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PROTEINS AS THE SOURCE OF PHYSIOLOGICALLY AND FUNCTIONALLY ACTIVE PEPTIDES*

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Abstract. The market of functional foods and beverages develops dynamically. Biological activities of many food components which occur naturally become an issue of many scientific and industrial interests. The structural and chemical changes occurring during the proteins processing lead to the release of bioactive peptides. Their multifunctional activity is based on their structure and other factors including e.g. hydrophobicity, charge, or microelements binding properties. This article focuses on peptides with other physiological and functional activities such as antithromobotic, antioxidative, antibacterial and antifungal, sensory, and improving those nutritional value of food.

Key words: bioactive peptides (biopeptides), proteins, functional food

INTRODUCTION

Diet plays an important role for the proper body functioning and the peptides which are released during the digestion by pepsin and pancreatin enzymes can affect the organism more or less effectively. The physiological effect of biopeptides depends on their ability to reach the target site. Biofunctional peptides have the potential to be applied in the formulation of health enhancing-nutraceuticals with well-defined pharmaceutical effect [Haque and Chand 2006].

Depending on the amino acid sequence, biopeptides may exert a number of different activities *in vivo*, affecting, e.g. the cardiovascular, endocrine, immune and nervous systems in addition to nutrient utilization [Korhonen and Pihlanto 2003]. Peptide products which have ACE inhibitory effect are currently on the market and some of them are at the stage of being tested due to the strict requirements in order to demonstrate the efficacy of these bioactive peptides prior to their widespread utilization as physiologically beneficial functional foods/food ingredients [Murray and FitzGerald 2007]. Ac-

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cording to Korhonen and Pihlanto [2007] there is a need to develop methods to optimise the activity of bioactive peptides in food systems and to enable their optimum utilization in the body.

It is well known that milk-origin biopeptides show multifunctional activities and recent studies suggest that casein and its peptides, have antimutagenic properties. Animal models, usually for colon and mammary tumorigenesis, nearly always show that whey protein is superior to other dietary proteins for suppression of tumor development [Parodi 2007]. Many food and pharmaceutical companies consider the exploitation of bioactive peptides in human nutrition and health promotion. Although the consumers knowledge about the impact of foods on the body rise, the molecular studies as well as special processing protocols are required before the application of biofunctional peptides as the food components [Haque and Chand 2006].

The paper describes the function of peptides in the body as well as their practical application in the food industry as the functional food components.

ANTITHROMBOTIC PEPTIDES

Peptides that inhibit the blood platelet aggregation are recommended as diet components helpful in the prevention of thrombosis which often occurs in patients with coronary heart disease or other blood systems diseases [Maubois and Léonil 1989]. One of the stages of the platelet aggregation is non-covalent binding of the α- and β-fibrin chains (fibrin polymerization). The N-terminal fragment with the sequence GRP of α chain is the key factor in fibrin polymerization.

Casoplatelins are antithrombotic peptides derived from milk proteins. They come from the C-terminal fragment of bovine κ-casein (glycomacropeptide) and they are the inhibitors of platelet aggregation activated by ADP. The major antithrombotic peptides occurring in bovine κ-casein are its fragments: 106-116, 106-112, 112-116 and 113-116, (MAIPPKKNQDK; fragment 106-116) [Quian et al. 1995]. Fragment of kappa-casein (position: 106-110) is called a casopiastrin. It was produced by trypsin hydrolysis and exerted antithromobotic activity by inhibition of fibrinogen binding. Another fragment (103-111) of kappa-casein inhibitied platelet aggregation and no finbrinogen binding. Some casein-derived peptides were isolated from plasma of the five days old human and bovine newborns and they also showed an atithrombotic effect. The C-terminal residues of sheep kappa-casein (fragment 106-171) reduced thrombin and collagen platelet aggregation in a dose dependant manner. Thrombin-induced platelet aggregation was aldo inhibited with pepsin digests of human and sheep lactoferrin [Clare and Swaisgood 2000]. Peptides containing the Arg-Gly-Asp motif (RGD-containing peptides) derived from a snake venom were found to be antiplatelet aggregation agents. Crotalin from *Crotalus atrox* appeared not only to be the most efficacious agent in prolonging the time lapse for inducing platelet-rich thrombus formation in this model, but also exhibits this antiplatelet activity with a longer duration [Chang et al. 1998]. Luzak et al. [2003] discovered that the shortest collagen type I-derived motif DGEA (Asp-Gly-Glu-Ala) significantly inhibited adhesion, aggregation and release reaction of collagen activated blood platelets.

