学位論文の要約

Bofu-tsu-shosan, an oriental herbal medicine, exerts a combinatorial favorable metabolic modulation including antihypertensive effect on a mouse model of human metabolic disorders with visceral obesity

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Introduction

Accumulating evidence indicates that metabolic dysfunction with visceral obesity is a major medical problem associated with the development of hypertension, type 2 diabetes (T2DM) and dyslipidemia, and ultimately severe cardiovascular disease. Since obesity with visceral fat is related to a variety of metabolic disorders and has a serious impact on the cost of health care, the treatment of obesity has become a critical issue. Although the standard treatment for obesity is a combination of diet and exercise therapy, it is often extremely difficult for obese people to reduce their body weight in this way compared with healthy people, in part because of their excessive appetite. Therefore, to prevent the development of obesity, various anti-obesity drugs and bariatric surgery have been developed as adjunct therapies of obesity in western medicine. However, anti-obesity drugs and bariatric surgery have only been able to help a limited number of severely obese people because of side effects and invasiveness of the procedure (Dietrich MO and Horvath TL, 2012).

Bofu-tsusho-san (BOF) is one of oriental herbal medicine and is clinically available to treat obesity in Japan. In previous studies, BOF has been reported to exert its anti-obesity effect in obese patients as well as various obesity-model animals (Hioki C et al., 2004; Yoshida T et al., 1995). However, the mechanism of its beneficial effect is not fully elucidated. Here, we investigated mechanism of therapeutic effects of BOF on KKAy mice, a model of human metabolic disorders with visceral obesity.

Methods

Male KKAy mice (9 weeks old) were divided into two groups and fed a standard powdered diet (CE-2, the control group) or a powdered diet containing BOF (CE-2 containing 4.7% BOF, the BOF group) for 8 weeks. During the experiment, body weight, food intake and systolic blood pressure (SBP) by tail-cuff method were measured. The tissues were collected under anesthesia at the end of the experimental period.

To examine the acute effects of BOF on food intake and an orexigenic hormone, KKAy mice (13 - 14 weeks of age) fed a standard diet were fasted for 24 hours and were then administered BOF (5000 mg/kg) dissolved in 1mL of distilled water per 100 g of body weight via a stomach tube, and then 24-hour food intake and plasma acylated-ghrelin level were measured.

Results

Chronic BOF administration persistently decreased food intake, body weight gain, LDL-C and SBP (Control vs BOF; SBP, 122 ± 4 vs 113 ± 2 mmHg, $P < 0.05$). In addition, both tissue weight and cell size of visceral white adipose tissue (WAT) were decreased, with concomitant increases in the expression of adiponectin and peroxisome proliferator-activated receptors (PPARs) genes in visceral WAT as well as the circulating adiponectin level by BOF treatment (Control vs BOF; plasma adiponectin level, 6.1 ± 0.2 vs 7.9 ± 0.3 μg/ml, $P < 0.001$). Furthermore, gene expression of uncoupling protein-1, a thermogenesis index by mitochondria, in brown adipose tissue (BAT) and rectal temperature were both elevated by BOF. Intriguingly, plasma acylated-ghrelin, an active form of orexigenic hormone, and short-term food intake were significantly decreased by single bolus administration of BOF (Control vs BOF; plasma acylated-ghrelin level, 25.1 ± 1.1 vs 20.5 ± 1.7 fmol/ml, $P < 0.05$).

Discussion

In the present study, we showed that 1) BOF persistently decreased food intake and body weight gain; 2) BOF consistently decreased blood pressure without affecting heart rate; 3) BOF decreased WAT weight and adipocyte hypertrophy, and ameliorated the adipocytokine dysregulation in WAT; 4) BOF increased UCP-1 mRNA expression in BAT and also the rectal temperature and 5) BOF decreased the short-term food intake and the plasma acylated-ghrelin level in KKAy mice, a model of human metabolic disorders with visceral obesity, T2DM, dyslipidemia and hypertension.

PPARs are critical regulators of adipocyte differentiation and are reported to activate adiponectin gene expression in WAT (Hiuge A et al., 2007; Maeda N et al., 2001). Furthermore, adiponectin is reported to play a protective role against hypertension (Ohashi K et al., 2006; Wang ZV and Scherer PE, 2008). UCP-1 is specifically expressed in BAT and uncouples mitochondrial oxidative phosphorylation by bypassing the electrochemical gradient across the inner membrane from the F1-ATPase and thereby consumes energy as heat (Yoshida T et al., 1995). Thus, the elevated rectal temperature, induced by activating BAT thermogenesis may contribute to the efficient suppression of adipocyte hypertrophy in WAT. Ghrelin, an orexigenic hormone secreted mainly from the stomach, plays an important role in the regulation of food intake (Kojima M et al., 1999). Ghrelin is reported to cause a significant increase in food intake by exerting a potent appetite-stimulating effect by altering orexigenic neuropeptides in the hypothalamus (Kamegai J et al., 2000; Seoane LM et al., 2003; van der Lely AJ et al., 2004). Thus, we hypothesized that BOF exerts a potent appetite-inhibitory effect possibly via suppression of the ghrelin system. We demonstrated that the acute BOF administration significantly decreased the 24-hour food intake with a concomitant reduction of circulating concentration of activated ghrelin. This is the first report showing that BOF exerts an appetite-inhibitory effect via its suppression on the ghrelin system.

