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Journal of Nutritional Biochemistry 17 (2006) 365–373

Journal of Nutritional Biochemistry

REVIEWS: CURRENT TOPICS

Regulation of lipid metabolism by soy protein and its implication in diseases mediated by lipid disorders

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Received 6 August 2005; received in revised form 30 September 2005; accepted 1 November 2005

Abstract

Soybeans have a high-quality protein that has been consumed for approximately 5000 years in Oriental countries. The awareness that soy products are healthy has increased their consumption in Western countries. Substantial data from epidemiological surveys and nutritional interventions in humans and animals indicate that soy protein reduces serum total and low-density lipoprotein (LDL) cholesterol and triglycerides as well as hepatic cholesterol and triglycerides. This review examines the evidence on the possible mechanisms for which soy protein has beneficial effects in diabetes, obesity and some forms of chronic renal disease. Consumption of soy protein due to low methionine content reduces serum homocysteine concentration, decreasing the risk of acquiring a cardiovascular disease. On the other hand, soy protein reduces the insulin/glucagon ratio, which in turn down-regulates the expression of the hepatic transcription factor sterol regulatory element binding protein (SREBP)-1. The reduction of this factor decreases the expression of several lipogenic enzymes, decreasing in this way serum and hepatic triglycerides as well as LDL cholesterol and very LDL triglycerides in diabetes and obesity, reducing lipotoxicity in the liver. Soy protein intake also reduces hepatic lipotoxicity by maintaining the number of functional adipocytes, preventing the transfer of fatty acids to extra adipose tissues. Furthermore, soy protein isoflavones stimulate the transcription factor SREBP-2, increasing serum cholesterol clearance. The reduction of serum cholesterol and triglyceride concentrations by soy protein intake produces beneficial effects in the kidney preventing the inflammatory response, increasing the renal flow by releasing endothelial nitric oxide (NO) synthase from the caveolae, facilitating the synthesis of NO. Thus, soy protein consumption may reduce the clinical and biochemical abnormalities in diseases mediated by lipid disorders.

Keywords: Diabetes; Kidney; Lipotoxicity; Lipogenesis; Obesity; SREBP-1

1. Introduction

Soybean is a legume with a high protein content (~35–40%) in comparison with most other legumes. Soy protein, after correcting for digestibility, provides amino acids equal to or in excess of requirements and receives a protein digestibility corrected amino acid score of 1, indicating that it is able to meet the protein needs of infants and adults when consumed as the only source of protein at the recommended level of protein intake [1]. The importance of soy protein has been undervalued because the limiting amino acid in soy protein is methionine. However, despite the fact that the rat requirement for methionine is ~50% higher than that for humans, the weight gain of growing animals is similar to that of rats fed with casein [2] (Fig. 1). Furthermore, methionine is a precursor of homocysteine (Hcy), which is an independent cardiovascular risk factor. Rats fed with a soy protein diet show a lower serum Hcy concentration than do those fed with a casein diet [3] (Fig. 2). Similarly in humans, soy intake is inversely associated with serum Hcy levels [4], indicating that substitution of animal protein for soy protein can result in lower Hcy levels, potentially reducing coronary heart disease risk.

2. Hypocholesterolemic effect of soy protein

In addition to the nutritional properties of soy protein in meeting amino acid requirements, the beneficial effects of dietary soy protein on serum lipid concentrations have been fully demonstrated in a variety of animal models and in humans [3,5–8]. Some of the questions posed by several researchers are whether soy protein is hypocholesterolemic

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doi:10.1016/j.jnutbio.2005.11.005

and whether casein is hypercholesterolemic. In general, proteins from animal sources are more hypercholesterolemic than those from plant sources [9]. Epidemiological data from different countries have also shown a strong positive correlation between coronary heart disease and consumption of animal protein [10]. Furthermore, replacement of animal protein in the diet with soybean protein has been reported to lower the level of plasma lipids in human subjects [11,12]. Two meta-analyses of the effects of soy protein on lipid profile in humans [13,14] revealed that soy protein intake reduced total serum cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides by 3.8–9.3%, 5.3–12.9% and 7.3–10.5%, respectively, and increased HDL cholesterol by 2.4–3.0%. These beneficial effects have been used to develop dietary strategies for the treatment of patients with hypercholesterolemia [15,16].

