Antioxidants and Skin Aging

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Abstract

Intracellular and extracellular oxidative stress initiated by reactive oxygen species (ROS) advances skin aging, which is characterized by wrinkles and atypical pigmentation. Because UV enhances ROS generation in skin cells, skin aging is generally discussed in relation to UV exposure. The use of antioxidants is one of

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the effective approaches to prevent symptoms related to photo-induced aging of the skin. In this chapter, alterations of the skin caused by chronic solar exposure are discussed in relation to the influence of ROS/oxidative stress. After summarizing the mechanisms of the generation and elimination of ROS in the body, the roles of ROS in altering the skin are discussed. Finally, the effects of representative antioxidants on the skin are introduced with a focus on skin aging.

Keywords
Fibroblasts • Keratinocytes • Melanocytes • ROS • UVA • UVB

Alterations in Solar UV-Exposed Human Skin

Solar UV radiation (SUV) is an important factor that increases oxidative stress in the skin through the generation of ROS. The skin is easily affected by SUV because of its outermost location on the body. In this section, alterations in the skin caused by chronic SUV exposure are introduced to define points to be discussed later.

Skin Hydration and Skin Barrier Function

Skin hydration levels at chronic SUV-exposed sites in elder subjects are lower than those at UV-protected sites. In addition, there is a tendency for higher levels of transepidermal water loss (TEWL) at chronic UV-exposed sites than at UV-protected sites in all subjects (Wang et al. 2010). Alterations of skin hydration and barrier function following UV exposure have been demonstrated by changes induced by a single UV exposure of human skin (Lim et al. 2008).

A single exposure of human skin to one minimal erythema dose (MED) of solar-simulated UV radiation (SSUV) causes an abrupt increase of TEWL which is an important parameter of skin barrier function (Lim et al. 2008). The elevated level of TEWL then recovers gradually to the original level within 7 days. However, when the exposure to SSUV is at a high energy level, such as more than one MED, the disruption of TEWL continues for up to 4 weeks or more. On the other hand, the water-holding capacity, which reflects skin hydration, declines sharply after SSUV exposure and reaches its lowest level within 2 days. It then recovers to the original level starting at 3 days after the exposure. These results indicate that an accumulation of changes that occurs after a single SSUV exposure reflects chronic alterations.

Skin Color and Pigmented Spots

To assess the influence of solar UV radiation on skin color and wrinkles, an epidemiological survey of skin conditions was conducted using volunteers living at different latitudes in Japan (Hillebrand et al. 2007). In general, UV intensity at the surface of the ground depends on the latitude. A region at high latitude has a higher

intensity of UV irradiance than at lower latitudes. In that survey, Akita was selected as the northern region (high latitude) and Kagoshima as the southern region (low latitude). Subjects residing in each region were measured for their skin color both at sun-exposed and at sun-protected skin sites. The lightness (L*) at sun-exposed skin sites was significantly higher for Akita subjects (lighter skin) compared with their Kagoshima (darker skin) counterparts. However, there was no significant difference between Akita and Kagoshima subjects for L* at sun-protected sites. In addition, quantitative analysis of facial pigmented spots showed a higher frequency in the Kagoshima subjects. That survey indicates that chronic SUV exposure accelerates skin color darkening and the formation of pigmented spots.

Skin Wrinkles

Hillebrand et al. also measured the length of skin wrinkles by image analysis (Hillebrand et al. 2007). Although wrinkle length increases with increasing age both in Kagoshima and in Akita residents, the mean wrinkle length for Kagoshima subjects was significantly longer than for Akita subjects. That result indicates that chronic SUV exposure at a higher energy enhances wrinkle formation in the skin. As a possible mechanism, alterations in skin elasticity considered the following evidence: (1) In chronic SUV-exposed skin of elderly subjects, the skin elasticity was remarkably reduced compared with SUV-unexposed skin areas (Wang et al. 2010). (2) In addition, the reduction of skin elasticity was negatively correlated with the severity of wrinkles (Fujimura et al. 2007). (3) The reduction of skin elasticity is caused by the fragile dermal structure, which is associated with decreases and alterations of collagen fibers and elastin fibers (Moloney et al. 1992; Kadoya et al. 2005).

