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Research article

Free-fatty-acid-regulating effects of fermented red ginseng are mediated by hormones and by the autonomic nervous system

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ABSTRACT

Background: Understanding what causes changes in the flux of free fatty acids (FFA) is important to elucidate the etiology of metabolic syndrome. The first aim of this study was to test whether or not hormones and the autonomic nervous system influence blood FFA levels. A secondary aim was to test by means of a multiple group path analysis whether the consumption of fermented red ginseng (FRG; *Panax ginseng*) would influence those causal relationships.
Methods: Ninety-three postmenopausal women (age 50–73 yr) were randomly divided into two groups. One group (44 women; age, 58.4 ± 5.9 yr; body mass index, 23.6 ± 2.5 kg/m^2) was supplied placebo capsules and the other group (49 women, age 58.4 ± 5.5 yr; body mass index, 22.9 ± 2.4 kg/m^2) was supplied FRG capsules. Both prior to and after the study (2 wk), blood samples were collected from the participants and several blood variables were measured and analyzed.
Results: Squared multiple correlations of FFA were 0.699 in the placebo group and 0.707 in the FRG group. The unstandardized estimate of estradiol (E2) for FFA was 0.824 in both groups.
Conclusion: The path coefficients of cortisol and the branchial pulse for FFA were significantly different between the FRG group and the placebo group.

1. Introduction

Of the primary energy sources in the human body (carbohydrates, proteins, and lipids), lipids are the most efficient type of energy storage (9 kcal/g) and are hence much more prevalent than carbohydrates or proteins as a form of storage [1]. This makes the process of lipid release a crucial component in understanding human energy metabolism and pathology. Several studies have reported that the incidence of metabolic syndrome in postmenopausal women is higher than in premenopausal women and that the causes are related not only to estrogen levels but also to the levels of other hormones related to lipid metabolism [2].

The chronic override of free fatty acids (FFA) in the blood may be a risk factor in human energy metabolism. A high level of FFA often correlates with type 2 diabetes, hypertension, dyslipidemia, insulin resistance, hyper uric acid, and abnormal fibrinolysis [3]. Obese individuals commonly show insulin resistance; correspondingly, their levels of fatty acids are also elevated. The most common cause of the positive correlations between FFA and several diseases is the competition between override FFA and carbohydrates in the energy oxidation process [4]. Boden et al [5] reported that after lipids were administered to test volunteers, lipid oxidation increased and carbohydrate oxidation decreased simultaneously. Compared to healthy volunteers, diabetic patients showed a 40–55% decrease in their insulin-stimulated glucose absorption rates [6].

Energy metabolism differs between the postprandial and fasting states. In the postprandial state, carbohydrates are used as a major energy source and insulin is released. In the fasting state, adipocytes release triglycerides, which are broken down into FFA and glycerol, which then enter the circulatory system. During the overnight fasting period, the burst size of FFA during the daily cycle is maximized [7].

In a fasting state, over the long term, basal metabolic lipolysis occurs when insulin levels and catecholamine levels decrease.

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In the short term, acute lipolysis occurs in “fight or flight” (emergency) states. In this state, catecholamines are triggered by the sympathetic nerve system [8]. In cell membranes, those catecholamine signals stimulate β-adrenoreceptors, which activate adenylyl cyclase via simultaneous G-protein coupled receptors. Adenylyl cyclase then transforms adenosine triphosphate into cyclic adenosine monophosphate (cAMP). The cAMP then binds to the regulatory module of the protein kinase A, activating it, which then phosphates hormone-sensitive lipase (HSL) [9].

Both long- and short-term lipolyses are affected by several hormones. Glucocorticoid [10], adrenocorticotropic hormone (ACTH) [11], thyroid hormone, dehydroepiandrosterone [12], insulin [7], and estrogen [13] have all been shown to influence lipolysis through the functioning of β-adrenergic receptors, the production of adenylyl cyclase, the activities of G-proteins, or changes in cAMP production.

The lipolysis of white adipose tissue is influenced by the autonomic nervous system as well as the central nervous system. For example, when the sympathetic nerve directly stimulates the adrenal medulla, it causes catecholamine to be released. The catecholamine then stimulates adipocytes to trigger lipolysis. In addition to this catecholamine pathway, sympathetic nerves directly innervate within adipose tissue. Cousin et al [14] reported that the level of lipids in the peritoneum increased after denervation. This suggests that the sympathetic nervous system influences the activity or differentiation of white adipose cells.

Parasympathetic nerves as well as sympathetic nerves showed a relation with adipose tissue. Kreier et al [15] reported that when the parasympathetic nerve was removed, the HSL activity in white adipose tissue increased. However, the absorption of FFA and blood glucose decreased.