The different effects of plant and animal proteins on serum lipids appear to be largely caused by differences in their amino acid composition [1,9,17]. However, isolated soybean protein supplemented with seven indispensable amino acids to levels comparable with those found in animal proteins failed to produce a hypercholesterolemic response [18]. These results indicate the possibility that not only the protein but also the phytochemicals associated with the protein, mainly isoflavones, are involved in the mechanism for reducing the concentrations of serum lipids [19–21]; however, some evidences are controversial. The full effects of soy protein on lipid metabolism have been observed when soy protein contains isoflavones, indicating that both components are necessary for reducing blood and tissue lipids [18]. Because of the complex interactions between soy protein and isoflavones, the mechanism/mechanisms through which soy protein exerts its beneficial effects on lipid metabolism is/are not fully understood. Recent research in vitro, in animals and in humans suggest that soy peptides may mediate many of the actions of soy protein. In the following sections, some mechanisms of how lipid metabolism is influenced by soy protein are presented.

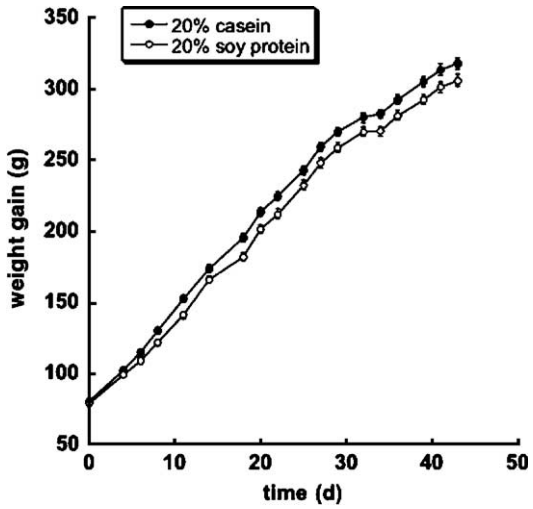

Fig. 1. Weight gain of growing rats fed with 20% casein or 20% soy protein for 45 days. Food intake was similar in both groups. There was no significant difference in both groups ($n = 20$/group).

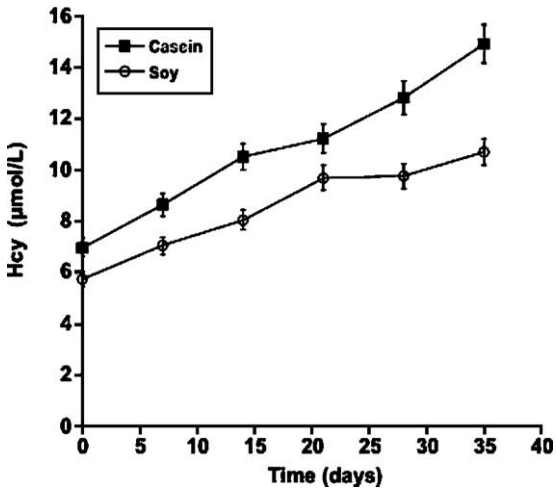

Fig. 2. Serum Hcy levels in rats fed with 20% casein or 20% soy protein for 35 days. Hcy concentrations were measured with a polarization of fluorescence immunoassay using an IMx analyzer (Abbott laboratories, USA) ($n = 10$/group).

3. Endocrine effects: regulation of insulin/glucagon ratio by soy protein

Insulin and glucagon participate in whole-body glucose and lipid homeostasis, producing opposite effects on the biosynthetic and catabolic pathways in the liver, skeletal muscle and adipose tissue. It has been shown that a high insulin/glucagon ratio is associated with an increased risk of developing cardiovascular diseases due to its hyperlipidemic and atherogenic effects [17]. Short-term studies in our laboratory provided evidence that postprandial serum insulin concentrations are 65% lower in rats fed with 18% soy protein than in those fed with an 18% casein diet whereas there is no difference in serum glucagon concentrations [2]. Interestingly, long-term consumption of a soy protein diet produces a 51% higher serum glucagon concentration compared with that of a casein diet. As a result of these hormonal changes, the insulin/glucagon ratio in rats fed with soy protein is lower than that in those fed with a casein diet (Table 1). The reduction in the insulin/glucagon ratio could be in part responsible for the hypolipidemic effect of soy protein. The capacity of soy protein to regulate the insulin/glucagon ratio might be explained by its amino acid composition [9,17]. The concentration of serum glucagon depends on the amount and composition of the ingested protein [2,22]. Generally, plant proteins have higher absolute amounts of dispensable amino acids such as arginine, glycine and alanine whereas animal proteins have higher amounts of indispensable amino acids such as lysine. A high arginine/lysine ratio is associated with high serum glucagon concentration, although some other amino acids are also associated with glucagon concentration [17,23,24]. These changes in the

