Chapter 11
Bioactive Compounds in Meat

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Introduction

Since health-conscious consumers have made functional foods the leading trends in the food industry, efforts have been taken in many countries to develop new functional foods and to establish regulations for functional foods (Arihara, 2004; Dentali, 2002; Eve, 2000; Hutt, 2000). For example, in 1991, the concept of foods for specified health use (FOSHU) was established by the Japanese Ministry of Health and Welfare (Arihara, 2004, 2006b). FOSHU are foods that, based on the knowledge of the relationship between foods or food components and health, are expected to have certain health benefits and have been licensed to bear the label claiming that a person using them may expect to obtain that health use through the consumption of these foods. As of June 2008, 786 FOSHU products have been approved in Japan. Also, in the United States and European countries, markets for functional foods have been expanding rapidly.

Chemicals found as natural components of foods that have been determined to be beneficial to the human body in preventing or treating one or more diseases or improving physiological performance are known as nutraceuticals (Wildman, 2000a, 2000b). Numerous food components with such physiological functions have been isolated and characterized (Hasler, 1998). Many vegetables, for example, have been shown to contain a variety of biologically active phytochemicals (Lindsay, 2000). There has been an accumulation of scientific findings regarding the roles of such components in the prevention of diseases. Rapid progress has been made in the development of functional foods based on the results of studies on food components that have positive health benefits other than the normal nutritional benefits (Arihara, 2004; Heasman & Mellentin, 2001).

In addition to various nutraceutical compounds found in vegetables (Lindsay, 2000) and milk (Chandan, 2007; Chandan & Shah, 2007), several attractive meat-based bioactive substances have been studied for their physiological properties (Arihara, 2004, 2006b; Williams, 2007). Such substances include conjugated

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linoleic acid (CLA), carnosine, anserine, L-carnitine, glutathione, taurine, coenzyme Q10 and creatine. Utilizing or emphasizing these physiological activities originating from meat is one possible approach for designing healthier meat and meat products, including functional foods. The composition of animal products could be improved through manipulation of animal feed. Several studies have shown that the feeding conditions of animals affect the contents of bioactive components, such as CLA and L-carnitine, in animal products (Krajcovicova-Kudlackova, Simoncic, Bederova, Babinska, & Beder, 2000; Mir et al., 2004). Various aspects of product processing, such as modification of constituents and incorporation of ingredients, are also important for developing functional meat products. Such efforts could lead to the creation of differentiated meat and meat products.

This chapter provides a brief overview of the potential benefits of representative meat-based bioactive compounds (e.g., CLA, carnosine, L-carnitine) on human health. Along with these compounds, this chapter focuses on the properties of meat protein-derived bioactive peptides (e.g., antihypertensive peptides), which have a potential for the development of functional meat products.

Meat-Based Bioactive Compounds

In the food guide pyramid, meat is categorized as a protein food group along with poultry, fish, and eggs (Lachance & Fisher, 2005). Since meat contains an abundance of proteins with high biological value, regarded nutritional, meat is a fundamental source of essential amino acids. Meat is also an excellent source of some valuable minerals and vitamins (Biesalski, 2005; Mulvihill, 2004). Some of these nutrients are either not present or have inferior bioavailability in other foods. In addition to these basic nutrients, much attention has recently been paid to meat-based bioactive compounds, such as conjugated linoleic acid.

Minerals and Vitamins

Meat plays an important role in supplying iron, zinc, selenium, and B vitamins to the diet. The contributions of meat and meat products to total dietary intakes of selected micronutrients are: 14% iron, 30% zinc, 14% vitamin B2, 21% vitamin B6, 22% vitamin B12, 19% vitamin D, and 37% niacin (Mulvihill, 2004). Red meat is rich in iron (e.g., 2.1 mg iron per 100 g of fillet steak). A large proportion of iron in meat is haem, which is a high absorbable form of iron, and meat proteins enhance the absorption of iron. Also, zinc in meat is highly bioavailable. For a detailed information on minerals and vitamins in meat, refer to other articles (Biesalski, 2005; Higgs, 2000; Mulvihill, 2004).

Fat and Fatty Acids

Unfortunately, consumers often associate meat and meat products with a negative health image. The **regretable** image of meat **is** mainly **due to** the content of fat, saturated fatty acids, and cholesterol and their association with chronic diseases, such as cardiovascular diseases, some types of cancer, and obesity (Chan, 2004; Fernández-Ginés, Fernández-López, Sayas-Barberá, & Pérez-Alvarez, 2005; Ovesen, 2004a, 2004b; Valsta, Tapanainen, & Mannisto, 2005). Dietary fat should provide between 15 and 30% of **the** total diet energy. Less than 10% of calorie intake should be from saturated fatty acids (SFA), 6–10% and 10–15% of that should be from polyunsaturated fatty acids (PUFA) and from monounsaturated fatty acids (MUFA) respectively. Furthermore, less than 1% of that should be from trans fatty acids, and cholesterol intake should be limited to less than 300 mg per day.

