11

Metabolism and Functions of Amino Acids in the Skin

F. Solano

Abstract

Amino acids are the building blocks of all proteins, including the most abundant fibrous proteins in the skin, as keratins, collagen and elastin. Sagging and wrinkled skin are features of chronic sun-damaged and aged uncared skin, and they are mainly associated with the deterioration of collagen and elastic fibers. The maintenance of skin structures by self-repair processes is essential to skin health. Thus, amino acids significantly impact the appearance of the skin. Amino acids are important nutrients required for (a) wound healing promotion and repair of the damaged skin; (b) acid-base balance and water retention in cellular layers, such as stratum corneum; (c) protection against sunlight damage; (d) maintenance of an appropriate skin microbiome. This review highlights the contribution of all proteinogenic amino acids and some related metabolites to the skin structures as constituents of the main cutaneous proteins or as signaling molecules for the regulation and determination of skin physiology.

Keywords

Amino acids · Skin · Epidermis · Dermis · Collagen · Elastin · Keratins · Melanin · Skincare

11.1 Introduction

Skin is a largest tissue in animals, with a surface of approximately 2 m^2 and around 4 kg in the adult human. It is a thin but wide tissue. In humans, its thickness goes from less than 1 mm on eyelids to more than 4 mm on the palms of hands and soles of feet. Skin is essential for general health as it is the first line of defense of the body against harmful external chemical, physical and biological agents in addition to other functions, such as the control of the corporal temperature. These agents include Vis-UV irradiation, chemical air pollutants, mechanical pressure, dehydration, as well as viral, bacterial and fungal infections. Skin cannot be considered just a physical barrier but it is also a dynamic tissue with its own metabolism and interactions between external and internal cells.

Anatomically, skin is a complex organ composed of two main compartments: epidermis and dermis, separated by the epidermal-dermal junction. Epidermis has several layers, and the most external one is the *stratum corneum* that constitutes an excretion system by losing old epidermal

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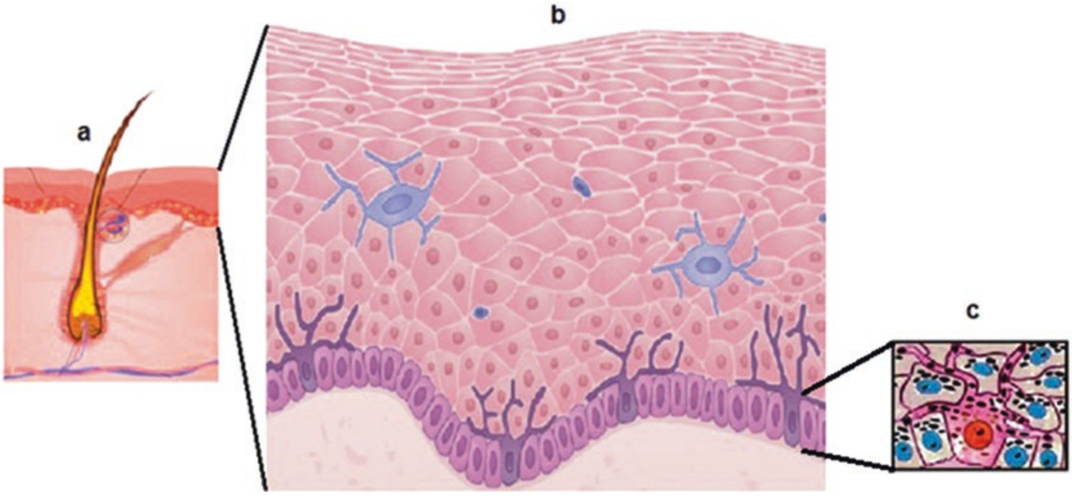

Fig. 11.1 Structure of skin. (**a**) Skin showing the three main parts, external epidermis, epidermal-dermal junction and dermis. Dermis contains fibroblast among extracellular matrix, with collagen and elastin as more abundant proteins; (**b**) Amplification of the epidermis layer showing abundant keratinocytes with some distribution of other cell types (Merkel and dendritic Langerhans cells). Melanocytes are also dendritic cells, but mostly found in the epidermal-dermal junction; (**c**) Detail of one melanocyte transferring melanosomes (melanin granules) to surrounding keratinocytes through its dendritic ramifications

cells with waste components. Epidermal cells are replaced about every month. The main cellular components of the epidermis are keratinocytes, and others include melanocytes, Langerhans cells, α-dendritic cells and Merkel cells (Fig. 11.1). Keratinocytes in the deepest layer of epidermis divide constantly and the new cells are pushed towards the external surface. Dermis contains fibroblasts as main cells among other components, such as blood vessels, touch and pain sensors, hair follicles, sweat and oil glands.

