Chapter 3 The relevance of the source of animal or vegetable proteins on the metabolic syndrome and its comorbidities

Capítulo 3 La relevancia de la fuente de proteínas animales o vegetales sobre el síndrome metabólico y sus comorbilidades

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Abstract

Metabolic Syndrome (MS) is one of the most serious health problems worldwide since 25% of the population suffers from it and 80% of these are at risk of cardiovascular diseases and diabetes mellitus. MS is defined as a series of metabolic abnormalities constituted by arterial hypertension (HTN), abdominal obesity, dyslipidemias, glucose intolerance and/or insulin resistance (IR). Proteins are long chains of amino acids and have a characteristic three-dimensional structure that is essential for their specific function. These are a source of bioactive peptides that can have beneficial effects on health. Bioactive peptides are small peptide chains composed of 2 to 15 amino acid residues, obtained by industrial food processing or during gastrointestinal digestion; after oral administration, they exert their beneficial effect on the cardiovascular, digestive, immune, and nervous systems. Therefore, the objective of this review is to describe investigations about the positive effects of different kinds and sources of protein, fractions, or peptides in MS.

Metabolic syndrome, Proteins, Bioactive peptides

Resumen

Actualmente el Síndrome Metabólico (SM) es uno de los problemas de salud más graves a nivel mundial, ya que el 25 % de la población lo padece y el 80% de éstos tiene riesgo de presentar enfermedades cardiovasculares y diabetes mellitus. El SM incluye una serie de anormalidades metabólicas como la hipertensión arterial (HTA), obesidad abdominal, dislipidemias, intolerancia a la glucosa y/o resistencia a la insulina (RI). Las proteínas son largas cadenas de aminoácidos y tienen una estructura tridimensional característica indispensable para que desempeñe su función específica. En los últimos años, estas macromoléculas han sido de gran interés debido a que son una fuente de péptidos bioactivos que pueden tener efectos benéficos en la salud. Los péptidos bioactivos son pequeñas cadenas peptídicas compuestas por 2 a 15 residuos de aminoácidos, su liberación es a través del procesado industrial de los alimentos o durante la digestión gastrointestinal; tras la administración oral, ejercen su efecto benéfico en los sistemas cardiovascular, digestivo, inmunológico y nervioso. Es por lo anterior que el objetivo de esta revisión es proporcionar información acerca del efecto de las proteínas y péptidos bioactivos provenientes de fuentes de origen animal y vegetal sobre algunos componentes del SM.

Síndrome metabólico, Proteínas, Péptidos bioactivos

3.1 Introduction

MS includes a series of metabolic abnormalities such as arterial hypertension (HTA), central obesity, dyslipidemias characterized by elevated triglyceride concentrations and decreased concentrations of high-density lipoprotein cholesterol (HDL- C), glucose intolerance, and/or insulin resistance (IR), as well as an increase in pro-inflammatory molecules (Pierlot *et al.*, 2017). Currently, it is one of the most serious health problems, since 25% of the world population suffers from it; among them, 80% have the risk of developing cardiovascular diseases and diabetes mellitus (Fernández, 2016).

Proteins are physically and functionally complex macromolecules, serving multiple crucial functions. They are long chains of amino acids composed of 50-55% carbon, 20-23% oxygen, 6-7% hydrogen, 0.2-0.3% sulfur, and are an important source of nitrogen (12-19%) that can be assimilated by the organism (Walstra and Van Vliet, 2010). Each protein has a characteristic three-dimensional structure that is essential for its specific function (Feduchi, 2011).

Currently, it is known that in addition to their nutritional and functional value, proteins are a source of bioactive peptides that can have beneficial effects on health. These peptides can be obtained through lactic fermentation methods, chemical hydrolysis and enzymatic processes (Daliri *et al.*, 2017).

Bioactive peptides are made up of 2 to 15 amino acid residues and their production can be through industrial food processing or during gastrointestinal digestion. After oral administration, the bioactive peptides exert their beneficial effect on the cardiovascular, digestive, immune, and nervous systems. They have different activities such as antimicrobials, opiates, antioxidants, antihypercholesterolemic, antithrombotic, antihypertensive, hypoglycemic, among others.

They have a positive impact on human health, beyond their nutritional function, in relation to the composition and sequence of the amino acids that compose them (Alvarado, 2010). Due to the different health benefits of oral administration of bioactive peptides, proteins of animal and vegetable origin have been used for their isolation by enzymatic hydrolysis (Mulero *et al.,* 2011).

