

Soybean and Obesity

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The human body is a beautiful specialized engine and there is not any other machine like it. Your body will always do everything possible to stay healthy; in its interior it will sacrifice some things for others in order to conserve the equilibrium.

1. Introduction

Obesity is an alteration of body composition characterized by excess adipose tissue, that involves an imbalance between energy intake and output, which can be produced by a series of genetic, biochemical, dietary and behavioral alterations; therefore, it could be viewed as a multifactorial disease, in which inside the body it can find various regulatory elements of the system of feeling hunger-satiety signals commanded by chemicals that regulate food intake. The environment plays an important role in the development of cultural elements of each individual, determining the amount, type, and frequency of consumption of foods; this also determines their nutritional status. Eastern societies have based their feeding in legumes such as soybeans. These groups have low rates of obesity, which has drawn wide attention towards these foods and especially soybeans. Soy is a valuable food from a nutritional standpoint, because its protein is among the highest biological value, its lipids are mostly polyunsaturated, contains fiber and carbohydrates, is rich in vitamins and minerals; additionally containing various phytochemicals with antioxidant and anti-obesity activity. Several studies in experimental animals and humans have shown that a diet whose protein content is based on soy protein, have a beneficial effect in obese individuals as measured by the decrease in body weight associated with the body calorie intake, liver triglycerides, cholesterol, hepatic synthesis of fatty acids, enzymes responsible for mRNA synthesis of fatty acids and hyperinsulinemia. Moreover, the soy protein has been shown to contribute to the increase in LDL receptors, the increase in insulin sensitivity, and also in the activity of enzymes responsible for fatty acid metabolism, especially those involved in the β -oxidation. Considering the above, in this chapter shall be reviewed how the consumption of soybean and soybean sprouts may reduce the incidence of obesity and diseases closely related to it as the Diabetes Mellitus and Cardiovascular Disease.

2. Obesity

Through the years, the world has lived terrible wars, in which many people survived in extreme conditions. Under these circumstances, the body created defense mechanisms that would allow it survives on similar conditions relying on fat. This is particularly important in any energy deprivation state such as prolonged fasting, skipping meals, performing to much exercise and not feeding correctly. However, nowadays there is a general tendency to cumulate fat; the excess of this component is associated with obesity.

When a disease is produced by multiple factors, a lot of different definitions and etiological explanations arise, such is the case of obesity, in which the conceptual analysis can be as diverse depending on the focus from which it is signaled. The definition varies from the clearest and simplest concept: *"the alteration of the body composition characterized for an excess of adipose tissue"*, through the most complex concept: *"Unbalance between food intake and energy expenditure produced by series of genetic, biochemical, dietary and behavior alterations."* Besides, the problem gets worse when it involves different population factors as ethnicity, dietary habits and the decrease of the vulnerability to diseases that previously limited life expectancy and conferred the opportunity to gain weight.

In many affected subjects it is clear that overfeeding and low physical activity causes an accumulation of excessive body fat. Currently there are many individual differences in the energy processing and tendency to calorie storing. Below we will provide a brief description of the great complex interrelated factors. Exposing different causes, we can constitute a group of syndromes based on diverse origins. Unfortunately it is a combination of these factors the ones that affect the majority of the population (**Figure 1**).

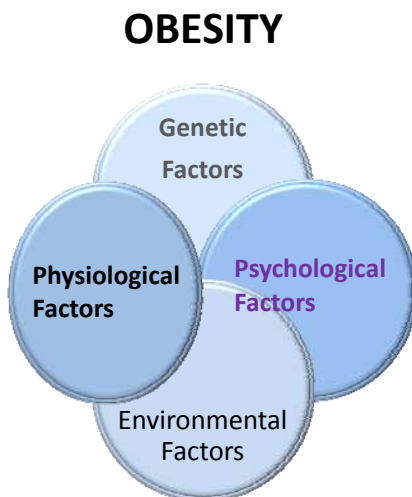


Fig. 1. Obesity Etiology. The obesity has origin in four main factors: genetic, physiological, environmental and psychosocial.

Genetic Factors

Genetics seems to establish the obesity scenario; nevertheless, diet, exercise and life style will be the ones determining the magnitude of the problem, for that reason it is convenient to analyze the physiological pathology of obesity from a wider focus.

Some studies based on comparing the behavior of identical twins exposed to different environmental conditions established that the impact of genetics, as an obesity causal factor, was approximately 30-40%, while environment was ascribed 60-70% (Bouchard, et al. 1993). Although other researches report an interval between 20 to 80%, depending on some particular characteristics of obesity or age of appearance (Groop & Orho-Melander, 2001).

In the research of the genetic factors that modulate satiety and body mass, several studies have been realized in animal models. In transgenic animal models has been studied the role of genes involved in the body fat increase as the effect related to the suppression of melanocortin-4 receptor, the reduction of glucocorticoid receptor in brain, the over expression of the corticotrophin releasing hormone, suppression of uncoupling protein in brown adipose tissue, the over expression of agouti protein, the suppression of β -3 adrenergic receptor and dysfunction of GLUT-4 in fat and intracellular adhesion molecule-1.

