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Research Article

Gum Arabic Increases Hypothalamic POMC mRNA Expression Associated with Decreased Plasma Lipids Profile in Mice

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Abstract

Objectives: Obesity is a worldwide health concern linked with high morbidity and mortality. Therapeutic strategies such as surgical operation and synthetic drugs ultimately cause high costs and serious complications. The anti-obese effect of dietary fiber is usually accepted to reduce body weight gain. Gum Arabic (GA) Acacia senegal used as a dietary fiber to reduce body weight.

Aim: The aim was to study the effects of GA on visceral adipose tissue (VAT) and its relation with hypothalamic expression of energy homeostasis related genes. We offered GA to 90 days old female mice in drinking water (10% w/v) for 84 days. Food consumption, body weight, plasma glucose, plasma lipid profile, plasma leptin, PYY and GLP-1 and mRNA of pro-opiomelanocortin (POMC) were measured. GA in drinking water significantly ($P<0.05$) decreased food intake associated with reduction of body weight and VAT accumulation compared to control. In addition, GA significantly ($P<0.05$) decreased plasma glucose, plasma total cholesterol, LDL and VLDL whereas increased HDL compared to control. The treatment of GA significantly increased plasma PYY and GLP-1 concentration whereas decreased leptin concentrations compared to the control. Moreover, GA significantly increased hypothalamic expression of POMC mRNA. However, GA treatment did not alter plasma triglycerides.

Conclusion: We conclude that GA decreases food intake, reduces body weight, as well as plasma lipids associated with reduction of VAT. GA also increases plasma PYY and GLP-1 concentration and on hypothalamic expression of POMC mRNA.

Keywords: Gum Arabic; Pro-Opiomelanocortin; Hypothalamus; Mice

Introduction

Obesity is defined as a state of increased abdominal fat deposition consequential from chronic nutrient intake, where energy intake much exceeds energy expenditure [1]. Energy intake is balanced by food intake and energy expenditure was influenced by several factors including basal metabolism rate, physical activity [2], body size and lifespan [3], and thermogenesis [4]. Disturbances of either central [5] or peripheral signals lead to a state of obesity or anorexia. The increase in obesity, a predisposing factor for developing, hypertension, diabetes, hyperlipidemia, cancer and other metabolic disorders, has driven a major interest in the regulation of food intake, appetite and fat deposition [6]. Energy homeostasis is regulated by a complex neuroendocrine system including appetite regulatory hypothalamic peptides [7], as well as adipocytes derived peripheral signals such as leptin [8]. These signals act in a reciprocal manner to integrate information about energy status, a system referred to as the hypothalamus-adipose tissue axis [9].

The central nervous system (CNS), including the hypothalamus, is involved in the regulation of feeding behavior and energy balance

in mammals and birds [10]. A variety of orexigenic and anorexigenic neuropeptides have been reported to play a critical role in food intake and energy balance [11,12]. Orexigenic neuropeptides include, orexin (ORX) [13], agouti-related protein (AGRP) [14] and neuropeptides Y (NPY) are known to stimulate food intake. On the other hand, anorexigenic neuropeptides include corticotropin releasing hormone (CRH) [15], proopiomelanocortin (POMC) [16], glucagon-like peptide-1 (GLP-1) [17], and adenosine monophosphate-activated protein kinase (AMPK) [18] are known to control food intake. The Fat Mass and Obesity Associated gene (FTO) is found to associate with body mass index (BMI) and increased food intake without significant effects on metabolic rates or physical activity [19]. The role of hypothalamic expression of NPY, FTO [20], POMC [21], AMP [22], and agouti [23] on food intake and energy homeostasis is well documented.

