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Mechanism of Lipid Peroxidation in Meat and Meat Products -A Review

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Abstract Lipid peroxidation is a primary cause of quality deterioration in meat and meat products. Free radical chain reaction is the mechanism of lipid peroxidation and reactive oxygen species (ROS) such as hydroxyl radical and hydroperoxyl radical are the major initiators of the chain reaction. Lipid peroxyl radical and alkoxyl radical formed from the initial reactions are also capable of abstracting a hydrogen atom from lipid molecules to initiate the chain reaction and propagating the chain reaction. Much attention has been paid to the role of iron as a primary catalyst of lipid peroxidation. Especially, heme proteins such as myoglobin and hemoglobin and "free" iron have been regarded as major catalysts for initiation, and iron-oxygen complexes (ferryl and perferryl radical) are even considered as initiators of lipid peroxidation in meat and meat products. Yet, which iron type and how iron is involved in lipid peroxidation in meat are still debatable. This review is focused on the potential roles of ROS and iron as primary initiators and a major catalyst, respectively, on the development of lipid peroxidation in meat and meat products. Effects of various other factors such as meat species, muscle type, fat content, oxygen availability, cooking, storage temperature, the presence of salt that affect lipid peroxidation in meat and meat products are also discussed.

Keywords: Lipid peroxidation, mechanism, reactive oxygen species, catalyst, meat

Introduction

Consumer concerns on the quality of meat and meat products have greatly increased during past decades. "Quality" and "healthfulness" were reported to be one of the most important factors for influencing consumers choice for foods (1). Three sensory quality characteristics appearance/color, texture, and flavor are the main quality attributes that affect consumer acceptance of meat, and lipid peroxidation is the primary cause of these quality deteriorations in meat and meat products (2).

Lipid peroxidation primarily occurs through a free radical chain reaction, and oxygen is the most important factor on the development of lipid peroxidation in meat (3, 4). Theoretically, oxygen molecule and polyunsaturated fatty acid (PUFA) cannot interact with each other because of thermodynamic constraints. Ground state oxygen does not have strong enough reactivity, but can be converted to reactive oxygen species (ROS) such as hydroxyl radical ($\cdot OH$), superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), hydroperoxyl radical ($HO_2^{\cdot}$), lipid peroxyl radical ($LOO^{\cdot}$), alkoxyl radical ($LO^{\cdot}$), iron-oxygen complexes (ferryl- and perferryl radical) and singlet oxygen ($^1O_2$), some of which are highly reactive to initiate lipid peroxidation. In addition, numerous agents such as enzymes and transition metals can directly or indirectly catalyze these oxidative processes through enzymic and nonenzymic mechanisms. Especially, iron plays a critical role in lipid peroxidation process as a major catalyst.

Many comprehensive reviews on the mechanism of lipid peroxidation in muscle foods, including the major initiators and catalysts for the oxidative process (5-8), have been published. This review is focused on the potential roles of reactive oxygen species (ROS) and iron as primary initiators and a major catalyst, respectively, on the development of lipid peroxidation in meat and meat products.

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Mechanism of lipid peroxidation

Lipid peroxidation is a free radical chain reaction that is comprised of three primary steps: initiation, propagation, and termination. Initiation of lipid peroxidation takes place by attack of any species that has sufficient reactivity to abstract a labile hydrogen atom from a methylene group in lipid molecules (LH) to form lipid radicals ($L^{\cdot}$) (Equation 1).

$$LH + Initiator^{\cdot} + L^{\cdot} + InitiatorH \text{ (reduced form)} \quad \text{(Equation 1)}$$

Wagner et al. (9) reported that the amount of lipid radical generated increased with the total number of bis-allylic carbons, and suggested that the number of bis-allylic carbons in lipid molecules determines their susceptibility to lipid peroxidation. More importantly, the rate of lipid peroxidation exponentially increased with the number of bis-allylic carbons although lipid chain length had no relationship with the rate of radical formation. The differences in the initiation rate of lipid peroxidation are closely related to the dissociation energies of various carbon-hydrogen (C-H) bonds in fatty acid chains. The weakest C-H bond is at bis-allylic position, whose bond energy is 75-80 kcal/mol, and those at allylic position and alkyl C-H bond are ≈ 88 kcal/mol and ≈ 101 kcal/mol, respectively (10, 11). Consequently, the C-H bond at the bis-allylic position is the most reactive site for hydrogen abstraction. The well-known species capable of abstracting hydrogen atom are ROS, especially $\cdot OH$. Koppenol (10) estimated that the reduction potential of PUFA radical/PUFA couple was +0.60 V at neutral pH, suggesting that PUFA could be readily oxidized by $\cdot OH$ (+2.31 V) as well as other ROS.

The abstraction of hydrogen atom ($H^{\cdot}$) from lipid chain

leaves unpaired electron on the carbon of the chain ($L^{\cdot}$) because $H^{\cdot}$ has only one electron. This carbon radical tends to be stabilized by a molecular rearrangement to form a conjugated diene. The conjugated diene formed can go through various reactions, depending on O_2 concentration in biological system. Under aerobic conditions, the most likely fate of conjugated dienes is to react with oxygen molecules (O_2) to form a LOO (Equation 2):

$$L^{\cdot} + O_2 \ddagger LOO^{\cdot} \quad \text{(Equation 2)}$$

On the other hand, under very low O_2 conditions, a conjugated diene can react to each other within the membranes or other membrane components such as protein and cholesterol (12). The formation of conjugated dienes is accompanied by the configuration changes of the double bond from *cis* to *trans* form, which may allow unsaturated fatty acids to pack more tightly, leading to the creation of more rigid domains within bilayer of oxidized lipid (13). This abnormal conjugated diene can be one of the most important markers for lipid peroxidation in various meat systems.

