The worldwide increase in degenerative diseases is in part due to modifications in the lifestyle including the diet. Epidemiological, clinical, and experimental evidence shows that soy protein may prevent lipotoxicity in non-adipose tissues during obesity. The molecular mechanism by which soy protein prevents lipotoxicity involves a reduction in the insulin/glucagon ratio, resulting in a down-regulation of lipogenic genes mediated by the transcription factor sterol regulatory element-binding protein (SREBP)-1, and up-regulation of SREBP-2 to reduce serum cholesterol. In addition, soy protein maintains the functionality of adipose tissue-liver axis to prevent hepatic steatosis during the development of obesity.

Key words: adipose tissue, diabetes, lipotoxicity, obesity, soy protein

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INTRODUCTION

Lifestyle-related diseases such as obesity, diabetes mellitus, hyperlipidemia, hepatic steatosis, and coronary artery disease are associated with chronic consumption of a high-fat or high-carbohydrate diet. However, dietary protein may also play a role in the development of these diseases. There is considerable epidemiological evidence suggesting that a vegetarian lifestyle is associated with lower risk for these diseases, and that an animal protein diet is associated with the development of atherosclerosis. In general, animal proteins tend to contain a higher concentration of indispensable amino acids than do vegetable proteins. However, some vegetable proteins have similar chemical scores as animal proteins and are useful for the treatment of human hyperlipidemia. For example, the nutritional value of soy protein is roughly equivalent to that of animal protein of high biological value. Isolated soy protein has a protein digestibility-corrected amino acid score of 1.0, which is the same as casein or egg protein and has additional benefits on health. Several studies in humans and animals have shown that soy protein reduces plasma total and low-density lipoprotein (LDL) cholesterol. It has been demonstrated that a soy protein diet lowers serum cholesterol to a greater extent than a low-cholesterol, low-saturated-fat diet containing an equivalent amount of protein of animal origin. The beneficial effects of soy protein is the result of its amino acid pattern, the biological activities of soy protein peptides, and non-protein compounds such as isoflavones.

Dietary protein triggers the release of both insulin and glucagon. In general, animal proteins are relatively more effective for releasing insulin, whereas vegetable proteins preferentially release glucagon. However, the pancreatic islets do not detect “protein” per se, but rather the postprandial increase in circulating amino acids. Long-term soy protein consumption increases the release of glucagon (Figure 1) and maintains insulin at normal levels, resulting in a low insulin/glucagon ratio compared with animals fed a casein diet. This low insulin/glucagon ratio is sensed by the transcription factor sterol regulatory element-binding protein-1 (SREBP-1), which in turn decreases the gene expression of lipogenic enzymes that lead to the hypolipidemic effect of vegetable proteins such as soybean and other legumes.

Molecular Mechanism of Action of Soy Protein to Explain its Hypolipidemic Effect

Insulin and glucagon are key controllers of cholesterol and triglyceride biosynthesis in liver and act by modulating the activity or expression levels of enzymes involved in cholesterol synthesis or uptake and fatty acid synthesis. The transcriptional control of these enzymes is mediated by a family of transcription factors designated SREBPs. SREBPs are transcription factors that belong to the basic helix-loop-helix-leucine zipper family. They are synthesized in the endoplasmic reticulum (ER) in the form of a precursor protein. To become transcriptionally
active, the SREBs are escorted by the SREBP cleavage-activating protein (SCAP) from the ER to the Golgi, where its NH2-terminal region is cleaved by two membrane-bound proteases. SCAP is activated when the intracellular concentration of sterols is low or in the presence of insulin.14 The NH2-terminal domain translocates to the nucleus, where it activates the transcription of multiple target genes by binding to sterol response elements in the promoter/enhancer regions of genes coding for enzymes responsible for the synthesis of cholesterol, fatty acids, and triglycerides. There are three SREBP isoforms: SREBP-1a and SREBP-1c, which preferentially regulate enzymes involved in fatty acid and triglyceride biosynthesis, and SREBP-2, which preferentially binds to promoters of genes involved in cholesterol uptake and biosynthesis.13 SREBP-1 is induced by insulin12 and regulates enzymes involved in fatty acid synthesis, whereas SREBP-2 is induced by low cellular cholesterol content.15

Interestingly, we demonstrated that animals fed a soy protein diet showed lower serum insulin concentration and SREBP-1 mRNA expression than animals fed a casein diet.16 In addition, we found that long-term soy protein consumption significantly increases serum glucagon concentration (Figure 1A), and is associated with up-regulation of SREBP-2 (Figure 1B). The possible mechanism for which glucagon increases SREBP-2 is not known; however, it could be mediated via cAMP by activating CREBP, because the SREBP-2 gene promoter shows three potential cAMP response elements.17 Once inside the nucleus, SREBP-2 activates cholesterogenic target genes through binding to the sterol regulatory elements present in their promoters. After long-term soy protein consumption, the hepatic cholesterol concentration decreases, even in diabetic rats,16,18 and this is the signal to activate the processing of SREBP-2 in the ER to produce the mature form of this transcription factor. This in turn increases the gene expression of SREBP-2 target genes such as HMGCoAR and LDLr19 as a feedback mechanism to synthesize and capture cholesterol. Thus, the hypolipidemic effect of soy protein is in part mediated by reducing SREBP-1 and increasing SREBP-2, with or without other lifestyle changes (Figure 2).

The role of soy protein in the prevention of lipid abnormalities is important, because it could be used as a dietary therapy to prevent the accumulation of lipids in different tissues. For this reason, some of our research has been focused on studying the effect of soy protein during obesity.