Gum arabic (GA), an edible dried sticky exudate from Acacia seyal and Acacia senegal is rich in non-viscous soluble fiber. It is generally used in food industry and pharmaceutical field as an emulsifier and preservative. In the North Africa and Middle East, it used as an oral hygiene material by different communities for centuries [24]. Previous studies revealed that a high ingestion of dietary fiber, including GA was associated with beneficial effects on fat metabolism [25,26]. Dietary fiber promotes satiation and satiety, alter glycaemic index, affects gastric emptying, gut hormone secretion and thus helps to manage weight [27]. Baulk of research have identified the major role of the gastrointestinal peptide hormones in the regulation of food intake and satiety/hunger [28]. Thus, the secretion of peptide tyrosine tyrosine (PYY) and glucagon-like peptide-1 (GLP-1) from the intestine signal satiety and decreases food intake [29]. It is hypothesized that the satiety effects of dietary fibre are mediated by the gut hormones.

Previously, we have reported the effect of GA on lipid metabolic genes expression in mice liver [30] and on downregulation of 11β-hydroxysteroid dehydrogenase mRNA expression in mice liver and muscle [31]. Yet, the effect of Gum Arabic on energy intake, body weight, visceral adipose tissue accumulation and its association with hypothalamic expression of POMC has not reported. Therefore, in the present study, we hypothesized that the GA may alter energy intake, body weight, VAT, and POMC genes expression in mice hypothalamus.

Materials and Methods

Animals

Forty female white mice (age, 13-week) were 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 mice were allowed free access to a commercial pellet diet for the adaptation and drinking water throughout the experiment. After 7 days of acclimatization, the mice were randomly divided into two groups of 20 mice each group. Control group and GA group. The GA group was offered drinking water containing GA while control group was given tape water. These mice received 0.5% of GA aqueous solution as drinking water for 7 days, and then 10% solution for further 63 days. Body weight and food intake was recorded during the experiment.

Mice were killed at the end of the experiment, liver and visceral adipose tissue were dissected and weighed. The experiment procedures were approved by the Animal Ethics Committee of the University of Nyala.

Microdissection of the ARC in the hypothalamus

Brains from decapitated mice were removed, quickly frozen on dry ice and stored at −80 °C. The middle brain was dissected using a cryostat. Microdissection of the ARC was performed using the procedure described elsewhere. Five continuous coronal sections were collected starting from Bregma −2.12 to −3.4 mm for the ARC micropunch. The thicknesses of sections were 300 μm each. The micropunch was performed bilaterally under a microscope, using a needle (Stoelting, Chicago, IL) with an inner diameter of 0.51 mm.

Plasma lipid analysis

Blood was collected in EDTA tubes and centrifuged at 4,000 RPM for 20 min to extract plasma. Plasma triglycerides, total cholesterol, LDL, VLDL, and HDL were determined using automated chemical analyzer and commercially kits (China, if possible, more details for kits, like below in green color). All assessment assays and control kits were performed in accordance with the manufacturers' instructions and protocols.

Plasma PYY, GLP-1, and leptin

The blood samples were collected in EDTA containing tubes and centrifuged at 4,000 RPM for 20 min to obtain plasma. The plasma PYY and GLP-1 were measured by radioimmunoassay method using the RIA kits from (China if possible, more details for kits, like below in green color). The intra-assay and inter-assay coefficients of variation are 9.4 and 3.2% for 10 for GLP-1 and for PYY, 29%, respectively.

RNA extraction and Real-time PCR

RNA was extracted from dissected ARC 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 (β-actin) 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. Real-time PCR was performed in Mx3000P (Stratagene, USA) according to the previous publication [32]. Mock RT and No Template Controls (NTC) 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 for POMC (Table 2) were synthesized by Geneary (Shanghai, China). Mice GAPDH were used as a reference gene for normalization purposes. The method of $2^{-\Delta\Delta Ct}$ was used to analyze the real-time PCR data [33]. The mRNA abundances were presented as the fold change relative to the average level of the control group.