In humans, there are clearly identified genetic syndromes in which obesity is a characteristic, such as Prader-Willi and Bardet-Biedl syndrome. However, obesity-related genetic alterations have been identified only in very few individuals. These alterations may be mutations in leptin and its receptor, melanocortin-4 receptor, proopiomelanocortin, endopeptidase, prohormone convertase-1, in β -3 adrenergic receptor, peroxisome proliferator-activated receptor- γ 2, among others (**Figure 2**). Despite the discovery of these single-gene disorders, the genetic model in the most cases of obesity in humans is non-Mendelian polygenic. In the genomics of obesity in humans, it has been determined that there are at least 15 genes that were significantly associated with body fat or the percentage of body fat, and 5 genes are associated with abdominal visceral fat (Sims, 2001), although surveys of large populations have identified over 250 genes, markers and chromosomal

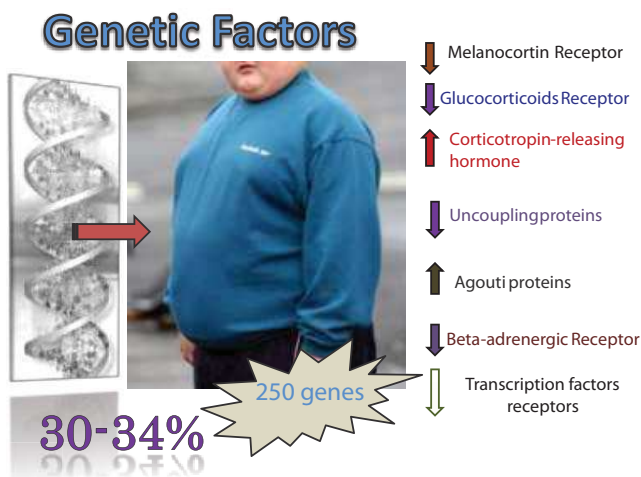


Fig. 2. Genetic factors of obesity. Two hundred and fifty genes have been related with obesity. Melanocortin and glucocorticoid receptors, corticotrophin-releasing hormone, uncoupling proteins, Agouti protein and transcription factors

regions associated with obesity (Perusse et al., 2000). Therefore, in humans, the potential interactions among multiple genes and their interaction with the environment, lead to the phenotypic expression of obesity.

Physiological factors

The accumulation of body fat requires an increment on the relation between intake and energy expenditure during a long period. However the simplicity of this premise vanishes when the modulator effect of other physiological variables as intrauterine development influences, hormonal functions (growth hormone and reproductive hormone) and the fine regulation of the feedback systems that try to keep a constant energy balance are included.

In a study of obese and non-obese subjects with periods of caloric restriction and excess of calorie consumption, it was observed a decrease in the total and resting energy expenditure when they lost 10-20% body weight, possibly due to the adaptation of caloric deprivation. With the increase of weight it was observed increment on the energy expenditure, which delayed weight gain. These findings suggest the existence of a compensator mechanism that tends to maintain body weight (Leibel et al., 1995).

Physiologically, there are many hormones and peptides that act in a feedback system composed of gastrointestinal system, adipocytes, hypothalamus and the hypothalamic-pituitary-adrenal axis. The main appetite suppressants, at gastrointestinal level, are the glucagon-like peptide-1, the 6-29 amino acid segment of glucagon, cholecystokinin, enterostatin, the peptide YY 3-36 and the ghrelin. In addition, gastric distension and contractions produce signals of satiety and decreased appetite. This highly accurate system is also influenced by the serum glucose concentrations. When glycemia is reduced about 10% it causes an increase of appetite (Campfield et al., 1985).

The discovering of leptin and its receptor interactions has established new paths for investigation on obesity physiopathology. Although it have been established that leptin is a fundamental protein in the energy equilibrium in rodents, the physiological role and the regulatory mechanisms of its secretions in humans have been object of great interest.

This protein hormone is secreted by adipocytes in response to activation of insulin receptors, adipogenic hormones, adrenergic receptor, and also when detecting fat repletion. That secretion has a periodicity of 7 min and diurnal variation. When the hormone is liberated, it stimulates to its receptor located in the paraventricular nucleus of the hypothalamus which induces the release of the neurpeptide, whose main functions are appetite suppression and the stimulation of the thyroid function, the sympathetic nervous system and, of the thermogenesis. All these effects tend to limit weight gain. Therefore, the adipocyte and the hypothalamus form a classic feedback mechanism in which the adipogenesis and lypolysis are revealed as highly regulated processes (Figure 3).

Aside of this path there are many afferent signals that affects the intake and energy expenditure. The adipocyte also receives signals from the gastrointestinal tract, the peripheral nervous system and the endocrine system. The integration of these systems involves the adequate adaptation to food deprivation periods, but it also leads to a poor adaptation to overfeeding.

Several studies have confirmed direct interaction between hyperleptinemia and the percentage of body fat that suggests a leptin resistance (Rosenbaum et al., 1997). This resistance can occur at different levels: in the transport across the hematoencephalic barrier, in its hypothalamic receptor and/or other neural circuits in which this hormone influences. Recent studies have shown hypertriglyceridemia-mediated alterations in the transport of leptin through the hematoencephalic barrier (Banks et al., 2004).

