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Oral administration of γ-aminobutyric acid and γ-oryzanol prevents stress-induced hypoadiponectinemia

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ABSTRACT

Metabolic syndrome is a cluster of risk factors including insulin resistance and type 2 diabetes and is found to associate partly with chronic stress at work in human. Adiponectin circulates in mammal blood mainly as a low molecular weight (LMW) trimer, hexamer, and a high molecular weight (HMW) multimers. Low circulating levels of adiponectin are related to metabolic syndrome. We have then investigated the influence of immobilization stress on plasma adiponectin concentrations in mice. Relative LMW and HMW adiponectin levels were markedly reduced by immobilization stress (0.66 ± 0.07 and 0.59 ± 0.06 after 102 h, respectively), significantly different from the control values ($p < 0.01$ and 0.05, respectively). γ-Aminobutyric acid (GABA) and γ-oryzanol abundantly contained in germinated brown rice have some physiological functions. We further investigated the effect of GABA, γ-oryzanol, GABA plus γ-oryzanol on adiponectin levels in mice subjected to immobilization stress. GABA and γ-oryzanol significantly increased the relative LMW and HMW adiponectin levels under immobilization stress (1.10 ± 0.11 and 0.99 ± 0.19 after 102 h, respectively, for GABA; 1.08 ± 0.17 and 1.15 ± 0.17 after 102 h, respectively, for γ-oryzanol). Additionally, the co-administration of GABA and γ-oryzanol also increased both relative LMW and HMW adiponectin levels (1.02 ± 0.07 and 0.99 ± 0.10 after 102 h, respectively) and was effective in an earlier phase from 30 to 54 h. The results indicate that the co-administration of GABA and γ-oryzanol might be effective in preventing stress-induced hypoadiponectinemia in mice and be also a promising tool for improving metabolic syndrome aggravated by chronic stress.

Introduction

The metabolic syndrome represents a cluster of metabolic risk factors, including central obesity, insulin resistance, dyslipidemia, hyperglycemia, and hypertension for type 2 diabetes and cardiovascular diseases. Metabolic syndrome is rapidly prevailing worldwide. Chronic stress, including psychological and physical stresses, is found to link with metabolic syndrome, and is believed an important risk factor for the development of metabolic syndrome (Vitaliano et al. 2002; Chandola et al. 2006).

Adiponectin is secreted from adipose tissue, exists in the circulation, and has been postulated to play an important role in the modulation of glucose and lipid metabolisms in insulin-sensitive tissues such as liver and skeletal muscle. Plasma adiponectin levels are decreased in the obese and insulin-resistant state (Arita et al. 1999; Yamauchi et al. 2001). Low adiponectin level is associated with metabolic syndrome (Saely et al. 2007; Devaraj et al. 2008). Plasma adiponectin consists of trimer (presented as a low molecular weight multimer, LMW, in the present study) and over-hexamer (presented as high molecular-weight multimers, HMW). Among them, the HMW multimers are believed the most bioactive forms (Pajvani et al. 2004; Waki et al. 2003). The reduced quantity of HMW adiponectin is in special associated with metabolic syndrome (Lera-Castro et al. 2006).

γ-Aminobutyric acid (GABA) is one of the many nutritional components in brown rice and pre-germinated brown rice (PGBR) with slight germination. It has been reported that PGBR rich in GABA effectively reduced glucose levels in diabetic rats (Hagiwara et al. 2004). We have also demonstrated that rice germ extract increased serum adiponectin levels of mouse and that its active compound was GABA (Uchida et al. 2008).

