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Gum Arabic Modifies Glucocorticoid Metabolic Enzymes Gene Associated with Decreased Plasma Corticosterone Levels in Mice

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ABSTRACT

Glucocorticoids (GCs) are a class of stress hormones that play a large number of biological actions in the body. The levels of GCs regulated by the intracellular enzyme 11β-hydroxysteroid dehydrogenases (11β-HSD 1 & 2) and are associated with the pathogenesis of metabolic syndrome. Here we aimed to investigate effect of Gum Arabic (GA) on GCs plasma corticosterone concentrations and its metabolic enzymes gene expression in mice. In the present study, 40 female CD-1 mice of 90 days old were randomly divided into two groups (20 of each group). Control group and GA group offered GA in the form of drink (10% w/v) for 15 weeks. GA in drinking water significantly ($P<0.05$) decreased food intake, body weight associated with reduction of visceral adipose tissue. GA supplementation significantly ($P<0.01$) decreased blood glucose, total cholesterol, and very low-density lipoprotein (VLDL) whereas increased high-density lipoprotein (HDL) concentrations compared to the control. However, supplementation of GA did not change triglycerides or very LDL. Interestingly, GA significantly ($P<0.05$) decreased plasma corticosterone associated with downregulation of hepatic 11β-HSD1 and glucocorticoid receptor (GR) mRNA expression compared to the control. Conversely, the treatment of GA increased hepatic 11β-HSD2 mRNA expression. In addition, the treatment of GA significantly ($P<0.05$) decreased muscular 11β-HSD1 compared to the control. No changes were observed in muscular GR and mineralocorticoid receptor. In conclusion, GA may enhance metabolic disorders through modification of hepatic 11β-HSDs mRNA expression which may ameliorate metabolic disorder complications. Further studies required to elucidate the molecular mechanisms of GA on GCs.

Introduction

Glucocorticoids (GCs), corticosterone in rodents and cortisol in humans are endogenous stress hormones that exert key physiological functions [1] on various tissues [2] including liver [3] and skeletal muscle [4]. GCs affect almost all organs and

tissues in the body [5], regulating various physiological processes [6] including stress response [7], immune response [8], energy metabolism [9], cell proliferation [10], skeletal muscle growth [11], and reproduction [12]. GCs exert their action through the glucocorticoid receptor (GR) [13], which is a transcription factor that belongs to the superfamily of nuclear hormone receptors [14]. GR acts via different mechanisms [15,16], one of the major mechanisms is transcriptional regulation of its primary target genes through genomic glucocorticoid response elements thereby directly binding to DNA or tethering onto other DNA-binding transcription factors [17]. Their secretion is mainly regulated by the hypothalamic-pituitary-adrenal axis [18].

The bioactivity of GCs is regulated via the intracellular metabolism involving 11β-hydroxysteroid dehydrogenases (11β-HSDs) and 20-hydroxysteroid dehydrogenase (20HSD) [19]. Elevations of GCs modify metabolic homeostasis such as hypoglycemia [20], infections [21], trauma [22], ambiguous temperature [23] or cold and stressful situations [24]. 11β-HSD type 2 catalyzes the interconversion of inactive and active GCs [25]. catalyzes the production of active corticosterone (CORT) from 11-dehydrocorticosterone in rodents, including in liver [26] and muscles [27]. Deregulation regulation of these enzymes has been associated various metabolic disorders including obesity [28], diabetes [29], hypertension [30], and cardiovascular disease [31]. Overexpression of 11β-HSD1 in the liver [32] or muscle [33] results in increased GCs action [34] and insulin resistance [35], while targeted downregulation of 11β-HSD1 protect against insulin resistance [29]. The inhibition of 11β-HSD1 decreases intracellular GCs concentrations [36] and thus enhances insulin sensitivity both in murine and mice [36].

On the other hand, the increased activity of 11β-HSD type 2 resulted in tissue-specific conversion of active cortisol to inactive cortisone [37], thereby decreasing the local of active GCs levels. Deregulation of HSD2 enzyme activity has been associated with a number of metabolic diseases [38]. In addition, inhibition of 11βHSD type 2 has been obviously shown to induce a congenital or acquired syndrome of mineralocorticoid exposure [27], thus contribute to essential hypertension [30].