Meat fat contains less than 50% SFA and up to 65–70% unsaturated fatty acids (Jiménez-Colmenero, 2007a). Various modifications, including reduced fatty acid levels, raised MUFA and PUFA levels, improved n-6:n-3 PUFA balances, and limited cholesterol contents, can be achieved by animal breeding and feeding, material formulation, and technological processing (Jiménez-Colmenero, Reig, & Toldrá, 2006). Also, numerous studies have demonstrated the possibility of changing the image of meat and meat products by the addition, elimination and reduction of fat and fatty acids (Jiménez-Colmenero, 2007b).

Conjugated Linoleic Acid

Conjugated linoleic acids (CLA) are a group of fatty acids found in meat and milk of ruminants (Gnadig, Xue, Berdeaux, Chardigny, & Sebedio, 2000; Nagao & Yanagita, 2005; Watkins & Yong, 2001). Since rumen bacteria convert linoleic acid to CLA by their isomerase, it is most abundant in the fat of ruminant animals. After its absorption in a ruminant animal, CLA is transported to the mammary tissue and muscles. For example, beef fat contains 3–8 mg of CLA per g of fat (Table 11.1). CLA, which was initially identified as an anti-carcinogenic compound in **the** extracts of grilled beef, is composed of a group of positional and geometric isomers of octadecadienoic acid.

The CLA content in meat is affected by several factors, such as breed, age and feed composition (Dhiman, Nam, & Ure, 2005). For example, products of grass-fed animals have 3–5 times more CLA than in products of animals fed **on** the typical diet of 50% hay and silage with 50% grain. Interestingly, the CLA content of foods is also increased by heating (cooking and processing). Also, lactic acid

Table 11.1 Contents of conjugated linoleic acid (CLA) in animal products

Product	CLA (mg per g of fat)
Beef	2.9–8.0
Pork	0.6
Chicken	0.9
Turkey	2.5
Bovine milk	5.4–7.0
Egg Yolk	0.6

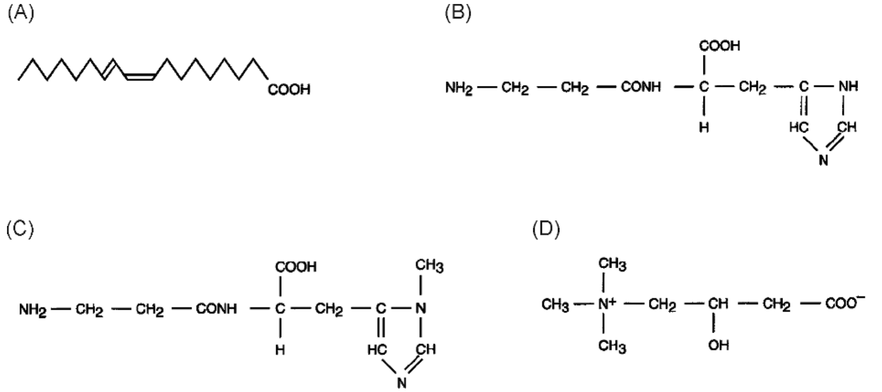

Fig. 11.1 Representative meat-based bioactive compounds (a) Conjugated Linoleic Acids (c9, t11-C18:2); (b) Carnosine; (c) Anserine; (d) L-Carnitine

bacteria promote the formation of CLA in fermented milk products (Alonso, Cuesta, & Gilliland, 2003; Coakley et al., 2003; Sieber, Collomb, Aeschlimann, Jelen, & Eyer, 2004; Xu, Boylston, & Glatz, 2005). Such conversion would be expected in fermented meat products. The most common CLA isomer found in beef is octadeca-*c*9, *t*11-dienoic acid (Fig. 11.1a). Since this fatty acid has **an** anti-carcinogenic activity, much interest has been shown in this compound. Recent epidemiological studies have suggested that high intakes of high-fat dairy foods and CLA may reduce the risk of colorectal cancer (Larsson, Bergkvist, & Wolk, 2005). In addition to its anti-carcinogenic property, CLA has anti-artheriosclerotic, antioxidative, and immunomodulative properties (Azain, 2003). CLA may also play a role in the control of obesity, reduction of the risk of diabetes and modulation of bone metabolism.

