GUM Arabic decreased visceral adipose tissue associated with downregulation of 11β-hydroxysteroid dehydrogenase type I in liver and muscle of mice

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Gum arabic decreased visceral adipose tissue associated with downregulation of 11β-hydroxysteroid dehydrogenase type I in liver and muscle of mice

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ABSTRACT

Objectives: Obesity is a global health concern associated with high morbidity and mortality. Therapeutic strategies include surgery and synthetic drugs, which may cause high costs and serious complications. High levels of glucocorticoid in adipose tissue generated by the intracellular enzyme 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) are associated with the pathogenesis of obesity. Gum arabic (GA, Acacia senegal) works as a dietary fiber that helps reduce body fat deposition. Yet, the effects of the dietary fiber, gum arabic (GA) on visceral adipose tissue (VAT) and its association with 11β-HSD1 have not been well studied.

Subjects/Methods: In the present study, 20 female CD-1 mice of 90 days old were randomly divided into two groups (10 of each group). Control group and GA group offered GA in the form of drink (10% w/v) for 63 days.

Results: GA supplementation significantly (P<0.05) decreased food intake associated with reduction of body weight. GA supplementation significantly decreased (P<0.01) VAT, blood glucose, low density lipoprotein (LDL), very low density lipoprotein (VLDL) and total cholesterol whereas increased high density lipoprotein (HDL) concentrations compared to the control group. However, GA supplementation did not alter plasma triglycerides. Interestingly, GA significantly (P<0.05) decreased 11β-HSD1 expression in the liver and muscle compared to the control group.

Conclusion: Our findings suggest that GA may decrease VAT deposition through reduction of food intake, plasma lipid, and glucose as well as 11β-HSD1 mRNA expression.

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1. Introduction

The prevalence of obesity is increasing in the populations worldwide (Nguyen & El-Serag, 2010). Obesity is often part of the metabolic syndrome (Wahba & Mak, 2007), a condition which includes insulin resistance (Qatanani & Lazar, 2007), dyslipidaemia (Klop, Elte, & Cabezas, 2013), reduced HDL cholesterol (Rashid & Genest, 2007) and hypertension (Hosick et al., 2014). Abdominal obesity is the most common manifestation of metabolic syndrome (Despres & Lemieux, 2006). Thus, metabolic syndrome is considered a fatal consequence of visceral obesity (Scaglione, Di Chiara, Argano, Corrao, & Licata, 2010). The reduction of visceral fat is crucial to reduce the risk of metabolic syndrome in this context (Fujikata et al., 1991). It has been reported that dietary fiber can prevent obesity through a numerous mechanisms such as reducing caloric density of food (Schneeman, 1987), limiting the absorption of fat in the small intestine (Vahouny et al., 1988). Moreover, a soluble dietary fiber for instance alginate has a significant capacity to limit lipid absorption (Brownlee et al., 2005).

Gum arabic (GA), an edible dried sticky exudate from Acacia seyal and Acacia senegal is rich in non-viscous soluble fiber (Slavin, 2013). It is generally used in food industry and pharmaceutical field as an emulsifier and preservative (Ali, Ziada, & Blunden, 2009). In the North Africa and Middle East, it used as an oral hygiene material by different communities for centuries (Tyler & Robbers, 1977). Previous studies revealed that a high ingestion of dietary fiber, including GA is associated with beneficial effects on fat metabolism (Ali et al., 2009; Slavin, 2003). Dietary fiber

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promotes satiation and satiety, alter glycaemic index, affects gastric emptying, gut hormone secretion and thus helps to manage weight (Chandalia et al., 2000).