**Effects of Dietary Soy Protein on Obesity and Diabetes**

Obesity and diabetes mellitus are nutritional disorders that have become major public health concerns in industrialized countries, not only because of their increasing prevalence, having reached epidemic proportions, but also because of their frequent association with

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Figure 1. Serum glucagon concentration (A) and hepatic sterol regulatory-binding protein 2 (SREBP-2) mRNA abundance (B) in rats fed a casein or soy protein diet for 180 days.
major cardiovascular risk factors (dyslipidemia, atherosclerosis, and coronary artery disease). Obesity is a disequilibrium between environmental factors including lifestyle habits and genetic predisposition and energy expenditure (Figures 3 and 4) that leads to weight gain. It is associated with hyperinsulinemia, insulin resistance, abnormalities in lipid metabolism, and nonalcoholic hepatic liver disease (NAFLD). NAFLD is the primary liver disease associated with obesity and the metabolic syndrome. Up to 70%–80% of obese individuals have the condition. The disease can progress from a normal liver, through steatosis, on to steatohepatitis, and finally cirrhosis.

After chronic high-energy food consumption, there is an increase in glucose and insulin concentrations that accelerate lipogenesis in adipose tissue, increasing the amount of fat stored in the form of triglycerides. Eventually, adipose tissue loses the capacity to respond to insulin, limiting the capacity to store fatty acids in the form of triglycerides, shifting the flux of fatty acids to non-adipose tissues mainly the liver. Additionally, hyperinsulinemia present during obesity stimulates hepatic lipogenesis via SREBP-1c. As a consequence of these events, there is an overaccumulation of lipids in the liver, leading to NAFLD (Figure 5). An accumulation of fatty acids that exceeds the capacity of non-adipose tissues to oxidize them enhances the metabolic flux of fatty acids to other harmful, nonoxidative pathways, producing ceramides in a condition called lipotoxicity.

Studies in obese-diabetic Zucker fa/fa rats fed a long-term soy protein diet have found decreases serum and hepatic triglycerides and cholesterol concentrations compared with animals fed a casein diet, even in the presence of hyperinsulinemia or hyperleptinemia. These reductions are the result of a decrease in the expression of lipogenic genes regulated by SREBP-1. These find-
ings suggest that soy protein consumption down-regulates hepatic SREBP-1 expression through an insulin-independent mechanism. Furthermore, soy protein consumption reduces serum concentrations of very-low-density lipoprotein (VLDL)-triglycerides and LDL-cholesterol, indicating its hypolipidemic effect even in the presence of insulin resistance or diabetes.

In addition, soy protein not only reduces hepatic lipogenesis through SREBP-1, but also increases the hepatic oxidation of fatty acids through the nuclear receptor peroxisome proliferator activator receptor-alpha (PPAR-α). This transcription factor is activated by certain ligands such as fatty acids, fibrates, and isoflavones, indicating that other compounds tightly associated with soy bean protein as isoflavones may play an important role in lipid metabolism. PPARα regulates the transcription of enzymes involved in lipid oxidation as carnitine palmitoyl transferase-1, acyl CoA oxidase, and uncoupling proteins.

Thus, the type of protein has an important role in the development of lipotoxicity through the intervention of different transcription factors involved in the regulation of lipogenesis and fatty acid oxidation. Interestingly, our findings showed that soy protein not only has an effect in the liver but also modulates lipid metabolism in adipose tissue.

As described earlier, obesity is associated with the presence of dysfunctional adipocytes. After long-term consumption of soy protein, animals exhibit smaller-size adipocytes and a higher number of adipocytes per area than animals fed a casein diet. This indicates that soy protein prevents hypertrophy and stimulates adipocyte hyperplasia associated with high PPARγ gene expression, preventing the release of excessive amounts of fatty acids to the circulation. PPARγ, a nuclear receptor mainly expressed in adipose tissue, is responsible for adipocyte differentiation, fatty-acid storage, and sensitizing the body to insulin. The absence of PPARγ in the adipose tissue is accompanied by hyperlipidemia and hepatic steatosis, demonstrating the essential role of PPARγ in adipogenesis and in maintaining the integrity and function of the mature adipocyte. This suggests that the type of dietary protein could regulate metabolism in adipocytes and liver, and possibly in other non-adipose tissues, thus preventing the development of lipotoxicity.

Soy protein may improve the functionality of the adipocytes during obesity and diabetes, reducing insulin resistance and adiposity by reducing insulin secretion from the pancreatic β cells. In fact, studies in healthy human subjects have shown that soy protein beverages have a low glycemic and insulimemic index that could be of benefit in obesity and diabetes treatment. Long-term consumption of soy protein as part of a low-energy diet may provide an additional benefit for weight reduction in obese subjects.

Collectively, these data indicate that our present affluent lifestyle, with its high proportion of animal protein and fat in the diet, exposes us to excessive levels of insulin, an activator of SREBP-1 and PPARγ, and disturbs the tightly regulated system present in our ancestors, who rarely ate animal protein and had an efficient energy conservation and storage that allowed survival through periods of food shortages. Being born with an affluent and often sedentary lifestyle now turns this once favorable energy conservation response into a detrimental one, which contributes to the pathogenesis of lifestyle-associated diseases, such as obesity, type 2 diabetes, and atherosclerosis. This also indicates that modulating (or inhibiting) SREBP-1, rather than activating it, and maintaining a balance between PPARα and PPARγ through diet, might be the preferred therapeutic strategy to treat metabolic disorders by improving glucose homeostasis to prevent lipogenesis and adipogenesis.

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