Solar UV Radiation Is a Generator of ROS and an Inducer of Oxidative Stress

UV radiation is a potent initiator of ROS ($O_2^{\bullet -}$: superoxide anion radical, $^1O_2$: singlet oxygen) generation in the skin. However, the type(s) of ROS generated depends on the wavelength of UV. UVB mainly stimulates the production of $O_2^{\bullet -}$ through the activation of NADPH oxidase and respiratory chain reactions in mitochondria (Masaki et al. 1995; Jurkiewicz and Buettner 1996), while UVA produces $^1O_2$ through a photosensitizing reaction with internal chromophores such as riboflavin and porphyrin. UVA also generates $O_2^{\bullet -}$ through the activation of NADPH oxidase (Valencia and Kochevar 2008) and the photosensitization of advanced glycation products in the dermal matrix (Masaki et al. 1999).

On the other hand, the major type of ROS produced on the skin surface is $^1O_2$ which is generated by a photosensitizing reaction with UVA and porphyrins from bacterial flora living on the skin (Ryu et al. 2009). $^1O_2$ on the skin surface is oxidized to squalene, cholesterol, and unsaturated acyl residues in the sebum to yield lipid hydroperoxides.

Endogenous Antioxidants

ROS cause mutations in various species depending on the environment. Several systems in mammalian tissues eliminate ROS and protect cells and organs against cellular damage. SOD (superoxide dismutase) catalyzes the dismutation of $O_2^{\bullet -}$ into O_2 (oxygen molecule) and H_2O_2 (McCord and Fridovich 1988), while catalase breaks down H_2O_2 (hydrogen peroxide) into O_2 and H_2O (Chelikani et al. 1988). The combination of SOD and catalase scavenges $O_2^{\bullet -}$ initiated ROS. In addition to catalase, glutathione peroxidase (GPx) breaks down H_2O_2 in the presence of the reduced form of glutathione (GSH). GPx also decomposes lipid hydroperoxides into their corresponding alcohols (Muller et al. 2007). Thioredoxin, a ubiquitous oxidoreductase enzyme, breaks down H_2O_2 in a NADPH-dependent reaction within cells (Mustacich and Powis 2000). Metallothionein, a heavy metal ion-induced cysteine-rich peptide, also functions as a ROS scavenger (Sato and Bremner 1993).

In response to excess oxidative stress, the nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway functions to reinforce intracellular antioxidant capacity. Nrf2, which is activated by the dissociation of Keap1, binds to an antioxidant response element and upregulates the transcription of several different genes (Zhang 2006). Nrf2 downstream genes identified to date can be categorized into several groups, including the following: (1) intracellular redox-balancing proteins, such as γ-glutamylcysteine synthetase (the rate-limiting enzyme of GSH synthesis), GPx, thioredoxin, thioredoxin reductase, peroxiredoxin, and heme oxygenase-1; (2) phase II detoxifying enzymes, such as glutathione S transferase, NAD(P)H quinone oxidoreductase-1, and UDP-glucuronosyltransferase; and (3) transporters, such as multidrug resistance-associated proteins (Ishii et al. 2000; Moinova and Mulcahy 1999; Banning et al. 2005; Kim et al. 2001; Sakurai et al. 2005; Yueh and Tukey 2007; Vollrath et al. 2006; Maher et al. 2005; Ishii and Yanagawa 2007).

Influence of Oxidative Stress/ROS in the Skin

Most dysfunctions/alterations in the skin caused by SSUV are triggered by ROS. This section discusses the role of ROS stress in various cellular processes.