In the propagation step (Equation 3), $LOO^{\cdot}$ formed is able to abstract $H^{\cdot}$ from another lipid molecule such as neighboring or surrounding fatty acids to form lipid hydroperoxide (LOOH):

$$LOO^{\cdot} + LH \rightarrow LOOH + L^{\cdot} \quad \text{(Equation 3)}$$

Hydrogen abstraction from a bis-allylic position on the fatty acid chain by $LOO^{\cdot}$ is favorable with Gibbs' free energy of -9 kcal/mol (10). In addition, because $LOO^{\cdot}$ has a higher standard reduction potential (+1.0V) than lipid molecule itself (+0.60 V) does, it can oxidize favorably an adjacent PUFA. Newly formed $L^{\cdot}$ can form another $LOO^{\cdot}$ by reacting with O_2, so the free radical chain reaction can continue. LOOH is a prominent non-radical intermediate of lipid peroxidation whose identification often provides valuable information on the related mechanisms. Since LOOHs are more polar molecules than normal fatty acids, LOOHs can disrupt the integral structure and function of the membrane, resulting in deleterious effect to cells and tissues. LOOHs may undergo various reactions, depending on environments in cell or tissue. Under low hydrogen-donating conditions, however, LOOH tends to undergo further reactions such as combination, intermolecular addition, intramolecular rearrangement, and further reactions with additional O_2 molecule, resulting in the formation of numerous secondary derivatives such as cyclic peroxides, prostaglandin-like bicycloendoperoxides, multi-hydroperxyl derivatives, etc., double bond isomerization, and formation of dimers and oligomers (14, 15). In addition, another complexity of LOOH derivatives formed is caused by the fact that hydrogen abstraction from PUFA can take place at different points on the fatty acid. Especially, hydroperoxyl cyclic peroxides and bicycloendoperoxides can be precursors of malonaldehyde, 2-thiobarbituric acid reactive substance (TBARS). The formation of various LOOHs and their derivatives possibly produced from primary PUFA has been reviewed by others (5, 15, 16).

The last step of lipid peroxidation is termination process in which the $LOO^{\cdot}$s react with each other and/or self-destruction to form non-radical products. Although LOOH is stable at physiological temperature, it can be decomposed by heating at high temperature or by exposure to transitional metal ions (17). Numerous secondary derivatives of hydroperoxides can be decomposed via homolytic and heterolytic â-scission catalyzed by transitional metal ions to generate a huge range of volatile and nonvolatile compounds such as carbonyls (e.g. ketones and aldehydes), alcohols, hydrocarbons (e.g. alkane, alkene), and furans that contribute to the flavor deterioration in many foods (18). Hexanal, 1-octen-3-ol, 2-nonenal, and 4-hydroxy-2-trans-nonenal (HNE) are reported to be originated from n-6 fatty acids and propanal, 4-heptenal, 2,4-heptadienal, 2-hexenal, 2,4,7-decatrienal, 1,5-octadien-3-ol, 2,5-octadien-1-ol, 1,5-octadien-3-one, and 2,6-nonadienal are from n-3 fatty acids (5, 19). Among these volatiles, aldehydes are one of most abundant, and are highly reactive and regarded as second toxic messengers that disseminate and augment initial free radical reactions (20). Aldehydes generated from lipid peroxidation were reported to be capable of reacting with protein to form adducts which may be related to the deterioration of protein stability and functionality (21). Also, Lynch and Faustman (22) suggested that aldehydes increase oxymyoglobin oxidation and prooxidant activity of metmyoglobin and decrease the enzymatic reduction of metmyoglobin, which is directly related to the deterioration of meat color and flavor. The primary aldehydes generated during lipid peroxidation in stored beef are propanal, pentenal, hexanal, and 4-hydroxynonenal (HNE) (21). Hexanal among aldehydes is the most prevailing volatile generated from cooked meat. It has been suggested as an index of meat flavor deterioration (MFD) during early storage stages of cooked meat because its concentration increased more quickly than any other aldehydes (23). In addition, HNE is known to have cytotoxic properties for human and animals by binding to proteins to inhibit their functions (24).

Reactive oxygen species (ROS) in lipid peroxidation

Although oxygen is essential for life, it can cause damages to various cells. The toxicity of oxygen is caused not by oxygen itself, but by the increased production of ROS. ROS can be produced under normal physiological conditions, but the amounts do not exceed the capacity of natural defense systems in body. The reduction of oxygen molecule by way of one-electron reduction processes produces short-lived but highly reactive oxygen products such as hydroxyl radical ($^{\cdot}OH$), superoxide anion ($O_2^{\cdot -}$), hydrogen peroxide (H_2O_2), hydroperoxyl radical ($HO_2^{\cdot}$), and iron-oxygen complexes (ferryl and perferryl radical), all of which may directly or indirectly participate in lipid peroxidation processes in meat and meat products.

Superoxide anion radical ($O_2^{\cdot -}$) and hydroperoxyl radical ($HO_2^{\cdot}$) Superoxide anion radical ($O_2^{\cdot -}$) is produced by one-electron reduction of oxygen, which acts as an intermediate in a number of biochemical reactions in body. Under physiological conditions, $O_2^{\cdot -}$ could be generated by numerous ways in muscle tissues. One of major sources of $O_2^{\cdot -}$ in muscle tissues are various

components of electron transport chain in mitochondria such as NADPH-dependent dehydrogenase and ubiquinone which may leak electrons onto O_2 (25, 26). The autoxidation of heme proteins (27, 28) and enzymes associated with metabolism such as xanthine oxidase (29) are other major sources. Activation of several leukocytes present in the vasculature of muscle tissue by the internalization of bacteria causes production of $O_2^{\cdot -}$ because $O_2^{\cdot -}$ is one of the major bactericides (30).