Group	Glucose (mmol/L)	Triglyceride (mg/dL)	Total cholesterol (mg/dL)	HDL (mg/dL)	LDL (mg/dL)	VLDL (mg/dL)	GLP-1 (pmol/l.)	PYY (pmol/l.)	leptin (ng/ml)
Control	5.08 ± 0.8[a]	35.5 ± 2.3[a]	68.9 ± 2.2[a]	52.5 ± 2.2[a]	33.5 ± 2. 3a	8.51 ± 0.3a	35.03 ± 1.8a	103.6 ± 3.3a	2.8 ± 2.1a
Gum Arabic	2.71 ± 1.4[b]	37.6 ± 2.1[a]	52.9 ± 2.1[b]	64.1 ± 4.6[b]	22.5 ± 2.4b	4.5.3 ± 1.1b	62.71 ± 1.5b	135.2 ± 4.6 b	1.3 ± 1.3 b

Table 1: Effect of GA on plasma glucose and 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. Effect of GA on plasma leptin, PYY and GLP-1. The values are the means ± SEM, n=20/group. Different small letters in the column indicate significantly different mean values at P<0.05.

Target genes	PCR products (bp)	Primer sequences
GAPDH	300	F : 5′- ACATGGTCTACATGTTCCAGTA -3′ R : 5′- GGAGTCTACTGGTGTCTTCA -3′
POMC	160	F: 5′- TCCTGCTTCAGACCTCCAT-3′ R: 5′- GGCTGTTCATCTCCGTTGC -3′

Table 2: Sequences of primers used for Q.PCR.

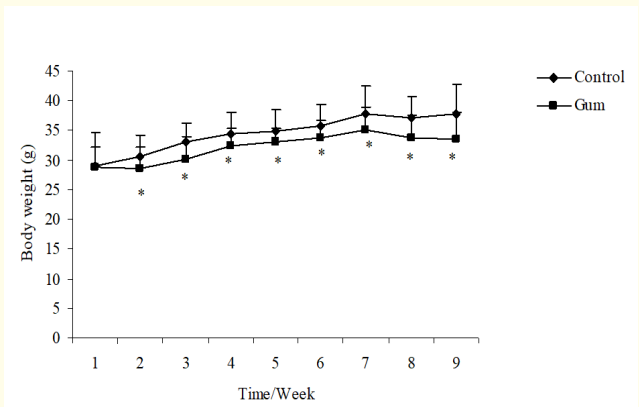
Statistical analysis

Descriptive statistics was performed to check the normality and homogeneity of variances before using parametric analyses. Body weight, organs weight, plasma lipid, plasma glucose, hormones as well as the relative quantitative data of gene expression were analyzed by one-way ANOVA using SPSS 16.0 for Windows, followed by a least-significant difference (LSD) test for individual comparisons. A P-value ≤0.05 was considered significant.

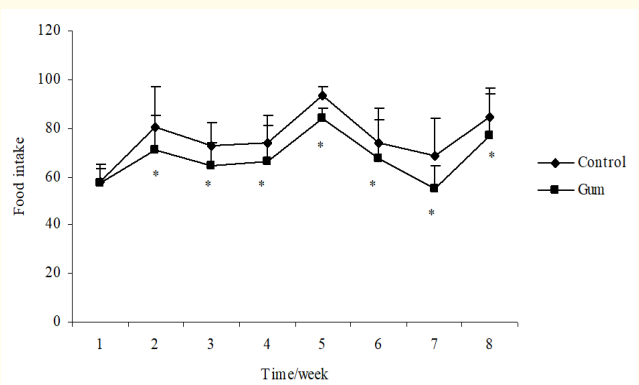
Results

Body weight, food intake and organs weight

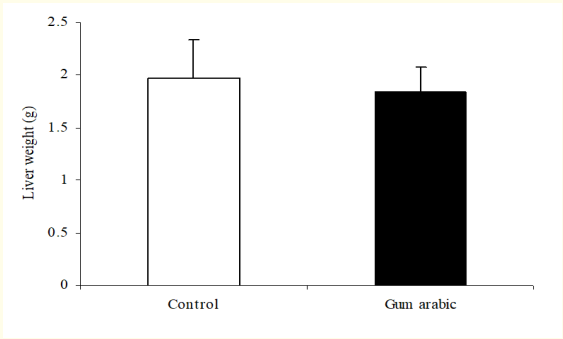
GA was significantly (P<0.05) decreased body weight compared to the control group (Figure 1A). In addition, GA was significantly (P<0.05) reduced food intake compared to the control group (Figure 1B). Moreover, GA was significantly (P<0.01) decreased visceral adipose tissue accumulation compared to control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