Inflammation

UVB radiation induces erythema in the skin, which is called sunburn. UVB-induced erythema is attenuated by the NOS inhibitor, NG-monomethyl-L-arginine, and the cyclooxygenase (COX) inhibitor, indomethacin (Warren 1994). ROS, including NO, induce skin erythema through prostaglandin E_2 synthesis (Ahn et al. 2002). Expression of COX-2, a pivotal enzyme in prostaglandin E_2 synthesis, is upregulated by ROS to stimulate the inflammatory process (Rhodes et al. 2009).

Oxidation on the Skin Surface

Oxidized lipids and proteins induce alterations in skin conditions. Topical application of oxidized squalene (squalene monohydroperoxide) on the skin disrupts skin barrier function as an acute response and induces skin roughness as a chronic response (Chiba et al. 2003). Alkyl aldehydes further oxidize proteins to produce carbonylated proteins in the stratum corneum (SCCP). Levels of SCCP increase following UV exposure (Fujita et al. 2007) and during the winter season (Kobayashi et al. 2008). SCCP could be one cause that induces skin dullness, "kusumi," by reducing the transparency of the stratum corneum (Iwai et al. 2008). In addition, patients suffering from atopic dermatitis have higher levels of SCCP compared with normal subjects (Niwa et al. 2003). SCCP levels appear to reflect the degree of oxidative stress in the skin induced by the environment. Thus, oxidative stress initiated by ROS alters skin conditions with respect to biological and cosmetic characteristics.

Melanogenesis

ROS has a paradoxical action on melanocytes because they not only cause depigmentation but can also increase pigmentation in the skin. An example of melanocyte degeneration induced by oxidative stress is vitiligo vulgaris, which is characterized by circumscribed depigmented macules in the skin (Schallreuter et al. 1999, and see chapter ▶ Reactive Oxygen Species and Reactive Nitrogen Species in Vitiligo). The skin of patients with vitiligo vulgaris have high levels of ROS and reduced levels of catalase (Sravani et al. 2009). An imbalance of the ROS scavenging system results in the accumulation of H_2O_2 in the skin. Keratinocytes are one source of the H_2O_2 that affects melanocytes (Pelle et al. 2005). H_2O_2 readily crosses cell membranes and is therefore easily transferred to melanocytes from keratinocytes. The transfer of H_2O_2 is thought to be one of the pathogenetic mechanisms of vitiligo.

ROS can also accelerate skin pigmentation. Keratinocytes adjacent to melanocytes significantly contribute to UV-induced skin pigmentation. Among ROS, $NO^{\bullet}$ derived from keratinocytes acts to induce melanogenesis by increasing levels of the melanogenic factors tyrosinase and tyrosinase-related protein 1 (Roméro-Graillet et al. 1997; Sasaki et al. 2000).

The contribution of ROS to melanogenesis has been demonstrated by studies using antioxidants. The effects of α-Melanocyte-stimulating hormone, which is increased by UVB, are abolished by N-acetylcysteine, a precursor of glutathione (GSH) (Chakraborty et al. 1996). In addition, stimulation by an endogenous antioxidant, metallothionein, also suppresses melanogenesis in melanocytes (Sasaki et al. 2004).

Furthermore, H_2O_2 activates phenylalanine hydroxylase (PAH), an enzyme that produces L-tyrosine from the essential amino acid L-phenylalanine, and thus contributes to melanogenesis by increasing the pool of L-tyrosine, the initial substrate of tyrosinase. In fact, PAH activity positively correlates with skin

phototypes (I–VI), and exposure to one MED of UVB increases PAH activity for up to 24 h. The H_2O_2 generated by UVB radiation activates PAH, thereby playing a critical role in UVB-induced melanogenesis (Schallreuter et al. 2004).

Dermal Matrix

ROS have an established role in UV-induced skin aging, characterized by wrinkles. In general, wrinkles are created by alterations of the dermal matrix in which collagen levels are decreased by the accelerated breakdown and reduction of collagen synthesis.