Table 1
Insulin/glucagon ratios in rats fed with 20% soy protein or 20% casein at 90 and 180 days

Diet	Insulin/glucagon ratio (pg/ml)	
	Day 90	Day 180
20% Casein	9.58±1.9	10.94±1.23
20% Soy protein	6.17±0.92	6.18±1.64

insulin/glucagon ratio can produce profound changes in the expression of genes of intermediary metabolism.

4. Regulation of the sterol regulatory element binding protein transcription factors by soy protein

Insulin and glucagon are key controllers of cholesterol and triglyceride biosyntheses in the liver by modulating activity or expression levels of enzymes involved in cholesterol synthesis or uptake as well as in fatty acid synthesis. The transcriptional control of these genes is mediated by a family of transcription factors designated as sterol regulatory element binding proteins (SREBPs) [25].

SREBPs are transcription factors that belong to the basic helix–loop–helix–leucine zipper family. SREBPs are synthesized in the endoplasmic reticulum (ER) in the form of a precursor protein. They are escorted by the SREBP cleavage-activating protein (SCAP) from the ER to the Golgi, where their NH_2-terminal region is cleaved by two membrane-bound proteases, for them to become transcriptionally active [26,27]. SCAP is activated when the intracellular concentration of sterols is low or by the presence of insulin [28]. The NH_2-terminal domain translocates to the nucleus, where it activates 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 [29].

There are three SREBP isoforms with specific and overlapping transcriptional targets. SREBP-1a and -1c preferentially regulate enzymes involved in fatty acid and triglyceride biosyntheses such as acetyl–CoA carboxylase, fatty acid synthase and the microsomal triglyceride transfer protein [30]. SREBP-2 preferentially binds to promoters of genes involved in cholesterol uptake and biosynthesis such as hydroxymethyl glutaryl–CoA reductase (HMG–CoA reductase) and the LDL receptor (LDLr) [31]. Multiple lines of evidence suggest that insulin stimulates fatty acid synthesis mediated by an increase in the expression and excision of the active form of SREBP-1c whereas that glucagon counteracts insulin activity by repressing SREBP-1c expression through a cAMP-dependent mechanism [32,33].

The induction of SREBP-1 in the liver by insulin is a rapid process [34]. In fasted rats, after the consumption of a casein diet, serum insulin concentration rises rapidly, reaching its maximal concentration after 1 h. In these animals, hepatic SREBP-1 mRNA concentration increases in proportion to serum insulin levels. Interestingly, when casein is replaced with soy protein, there is a 36% reduction