Glucocorticoids (GC) play a vital role in the regulation of multiple physiological processes, including stress responses (Scheuer, 2010), energy intake (Tataranni et al., 1996) and the development of central obesity (Dallman et al., 2004). The intracellular concentrations of active GC is under control of a number of metabolizing enzymes which is called pre-receptor modulation (Edwards, Benediktssson, Lindsay, & Seckl, 1996). The 11β-hydroxysteroid dehydrogenase (11β-HSD1) activates, while 11β-hydroxysteroid dehydrogenase (11β-HSD2) deactivates GCs (Diederich et al., 1998; Harris, Kotelevtsev, Mullins, Seckl, & Holmes, 2001; Holmes & Seckl, 2006; Holmes, Yau, Kotelevtsev, Mullins, & Seckl, 2003; Stewart & Krozowski, 1999). Over expression of 11β-HSD1 in liver and visceral adipose tissue associated with metabolic syndrome in obese patients (Baudrand et al., 2011). The inhibition of 11β-HSD1 found to decrease the differentiation of white adipocytes, reduced white adipose accumulation, and enhanced the function of white adipose tissue (Staab & Maser, 2010). Recent studies proposed that the suppression of 11β-HSD1 is a novel molecular target for the treatment of metabolic syndrome and type 2 diabetes (Anagnostis et al., 2013; Wang, 2011).

The majority of studies investigating the biological effects of GA focused on body mass index (Babiker et al., 2012) and fat deposition (Ushida, Hatanaka, Inoue, Tsukahara, & Phillips, 2011). However, the effect of GA on visceral fat deposition its association with downregulation of 11β-HSD1 genes mRNA remain unclear. In the present study, we used mice to test our hypotheses that GA may be decrease visceral adipose tissue (VAT) and the changes in VAT may be associated with downregulation of 11β-HSD1 mRNA in the liver of mice administrated with GA.

2. Materials and methods

2.1. Animals

Twenty female albino SCID laboratory mouse (age, 13-week) old were housed in 4 plastic cages (each containing 5 mice) in a room kept at 25 °C with a 12-h light and dark cycle. The mice were allowed free access to a commercial pelleted diet for the adaptation and drinking water throughout the experiment. After 3 days of acclimatization, the mice were divided into two groups of 10 mice each group. Control group and GA group. GA group was offered drinking water containing GA while control group was given tap water. These mice received 0.5% of GA aqueous solution as drinking water as in the acclimatization. Body weight and food intake was recorded during the period of the experiment. By the end of the experiment, the mice were killed. Liver and visceral adipose tissue dissected and weighed. The tissue samples were collected and stored at −80 °C.

2.2. Plasma lipid profile

Blood glucose, plasma triglycerides, total cholesterol, LDL, VLDL, and HDL were determined using commercially kits (At Nanjing Military Hospital., Nanjing, China). Mice drank water as in the acclimatization. Body weight and food intake was recorded during the period of the experiment. By the end of the experiment, the mice were killed. Liver and visceral adipose tissue dissected and weighed. The tissue samples were collected and stored at −80 °C.

2.3. RNA extraction and real-time PCR

About 100 mg of liver was ground in liquid N2, and a portion of about 50 mg was used for RNA extraction using TRIzol total RNA kit (Invitrogen, Biotechnology Co, Ltd, Carlsbad, CA, USA) according to the manufacturer’s instruction. Two approaches were taken to ensure that all the total RNA preparations are free of genomic DNA contamination. Firstly, total RNAs were treated with 10 U DNase I (RNase Free, D2215, Takara, Japan) for 30 min at 37 °C, and purified according to the manufacturer’s protocol. Secondly, the primers for the reference gene were designed to span an intron, so any genomic DNA contamination can be reported easily with an extra product in the melting curves for real-time PCR. For establishing the effect of in ovo injection CORT on hypothalamic genes expression, real-time PCR was performed in Mx3000P (Stratagene, USA) according to the previous publication (Li et al., 2011). Mock RT and No Template Controls were included to monitor the possible contamination of genomic and environmental DNA at both RT and PCR steps. The pooled sample made by mixing equal quantity of RT products (cDNA) from all samples was used for optimizing the PCR condition and tailoring the standard curves for each target gene, and melting curves were performed to insure a single specific PCR product for each gene. The PCR products were sequenced to validate the identity of the amplicons. Primers specific 11β-HSD1 (Table 2) was synthesized by Geneary (Shanghai, China). Mice β-actin was used as a reference gene for normalization purposes. The method of 2−ΔΔCt was used to analyze the real-time PCR data (Livak & Schmittgen, 2001). The mRNA abundances were presented as the fold change relative to the average level of the control group.

