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Dietary soy and tea combinations for prevention of breast and prostate cancers by targeting metabolic syndrome elements in mice,,[1,2,3,4]

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Abstract

Background—The prevalence of metabolic syndrome is high and is increasing in parallel with increasing incidences of breast and prostate cancers. The combination of soy with tea was shown to have synergistic effects on preventing breast and prostate tumors, but the effects of soy and tea combinations on metabolic syndrome–related elements have not been investigated.

Objective—We aimed to determine the effects of soy and tea components, alone and in combination, on abdominal adipose mass and serum concentrations of adipokines, growth factors, and sex hormones in male and female mice.

Design—Male and female FVB/N mice were treated with soy, tea components, or both. Food intake and body weight were monitored weekly. At the end of the experiment, abdominal white adipose tissue was weighed, and serum concentrations of biomarkers were measured.

Results—Whole teas, but not the tea polyphenol extracts, significantly reduced abdominal white adipose tissue by 43–60% in female mice and by 65–70% in male mice. The combination of soy phytochemical concentrate and green tea reduced serum insulin-like growth factor-I concentrations in both male and female mice in a synergistic manner. The soy phytochemical concentrate and tea combinations reduced serum estrogen concentrations in female mice in a synergistic manner. Soy phytochemical concentrate and teas also significantly reduced serum leptin concentrations in both male and female mice and testosterone concentrations in male mice.

Conclusion—Further research is warranted to investigate whether soy and tea combinations may prevent breast or prostate cancer in a synergistic manner in part by alleviating metabolic disorders.

Keywords

Metabolic syndrome; cancer prevention; tea; soy; insulin-like growth factor-I; IGF-I; leptin; synergy

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INTRODUCTION

The metabolic syndrome (MS) is characterized by visceral or intraabdominal obesity, glucose intolerance, hypertension, low serum HDL-cholesterol, and high serum triacylglycerols. The prevalence of MS is high and increases in parallel with increased risks of certain types of cancer, such as breast cancer and prostate cancer (1,2). Recent epidemiologic studies have shown associations between MS or MS-related elements and increased risks of breast cancer (3–5) and prostate cancer (6–9), which suggests that MS may be an important etiologic risk factor for these cancers.

Despite established epidemiologic associations between MS and increased risks of breast and prostate cancers, little experimental evidence is available to support whether MS plays a direct causal role in breast or prostate cancer. On the other hand, previous experimental research has provided mechanistic plausibility that MS may play an important role in cancer development, progression, or both. MS is associated with altered concentrations of adipokines, growth factors, and sex hormones. Insulin resistance is considered to be the underlying factor for MS. Evidence has linked chronic hyperinsulinemia to greater cancer risks (2). Obesity is associated with higher concentrations of insulin (10–12). Elevated serum insulin concentrations increase the concentration or bioavailability of insulin-like growth factor-I (IGF-I), which also plays a critical role in the development of some breast and prostate cancers (13–16).

Considerable data from animal studies indicate that combinations of agents can be more effective for cancer prevention than any single constituent (17). Research suggests that increased consumption of soybean products or tea contributes to the lower risks of breast and prostate cancers in Asian populations than in industrialized Western nations (18,19). Asian people consume soy products and tea regularly. It is possible that the effective cancer prevention activity of Asian diets may result at least in part from interactions between soy and tea active components.

We evaluated the effects of soy and tea components on breast and prostate cancers in clinically relevant animal models (20,21). The combination of soy phytochemical concentrate (SPC) and black tea (BT) synergistically inhibited prostate tumorigenicity, final tumor weight, and metastases to lymph nodes (20). The combinations of soy phytochemicals and tea [BT or green tea (GT)] also inhibited the growth of breast tumors (21) in a synergistic or an additive manner. The combinations also synergistically reduced serum IGF-I concentrations (21) and androgen concentrations (20).

To further define the activity of soy and tea combinations in the prevention of breast and prostate cancers and to determine whether modulation of metabolic elements is in part responsible for the cancer prevention activity of the combination regimens, we evaluated the combined effects of soy and tea components on abdominal white adipose tissue (WAT) and serum concentrations of adipokines (leptin, adiponectin), growth factors (insulin, IGF-I), and sex hormones (androgen in male mice or estrogen in female mice) in mice consuming a normal-fat diet.