Superoxide anion radical ($O_2^{\cdot -}$) is a poorly reactive radical in aqueous solution although it is highly reactive in hydrophobic environments. Hydroperoxyl radical ($HO_2^{\cdot}$), the protonated form of $O_2^{\cdot -}$, is a more reactive than $O_2^{\cdot -}$ itself (Equation 4).

$$HO_2^{\cdot} \leftrightarrow O_2^{\cdot -} + H^+ \quad \text{(Equation 4)}$$

The pK_a of this reaction is approximately pH 4.8 in aqueous solution. Therefore, less than 1% of $O_2^{\cdot -}$ produced exists in this protonated form under physiological conditions (pH 7.4). The negative charges of membrane surface due to phosphatidyl moiety of phospholipid may cause pH drop around the membrane, resulting in the increase of $O_2^{\cdot -}$ concentration at the membrane surface (31). The pH in muscle tissue after post-rigor also decreases from around 7 to 5.5-6.0, so the amount of $HO_2^{\cdot}$ could be 10-20% of total $O_2^{\cdot -}$. The poor reactivity and relatively long half-life of $O_2^{\cdot -}$ in cytosol allows it to diffuse more effectively from its generation site to targets such as membrane lipid bilayers than $HO_2^{\cdot}$ or other reactive species. Furthermore, much of $O_2^{\cdot -}$ generated in cell may be produced near membrane by membrane-bound systems such as electron transport system of mitochondria (25, 26) However, $O_2^{\cdot -}$ was suggested not to be able to permeate deep into liposomal bilayer (32). Subsequently, some part of $O_2^{\cdot -}$ present near membrane could exist as $HO_2^{\cdot}$. Uncharged conditions of $HO_2^{\cdot}$, unlike $O_2^{\cdot -}$, allow it to permeate into membrane lipid bilayer, where it could initiate lipid peroxidation process by abstracting hydrogen atom from bis-allylic position of PUFA in phospholipids (33, 34). Aikens and Dix (35, 36) indicated that the initiating effectiveness of $HO_2^{\cdot}$ is directly related to the initial concentration of LOOH in lipids because LOO$^{\cdot}$s generated by either direct or indirect hydrogen atom transfer between $HO_2^{\cdot}$ and LOOH can initiate lipid peroxidation more efficiently than $HO_2^{\cdot}$ itself. However, the evidence for the ability of $HO_2^{\cdot}$ to mediate directly the initiation of free radical chain reaction has not been proven yet.

A major toxicity of superoxide in lipid peroxidation is attributed to its ability to reduce ionic irons which are re-oxidized by H_2O_2 to produce $^{\cdot}OH$ (Equations 5 and 6) - the most reactive oxygen species that can abstract hydrogen atom from bis-allylic position of PUFA chains and initiates lipid peroxidation (37):

$$\text{Fe(III)-complex} + O_2^{\cdot -} \rightarrow \text{Fe(II)-complex} + O_2 \quad \text{(Equation 5)}$$

$$\text{Fe(II)-complex} + H_2O_2 \rightarrow \text{Fe(III)-complex} + OH^- + {}^{\cdot}OH \quad \text{(Equation 6)}$$

In addition, Liochev and Fridovich (37) and Fridovich (38) suggested that $O_2^{\cdot -}$ *in vivo* oxidizes the [4Fe-4S] clusters of dehydratases such as mammalian aconitase causing inactivation of enzyme and release of Fe(II) ion. Also, $O_2^{\cdot -}$ is suggested to decrease the activity of antioxidant defense enzymes such as catalase and glutathione peroxidase (39). Meanwhile, $O_2^{\cdot -}$ is indicated to serve not only as a reducing agent for Fe (III), but also as an oxidant for Fe(II) depending on the ligands or chelators of iron. Ahn et al. (4) and Ahn and Kim (40) in their mechanism study with $O_2^{\cdot -}$-generating systems associated with various iron sources indicated that $O_2^{\cdot -}$ is a strong oxidant rather than a reducing agent and the antioxidant effect of $O_2^{\cdot -}$-generating systems, especially xanthine oxidase system, in oil emulsion is due to the oxidation of Fe(II) to Fe(III) by $O_2^{\cdot -}$ and/or H_2O_2.

Hydrogen peroxide (H_2O_2) Low concentrations of hydrogen peroxide (H_2O_2) are present in aerobic cells as a metabolite under physiological conditions. An $O_2^{\cdot -}$-generating system would be expected to yield H_2O_2 by non-enzymatic or superoxide dismutase (SOD)-catalyzed dismutation. Hydrogen peroxide (H_2O_2) generation has been easily detected in mitochondria, microsomes, peroxisomes, and phagocytic cells. Also, several enzymes, including aldehyde oxidase, xanthine oxidase, urate oxidase, glucose oxidase, glycolate oxidase, and D-amino acid oxidase, etc., can directly produce H_2O_2 (7, 17). Giulivi et al. (41) reported that H_2O_2 is generated at a rate of approximately 3.9×10^{-9}M/h*g hemoglobin and the concentration of H_2O_2 in the steady-state red blood cells is around 2×10^{-10}M, indicating that the main source of H_2O_2 in red blood cells is probably oxyhemoglobin autoxidation. Chan et al. (42) suggested that H_2O_2 generated during oxymyoglobin oxidation plays an important role in lipid peroxidation. Harel and Kanner (43) reported that turkey muscle tissues stored at 37°C for 30 minutes generated almost 14.0 nmol H_2O_2 per gram of fresh weight and its generation increased with storage at 4°C.

H_2O_2 is not a radical because it has no unpaired electron, and has limited reactivity and permeability to biological membrane unlike the charged $O_2^{\cdot -}$ (44). The poor reactivity and relatively long half-life of H_2O_2 like $O_2^{\cdot -}$ enables it to diffuse more effectively from its generation site to targets such as membrane lipid bilayers. However, H_2O_2 can perform most of its damaging effects by generation of more reactive species such as $^{\cdot}OH$ by catalysis of Fe(II) (45). In addition, H_2O_2 can denature heme proteins to release free irons and heme group or convert heme protein to ferryl or perferryl radical, depending on its concentration (28)

Hydroxyl radical ($^{\cdot}OH$) Hydroxyl radical ($^{\cdot}OH$) is the most reactive oxygen radical with high positive reduction potential (39). Usually, the steady-state concentration of $^{\cdot}OH$ is effectively zero *in vivo* because it would react at or close to its site of formation with every molecule in living cell, such as DNA, protein, phospholipid, amino acid, sugar, etc. as soon as $^{\cdot}OH$ is produced. Pryor (46) hypothesized that the high reactivity of $^{\cdot}OH$ is due to a rare combination of three characteristics: high electrophilicity, high thermochemical reactivity, and a mode of production that can occur near target molecules.