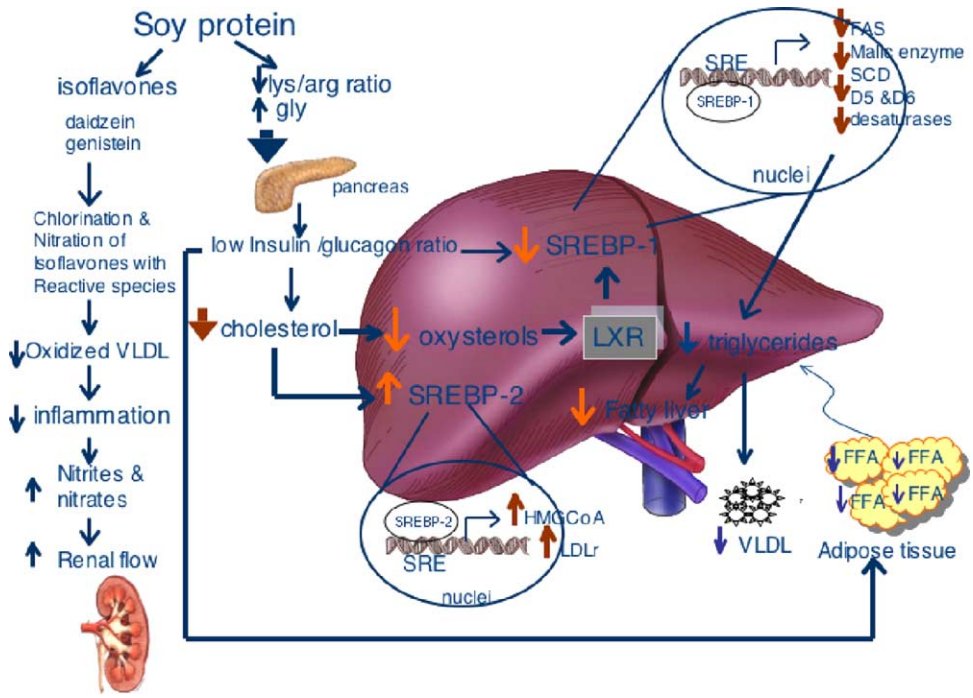

Fig. 3. Mechanism of action of soy protein. Soy protein consumption decreases the insulin/glucagon ratio and reduces the expression of SREBP-1, which in turn decreases the expression of lipogenic genes. Isoflavones stimulate SREBP-2, increasing serum cholesterol clearance. Low hepatic cholesterol reduces oxysterol concentrations, preventing the stimulation of LXR-α, which additionally reduces SREBP-1 expression. As a consequence of soy protein consumption, there is a low concentration of VLDL particles. In addition, low serum cholesterol levels observed with soy protein diets prevent kidney damage, decreasing inflammatory response and increasing NO production.

in insulin concentration, which in turn reduces SREBP-1 mRNA levels in the liver by approximately 54% [35]. Recent results in our laboratory have shown that repression of SREBP-1 expression by soy protein is also due to an increase in serum glucagon concentration, decreasing the insulin/glucagon ratio (unpublished results). As a consequence, reduction of SREBP-1 by soy protein intake reduces gene expression of enzymes involved in fatty acid biosynthesis (Fig. 3).

5. Regulation of hepatic lipid metabolism enzymes by soy protein

Insulin stimulates fatty acid synthesis in the liver after the consumption of a casein diet. However, the low insulin/glucagon ratio in animals fed with soy protein represses the expression of SREBP-1, which in turn reduces the expression of lipogenic genes. There is no evidence that isoflavones regulate the activity or the expression of SREBP-1 [36]. In addition, SREBP-1 regulates the expression of stearoyl–CoA desaturase 1 (SCD-1), Δ5 desaturase and Δ6 desaturase involved in fatty acid desaturation to form monosaturated and polyunsaturated fatty acids. The balance between saturated, monosaturated and polyunsaturated fatty acids is essential for the formation of triglycerides and phospholipids in the liver [29,37]. Hepatic SCD-1 activity determines the metabolic fate of endogenous lipids, driving newly synthesized fatty acids preferentially to triglyceride esterification and very LDL (VLDL) assembly and secretion rather than mitochondrial influx and β-oxidation [38,39]. The reduction of SCD-1 mRNA in the liver of rats fed with soy protein appears to be an important mechanism to reduce hepatic triglycerides and circulating VLDL particles [40].

Interestingly, serum and hepatic cholesterol concentrations are also low in rats fed with a soy protein diet in comparison with those fed with a casein diet [3,40]. Several mechanisms have been proposed to explain this response, including an increase in the activity of LDLr and an increase in bile acid secretion [41,42]. LDLr gene expression is regulated preferentially by the transcription factor SREBP-2.

When cells of animals fed with a soy protein diet sense a low cholesterol content in the liver, the nuclear mature form of SREBP-2 increases by 119% with respect to rats fed with a casein diet [43] and increases the expression of HMG–CoA reductase and LDLr [35]. In addition, new evidence shows that SREBP-2 expression is also up-regulated by soy isoflavones [36]. Thus, the low hepatic cholesterol content and the presence of isoflavones increase the expression of the LDLr, which in turn increases serum cholesterol clearance.

It has been demonstrated that SREBP-1 expression in the liver is up-regulated in rodent models of obesity and diabetes [44,45]. Feeding ZDF *fa*/*fa* rats with soy protein reduces their serum and hepatic triglyceride levels, as well as VLDL triglycerides, as compared with feeding them with casein. This reduction is associated with lower hepatic SREBP-1 mRNA content in rats fed with soy protein, as well as several of its target genes, indicating a decrease in lipogenesis, even in the presence of hyperinsulinemia [40]. These data indicate that other transcription factors may modulate the expression of lipogenic genes controlled by the consumption of soy protein. Recent evidence shows that the orphan receptor LXRα is probably involved in the mechanism by which soy protein reduces fatty acid and cholesterol syntheses [40,46].