Keratinocytes synthesize high amounts of keratins, which are fibrous proteins providing the skin with a durable overcoat to protect from drying, mechanical damage and infection. Around 95% of epidermal proteins are keratins. Other important protein is filaggrin. Dermal fibroblasts are producers of two important proteins in the skin, collagen and elastin. Those proteins begin to decrease from age 25 in humans, and about 70% of the dry skin mass is collagen.

Keratinocytes and fibroblasts produce the essential proteins for cutaneous fibers. An unbalanced ratio of amino acids, the building blocks of proteins, will cause a reduction in protein synthesis in the skin (Li and Wu 2018). Those proteins prevent skin thinning, loss of skin elasticity and dehydration and minimize the conditions that lead to the appearance of sagging and wrinkles. Furthermore, deficit or dysfunction of these proteins lead to severe diseases, such as urticaria, xerosis, eczemas, thrush, itching and skin ulcers. In addition to internal requirements, epidermal keratinocytes need amino acids to synthesize some antimicrobial peptides to kill pathogens (Park et al. 2013), although at the same time skin provides an interface to host the epidermal common microbiota. The metagenomic DNA sequencing studies in the skin microbiota has been recently focused on *Propionibacterium acnes*, *Staphylococcus epidermidis* and *Staphylococcus aureus* (Byrd et al. 2018). Amino acid replacement is especially important in the skin where they are lost due to shedding of *stratum corneum* cells. This requirement of particular amino acids is related to: (1) their relative abundancy in the sequence of main skin proteins, and (2) their forming-capacity. As it is well known, human cells cannot synthesize all the proteinogenic amino acids (Wu 2013). From this point of view, amino acids had traditionally been classified as nutritionally essential or non-essential (Hou et al. 2015). Essential amino acids cannot be formed de novo, so that they must be obtained from foods or supplements and any deficiency can result in health problems. The “non-essential” term means that the human cells can synthesize them de novo, but it does not mean that those amino acids are less important for skincare. Some of these non-essential (arginine, glycine and tyrosine) are also known as “conditionally essential” amino acids, meaning they cannot be formed sufficiently under certain conditions. The term “nutritional nonessential amino acids” is now considered as a misnomer in nutritional sciences and should no longer be used (Hou and Wu 2017).

The most common amino acids in skincare products are the 3 cationic ones (His, Lys and Arg), and 3 neutral ones that are especially abundant in collagen (Gly, Pro and Leu). Amino acids are not only needed for protein synthesis, but they play specialized roles in maintaining healthy skin. None of them can be considered as the most important one, as they are complementary to each other. For example, a combination of Lys and Arg can effectively treat certain skin injuries by accelerating would healing, while Pro and Leu can attenuate wrinkles when paired together. A mixture of four amino acids supplemented with other components are effective to decrease the time of wound healing (Corsetti et al. 2010). It should bear in mind that they act in combination with other components of the skin, including lipids (e.g., glycerin, ceramides and ω^3 fatty acids), polysaccharides (e.g., hyaluronate, vitamins D and E, and some inorganic ions such as Zn).

Thus, amino acids are active compounds used in cosmetic and therapeutic treatments for a number of skin diseases and just for hydrated and young skin maintenance. This review is devoted to amino acids and skin health. The specific roles of each of them will be described in the next paragraphs.

11.2 Histidine (His)

This amino acid has important roles in the skin. His is related to the formation of several biomolecules, not always proteins. This paragraph will be focused on a very important protein in the stratum corneum, filaggrin and a His-derivative, urocanic acid (UCA, Fig. 11.2). In fact, both molecules are correlated because filaggrin could be a reservoir of His for its transformation into UCA. Increased filaggrin expression and urocanic concentration have been found to be correlated in chronic spontaneous urticaria (Le Pharm et al. 2017). Other roles of His are related to the prevention against certain fungal infections, as the systemic candida, due to the synthesis of one antifungal histidine-rich glycoprotein that breaks the cell walls of fungal cells by specific interactions with ergosterol (Rydengård et al. 2008) or the formation of histamine in dermal mast cells, and an involvement in inflammatory and allergic responses. The formation of antimicrobial peptides or the role of histamine are out of the scope of this review.

