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Replacement of Dietary Soy Protein Isolate with Concentrates of Soy 7S or 11S Globulin Has Minimal or No Effects on Plasma Lipoprotein Profiles and Biomarkers of Coronary Risk in Monkeys

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Abstract

Effects of soy peptide fractions on risk factors for coronary heart disease are unknown. We compared the effects of a soy protein isolate, a soy 7S fraction concentrate and a soy 11S fraction concentrate on total plasma cholesterol, HDL cholesterol, LDL + VLDL cholesterol and triacylglycerol in adult male cynomolgus monkeys. Effects on biomarkers of coronary risk [soluble E-selectin, vascular cell-adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1), transforming growth factor β -1 (TGF- β -1) and plasminogen activator inhibitor-1 (PAI-1)] were also determined. Relative to a soy- and isoflavone-free diet (casein and lactalbumin as the source of protein), soy protein isolate had the predicted favorable effects on plasma lipoproteins, i.e. reductions in total and VLDL + LDL cholesterol (8% and 14% respectively) (P 's<0.05) and a 41% increase in HDL (P <0.05). Effects of 7S and 11S on these variables were less favorable. In fact, there was a 7% increase in total plasma cholesterol concentration (P <0.05) in monkeys fed 7S that was accounted for primarily by an increase in VLDL + LDL cholesterol. There was no effect of any protein source on cardiovascular biomarkers. Replacement of dietary soy protein isolate with concentrated 7S or 11S does not result in improvement of plasma lipoprotein profiles or cardiovascular biomarkers in monkeys.

Keywords

lipoproteins; monkeys; 7S globulin; 11S globulin; soy; biomarkers

1. Introduction

While the effect of increased soy consumption on risk of coronary heart disease remains uncertain, it is known that consumption of 25 g or more of soy protein/d results in modest improvements in plasma lipoprotein profiles in some subjects. However, dietary soy or isoflavone supplements seem to have little or no effect on biomarkers of inflammation that have been associated with increased coronary risk [1]. We have hypothesized that the apparent

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lack of a robust effect of soy protein isolates or other soy products on coronary risk factors or biomarkers can be explained by the fact that the cardioprotective activity of soy protein may reside in one or more of its peptide fractions. Since the responsible fraction(s) are present in relatively small amounts in typical soy products, their effects may be less than optimal. It is also possible that antagonistic actions of other soy peptides or the many non-peptide constituents of commonly-consumed soy products may tend to negate favorable influences. Supporting this hypothesis, we have recently shown that consumption of concentrated β -conglycinin, or 7S globulin, a fraction accounting for about 30% of soy protein, has an inhibitory effect on atherosclerosis in mice that greatly exceeds the effect of a soy protein isolate commonly used in dietary supplements [2].

Effects of soy peptide fractions on risk factors for atherosclerosis and coronary heart disease in human subjects remain unclear. However, studies of cultured human hepatocytes [3,4] have found that 7S globulin stimulates the expression of LDL receptors and the degradation of LDL. Another study by this group [5] showed that, when fed to rats, 7S globulin reduced plasma cholesterol concentration by 35%. More recently, it was found that consumption of the α' subunit of 7S globulin caused an upregulation of hepatic β -VLDL receptors and a 38% reduction in plasma cholesterol concentration in rats [6]. These investigators [7] have also shown that small peptides (3 to 20 kDa) produced by enzymatic digestion of soy protein and a small synthetic peptide (2271 Da) which corresponds to certain sequences of the complete 7S globulin produce the same effects on cultured hepatocytes as the complete 7S globulin. This has led to speculation that there are bioactive small peptide fractions produced by the digestion of soy protein that are absorbed from the intestinal tract and have favorable effects on lipoprotein metabolism and cardiovascular health [7,8]. However, other studies with rats have found either no effect of 7S on plasma total or LDL cholesterol concentrations [9] or a modest effect that was similar to that of a typical soy protein isolate [10]. Furthermore, we have shown that, while effects of 7S on plasma lipoproteins in mice are not different than those of soy protein isolate, 7S has marked athero-inhibitory influences in mice that exceed those of soy protein isolate and are unrelated to plasma lipoprotein concentrations [2].

To our knowledge there are no data on the effects of consumption of 7S fraction on atherosclerosis, coronary heart disease risk, plasma lipoproteins or other cardiovascular biomarkers in human or nonhuman primates. For this reason we studied the effects of consumption of 7S fraction on plasma total cholesterol, HDL cholesterol, VLDL+LDL cholesterol and triglycerides in a monkey model of atherosclerosis. Effects on known or suspected soluble markers of coronary risk were also assessed. In addition, the effects of glycinin, or 11S globulin, which is not thought to influence lipoprotein metabolism, atherosclerosis or coronary risk were also studied.