Collectively, from the results of present study, we present a schema that would explain the mechanisms of the combinatorial favorable metabolic modulation including antihypertensive effect mediated by BOF (**Figure 1**). BOF acts on adipose tissue to decrease adipocyte hypertrophy in WAT by activation of BAT thermogenesis and amelioration of adipocytokine dysregulation. BOF probably acts on the ghrelin system to exert an appetite inhibitory effect. The improvement in adipose tissue function by amelioration of adipocytokine dysregulation and the reduction of food intake by appetite inhibition may contribute to the blood pressure lowering effect as well as favorable metabolic modulation by BOF in KKAy mice. A limitation of the present study is that other factors such as a diuretic effect and/or an inhibitory effect on sympathetic nerve activity, in addition to a decrease in food intake via appetite suppression, may be involved in the BOF-mediated blood pressure lowering, and these issues should be also addressed by further studies.

In conclusion, these results indicate that BOF exerts a combinatorial favorable metabolic modulation including antihypertensive effect, at least partially, via its beneficial effect on adipose tissue function and its appetite-inhibitory property through suppression on the ghrelin system.

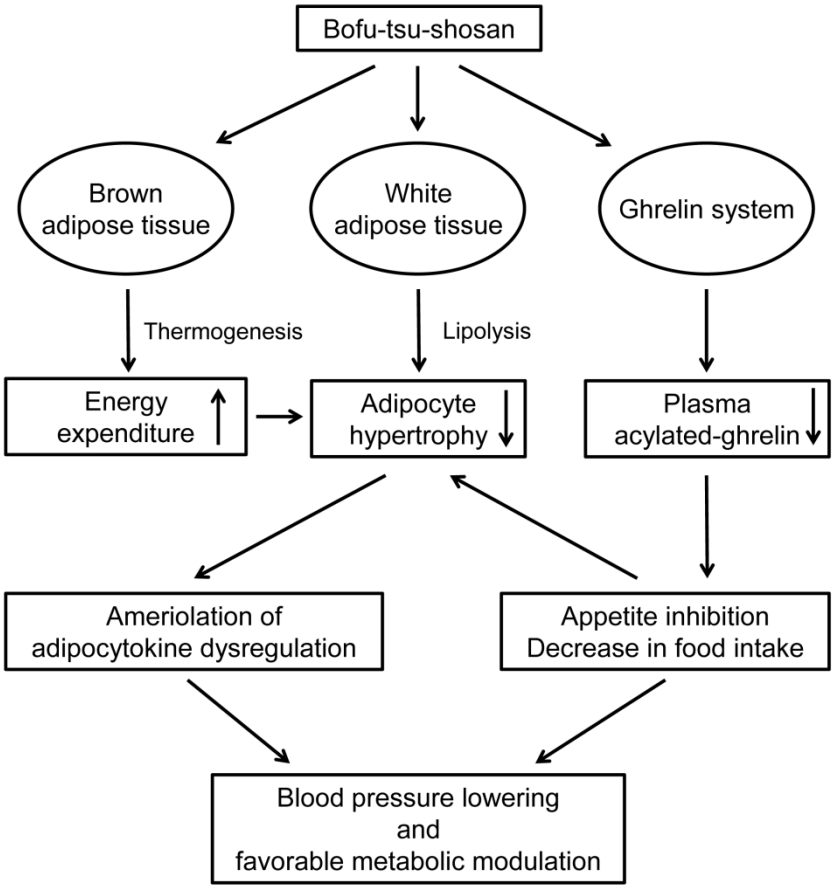

Figure 1. Schema of the mechanisms of beneficial effects induced by BOF.

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論文目録

Ⅰ　主論文

Bofu-tsu-shosan, an Oriental Herbal Medicine, Exerts a Combinatorial Favorable Metabolic Modulation Including Antihypertensive Effect on a Mouse Model of Human Metabolic Disorders with Visceral Obesity.

Kengo Azushima, Kouichi Tamura, Hiromichi Wakui, Akinobu Maeda, Masato Ohsawa, Kazushi Uneda, Ryu Kobayashi, Tomohiko Kanaoka, Toru Dejima, Tetsuya Fujikawa, Akio Yamashita, Yoshiyuki Toya, Satoshi Umemura: PLoS One. Volume 8, Issue 10: e75560, October 2013.

Ⅱ　副論文

Effects of the oriental herbal medicine Bofu-tsusho-san in obesity hypertension: A multicenter, randomized, parallel-group controlled trial.

Kengo Azushima, Kouichi Tamura, Sona Haku, Hiromichi Wakui, Tomohiko Kanaoka, Masato Ohsawa, Kazushi Uneda, Ryu Kobayashi, Kohji Ohki, Toru Dejima, Akinobu Maeda, Tatsuo Hashimoto, Jin Oshikawa, Yusuke Kobayashi, Koichiro Nomura, Chieko Azushima, Yasuyo Takeshita, Ryota Fujino, Ken Uchida, Ken Shibuya, Daisaku Ando, Yasuo Tokita, Tetsuya Fujikawa, Yoshiyuki Toya, Satoshi Umemura: Submitted.

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