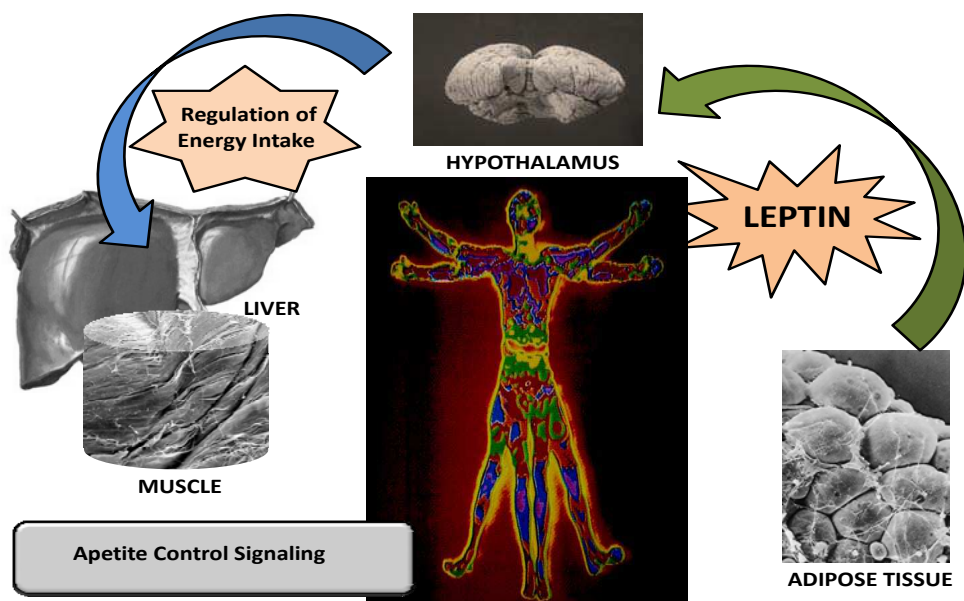


Fig. 3. Role of leptin on energy intake. Leptin is a 16 kDa protein hormone that plays a key role in regulating energy intake and energy expenditure, including appetite and metabolism.

Besides the role of leptin in the origin of obesity, have emerged reports about the deleterious effect of hyperleptinemia on the complications of obesity. It has been reported that leptin causes insulin resistance in hepatocytes (effect mediated by the dephosphorylation of insulin receptor substrate-1) and has fibrosis-inducing effects in various chronic liver diseases of metabolic or toxic etiology (Cohen et al., 1996; Crespo et al., 2002; Leclercq et al, 2002).

The hypothalamus exerts control over appetite, satiety and thermogenesis. To carry out this function, the hypothalamus requires mediators such as afferent hormonal signals (leptin, glucose), and regulation by the autonomic nervous system, through vagal afferents from gastrointestinal system and even from oropharyngeal stimulus. The main sites involved in this regulation are the nucleus of the solitary tract, the arcuate and paraventricular nucleus, as well as the ventromedial and lateral regions of the hypothalamus and amigdala. Leptin acts on the control of satiety in the arcuate and ventromedial nucleus. When there is destruction of the ventromedial hypothalamus, leptin is unable to suppress food intake at this level. In this process is also involved a large number of monoamines (such as norepinephrine and serotonin) and other neurotransmitters or neuromodulators (Campfield, 2000) (Figure 4).

Other metabolic abnormalities related to obesity pathogeny are the defects on the lypolysis regulation (Sheehan & Jensen, 2000), actions in adipose tissue of rennin-angiotensin system (Goossen et al., 2003), tumor necrosis factor (TNF) (Bulló et al., 1999), and several neuropeptide systems (Cummin & Schwartz, 2003; PI-Sunyer, 2002). In this final sections, it

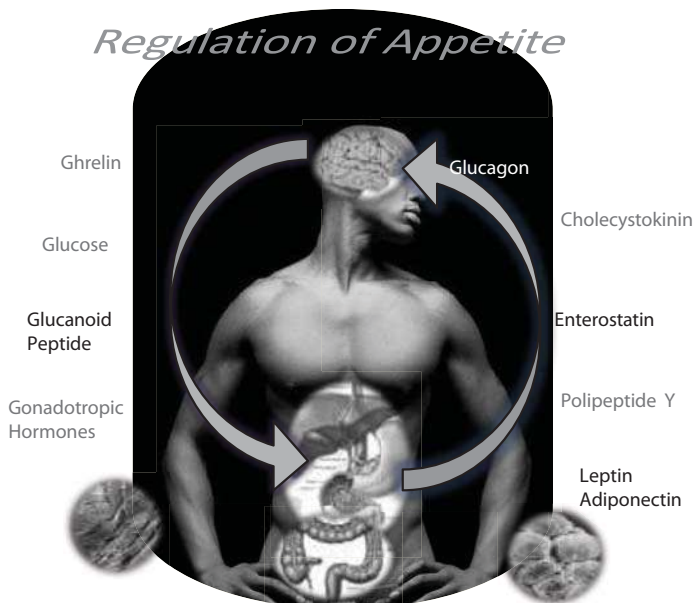


Fig. 4. Appetite control. The fluctuation of some molecules and hormone levels results in the motivation of an organism to consume food.

has been implicated the autonomic nervous system imbalance with obesity and metabolic syndrome. In animal models with beta-adrenergic receptors suppressed, there is a severe obesity due to failure in diet-induced thermogenesis (Bachman et al., 2002). Pima population studies have linked the low adrenal sympathetic activity to weight gain (Tatarann, 1997).

Another etiological factor of supreme importance is the aging process, in which, there are various elements that determine the weight gain and the changes in body fat distribution, such as the decreased physical activity and metabolic responses to dietary or environmental modifications; hormonal changes, for example, the decline in estrogens and progesterone that alters the adipocyte biology; the emergence of comorbidities, as well as behavioral disturbances and depression among others.

As we move on obesity knowledge, new routes and pathophysiological interactions are discovered and it will be increasingly difficult to attribute them a greater pathogenic impact.

Environmental factors

The exaggerated increase in the prevalence of obesity in the last 20 years has been favored by changes in the environment that determine the increasing energy input and the reduction of the physical activity, included individuals without genetic predisposition.

The environment influence can initiate since gestation. Diverse studies have related obesity with prenatal exposure to an excess of caloric intake, diabetes, smoking and the lack of breastfeeding (Dabelea, et al., 2000; Power & Jefferis, 2002; Silverman et al., 1998).

The weight gain is very common in people that quit smoking. This fact has been attributed to the suppression of nicotine exposure. The average weight gain is about 4 - 5 Kg in 4 to 6 months. It has estimated that suppression of smoking increase to 2.4 times the risk of obesity in comparison to non smoking people (Flegal, 1995).