Bannister and Thornalley (47) presented a direct evidence for the generation of ·OH by adrianmycin in intact red blood cells using the electron paramagnetic resonance (EPR) technique of spin trapping. Most of the ·OH generated *in vivo* or *in situ* came from Fe(II)-catalyzed decomposition of H_2O_2 (45). In addition, ·OH can also be generated by various sources: sunlight (48), ultraviolet radiation (49), ionizing irradiation (50), the reaction of hypochlorous acid with $O_2^{\cdot-}$ (51), and sonolysis of water (ultrasound) (52).

The reaction of ·OH can be inhibited by ·OH scavengers such as mannitol, formate, thiourea, dimethylthiourea, methanol, ethanol, 1-butanol, glucose, tris-buffer, or sorbitol (17). Although ·OH scavengers usually inhibit the reaction of ·OH with other molecules including lipid molecules, sometimes they do not act effectively. There are a couple of reasons that should be considered: 1) the reaction of ·OH with a scavenger may generate scavenger radicals that might react with other molecules in the system. The production and reactivity of secondary radicals may sometimes be responsible for the unsuccessful protection by one scavenger (53). 2) More attention has been paid on the possibility of the metal-mediated site-specific mechanism (45): ·OH generated *in vivo* by the reaction of H_2O_2 with metal ions bound to macromolecules in cells can reacts with the metal-binding molecules or the nearest molecules immediately after production before the scavengers give access to them. Auroma et al. (54) demonstrated the evidence for the formation of complex of Fe(II) ion and 2-deoxyrebose, suggesting that Fe(II) ion bound to DNA reacts with H_2O_2 to form ·OH that immediately damages DNA. Baysal et al. (55) suggested that Fe(III) ion binds to membrane and then generates free radicals at the binding site. Although the specific binding site of iron to membrane was not found, they suggested that carboxyl groups of sialic acids, sulfate group of glycolipids and glycoproteins, and sulfin and sulfon group together with phosphate head group of the phospholipids are considered as the major binding sites on erythrocyte membrane. Gutteridge (56) indicated that ·OH scavengers inhibited ·OH generation effectively in the presence of EDTA because EDTA may allow Fe(II) ions to be removed from these binding site. Therefore, the actual toxicity of $O_2^{\cdot-}$ and H_2O_2 may be dependent on the availability and distribution of metal ion catalysts to generate ·OH in cells.

Iron-oxygen complexes (ferryl and perferryl radical) The ferryl [Fe(IV)] and perferryl [Fe(V)] radicals are catalytically active in numerous biological processes, and these ferryl/perferryl moiety, whether as components of enzyme or simple iron complex, can be very powerful oxidants capable of abstracting hydrogen atom in lipid peroxidation (57). It has been indicated that an oxidizing intermediate generated in Fe(II)-EDTA-H_2O_2 system does not undergo the characteristic reactions of ·OH but shows a pattern of reaction more associated with ferryl complex (58, 59). Also, it has been suggested that the reaction of metmyoglobin and methemoglobin with low concentration H_2O_2 generates a short-lived ferryl species that contain one oxidizing equivalent on heme and another one on globin, and is not affected by all efficient ·OH scavengers (60-63). Xu et al. (64) reported that free radicals generated by H_2O_2 activation of metmyoglobin by electron spin resonance (ESR) techniques may be a ferryl species.

Iron in lipid peroxidation

Iron is the most abundant transitional metal in biological systems. Although iron has the possibility of various oxidation states (from -II to +VI), the forms of Fe(II) and Fe(III) is dominated in biological systems. The ability of iron with various oxidation state, reduction potential, and electron spin configuration depending upon different ligand environments allows it to serve in multifunctional roles as a protein cofactor (65). Metal-binding proteins in biological system are usually classified by the functional role of metal ion: structural, metal-ion storage and transport, electron transport, dioxygen binding, and catalytic protein (66). However, the versatile potential of iron allows it to catalyze the detrimental oxidation of biomolecules such as DNA, protein, lipid, etc. Therefore, iron metabolism *in vivo* should be tightly regulated by iron-binding proteins in order to ensure the absence of free forms of iron existing.

Iron distribution in tissue Iron is distributed in five distinct pools, including transport, storage, oxygen-carrying, functional, and low molecular weight irons, represented by transferrin, ferritin, hemoglobin/ myoglobin, iron-dependent enzymes, and small transit pool of iron chelates, respectively. About two-thirds of body iron is found in hemoglobin, with smaller amounts of myoglobin, various iron-containing enzymes, and transferrin. The rest not used for these is stored in intracellular storage protein, ferritin and hemosiderin. Intracellular concentration of free ionic iron seems to be extremely small.

The concentrations of myoglobin and hemoglobin in muscle tissue are dependent on animal species, muscle type, and anatomical location of muscle (67). Both myoglobin and hemoglobin-bound iron accounted for 73.3, 47.0, and 28.5% of total iron concentration in beef, pork, and chicken thigh meat, respectively (68). Myoglobin (70%) is the predominant iron compound in beef. Myoglobin accounts for most of heme iron in beef and pork, but the level of myoglobin in chicken breast and thigh muscle is very low. Meanwhile, Schricker and Miller (69) suggested that the heating or addition of H_2O_2 caused the release of heme iron due to oxidative cleavage of porphyrin ring of heme. Han et al (70) reported that the iron content in water-soluble fractions of heated beef and chicken thigh muscle decreased due to the reduction of heme iron content, but that in water insoluble fractions increased because the denatured heme protein was also included in insoluble fraction.