MATERIALS AND METHODS

Soy and tea components and experimental diets

Both GT (China Green Tea, Shanghai Tea Import and Export Corporation, Shanghai, China) and BT (Keemun Black Tea, Shanghai Tea Branch, China National Native Produce and Animal By-Products Import and Export Corporation, Shanghai, China) were purchased from a local supermarket. BT extract (BTE) and GT extract (GTE) were prepared by hot water extraction of BT and GT leaves, respectively, followed by freeze-drying. Both BT polyphenols (BTPs)

and GT polyphenols (GTPs) were prepared by extraction of tea polyphenols from BTE and GTE, respectively. The tea polyphenols were analyzed by HPLC. The typical compositions of these tea components are shown in Table 1.

Four soybean components that represent commonly used soybean products were evaluated: *1*) isoflavone-depleted soy protein isolates (SPIs), representing soy protein and containing 0.002 mg isoflavone aglycones/g material; *2*) high-isoflavone-containing SPIs, representing a commonly used soy protein product in food industry and scientific research and containing 2.67 mg isoflavone aglycones/g material; *3*) the soy phytochemicals extract SPC, representing the soy phytochemicals profiles commonly consumed in soyfoods and containing 51.9% soy isoflavones by weight (50.8% genistein aglycone equivalents, 40.5% daidzein aglycone equivalents, and 8.7% glycitein aglycone equivalents; other phytochemicals not quantified); and *4*) the soy isoflavone genistein, a proposed active component in soy. Both isoflavone-depleted and high-isoflavone-containing SPIs were provided by Solae Co (St Louis, MO),SPCwas provided by Archer Daniels Midland Co (Decatur, IL), and genistein was purchased from LC Laboratories (Woburn, MA).

Diet formulations and treatment groups

The soy and tea components were used to prepared the experimental diets by Research Diets Inc (New Brunswick, NJ) for the following treatment groups: *1*) AIN-93G as the control diet; *2*) AIN-93 with isoflavone-depleted SPIs in place of casein, 20% by weight; *3*) AIN-93 with high-isoflavone-containing SPIs in place of casein, 20% by weight; *4*) AIN-93 with the addition of genistein at 0.07% of the diet; *5*) AIN-93 with the addition of SPC at 0.5% of the diet; *6*) AIN-93 with 1.2% BT infusion in place of drinking water; *7*) AIN-93 with 1.2% GT infusion in place of drinking water; *8*) AIN-93 with the addition of BTPs at 0.2% of the diet; *9*) AIN-93 with addition of GTPs at 0.2% of the diet; *10*) AIN-93 with 0.5% SPC and 1.2% BT infusion; and *11*) AIN-93 with 0.5% SPC and 1.2% GT infusion.

Animal study 1: effects of soy and tea components on abdominal WAT, adipokines, IGF-I, and estrogen in female mice—Female FVB/N mice (5–6 wk old) were randomly assigned into the experimental groups ($n = 12$ per group) and were treated with the corresponding experimental diets for 8 wk. Food intake and body weight were measured weekly. At the end of the experiment, 3-h fasting blood samples were collected, the animals were killed, and abdominal WAT and liver were collected and weighed. Serum concentrations of adipokines (leptin, adiponectin), growth factors (insulin and IGF-I), and estrogen were measured by using commercially available radioimmunoassay or enzyme-linked immunosorbent assay kits by following the procedures provided by the manufacturers (Diagnostic Systems Laboratories, Inc, Webster, TX, and Linco Research Inc, St Louis, MO). All procedures with animals were reviewed and approved by the Institutional Animal Care and Use Committee at Beth Israel Deaconess Medical Center according to National Institutes of Health guidelines.

Animal study 2: effects of soy and tea components on abdominal WAT, adipokines, IGF-I, and testosterone in male mice—The animal study was conducted by using the same experimental protocol as in animal study 1 except that male mice, rather than female mice, were used.