Nrf-2 deficient mice show acceleration of photoaging characteristics such as coarse wrinkle formation, loss of skin flexibility, epidermal thickening, and deposition of extracellular matrix in the upper dermis. As described in the previous section, Nrf-2 is an important transcription factors that maintains the cellular redox potential. The involvement of Nrf-2 and ROS in the development of photoaged skin has been recently reported (Hirota et al. 2011).

Collagen

The mechanisms involved in the contribution of ROS to collagen degradation have been demonstrated by the following observations: The $^1O_2$ generated by UVA radiation stimulates the expression of matrix metalloproteinase (MMP)-1 in dermal fibroblasts through the secretion of interleukins (IL)-1α and IL-6 (Scharffetter-Kochanek et al. 1993; Wlaschek et al. 1994). Oxidized lipids, such as linoleic acid hydroperoxide, also enhance the expression of MMP-1 and MMP-3 (Ohuchida et al. 1991). MMP-1 expression is stimulated by the activation of c-Jun N-terminal kinase (JNK), which is triggered by ROS after UV exposure. The activation of JNK due to activator protein (AP)-1 is due to the continuous phosphorylation of the epidermal growth factor receptor by ROS-dependent inactivation of protein tyrosine phosphatase (Denu and Tanner 1998). An in vivo study showed that the accumulation of H_2O_2 in the skin due to a decrease in catalase activity also stimulates MMP-1 expression (Shin et al. 2005).

On the other hand, the attenuation of new collagen synthesis is also regulated by AP-1 (Chung et al. 1996), due to a reduction of collagen synthesis modulated by ROS and effects on MMP-1 expression. In fact, exposure of human dermal fibroblasts to ROS also decreases collagen synthesis (Tanaka et al. 1993). Furthermore, extracellular thioredoxin restores the reduction in collagen synthesis initiated by UVA/UVB and by infrared radiation (Buechner et al. 2008). Thus, ROS also regulate collagen synthesis.

However, the effects of ROS on collagen synthesis show conflicting results. In the pathogenesis of scleroderma, which is characterized by excess collagen accumulation, ROS stimulates collagen synthesis. Fibroblasts from the skin of patients with scleroderma exhibit high levels of mRNAs encoding alpha1(I) and alpha2(I) collagens. In addition, they yield higher levels of $O_2^{\bullet -}$ and H_2O_2 than do normal fibroblasts. N-Acetylcysteine blocks the upregulation of collagen mRNA

expression (Sambo et al. 2001). Furthermore, adequate amounts of $NO^{\bullet}$ increase collagen synthesis in dermal fibroblasts by stimulating heat shock protein 47, which is a molecular chaperone of collagen synthesis (Obayashi et al. 2006).

Elastin

A recent study demonstrated the importance of elastic fiber alteration in wrinkle formation. The elastic fiber system consists of three types of fibers, oxytalan, elaunin, and elastic (Schwartz and Fleischmajer 1986). Among them, oxytalan fibers are fine and are localized in the papillary dermis showing candelabra-like structures toward the epidermis perpendicularly. In the process of wrinkling, oxytalan fibers also are progressively lost (Lee et al. 2008). In general, elastic fibers are decomposed by neutrophil elastase (Rijken and Bruijnzeel 2009), matrilysin-1 (MMP-7), and MMP-12 (Heinz et al. 2011; Saarialho-Kere et al. 1999). When focusing on the dermal microcirculating system, skin exposed to chronic solar SUV exhibits a gradual decrease in the size and number of dermal blood vessels (Chung et al. 2002) and dysfunction of lymphatic vessels (Kajiya et al. 2007). However, acute UV irradiation induced wrinkles are associated with hyperplasia of dermal blood vessels (Kawada et al. 2010). In any case, alterations in the blood and lymphatic systems increase the opportunity to damage dermal matrix components, because of the easy infiltration of cells from the blood such as neutrophils and macrophages into the dermis and the interfering excretion of infiltrated substances. The alterations in blood vessels are induced by imbalances of VEGF-A expression and its endogenous inhibitor, thrombospondin-1 (Yano et al. 2004). On the other hand, dysfunction of lymphatic vessels is induced by the attenuation of VEGF-C/VEGFR-3 signaling (Kajiya et al. 2009). Since some studies have indicated ROS-inducible expression of VEGF (Xia et al. 2007; Fay et al. 2006), ROS may also contribute to alterations of the dermal structure through the regulation of VEGF expression (Fig. 167.1).