Gum Arabic (GA), an edible dried sticky exudate from Acacia seyal and Acacia senegal is rich in non-viscous soluble fibers [39]. Pharmacologically, GA has been confirmed to have a number of therapeutic benefits including hypoglycemic [40], hypocholesterolemic [41] immunomodulatory [42], antioxidant [43], antiobesity [44], and many other health beneficial [45]. In our pervious publication, we reported that GA decreased visceral adipose tissue which was associated with downregulation of 11β-Hydroxysteroid dehydrogenase type I in the liver and muscles of mice [46]. To our knowledge, the effect of GA on stress hormone levels is not reported. Therefore, here we hypothesized that the supplementation of GA in the form of drinking water may alter plasma CORT levels in mice. In addition, the alteration in plasma CORT concentration by GA administration may associate with changes in glucocorticoid metabolic enzymes gene and mRNA in liver and muscle of mice. Moreover, it remains unknown whether the changes in 11β-HSD type 1 and type 2 may be linked with changes in glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) gene mRNA expression.

Materials and Methods

Animals and Experimental Design

Forty female albino laboratory mice (age, 90 days) old were obtained from Sudanese National Research Center and housed in 8 plastic cages (each containing 5 mice) in a room kept at 25 C with a 12-h light and dark cycle. The animals were allowed to access freely to a commercial pelleted diet for the adaptation and drinking water throughout the experiment at least for one weekday. After 7 days of adaptation, the animals were divided into two groups of 20 mice in each group. Control group and GA group. GA group was provided drinking water containing GA whereas; the control group was given tape water. These mice received 0.5% of GA aqueous solution as drinking water for 7 days to adapt GA, and then 10% solution for a further 15 weeks consecutively. The control group was remained on the same drinking water as in the acclimatization. Body weight and food consumption were recorded throughout the period of the experiment. On day 105, the mice were killed. Liver and visceral adipose tissues were dissected and weighed. The tissue and blood samples were collected and stored at-80°C.

Blood Lipid Profile Biochemistry

Plasma lipids biochemistry including total cholesterol, triglycerides, HDL, VLDL, and LDL were determined using commercially assay kits according to the manufacturers' instructions (Nanjing Jiancheng Bioengineering Company, Nanjing, China).

Blood Glucose Measurement

Plasma samples were obtained from blood through centrifugation (2,400 rpm, 20 min, and 3.5°C) and then stored at -20 °C until samples analyzed. Blood glucose concentrations were measured using assay kits according to the manufacturers' instructions. (Nanjing Jiancheng Bioengineering Company, Nanjing, China).

Plasma Corticosterone Measurement

After decapitation of mice, blood samples were obtained from the ruptured cervical blood vessels in heparinized tubes for corticosterone (CORT). The plasma samples were prepared after centrifugation (2,400 rpm, 20 min, 3.5°C) in a refrigerated device and frozen at –20°C until the measurement of the hormone. Plasma CORT levels were measured using radioimmunoassay method (RIA), using the CORT commercial kit according to the

manufacturers' instructions (Biochem Immuno System). All plasma samples were dosed in the same assay, to avoid inter-assay errors. The lower detection limit for CORT was 0.064 ng/mL, with a 4% intra-assay error.

Real-time PCR and Gene Expression

About 100 mg of liver and muscle were ground in liquid N2, and a portion of about 50 to 100 mg were used for extraction of RNA 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 liver and muscle glucocorticoid metabolic genes expression, real-time PCR was performed in Mx3000P (Stratagene, USA) according to the previous publication [46].

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 ensure a single specific PCR product for each gene. The PCR products were sequenced to validate the identity of the amplicons. Primers specific 11β-HSD1, 11β-HSD2, GR and MR (Table 2) were synthesized by Geneary (Shanghai, China). A mouse GAPDH was used as a reference gene for normalization purposes. The method of 2−ΔΔCt was used to analyze the real-time PCR data [47]. The mRNA abundances were presented as the fold change relative to the average level of the control group.