The increasingly sedentary lifestyle is an important determinant of obesity. Some authors suggest that the decrease in energy expenditure may have more impact than the increase in the caloric intake (Prentice & Jebb, 1995). A health study reported that watching television for 2 hours a day is associated with an increment of about 23 and 14% of obesity and diabetes risk respectively (Hu et al., 2003). The reduction in the number of hours watching television has been demonstrated to decrease the appearance of obesity (Robinson, 1999). Obesity is more prevalent in adults with physical or sensorial incapacity, or with mental diseases (Levine et al., 2000).

The relationship between environment and physiology is an important factor on the obesity epidemic in industrialized countries. It has emerged an abundant availability of food; the food intake prevails at the end of day and the physical activity has been reduced. This supposed "environment mutation" causes that the susceptible central nervous system (CNS) loses its capability to detect the internal and external rhythm. Since CNS employs the autonomous nervous system (ANS) to regulate internal rhythm, it has been proposed that unbalance and loss of rhythm could be the most important mechanisms in the origin of the metabolic syndrome. The metabolic syndrome is a clinic concept that is characterized by the association of Diabetes Mellitus, glucose intolerance, hypertension, central obesity, dyslipidemia, micro albuminuria and atherosclerosis (Kreier et al., 2003).

Psychosocial factors

There are descriptions about some psychiatric disorders related to obesity. The "night eating" syndrome is defined as the consumption of at least 25% (generally more than 50%) of the energy between dinner and the next morning breakfast. It is an eating disorder of the obese that is accompanied by sleeping disorders and it has been considered as a component of the sleep apnea. It occurs in 10-64% of the obese subjects. Binge eating disorder is a psychiatric disease characterized by ingesting large amounts of food in a relatively short time period, with the subjective feeling of control loss and without a compensatory behavior. Its prevalence is 7.6 to 30% in different groups of obese (Stunkard et al., 1996). Progressive hyperphagic obesity starts from childhood, and affected individuals which generally exceed 140 Kg of weight at age 30 (Bray, 1976). Obesity is more prevalent in subjects of low socioeconomic level, but it has not determined the precise reason of this finding.

Although increasingly new evidence about genetic influence and neuroendocrine unbalance of obesity are emerging, is necessary to consider a holistic model in which the biological and psychological factors interact in a complex way. Thus we can expect better results in the comprehension, prevention and treatment for this important health problem.

There have been many attempts to find an adequate treatment that contributes to diminish the amount of body fat of individuals that for any of the previously mentioned reasons have acquired a *Body Mass Index (BMI)* above to the standard established for health care (**Figure 5**). Due to the multifactorial etiology of this disease, it has been complicated to find a unique or standard therapeutic, since each individual has a different development of the disease.

Looking for options that can contribute to the decrease of the exceeding body fat in the population that have obesity, it has been observed that some populations tend to develop in a lesser frequency this disease, such is the case of the eastern populations which have an obesity incidence about 5% in subjects over 18 (WHO, 2002), compared to the highest incidence in countries as USA, where 1 of every 3 habitants are obese. It has been observed that the eastern populations have healthier life styles and also a diet where soybeans have long been a major component.

BODY MASS INDEX (BMI)
IS ONE OF THE MOST IMPORTANT CRITERIA TO KNOW THE NUTRITIONAL STATUS OF ADULTS, CONSIDERING FACTORS AS CURRENT WEIGHT, HEIGHT AND SEX OF THE PERSON
<i>PARAMETERS ARE RANGING FROM 18 TO 24.9</i>
BMI OBESITY: 27 OVERWEIGHT : Over 25 and under 27 Malnutrition : EQUAL TO OR LESS THAN 18

<http://www.issste.gob.mx/aconseja/indice.html>

Fig. 5. BMI, over 80 developing countries have adopted BMI as part of their national policy to improve child health (WHO, 2002).

3. Soybean

Chemical composition

Soy (*Glycine max*, family Leguminosae, subfamily Papilionoidae) is a species of legume native to East Asia. The height of the plant varies from 0.50 m to 1.50 m. It has large trifoliate and pubescent leaves and the fruit is a hairy pod that grows in clusters of 3–5, and usually contains 2–4 spherical or elongate seeds (**Figure 6**). This legume has important feeding characteristics. Japan was the first country to consider the nutritional benefits of the soybean. The protein concentration of the soybean is the largest of all legumes. The soybean contains in sufficient amount the indispensable amino acids to satisfy the healthy adult requirements (Ridner, 2006). This legume also has lipids that are rich in poly-unsaturated fat acids, standing out for the high content of linoleic acid (51%). Approximately 1.5 to 2.5% of the lipids present in the soybean are found as lecithin, this has an emulsifier function. We can find also in considerable proportions tocopherols and vitamin E, both of them can act as antioxidants (FAO, 1992)



Fig. 6. Soybeans. Soy is a legume containing between one and four yellow or black seeds

This is the legume with the highest content of galactooligosaccharides, which constitute an important prebiotic (Ridner, 2006). The soybean also has significant amounts of minerals like: calcium, iron, copper, phosphorus and zinc; however, the availability seems diminished by the presence of phytate; this disadvantage decreases with cooking, fermentation or germination process (FAO, 1992).

In addition, soybean contains a series of compounds which are known to have specific functions in both the plant and the organisms that consume it; such as the isoflavones genistein, daidzein and glycitein (**Figure 7**), as well as flavonoids, lignin, saponins and sterols. Some of them have showed to have antioxidant capacity (Dixon, 2004; Mikstacka et al., 2010).