A



B



C

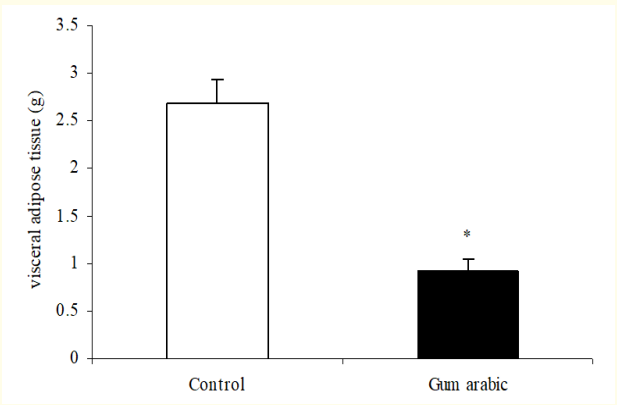


Figure 1: Effect of GA on body weight (A), Food intake (B), and liver weight (C), and VAT (D). The values are the means ± SEM, n=20/group. Different small letters on bars indicate significantly different mean values at P<0.05.

Plasma lipid profile and blood glucose

GA was significantly (P<0.05) decreased random blood glucose, plasma total cholesterol concentrations and LDL compared to the control group. However, GA was increased HDL concentrations compared to control group (Table 1). No changes were observed in triglycerides concentration regarding GA treatment.

Plasma PYY, GLP-1 and leptin levels

The GA was significantly (P<0.05) increased plasma PYY and GLP-1 concentrations compared to the control. While was significantly decreased plasma leptin concentrations compared to the control group (Table 1).

Hypothalamic expression of neuropeptides

In the present study, the treatment of GA in drinking water significantly upregulated hypothalamic expression of POMC mRNA (Figure 2A) compared to the control.

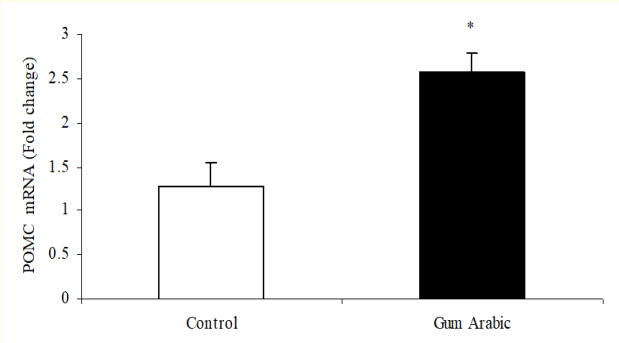


Figure 2: Effect of GA on hypothalamic POMC mRNA expression. The values are the means ± SEM, n=10/group. Different small letters on bars indicate significantly different mean values at P<0.05.

Discussion

The obesity plays a major role in the development of coronary heart diseases, type 2 diabetes and many other abnormalities, including cancer [34]. In the present study, supplementation with GA in drinking water significantly decreased body weight and food intake. The reduction of body weight by GA may be due to the fact that a high intake of dietary fiber, including GA, associated with beneficial effects on fat metabolism [25,26]. In addition, the dietary fiber was reported to promote satiety and satiation, alter glycaemic index, affects gastric emptying, stomach hormone secretion therefore, reduces weight [27]. Moreover, it has reported that GA inhibits absorption of glucose in the intestine via interaction with membrane abundance of SGLT1 in mice.