ANTIOXIDATIVE PEPTIDES

Many peptides and protein hydrolysates can lower the pace of lipid autooxidation process [Pena-Ramos and Xiong 2001]. They also play a role of the heavy metal acceptors and scavanage free radicals. The Maillard reaction products have also the properties to bind heavy metals and form inactive oxidative complexes. Protein hydrolysates can be potentially applied as additives to many of food products although their darkening and low fat solubility make it impossible to apply them as the antioxidative additives to fats and oils [Cunningham and O'Connor 1997, Dziuba 1997].

Antioxidative activity was detected in some peptides (e.g. LLPHH and VIPAGYP) derived from soybean β-conglycinin after enzymatic action of proteinase S [Chen et al. 1995]. These peptides with their synthetic analogues *in vitro* inhibit the oxidation of linoleic acid [Chen et al. 1998]. The main components of the antioxidative peptides derived from different proteins are mainly the amino acids known for their antioxidative properties such as histidine or tyrosine. Similar properties also display methionine, lysine and tryptophan. The composition of amino acids, their sequence and configuration also affect the antioxidative properties of peptides [Pena-Ramos and Xiong 2001]. The antioxidant activity increases due to the presence of proline residues and the presence of hydrophobic residues fosters the interaction of peptides with linoleic acid [Chen et al. 1996].

Carnosine (β-AH) is the natural dipeptide present in animal muscles. It has the ability to inhibit the oxidation reactions of lipids. These reactions are catalyzed *in vitro* by iron, haemoglobin, lipooxidase and atomic oxygen. Carnosine inhibits the oxidative rancidity of the roasted meat during the storage.

Liu et al. [2005] found out that soymilk-kefir has an antioxidant acitivity which suggests that fermented soy milk may be considered as the food component meaningful in the antioxidative processes prevention. The antioxidant activity of soy peptides is related to its structure – some of the amino acids present in the peptides are regarded to be the antioxidants (Tyr, Met, His, Lys, Trp) [Wang and Gonzalez de Meja 2005]. Manufacturing of soymilk and tofu produces large amount of spent residue (okara). This is as waste by-product containing about 27% protein (dry basis) and can be extracted with high yield at alkaline pH. Okara protein has low solubility but has nutritional and functional properties comparable to commercial soy isolates. Products derived from the okara protein have good essential amino acid profiles and the trypsin-hydrolysates also had increased in vitro digestibility and available lysine content [Chan and Ma 1999]. Yokomizo et al. [2002] isolated four antioxidative peptides from the okara protein with Protease N by size exclusion chromatography and RP-HPLC. They were composed of two and three amino acid residues, including aromatic amino acid at the C-terminal end. Their amino acid sequences were determined to be Ala-Tyr, Gly-Tyr-Tyr, Ala-Asp-Phe, and Ser-Asp-Phe, respectively. The antioxidative activity of Gly-Tyr-Tyr is nearly equal to that of carnosine.

Another source of antioxidants is an yellowfish sole (*Limanda aspera*) frame protein (YFP), which is normally discarded as industrial waste in the process of fish manufacture. Digestion of this protein by pepsin and mackerel intestines crude enzyme revealed that 10 N-terminal amino acid residues, RPDFDLEPPY (13 kDa) was found to be an antioxidant [Jun et al. 2004]. Gelatin extracted from Alaska pollack skin was hydrolyzed with Pronase E and the hydrolysate contained peptides ranging from 1.5 to 4.5 kDa.