Effects of Antioxidants on the Skin and on Skin Cells

Ascorbic Acid

Ascorbic acid eliminates most ROS due to the oxidation of ascorbate to monodehydroascorbate and then to dehtdroascorbate; important, ascorbic acid has diverse functions in maintaining the normal physiologic state in humans. UV radiation stimulates the translocation of SVCT (sodium-dependent vitamin C transporter-1) in keratinocytes from the cytosol to the cell surface to increase the incorporation of ascorbic acid (Kang et al. 2007). That translocation results in the protection of cells against UV-induced oxidative stress. In the skin, ascorbic acid is a cofactor required for the enzymatic activity of prolyl hydroxylase, which hydroxylates prolyl residues in procollagen and in elastin (Myllyla et al. 1984). In addition, ascorbic acid is widely used as a depigmentation agent due to its inhibitory effect on tyrosinase. Recent studies report newly discovered functions of ascorbic acid that contribute to

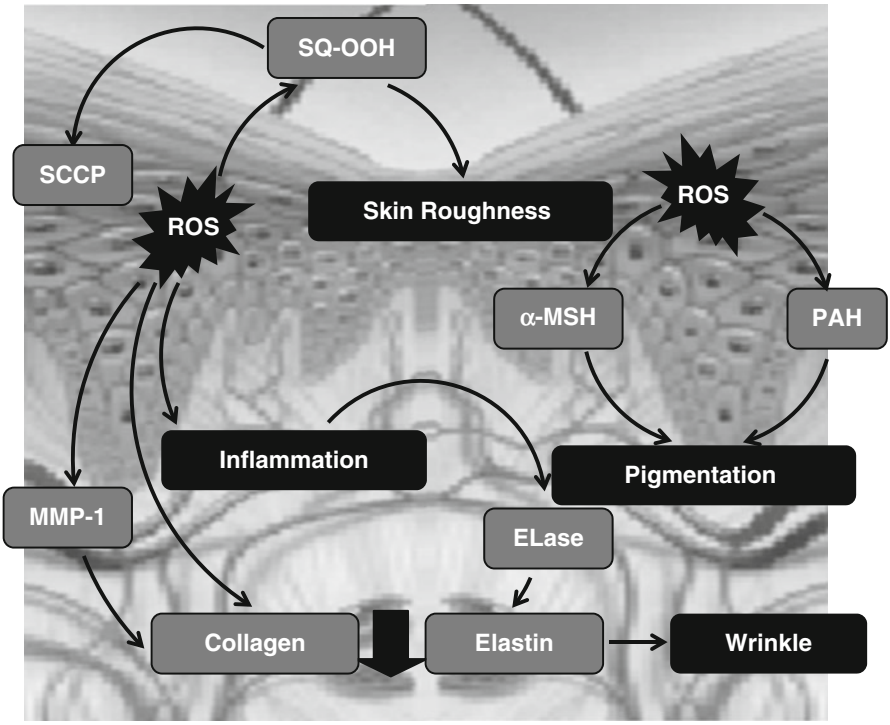

Fig. 167.1 ROS-initiated skin alterations. α-MSH: α-melanocyte stimulating hormone, ELase: elastase, MMP-1: matrix metalloprotease-1, PAH: phenylalanine hydroxylase, ROS: reactive oxygen species, SCCP: stratum corneum carbonylated protein, SQ-OOH: squalene monohydroperoxide