Statistical analysis

Measured values are expressed as means ± SEMs. The STAT-VIEW 5.0 program (SAS Institute Inc, Cary, NC) was used to calculate two-sided comparisons among experimental groups through analysis of variance followed by Tukey's test to determine significance between the treatment group and the control group (22). A P value of < 0.05 was considered

significant. The nature of the combined effects of SPC and tea was determined by using the method described by us and other laboratories (20,21,23). In brief, the expected value of a combination effect between treatment 1 and treatment 2 is calculated as [(observed treatment 1 value)/(control value)] × [(observed treatment 2 value)/(control value)]×(control value); the combination index is calculated as the ratio (expected value)/(observed value). A ratio of > 1 indicates a synergistic effect, and a ratio of <1 indicates a less than additive effect.

RESULTS

Effects of soy and tea treatments on food intake, body weight, and abdominal WAT mass in mice

The effects of different soy and tea components on food intake, body weight, and WAT weight in both male and female mice are shown in Table 2. Male mice consumed more diets, gained more weight, but had less WAT mass than did female mice. All experimental diets were well consumed by the animals. In fact, the mice in some treatment groups consumed even more food than did the controls. Male mice in the BTP, BT, and GT and SPC combination groups consumed 28.3% ($P < 0.0005$), 12.9% ($P < 0.05$), 16.7% ($P < 0.005$), and 16.1% ($P < 0.005$) more food, respectively, than did the control group. Female mice in the SPC and GT combination group consumed 13.6% ($P < 0.05$) more food than did the control group.

Soy and tea components showed different effects on food intake and body weight. In general, the soy components did not significantly alter food intake or body weight compared with the control in either male or female mice. Compared with the control, tea components resulted in significantly higher food intake (except the GTPs) in male mice, but significantly lower body weights of both male (except in the BTP and GTP groups) and female mice.

Male mice treated with isoflavone-depleted SPIs, high-isoflavone-containing SPIs, or genistein had significantly lower WAT mass by 65.2% ($P < 0.0005$), 42.9% ($P < 0.0005$), and 37.7% ($P < 0.005$); female mice treated with high-isoflavone-containing SPIs or genistein had significantly lower WAT mass by 21% ($P < 0.05$), respectively (Table 2). The SPC did not have a significant effect on WAT mass in either male or female mice. Similarly, male or female mice treated with tea polyphenols (BTPs and GTPs) did not have significantly lower WAT mass. Male mice treated with BT or GT had significantly lower WAT mass by 70% ($P < 0.0005$) and 65% ($P < 0.0005$), respectively. Female mice treated with BT or GT, on the other hand, had significantly lower WAT mass by 60% ($P < 0.0005$) and 43% ($P < 0.0005$), respectively. These results indicate that whole teas have potent effects on reducing abdominal WAT mass and that the effects of tea polyphenols extracts do not have significant effects on WAT and body weight.

Effects of SPC and tea combinations on food intake, body weight, and abdominal WAT mass in mice

The SPC and BT combination and SPC and GT combination were evaluated for their effects on food intake, body weight, and WAT mass. We selected SPC and whole tea combinations because these materials represent the soy and tea phytochemical compositions commonly consumed by humans, and their combinations showed significant and synergistic effects on inhibiting the growth of breast or prostate tumors in vivo. The combinations of SPC and tea did not further alter food intake, body weight, or WAT mass (Table 2).

Effects of SPC and tea combinations on serum concentrations of insulin, leptin, IGF-I, adiponectin, and sex hormones in mice

The effects of SPC and tea combinations on modulation of serum concentrations of adipokines (leptin and adiponectin), growth factors (insulin and IGF-I), and sex hormones (testosterone

in male mice and 17β-estradiol in female mice) are shown in Figure 1 and Figure 2. The treatments did not significantly alter serum concentrations of insulin in male or female mice. The SPC significantly lowered serum leptin concentrations by 20% in female mice. BT and GT significantly lowered serum concentrations of leptin by 92% ($P < 0.0005$) and 94% ($P < 0.0005$), respectively, in male mice and by 80% ($P < 0.0005$) and 73% ($P < 0.0005$), respectively, in female mice. The combinations of SPC with BT or GT significantly lowered serum concentrations of leptin by 93% ($P < 0.0005$) and 87% ($P < 0.0005$), respectively, in female mice. Analysis showed that the combination of SPC and BT or GT had a synergistic effect ($P < 0.05$) on lowering leptin concentrations in female mice.