11.2.1 Filaggrin

His plays an important role in preserving the moisture of stratum corneum. Filaggrin is one of the most important proteins specifically located in in granular keratinocytes and lower corneocytes of the stratum corneum (Hsu et al. 2011). Filaggrin aggregate with keratin intermediate filaments during terminal differentiation of mammalian epidermis and it is a component of the cornified cell envelope. Human filaggrin is synthesized as a large, insoluble, highly phosphorylated precursor containing more than 20 tandem copies around 50 residues long (P20930, www.expasy.org) especially rich in histidine, but also serine and arginine.

The stratum corneum maintains its hydration level at ~15% by retention of free amino acids that act as emollient factors (Jacobson et al. 1990; Seguchi et al. 1996; Kim et al. 2012). Many data suggest that selective proteolysis of filaggrin is the source of those amino acids. First, the composition of free amino acids in skin shows a high degree of similarity to the composition of filaggrin. Secondly, a decrease in the amount of amino acids contributes to the pathogenesis of xerotic skin conditions (Horii et al. 1989), and this is correlated with low filaggrin content in the epidermis. Thus, during terminal differentiation filaggrin acts as a natural moisturizing factor. It is phosphorylated and proteolytically cleaved by calpain-1 (Senshu et al. 1996; Hsu et al. 2011). In addition, some His and Arg residues in filaggrin undergoes deimination, so that UCA and citrulline residues appear. Thus, filaggrin can be considered the major source of His in the stratum corneum (Koyama et al. 1984), and then this amino acid could be transformed to UCA, which is an important signal of stress conditions in the skin.

11.2.2 Urocanic Acid

UCA is produced by His deamination (Fig. 11.2). Significant amounts of this metabolite are found in blood, but interestingly it is mostly concentrated in skin, particularly in the *stratum corneum* (Tabachnick 1957). Due to that location and its light-absorbing properties, the initial studies of this chromophore indicated that it could play a role as a physiological sunscreen, as its main UVR absorption band around 260 nm is coincident with the absorption band of the bases contained at nucleic acids. This proposal was supported with the direct evidence of the photoprotective effect of UCA (Barresi et al. 2010). However, UCA content does not correlate with the pigmentation level or the minimal erythema doses. Therefore, the other roles of UCA were proposed, such as a buffering effect to maintain the relatively acidic pH of the stratum corneum (around 5.5) that contributes to the inhibition of pathogenic bacterial and fungal growth.

The interest in UCA has been increased in recent years and its two other possible physiological roles have been proposed, involving not only the skin but other tissues. For instance, it has been detected that the His-derived isomer t*rans*-UCA is photoisomerized to *cis*-UCA by exposure to UVR. Opposite to the trans-isomer, *cis*-UCA produces proapoptotic intracellular acidification and oxidative DNA damage, and triggers specific immunologic responses. Some authors describe immunosuppression (Kaneko et al. 2008) and others reported an IgE-mediated basophil activation (Le Pharm et al. 2017). Relative "beneficial" versus "detrimental" properties of UCA have been reported. Thus the formation of UCA in the stratum corneum is important, but its roles are complex and remain largely unknown (Gibbs and Norval 2011).

On the other hand, a novel metabolic pathway that transforms UCA to glutamate in neurons have been suggested (Zhu et al. 2018). The UV exposure of skin increases the levels of UCA, which then could be able to cross the blood-brain barrier and be transformed into glutamate by neuronal urocanase. If so, this mechanism reveals a new glutamate biosynthetic pathway that may contribute to some of the sunlight-induced neurobehavioral changes related to the ancient belief that sunlight exposure affects mood, learning, memory and cognition. The underlying mechanisms may involve diverse signaling molecules, such as melatonin, without a total satisfactory correlation (Goswami and Haldar 2015).