Histidyl Dipeptides

Consumption of antioxidant-rich foods, such as fruits and vegetables, has been shown to have a preventative effect on oxidative damage in the body (Lindsay, 2000). This beneficial action of food is attributed to neutralization and reduced release of free radicals by the antioxidant potency of various compounds (Langseth, 2000). Ascorbic acid, vitamin E, β-carotene and polyphenolic compounds are representative food-derived antioxidants. Such compounds may decrease the risk of many diseases, including cancer. Several endogenous antioxidants (e.g., tocopherols, ubiquinone, carotenoids, ascorbic acid, glutathione, lipoic acid, uric acid, spermine, carnosine, anserine) in meats have been studied (Decker, Livisay, & Zhou, 2000).

Both carnosine (β-alanyl-L-histidine; Fig. 11.1b) and anserine (N-β-alanyl-1-methyl-L-histidine; Fig. 11.1c) are antioxidative histidyl dipeptides and the most abundant antioxidatives in meats. The concentration of carnosine in meat ranges from 500 mg per kg of chicken thigh to 2700 mg per kg of pork shoulder. On the other hand, anserine is especially abundant in chicken muscle. Their antioxidant activities may result from their ability to chelate transition metals such as copper (Brown, 1981) These antioxidative peptides have been reported to play a role in wound healing, recovery from fatigue and prevention of diseases related to stress. A recent study demonstrated the bioavailability of carnosine by determining its concentration in human plasma after ingestion of beef (Park, Volpe, & Decker, 2005). Increasing attention to these meat-based bioactive compounds has resulted in the development of a new sensitive procedure for determining these compounds including carnosine (Mora, Sentandreu, & Toldrá, 2007).

L-Carnitine

L-Carnitine, β-hydroxy-gamma-trimethyl amino butyric acid (Fig. 11.1d), is detected in **the** skeletal muscle of various animals (Shimada et al., 2005). L-Carnitine is especially abundant in beef (e.g., 1300 mg per kg of the thigh). It assists the human body in producing energy and in lowering **the** levels of cholesterol. Also, it helps the body to absorb calcium to improve skeletal strength and chromium picolinate to help build lean muscle mass. A recent study demonstrated that L-carnitine blocked apotosis and prevented skeletal muscle myopathy in heart failure (Vescovo et al., 2002). A drink product containing L-carnitine, which is marketed in the United States, is advertised as having several beneficial effects, such as maintenance of stamina and fast recovery from fatigue. Also, a product containing **a good amout of** L-carnitine and carnosine, which is used as a functional food ingredient, has been marketed in Japan. This product is made from a by-product of corned beef.

Other Bioactive Components

Glutahione is an important antioxidative compound providing cellular defense against toxicological and pathological processes. Red meat is a good source of glutathione (12–26 mg per 100 g of beef; Jones et al., 1992). Taurine is a conditionally essential amino acid during lactation and at times of immune challenge (Bouckenooghe, Remacle, & Reusens, 2006). Also, taurine may protect our body from oxidative stress. Meat is the most excellent dietary source of taurine (77 mg per 100 g of beef; Purchas, Rutherfurd, Pearce, Vather, & Wilkinson, 2004). Coenzyme Q10 (ubiquinone) shows antioxidative activity and its content in beef is 2 mg per 100 g (Purchas & Busboom, 2005). Creatine and creatine phosphate have a critical role in muscle energy metabolism. Beef contains 350 mg of creatine per 100 g (Purchas & Busboom, 2005). Other components such as choline, balenine, creatinine, lipoic acid, putrescine, spermidine, and spermine should also be listed as meat-based bioactive compounds.

Meat Protein-Derived Bioactive Peptides

In addition to **the** meat-based bioactive compounds described above, meat protein-derived peptides are another group of promising bioactive components of meat (Arihara, 2004, 2006a, 2006b). Several bioactive peptides from hydrolyzates of muscle proteins have been found. Although the activities of these peptides in the sequences of **the** parent proteins are latent, they are released by proteolytic enzymes. In this aspect, meat proteins have possible bioactivities beyond a nutritional source of amino acids alone.

Bioactive Peptides Derived from Food Proteins

Information on bioactive peptides generated from meat proteins is still limited. However, various physiologically functional peptides **have** been found from enzymatic hydrolyzates of food proteins, such as milk and soy proteins (Arihara, 2006a; Korhonen & Pihlanto, 2007; Meisel, 1998; Mine & Shahidi, 2005; Pihlanto & Korhonen, 2003). Thus, bioactive peptides generated from food proteins are covered briefly at the beginning. Bioactive peptides from food proteins were first reported by Mellander (1950). He described the effect of casein-derived phospho-related peptides on vitamin D-independent bone calcification of rachitic infants. Since then, there have been numerous studies on bioactive peptides generated from food proteins.