2. Methods

2.1 Animals and diets

Adult male cynomolgus monkeys (*Macaca fascicularis*) (n=32) were imported from Indonesia (Institut Pertanian Bogor). The animal facilities of Wake Forest University are fully accredited by the American Association for the Accreditation of Laboratory Animal Care. All procedures involving animals were approved by the Institutional Animal Care and Use Committee of Wake Forest University. For their first 18 months at our facilities, the monkeys were subjects in a study involving the feeding of moderately atherogenic diets containing varied amounts of isoflavones. At the end of this study, monkeys were fed a moderately atherogenic soy- and isoflavone-free control diet (Table 1) for a seven-month washout and pretreatment period. The monkeys were then randomly assigned to a crossover protocol (4 $\times$ 4 Latin Square design). For successive six month treatment periods, subsets of eight monkeys were randomly assigned to being fed either the soy-free control diet or one of three soy-containing diets (Table 1). These

diets differed by the source of protein. For the soy-free control diet, casein and lactalbumin were the protein source. The source of protein for a second diet was a soy protein isolate containing 1.85 mg (aglycone units) isoflavones/g of isolate. For the third and fourth diet, the source of protein was a concentrate of 7S fraction or 11S fraction. These protein sources were made from defatted soy flake using the typical isolate process with the exception of precipitation pH. This soy protein isolate was then fractionated based on isoelectric points of the two protein types and the fractions were spray dried for use in the experimental diets. The three soy protein sources varied in respect to their isoflavone content. Therefore, to control for the possibility that differences in isoflavone content may contribute to differences in effects of protein source, the diets containing 7S and 11S were supplemented with isoflavone glycoside concentrate added in amounts sufficient to equalize isoflavone consumption across soy protein groups. Therefore, the total isoflavone content of these diets was similar to the amount consumed by monkeys fed the diet with the isoflavone-replete soy protein isolate. Isoflavone concentrate was produced by ethanol extraction of defatted soy flake. Isoflavone concentrate produced in this way has been shown to have no independent effects on plasma lipoproteins in monkeys or human beings [reviewed in 11]. The isoflavone content of all products was determined using high-performance liquid chromatography [12].

2.2 Plasma lipoproteins

Plasma total cholesterol [13], HDL cholesterol [14] and triacylglycerol [15] were determined at baseline and the end of each six-month treatment period. Plasma VLDL + LDL was calculated as the difference between total and HDL cholesterol. Analyses were performed on a COBAS FARA II Autoanalyzer (Roche). The laboratory subscribes to the Centers for Disease Control and Prevention-National Institutes of Health Lipid Standardization Program.

2.3 Biomarkers of inflammation, proliferation, and anti-fibrinolytic activity

Plasma concentrations of E-Selectin, vascular cell-adhesion molecule-1 (VCAM-1), monocyte chemoattractant protein-1 (MCP-1), transforming growth factor β -1 (TGF- β -1) and plasminogen activator inhibitor-1 (PAI-1) were measured at baseline and the end of each treatment period by enzyme-linked immunosorbent assay (R & D Systems or America Diagnostica).

2.4 Data analysis

Data sets that were not normally distributed underwent logarithmic transformation prior to analysis. Data were analyzed using a general linear mixed effects model approach to account for the correlation between the multiple measurements for each animal. Baseline measurements were used as covariates in the models. No significant carryover effects were found for the outcomes in this crossover study. Pair wise *post hoc* comparisons were made using Tukey's method. Differences with $P < 0.05$ were considered significant. Data are presented as mean $\pm$ SEM.

3. Results

3.1 Plasma lipoproteins

Total plasma cholesterol concentration was reduced similarly in monkeys fed soy protein isolate and 11S (P 's < 0.05), but increased in monkeys fed 7S ($P < 0.04$) (Table 2). Plasma VLDL + LDL cholesterol was reduced similarly in monkeys fed soy protein isolate and 11S (P 's < 0.005) but was unchanged in monkeys fed 7S ($P > 0.4$) (Table 2). Plasma HDL cholesterol was increased in all groups fed soy protein ($P < 0.001$). However, the magnitude of this increase in monkeys fed soy protein isolate was greater than that seen in monkeys fed

7S or 11S (P 's < 0.001) (Table 2). There was no effect of protein source on total plasma triglyceride concentrations (P 's > 0.2) (data not shown).