6. Soy protein reduces lipotoxicity in liver

Lipid overaccumulation in tissues other than adipocytes impairs normal cellular metabolism, compromising cell viability. This fatty acid-induced damage termed as "lipotoxicity" has been recognized to be the primary cause of some obesity-related disorders such as insulin resistance, heart failure and Type 2 diabetes [47–49]. In the liver, lipotoxicity causes hepatic steatosis often referred to as nonalcoholic fatty liver disease (NAFLD). NAFLD is a clinicopathological term that encompasses a disease spectrum ranging from simple triglyceride accumulation in hepatocytes to hepatic steatosis with inflammation (steatohepatitis), fibrosis and cirrhosis. In humans, hepatic steatosis strongly associates with obesity [50–52]. The primary event in the progression of NAFLD constitutes the deposition of triglycerides in the cytoplasm of hepatocytes [48,53,54]. It has been shown that excess triglycerides may cause fibrosis in nonadipocyte cells. Hepatic fibrosis is a common finding in obese nonalcoholic patients with an excessive hepatic triglyceride deposition [55,56].

Soy protein consumption prevents triglyceride accumulation in the liver, decreasing the deleterious effects of lipotoxicity [35]. The mechanisms by which soy protein prevents triglyceride accumulation are by reducing hepatic fatty acid and triglyceride biosyntheses and by increasing fatty acid oxidation through the activation of the transcription factor peroxisome proliferator-activated receptor α (PPARα) [40]. PPARα is a ligand-dependent transcription factor of the nuclear receptor superfamily [57]. It controls fatty acid oxidative metabolism through the transcriptional induction of carnitine–palmitoyl transferase 1 (CPT-1) and several enzymes for β-oxidation [58–60]. A soy protein diet up-regulates PPARα gene expression in the liver and is associated with a higher content of CPT-1 mRNA, with respect to rats fed with casein [40]. This pattern of gene expression is associated with an increased carbohydrate and lipid oxidation and energy expenditure as seen in Type 2 diabetic mice [61].

7. Adipocyte metabolism and hepatic lipotoxicity: restoration of normal cross-talk by soy protein

Our understanding of fat cells, once considered simple storage depots for lipids, has changed dramatically in recent times. Adipocytes synthesize several hormones called

adipocytokines or adipokines, which are secreted in response to energy intake and fat cell mass to regulate energy balance and lipid homeostasis [48,62].

Adipocytes protect nonadipose tissues from lipid overload, driving fatty acid uptake and triglyceride esterification into adipose tissue, reducing lipid deposition in other tissues. This protection is mediated by the coordinated action of the adipocyte hormones leptin and adiponectin [63,64]. However, several studies on humans and rodents have found altered adipocyte metabolic activity producing abnormal circulating levels of leptin and adiponectin in the development of obesity and related disorders [65,66]. The increase in adipose tissue mass in obesity is primarily due to a hypertrophic cell growth rather than a hyperplastic growth [67–69].

Rats fed with soy protein show a higher plasma concentration of adiponectin and its mRNA in adipose tissue in comparison with rats fed with casein [70]. One possible mechanism of soy protein diet-enhanced expression of adiponectin is that dietary soy protein promotes the conversion of large adipocytes to smaller ones [40], exhibiting appropriate adipocytokine-producing activities [70]. Histological analysis of adipose tissue in ZDF *fa*/*fa* rats fed with soy protein shows an increase in the adipocyte number per area and a reduction in cell diameter compared with rats fed with a casein diet, suggesting an increased hyperplastic growth in the adipose tissue of rats fed with soy protein in contrast with a more pronounced hypertrophic cell growth in the adipose tissue of rats fed with casein [40].

Some of the metabolic alterations that follow hypertrophic fat cell growth in obesity are associated with the expression of the PPARγ [67,71]. PPARγ is highly expressed in adipose tissue and is involved in critical physiological functions such as adipogenesis and glucose and cholesterol metabolism. This transcription factor induces a preadipocyte differentiation program leading to mature functional adipocytes. PPARγ stimulates fatty acid uptake and triglyceride esterification in a concerted action with SREBP-1 that regulates lipogenesis to fill the lipid droplet [71].