SPC and BT treatment alone did not significantly lower serum concentrations of IGF-I, whereas GT significantly lowered serum concentrations of IGF-I by 13.3% ($P < 0.05$) in male mice (Figure 1). The combination of SPC and GT further lowered serum IGF-I by 25.7% ($P < 0.0005$) in male mice, and the combination effect was synergistic. In female mice, SPC, BT, and GT did not show significant effects on IGF-I concentrations (Figure 2). The combination of SPC and GT, however, significantly lowered IGF-I concentrations by 14% ($P < 0.05$), and the combination had a synergistic effect ($P < 0.05$).

The SPC and tea treatments significantly lowered serum concentrations of adiponectin in male mice (except the SPC treatment, Figure 1), but not in female mice (Figure 2), compared with those of the control. Because adiponectin is produced only in adipose tissue, we also expressed adiponectin concentrations on the basis of WAT mass and as percentage of the control amount. SPC did not have a higher WAT-corrected adiponectin concentration compared with that of the control. Other experimental groups had significantly higher ratios (except for the SPC-BT combination in male mice). No synergistic effect was observed.

The experimental treatments significantly lowered the serum testosterone concentration in male mice (Figure 1). No apparent combination effects were observed, maybe in part because of the dramatic effects in individual treatments. In contrast, tea treatments alone did not significantly alter serum estrogen concentrations in female mice (Figure 2), and SPC significantly raised serum estrogen concentrations by 23% ($P < 0.05$). Interestingly, this estrogen-enhancing activity of SPC was reversed by its combination with BT or GT, and the combinations of SPC with BT or GT lowered serum estrogen concentrations by 14.6% (NS) or 32.5% ($P < 0.0005$), compared with the control. Calculation of the combination index showed that both the SPC-BT and the SPC-GT combinations had synergistic effects ($P < 0.05$) on lowering serum estrogen concentrations in female mice.

DISCUSSION

The results of the present study show that tea components significantly lowered body weights without significantly altering food intakes. Whole teas, but not tea polyphenol extracts, significantly lowered WAT mass by 65–70% in male mice and by 43–60% in female mice. SPC and teas, alone and in combination, significantly lowered serum leptin concentrations in both male and female mice. The combination of SPC and GT lowered serum IGF-I concentrations in both male and female mice in a synergistic manner. The SPC and tea combinations also lowered serum estrogen concentrations in female mice in a synergistic manner. Our results suggest that the combinations of soy and tea components may improve metabolic conditions by inhibiting abdominal WAT mass and by modulating certain MS-associated elements such as leptin, IGF-I, and sex hormones.

In this animal study, MS was not induced and the animals were treated with a 10%-fat diet. Even in this situation, the soy and tea components, especially in combinations, showed significant modulation of several MS-related elements, such as leptin, IGF-I, and sex

hormones, all favoring cancer-prevention activity. Indeed, the SPC and tea combinations inhibited the growth and progression of both breast and prostate tumors in our preclinical animal models. These findings may have significant effects on the prevention of breast cancer or prostate cancer in a healthy population because the dietary fat was at a “normal” level. Although not conducted in this report, we expect that certain soy and tea combinations may significantly prevent the development of MS and improve metabolic status. To directly establish the cancer-promoting effects of MS, it is also required to determine whether MS enhances the development or progression of breast or prostate cancer in appropriate animal models. Further animal studies are also required to define whether certain soy and tea combinations effectively prevent breast or prostate cancer in part by preventing the development of MS and improving metabolic profiles.

Previous research has primarily focused on the cancer prevention activity of soy or tea components alone (18,19) but not in combination. Evidence is emerging that soy components, such as soy isoflavones and soy protein, may play a beneficial role in obesity and diabetes. Soy protein associated with isoflavones improves glucose control, lipid profiles, and insulin resistance (24–29) and increases the serum adiponectin concentration (27,29). Soy isoflavones significantly lower fat mass, plasma glucose in both lean and obese rats (30,31), and serum concentrations of leptin (32,33) and improve glucose tolerance (34). Clinical intervention studies showed that soyfood reduces serum concentrations of insulin and leptin (35). Consumption of soy isoflavones is associated with lower body mass indexes and fasting insulin concentrations and higher HDL cholesterol and also lowers the insulin response to an oral glucose load in presumably normal-weight, postmenopausal women (36). Thus, it appears from these studies that soy-based diets may provide potential benefits in conditions associated with impaired glucose tolerance, hyperlipidemia, and reduced insulin sensitivity. On the other hand, some studies did not show significant effects of soy components on metabolic profiles (37, 38).