Angiotensin I-Converting Enzyme Inhibitory Peptides

Angiotensin I-converting enzyme (ACE) inhibitory peptides generated from food proteins have been studied most extensively (Meisel, Walsh, Murry, & FitzGerald, 2005; Vermeirssen, Camp, & Verstraete, 2004). ACE inhibitory peptides have been shown to have antihypertensive effects and have been utilized for pharmaceuticals and physiologically functional foods. ACE plays an important physiological role in the regulation of blood pressure (Fig. 11.2). ACE is a dipeptidyl carboxypeptidase that converts an inactive form of **the** decapeptide, angiotensin I, to a potent vasoconstrictor, octapeptide angiotensin II, and inactivates bradykinin, which has a depressor action (Li, Le, Shi, & Shrestha, 2004). Therefore, by inhibiting the catalytic action of ACE, the elevation of blood pressure can be suppressed.

ACE inhibitory peptides from food protein were first identified in the hydrolyzate of gelatin by Oshima, Shimabukuro, and Nagasawa (1979). Since then, ACE inhibitory peptides have been found in the hydrolyzates of many proteins from milk, fish, meat, eggs, soybean, corn, wheat, seaweed, and others (Arihara, 2006a; Vermeirssen et al., 2004). Some of these peptides have been reported to show antihypertensive effects in spontaneously hypertensive rats (SHR) by oral administration. ACE inhibitory peptides isolated from meat proteins are described later.

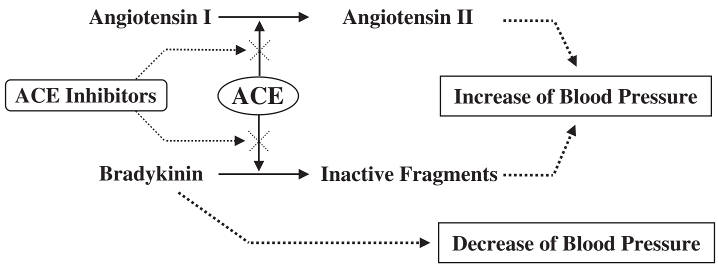

Fig. 11.2 Blood pressure regulation by Angiotensin I-Converting Enzyme (ACE)

Other Bioactive Peptides Derived from Food Proteins

In addition to ACE inhibitory (antihypertensive) peptides, it has been found that various bioactive peptides, such as opioid, immuno-modulating, antimicrobial, prebiotic, mineral-binding, antithrombotic, hypocholesterolaemic, and antioxidative peptides, are generated from food proteins (Arihara, 2006a; Korhonen & Pihlanto, 2007; Pihlanto & Korhonen, 2003). Since milk proteins are the main source of a range of these bioactive peptides (Gobbetti, Minervini, & Rizzello, 2007; Meisel, 1998; Silva & Malcata, 2005), representative examples of bioactive peptides generated from milk proteins are summarized in Table 11.2.

Opioid peptides have an affinity for an opioid receptor and have effect on the nerve system (Guesdon, Pichon, & Tomé, 2005). Immuno-modulating peptides stimulate **the** proliferation of lymphocytes and phagocytic activities of macrophages (Pihlanto & Korhonen, 2003). Antimicrobial peptides inhibit the growth of pathogenic bacteria (Chan & Li-Chan, 2005). Mineral-binding peptides, such as caseino-phosphopeptides (CPP) generated from milk proteins, function as carriers for minerals, including calcium (Bougle & Bouhallab, 2005). CPP also anti-carcinogenic activity (Cross, Huq, & Reynolds, 2005). Antithrombotic peptides inhibit fibrinogen binding to a specific

Table 11.2 Examples of milk protein-derived bioactive peptides

Bioactivity	Sequence[a]	Preparation	Reference
ACE-inhibitory Antihypertensive	IPP, VPP	Fermentation	Nakamura et al., 1995
Opioid agonistic	YIPIQYVLSR	Trypsin	Chiba, H., Tani, F., & Yoshikawa, 1989
Immunomodulating	VGPIPY	Trypsin-Chymotrypsin	Fiat et al., 1993
Antimicrobial	FVAPFPEVFG	Trypsin	Rizzello et al., 2004
Mineral-binding	Casein phosphopeptides	Trypsin	Gagnaire et al., 1996
Anticariogenic	Casein phosphopeptides	Trypsin	Cross et al., 2005
Antithrombotic	MAIPPKKNDQDK	Synthesis	Jollès et al., 1986
Hypocholesteromic	IIAEK	Trypsin	Nagaoka 2005
Antioxidative	YFYPEL	Pepsin	Suetsuna, Ukeda, & Ochi, 2000
Prebiotic	CAVGGCIAL	Synthesis	Lieple et al., 2002

[a] The one-letter amino acid codes were used.

receptor region on the platelet surface (Jollès et al., 1986). Hypocholesteromic peptides isolated from the hydrolyzate of milk β-lactoglobulin have a strong effect on serum cholesterol level (Nagaoka, 2005). Antioxidative and prebiotic peptides are described as meat protein-derived bioactive peptides later in this article.