The isolated peptides (P1 and P2) showed high antioxidative activity. They were composed of 13 and 16 amino acid residues. Both peptides contained a Gly residue at the C-terminus and the repeating motif Gly-Pro-Hyp. Peptide P2 had potent antioxidative activity on peroxidation of linoleic acid and the cell viability of cultured liver cells was significantly enhanced by addition of the peptide [Kim et al. 2001].

ANTIBACTERIAL AND ANTIFUNGAL PEPTIDES

Peptides with antibacterial activity play an important role in the innate immune response to bacterial challenge, and then they ensure the line defense of many species. They are mostly alpha-helical, with several positive charges and amphipathic character and they posses a wide spectrum range of activity against bacteria and fungi [Tam et al. 2000, Jia et al. 2000, Campagna et al. 2007].

Antibacterial peptides have been isolated so far from the many sources i.e. bacteria, insects, mammals and plants. They were mostly linear peptides containing Pro, Arg or occasionally Trp (e.g. cecropin, maigainin, mellitin) as well as bound with disulfide bonds (e.g. tachylepsin, the member of defensin family) [Zhong et al. 1995]. Antibacterial peptides from food proteins show the alkaline character. They damage the bacterial cell membranes. One of the precursors of such peptides are milk proteins (α_{s1}-casein, α_{s2}-casein and lactoferrin) [Dziuba et al. 1999]. One of them is lactoferrin, a glycoprotein that binds iron present in the majority of mammal biological liquids including milk. This is the one of main components which can prevent bacterial infections. The antibacterial effect is the combination of two mechanisms: iron binding which causes the limitation in the free iron availability – the basic factor of microorganisms growth, and the destabilization of the external membrane of Gram-negative bacteria, which as the consequence release the liposaccharides [Vorland 1999]. Comparing with the non-hydrolysed lactoferrin, the better antibacterial ability is assigned to its shorter fragment called lactoferricin (LF, fragment 17-41). The shorter chain of this peptide favours the access to the special sites of bacterial cells. Lactoferricin can be obtained *in vitro* by the pepsin hydrolysis of lactoferrin [Meisel and Schlimme 1996]. This 25-mer peptide KCRRWQWRMKKLGAPSITCVRRAF forms a cationic distorted beta-sheet joined together by a disulfide bridge with a cationic tail near the N-end. Lactoferricin is active against the Gram-negative and Gram-positive bacteria, fungi and protozoa [Chan and Li-Chan 2006].

According to Azuma et al. [1999] a peptide FQWQRNMRKVR, homologous to just over half the loop region of human lactoferricin, is thought to be responsible for antimicrobial properties of human lactoferricin. Multiple antigen peptides (MAP) of the 11-residue peptide exerted significant antibacterial effects against a broad spectrum of bacteria.

Cationic antibacterial peptides are potentially therapeutic in the treatment of sepsis, because of their amalgamated antibacterial and lipopolysaccharide-binding activities. The acyl analogues of the peptide fragment of human lactoferrin consisting of 12 enhanced the antibacterial activity and binding of lipopolysaccharide by up to two orders of magnitude. Lactoferrin-based lipopeptides approached the activity of polymyxin B, a lipopeptide of natural origin, but were also active against Gram-positive bacteria [Majerle et al. 2003].

There are many antibacterial peptides that contain lanthionine and thus called lanthibiotics. Lanthibiotics can be classified for two classes A and B according to their structure and biological function. The antibacterial effect of class A peptides is assigned to the pores formation in the cell membrane. Globular polypeptides, which are enzymes inhibitors belong to class B (e.g. duramycin from *Streptomyces cinnamoneus*, ankowenin from *Streptomyces* ssp.) [Hooven 1995]. Recio et al. [2000] proposed a method of production of the lanthibiotic nisin. It could be released with high efficiency by tryptic hydrolysis of its precursor polypeptide bound to the ionic membrane. Moreover, the same method was applied to produce a fraction enriched in a novel antibacterial domain from the N-terminal part of caprine lactoferrin. The same authors [Recio et al. 2000] revealed that peptide corresponded to fragment 14-42 of the sequence of mature caprine lactoferrin referred to as lactoferricin-C. It was concluded that purification procedure presented can be applied to isolate cationic peptides initially produced in a longer, inactive form by bacteria or naturally occurring antibacterial peptides generated by the digestion of proteins.