Transferrin and ferritin are major iron transport and storage proteins, which are capable of binding two and ~2500 Fe(III) ion at a time, respectively. The structure, function, physiological role, and relationship to oxidative processes of them are well reviewed by Crichton and Charloteaux-Wauters (71), Reif (72), and Welch et al (65). However, the role of transferrin as a catalyst for lipid peroxidation has not been yet demonstrated in muscle tissues although released irons from transferrin were suggested to be participated in lipid peroxidation process

in other tissues (73). Meanwhile, the concentrations of ferritin-bound iron in beef, pork, and chicken thigh muscles were reported to be 1.2%, 4.6%, and 11.1% of total iron concentration in each species, respectively (68). Ferritin has been suggested to be involved in oxidative deterioration by releasing Fe(II) in the presence of reducing compound such as $O_2^{\cdot -}$ and ascorbate (74, 75), heating, or refrigerated storage (76, 77, 70). Hemosiderin is an insoluble complex of iron, other metals and proteins, and is thought to be a ferritin decomposition or polymerization products (6). In pork and chicken muscles over a half of total iron (58%) was detected in insoluble fraction (68). Although the amount and precise nature of the insoluble fraction in muscle is unknown, some of them may be from hemosiderin. Hemosiderin may release its bound iron in the presence of reducing agents, resulting in the acceleration of $^{\cdot}OH$ generation, but is far less effective than ferritin. Therefore, it was proposed that the conversion of ferritin to hemosiderin *in vivo* is biologically favorable because it reduces the availability of iron to promote lipid peroxidation (78). The amount of hemosiderin in muscle tissues has not been known yet.

An extremely small amount of nonprotein-bound iron is present in cells. This cytosol iron pool is often considered as the transit pool because it is related to iron in transit between transferrin and ferritin (71). Although very low solubility of iron under physiological conditions causes the precipitation of iron with anions such as hydroxyl ion (OH^-), various chelators can increase its solubility significantly (79). Thus, the intermediate pool of iron is composed of iron associated with low molecular weight chelators such as organic phosphate esters (e.g. NAD(P)H, AMP, ADP, and ATP), inorganic phosphates, amino acids, and organic acids (e.g. citrate), which is called as low molecular weight iron (6, 17). The existence of low molecular weight iron pool has been identified in various tissues (80-82) as well as in mitochondria for heme synthesis (83). In muscle tissues, the content of low molecular weight iron accounts for 2.4~3.9% of total iron, depending on animal species and muscle types (68), and the concentration can be influenced by heating and in the presence of ascorbic acid and H_2O_2 (69) and storage (84). Neither the size nor the chemical nature of intermediate pool of iron has been clearly identified.

Importance of iron as a catalyst for initiation of lipid peroxidation

Nonenzymic catalysis: the initiation mechanism of lipid peroxidation is still an area of controversy. Iron is the most probable catalyst for the initiation of lipid peroxidation by catalyzing the generation of most $^{\cdot}OH$ *in vivo* or *in vitro* via Fenton reaction (Equation 6) and is cycled by reducing agents such as $O_2^{\cdot -}$ and ascorbic acid (37, 85). In general, ascorbic acid can serve as both an antioxidant and a prooxidant, depending on relative concentrations of ascorbate and iron present (6). Ascorbate at low concentration is most likely to promote lipid peroxidation in muscle tissue by the reduction of iron, whereas at high concentration it tends to reduce some of $LOO^{\cdot}$ directly to LOOH, resulting in breaking the free radical chain reactions and also regenerates α-tocopherol in biological membrane. In turkey muscle, reducing compounds were observed at the level of ~3 mg ascorbate equivalent/100 g of fresh weight, 80% of which would be ascorbic acid (86).

Many studies have tried to determine which form of iron is responsible for the catalysis of the lipid peroxidation in meat and meat products. In the beginning, the involvement of heme proteins as catalyzing agents of lipid peroxidation was first described by Robinson in 1924 (7). Many studies have indicated that heme pigments in meat play a pivotal role in catalysis of lipid peroxidation in the model systems with various meat species such as beef and fish (87- 90). Rhee and Ziprin (91) showed that the levels of lipid peroxidation were dependent on animal species and muscle type in raw meat, and beef was more susceptible to lipid peroxidation than pork and chicken muscle. They proposed that total pigment and myoglobin concentrations are well related to the differences in lipid peroxidation of stored, raw muscles in three species.

Alternatively, Kanner et al. (84, 92, 93) suggested that lipid peroxidation in minced turkey muscle is primarily affected by "free" ionic iron and this suggestion was confirmed by the chelating ability of ceruloplasmin to low molecular weigh iron. Hydrogen peroxide (H_2O_2) and ascorbate presented in the cytosol of muscle cells can release free iron from heme pigments and ferritin, respectively, which can catalyze lipid peroxidation in meat and meat products (43, 74). Also, Ahn et al. (94) and Ahn and Kim (95) suggested that free ionic iron played an important role in the catalysis of lipid peroxidation, but neither transferrin- and ferritin-bound irons nor heme pigments had any catalytic effect in raw turkey muscle. They suggested that the status of ionic iron is more important than the amount of iron. Ahn and Kim (95) in their study with oil emulsion systems indicated that Fe(III) catalyzed lipid peroxidation only in the presence of ascorbic acid while Fe(II) did it alone. In addition, studies using cooked meat model systems containing water-extracted muscle fractions indicated that nonheme iron released from heme pigments and ferritin by heating is the principal catalyst rather than myoglobin (76, 77, 96). Therefore, these researches indicated that free ionic iron released from heme pigments and ferritin may be considered as the major catalyst for lipid peroxidation in raw and cooked meat.