According to recent population studies, the prevalence of MS components is increasing worldwide, so it is necessary to find non-pharmacological alternatives that allow their prevention and treatment. This chapter presents a review of the effect of bioactive proteins and peptides from animal and plant sources on some components of MS.

Table 3.1 shows the effects of plant and animal proteins, because they can interfere with different mechanisms for lowering blood pressure, improving diabetes or dyslipidemia.

Table 3.1 Health effects of animal vs vegetable protein consumption

Animal protein	Vegetal protein
- Reduction of glucose levels - Prevention of liver and kidney toxicity - Increase in catabolism of hepatic fatty acid - Increase hepatic gene expression of the fernesoid X receptor (Fxr) - Reduction of low-density lipoprotein (LDL) cholesterol levels - Inhibition of angiotensin-converting enzyme I (ACE I) - Improved ex vivo vasodilation	- Inhibition of the DPP-IV enzyme - Reduction of glycosylated hemoglobin levels - Significant reduction in triglyceride levels - Improvement of hepatic stagtosis - Lower expression of transcription factor SREBP-2 - Reduction of low-density lipoprotein (LDL) cholesterol levels - Inhibition of angiotensin-converting enzyme I (ACE I)

Source: Own elaboration

3.2 Animal protein

Foods of animal origin generally contain a high Digestible Indispensable Amino Acid Index (DIAAS) and a high Protein Digestibility Corrected Amino Acid Score (PDCAAS), which places animal protein as having high biological value. This means that they contain a favorable ratio and quantity of the essential amino acids. The DIAAS method is used to know the quality of dietary proteins for regulatory purposes, this is defined as% DIAAS = 100 x [(mg of the amino acid of the diet indispensable digestible in 1g of the protein of the diet) / (mg of the same amino acid in 1g of the reference protein)]. The PDCAAS method also assesses the quality of the protein; however, this method has been found to overestimate the protein quality of some products. Foods of animal origin, in addition to being a good source of proteins and essential amino acids, are important sources of cobalamin or vitamin B12, zinc, phosphorus, and heme iron (Quesada and Gómez, 2019).

3.2.1 Effect of consumption of animal protein on glucose metabolism

Various investigations have suggested that proteins or protein hydrolysates can regulate blood glucose levels under different conditions, however, the mechanisms have not been fully elucidated.

There are different mechanisms by which bioactive proteins or peptides can reduce blood glucose levels. In the study of Nasri *et al.* (2015) the therapeutic effect of undigested goby fish muscle proteins (UGP) and their hydrolysates (GPHs) was investigated in rats fed a high-fat, high-fructose (HFFD) diet. In the rats that were fed with HFFD, hyperglycemia associated with an increase in oxidative stress was observed, while in those that were co-administered with GPHs, a significant decrease in their blood glucose levels and α-amylase activity was found; however, in UGP fed rats, blood glucose values did not decrease, which may be due to differences in length, chain and amino acid sequence of the peptides used. In addition to the hypoglycemic activity that GPH provides, results suggested its use for the prevention of liver and kidney toxicity induced by the consumption of a high-fat and high-fructose diet. Akhavan *et al*. (2010) evaluated the effect of the consumption of whey protein (WP) and its hydrolysate (WPH) on the blood concentrations of glucose and insulin in healthy young adults, and showed that the WP in small amounts and when consumed before a meal, reduces postprandial blood glucose levels as well as food intake; however, the consumption of WPH did not reduce blood glucose levels, suggesting that non-insulin tropic mechanisms require the stimulation that arises from the digestion of intact proteins.

3.2.2 Effect of consumption of animal protein on lipid metabolism

According to what has been mentioned by different researchers, proteins, hydrolysates or peptides can have effects on lipid metabolism. Ramsvik *et al.*, in 2013, evaluated the effect of krill protein hydrolysate (KPH) on lipid and bile acid (BAs) metabolism in mice. The animals were fed a high-fat diet for six weeks. One group was supplemented with casein (control) and the other with KPH. In the KPH group, hepatic fatty acid catabolism increased as the activity of the target PPARα CPT-2 gene increased. An increased hepatic gene expression of the farnesoid X receptor (FXR) was also found in KPH-treated mice compared to the control group. FXR is responsible for maintaining bile acid homeostasis and controlling plasma TAG levels by activating the PPARα gene. It has also been reported that PPARα induces the expression of genes that encode enzymes involved in the oxidation of mitochondrial fatty acids, so that the regulation of KPH of BAs may have the ability to modulate the oxidation of hepatic fatty acids, reducing the concentration of triglycerides in plasma. Mice with FXR deficiency have an increased synthesis of Apolipoprotein B (ApoB), resulting in a higher concentration of TG in serum and liver.