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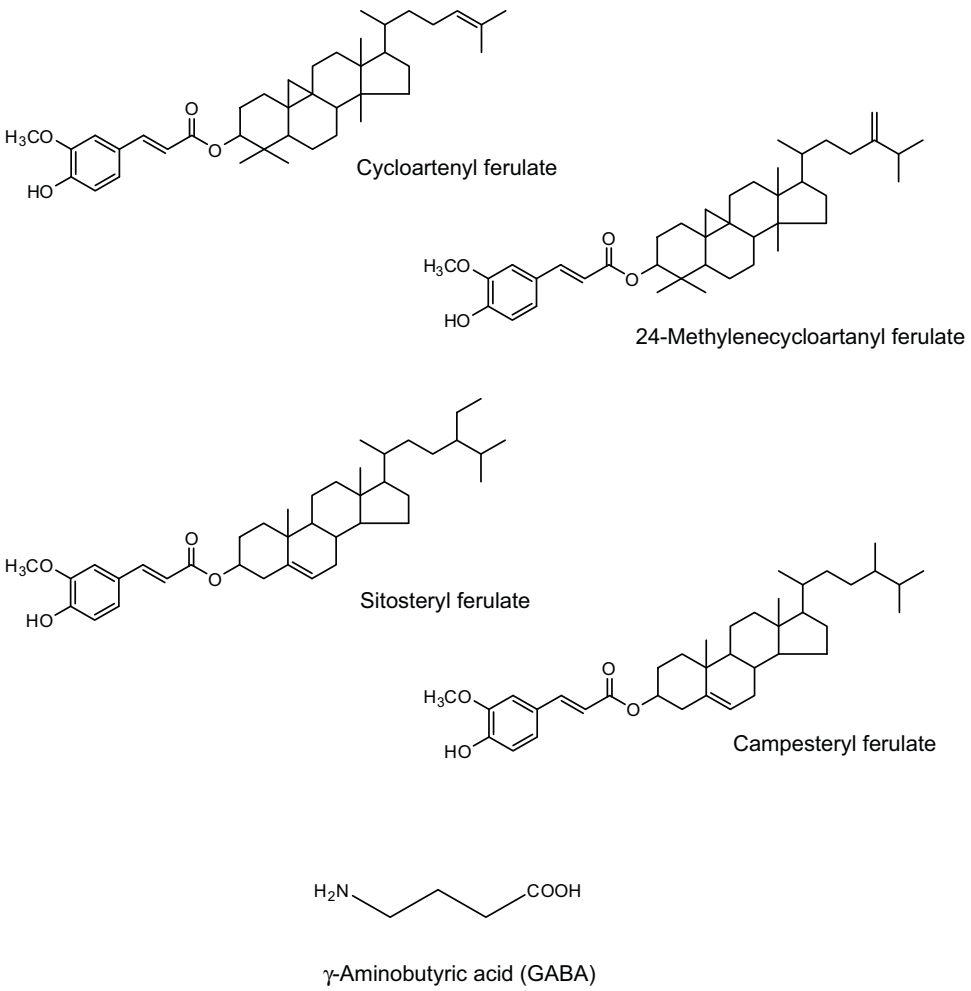

Fig. 1. Chemical structures of four major γ-oryzanol components and γ-aminobutyric acid (GABA) used in this study.

γ-Oryzanol is one of major bioactive components in rice bran, and has been suggested to possess effects of lowering serum cholesterol levels (Rong et al. 1997; Wilson et al. 2007), anti-inflammatory effects (Akihisa et al. 2000), and an anti-cancer effect (Yasukawa et al. 1998) and to function as an antioxidant (Isram et al. 2009; Xu et al. 2001). We have demonstrated that γ-oryzanol suppressed NF-κB activation (Nagasaka et al. 2007; Islam et al. 2008) and directly induced the adiponectin secretion of adipocytes in part through inhibition of NF-κB activation (Ohara et al. 2009). We have recently demonstrated that cycloartenyl ferulate, one component of γ-oryzanol, also prevents allergic inflammation (Oka et al. 2010).

In this study, we investigated the effect of immobilization stress on serum adiponectin levels in mice. We also evaluated the effects of GABA and γ-oryzanol on serum adiponectin levels in mice under immobilization stress.

Materials and methods

Chemicals

GABA (>98% in purity) was obtained from Wako (Osaka, Japan). γ-Oryzanol (>99% in purity) was obtained from Oryza Oil & Fat Chemical Co., Ltd. (Aichi, Japan). The chemical structures of GABA and main components in γ-oryzanol are shown in Fig. 1. Analytical grades were used for other chemicals.

Animals

Male c57BL/6J mice (9–10 weeks, an average weight of 25 g) were obtained from Clea Japan, Inc. (Tokyo, Japan). They were maintained at 50% relative humidity and a 12-h light/dark cycle at 20–22 °C. Mice were *ad libitum* given water and the commercial diet type MF from Oriental Yeast Co., Ltd. (Tokyo, Japan). All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, Tokyo University of Marine Science and Technology and approved by the Committee for the Care and Use of Laboratory Animals, Tokyo University of Marine Science and Technology.

GABA and γ-oryzanol administration

Each experiment was performed with 3–5 mice per group. Solutions of 30 μg/ml GABA, 14.5 μg/ml γ-oryzanol, or the mixture of 30 μg/ml GABA and 14.5 μg/ml γ-oryzanol in 0.0003% 3-[(3-cholamidopropyl) dimethylammonio] propanesulfonate (CHAPS) (Dojindo, Kumamoto, Japan) were prepared. 0.5 ml of GABA ($n = 4$), γ-oryzanol ($n = 3$), GABA plus γ-oryzanol ($n = 5$) or vehicle solution (0.0003% CHAPS, $n = 5$) was orally administered to each mouse after 24-h-fasting. After administration, about 30 μl of blood samples were immediately collected from tail vein (time 0). The mice were subjected to immobilization stress, widely used as one stress model as described in Paré and Glavin (1986). Mice were separately immobilized for 6 h in metal mesh cages. The blood samples (about 30 μl)