Given that the direct measurement of autonomic nervous activity by micrography is not feasible in a large epidemiological study, heart rate variability (HRV) is used as the measurement method for the autonomic nervous system [16]. HRV is measured by the variation of the beat-to-beat interval. The average R-R is calculated by 60 divided by the average heart rate in beats/min. Chang et al [17] showed that HRV is related to several component of metabolic syndrome (MtS). When they separated 1,298 individuals into four groups based on the components of MtS, those who had one or more components of MtS showed a lower standard deviation of the R-R interval compared to a healthy control group.

The recorded use of ginseng dates back 2,000 years. It has been one of the most popular herbal supplements in Asia, especially in Korea, China, and Japan. In the USA, ginseng ranked as one of the top-10 selling herbal supplements in 2003 [18]. The primary effective components of ginseng are known as ginsenosides, and these include compound K (CK), Rg3, Rk1, and Rg5, all of which have a steroidal skeleton.

In the results of this study, CK served as the ligand of glucocorticoid receptor (GR) [19] and Rg3 functioned as the ligand of estrogen receptor (ER) [20], which implies a possible effect of ginseng on lipolysis. In fact, when CK was administered to a 3T3-L1 adipocyte cell line, the storage of triglycerides was suppressed. On the other By contrast, Rg1 stimulated triglyceride storage in adipocytes [21]. Rg3, Rk1, and Rg5 treatments in 3T3-L1 suppressed lipid accumulation [22].

As well as the reported effects of ginseng on FFA, red ginseng has also been shown to have a beneficial effect on insulin and glucose regulation. Vuksan et al [23] reported that red ginseng consumption improved insulin and glucose regulation in type 2 diabetes patients. Lee et al [24] showed that red ginseng has a beneficial effect on insulin sensitivity. We also reported that fermented red ginseng (FRG) showed a serial causal effect on the level of hormones, insulin resistance, and insulin levels. In an analysis of the effects of hormones on glucose blood levels, the difference between the FRG group and the placebo group was due to the level of aldosterone [25].

According to an experiment with mice, ginsenosides stimulated an acetylcholine release in the terminal of cholinergic neurons [26]. In a human study with 120 adult men, wild ginseng increased the activity of the autonomic nerves and increased the heart rate [27].

The first aim of this study was to test the hypothesis that hormones (including insulin) and the branchial pulse rate (the autonomic nervous system activity) affected the flux of FFA in the blood. For this analysis, a path model was established and estimates of the model fit and the hypothesis were then tested. The second aim of this study was to test whether FRG consumption affects the relationship between the independent variables of several hormones and the autonomic nervous system and the dependent variable of FFA.

The study hypotheses were: (1) ACTH, growth hormone (GH), E2, glucocorticoid, tri-iodothyronine (T3), thyroid-stimulating hormone, and/or insulin influence the release of FFA; (2) the brachial pulse rate, which represents the activity of the autonomic nervous system and affects the release of FFA from adipocytes; and (3) the consumption of FRG changes the rate of FFA release, and this release is mediated by FRG on ER or GR.

2. Materials and methods

2.1. Participants and study design

This study was approved by the Institutional Review Board of Sahmyook University (Seoul, Korea). The study participants were 117 postmenopausal women (age 50–73 yr) who were recruited from four Catholic churches. Participants with any disease, including diabetes, cardiovascular disease, dyslipidemia, and kidney disease, were excluded. None of the study participants took any supplements for 2 wk prior to or during the experiment.

Anthropometric parameters were used to evaluate and categorize the 117 participants, who then had their brachial and ankle blood pressure and brachial and ankle blood pulse measured twice, once in the supine position and again after a 10-min rest period. Although the brachial and ankle pressures and pulse rate vary according to the spectrum of life activity, the pressure and the pulse in the supine position can be considered as the pressure and the pulse of a participant in a resting state.

After overnight fasting, blood and urine samples from the 117 participants were collected from 8:00 AM to 10:00 AM. The study participants were then divided into two groups according to the double-blind method of drawing lots. One group was supplied with capsules containing FRG powder (Bifido Inc., Gangwon-do, Korea), and the other group was supplied with placebo capsules containing edible starch for 2 wk. Because a hypothesis of this study was that ginsenosides are ligands of nuclear receptors and that the effects of a nuclear receptor can begin within 2 h, we considered that 2 wk of FRG consumption was sufficient.

The ingredients of the FRG capsules were as follows: crude saponin, 258.6 mg/g; compound K, 57.05 mg/g; Rg3, 53.85 mg/g; Rh2, 11.97 mg/g; Rg2, 5.72 mg/g; Rh1, 2.99 mg/g; and Rb1, 0.023 mg/g. The total weight of the FRG capsule powder was 2.1 g. After 2 wk, 24 women dropped out of the study; therefore, 93 women (49 in the FRG group and 45 in the placebo group) participated in the second blood sample collection. The reported cause of departure for 23 of the women was individual personal reasons not related to FRG consumption. One woman left the experiment after reporting insomnia associated with her consumption of FRG (Fig. 1).

Blood samples were measured at the Green Cross Reference Laboratory (Gyeonggi-do, Korea). The methods of sample analysis are listed in Appendix I.