Peptide Generation from Meat Proteins

Since many bioactive sequences of food proteins are inactive within the parent proteins, food proteins have to be digested for liberating **the** bioactive peptides. Gastrointestinal proteolysis, aging, fermentation, and enzymatic treatment are the principal means for digestion of meat proteins to generate bioactivities (Fig. 11.3).

Gastrointestinal Proteolysis

Bioactive peptides are thought to be generated from food (meat) proteins during gastrointestinal digestion. Ingested proteins are attacked by various digestive enzymes, such as pepsin, trypsin, chymotrypsin, elastase and carboxypeptidase (Pihlanto & Korhonen, 2003). Digestive enzymes (i.e., pepsin, trypsin, and α-chymotrypsin) in the gastrointestinal tracts generated ACE inhibitory activity from porcine skeletal muscle proteins (Arihara, Nakashima, Mukai, Ishikawa, & Itoh, 2001). Also, ACE inhibitory peptides were generated from meat proteins, such as myosin, actin, tropomyosin, and troponin, by pancreatic protease treatment (Katayama, Fuchu, et al., 2003). Since denatured proteins are particularly liable to attack by proteolytic enzymes, peptides would be easily generated from cooked meat and meat products.

Aging of Meats

After slaughter of a domestic animal, the skeletal muscle is converted to meat via aging. During aging or storage, meat proteins are hydrolyzed by muscle endogenous proteases, such as calpains and cathepsins (Etherington, 1984; Koohmaraie, 1994).

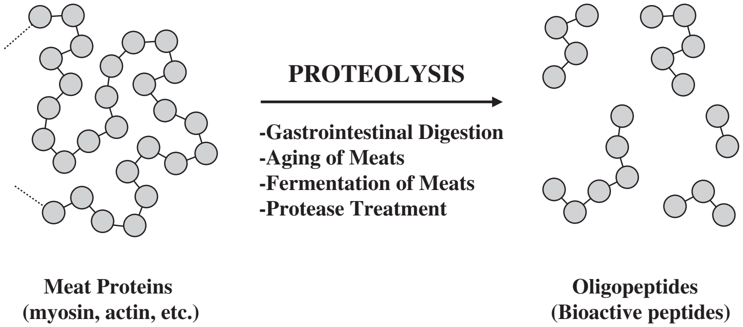

Fig. 11.3 Generation of bioactive peptides from meat proteins

Thus, the content of peptides in meat increases during post-mortem aging. Such changes in the levels of oligopeptides occur during storage of beef, pork, and chicken (Nishimura, Rhue, Okitani & Kato, 1988). For example, the content of peptide in pork increased from 2.40 mg at day 1 to 3.05 mg per g meat at day 6. Also, Mikami, Nagao, Sekikawa, and Miura (1995) reported that peptide contents of beef varied widely, ranging from 0.69 to 1.44 mg and from 2.64 to 4.65 mg per g meat 2 and 21 days after slaughter, respectively.

It is well recognized that enzymatic hydrolysis of meat proteins during aging or storage contributes to improvement of sensory properties of meat, such as texture, taste, and flavor. However, there has been no report about the generation of bioactive peptides in meat during post-mortem aging. Our preliminary study showed an increase in ACE inhibitory activity of beef during storage (unpublished data). Further studies are expected to reveal the novel meaning of meat aging.

Fermentation of Meats

Components generated from meat proteins by proteolytic reactions during fermentation of raw sausages and dry-cured hams are important for the development of sensory characteristics of fermented meat products (Hammes, Haller, & Gänzle, 2003; Toldrá, 2004; Toldrá & Flores, 1998). The content of peptides and amino acids of fermented sausages reaches about 1% dry matter of products during fermentation (Dainty & Blom, 1995). Meat proteins are mainly degraded into peptides by endogenous enzymes (cathepsin B, D, H, and L) during the fermentation process. Although microbial proteolytic enzymes are involved in meat fermentation, most bacteria such as lactic acid bacteria grown in fermented meat products have only weak proteolytic activity (Hierro, de la Hoz, & Ordonez, 1999). However, lactic acid bacteria contribute to degradation of meat proteins by causing a decrease in pH, which increases the activity of muscle proteolytic enzymes (Kato et al., 1994).