Similar to the soy studies, previous studies have shown the MS-preventive activity of tea components. Tea components, especially epigallocatechin gallate, had antiobesity activity and improved metabolic disorders via modulation of adipokines and growth factors (39–41), especially suppression of leptin concentrations (39,41,42). Besides tea polyphenols, caffeine had antiobesity activity and modulated related adipokines such as leptin (43). GT lowered adipose tissue weight without any change in body weight, other tissue weights, and food and water intakes, and also significantly lowered the plasma concentrations of cholesterol and free fatty acids (41).

Our results suggest that one of the mechanisms by which SPC and tea combinations may have synergistic cancer prevention activity is via synergistic effects on lowering IGF-I concentrations. IGF-I has been shown to play an important role in the development of breast and prostate glands and in carcinogenesis and tumorigenesis. Epidemiologic investigations in general indicated that the increased serum concentrations of IGF-I were significantly associated with breast cancer risk (44–48) and prostate cancer risk (46,49,50). On the other hand, the results from epidemiologic investigations on the association between soy components, mostly soy proteins, and serum concentrations of IGF-I are inconsistent, ranging from a positive association (48,51–54), a negative association (55), to no association (55–59). Our results showed that although SPC and tea alone did not have significant effects on serum IGF-I concentrations, the combination of SPC and GT significantly lowered IGF-I concentrations in a synergistic manner. Our results support further investigation to apply appropriate dietary combination regimens, such as soy and tea combinations, for cancer prevention by targeting IGF-I function.

Our results also showed that SPC and tea combinations had a synergistic effect on lowering the serum estrogen concentration in female mice. Estrogen plays a key role in estrogen-dependent breast cancer development and growth. Obesity has been shown to enhance circulating concentrations of estrogen and thus may favor promotion of breast cancer development. Administration of anti-estrogen tamoxifen is a successful adjuvant therapy for patients with estrogen-dependent breast cancer and significantly improves the survival of those women (60). The results from our study may provide a mechanistic explanation for the finding in our breast cancer study of a synergistic effect of SPC and GT on inhibiting the growth of breast tumors (21). Further research is warranted to investigate the mechanisms by which SPC and tea combinations may reduce circulating estrogen concentrations in a synergistic manner.

Our results also showed that the combination of BT or GT with SPC reduced leptin concentrations in a synergistic manner in female mice. Due to dramatic effects of soy and tea treatment alone, the potentiating effects between soy and tea combinations were not apparent in male mice. Plasma leptin concentrations correlate with fat stores and the volume and number of adipocytes. Epidemiologic and experimental studies in general have shown that leptin promotes the development and progression of breast cancer (61–65) and prostate cancer (66–73). Our findings suggest that one of the mechanisms by which the soy and tea combination may synergistically prevent breast cancer may be through synergistic effects on lowering leptin concentrations in female mice.

In summary, the results of the present study show that the soy and tea combinations lowered abdominal WAT mass, serum concentrations of IGF-I and leptin in both male and female mice, and estrogen concentrations in female mice in a synergistic or an additive manner. The results suggest that the soy and tea combination may prevent MS and improve metabolic profiles, and this MS-preventive activity may be in part responsible for the synergistic effects of the soy and tea combinations on the prevention of breast or prostate cancer observed in the animal studies. The results provide the rationale to support future research to define the causal role of MS in the development and progression of breast or prostate cancer and to apply dietary combination strategies, such as the soy and tea combinations, to cancer prevention by preventing MS.