At present the application of antibacterial peptides especially those which are isolated from non-conventional sources (e.g. insects) is in interest of pharmaceutical industry [Otvos et al. 2000]. The cecropin-like linear peptides without cysteine were found first in insects, whereas the defensin type with three disulphide bridges were found in rabbit granulocytes. Some antibacterial peptides are clearly multifunctional and an attempt to predict this property from the hydrophobicity of all amino acid side chains are given. Humans need two classes of defensins and the cathelicidin-derived linear peptide LL-37. Clinical cases show that deficiencies in these peptides give severe symptoms. Examples given are morbus Kostmann and atopic allergy. Several antibacterial peptides are being developed as drugs [Boman 2003].

Campagna et al. [2007] isolated an antibacterial peptide from the mast cells of striped bass. It was called a piscidin (FFHHIFRGIVHVGKIHRLVTG-NH_2) and showed the activity against a broad spectrum of pathogens *in vitro.* Another peptide – astacidin 1 (FKVQNQHGQVVKIFHH-COOH) was isolated from the freshwater crayfish, *Pacifastacus leniusculus*. Astacidin 1 has a broad range of antibacterial activity, and it inhibits growth of both Gram-positive and Gram-negative bacteria [So et al. 2003].

NEUROPEPTIDES

Neuropeptides are synthetized and released in the peptidergic neurons (they synthetize peptide transmitters) and they are involved in signal functions for other cells. In the group of neuropeptides one can find the neurohormones which are formed in the neural cells. Neurohomormones play secretory function and they are released to the transporting systems.

These systems transfer the hormones to the specific target cells, bind with their receptors and then generate biological effect. Most of the neuropeptides belong to peptide families while a few, such as protocolin, are orphan peptides. They have the same amino acid sequence in all species from which they have been isolated. Neuropeptides released in synaptic cleft are defined as neurotrasmitters. They are: substance P, protocolin, and tyroliberin [Skiebe 2001]. The other peptides are: calcitonin gene-related peptide, vasoactive intestinal peptide and somatostatin to the regulation of T cell activation.

These neuropeptides are released not only from nerve endings but also from inflammatory immune cells such as monocytes, dendritic cells, eosinophils and mast cells. During release they can exert both direct stimulatory and inhibitory effects on T cell activation and also indirect effects through their influence on the recruitment and activation of professional antigen-presenting dendritic cells. Neuropeptides should therefore be included in the conceptual framework of the immune regulation of T cell function by dendritic cells [Lambrecht 2001]. Most neuropeptides were isolated using bioassays based on physiological effects such as light adaptation, spontaneous contractions of the gut or changes in heartbeat frequency [Skiebe 2001]. There are hundreds of peptides detected in brain and other tissues, but it is worth to be noticed that a fraction is known as biologically functional. The biological activity of neuropeptides is usually mediated by G-protein coupled receptors, or in some cases, by enzyme-linked receptors (e.g. the insulin receptor). Because there is a large number of orphan G-protein coupled receptors, it is likely that there are peptides with undiscovered functions. Analysis of hundreds of peptide precursor cleavage sites in a variety of organisms confirmed that Lys-Arg and Arg-Arg constitute the vast majority of all cleavage sites, while Arg-Lys and Lys-Lys are found with much lower frequency [Fricker 2005].

The definition of "neuroactive peptides" includes all natural peptides, their partial reactions and synthetic analogues which are able to generate the nervous system reaction. Among these peptides are: corticotropin (ACTH), α- and β-melanotropin (α- and β-MSH), oxitocin, vasopressin, gastrin. The consequences of the action of such peptides in the central nervous system can be very different. They can act as neurotransmitters (substance P), control the physiological sleep (DSIP), affect the learning processes, and palliate. The examples of such peptides are: protocoline (RYPT), neurotransmitter of the intestine muscles and neuropeptide Y (NPY), which inhibits the substance P and the other "pain neurotransmitters" from the spinal cord [Naveilhan et al. 2001].

