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Mini Review

Antihypertensive Peptides in Dairy Products

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Abstract

Dairy products are a fundamental source of protein. Also, they are popular foods for the intake of bioactive peptides with their sensory properties and high consumption. Among various bioactivities, antihypertensive activity has special importance due to high blood pressure, which has become a growing health problem in recent years. Milk proteins are the main precursors for ACE inhibitor peptides. The antihypertensive effect of a few bioactive peptides found in dairy products has been confirmed in vivo, and a few commercial products have shown to reduce blood pressure. This review discusses the studies about the antihypertensive specifically ACE inhibitor peptides found in milk and dairy products as an essential source of bioactive peptides.

Keywords: Bioactive Peptides; Milk; Dairy Products; ACE Inhibitor; Antihypertensive

Introduction

Milk and dairy products are rich in protein content, and main proteins in milk casein and whey proteins are the principle bioactive peptide precursors [1]. Although there are numerous studies on bioactive peptides, the first discoveries of bioactive peptides from foods are dairy products. These bioactive peptides have different functions such as antihypertensive, opioid, immune-modulatory, antimicrobial, and antioxidant [2-5]. Hypertension is a condition in which the blood vessels have persistently raised pressure [6]. It affects approximately 30% of the adult population worldwide [7]. It is a prominent risk factor for cardiovascular diseases such as coronary heart disease, peripheral artery disease, and stroke. Even though it is a controllable disease high prevalence, and serious consequences make hypertension an important comprehensive health threat [7]. ACE (peptidyldipeptide hydrolase, EC 3.4.15.1) is an exopeptidase which splits various peptides from C-terminal and forms dipeptides. ACE performs a critical role in regulating the blood pressure by the renin-angiotensin and bradykinin pathways. Angiotensin I is a decapeptide and inactive in its intact form. ACE catalyzes hydrolyzation of angiotensin I to the potent vasoconstrictor octapeptide angiotensin II [8]. Bradykinin, a vasodilator, is involved in the blood pressure system. ACE also controls the blood pressure by degrading bradykinin. Thus, inhibition of ACE results in an antihypertensive effect. Consequently, synthetic ACE inhibitors such as captopril and enalapril, are used in the treatment of hypertension and other related heart diseases [9]. However, they can cause adverse effects such as hypotension, cough, altered taste, rash and angioedema [10]. Bioactive peptides are natural and healthier alternatives to synthetic ACE inhibitors without side effects [11]. Although there are many different protein sources of ACE inhibitor peptides, milk proteins are accepted as the primary sources [12]. Chemical structures of peptides are important for binding to the catalytic sites of ACE [13,14]. The presence of aromatic or branched hydrophobic structures in the tripeptide structure at the carbon end of the peptide is necessary for binding [13,15]. Several functional dairy products are present in the market comprising antihypertensive peptides. Calpis sour milk in Japan (Calpis Co Ltd, Tokyo, Japan) cultured via Saccharomyces cerevisiae and Lactobacillus helveticus poses two potent ACE inhibitory peptides, Val-Pro-Pro and Ile-Pro-Pro [15]. These two peptides are also present in calcium-enriched fermented milk drink in Finland [16]. In short- and long-term human studies have shown that IPP and VPP peptides decrease blood pressure [4]. BioZate contains β-lactoglobulin fragments as functional bioactive peptides [16].

This paper will review studies on antihypertensive especially, ACE inhibitor peptides and their production in dairy products.

Factors Affecting Occurrence of Bioactive Peptides in Dairy Products

The bioactive peptide profile of a dairy product is tightly dependent on processes used such as thermal processes, homogenization, pressure applications, coagulation of milk, fermentation, and ripening [17]. Thermal processes are essential in the production of almost all dairy products. Reactions that occurred during thermal processes can affect the structure of proteins and the bioactive peptide content of the product [17,18]. Thermal processes affect activities of natural enzymes found in milk, thus affect the peptide profile of the last product. Caseins are hydrolyzed through the action of enzymes from different sources such as casein residue coagulants, natural milk enzymes, starter culture enzymes, enzymes of seconder cultures and non-starter lactic acid bacteria [5].