2.4. Statistical analysis

Data are expressed as the mean ± SEM and compared by one way analysis of variance (ANOVA) and Student’s T test. P<0.05 as considered significant. All statistical analyses were performed using SPSS 16.0 software (SPSS, Chicago, IL, USA).

3. Results

3.1. Body weight, food intake and organs weight

The treatment of GA significantly (P<0.05) decreased body weight (Fig. 1 A) but not food intake (Fig. 1B) compared to the control. In addition, the treatment GA significantly (P<0.01) decreased visceral adipose tissue accumulation compared to control group (Fig. 1C). However, the treatment of GA did not change liver weigh (Fig. 1D).

3.2. Plasma lipid profile and Blood glucose

Supplementation of GA significantly (P<0.05) decreased blood glucose (P<0.05) total cholesterol (P<0.05), and LDL whereas increased HDL concentrations compared to control (Table 1). No changes were observed in triglycerides concentration regarding GA supplementation. Fig. 2

3.3. Liver and muscle 11β-HSD1 mRNA expression

In the present study, supplementation of 10% GA in the form of drinking water significantly (P<0.05) downregulated 11β-HSD1 mRNA expression in liver and muscle compared to the control group (Table 2).

4. Discussion

There are several studies suggesting the association between dietary fiber intake and obesity (Brauchla, Juan, Story, & Kranz, 2012), food intake (Kristensen & Jensen, 2011), body weight (Adam
Fig. 1. The effect of GA on body weight (A), Food intake (B), Liver weight (C), and VAT (D). The values are the means ± SEM, n=10/group.

Table 1
Effect of GA on serum lipid profile. The values are the means ± SEM, n=20/group. Different small letters in the column indicate significantly different mean values at P < 0.05.

<table>
<thead>
<tr>
<th>Group</th>
<th>Glucose (mmol/L)</th>
<th>Triglyceride (mg/dL)</th>
<th>Total cholesterol (mg/dL)</th>
<th>HDL (mg/dL)</th>
<th>LDL (mg/dL)</th>
<th>VLDL (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>7.01 ± 0.42a</td>
<td>38.8 ± 3.09a</td>
<td>73.8 ± 2.5a</td>
<td>52.73 ± 3.41a</td>
<td>72.36 ± 5.51a</td>
<td>10.36 ± 5.51a</td>
</tr>
<tr>
<td>Gum</td>
<td>3.08 ± 0.80b</td>
<td>35.5 ± 2.3a</td>
<td>58.9 ± 2.18 b</td>
<td>64.46 ± 2.15b</td>
<td>33.51 ± 2.13b</td>
<td>8.51 ± 0.13b</td>
</tr>
</tbody>
</table>
et al., 2014) and blood glucose (de Leeuw, Jongbloed, & Verstegen, 2004). In the present study, supplementation of gum arabic (GA) in drinking water significantly decreased body weight, food intake and blood glucose. The reduction of body weight or food intake by GA may be due to the fact that a number of epidemiological reported that the dietary fiber promote satiety and satiation (Burton-Freeman, 2000), alter glycaemic index (Barclay, Flood, Rochtouwen, & Mitchell, 2001), affect gastric emptying, gastric hormone secretion (Weickert & Pfeiffer, 2008) therefore, it reduces body weight (Chandalia et al., 2000). In addition, it was reported that GA inhibits absorption of glucose in the intestine via interaction with membrane abundance of sodium-glucose transporter 1 (SGLT1) in mice (Nasir et al., 2010). Moreover, GA may reduce body weight via lowering caloric density of food (Schneeman, 1987), decreasing fat absorption in the small intestine (Vahouny et al., 1988), and limit intestinal cholesterol and fatty acid absorption (Brownlee et al., 2005). Recent studies suggested the dietary fibers are reducing body mass through increasing mitochondrial biogenesis and fatty acid oxidation or visceral obesity (Islam, Civitarese, Hesslink, & Gallaher, 2012). However, the mechanism of GA is not yet fully elucidated, due to the lack of research in this field.