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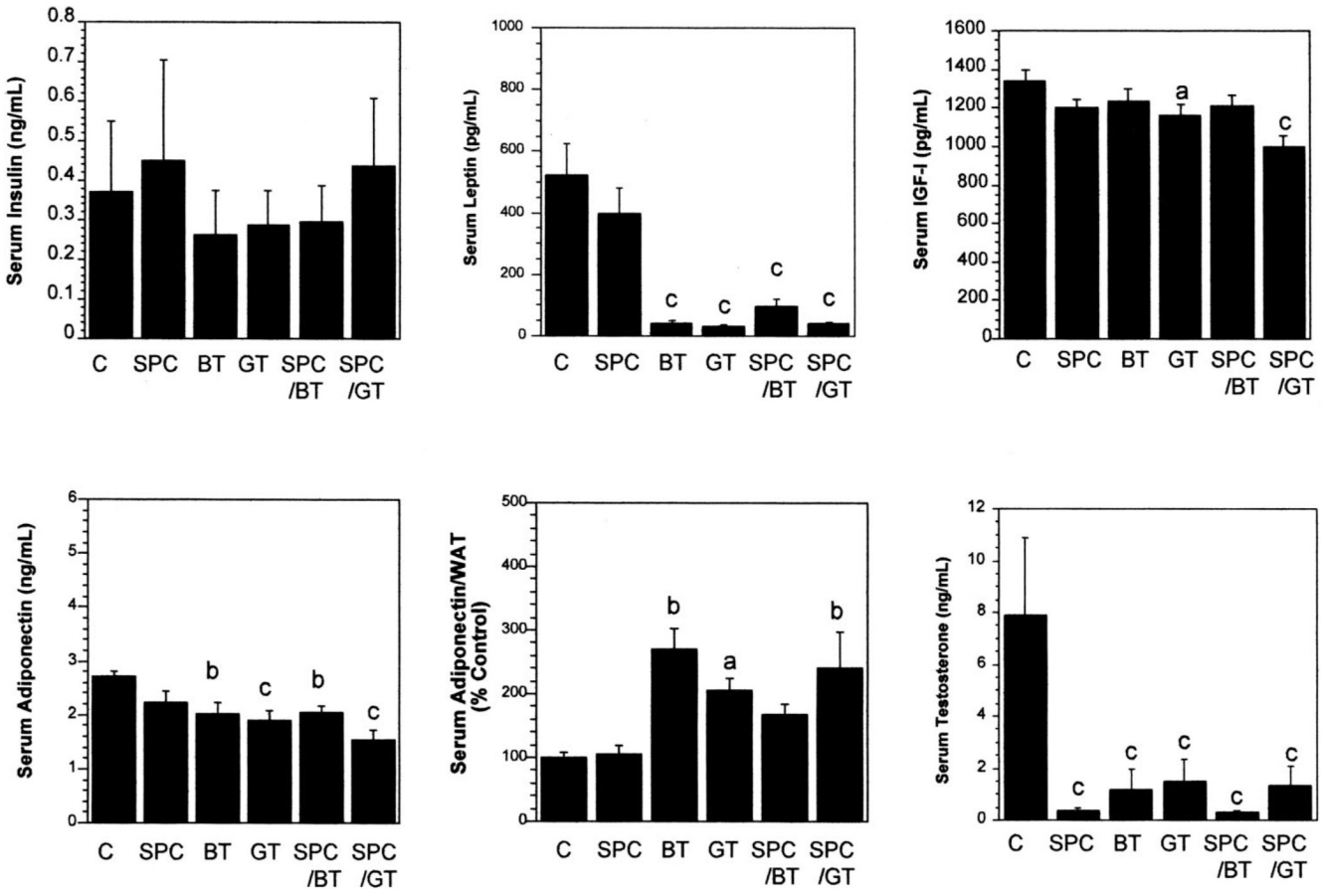

FIGURE 1.

Effects of soy phytochemical concentrate (SPC) and tea combinations on serum concentrations of insulin, leptin, insulin-like growth factor-I (IGF-I), adiponectin, adiponectin corrected for white adipose tissue (WAT), and testosterone in male mice. C, control; BT, black tea; GT, green tea. Values are $\bar{x} \pm$ SEM, $n = 12$/group, and were analyzed by ANOVA followed by Tukey's test. Within each panel, the value with a letter is significantly different from the control: $^{a}P < 0.05$, $^{b}P < 0.005$, $^{c}P < 0.0005$.