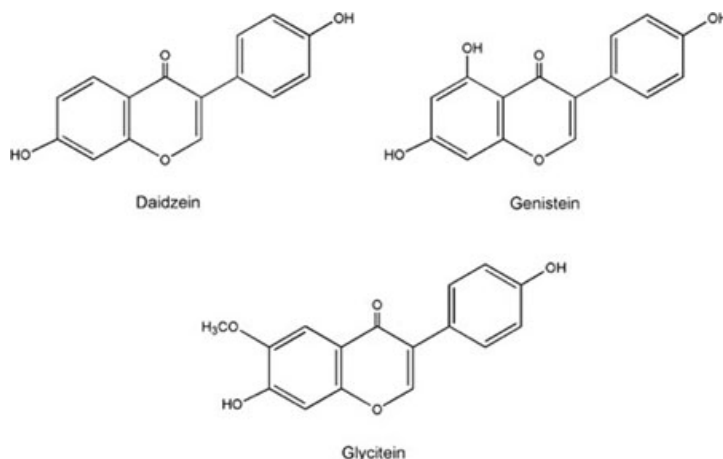


Fig. 7. Soy Isoflavones. Isoflavones comprise a class of organic compound, often naturally occurring, related to the isoflavonoids. Many act as phytoestrogens and antioxidants.

Soybean and obesity

Metabolic syndrome is a combination of medical disorders that increase the risk for cardiovascular disease and Type II diabetes. Obesity may lead to metabolic syndrome because it increases the prevalence of visceral obesity, insulin resistance, increased very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol, decreased high-density lipoprotein (HDL) cholesterol, elevated triglycerides, hypertension (high blood pressure), and fatty liver, which are important factors of metabolic syndrome.

Visceral obesity, a hallmark for the male obese phenotype, which is characterized by excess fat storage around the abdomen, is the prime cause of metabolic abnormalities; therefore, men are usually at higher risk of cardiovascular disease than women. Along with the realization of many studies it has been observed that animals and humans fed with seeds of soybean tend to lose more weight than those who were fed animal protein such as casein (Hurley et al., 1998; Iritani et al., 1997).

The mechanisms of action by which the soy protein isolates have beneficial effects on obesity are not completely clear yet. However, there are many studies confirming that different components included in the soybean have specific functions in the human body such as the absorption of the lipids, the insulin resistance, fat acid metabolism and other hormonal, cellular and molecular changes related with adipose tissue (Wang & González, 2005).

Soybean, obesity and Diabetes Mellitus II

Murine Models

Some researches performed on animal models have demonstrated that the consumption of soy has effects on the diminution of glucose levels and in insulin resistance, and also the increase in insulin receptors. Hurley et al. (1998) examined the metabolic effects of different types of protein in male Sprague-Dowley rats. Plasma glucose and insulin concentrations, in addition to total and metabolizable energy intake and body weight gain, were lower in rats fed soy protein isolate- cornstarch diet compared with casein-cornstarch diet. In the study of Lavign et al. (2000), it was evaluated the effect of feeding different types of proteins (cod, soy and casein) in Wistar rats finding that cod and soy protein improved fasting glucose tolerance and peripheral insulin sensitivity when compared with casein.

Subsequently, based on these findings, further studies were done in animal models with specific features of obesity and various chronic degenerative diseases.

Iritani et al. (1997) investigated the effects of different dietary fatty acids and proteins on glucose tolerance and insulin receptor gene expression, in Wistar fatty rats (genetically obese, noninsulin-dependent diabetes mellitus). After three weeks, dietary soybean protein could help to reduce the insulin resistance, but only when a diet low in polyunsaturated fatty acids was consumed. In addition, dietary soybean protein stimulated insulin receptor gene expression in comparison with casein.

Another possible mechanism of action of soy protein is by stimulation of adiponectin, a cytokine produced by fat cells that has an important role in regulating differentiation and secretory function of adipocytes by increasing insulin sensitivity (Anderson et al, 2004). High blood levels of this hormone reduce obesity (Arita et al, 1999; Weyer et al., 2001). There is a report indicating that the consumption of soy isolate reduces the adiponectin concentration in Wistar rats genetically engineered to develop obesity (Dietze et al., 2005).

In another study it was compared the effects with an energy-restricted diet, low fat intake (5%) and high protein content (35%) from soy and casein in male genetically obese yellow KK mice. The plasma total cholesterol and glucose levels as well as the body fat and body weight were lower in mice fed soy protein isolate (SPI) compared to group fed whey protein isolate (Aoyama et al., 2000).

Nagasawa et al. (2002) studied the effects of energy-restricted diet containing soy protein isolate (SPI) on body composition, blood glucose, lipid and adiponectin levels and the expression of genes involved in the metabolism of glucose and fatty acid in male obese mice KK-A. Body weight and brown adipose and mesenteric tissues were lower in animals fed SPI compared with animals fed casein diet. There no was significant difference in gene expression between both diets. It was concluded that SPI diminishes body fat quantity and glucose levels more efficiently than hypocaloric diets based in casein in obese mice.

The content of isoflavones of the soy protein is important to the antiobesity effect, because has been shown to decrease fat accumulation in animal models of obesity (Manzoni et al., 2005; Banz et al., 2004).

Human research

Positive results obtained with murine models supported researches to evaluate the effect of SPI diets in human subjects.

Mikkelsen et al. (2000) compared the effect of feeding low-fat diets containing pork, soy protein or carbohydrates in 12 young people with overweight and grade II obesity and a body mass index (BMI) between 26 and 32. Energy expenditure was measured in a respiratory chamber and was significantly higher (by >3%) in subjects consuming protein-rich diets. This indicates that protein has a thermogenic and satiety effect greater than carbohydrates, a fact that may be relevant in the prevention and treatment of obesity.

Allison et al. (2003) evaluated the efficiency and the safety of a low-calorie diet based on soy in the treatment of obesity in obese individuals. Soy diet induced a higher weight loss than animal protein diet. Anderson et al. (2004) demonstrated, in human studies, that SPI consumption had an effect on reduction of appetite compared to egg protein.

In another study (Deibert et al, 2004) it was compared diets from two different lifestyles (balanced nutrient reduction diet, and soy protein substitution diet with and without physical activity program). It was shown that a high-soy-protein low-fat diet induced a higher weight loss through fat but not muscle mass in overweight and obese people.