ACE Inhibitor Peptides Naturally Found in Milk and Dairy Products

In general, dairy products, in particular, fermented dairy products, are the most popular foods for the intake of bioactive peptides with their sensory properties and high levels of consumption favored by consumers [1]. Some of these studies summarized in Table 1. Among the dairy products, ripened cheeses contain numerous peptides, affecting the properties of the final product such as taste, odor, and texture due to the variety and complexity of the production methods. ACE inhibitor peptides in Spanish cheeses (Cabrales, Idiazábal, Roncal, Manchego, Mahón and goat's milk) are identified [14]. In this study, researchers confirmed ACE inhibition effect of 8 synthetic peptides (VRGP, PFP, QP, DKIHP, PKHP, FP, PP, and DKIHPF). Since proteolysis and peptide formation continue during cheese ripening, the ACE inhibitor effect may alter during the cheese maturation period. Further proteolysis during ripening may cause hydrolyzation of bioactive peptides and inactivation of them. Gomez-Ruiz et al. [19] determined the ACE-inhibitor peptides in Manchego cheese. The antihypertensive activity reached the maximum level after eight months of maturation and decreased again after twelve months of maturation. Likewise, Gouda ripened for 8 months decreased more strongly the blood pressure of spontaneously hypertensive rats than 24-month-old Gouda, although they have a similar ACE inhibitor activity *in vitro* [3]. In view of composition rich in proteins, cheese whey can be considered as a valuable source of bioactive proteins [20]. Alongside studies on bioactivities of cheese varieties some researchers identified ACE inhibitor peptides (FVAPFPE, NLHLPLPLLQ, FVAPFPEVFG, NLHLPLPLQ originated from αs1-casein, β-casein, αs1-casein, β-casein, respectively) in a liquid waste deriving from Ricotta cheese production [21]. Probiotic fermented milk beverage from milk of different species also have antihypertensive activity [22,23]. Caseins are the best precursors for the production of angiotensin I am converting enzyme (ACE) [de Gobba et al. 2014].

Table 1: Antihypertensive peptides found in dairy products.

Dairy Product	Peptide Sequence and Precursor Protein	Bioactivity	Reference
Gouda, Emmental, Blue, Camembert, Havarti Cheese	RPKHPIKHQ αs1-casein (f 1–9), RPKHPIKHQGLPQ αs1-casein (f 1–13), YPFPGPIPN β-casein (f 60–68) MPFPKYPVQPF β-casein (f 109–119)	ACE inhibitor activity in vivo and in *vitro*	3
Commercial caprine kefir	PYVRYL and LVYPFTGPIPN β-casein	ACE inhibitor effect of peptides similar after simulated gastrointestinal digestion	23
Cabrales, Idiazábal, Roncal, Manchego, Mahónand goat's milk cheese (Spain)	VRGP, PFP, QP, DKIHP, PKHP, FP, PP, DKIHPF	ACE inhibitor activity concentrated in the permeate of molecular weight <1000 kDa	14
39 Swiss cheeses and matured Gouda, Allgauer Limburger, Munster, Reblochon, Gorgonzola, Roquefort, Manchengo, Feta Cheese	IPP and VPP	The quantities of ACE inhibitor peptides IPP andVPP is higher in ripened cheeses produced from raw milk	4
Different types of ovine cheeses from Southern Brazil and Uruguay	KEMPFPKYPVE β-casein f(122–132)	ACE inhibitor	24
Scotta (liquid waste from Ricotta cheese production)	FVAPFPEVFG αs1-casein (f 24-33), FFVAPFPEVFGK αs1-casein (f 23-34), YQEPVLGPVRGPFPIIVβ-casein (f 193-209)	Known ACE inhibitor peptides identified by using peptidomics approach	21
Kefir	EMPFPKYPVEPF, FVAPFPEVFG, KVGINYWLAHK, VAPFPEVFGK	Antihypertensive effect in *vivo*	22

Chiapas (Mexico)	-	Antihypertensive and ACE inhibitor effect	25
Buffalo cheese	YQEPVLGPαVRGPFP and VLNENLLRF β-casein, AYFYPEL αs1-casein (f86-98)	ACE inhibitor	26

Production of ACE Inhibitor Peptides from Milk Proteins

Basically, there are two approaches to generate ACE-inhibitor peptides from milk proteins. One approach is to utilize the proteolytic enzymes of lactic acid bacteria in fermented dairy products. The other approach is to hydrolyze milk proteins in vitro by one protease or a combination of various proteases or peptidases.