Kanner and Harel (97) suggested that ferryl species generated by the interaction of H_2O_2 with metmyoglobin or methemoglobin can initiate lipid peroxidation in muscle tissue. They showed that H_2O_2 alone or metmyoglobin alone could not stimulate oxidation reaction in sarcosomal fraction of turkey dark muscle whereas the membranal lipid peroxidation was readily promoted in the presence of H_2O_2 and metmyoglobin. H_2O_2- or cumene hydroperoxide-activated metmyoglobin was shown to catalyze lipid peroxidation in model systems containing PUFA (98, 99). Also, H_2O_2- activated metmyoglobin was reported to be able to oxidize a series of compounds such as phenols, β-carotene, methional, reducing agents, and uric acid (61, 100). The ratio of H_2O_2 to metmyoglobin seemed to be important for the generation of the ferryl species. Rhee et al. (101) demonstrated that the catalytic activity of metmyoglobin-H_2O_2 treatment was the highest at the molar ratio of ~1:0.25 in raw microsomal system of beef and at the molar ratio of 1:1.5 or 1:2 in the cooked system

although metmyoglobin alone had little catalytic activity. Moreover, nonheme iron concentration in this system was shown to increase as the added concentration of H_2O_2 increased. Hence, they suggested that the catalytic effect of metmyoglobin-H_2O_2 treatment is most likely to be attributed to both H_2O_2-activated metmyoglobin and nonheme iron released from metmyoglobin. Also, H_2O_2, the essential element for the activation of metmyoglobin, was shown to be endogenously generated in ground turkey muscle tissue (43). Meanwhile, Baron et al. (102) reported that metmyoglobin can be activated to ferryl species in the presence of lipid hydroperoxide and suggested that the presence of lipid hydroperoxide is a crucial factor for heme protein-catalyzed lipid peroxidation. In addition to lipid hydroperoxide, the prooxidant activity of metmyoglobin is dependent on a linoleate-to-heme ratio (28, 102, 103). They indicated that at a low linoleate-to-heme ratio (1:100), metmyoglobin did not show prooxidant activity because it was converted to hemichrome by binding of fatty acid which is known to poor prooxidant. However, at higher ratio (1:200 and 300), metmyoglobin showed prooxdant activity because it was denatured by the high concentration of fatty acids, resulting in exposure or release of heme group to lipids, leading to the initiation of lipid peroxidation. Also, it was indicated that ferryl species produced in the presence of H_2O_2 were likely to attack other heme "edge" molecule to produce porphyrin radical, resulting in the release of ionic irons (104). Therefore, all of ferryl species, exposed or released heme, and ionic irons may be responsible for myoglobin-mediated lipid peroxidation, depending on the environment.

In addition to the role of iron as the catalyst for the initiation of lipid peroxidation, iron plays another role in lipid peroxidation process. Pure LOOH can be decomposed by heating or in the presence of transitional metal ions although it is pretty stable at physiological temperature (17). Davies and Slater (105) indicated that reduced iron complexes react with LOOHs to produce $LO^{\cdot}$ by one-electron reduction. A Fe(II) complex causes the fission of O-O bonds to form $LO^{\cdot}$ in a similar way to their reaction with H_2O_2, and the reactions of Fe(II)-complexes with LOOHs are much faster than their reactions with H_2O_2 (the rate constant (k_2) for Fe(II)+ROOH is~$1.5\times10^3 M^{-1}s^{-1}$; that for Fe(II)+$H_2O_2$ is about 76 $M^{-1}s^{-1}$) (39, 106) (Equation 7). Garnier-Suillerot et al. (106) proposed that the mechanism of LOOH decomposition by Fe(II) in their small unilamellar vesicle with phospholipids consists of two steps; the fixation of Fe(II) to membrane as a first step, and then the decomposition of LOOH to form $LO^{\cdot}$.

$$\text{LOOH} + \text{Fe(II)-complex} \rightarrow \text{Fe(III)-complex} + OH^- + LO^{\cdot} \quad \text{(Equation 7)}$$

Subsequently, this $LO^{\cdot}$ reacts with another lipid molecules (L*H) and/or L*OOH to produce both $L^{*\cdot}$ and/or $L^*OO^{\cdot}$, respectively, depending on the concentration of reactants (105). The ability of $LO^{\cdot}$ to abstract a hydrogen atom from PUFA and LOOH was demonstrated on the basis of the reduction potential of $LO^{\cdot}$ (+1.6V) and the Gibbs free energies changes (ΔG^o) in the reaction of $LO^{\cdot}$ with hydrogen at bis-allylic carbon in propene (-23 kcal/mol) and LOOH (-14 kcal/mol) (10) (Equation 8 and 9). Fe(III)-complexes can also decompose LOOH to $LOO^{\cdot}$. Davies (62) showed that the reaction of metmyoglobin and methemoglobin with t-butyl hydroperoxide generated its $LOO^{\cdot}$ (Equation 10)

$$LO^{\cdot} + L^*H \ddagger LOH + L^{*\cdot} \quad \text{(Equation 8)}$$

$$LO^{\cdot} + L^*OOH \ddagger LOH + L^*OO^{\cdot} \quad \text{(Equation 9)}$$

$$\text{LOOH} + \text{Fe(III)-complex} \rightarrow \text{Fe(II)-complex} + H^+ + LOO^{\cdot} \quad \text{(Equation 10)}$$

The $LOO^{\cdot}$ formed in equations 9 and 10 subsequently is involved in the propagation step of lipid peroxidation process. However, the reaction rate of Fe(III) with LOOH (equation 10) is much slower than that of Fe(II) (equation 7) (39). Moreover, $LO^{\cdot}$ is more reactive for the abstraction reaction than $LOO^{\cdot}$ (equation 10). In usual, the micelles or liposomes from commercially available lipid and microsome isolated from disrupted cell are contaminated with a trace amount of LOOH. Therefore, when iron is added, LOOH present can react with iron via equations 7 and 10 to form $LO^{\cdot}$ and $LOO^{\cdot}$ that can participate in the initiation and propagation of lipid peroxidation.