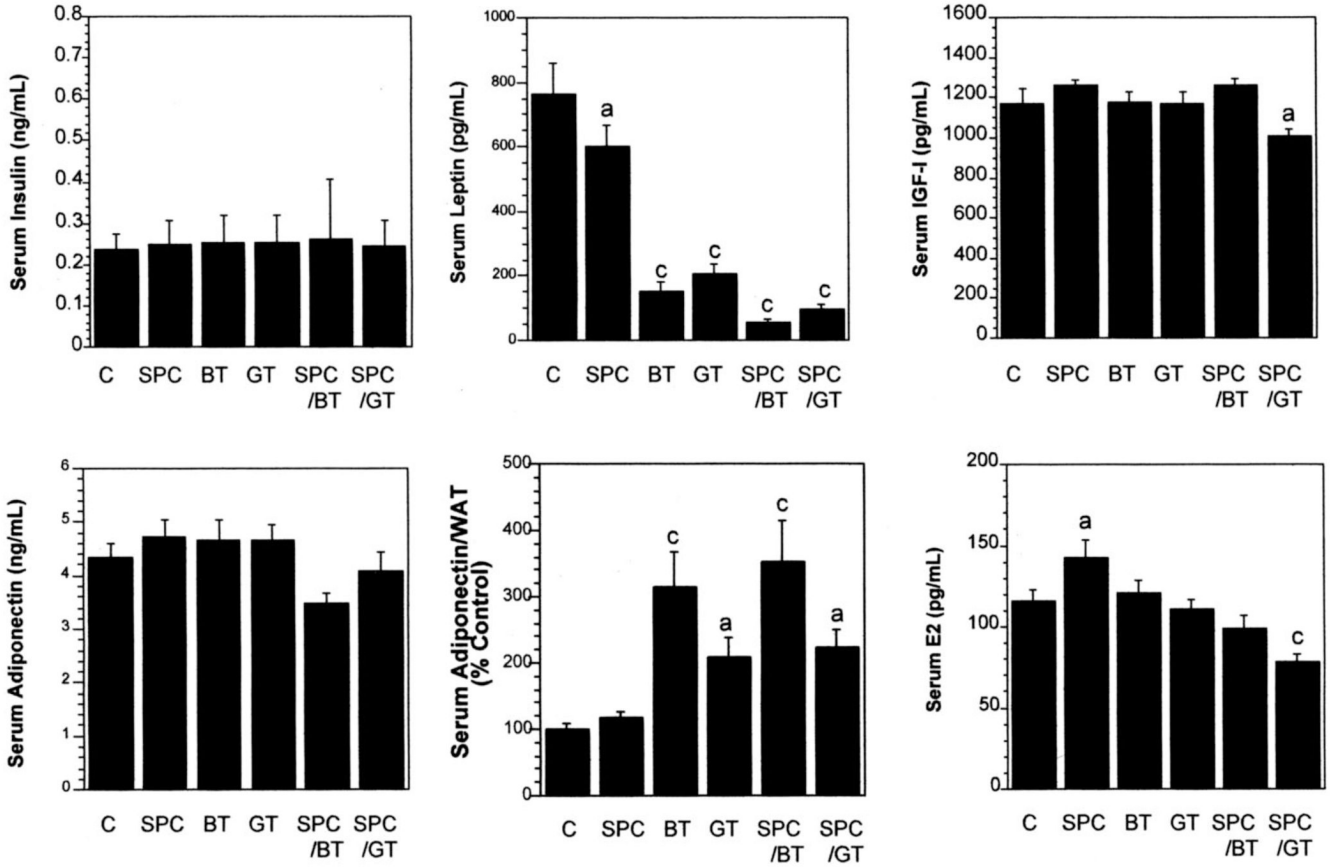

FIGURE 2.

Effects of soy phytochemical concentrate (SPC) and tea combinations on serum concentrations of insulin, leptin, insulin-like growth factor-I (IGF-I), adiponectin, adiponectin corrected for white adipose tissue (WAT), and estradiol (E2) in female mice. C, control; BT, black tea; GT, green tea. Values are $\bar{x} \pm$ SEM, $n = 12$/group, and were analyzed by ANOVA followed by Tukey's test. Within each panel, the value with a letter is significantly different from the control: $^{a}P < 0.05$, $^{c}P < 0.0005$.