11.3 Lysine (Lys)

Lysine is one of the essential amino acids that have been extensively studied. Its recommended daily allowance is from 41 mg per kilogram of

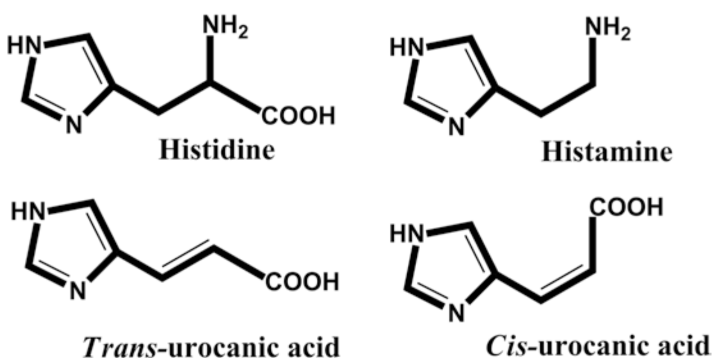

Fig. 11.2 Chemical structure of Histidine and derived molecules with relevance in the skin: histamine; trans-urocanic acid; cis-urocanic acid

body weight per day in adults to 89 mg/kg of body weight in children, although the estimated requirements are lower since its absorption is dependent on other nutrients in diets. Lysine is especially important for proper collagen and elastin functions. Once Lys is incorporated into skin proteins, and some post-translational modifications on the side chain make Lys residues essential for maturation of those proteins. Those modifications are catalyzed by different types of enzymes, lysyl hydroxylases and lysyl oxidases. In preprocollagen chains, some lysyl residues are intracellularly hydroxylated at the 5-carbon by vitamin-C dependent lysyl hydroxylases. Human collagen analysis shows that approximately 20% of the Lys residues are 5-hydroxylated (Veis and Anesey 1965). Subsequently some glycosyl transferases add carbohydrate moieties at the 5-hydroxy-Lysine residues. On the other hand, once the tropocollagen or proelastin are secreted to the extracellular matrix, some ε-amine groups of lysyl or 5-hydroxylysyl residues are oxidized to aminoadipic semialdehyde (also named al-lysine, Fig. 11.3) by lysyl oxidases (Lox), a specific type of copper amine oxidase present in the skin. The aldehyde group of al-lysine reacts with other ε-NH_2 groups of unaltered lysyl residues to form covalent cross-linked bonds among tropocollagen units, thereby providing tensile strength and insolubility to protein fibers. Other cross-linking reactions are possible, forming structures such as lysinonorleucine (two cross-linked chains), merodesmosine, (3 cross-linked chains) and desmosine or isodesmosine (4 cross-linked chains with the formation of a complete pyridinoline ring). Desmosine, which is much more abundant in elastin than in collagen, is primarily responsible for the elasticity and is commonly used as a marker for elastin.

It is worth to mention that Lys supplementation has been also proposed for prevention of acne and cold sore. Complex factors, such as hormone fluctuations and stress are involved in the appearance of acne. In fact, acne is the result of a combination of bacteria, oil (sebum) and dead skin cells trapped in hair follicles, clogging pores. There is no doubt that acne repair would require collagen turnover, so that adequate intakes of amino acids, along with other nutrients, may help to treat acne. However, there is no particular scientific evidence that Lys improves the lesions of this skin disorder.

Finally, unrelated of collagen production, a tripeptide containing Lys and His has been proposed as a skin moisture agent used in skincare products (Choi et al. 2012). Gly-His-Lys is a copper(II)-chelating motif occurring in some serum proteins that promotes the survival of basal