There has been no report on the generation of bioactive peptides from meat proteins in fermented meat products. However, we measured the ACE inhibitory activities of extracts of several fermented meat products (i.e., raw sausages and dry-cured ham) and found that activity levels of all extracts were higher than those of the extracts obtained from non-fermented pork products (unpublished data). Also, ACE inhibitory and antihypertensive activities were experimentally generated from porcine skeletal muscle proteins by lactic acid bacteria (Arihara, Nakashima, Ishikawa, & Itoh, 2004). Sentandreu et al. (2003) identified several small peptides in dry-cured ham. Such small peptides generated from meat proteins could have some bioactivities in fermented meat products. Sentandreu and Toldrá (2007a, 2007b) suggested that the proteolytic action of porcine muscle dipeptidyl peptidases during the ripening period of dry-cured ham could contribute to the generation of ACE inhibitory peptides.

Protease Treatment

In the food industry, many proteolytic enzymes are utilized for food processing, such as tenderization. Utilizing commercial proteases is an efficient method for releasing bioactive peptides from food proteins. Many bioactive peptides have been experimentally generated by commercial proteases (Korhonen & Pihlanto, 2003; Pihlanto & Korhonen, 2003). Proteases from animal, plant, and microbial origins have been used for the digestion of food proteins. In the meat industry, proteolytic enzymes have been used for meat tenderization (Dransfield & Etherington, 1981). The most commonly used enzymes for meat tenderization are the plant enzymes papain, bromelain, and ficin. In meat treated with enzymatic tenderization, peptides having bioactivities could be generated. On the other hand, effects of commercial proteases on protein breakdown and sensory characteristics of dry fermented sausages have been investigated (Bruna, Fernandez, Hierro, Ordonez, & de la Hoz, 2000). Such treatment would also generate bioactive peptides in meat products.

ACE Inhibitory Peptides from Meat Proteins

As stated above, the most extensively studied bioactive peptides derived from food proteins are ACE inhibitory peptides. Also, among the bioactive peptides derived from meat proteins, ACE inhibitory peptides have been studied extensively (Arihara, 2006a, 2006b; Vercruysse, Van Camp, & Smagghe, 2005). ACE inhibitory peptides generated from meat proteins are summarized in Table 11.3.

Table 11.3 ACE inhibitory peptides derived from meat proteins

Sequence[a]	Source	IC50[b] (μM)	SHR[c]	References
IKW	Chicken muscle	0.2	+	Fujita et al., 2000
LKA	Chicken muscle (creatine kinase)	8.5	nt	Fujita et al., 2000
LKP	Chicken muscle (aldolase)	0.3	+	Fujita et al., 2000
LAP	Chicken muscle	3.5	+	Fujita et al., 2000
VWI	Porcine muscle (actin)	1.1	+	Arihara et al., 2005
ITTNP	Porcine myosin	549.0	+	Arihara et al., 2001 Nakashima et al., 2002
MNPPK	Porcine myosin	945.5	+	Arihara et al., 2001 Nakashima et al., 2002 Fujita et al., 2000
FQKPKR	Chicken muscle (myosin)	14.0	nt	Jang & Lee, 2005
VLAQYK	Bovine muscle	23.2	+	Fujita et al., 2000
FKGRYYP	Chicken muscle (creatine kinase)	0.6	-	Arihara et al., 2004
VFPMNPPK	Fermented pork (myosin)	66.0	nt	Fujita et al., 2000
IVGRPRHQG	Chicken muscle (actin)	2.4	-	Katayama, Tomatsu et al., 2003
RMLGQTPTK	Porcine troponin C	34.0	nt	Katayama et al., 2004 Saiga, Okumura et al., 2003
GFXGTXGLXGF	Chicken muscle (collagen)	42.4	nt	

[a] The one-letter amino acid codes were used.
[b] The concentration of peptide needed to inhibit 50% of the ACE activity.
[c] Antihypertensive activities in spontaneously hypertensive rats (+, positive activity; -, no activity; nt, not tested).