Production of ACE Inhibitor Peptides with Enzymes

Most of the researches about the production of bioactive peptides with enzymes have utilized digestive enzymes, and commercial dry cheese whey, purified whey proteins or microfiltration permeates as a substrate [27]. Besides, other digestive enzymes from different sources and various milk protein preparations have been studied to generate antihypertensive peptides (Table 2). Different bioactive peptides are produced from caseins of milk from different species, which implicates the sequence and conformation of the caseins affect the bioactive peptide yield [28]. Minervini et al. [28] used a proteinase from *Lactobacillus helveticus* PR4 to obtain ACE inhibitor and antimicrobial peptides from casein of milk from six different species (bovine, sheep, goat, pig, buffalo, and human). Abdel-Hamid et al. [29] identified new peptide sequences (FPGPIPK, IPPK, QPPQ) showing ACE inhibitor activity generated from buffalos' skim milk hydrolyzed with papain.

Table 2: Using proteases to generate ACE inhibitor peptides from milk proteins.

Protease	Substrate	Hydrolysis and/or Fermentation Conditions	Peptides	Reference
Lactobacillus helveticus PR4 Proteinase	Bovine, sheep, goat, pig, buffalo, and human milk	pH 4.6, 35°C, 10 min	Bovine LVYPFPGPIPNSLPQNIPP, LVYPFPGPIPNSLPQNIPP, LVYPFPGPIPNSLPQNIPP β-casein FVAPFPEVFGKEKVNELSKDIGSE, FVAPFPEVFGKEKVNELSKDIGSE, LGTQYTDAPSFSDIPNPIGSENSEK, FVAPFPEVFGKEKVNELSKDIGSE αS1-casein Sheep RPKHPI, RPKH, HPIKH αS1-casein TVDQ and HQK αS2-casein Goat LVYPFPGP β-casein TVDQHQ αs2-casein Buffalo LVYPFPGPI β-casein Human QPQ, VPQ, IPQ β-casein	28
Protease from Bacillus sp. P7	Sheep cheese whey	pH 8.0, temperature 45°C, 0.5,1,2,3,4,5,6 hour	LAFNPTQLEGQCHV (β-lactoglobulin, f 149-162)	20
Papain, pepsin, and trypsin	Buffalo milk	pH 6, 8, 2 for papain, trypsin, and pepsin, respectively, temperature 37°Cs, 4 hour	IPPK (κ-casein), IVPN and APFPE (αs1-casein), QPPQ, DMPIQ, LPVPQ, FPGPIPK, YPVEPFT, GPFPIIV, YPFPGPIPK (β-casein)	29
L. helveticus strain 881315 and Flavourzyme®	Skimmed milk	37 °C, 12 h	-	1
Trypsin	Cheese whey	pH 7.5-9.0, temperature 37°C-50°C, 1 hour	-	27

ACE inhibitor and antioxidant capacity of 6 synthetic peptides (WY, WYS, WYSL, WYSLA, WYSLAM, WYSLAMA) deriving from β-lactoglobulin were evaluated [30]. Dipeptide WY β-lactoglobulin fragment f (19-20) showed potent ACE inhibitor activity. ACE inhibitor activity depends on the amino acid sequence in the C-terminus of the peptide, and the amino acid Ser at the C –terminus showed a potential decreasing effect on ACE inhibitor activity. Sheep cheese whey hydrolyzed using proteinase from *Bacillus sp.* P7 to generate ACE inhibitor peptides [20]. ACE inhibitor activity was dependent on hydrolysis time. In a recent work, trypsin from bovine pancreas employed to hydrolyze whey from the production of panela cheese to generate bioactive peptides [27]. The researchers found a significant correlation between antioxidant and ACE inhibitor activity.

Production of ACE Inhibitor Peptides through Fermentation

In the dairy industry mainly highly proteolytic starter cultures are preferred. Bioactive peptides can be generated by the starter culture or non-starter bacteria added as an adjunct culture (Table 3).

Table 3: Obtaining ACE inhibitor peptides by using adjunct culture and fermentation.