Statistical Analysis

Descriptive statistics analysis was performed to check the normality and homogeneity of variances before using parametric analyses. Body weight, food intake, organs weight, blood lipids profile, CORT, as well as the relative quantitative data of gene expression were analyzed by one-way ANOVA using SPSS 21.0 for Windows, followed by a least-significant difference (LSD) test for individual comparisons. A P-value ≤0.05 was considered significant.

Results

Body Weight, Food Intake Visceral Adipose Tissue Weight, and Liver Weight

In the present study, the supplementation of GA significantly (P<0.05) decreased VAT (Figure 1A) food intake (Figure 1B), and body weight (Figure 1C) compared to the control group. No significant differences were observed in liver weight regarding the treatment of GA (Figure 1D).

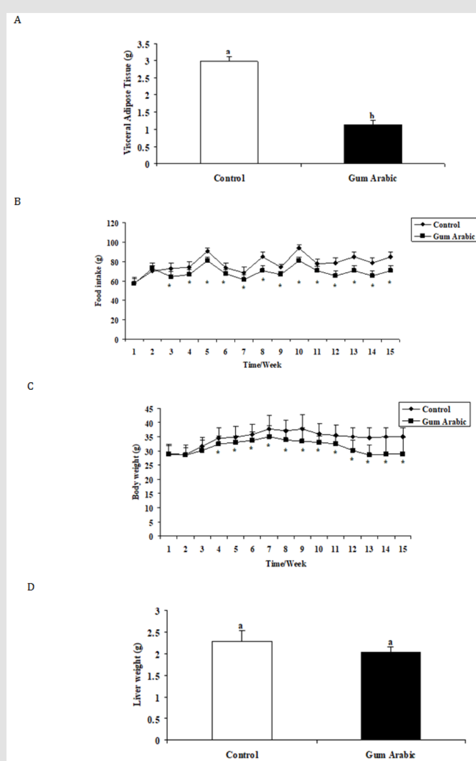

Figure 1: Effect of GA treatments on liver food intake (A) body weight (B), visceral adipose tissue (C) and liver weight (D). The values are the means ± SEM, n=20/group.

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Blood Glucose Lipid Profile

In this study, the treatment of GA significantly (P<0.05) decreased final blood glucose concentration compared to the control group. In addition, the administration of GA significantly (P<0.05) decreased total cholesterol (P<0.05) compared to the control group. Likewise, the supplementation of GA significantly reduced plasma LDL-c concentrations compared to the control group. On the other hand, the treatment of GA significantly (P<0.05) increased HDL-c concentrations when compared to the control group (Table 1). No changes were observed both in triglycerides or VLDL concentrations regarding GA administration.

Table 1: Effect of GA treatments on blood lipid profile and glucose concentrations. Data were expressed as means ± S.E.M. of 20 /group. Different letters in the rows indicate significantly different mean values at p<0.05

Group	Triglyceride (mg/dL)	Total cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	Glucose (mmol/L)
Control	42.3±3.05a	74.5±3.2a	53.51±2.20a	73.43±5.60a	11.26±4.52a	8.70±.53a
Gum	33.4±1.5a	47.3±2.16 b	70.55±3.11b	31.62±4.13b	9.32±0.12a	4.30±0.50b

Plasma Corticosterone and Blood Glucose Concentrations

In the current study, the treatment of GA significantly (P<0.05) decreased plasma CORT concentrations when compared to the control group (Figure 2A). In addition, the administration of GA significantly (P<0.05) decreased blood glucose compared to the control group (Table 1).

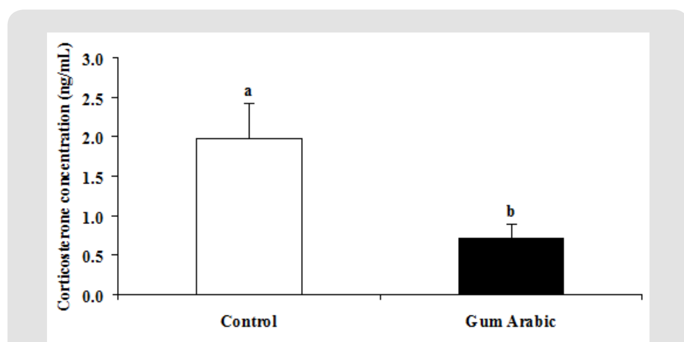

Figure 2: Effect of GA treatments on plasma corticosterone concentrations (A). The values are the means ± SEM, n=20/group. Bars with different letters are significantly different at p<0.05