Fujita, Yokoyama, & Yoshikawa (2000) isolated the ACE inhibitory peptides (Leu-Lys-Ala, Leu-Lys-Pro, Leu-Ala-Pro, Phe-Gln-Lys-Pro-Lys-Arg, Ile-Val-Gly-Arg-Arg-Arg-His-Gln-Gly, Phe-Lys-Gly-Arg-Tyr-Tyr-Pro, Ile-Lys-Trp) generated from chicken muscle proteins by thermolysin treatment. Arihara et al. (2001) reported ACE inhibitory peptides in hydrolyzates of porcine skeletal muscle proteins. Two ACE inhibitory peptides (Met-Asn-Pro-Pro-Lys and Ile-Thr-Thr-Asn-Pro), which are found in the sequence of the myosin heavy chain, have been identified in the thermolysin digest of porcine muscle proteins. These peptides showed antihypertensive activity when administered orally to SHR (Nakashima, Arihara, Sasaki, Ishikawa, & Itoh, 2002). Katayama, Fuchu, et al. (2003), Katayama, Tomatsu et al. (2003), Katayama et al. (2004) utilized porcine skeletal muscle and respective muscle proteins for proteolytic digestion. They isolated a corresponding peptide (Arg-Met-Leu-Gly-Gln-Thr-Pro-Thr-Lys) from hydrolyzed porcine troponin C with pepsin. Saiga, Okumura, et al. (2003) reported antihypertensive activity of *Aspergillus* protease-treated chicken muscle extract in SHR. They also isolated four ACE inhibitory peptides from the hydrolyzate. Three of those four peptides possessed a common sequence, Gly-X-X-Gly-X-X-Gly-X-X, which is homologous with that of collagen. Jang & Lee (2005) assayed ACE inhibitory activities of several enzymatic hydrolyzates of sarcoplasmic protein extracts from beef rump. An ACE inhibitory peptide (Val-Leu-Ala-Gln-Tyr-Lys) was isolated from the hydrolyzate with the highest level of ACE inhibitory activity obtained by using the combination of thermolysin and proteinase A.

ACE inhibitory peptides have shown antihypertensive effects by oral administration in animal experiments using SHR. However, the inhibitory potencies of peptides do not always correlate with their antihypertensive effects in vivo. Some peptides with potent ACE inhibitory activities in vitro are inactive by oral administration. Such a phenomenon between the inhibitory activity and antihypertensive effect and the structure-activity relationships of peptides has been reviewed (Arihara, 2006a; Li et al., 2004; Meisel et al., 2005).

Antioxidative Peptides from Meat Proteins

Information on meat protein-derived bioactive peptides other than **the** ACE inhibitory peptides is still limited. Several antioxidative peptides have been reported to be generated from meat proteins by enzymatic digestion. Saiga, Tanabe, and Nishimura (2003) reported that hydrolyzates obtained from porcine myofibrillar proteins by protease treatment (papain or actinase E) exhibited high levels of antioxidant activity in a linolenic acid peroxidation system. Among **the** five antioxidative peptides identified from papain hydrolyzate, Asp-Ala-Gln-Glu-Lys-Leu-Glu, corresponding to a part of the sequence of porcine actin, showed the highest level of activity. Arihara et al. (2005) investigated antioxidative activities of enzymatic hydrolyzates of porcine skeletal muscle actomyosin using a hypoxanthine-xanthine oxidase system as the source of **the** superoxide anion. Three antioxidative peptides were isolated from a papain-treated hydrolyzate of pork actomyosin and they were sequenced as Asp-Leu-Tyr-Ala, Ser-Leu-Tyr-Ala, and Val-Trp. In addition to the antioxidative activity in vitro, these peptides showed physiological activity in vivo. Each of these peptides had an anti-fatigue effect when orally administered to mice in an experiment using a treadmill.

Prebiotic Peptides from Meat Proteins

Prebiotics are defined as "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon and thus improve the health of the host" (Gibson, & Roberfroid, 1995). Oligosaccharides are representative prebiotic substances, which are known to enhance the activity of probiotic bacteria (i.e., intestinal lactobacilli and bifidobacteria). The presence of prebiotic peptides has been suggested. Lieple et al. (2002) first reported nonglycosylated peptides that selectively stimulate the growth of bifidobacteria. Recently, we found that the hydrolyzate of porcine skeletal muscle actomyosin, digested by papain, enhanced the growth of *Bifidobacterium* strains (Arihara, Ishikawa, & Itoh, 2006). One corresponding prebiotic peptide was identified as Glu-Leu-Met.

Other Promising Peptides from Meat Proteins

Opioid peptides are defined as peptides that have an affinity for an opiate receptor as well as opiate-like effects (Pihlanto & Korhonen, 2003). Opioid peptides have effects on the nerve system and gastrointestinal functions. Typical opioid peptides (e.g., endorphins, enkephalin, and prodynorphin) have the same N-terminal sequence, Tyr-Gly-Gly-Phe. Several opioid peptides derived from food proteins have been reported. The N-terminal sequence of most of these peptides is Tyr-X-Phe or Tyr-X1-X2-Phe. The N-terminal tyrosine residue and the presence of an aromatic amino acid at the third or fourth position form an important structure that fits with the binding site of opioid receptors (Pihlanto-Leppälä, 2001). There has been no report on the generation of opioid peptides from meat proteins. However, since opioid sequences are thought to be present in the sequences of muscle proteins, it should be possible to find opioid peptides in meat proteins by proteolytic treatment. Although bovine blood hemoglobin is regarded as a minor component of meat and meat products, in some meat products, such as blood sausage, hemoglobin is a major component. Investigation of hemoglobin peptic hydrolyzate has revealed the presence of biologically active peptides with affinity for opioid receptors (Nyberg, Sanderson, & Glämsta, 1997; Zhao, Garreau, Sannier, & Piot, 1997).