Microorganism	Dairy Product	Peptides	Reference
Bifidobacterium longum 1941, Lactobacillus casei 279, Lactobacillus acidophilus 4962, Bifidobacterium animalis subsp. lactis LAFTI® B94, *L.casei*LAFTI®L26, L. *acidophilus* LAFTI® L10	Cheddar	ARHPHPH κ-casein (f 96-102), RPKHPIKHQ αs1-casein (f 1-9), RPKHPIK αs1-casein (f 1-7), RPKHPI αs1-casein (f 1-6), FVAPFPEVF αs1-casein (f 24-32), YQEPVLGPVRGPFPIIV β-casein (f 193-209)	32

L. casei 279, *L. casei* LAFTI®L26	Cheddar	RPKHPIKHQ αs1-casein (f 1–9), RPKHPIK αs1-casein (f 1–7), RPKHPI αs1-casein (f 1–6), DKIHPF β-casein (f 47–52), FVAPFPEVF αs1-casein (f 24–32), KKYKVPQLE αs1-casein (f 102–110), YQEPVLGPVRGPFPIIV β-casein (f 193–209)	13
Lactococcus. lactis ssp. *lactis, Enterobacter faecium*, *L. casei*, and 1:1 mixtures of *Lc. lactis* ssp. *lactis–L. casei* and *Lc. Lactis* ssp. *lactis–E*. faecium	Fresco cheese (Mexico)	YQEPVLGPVRGPFPIIV, YQEPVLGPVRGFP, YQEPVLGPVRGPFPIIV, YQEPVLGPVRGPFPI (β-casein), FVAPFPEVFGK, EVLNENLLRF, RPKHPIKHQGLPQEV, RPKHPIKHQGLPQEVLNENLLR, FVAPFPEVFGK, EVLNENLLRF (αs1-casein)	33
Kluyveromyces marxianus	Fermented milk	VLSRYP (κ-casein f31-36) and LRFF (αs1-casein f21-24)	12
Set of *L. casei*, *Lactobacillus rhamnosus Lactobacillus paracasei* non-starter strains	Fermented milk	IPP and VPP (quantification)	31
L. casei PRA205 and *L. rhamnosus* PRA331	Yoghurt	IPP and VPP (quantification)	34
L. helveticus LH-B02	Prato cheese	GQPVLGPVRGPFPII β-casein (f193-206) and GQPVLGPVRGPFPIIV β-casein (b194-209)	5
L. acidophilus 2499 *L. rhamnosus* 489, *Lactobacillus delbrueckii* 490, *L. casei* 2639	Dutch type cheese	-	35

Ahtesh et al. [1] produced a new fermented functional dairy product with combination of *L. helveticus* and Flavourzyme® using a bioreactor. They have achieved to obtain an acceptable product with high ACE inhibitor activity. *L. helveticus* is a highly proteolytic bacterium, thus, there are many studies on both fermentation with this bacterium and hydrolysis with proteinases of this bacterium [22,28].

Similarly, researchers utilized *L. helveticus* LH-B02 strain in order to improve the ACE inhibitor activity in Prato cheese [5]. They observed that levels of ACE inhibitor peptides β-casein (f193-206) and β-casein (f194-209) increased while relative intensity of αS1-casein (f1-9) reduced. Gonzalez Gonzalez et al. [25] isolated highly proteolytic lactic acid bacteria from Chiapas cheese and evaluated tendency of releasing bioactive peptides of selected strains. They employed four selected strains for fermentation of milk and observed that most proteolytic strain has lowest ACE inhibitor activity, presumably according to further breakdown peptides to inactive amino acids. Solieri et al. [31], fermented bovine milk with non-starter lactic acid bacteria (*Lactobacillus casei, Lactobacillus paracasei* and *Lactobacillus rhamnosu*s strains) to evaluate their potential to produce fermented milk with enhanced ACE inhibitor activity [32-35]. They concluded that the strains used in the study especially *L.casei* PRA205 can produce high amounts of VPP and IPP peptides.

Conclusion

In recent years, the tendency to consume functional health-promoting foods has increased the interest in bioactive peptides. There are numerous studies on bioactive peptides in foods in the literature. Dairy products, which are an indispensable part of a healthy and balanced diet, are considered as ideal sources for bioactive peptides and natural alternatives to therapeutic drugs due to their high protein content and technological processes in production. However, the mechanism of action of bioactive peptides is not fully described. Molecular studies employing new technologic enhancements and peptidomics approach are necessary to understand the mechanisms of antihypertensive peptides as well as to design functional products.

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