Recently, some researchers suggested iron-catalyzed LOOH-dependent lipid peroxidation as an initiation mechanism of lipid peroxidation (107-109). Tandolini et al. (108) also showed that added Fe(III) to their model system did not affect LOOH-independent but affected LOOH-dependent lipid peroxidation, which suggested that Fe(III) played in an important role in the control of LOOH-dependent lipid peroxidation. Tang et al. (109) reported that the removal of pre-existed LOOH in liposome prevented Fe(II) from initiating lipid peroxidation, but re-addition of LOOH promoted lipid peroxidation after short latent period. They suggested that pre-existing LOOH is required for the "Fe (II)-initiated" lipid peroxidation. Also, they showed that scavenging $LOO^{\cdot}$ inhibited the initiation of lipid peroxidation. They proposed that Fe(II) initiated lipid peroxidation by decomposing LOOH, resulted in the formation of $LOO^{\cdot}$, which may be the real initiator of "Fe (II)-initiated" lipid peroxidation. However, according to equation 7, Fe(II) reduces LOOH to form $LO^{\cdot}$, which is more reactive for H atom abstraction than $LOO^{\cdot}$ (10). They also suggested that the latent period before initiating lipid peroxidation is due to the suppression of $LOO^{\cdot}$ and $LO^{\cdot}$ activity via reduction to LOOH and LOH by Fe(II) (Equation 11 and 12) and lipid peroxidation is initiated below certain concentration of Fe(II).

$$\text{Fe(II)-complex} + LOO^{\cdot} + H^+ \rightarrow \text{Fe(III)-complex} + \text{LOOH} \quad (11)$$

$$\text{Fe(II)-complex} + LO^{\cdot} + H^+ \rightarrow \text{Fe(III)-complex} + \text{LOH} \quad (12)$$

Enzymic catalysis: Isolated microsomes from animal tissues undergo lipid peroxidation when incubated with NADPH or NADH and Fe(II) or Fe(III) salt. Sevanian et al. (110) observed that both NADPH-cytochrome P450 reductase and cytochrome P450 contained in microsomes were involved in NADPH- and ADP-Fe(III)-dependent lipid peroxidation. The enzyme may generate $O_2^{\cdot -}$ that dismutate H_2O_2 and reduce Fe(III)-chelates to Fe(II)-chelates to form $^{\cdot}OH$, which stimulate microsomal lipid

peroxidation (111, 112). However, it has been proposed that NADPH-dependent lipid peroxidation in liver microsome in the presence of Fe(III) chelates is initiated by the reduction of Fe(III), followed by addition of O_2 to perferryl species which then stimulates the abstraction of an hydrogen atom from PUFA chain (110, 113).

The presence of enzyme systems in microsomal fractions from beef, pork, and turkey muscle that catalyze lipid peroxidation of microsomal lipids has been reported (91, 114, 115). Rhee (116) suggested that enzymic lipid peroxidation in skeletal muscle microsomes is dependent on NADH or NADPH and requires ADP and Fe(II) or Fe(III) for maximum rate. The reaction rate is higher with NADH for the microsomal systems of fish muscles than NADPH for those of poultry and red-meat muscles. The reaction rate is also higher with Fe(II) than Fe(III).

The role of lipoxygenase in fish tissues as the enzymic initiator of lipid peroxidation has been actively investigated. German and Kinsella (117) found that 12-hydroxyeicosate-traenoic acid was observed as a major monohydroxy product from arachidonic acids, indicating a 12-lipoxygenase activity in fish skin. They suggested that endogenous skin 12-lipoxygenase released post-mortem may be a major source for the initiation of lipid peroxidation in fish tissues. Saeed and Howell (118) demonstrated the presence of 12-lipoxygenase in Atlantic mackerel, which has the possibility of enzymatical initiation of lipid peroxidation in chilled and frozen stored fillets of mackerel. Meanwhile, lipoxygenase has been found in various mammalian species such as human, rat, mouse, pig, cattle, chicken, etc. (119). Kuhn and Borchert (120) reported that among currently known mammalian lipoxygenase isoforms only 12/15-lipoxygenases can directly oxygenate lipid esters to generate lipid hydroperoxy esters even when lipids are bound to membranes and lipoproteins.

Factors affecting lipid peroxidation in meat and meat products

Lipid peroxidation process probably starts immediately after slaughtering and during certainly post-slaughtering events. The biochemical changes during the conversion of muscle to meat such as post mortem aging cause the destruction of the balance between prooxidant and antioxidant factors. The rate and extent of lipid peroxidation in muscle tissues appears to be dependent on degree of muscle tissue damages during pre-slaughtering events such as stress and physical damage and post-slaughtering events such as early post mortem, pH, carcass temperature, shortening, and tenderizing techniques such as electrical stimulation (121). In addition, various processing factors can influence the rate of lipid peroxidation in meat and meat products: composition of raw meat, aging time, cooking or heating, size reduction processes such as grinding, flaking, and emulsification, deboning, especially mechanical deboning, additives such as salt, nitrite, spices, and antioxidants, temperature abuse during handling and distribution, oxygen availability, and prolonged storage (7, 116).

Differences in total lipid content and fatty acid composition in meat are dependent on animal species, muscle type, and anatomical location of muscle (122). Several studies have demonstrated that phospholipids play a critical role in the development of lipid peroxidation in raw and cooked meat. Pikul et al. (123) suggested that the phospholipid fraction contributed about 90% of the malonaldehyde measured in total fat from chicken meat. Also, the PUFA content of phospholipids was positively related to the development of rancidity (124). Yin and Faustman (125) indicated that the level of lipid peroxidation is more strongly influenced by oxidative stability of membrane components rather than that of cytosolic components. Sasaki et al (126) indicated that the extent of lipid peroxidation was correlated with phospholipid peroxidation in the initial period of storage, but was directly correlated with total lipid content in a later period. The content, composition, and quality of dietary fat in feed and the tendency of animal species to store fatty acids into membrane phospholipids can affect the fatty acid composition of membrane and its susceptibility to lipid peroxidation (127-129).

The susceptibility of meat to lipid peroxidation is depending on animal species, muscle type, and anatomical location (91, 130). They reported that frozen raw beef and pork muscle had higher TBARS value than frozen raw chicken muscle as was heme iron content, but cooked chicken meat was more susceptible to lipid peroxidation than cooked beef and pork. Thus, they concluded that heme pigment content in conjunction with catalase activity determines lipid peroxidation potential of raw meat and the content of PUFA is the major determinant for lipid peroxidation in cooked meats. Salih et al. (131) reported that turkey thigh meat was more susceptible to oxidation than turkey breast meat. Also, Kim et al. (132) reported that beef showed higher susceptibility to lipid peroxidation than pork and turkey breast muscle.