Soybean, obesity and cardiovascular diseases

Murine models

There are *in vivo* evidences showing that soy protein influences the lipogenesis on the liver. It was demonstrated that triglycerides (TGC) in the blood and especially in the liver were decreased by the consumption of a diet with a protein input based on soybean. These effects were associated with the activity reduction of lipogenic enzymes, particularly dehydrogenase 6-phosphate, malic enzyme, synthetase fatty acid, as well as acetyl CoA carboxylase (ACC) meaning that soy protein decreases the liver TGC inhibiting the synthesis in the same (Xiao et al., 2006)

Recently in a study with obese Zucker rats that were fed isoflavones-rich SPI, it was showed a decrease on fatty liver and reduced alanine and aspartate transaminases levels in plasma. These effects were accompanied by an increase in mitochondrial and peroxisomal β -oxidation activity and acetyl CoA carboxilase activity, among others. The ACC is the rate limiting enzyme in catalyzing the carboxylation of acetyl CoA to form malonyl CoA and is the main enzyme in the biosynthesis of long chain fatty acids. Aoki et al. (2006) reported that SPI feeding decreased the hepatic contents of ACC alpha mRNA mainly by regulating PI promoter in rats.

In addition, it was shown that soy protein decreased levels of TGC in rat liver also reducing the adipose tissue weight. These changes were associated with increased gene expression of skeletal muscle enzymes which produce the fatty acid oxidation, including carnitin palmitoyl-transferase (CPT1), β -hydroxyacyl-CoA dehydrogenase (HAD), acyl CoA-oxidase and the medium-chain acyl CoA-dehydrogenase activities.

It has been reported that soybean saponins can also reduce serum cholesterol (Oakenful et al, 1984), but their role in lipid metabolism is not completely clear. A study on hamsters reported that a diet containing soy saponins without isoflavones induced a reduction in cholesterol and TGC levels as well as in total cholesterol/HDL ratio. The phospholipids may have an antilipidemic effect, since they reduced the hepatic synthesis of fatty acids along

with the malic enzyme, glucose-6-phosphate dehydrogenase and pyruvate kinase activities in a study in rats (Rouyer et al, 1999).

Human studies

The consumption of soy protein in a group of patients with hyperlipoproteinemia, reduced the low density lipoproteins (LDL) cholesterol and TGC levels by 16.4% and 15.9%, respectively, in blood and liver, besides to reduce intestinal absorption of endogenous and exogenous cholesterol (Wright & Salter, 1998). Soy protein has also been shown to directly affect LDL hepatic metabolism and the activity of LDL receptors. Lovati et al. (1987) found that SPI diet dramatically affected the degradation of LDL by mononuclear cells.

In another research in humans, it was found that soybean can reduce the insulin/glucagon ratio which increases its antihypercholesterolemic effect (Gudbrandsen et al., 2006; Hubbard et al., 1989). In a similar work it was evaluated the effect of a hypocaloric diet containing casein or soy protein in a long and short term assays. The measured parameters were body weight reduction in subjects with 50% over ideal weight and lipoproteins levels. All participants lost weight (in a similar way in both diets), but the high density lipoproteins (HDL) level was lower in individuals consuming casein. Authors concluded that soy protein could have a greater benefit than casein in patients who need hypocaloric diet for long periods (Bosello et al., 1998).

In a twelve-week trial with obese subjects, it was compared the soy protein effects against milk protein in hypocaloric diets of 1200 kcal/day. People who consumed soy lost more weight than those who consumed milk (9% vs 7.9%) but the difference was not statistically significant. However, the reduction of LDL cholesterol and TGC levels were significant (Anderson et al., 2005).

Soy and its relation with PPAR and SREBP-1

The type of foods that are ingested has effect in the phenotype of an individual by modulating transcription factors that modifies the expression of genes and determines individual characteristics.

The transcriptional control of these genes is mediated by a family of transcription factors designated as sterol regulatory element binding proteins (SREBPs) (Torres, 2006). The isoflavones acts through multiple mechanisms that include inhibition of cholesterol synthesis and esterification of fat (Orgaard & Jensen, 2008). Isoflavones regulate the activity or the expression of SREBP-1. In addition, SREBP-1 regulates the expression of stearoyl-CoA desaturase 1 (SCD-1), D5 desaturase and D6 desaturase involved in fatty acid desaturation to form monounsaturated and polyunsaturated fatty acids. The balance between saturated, monounsaturated and polyunsaturated fatty acids is essential for the formation of triglycerides and phospholipids in the liver. 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 C-H oxidation (Torres, 2006). Soy protein causes an increase in bile acid secretion and inhibits intestinal cholesterol absorption.

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 (PPAR α). PPAR α is a ligand-dependent transcription factor of the nuclear receptor superfamily. A soy protein diet up-regulates PPAR α gene expression (Tovar, 1998). PPAR γ

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. PPAR γ stimulates fatty acid uptake and triglyceride esterification in a concerted action with SREBP-1 that regulates lipogenesis to fill the lipid droplet. The differentiation of adipose tissue protect to other organs of fat accumulation called lipotoxicity. Many studies have demonstrated that the soy protein associated isoflavone genistein is able to activate PPAR γ , resulting in an up-regulation of adipogenesis and probably fatty acid uptake from plasma (Mezei, 2003).

Another molecule related in the energy homeostasis is AMP-activated protein kinase (AMPK). AMPK induces a cascade of events within cells in response to the ever changing energy charge of the cell. The role of AMPK in regulating cellular energy charge places this enzyme at a central control point in maintaining energy homeostasis. In a recent research the consumption or administration of soy peptides increased AMPK level, and promoted the fat mass loss (Jang, 2008).