In 2012, Xue *et al.* determined the effects of chickpea albumin hydrolysate (CAH) on the lipid profile of mice fed a high-fat diet. The mice were divided into the following groups: control normal diet, high-fat diet, and CAH with a low (LD), medium (MD), and high dose (HD). The triglyceride content of the three CAH groups decreased by 15.50% (LD), 19.01% (MD), and 36.55% (HD), compared to the high-fat diet group; triglyceride levels of the CAH-HD group were similar to those of the normal diet group. The high-fat diet also caused an increase in low-density lipoprotein (LDL) cholesterol levels, however, after four weeks of CAH administration these levels were decreased in a dose-dependent manner. For high-density lipoprotein (HDL) cholesterol, levels increased showing a dose-dependence. The researchers concluded that the mechanism of action of CAH for cholesterol reduction cannot be fully understood yet and suggested that it may involve the enhancement of LDL cholesterol catabolism through hepatic receptors and/or the increased lipoprotein lipase activity.

3.2.3 Effect of consumption of animal protein on blood pressure

Studies on the relationship between the consumption of protein, protein hydrolysates, or bioactive peptides and the control of blood pressure associate the effect with the inhibition of the angiotensin-converting enzyme (ACE).

A study by Girgih *et al.* in 2015 evaluated the ACE inhibitory activity of a cod hydrolysate (CPH) and its bioactive peptides (CF3) obtained through proteolysis. The experimentation was carried out in four groups of rats (CHP, CF3, captopril, and phosphate-buffered saline), to which the aforementioned were administered by oral gavage, and systolic blood pressure was measured at 2, 4, 6, 8, and 24 hours. It was found that the CF3 peptide reduced blood pressure within the first 2 hours after oral administration and was maintained until after 24 hours, which suggests that its absorption was faster in the gastrointestinal tract of rats compared to CPH.

Another study that evaluated the effect of animal protein and on blood pressure was carried out by Jahandideh *et al.* in 2016, who used an egg white hydrolysate (EWH) in spontaneously hypertensive rats. Three groups were assigned, the control group, low dose EWH (250 mg/kg body weight), and high dose EWH (1000 mg/kg body weight). Treatments were administered orally once a day for 12 days, and blood pressure (BP) was measured on days 0, 3, 6, 9, and 12. It was reported that both EWH doses decreased BP values compared to the control group, but the reduction was only significant in those rats that were administered with the high dose. This could be associated with improved ex vivo vasodilation that reduced oxidative stress because spontaneously hypertensive rats show impaired vasodilation. It also reduced ACE, as well as the expression of the angiotensin II receptor.

3.2.4 Vegetal protein

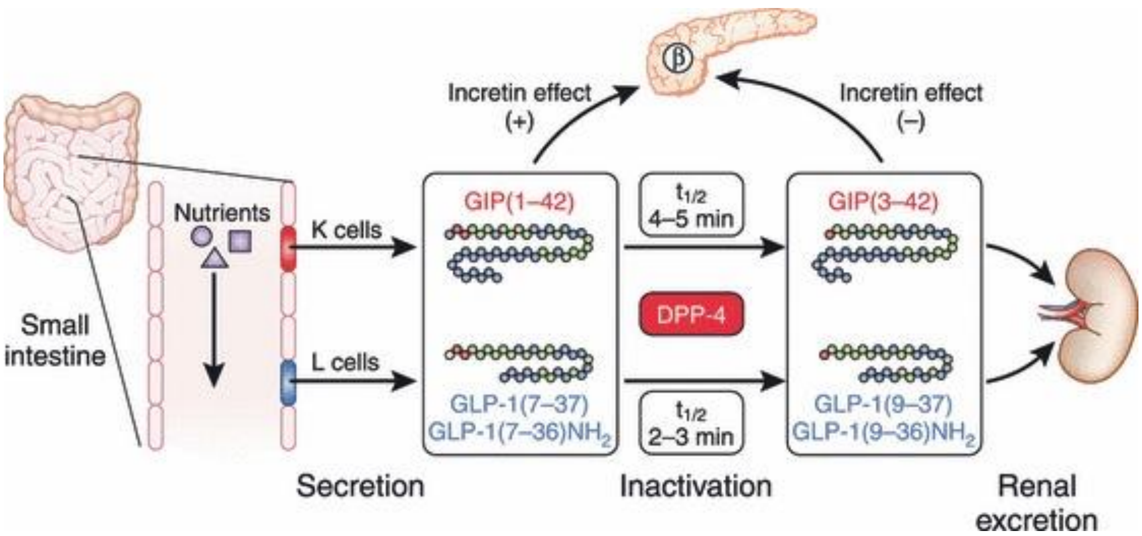
Vegetable proteins are presented in a wide variety, availability and low cost, and great versatility in terms of physicochemical characteristics, which is why it is sought to improve their functionality through chemical or enzymatic modifications. They are obtained from crushed seeds or defatted flour by different methods (Bonino, 2016). Grains are the most abundant and valuable source of vegetable protein since, in addition to being of high quality, they have an adequate content of essential amino acids.