Oxygen availability is one of the most important factors for the development of lipid peroxidation in raw and cooked meat. Any process causing disruption of the membranes such as size reducing processes (grinding, flaking, mincing, etc), deboning, and cooking results in exposure of the phospholipids to oxygen, and, therefore, accelerates development of oxidative rancidity (6). The level of oxygen content in modified atmosphere and vacuum packaged raw and cooked beef was proportional to that of lipid peroxidation (133, 134). Ahn et al. (135, 136) reported that vacuum-packaged meat immediately after cooking while the meat is still hot ("hot-packaging") developed significantly lower TBARS during storage than the one with vacuum packaged after chilling, which suggested that the 3-hr chilling provided enough time for oxygen to stimulate lipid peroxidation in cooked meat. They also showed that when oxygen is not present, prooxidants such as ionic iron, hemoglobin, NaCl, fat content, and fatty acid composition had little effect on the oxidation of cooked meat during storage. In addition, the combination of "hot"packaging and antioxidants such as reducing agents and free radical terminators provided cooked turkey meat patties with better protection from lipid peroxidation than either treatment alone mainly because antioxidants protected meat from oxidation during raw meat preparation and brief exposure to air (137). Andersson and Lingnert (138) indicated that the production of volatiles showed different patterns depending on oxygen

concentration and some compounds were produced in larger amounts at lower oxygen concentration than at higher one.

The term "warmed-over flavor" was first introduced by Tims and Watts in 1958 to describe the rancidity in cooked meat during refrigerated storage. Rancid flavors are readily detectable after 2 days in cooked meat, in contrast to much more slowly developing rancidity in raw meat (139). Generally, heating increases the level of lipid peroxidation such as TBARS and volatile productions. Heating can promote lipid peroxidation by disruption of muscle cell structure, inactivation of antioxidant enzymes, and release of oxygen and iron from myoglobin. The disrupted membranes by heating are exposed to and readily accessed by oxygen, followed by rapid lipid peroxidation (140). Mei et al. (141) and Lee et al. (142) suggested that the inactivation of catalase and glutathione peroxidase (GSH-Px) by heating could be partially responsible for the rapid development of lipid peroxidation in cooked meat. Meanwhile, Chen et al. (143) showed that heating rate and final temperature affected the release of non-heme iron from heme pigment. Slow heating increased the release of non-heme iron than fast heating. Also, high temperature provides reduced activation energy for oxidation and breaks down preformed hydroperoxide into free radicals, which stimulates further lipid peroxidation processes and off-flavor development (7). On the other hand, freezing slows down lipid peroxidation, but cannot stop the process. Eun et al. (144) demonstrated that freezing retarded the development of NADH-dependent lipid peroxidation in channel catfish muscle microsomes by inactivating enzymes, but thawing resulted in reactivation of peroxidase system. $LOO^{\cdot}$ is soluble in oil fraction and are more stable at low temperature, which they can diffuse to longer distances and spread the reaction potential during freezing (7).

Sodium chloride is one of the most important additives in meat industry for enhancing preservation, flavor, tenderness, water holding capacity, binding ability, and juiciness (145). It has been known that sodium chloride has a prooxidant effect in meat and meat products, depending on its concentration. Rhee et al. (146) showed that the level of lipid peroxidation increased with the sodium chloride up to 2% while over 3% of sodium chloride had little or no prooxidant effect, and proposed that the prooxidant effect of sodium chloride is decreased and/or inhibited over a certain high concentration. Although the mechanism by which sodium chloride promotes muscle lipid peroxidation has not been clearly understood, but one of the possible explanations is that sodium chloride may disrupt the structural integrity of the membrane to enable catalysts easily access to lipid substrates (145). Kanner et al. (147) showed that the prooxidant effect of sodium chloride was inhibited by EDTA and ceruloplasmin, and suggested that sodium chloride enhances the activity of ionic irons for lipid peroxidation. Rhee and Ziprin (148) also reported that non-heme iron content in ground beef and chicken breast muscle increased with sodium chloride concentration. This effect of sodium chloride may be in part related to its capability to release ionic irons from iron-contained molecules such as heme proteins. In addition, sodium chloride can promote the formation of metmyoglobin, which reacts with H_2O_2 to form ferryl-myoglobin to catalyze lipid peroxidation (145). Meanwhile, Lee et al. (149) showed that sodium chloride lowered the activity of antioxidant enzymes, catalase, glutathione peroxidase, and superoxide dismutase by 8%, 32%, and 27 %, respectively, and suggested that the capability of sodium chloride to decrease the activity of those antioxidant enzymes could be partially responsible for the acceleration of lipid peroxidation in muscle tissue. Hernandez et al. (150) drew similar conclusions, but they suggested that the accelerated lipid peroxidation in salted pork may be partly related to the reduction of glutathione peroxidase activity rather than that of catalase activity. Rhee et al. (146) reported that sodium chloride and magnesium chloride increased rancidity of raw and cooked ground pork but potassium chloride did not increased in cooked samples, and suggested that replacement of sodium chloride with potassium chloride is effective for decreasing rancidity in processed meat. Potassium chloride, however, has a limitation for using in the industry because of its bitter taste (116).

Conclusion

Lipid peroxidation is a major cause of quality deterioration in meat and meat products. NRC (151) indicated that lipid peroxidation is a major problem in meat. In order to prevent or retard lipid peroxidation in meat effectively, the mechanism of lipid peroxidation should be comprehensively understood. Especially, the control of catalyst is very important because catalyst can be rapidly amplified by free radical chain reactions. Much attention has been paid to the role of iron, which can directly and/or indirectly catalyze the initiation of lipid peroxidation. Many researches have tried to elucidate which iron type and how iron is involved in lipid peroxidation in meat as well as what is the "real" initiator to be able to abstract hydrogen atom from lipid molecule at the beginning. Yet, these areas are still debatable even though tremendous research have been done and doing. In addition, the relationship of various factors involved in pre- and post-slaughtering and further processing to lipid peroxidation should be clarified, and development of the prevention strategies using the information from mechanism studies deserve more attention.

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