Table 2: Primers sequences used for Real-time PCR

Target genes	Gene bank number	Primer sequences
11β-HSD1	NM_001044751.1	F: 5′- TGCAGGTTTTCTTCGTGTGT-3′
		R: 5′- GAGGAGATGACGGCAATGCT-3′
11β-HSD2	NM_008289.2	F: 5′- ATAGCCCTGGTGCCCTAGAA-3′
		R: 5′- AAGGGCTGAAGAAGCCCATC-3′
GR	X66367.1	F: 5′- CGTCGGGGACGGATTCTAAG-3′
		R: 5′- AAACCGAAAAGGACGCCAGA-3′
MR	NM_001083906.2	F: 5′- CACATAAGCAAGACAGTGGCA-3′
		R: 5′- TGGTGAACCCTGTGGGAAAC-3′
GAPDH	NM_008084.2	F: 5′- ACATGGTCTACATGTTCCAGTA -3′
		R: 5′- GGAGTCTACTGGTGTCTTCA-3′

Hepatic and Muscular 11β-HSD1 and 11β-HSD2 mRNA Expression

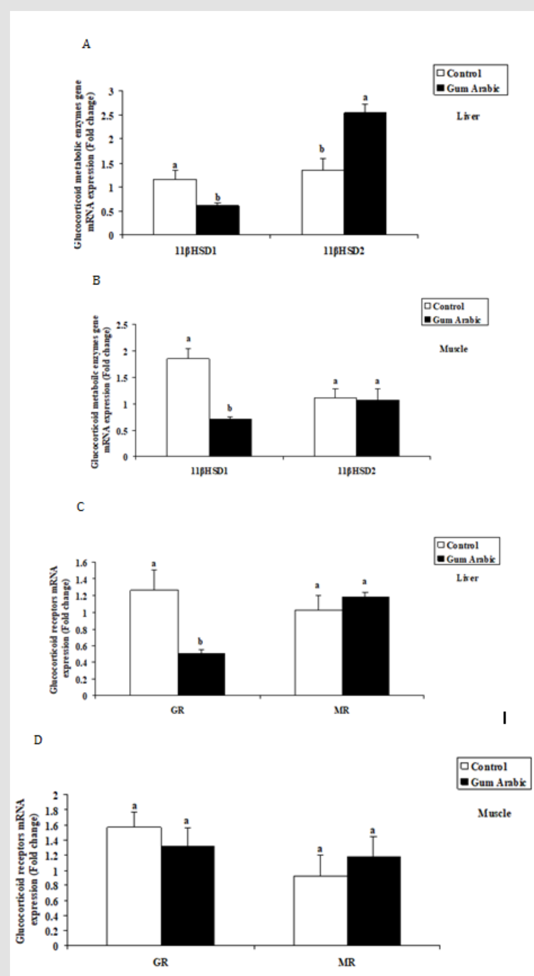

Figure 3: Effect of GA treatments on hepatic 11βHSD1 and 11βHSD2 (A), muscle 11βHSD1 and 11βHSD2 (B), hepatic GR and MR (C) and muscle GR and MR (D) mRNA expression. The values are the means ± SEM, n=20/group. Bars with different letters are significantly different at p<0.05.

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In the present study, treatment of GA significantly ($P<0.05$) decreased hepatic11β-HSD1 (Figure 3A) mRNA expression whereas, increased hepatic 11β-HSD2 (Figure 3A) mRNA expression compared to the control group. Similarly, the treatment of GA significantly ($P<0.05$) decreased muscular 11β-HSD1 (Figure 3B) mRNA expression but not 11β-HSD2 (Figure 3B) compared to the control group.

Hepatic and Muscle GR and MR mRNA Expression

In the present study, the treatment of GA significantly ($P<0.05$) decreased hepatic GR (Figure 3C) mRNA expression when compared to the control group. However, no significant differences observed in hepatic MR (Figure 3C) mRNA expression compared to the control group. Likewise, no significant differences were observed both in muscular GR and MR mRNA expression regarding to the treatment of GA (Figure 3D).