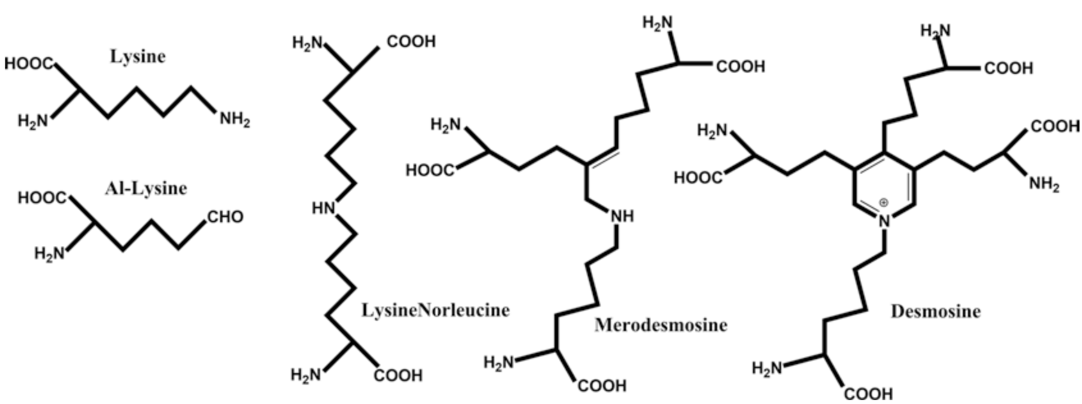

Fig. 11.3 Chemical structure of Lysine and the derivative aldehyde Al-Lysine formed by Lox action. During the process of cross-linking in collagen and elastin, the side chain of these amino acids can react to form Lysinenorleucine (1 Lys and 1 Al-Lys), Merodesmosine (1Lys and 2 Al-Lys) or Desmosine (1 Lys and 3 Al-Lys residues forming the pyridinoline ring). Isodesmosine is similar to desmosine, but the positions of the 4 side chains are 1,2,3 and 5

stem cells in the skin and the proliferation of keratinocytes with increased expression of integrin.

11.4 Branched-Chain Amino Acids: Isoleucine, Leucine and Valine

These branched-chain amino acids are nutritionally essential for humans (Wu 2013). Formation of keratins, collagen and skin proteins is affected by the availability of these nutrients, especially for replacement of damaged collagen. However, their specific effects on the skin have been rarely studied. Amino acid mixtures consisting of branched-chain amino acids (Ile, Leu and Val) plus Arg, Gln or Pro significantly increased the synthesis of dermal collagen in hairless mice submitted to UVR irradiation (Murakami et al. 2012). The stimulatory effect does not occur when the amino acids are supplied individually, but the presence of all the three branched-chain amino acids seems to be necessary for beneficial effects (Murakami 2014). Leu has also been used for attenuation of skin wrinkles in conjunction with Gly and Pro (Kawashima et al. 2013). Beyond the general effect as building blocks of the protein, recent data suggest that deficiencies of Leu and Ile reduce collagen synthesis in skin by suppressing the action of mTOR (Yamane et al. 2018). Thus, these amino acids could be involved in regulatory mechanisms, such as autophagy or transcription.

To strength muscles for exercise, a Leu metabolite HMB (β-Hydroxy-β-methylbutyrate) has been used as a dietary supplement. This substance has been proposed to promote wound healing, and therefore it has been added to some skincare products (Williams et al. 2002; Morfino et al. 2013). However, recent studies have shown that supplementation with Gln, Arg and HMB does not have any beneficial effect in enhancing healing of open wounds in rats (Bozkirli et al. 2015). Ile has been also used as a complement component of ceramides-based emollient cream for treatment of facial atopic eczema (Puviani et al. 2014), but the precise role of this amino acid is unclear.

11.5 Phenylalanine (Phe) and Tyrosine (Tyr)

Tyr and Phe are not very abundant in collagen, elastin or keratins, so that the correlation between the supply of these amino acids and the synthesis of skin proteins has not been reported. However, these aromatic amino acids are important as precursors of melanin (Fig. 11.4). Melanin absorbs the harmful sunlight UV and thus is the main cutaneous photoprotective pigment for avoiding DNA damage and skin cancer types (Brenner and Hearing 2008; Solano 2016; Fajuyigbe et al. 2018). Phe can be converted into Tyr by phenylalanine hydroxylase. This enzyme generates Tyr from essential Phe. Of note, Phe hydroxylase is activated in human melanocytes by ROS and the oxidant conditions created after UV exposure (Schallreuter et al. 2004). Then, Tyr is further oxidizes to melanin by tyrosinase (Solano 2014). Phe hydroxylase (a tetrahydrobiopterin-dependent enzyme) and tyrosinase (a copper enzyme, Solano 2018) are present in melanocytes, the specialized cells for melanin synthesis