3.2 Biomarkers of inflammation, proliferation, and anti-fibrinolytic activity

There was no effect of protein source on any biomarker (all P 's ≥ 0.4) (Table 3).

4. Discussion

Soy protein isolate had the predicted favorable effect on plasma lipoproteins, i.e., reductions in total and VLDL + LDL cholesterol (8% and 14% respectively) and a 41% increase in HDL cholesterol relative to monkeys fed casein/lactalbumin. Effects of 7S and 11S globulin were less favorable. In fact, there was an increase in total plasma cholesterol concentration in monkeys fed 7S that was accounted for primarily by an increase in VLDL + LDL cholesterol. Because some studies have found that 7S or its subunits can upregulate hepatic LDL receptors *in vitro* and reduce plasma cholesterol concentrations in rats [3–7], this finding was somewhat unexpected. However, other studies in rats [9,10] and mice [2] have found no effect of 7S on plasma cholesterol concentrations. Furthermore, a study of normocholesterolemic human volunteers found that consumption of 5 g of 7S/d for 16 weeks resulted in an increase in total plasma cholesterol concentrations [16]. The present results seem to agree with these latter findings.

To our knowledge, there are no published data on the influence of soy protein fractions, e.g., 7S or 11S, on soluble markers of coronary risk. However, a recent review [1] concluded that there is no evidence that consumption of soy products influences inflammatory biomarkers. Furthermore, published data generally agree with the lack of an effect of soy consumption on the specific biomarkers studied here. We chose to measure plasma concentrations of three biomarkers of vascular inflammation (E-selectin, VCAM-1 and MCP-1), a cytokine involved in maintenance of normal arterial architecture and cell proliferation (TGF- β -1) and a biomarker of fibrinolysis and hemostasis (PAI-1). Most studies have found that there is no effect of dietary soy protein isolate or soy isoflavone concentrates on soluble VCAM-1 [17–21], E-selectin [19–22], MCP-1 [18,20,22], TGF- β -1 [23] or PAI-1 [23–25] in human or nonhuman primate subjects. However, two studies have found a reduction in VCAM-1 [22,25] and one study a reduction in E-selectin [25] attributable to soy or isoflavone consumption. The present results seem to agree with the preponderance of the published data and, furthermore, indicate that, like soy protein isolates and isoflavone concentrates, 7S and 11S have no influence on soluble coronary risk biomarkers.

While consumption of 7S did not favorably influence plasma lipoproteins or biomarkers of coronary risk, it is important to note that possible effects of 7S on atherosclerosis and coronary heart disease were not addressed directly in this study. There remains reason to think that dietary 7S may inhibit the development of atherosclerosis, the underlying cause of coronary heart disease. We have described evidence for a marked lipoprotein-independent inhibitory effect of 7S on the development of atherosclerotic lesions in mouse models of atherosclerosis. If not by plasma lipoproteins, how might these atheroprotective effects have been mediated? Since large peptides like 7S globulin are hydrolyzed in the gastrointestinal tract and are not likely to be absorbed intact in meaningful amounts, it seems unlikely that these effects are attributable to the intact peptide. However, it is likely that smaller peptide digestion products escape further digestion, are absorbed and reach the circulation. Supporting this possibility are the findings of Masuda, et al. [26] who administered sour milk containing small antihypertensive peptides to spontaneously hypertensive rats and found a reduction in angiotensin I-converting enzyme in association with a reduction in blood pressure. Furthermore, the intact peptides were detected in the aorta. While there are no published data demonstrating the absorption and transport of soy protein digestion products to the liver or

cardiovascular system, Lovati, et al. [7] have described the *in vitro* effects of small peptides produced by the digestion of a soy protein concentrate and a synthetic peptide (2271 Da) corresponding to specific sequences of 7S soy globulin. In these studies, both peptide products had significant effects on LDL metabolism in cultured Hep G2 cells. This indicates that, if such products do survive digestion and reach the circulation they may have *in vivo* biologic activity within the cardiovascular system. We can only speculate on the processes that might be involved. Angiotensin I-converting enzyme inhibitory activity has been described for several peptides derived from nutritional products, e.g., sour milk [reviewed in 27]. A direct role for angiotensin-II in the development of atherosclerosis is well-established [reviewed in 28]. Among other biologic effects that have been attributed to bioactive peptides are anti-oxidation, anti-proliferation, and anti-inflammation [reviewed in 27]. Since the initiation and progression of atherosclerosis are known to involve the oxidation of plasma lipoproteins in the arterial intima, cell proliferation and a localized inflammatory reaction these represent potential pathways by which soy peptides could directly inhibit atherosclerosis.