Although proteins of vegetable origin can be considered as an incomplete protein source due to their null or limiting content of some amino acids, it is possible to obtain high-quality proteins by combining vegetable sources (Quesada and Gómez, 2019).

3.2.5 Effect of consumption of vegetal protein on glucose metabolism

After food intake (Figure 3.1), insulin secretion is stimulated by the combined action of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These are the main hormones of the incretin effect, which exert their metabolic effects by activating their receptors. It has been suggested that GLP-1 modulation can help normalize blood glucose levels in individuals suffering from type 2 diabetes (DM2) (González *et al.*, 2018). However, these hormones are degraded by the enzyme dipeptidyl peptidase IV (DPP-IV), turning them into inactive peptide fragments, so their circulating half-life is very short (Romero, 2007). Therefore, the inhibition of DPP-IV can be considered as an alternative for the management of DM2, as well as the blockade of salivary α-amylase and intestinal α-glucosidase.

Figure 3.1 Mechanism of inhibition of the DPP-IV enzyme



Source: Seino et al., 2010

González *et al.* in 2018, investigated *in vitro* the effect of soybean sprout peptides on the inhibition of DPP-IV, salivary α-amylase, and intestinal α-glucosidase. Germinated soy protein was digested for six days (6GSPD) and peptide fractions were obtained by ultrafiltration. Results showed that the inhibition of DPP-IV activity by 6GSPD was dose-dependent. In addition, peptides of 5-10 and >10 kDa were effective in inhibiting the DPP-IV enzyme but peptides of 5-10 and <5 kDa showed better inhibition of the enzymes α-amylase and α-glucosidase, suggesting that the amino acid composition of the peptides determines the interaction with the enzymes in the inhibitory mechanism.

Hernández *et al.,* in 2020 evaluated the effect of consuming a bean protein concentrate (BPC) and a cooked bean flour (WCB) in male Wistar rats given a control diet (casein) or a high-fat diet with 5% sucrose in drinking water. Rats fed the high-fat diet and supplemented with BPCs had 33.6% less body weight, a 11% loss of body fat, and a 5.5% increase in lean mass compared to those fed the same diet but supplemented with casein. Animals fed a high-fat diet and supplemented with WCB had a lower percentage of body fat and a higher percentage of lean mass compared to BPCs group. These results were associated with a significant increase in energy expenditure in BPCs and WCB groups. In addition, a significant reduction in triglyceride, glucose and insulin levels were found in both groups compared to the control group, despite being fed with the high-fat diet, suggesting a lower expression of lipogenic genes in the liver.

In 2019, Marthandam *et al.* studied the efficacy of a decapeptide obtained from potato protein hydrolysated with alcalase (APPH) administered to male mice induced to diabetes by streptozotocin, and observed that animals administered with APPH showed regulated blood glucose levels, and a reduction in the levels of glycated hemoglobin (HbA1c), triglycerides (TG), and total cholesterol (TC).

Another important aspect was the significant improvement in the morphology of the liver and kidney when compared with the diabetic group, who showed loss of normal architecture of the hepatocytes, necrosis, hydropic degeneration, and congestion of the central vein, as well as diabetic nephropathy.

3.2.6 Effect on lipid metabolism

In vivo studies have determined the different effects of vegetal protein on lipid metabolism, total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein (LDL), and triglycerides (TG). Moriyama *et al.* in 2004, evaluated the effects of soybean β-conglycinin and glycinin on the lipid profile in normal and obese mice. They observed that triglycerides and glucose levels in the group of mice with a diet supplemented with β-conglycinin were lower than in control (casein) and conglycinin groups. The researchers reported that the activities and expression of the enzymes related to β-oxidation were higher in the β-conglycinin group than in the other groups. Furthermore, the activity of the fatty acid synthase in the β-conglycinin group was significantly lower when compared to other groups. The aforementioned suggests that the activities of the enzymes involved in fatty acids metabolism could alter the levels of TG in the liver and probably the levels of TG as VLDL (very low-density lipoprotein).