Neuropeptides were relatively successfully isolated from several invertebrate systems such as *Lymnaea stagnalis*, *Drosophila melanogaster*, and *Aplysia californica*. It led to identification of several invertebrate neuropeptide families e.g. 23 FMRFamide--related proteins (FaRP) neuropeptide genes from *Caenorhabditis elegans* [Nanthoo et al. 2001]. Research conducted on insect neuropeptides that are similar to vertebrate neuropeptides may be applicable to higher organisms; and research on insect neuropeptides that are distinct from vertebrate neuropeptides may identify targets for the development of safe and effective pest-management tools. E.g. 28 neuropeptides were found in the extract of 50 *D. melanogaster* larvae [Nichols 2002].

According to Jimenez-Corral et al. [2006] out of 800 neuropeptides that exist and function in the body 20 of them are related to Alzheimer's disease. One of them is amyloid-beta peptide – a pathogenic agent in Alzheimer's syndrome [Saito et al. 2003].

Neuropeptides such as melanin-concentrating hormone (MCH), neuropeptide Y (NPY), and α-melanocyte-stimulating hormone (α-MSH) are known as mediatiors of energy balance through centrally mediated pathways, also have direct acute effects on the lipolytic activity of murine adipocytes [Bradley et al. 2005].

PEPTIDES WITH SENSORY PROPERTIES

Until recently, according to different textbooks, human beings could distinguish four tastes: sweet, bitter, sour and salty. At the beginning of the 20th century Japanese identified a fifth taste called umami (taste impression corresponding to monosodium glutamate – MSG) [Lindemann 2000]. Recent studies confirm that there is another perception of dietary fat in the oral cavity. Results obtained by Hiraoka et al. [2003] suggest that long chain fatty acids trigger chemical reception in the oral cavity, and the length of the fatty acid chain and the presence or absence of carboxylate groups are related to recognition of fat. Relatively short oligopeptides derived mainly from the protein hydrolysis play the important role in the featuring the food sensory properties. There was a research in the field of peptides structure and their taste. Many models were proposed to explain the relation between the taste impression and the presence of specific amino acids, their location in the polypeptide chain, as well as their conformation. For example Kamei et al. [1992] determined the complete sequence of the polypeptide responsible for sweet taste. The peptide was gurmarin and it was derived from the leaves of *Gymnema sylvestre* obtained with *Staphylococcus aureus* V8 protease, pyroglutamyl aminopeptidase, and lysyl endopeptidase. Gurmarin consists of 35 amino acid residues with an amino-terminal pyroglutamyl residue and has the molecular weight of 4.209.

In case of the bitter taste it was concluded that the bitterness is the result of the presence of hydrophobic and basic amino acids in the peptide structure. Fragment of beta--casein [193-209] was isolated and detected confirmed for its bitterness in cheeses [Singh et al. 2005]. Basic and hydrophobic amino acids are also characteristic for the sour taste and umami. According to Lioe et al. [2006] free Glu, in the presence of sodium salt, as well as free Asp and several sweet-taste eliciting free amino acids were considered to be the main contributors to the umami taste of the soy sauces. This study of Japanese soy sauces gives a clear explanation of the frequently questioned peptide contribution to the taste of savoury food product.

The role of peptides with sensory properties is not limited only to the featuring the basic tastes. Dipeptides such as GL, PE or VE improve the taste of food products due to their buffer properties. Addition of Glu oligomers to the fruit or vegetable juices disguises their bitterness. Peptides can also be the precursors of taste and flavour components of the natural and processed food. Short peptides enzymatically released during the fermentation processes of bread, cocoa and peanuts initialize the formation of many heterocyclic, aromatic components in the baking or roasting [Dziuba 1997]. Park et al. [2002] fractionated some high-molecular-weight peptides (rich in nitrogen) from a Vietnamese fish sauce *Nuoc mam*. The large amounts of peptides produced during the long-term fermentation of fish sauce were responsible for the complicated taste of the sauce. 17 peptides (di-, tri- and tetra-peptides) any one of bitter, sour, umami taste, or practically no taste in the absence of salt. In the presence of 0.3% NaCl, almost all of fractionated peptides showed sweet and umami tastes. Park et al. [2002] found also other peptides in the fish sauce contributing to its taste. White wine was the subject of research on taste peptides. Peptides were fractionated by gel filtration and then compared to synthetic peptides (Ile-Arg, Ile-Val, Phe-Lys, Tyr-Lys, Val-Ile, Lys-Met-Asn, Phe-Arg-Arg, and Ser-Lys-Thr-Ser-Pro-Tyr) in terms of sensory tests. Three tastes: bitter, sour, and umami were recognized [Desportes et al. 2001].