the formation of the skin barrier by enhancing epidermal differentiation (Boyce et al. 2002) and by stimulating blood flow through $NO^{\bullet}$ production via increases in the stability of tetrahydrobiopterin, a cofactor of constitutive NO synthase (Heller et al. 2001). Oshima et al. indicated that the dark circles on the lower eyelid, which are caused by hyperpigmentation and poor blood circulation, can be improved by ascorbic acid. In fact, in an in vivo study, sodium ascorbate significantly improved dark circles due to effects on melanin, erythema, and dermal thickness (Ohshima et al. 2009). These findings demonstrate the effects of ascorbic acid to suppress melanogenesis, to stabilize NOS, and to stimulate collagen synthesis.

Although ascorbic acid is widely applied to the skin to achieve these clinical improvements, its poor skin penetration and its instability in formulations reduce its clinical efficacy (Ebihara et al. 2003). To overcome those disadvantages, several ascorbic acid derivatives, such as magnesium L-ascorbyl-2-phosphate (Kameyama et al. 1996), ascorbic acid 2-*O*-α-glucoside (Miyai et al. 1996), 6-acylated ascorbic

acid 2-*O*-α-glucoside (Zhou et al. 2003), and tetra-isopalmitoyl ascorbic acid (Ochiai et al. 2006), have been synthesized and evaluated for their potential as pro-ascorbic acid derivatives.

Tocopherols (Vitamin E)

Tocopherols are chemical compounds comprised of a chromanol ring and a hydrophobic side chain of an isoprene molecule and are present in eight different forms based on the distinct substituted position of the methyl group in the chromanol ring and by the distinct unsaturation of the hydrophobic side chain. The antioxidative mechanism of tocopherols is partially due to the hydroxyl group in the chromanol ring which donates a hydrogen atom to reduce free radicals.

Under physiologic conditions, α-tocopherol stimulates GSH synthesis in HaCaT keratinocytes through the upregulation of γ-glutamylcysteine synthetase mRNA (Masaki et al. 2002). This finding suggests that tocopherol has biologic effects through the modulation of cellular responses.

Tocopherol has preventive effects on various types of oxidative stress. 12-*O*-Tetradecanoylphorbol-13-acetate, which is a well-known tumor promoter, also induces oxidative stress (Wei and Frenkel 1993). The application of tocopherol to the skin 30 min prior to treatment with 12-*O*-tetradecanoylphorbol-13-acetate inhibits the induction of H_2O_2, myeloperoxidase activity, xanthine oxidase activity, and lipid peroxidation (Rahman et al. 2008). α-Tocopherol acetate suppresses UVB-induced edema, erythema, and lipid peroxidation. UVA dramatically upregulates the expression of IL-8 mRNA and the secretion of IL-8 protein and enhances AP-1 DNA-binding activity. These effects of UVA are effectively reduced by α-tocopherol in a dose-dependent manner (Wu et al. 2008).

α-Tocopherol is expected to downregulate MMP-1 through its suppressive effects on AP-1 binding to DNA. Dermal fibroblasts isolated from older donors produce higher levels of MMP-1 than those from younger donors. α-Tocopherol attenuates the increased MMP-1 gene transcription in aging fibroblasts without altering the level of its natural inhibitor, tissue inhibitor of metalloproteinase, through the inhibition of protein kinase C-α activity (Ricciarelli et al. 1999). A detailed study of the ROS scavenging activity of tocopherols showed that γ-tocopherol is superior to α-tocopherol in its ability to scavenge $NO^{\bullet}$ (Yoshida et al. 2006). Tocopherol, therefore, is expected to suppress melanogenesis.