Amaral *et al.*, in 2014, evaluated the effect of the consumption of 11S globulin isolated from chickpea on the lipid profile of adult male Wistar rats with hypercholesterolemia and found that serum triglycerides levels were 28.77% lower than those of the hypercholesterolemic group, and similar to control group. The researchers mentioned that 11S globulin could be involved in triglycerides metabolism, which could be attributed to the possible regulatory effects of this fraction on the transcription factor SREBP-1 (sterol regulatory element-binding protein) found associated with genes involved in fatty acid biosynthesis. Another important observation was the improvement in liver steatosis in the group treated with 11S globulin.

In 2016, Zhang *et al.* evaluated the effects of defatted rice bran protein (DRBP), fresh rice bran protein (FRBP), DRBP hydrolysate (DRBPH), and FRBP hydrolysate (FRBPH) on the lipid profile of mice fed a high-fat diet. In all protein-supplemented groups, decreased levels of very-low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) cholesterol were observed. In the group supplemented with FRBPH, a lower expression of the transcription factor SREBP-2 was observed; SREBP-2 is responsible of cholesterol biosynthesis regulation. Authors concluded that rice bran proteins, as well as their hydrolysates, intervene in mice lipid metabolism, since they can reduce cholesterol biosynthesis.

3.2.7 Effect of vegetal protein consumption on blood pressure

Different *in vitro* investigations have been carried out to analyze the effect of vegetal proteins on the angiotensin-converting enzyme (ACE). Boye *et al.*, in 2010, characterized the proteins present in red lentils, obtaining different fractions such as albumins, legumes and vicilins, which underwent tryptic hydrolysis to release bioactive peptides. Each fraction showed an ACE inhibition property, however, legumin showed higher activity compared to the other fractions, which could be due to its particular peptide composition or higher protein content.

A study conducted in 2014 by García *et al.* evaluated different proteases (alcalase, savinase, protamex and corollase 7089) at different hydrolysis times, to obtain multifunctional hydrolysates from lentil protein concentrates. Once the hydrolysates were obtained, their antioxidant and ACE inhibitor activities were measured. It was found that the hydrolysate produced by the protease Savinase after 2 h of hydrolysis (S2) showed the highest ACE inhibitory activity and antioxidant activity, concluding that the peptides of this hydrolysate could preserve or improve its multifunctionality in the gastrointestinal tract. Authors identified peptides with hydrophobic amino acids, which makes them potential contributors to the double bioactivity detected.

García *et al.* in 2017, identified peptides with antioxidant and ACE inhibitory activity, released by hydrolysis of lentil protein by protease Savinase, and studied the functional stability of bioactive peptides after simulation of gastrointestinal digestion. The most abundant peptides identified were in the vicilin, convicilin, and legumin fractions.

The researchers found that 3 peptides (LLSGTQNQPSFLSGF, NSLTLPILRYL, TLEPNSVFLPVLLH) showed the highest antioxidant activity (0.013-1.432μmol Trolox eq./μmol peptide) and ACE inhibition (IC 50 = 44-120μM). Inhibition of ACE is based on the formation of hydrogen bonds between the C-terminal residues of bioactive peptides and the residues of the catalytic site of ACE. To confirm gastrointestinal stability, bioactive peptides from lentils were treated *in vitro* with the enzyme pepsin and subsequently with pancreatin at 37ºC in simulated gastrointestinal digestion, and it was found that the action of digestive enzymes increased the double activity of the peptides.

3.3 Conclusions

Metabolic Syndrome (MS) is a condition that afflicts an alarming percentage of society. The drugs used for the treatment of MS and its comorbidities have, in the long term, a series of adverse health effects. Therefore, it is necessary to identify alternative food sources that are less aggressive and that can alleviate and/or prevent the appearance of the syndrome.

There is evidence that suggests that bioactive peptides, whether of animal or plant origin, could be an alternative that helps in the treatment of MS and its associated comorbidities. However, the mechanisms of action of these have not yet been fully elucidated, which opens up a field of opportunity for new research using *in vitro* and *in vivo* models.

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