PEPTIDES IMPROVING THE NUTRITIONAL VALUE OF FOODS

Since 1980s the production of protein hydrolysate preparations with the specific taste profile has been developed. These preparations are frequently used as the source of protein substances in different kind of dietetic, nutritional, and medicinal specimen. They can be applied in:

- food enrichment, especially fruit beverages
- diets composed for elderly people with the deficiency of the stomach juice secretion
- diets for sportsmen – as the food being the source of available nitrogen provided as peptides and amino acids
- specially composed diets for patients with the metabolic problems and digestive tract diseases such as: chronic pancreatitis, syndrome of loop intestine
- preparations necessary in parenteral and enteral feeding
- food formulae for children and infants with the allergy for bovine milk proteins [Świderski and Waszkiewicz-Robak 2000].

Di- and tripeptides are absorbed in the digestive tract faster and more efficiently than free amino acids, peptides rich in glutamic acid, methionine are the important components of the supplemementing food for the patients with the special nutritional requirements.

Short peptides are also used as the additives to some of the food products which are poor in individual necessary amino acids. E.g. peptide γ-EK is a good source of lysine and is used to the wheat gluten (wheat flour) enrichment in bread production. Other oligopeptides are applied in composing of specific diets especially where the conventional additives cannot be used because of intolerance of specific amino acids. The typical example are the formulae with no peptides containing phenylalanine for patients suffering from the phenylketonuria [Dziuba 1997]. Casein-derived phosphorylated peptides (CPPs) enhanced a mineral uptake due to the formation of soluble organophosphate salts. Because CPPSs have the ability to bind and solubilize minerals they can be the valuable agents in the prevention of osteoporosis, dental caries, hypertension and anemia. Many of dental care products that contain CPPS are available on the market [Haque and Chand 2006]. According to Hansen and co-workers [1996] preformed CPPs might be useful as the components of baby foods and non-dairy products. Addition of casein-derived phosphopeptides to soy formulae or cereal – based infant diets may contribute to the more efficient zinc bioavailability It is very important from nutritional point of view, especially that inadequate zinc ingestion leads to acrodermatitis enteropathica, diarrhea, retarded growth, exposure to infections and hypogonadism [Miquel and Farré 2007].

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BIAŁKA JAKO ŹRÓDŁO FIZJOLOGICZNIE I FUNKCJONALNIE AKTYWNYCH PEPTYDÓW

Streszczenie. Rynek napojów i żywności funkcjonalnej rozwija się dynamicznie. Aktywność biologiczna wielu składników naturalnie występujących w żywności jest przedmiotem zainteresowania ośrodków naukowych i przemysłowych. Zmiany strukturalne i chemiczne zachodzące podczas produkcji żywności prowadzą do uwalniania bioaktywnych peptydów. Wielofunkcyjna aktywność peptydów wynika z ich struktury oraz innych czynników takich, jak hydrofobowość, ładunek, zdolność wiązania mikroelementów. W artykule skoncentrowano się na peptydach wykazujących aktywności fizjologiczne i funkcjonalne, np. przeciwkrzepliwą, antyoksydacyjną, antybakteryjną i przeciwgrzybiczą, poprawiającą właściwości sensoryczne oraz wartość odżywczą żywności.

Słowa kluczowe: bioaktywne peptydy (biopeptydy), białka, żywność funkcjonalna

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