γ-Tocopherol is useful for suppressing melanogenesis and reducing the mRNA expression of tyrosinase and tyrosinase-related protein-2 in B16 melanoma cells (Kamei et al. 2009). A novel hydrophilic γ-tocopherol derivative was recently synthesized to improve its biologic effects. γ-Tocopherol-*N*,*N*-dimethylglycinate hydrochloride significantly reduces the formation of edema and tempers the increase in the COX-2-catalyzed synthesis of prostaglandin E_2 induced by UV. Further, γ-tocopherol-*N*,*N*-dimethylglycinate hydrochloride strongly suppresses $NO^{\bullet}$ production through the downregulation of inducible nitric oxide synthase mRNA expression (Cooney et al. 1993).

Carotenoids

Carotenoids are organic pigments naturally produced by plants, algae, some types of fungus, and some bacteria. β-Carotene and astaxanthin are members of carotenoids. In general, carotenoids possess the ability to quench $^1O_2$. Carotenoids are useful to protect against UV-induced damage. In this section, the effects of astaxanthin, lycopene, and fucoxanthin are introduced as representative carotenoids. The mechanisms underlying the protective effects of carotenoids have been studied in a model of UVA-irradiated human dermal fibroblasts. Moderate doses of UVA have various effects on fibroblasts, such as increasing apoptosis, increasing oxidative stress due to ROS generation, decreasing antioxidant enzyme activities, promoting membrane perturbation, and inducing the expression of heme oxygenase-1. Among astaxanthin, canthaxanthin, and β-carotene, astaxanthin preloaded in fibroblasts protects against the UVA-induced changes described above, indicating that astaxanthin has a superior preventive effect toward photooxidative changes in cells (Camera et al. 2009).

Lycopene concentrations in the skin correlates significantly with skin roughness, suggesting that higher levels of antioxidants in the skin effectively decrease skin roughness, which is an early stage of wrinkle formation (Darvin et al. 2008).

Fucoxanthin, a major carotenoid in brown algae, significantly decreases UVB-induced epidermal hypertrophy, VEGF and MMP-13 expression in the epidermis, and thiobarbituric acid reactive substances (TBARS) in the skin of hairless mice. These results indicate that fucoxanthin prevents the photoaging of UVB-irradiated skin, possibly via antioxidant and antiangiogenic effects (Urikura et al. 2011).

In human volunteers, the relationship between cutaneous carotenoid concentration and the reduction of topically applied nitroxide radicals was investigated using in vivo electron paramagnetic resonance spectroscopy. The rate constant of the nitroxide decrease correlated with the cutaneous carotenoid concentration, which indicates that cutaneous carotenoids scavenge exogenous radicals in the skin (Haag et al. 2011).

Natural Substances

Coenzyme Q10 (CoQ10) is also an intracellular antioxidative and energizing molecule, which reduces DNA damage triggered by UVA irradiation of human keratinocytes in vitro. CoQ10 suppresses MMP-1 production in dermal fibroblasts due to the downregulation of IL-6 expression in UVB-irradiated keratinocytes (Inui et al. 2008). Furthermore, CoQ10 accelerates the production of laminin 332 and type IV and VII collagens of basement membrane components due to effects on keratinocytes and fibroblasts, respectively. However, it has no effect on type I collagen production by fibroblasts. These findings suggest that CoQ10 has antiaging effects through the accelerated production of components of the epidermal basement membrane (Muta-Takada et al. 2009).

Ergothioneine is a sulfur-containing amino acid presumed to function as a natural antioxidant. In cultured fibroblasts, ergothioneine suppresses the UVB-induced upregulation of tumor necrosis factor-α. In addition, ergothioneine suppresses the expression of MMP-1 protein in fibroblasts exposed to UVA by quenching $^1O_2$ (Obayashi et al. 2005).

Zn(II)-glycine, a coordinated compound of Zn^{2+} and glycine, which is a cell-membrane permeable inducer of metallothionein and GSH, protects against UVB-induced cell damage and also suppresses IL-1α secretion and prostaglandin E_2 synthesis in human keratinocytes (Ochiai et al. 2008). In addition, Zn(II)-glycine reduces pro-MMP-1 production in dermal fibroblasts induced by the conditioned medium of UVB-irradiated keratinocytes.