TABLE 1

HPLC analysis of tea polyphenol compositions in typically prepared black tea extract (BTE), black tea polyphenols (BTPs), green tea extract (GTE), and green tea polyphenols (GTPs)[1]

Tea component	BTE	BTPs	GTE	GTPs
		% of Solids		
EC	1	4.4	3.8	8.7
EGC	1	1.6	8.7	13.9
ECG	2	12.7	4.3	7.6
EGCG	3	20.1	15.1	47.7
TF	1	4.3	NA	NA
TF-3-gallate	<1	4.7	NA	NA
TF-3'-gallate	<1	2.5	NA	NA
TF-3,3'-digallate	<1	3.8	NA	NA
Gallic acid	1	3.2	0.2	0.2
Caffeine	7	0.6	5.4	1.2
Total polyphenols	12	57.3	32.1	78.1

[1] EC, epicatechin; EGC, epigallocatechin; ECG, epigallocatechin gallate; EGCG, epigallocatechin gallate; NA, not analyzed; TF, theaflavin.

TABLE 2

Effects of soy and tea components on food intake, body weight, and abdominal white adipose tissue mass (WAT) in male or female mice[1]

	Food intake		Final body weight		WAT	
Treatment	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
	g/d		*g*		*g*	
Control	3.11 ± 0.26	2.50 ± 0.21	29.7 ± 1.5	24.4 ± 2.0	0.77 ± 0.23	0.90 ± 0.28
IDSPIs	3.32 ± 0.24	2.64 ± 0.23	30.5 ± 1.3	24.2 ± 1.5	0.26 ± 0.11[2]	0.75 ± 0.21
HISPIs	3.13 ± 0.09	2.51 ± 0.20	29.7 ± 1.6	23.9 ± 2.4	0.44 ± 0.15[2]	0.71 ± 0.23[3]
Genistein	3.13 ± 0.34	2.43 ± 0.22	29.2 ± 2.4	23.6 ± 1.5	0.48 ± 0.31[4]	0.71 ± 0.18[3]
SPC	3.00 ± 0.23	2.32 ± 0.25	28.6 ± 1.8	24.0 ± 1.9	0.64 ± 0.28	0.82 ± 0.22
BTPs	3.99 ± 0.31[2]	2.48 ± 0.31	29.0 ± 2.6	23.0 ± 1.3[3]	0.62 ± 0.42	0.79 ± 0.19
GTPs	3.49 ± 0.34	2.68 ± 0.37	31.0 ± 2.6	23.7 ± 1.2[3]	0.86 ± 0.23	0.85 ± 0.22
BT	3.51 ± 0.11[3]	2.77 ± 0.41	27.4 ± 2.6[3]	21.1 ± 1.7[2]	0.23 ± 0.10[2]	0.36 ± 0.17[2]
GT	3.63 ± 0.10[4]	2.72 ± 0.33	27.1 ± 2.2[4]	22.4 ± 1.6[4]	0.27 ± 0.12[2]	0.51 ± 0.21[2]
BT/SPC	3.33 ± 0.15	2.79 ± 0.18	27.0 ± 1.6[4]	21.9 ± 1.1[2]	0.37 ± 0.14[2]	0.24 ± 0.11[2]
GT/SPC	3.61 ± 0.20[4]	2.84 ± 0.28[3]	26.4 ± 2.9[2]	21.8 ± 1.4[2]	0.31 ± 0.24[2]	0.40 ± 0.16[2]

[1] All values are $\bar{x}$ ± SEM. IDSPIs, isoflavone-depleted soy protein isolates; HISPIs, high-isoflavone soy protein isolates; SPC, soy phytochemical concentrate; BTPs, black tea polyphenols; GTPs, green tea polyphenols; BT, black tea; GT, green tea. Values were analyzed by ANOVA followed by Tukey's test.

[2] Significantly different from control: $P < 0.0005$

[3] Significantly different from control: $P < 0.05$

[4] Significantly different from control: $P < 0.005$.