After terminal differentiation, the PPARγ gene is constitutively expressed to maintain a mature phenotype; however, in the adipose tissue of obese mice and humans, PPARγ mRNA content is significantly decreased [72]. As a consequence, the adipocytes, although lipid engorged, have a significantly reduced capacity to esterify fatty acids into triglycerides, thus increasing fatty acid release to the bloodstream and uptake by tissues other than adipose, such as the liver and pancreas [53].

A recent study demonstrated that the soy protein-associated isoflavone genistein is able to activate PPARγ, resulting in an up-regulation of adipogenesis and probably fatty acid uptake from plasma [73]. In ZDF *fa*/*fa* rats fed with a soy protein diet, mRNA levels of PPARγ in adipose tissue are significantly increased compared with those in rats fed with a casein diet [40]. In addition, adipose tissue SREBP-1 gene expression is lower in rats fed with soy protein, indicating a reduced lipogenic rate reflected in decreased fat cell hypertrophy [69]. Furthermore, PPARγ also regulates synthesis and release of adiponectin [74], and soy protein intake probably increases circulating adiponectin concentrations in obesity through the selective activation of PPARγ in adipose tissue.

8. Effect of soy protein on intestinal cholesterol absorption and bile acid synthesis

As indicated above, one of the mechanisms proposed to explain the hypocholesterolemic effect of soy protein is through an increase in bile acid secretion. Measurement of intestinal cholesterol absorption provides evidence that rabbits, which are susceptible to hypercholesterolemia, absorb cholesterol more readily when fed with casein than those fed with soy protein [18,41]. Rabbits fed with a casein diet excrete less neutral steroids and produce less bile acids than animals fed with a soy protein diet. In addition, rabbits fed with casein excrete mainly cholesterol whereas those fed with soy protein excrete coprostanol, which is unabsorbable and increases the amount of cholesterol excreted, suggesting that soy protein favors the bacterial conversion of cholesterol to coprostanol. Furthermore, rabbits taking soy protein synthesize about twice as much cholesterol as those taking casein [41]. This is due to an increase in the mRNA expression of LDLr and HMG–CoA reductase, increasing the uptake and synthesis of cholesterol, respectively [3]. Since there is low hepatic cholesterol concentration in rats fed with soy protein, this increases SREBP-2 expression. More research is needed to understand the effects of soy protein on the molecular mechanisms of bile acid synthesis and transport.

9. Biologic activities of soybean peptides

The main soybean proteins, β-conglycinin (7S globulin) and glycinin (11S globulin), comprise up to 90% of the total protein [75]. Evaluation of these dietary proteins has become of major interest because their hydrolysis with proteases produces peptides with biologic activities. It has been shown that the variability in cholesterolemic responses to different soy-based diets in clinical studies is related to the specific protein composition of the soy variant used [75]. For instance, the soy variant Keburi does not regulate the LDLr because it lacks the α′ subunit of β-conglycinin (7S), indicating that this subunit is involved in the regulation of the LDLr [76]. In fact, studies on culture cells demonstrate that soybean 7S globulin and peptides derived from this protein are able to up-regulate LDL-receptor activity [77,78]. Some soy peptides derived from 7S globulin, mainly from subunit 7S α′, are partially resistant to digestion with endoproteases and may enter the bloodstream as functional oligopeptides [79]. Information in a U.S. patent indicated more marked cholesterol- and triglyceride-lowering effects in animals fed with a

β-conglycinin-enriched soy product in comparison with those fed with a soy protein isolate [80]. Initial testing of custom-designed peptides that regulate cholesterolemia by activation of LDLr's has been reported [79]. In addition, it has been shown that soy protein peptides decrease intestinal cholesterol absorption and bile acid uptake, promoting a serum cholesterol-lowering effect [81]. Also, soybean β-conglycinin reduces the aortic accumulation of cholesteryl esters, protecting against cardiovascular diseases [82].

Peptides from digested proteins provide satiety signals through intestinal opioid and cholecystokinin-A receptors, independent of the type of protein [83]. Soybean β-conglycinin subunits suppress food intake and gastric emptying by increasing cholecystokinin levels in rats [84]. Specific fragments of soy peptides rich in arginine residues have strong food intake suppressor activity [85].

The second major soybean protein, glycinin, also possesses biologic activities, including angiotensin-converting enzyme inhibition, antithrombotic activity and antioxidant properties [86]. Soy glycinin subunits A1aB1b and A2B1a have bile acid-binding capacity similar to β-conglycinin [87].