Polyphenols

Polyphenols include a group of chemical molecules produced in plants characterized by the presence of phenol units in their molecular structure. In an in vitro study, green tea polyphenols inhibited UVB-induced protein oxidation in human skin fibroblasts and suppressed UVB-induced expression of MMPs, such as MMP-2, MMP-3, MMP-7, and MMP-9, in hairless mouse skin (Vayalil et al. 2004).

Epigallocatechin gallate (EGCG) is a representative polyphenol. Oral administration of EGCG for 8 weeks significantly increases the MED to UV and prevents disruption of the epidermal barrier function by UV irradiation. These findings suggest that EGCG strengthens the tolerance of the skin to UV-initiated stress (Jeon et al. 2009). Furthermore, EGCG markedly reduces UVB-induced MMP-1, MMP-8, and MMP-13 in a dose-dependent manner, suggesting that EGCG attenuates the UVB-induced production of MMP via its interference with mitogen-activated protein (MAP) kinase-responsive pathways (Bae et al. 2008).

A recent study on longevity (Borra et al. 2005) revealed the importance of SIRT1 and its activator resveratrol, which is an important antioxidant. Resveratrol increases cell survival and concomitantly reduces ROS in UVB-exposed HaCaT keratinocytes. In addition, resveratrol suppresses the activation of caspases-3 and 8 in HaCaT cells (Park and Lee 2008).

Resveratrol prevents UV-induced skin aging through activation of SIRT1 (Cao et al. 2009). In addition, resveratrol directly inhibits tyrosinase activity and suppresses tyrosinase maturation, which decreases the pigmentation stimulated by the cAMP signaling pathway (Newton et al. 2007).

Hesperidin and mangiferin, which are the two most abundant polyphenols in honeybush, reduce signs of sunburn, such as erythema, peeling, and hardening of the skin, and also significantly attenuates edema, epidermal hyperplasia, and the induced expression of cyclooxygenase-2 (COX-2), ornithine decarboxylase (ODC), GADD45, and OGG1/2 expression (Petrova et al. 2011). Luteolin also inhibits both UVB-induced skin erythema and the upregulation of COX-2 and PGE_2 production in human skin via interference with the MAPK pathway. These data suggest that luteolin may protect human skin from UVB-induced damage (Wölfle et al. 2011).

Others

Hydrogen can selectively neutralize hydroxyl radicals ($OH^{\bullet -}$) and peroxynitrite ($ONOO^-$) in cell-free systems. A recent study reported the protective effects of hydrogen on intracellular oxidative stress caused by mannitol and high glucose. A hydrogen-rich medium significantly reduced the level of intracellular $O_2^{\bullet -}$, stabilized the mitochondrial membrane potential, and attenuated levels of cellular malonaldehyde, 8-OHdG, and 3-nitrotyrosine through efficient enhancement of the antioxidative defense system (Yu et al. 2011).

Nitroxides are a class of compounds endowed with versatile antioxidant activities, and recently, nitroxide-based UV filters, such as 4-(1-oxyl-2,2,5,5-tetramethyl-1,5-dihydro-1H-pyrrol-3-yl) methoxycinnamic acid ethylhexyl ester, in which a nitroxide moiety has been attached to the most popular UV filter present in sunscreens, have been developed. A tenfold increase in MMP-1 mRNA expression levels was observed 24 h post-UVA treatment, which was significantly reduced by all nitroxide compounds (Venditti et al. 2011).

Conclusions

Oxidative stress initiated by ROS generation is an important factor accelerating skin aging. The human body has several endogenous oxidative stress-eliminating systems to overcome damage induced by oxidative stress. In addition, treatment with some antioxidants, such as ascorbic acid, tocopherols, and polyphenols, enhance resistance to oxidative stress and prevents / improves skin aging. The information in this review will contribute to the development of future clinical and basic studies of the skin and potential treatments for skin diseases and skin aging.

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