Abdominal obesity is the most prevalent manifestation of metabolic syndrome (Despres & Lemieux, 2006). Therefore, metabolic syndrome is considered a fatal consequence of visceral obesity (Scaglione et al., 2010). A number of studies reported that a high intake of dietary fiber, including gum arabic (GA) associated with beneficial effects on fat metabolism (Ali et al., 2009; Slavin, 2003). In the current study, 10% of GA given to mice in the form of drinking water decreased accumulation of visceral adipose tissue (VAT). Our findings are in line with previous studies that dietary fiber reduced adiposity in rat (Islam et al., 2012). Several mechanisms are proposed that the dietary fiber prevent obesity, for example dietary fiber usually has lower energy content, which contributes to the reduction of the energy density (Slavin, 2005). Dietary fiber needs to be eaten longer, resulted in an increase of time needed food chew and thus, the feeling of satiety. The fiber makes up viscous solutions which may delay the passage of food through gastrointestinal tract (GIT) and contribute to an increase in satiety and a reduce energy consumption (Pasman, Saris, Wauters, & Westerterp-Plantenga, 1997). It is also important to know that the effects of dietary fiber on body weight may be due to the influences to different gut hormones and enzymes which regulate energy intake, satiety, and/or pancreatic functions (Alexandre & Miguel, 2008).

Dietary fibers are well known to have very important physiological benefits, reducing the postprandial glucose and lowering plasma cholesterol concentrations (Babio, Balanza, Basulto, Bullo, & Salas-Salvado, 2010). In the present study, we reported that GA supplementation significantly decreased plasma total cholesterol and low density lipoprotein (LDL) whereas increased high density lipoprotein (HDL) concentrations. Various mechanisms have been proposed to explain the hypercholesterolemic effect of GA (Kelley & Tsai, 1978; Moudras, Behr, Demigne, Mazur, & Remesy, 1994). Some studies have suggested that the viscosity of fermentable dietary fibers contribute substantially to the lipid lowering effects in animals and humans (Gallaher, Hassel, & Lee, 1993; Moudras et al., 1994). While other proposes that this property does not relate to plasma lipids (Evans, Hood, Oakenfull, & Sidhu, 1992). The mechanism most clearly implicated is that GA increased fecal bile acid and neutral sterol excretion or a modification of lipid digestion and absorption (Eastwood, 1992).

The enzyme 11β-HSD1 catalyzes intracellular glucocorticoid (GC) reactivation via conversion of cortisone to cortisol in liver (Stimson et al., 2011). 11β-HSD1 has been involved in a number of metabolic disorders associated with obesity (Joharapurkar, Dhanesha, Shah, Kharul, & Jain, 2012; Morton & Seckl, 2008). Inhibition of 11β-HSD1 is being pursued as a new therapeutic drug for the treatment of metabolic syndrome and obesity (Wang et al., 2012). Therefore, it’s very important to establish the effect of 11β-HSD1 inhibitor, which suppresses GC action, in GC target tissues. Here we reported for the first time, that the supplementation of GA in drinking water for several weeks decreased 11β-HSD1 mRNA expression in the liver and muscle of mice. The reduction of 11β-HSD1 mRNA expression may play a role in the reduction of VAT or plasma lipid profile. It will be remain unclear the mechanism of action through which GA reduces 11β-HSD1 mRNA. Further studies are required to reveal such effects.

5. Conclusion

In conclusion, GA in the form of drinking water decreased body weight, food intake and abdominal fat deposition in female mice associated with reduction of plasma lipids, blood glucose and reduction of 11β-HSD1 mRNA expression in the liver.

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