Morimatsu et al. (1996) demonstrated hypocholesterolemic effects of papain-hydrolyzed pork meat. However, the corresponding peptides were not identified. Immuno-modulating peptides have been discovered in enzymatic hydrolyzates of proteins from various foods, such as milk, eggs, soybeans, and rice. However, to date, meat protein-derived immuno-modulating peptides have not been reported. In addition to bioactive peptides described here, several bioactive peptides (e.g., antimicrobial, mineral-binding, antithrombotic, and hypocholesterolemic peptides) have been found from enzymatic hydrolyzates of various food proteins (Mine & Shahidi, 2005). It is expected that interest will be directed to research aimed at finding such meat protein-derived peptides.

Apart from bioactivities, meat protein-derived peptides also contribute to organo-leptic properties of meat (Nishimura & Kato, 1988; Nishimura et al., 1988; Arihara, 2006a). Meat products can be modified by adding functional ingredients beneficial for health or by eliminating or reducing components that are harmful. However, these modifications could result in products with inferior sensory properties. Therefore, generation of peptides from meat proteins has a great potential to produce novel functional foods with good organo-leptic properties. Also, from the aspect of food allergies, enzymatic treatment of food proteins, including meat proteins, warrants attention. Protein hydrolyzate based products have been produced and considered suitable for the diet of allergic patients. Although meat is less allergic than common allergy-inducing foods, such as milk, eggs, and soya, meat proteins (e.g., serum albumin, gamma globulin, actin, myoglobin and tropomyosin) sometimes cause allergic reactions (Tanabe & Nishimura, 2005).

Utilization of Peptides for Functional Meat Products

Although bioactive peptides have not yet been utilized in the meat industry, such peptides are promising candidates for ingredients of functional foods. Several food products containing ACE inhibitory peptides have been successfully marketed for hypertensives (Arihara, 2006b). There are two commercial dairy products containing Ile-Pro-Pro and Val-Pro-Pro, which are generated from milk protein by fermentation (Nakamura, Yamamoto, Sakai, & Takano, 1995; Seppo, Jauhiaine, Poussa, & Korpela, 2003). Calpis Amiel-S drink has been approved as a FOSHU in Japan. The Finnish fermented milk drink Evolus, developed by Valio Ltd., contains the same tripeptides as those in Amiel-S. The enzymatic digest of dried bonito containing antihypertensive peptides has also been used in a soup product in Japan. A FOSHU sour milk product utilizing casein-phosphopeptide (CPP) has been developed in Japan. CPP milk protein-derived peptides act as mineral trappers resulting in enhancement of the absorption efficiency of calcium (Gagnaire, Pierre, Molle, & Leonil, 1996). Hydrolyzates of meat proteins and their corresponding bioactive peptides would be utilized for functional foods.

Accumulation of bioactive peptides in meat products by fermentation is a good strategy for developing functional meat products. Bioactive peptides would be generated in fermented meat products, since meat proteins are hydrolyzed by proteolytic enzymes during fermentation and storage. Rediscovery of traditional fermented meats as functional foods is also an interesting direction. In the dairy industry, many traditional fermented foods, such as fermented dairy products, have been rediscovered as functional foods (Farnworth, 2003). Numerous physiologically active components, including bioactive peptides, have been discovered in these traditional fermented foods. Thus, traditionally fermented meats are attractive targets for finding new functional meat products.

Concluding Remarks

Although there has been extensive research and development of functional foods in the dairy industry (Chandan, 2007; Chandan & Shah, 2007; Mattila-Sandholm & Saarela, 2000; Playne, Bennett, & Smithers, 2003), little attention has been paid to functional meat products until recently. However, efforts have been directed in recent years to research and development of functional meat products (Arihara, 2004, 2006a, 2006b; Fernández-Ginés et al., 2005; Jiménez-Colmenero, 2007a, 2007b; Jiménez-Colmenero, Carballo, & Cofrades, 2001; Jiménez-Colmenero et al., 2006). Since meat and meat products are important in the diet in most developed countries, healthier meat and meat products would contribute to human health. Utilizing or emphasizing meat-based bioactive compounds, including bioactive peptides generated from meat proteins, is a promising means for developing attractive functional meat products. Such efforts would also contribute to the demonstration for consumers of the scientific benefits of meat and meat components for human health.

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