Soybean germination, obesity and cardiovascular diseases

Germination of soybean and changes in chemical composition and aminoacid profile

Germination is a simple, low-cost process that produces a natural product, eliminates or inactivates certain antinutritional factors, and increases the digestibility of proteins and starches in legumes. Germination process has been developed to overcome the disadvantage of soybean seeds used in food products. Germination causes changes in secondary metabolite distribution, mobilizes the reserve proteins stored in the cotyledon protein bodies, changes amino acids composition (Davila et al., 2003) and produces intermediate molecular weight peptides (Mora-Escobedo et al., 2009). Germination could improve the nutritional and nutraceutical properties of legumes by modifying metabolites content and generating peptides and amino acids with possible biological activity. Paucar-Menacho et al., (2009) found that germination of soybean for 42 h at 25 °C resulted in an increase of 61.7% of lunasin, decrease of 58.7% in lectin and 70.0% in lipoxygenase activity. Optimal increases in the concentrations of isoflavone aglycones were observed in combination of 63 h of germination and 30°C. A significant increase of 32.2% in the concentration of soy saponins was observed in combination of 42 h of germination at 25 °C.

Our group conducted an investigation in which soybean seeds (BM2 donated by the Forestry Research Institute of Agricultural and Livestock, INIFAP, México) were germinated according Mora-Escobedo et al. (2009). The germinated seeds were harvested at different times (0, 48, and 72 h), lyophilized and ground. In order to evaluate the effect of germination on the main nutrients provided by the soybeans, were characterized the flours obtained at different times of germination. Table 1 shows the results. The protein content of the soybean was of 34.85 ± 0.65 to 35.63 ± 0.87 , with no significant difference ($p > 0.05$) between different times of germination. In germinated flour was an increase in the lipid content of 11.14% ($p \leq 0.05$) for 48 h and 16.18% ($p < 0.05$) for 72 h compared to ungerminated flour. The increase in lipid content observed in this study probably was due to the decrease of other seed components, as some carbohydrates. Paredes-López and Mora-Escobedo (1989) reported a decrease in starch content of 25% in germinated amaranth flour by 72 h.

Soybean flour	Carbohydrates	Protein	Fat	Ashes
Ungerminated	37.52	34.85 ± 0.65	22.43 ± 1.04	5.20 ± 0.03
48h of germination	34.66	35.63 ± 0.87	24.93 ± 0.8*	4.78 ± 0.02
72h of germination	33.62	35.18 ± 0.64	26.06 ± 0.8*	5.14 ± 0.10

*p<0.05 regarding non-germinated flour

Table 1. Composition of soybean flour with different times of germination (g/100 g meal dry basis)

Amino acid content of germinated soybean proteins

The method proposed by Rickert et al., (2004) was used with slight modifications in order to obtain soybean proteins. The protein yield was 59.7%. The total protein content and amino acid analysis of germinated soy proteins are shown in Table 2. The protein content in the sample obtained at 72 h of germination decreased. The amino acid composition was altered significantly compared to the different times of germination. Analyzing the essential amino acids, it was observed in the isolate of soy germinated for 48 h, a significant increase ($p \leq 0.05$), between 10 and 21% for phenylalanine, leucine, threonine, and isoleucine. These results were consistent with those reported by Dasinova (1994), who observed an increase of 5 to 23% in soybean, lentils, barley and wheat sprouts, for the essential amino acids leucine, phenylalanine and tryptophan. By extending the germination time to 72 h, this group of amino acids showed a more significant increase of 16 to 25%. Valine was the amino acid with the greatest increase and it was seen in the germination of 48 h (54.06% at $p \leq 0.05$).

Lysine is an amino acid important for human consumption, since it intervenes in the metabolism of carbohydrates and fats and is needed for protein synthesis. It is the main limiting amino acid in cereals, especially wheat. The isolate obtained from soybean germinated for 72 h, was able to increase the contribution of lysine by 26% ($p \leq 0.05$). Contrary to expectations, the methionine content increased with germination time up to 23.98% at 72 h ($p \leq 0.05$). This is the limiting amino acid in soy and the germination was able to increase their concentration; a significant event when viewed from the nutritional point of view. However, methionine is the precursor of homocysteine, a compound that at high levels in the blood can be an independent risk factor for cardiovascular disease (Steed & Tyagi, 2010).

The amino acid of interest for this study was arginine. This amino acid was link with the decrease in the progression of atherosclerotic plaque and protection against damage produced by ischemia-reperfusion (Piñeiro et al., 2010). In this research after germination for 72 h, there was an increase of 8.5% ($p \leq 0.05$). Considering these results it was decided to continue the study using the isolated protein obtained from soybeans germinated for 72 h, free of isoflavones, because the objective was to study only the effect of proteins, since Orgaard and Jensen (2008) studied the effect of soy isoflavones on obesity in humans and they found that this effect may depend on whether the isoflavones are consumed in combination with soy protein.

Germination induced degradation of the α and α' fractions of β -conglycinin, after third day of germination generating low molecular weight peptides (Figure 7). At least six polypeptides, ranging from 25 to 37 kDa molecular weight, appeared as apparent degradation products of β -conglycinin (Mora-Escobedo et al. 2009). Analyzing the electrophoretic profile, it is demonstrated that there was a turnover of proteins and

	Ungerminated	48 h of germination	72 h of germination
Proteins	84.6%	81.39%	76.90%
Essential amino acids (g/100 g of protein)			
Valine	3.64	5.60*	4.12
Isoleucine	3.33	4.05*	4.17*
Treonine	3.48	4.09*	4.07*
Fenilalanine	4.96	5.48*	5.83*
Leucine	7.46	8.42*	8.67*
Lisina	5.61	5.91	7.06*
Metionine	0.98	1.19*	1.22*
Cisteine	1.37	1.64*	1.68*
Non essential amino acids (g/100 g of protein)			
Histidine	2.43	2.69	2.69
Aspartic Acid	11.47	11.95*	12.29*
Serine	7.69	8.3*	8.32*
Glutamic Acid	18.58	18.36	17.93*
Proline	5.18	5.32	5.28
Glicine	4.32	4.76*	5.67*
Alanine	4.27	5.07*	5.12*
Tirosine	3.68	4.41*	4.51*
Arginine	4.90	5.07	5.31*

*p<0.05 regarding non-germinated flour

Table 2. Protein and amino acid content of soybean proteins obtained at different times of germination of BM2 variety.

