [14].

Fetal and neonatal environmental and nutritional influences may change some physiological parameters in adulthood, a phenomenon known as programing [15–18]. Epidemiological and experimental studies indicate a relationship between the periconceptional, fetal and early infant phases of life and the subsequent development of diseases as an adult [19]. For instance, maternal low-protein diets are early-life inducers of glucose intolerance, hypertension, renal disease and obesity [20–22]. Our previous report showed that green tea extract intake during lactation modulates AMPK expression in the kidneys of adult male offspring of dams fed a protein-restricted diet and may induce long-term alterations in the expression of that protein in the kidneys [23]. Another investigation showed the potential protective effects of vinifera grape skin extract on programming-induced renal endowment in mice offspring of dams submitted to protein restriction during pregnancy, and its possible effects on oxidative stress associated with malnutrition [24]. These results indicated that maternal resveratrol intake during lactation modulates programing-induced changes of