Discussion

There are several reports confirming the association between dietary fibre consumption and stress relief [48-50]. Gum Arabic (GA) is a profitable natural source of dietary fiber that reaches 85% of its weight [51]. It has a wide spectrum of health benefits including oxidative stress [52], dyslipidemic [41], anti-obesity [53], and anti-inflammatory [54]. In the present study, administration of GA significantly decreased food intake associated with reduction in body weight and blood glucose. These findings are agreed with earlier reports that the treatment of GA associated with a reduction in food intake [36], body weight [55] and blood glucose levels [40]. The reduction effect of GA on food intake and body weight may be due to the fact that several studies confirmed that the dietary fiber have bulk properties [56] and viscosity [57] therefore, it promoting satiety [58], satiation [59, 60] and lowering body weight [61].

In addition, intake of dietary fiber associated with increases in satiety and decreased blood glucose levels [61]. Moreover, it was confirmed that supplementation of GA inhibited glucose absorption in intestine through interference of membrane abundance of sodium-glucose transporter 1 in mice [62]. Abdominal obesity is considered the most common signs of metabolic syndrome [63]. As a result, metabolic syndrome is a fatal consequence of visceral obesity [64]. Here we reported that supplementation of GA decreased visceral adipose tissue (VAT) accumulation associated with reduction in blood cholesterol, and VLDL. However, the treatment of GA increased HDL concentrations. Our findings are consistent with previous reports that dietary fibre decreased adiposity [65], lowered blood cholesterol [66] and blood VLDL levels [67]. A variety of mechanisms have been suggested to elucidate the hypercholesterolemic effect of GA [68,69]. Some reports suggested that the viscosity of fermentable dietary fibers in GA contribute significantly to lipid lowering action [65,70]. In addition, mechanism it was found that administration of GA increased fecal bile acid excretion together with decreased medication in lipid digestion and absorption [71].

Glucocorticoids (GCs) play a vital role in a wide array of physiological processes in the body. The 11β-hydroxysteroid dehydrogenases (11β-HSDs) enzyme catalyze interconversion of intracellular GC in liver [72]. Deregulations of both 11β-HSD1 and 11β-HSD2 have been associated with several types of metabolic disorders [73]. In the present study, the supplementation of GA in drinking water downregulated hepatic and muscular 11β-HSD1 mRNA expression associated with decreases in plasma corticosterone concentrations. These results are consistent with our previous publication showed that administration of GA decreased 11β-HSD1 mRNA expression in mice liver [46]. The downregulation of hepatic and muscular 11β-HSD1 mRNA may play a critical a role in the inhibition of abdominal adiposity [36] and blood lipid profile, thus may attenuate atherosclerosis [74]. Downregulation of muscular 11β-HSD1 within the muscle may also protect against the unfavorable effects of local inflammation [75]. However, the mechanism through which GA downregulates 11β-HSD1 mRNA is unclear the.

Therefore, additional studies are essential to disclose such effects. 11β-HSD2 plays a crucial role in the prevention of inappropriate activation of the mineralocorticoid receptor (MR) from improper activation via GCs by inactivating GCs in mineralocorticoid target tissues [76]. In the present study, the treatment of GA upregulated hepatic 11β-HSD2 mRNA expression. Overexpression of hepatic 11β-HSD2 mRNA may imply the prevention from various metabolic disorders such as atherogenesis [36], hypertension [77] and proinflammatory changes [76]. Chronic exposure elevated levels of GCs cause metabolic disorders such as insulin resistance [78] elevation of fasting glucose [79] and development of type 2 diabetes mellitus [80]. Here we reported for the first time that the administration of GA decreased GR mRNA expression in the liver but not muscle. Downregulation of hepatic GR mRNA could therefore decrease the development of metabolic risk factors [81] such as obesity [82], cardiovascular diseases [83], and diabetes [84].

Conclusion

We concluded that the supplementation of GA reduced food intake, body weight, VAT, plasma lipids profile and plasma CORT concentration which were associated with modification of hepatic 11β-HSD1, 11β-HSD2 and GR mRNA expression. Thus, GA may be useful in the treatment of metabolic disorder related diseases that induced by GCs deregulation.

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