Abdominal obesity is associated with metabolic syndrome. Therefore, metabolic syndrome is considered a fatal consequence of visceral obesity [35]. In the current study, GA significantly decreased the accumulation of VAT in mice given 10% of GA in drinking water. Our findings are agree with previous report that 1% of GA in drinking water reduced visceral adipose tissue [36]. GA; a dietary fiber may prevent obesity by several mechanisms for example via lowering caloric density of food [37], and/or decreasing fat absorption in the small intestine. Since there was no significant difference in food intake for both groups, the reduction in the VAT mass may be not a consequence of a lower caloric intake. This point is noteworthy because dietary fibers are believed to reduce food intake [37]. According to our finding, soluble dietary fiber, generally may have the potential effects to limit cholesterol and fat absorption as proposed previous [38].

In the present study, we reported that GA supplementation significantly decreased plasma total cholesterol and LDL whereas increased HDL concentrations. The effects of GA on blood lipid profile are variable. It is found to increase cholesterol biosynthesis in rat fed with cholesterol containing diet, while had no effect in rat fed with cholesterol-free diet [39]. The effect of GA has shown decrease in both [40] or increase or had no effect on plasma lipid profile. Various mechanisms have been proposed to explain the hypercholesterolemic effect of GA [41]. Some studies have suggested that the viscosity of fermentable dietary fibers contribute substantially to the lipid lowering effects in animals and humans [42]. While other proposes that this property does not relate to plasma lipids [43]. The mechanism most clearly implicated, is that GA increased fecal bile acid and neutral sterol excretion or a modification of lipid digestion and absorption [44]. Dietary fibre plays a key role in controlling food intake via modulation of gastrointestinal hormones [45]. Here we reported for the first time that GA treatment increased plasma increased plasma PYY and GLP-1 whereas decreased plasma leptin concentrations. Our findings are consistent with previous publications that the dietary fibre decreased plasma in rat and increased plasma PYY and GLP-1 concentrations in rat [46].

Hypothalamic neuropeptide signaling network play major roles in the regulation of energy balance. In this study, we found that GA increased hypothalamic POMC expression in mice. This findings are agree with earlier report that viscous dietary fiber reduced adiposity and plasma leptin associated with increases of muscle expression of fat oxidation genes in rats [47]. Although there are differences between our experiment with previous experiment such as experimental deign and animal models used, these findings indicate that dietary fibre whether from GA or any other sources has a potentiality to induce Antiobesity effect ant molecular level. To our knowledge, our results provide the first evidence that dietary GA alters hypothalamic neuropeptide expression in mice. We suggested that GA increased POMC expression in mice, because GA may potentially have three major properties as a part of the diet: metabolically energy dilution, a bulking and satiety effect, or fermentation to produce short-chain fatty acids and increase GLP-1 and PYY [48]. The bulking and satiety effect may be due to the high fiber content in GA diet. If the bulking makes the alterations in POMC, destroying vagal afferent nerves supposed prevent the alterations, as distension signals from the stomach to the brain are vagal afferent nerve dependent [49]. Unfortunately, we did not measure the effect of GA on water consumption in the current study which will be remaining to be investigated. Moreover, it's difficult to control the dose of GA extract administration by this way.

A numerous research has reported positive relationship between fiber utilization and the risk for coronary heart diseases and several types of metabolic diseases [50]. The mechanisms behind these reports are still unclear. Yet, it is considered to be endorsed to several factors such as decreased caloric intake, increasing bile acid excretion, and increased short chain fatty acid production. The viscosity and digestive characteristics of GA are the possible mechanism of action which impacts obesity and diabetes risk. These modes of actions seem to reduce nutrient absorption, consequently, decreasing metabolizable energy. GA may also be able to reduce gross energy of the food because of its lower energy density.

Conclusion

In conclusion, GA in drinking water decreases food intake, body weight and abdominal fat accumulation, plasma lipids associated with increased plasma PYY and GLP-1 concentration and on hypothalamic expression of POMC mRNA in female mice. Our results provide a further understanding of how GA works as a dietary ingredient to decrease body weight and body fat.

Acknowledgment

This study is a collaboration project from four universities, University of Nyala, Sudan; University "G. d'Annunzio" of Chieti-Pescara, Italy; Islamia University, Bahawalpur, Pakistan and National Ribat University, Khartoum, Sudan.

Conflicts of Interest

None.

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