We conclude that replacement of soy protein isolate with concentrated 7S or 11S globulin in the diet does not result in improvement of plasma lipoprotein profiles or cardiovascular biomarkers in monkeys. However, effects of these fractions of soy protein on the development of atherosclerosis or coronary risk in human beings or other primates remain unknown.

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Table 1

Composition of Experimental Diets Fed to Monkeys

INGREDIENT ¹	CONTROL	SPI	7S	11S
Casein	8.50			
Lactalbumin	8.50			
SPI ²		17.08		
7S fraction ³			16.81	
11S fraction ⁴				18.30
Isoflavone concentrate ⁵			0.032	0.004
DL-methionine		0.30	0.30	0.30
Wheat Flour, self-rising	35.76	35.76	35.76	35.76
Dextrin	9.00	8.90	8.59	7.54
Sucrose	7.00	7.00	7.00	7.00
Alphacel	8.03	8.23	8.19	8.30
Lard	5.00	5.00	5.00	5.00
Beef Tallow	4.00	4.00	4.14	4.00
Butter, lightly salted	3.10	3.10	3.10	3.10
Safflower Oil (linoleic)	3.00	2.56	3.00	2.60
Crystalline Cholesterol	0.061	0.061	0.061	0.061
Complete Vitamin Mix ⁶	2.50	2.50	2.50	2.50
Mineral Mix ⁷	5.00	5.00	5.00	5.00
Calcium Carbonate	0.400	0.357	0.369	0.349
Calcium Phosphate, Monobasic	0.150	0.145	0.150	0.186

¹ g/kg dry weight

² Soy protein isolate (Lot 241-2): Provided by the Solae Company, St. Louis, MO. Contains 1.08 mg genistein, 0.69 mg daidzein, 0.08 mg glycitein/g soy protein isolate.

³ 7S-rich soy protein isolate (88% protein) provided by the Solae Company, St. Louis, MO. Contains 0.78 mg genistein, 0.50 mg daidzein, 0.13 mg glycitein/g soy protein isolate

⁴ 11S-rich soy protein isolate (80% protein) provided by the Solae Company, St. Louis, MO. Contains 0.96 mg genistein, 0.62 mg daidzein, 0.16 glycitein/g soy protein isolate

⁵ Isoflavone concentrate provided by the Solae Company, St. Louis, MO. Contains 145.1 mg genistein, 116.3 mg daidzein, 21.7 mg glycitein/g concentrate

⁶ Complete vitamin mixture [29] obtained from Harlan Teklad, Madison, WI

⁷ Mineral mix [29] obtained from Harlan Teklad, Madison, WI.

Table 2
Plasma lipoprotein cholesterol concentrations in monkeys fed diets with different sources of protein

	Total cholesterol	VLDL + LDL cholesterol	HDL
	<i>mmol/L</i>		
Casein/lactalbumin	12.0 ± 0.3 ^a	11.1 ± 0.3 ^a	0.95 ± 0.04 ^a
Soy protein isolate	11.0 ± 0.3 ^b	9.6 ± 0.3 ^b	1.34 ± 0.04 ^b
7S fraction	12.8 ± 0.3 ^c	11.6 ± 0.4 ^a	1.19 ± 0.04 ^c
11S fraction	11.4 ± 0.3 ^b	10.2 ± 0.3 ^b	1.15 ± 0.04 ^c

Values are mean ± SEM, n=32. Within columns, means without a common letter differ, P<0.05.

Table 3
Concentrations of soluble cardiovascular biomarkers in monkeys fed diets with different sources of protein

	E-selectin	VCAM-1	MCP-1	TGF-β-1	PAI-1
	ng/ml	ng/ml	pg/ml	pg/ml	ng/ml
Casein/lactalbumin	91.5 ± 3.6	264.6 ± 13.7	273.4 ± 19.2	1328 ± 174	8.6 ± 2.9
Soy protein isolate	94.7 ± 3.5	274.7 ± 12.2	240.4 ± 18.1	1520 ± 157	2.2 ± 3.7
7S fraction	93.6 ± 4.1	274.1 ± 16.3	250.1 ± 15.2	1778 ± 191	1.9 ± 5.2
11S fraction	92.1 ± 3.8	261.5 ± 15.5	281.3 ± 20.5	1616 ± 176	2.9 ± 3.7

Values are mean ± SEM, n=32. There were no effects of protein source, all P's ≥ 0.4.