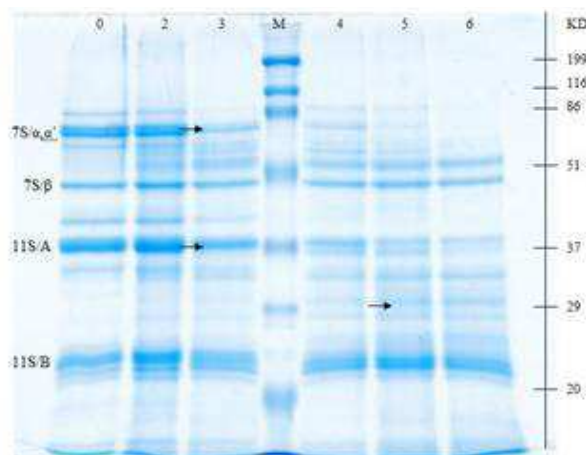


Fig. 7. Electrophoretic profile of the soy protein isolates germinated at different times (0-6 days) (Mora-Escobedo, 2009).

nonprotein nitrogen; equilibrium resulting of the degradation and synthesis processes during germination.

Biological experiments

Rat experimental design: 27 female rats were randomly distributed in 3 groups with 9 rats each. Group 1 (control): hypercholesterolemic diet (HCD); Group 2 (soybean): 0.43 g of germinated soybean protein/Kg of weight and Group 3 (blank): milled Rodent chow 5008. The weight of the rats was registered in order to adjusting the doses. HDC was: Cholesterol 1% (C8503, Sigma), Sodium Cholate 0.5% (C1254, Sigma), butter without salt 5%, glass sugar 30%, casein 10% (Teckland, MA) and Rodent food 5008 53.5% (Matsuda, 1986). The soybean protein/ treatment were administered orally for a period of 40 days. On day 40, myocardial infarction was provoked in all animals, following the procedure reported by Piñeiro et al., 2010.

Table 3 shows weight increase of different groups at the end of the treatment. Analyzing body weight in all groups it was observed a significant decrease in Group 2 ($p \leq 0.05$). It was an important finding since it indicates that consumption of soy protein may help control weight. Bau et al., (2000) found that a diet rich in germinated soybean seeds may possibly have beneficial effects in preventing obesity (Bau et al., 2000). On the other hand the results found in this work showed protein soy tendency to diminish the problems generated by ischemic reperfusion and then it is possible to say that the changes in aminoacid profile could be responsible for the protector effect.

	Group 1 (Control)	Group 2 (Soybean)	Group 3 (Blank)
Weight increase (%)	41.5 ± 6.24	37.67 ± 5.03*	34.5 ± 4.45*
Heart (relative weight)	0.47 ± 0.05	0.43 ± 0.03	0.44 ± 0.07
HAA/TA	0.75	0.59	0.58

*Significant difference ($p < 0.05$) respecting to control. Relative weight: heart weight/100 g of rat weight. HAA/TA=Heart attack area/Total area.

Table 3. Weight increase; heart relative weight and damaged area in dyslipidemic rats

Studies *in vitro* and *in vivo* suggest that consumption of soy protein have favorable effects on obesity and lipid metabolism. Cell culture has been used as a model for the study of obesity, supporting the study of phenomena such as disorders in the metabolism of carbohydrates and lipids. It is useful to elucidate the possible mechanisms by which soy protein has beneficial effects on diabetes, cardiovascular disease and obesity (Jang et al, 2009; Gonzalez, et al. 2009; Tsou, et al. 2010).

Taking into account the results obtained with studying the germinated soy protein it was realized an *in vitro* study of antiobesity effect of germinated soy proteins using 3T3-L1 adiposities. This research was done to determine if germination improves the antiobesity properties of soybean protein through generation of amino acids or bioactive peptides. Soybean was germinated during 1 to 6 days and proteins were isolated from germinated samples. The protein isolates were hydrolyzated by sequential *in vitro* digestion using pepsin and pancreatin, the protein profile was observed by SDS-PAGE.

These hydrolysates were tested in 3T3-L1 cells (mice fibroblast) differentiated into adiposities. The amount of accumulated lipid was measured by red oil technique. Degrees

of hydrolysis ranged from 60-63%. The 2 days germinated soy protein hydrolysate with isoflavones had the best effect antiadipogenic. These results indicate that the consumption of germinated soybean could have an impact on reducing body fat and thereby mitigate the effect of obesity, promoting the use of germinated soybean for the elaboration of functional foods. The development of products from germinated soybean could further increase the versatility and utilization of soybean.

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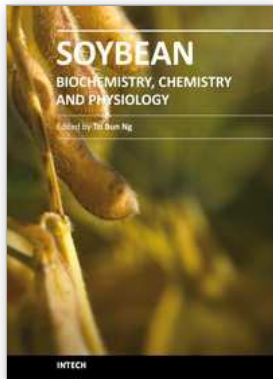
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Soybean is an agricultural crop of tremendous economic importance. Soybean and food items derived from it form dietary components of numerous people, especially those living in the Orient. The health benefits of soybean have attracted the attention of nutritionists as well as common people.

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