Other proteins present in the soybean are important suppressors of carcinogenesis, such as the Bowman–Birk inhibitor [88] and lunasin, which was recently identified as a soy-derived peptide with chemoprotective activity [89].

Another promising bioactive peptide isolated from soy protein is osmotin. It has been shown that osmotin can bind to and activate the adiponectin receptor. Osmotin and adiponectin bind to the same receptor although they do not share sequence similarity activating lipid and carbohydrate metabolism [90].

10. Effect of soy protein on renal function

In addition to the beneficial effects of soy protein on serum lipids, it has been demonstrated that consumption of soy protein has a beneficial effect on renal function. Renal injury during nephrotic syndrome is accompanied by severe hyperlipidemia, which is a factor that accelerates kidney dysfunction. It has been shown during experimental nephritic syndrome that there is an increase in the number of damaged glomeruli that is accompanied by an increase in mediators of the inflammatory response. As a consequence of the injury of the glomerulus, there is an increase in the permeability of the glomerular capillaries to plasma proteins, increasing proteinuria that is exacerbated by consumption of a high-protein diet. Ingestion of a low-protein diet improves not only proteinuria but also hyperlipidemia of rats with nephrotic syndrome [3,43].

Low-protein diets, however, retard the growth of rats despite their beneficial effects. Interestingly, a diet based on the use of 20% soy protein, which meets the protein requirement of rats, reduces hyperlipidemia, VLDL triglycerides and LDL cholesterol [3,35]. In addition to its hypocholesterolemic properties, soy protein reduces kidney damage and inflammation [3] through other mechanisms that probably involve soy isoflavones [19,20]. The main isoflavones present in soy protein, genistein and daidzein, may reduce glomerular damage during nephrosis by protecting LDL particles from oxidation [91]. In addition, isoflavones can react with reactive oxygen species [92]. These species are produced as part of the inflammatory response in the kidney during nephrotic syndrome. The main reactive species are hydrogen peroxide and superoxide anion, which react with chloride and nitric oxide (NO), leading to the formation of hypochlorous acid and peroxynitrite. Both compounds react with tyrosine residues on proteins, producing chlorinated and nitrated proteins with abnormal function. Because isoflavones have a phenolic ring, they can react competitively with hypochlorous acid and peroxynitrite, reducing the chlorination and nitration of proteins and preventing glomerular damage [3,93].

Another possible mechanism described to explain lower renal injury in obese Zucker rats fed with soy protein involves NO generation. Soy protein is high in L-arginine, twice the amount found in casein, and arginine is the precursor of NO. Caveolins, the resident scaffolding proteins of caveolae, modulate endothelial NO synthase (eNOS) activity to produce NO. Association of eNOS with the caveolae through caveolin-1, as found in obese rats, maintains eNOS in its inactive form, thus reducing NO production. Rats fed with a soy protein diet do the contrary, releasing eNOS from the caveolae, facilitating the synthesis of NO and improving renal flow [94]. All these evidence indicate that soy protein intake has a beneficial effect on health in different organs by different mechanisms.

The use of soy protein by humans with renal diseases instead of animal protein has been postulated as a new preventive and treatment option in chronic kidney diseases. Soy protein has beneficial effects on renal function in diabetic and nondiabetic patients with nephropathy, reducing the glomerular filtration rate and improving creatinine clearance [95–98].

11. Conclusions

Numerous advances have been made to explain the mechanisms by which soybean protein exerts beneficial effects on the concentrations of serum and hepatic cholesterol and triglycerides. It seems that there are several factors that have to be taken into account. These factors include the amount of dietary protein, hormones such as insulin and glucagon, several transcription factors including SREBPs and LXRα that sense the amount of lipids in the cells, enzymes involved in lipogenesis, cholesterol uptake and transport as well as enzymes responsible for bile acid production. The primary effect of soy protein on cholesterol metabolism is exerted in the liver; however, the adipose tissue, intestine, pancreas and kidney seem to play an important role in lipid metabolism (Fig. 3). The implications of studying soy protein in lipid metabolism are important in

primary disease prevention. For a patient with a moderately elevated LDL cholesterol level, a substantial substitution of animal protein for soy protein in the diet might be adequate when combined with a low-fat diet and exercise to bring the LDL cholesterol to the target concentration for the patient. Furthermore, it is important for the dietary support of patients with obesity, diabetes Type 2 and renal diseases, among others. The patients might then need less medication than would otherwise be required for their treatments.

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