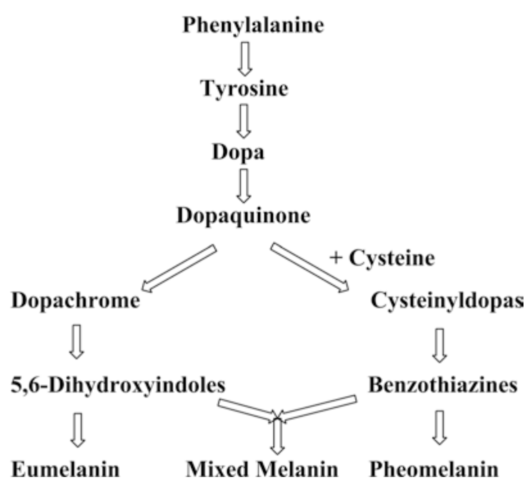

Fig. 11.4 Scheme of the melanogenesis pathway showing the role of Phenylalanine and Tyrosine as melanin precursors. Cysteine is also involved in pheomelanin formation

(Fig. 11.1). Melanogenesis takes place in a subcellular organelle of melanocytes called melanosomes (Slominski et al. 1988), and then melanosomes are transferred to keratinocytes (Serre et al. 2018). Freckles and moles are patches of skin with more melanocytes and therefore more melanin than the surrounding area.

The requirements of Phe and Tyr for melanin synthesis depends on the exposure to sunlight and the skin phototype. The amount and type of melanin determines the degree of tanning in each phototype and the skin color. Dark skin needs higher amounts of (eu)-melanin than fair skin. Fair skin contains predominantly pheomelanin, a type of melanin that is structurally different from the dark eumelanin. Pheomelanin formation needs lower amounts of Phe/Tyr but it needs Cys (Wu 2013; Solano 2014).

11.6 Tryptophan (Trp)

This is another aromatic amino acid that is not abundant in skin proteins. There are very few studies on the role of tryptophan in the skin health, but Trp is the precursor of melatonin, a hormone involved in skin protection against oxidative stress. Human skin contains all the enzymes necessary to transform Trp into melatonin, as the pineal gland does (Slomisnki et al. 2008). Absorption of sunlight in the skin, particularly UVA rays, induces the formation of photosensitizers (Wondrak et al. 2006). The endogenous chromophores in human skin serve as photosensitizers but are not well characterized. In addition to melatonin, the Trp derivative, 6-formylindolo[3,2-b]carbazole (FICZ) found in epidermal keratinocytes has been proposed as one possible UVA-photosensitizer. FICS may bind to a skin-occurring aryl hydrocarbon receptor (Syed and Mukhtar 2015), and could be formed as a consequence of spontaneous chemical damage of Trp residues in the skin proteins.

Impaired Trp transport is related to Hartnup disease. The mutated gene encoding a solute carrier protein is mainly expressed in the small intestine and renal tubules, causing malabsorption and neutral amino aciduria including Trp and other amino acids (Wan 2011). The Hartnup symptoms are photosensitivity and pellagra-like skin rash, suggesting that Trp deficiency affects skin integrity and function.

11.7 Sulphur-Containing Amino Acids: Methionine (Met) and Cysteine (Cys)

Oral ingestion of Met can be an endogenous source of Cys in keratins, and Cys plays an important role in the formation of the disulfide bridges present in the integumentary skin structures (Fraser et al. 1972; Miniaci et al. 2016). These sulfur-containing amino acids along with other sulfated compounds are the sources of sulfur for several functions. Adequate consumption of dietary Met and Cys is required to meet the body's requirements for the formation of skin structural polysaccharides and glycosaminoglycanes (Danzberger et al. 2018). Met can also be used as a zinc-vehicle rather than a sulfur-supplier for treating acne and inflammatory cutaneous lesions as antioxidant complexes (Sardana and Garg 2010).

11.8 Threonine (Thr)

The role of Thr in skin health has not been described in the literature. Thus, there are very few data concerning nutritional Thr requirements for the maintenance of the skin or any other tissue. Thr and Ser are appropriate amino acids for keeping the stratum corneum in a hydrated state. In proteins, Thr and Ser may be phosphorylated by a number of kinases. Several epidermal proteins must be phosphorylated for a proper structural function and control of skin metabolism.

11.9 Amino Acids that Are Synthesized in Animals (AASA)

These amino acids are synthesized de novo by humans (Wu et al. 2013), and are Arg, Gly, Pro, Ala, Ser, Asp, Glu, Gln and Asn. Tyr and Cys are formed from Phe and Met, respectively, as noted previously.

11.9.1 Arginine (Arg)

Arg can formed as an intermediate in the urea cycle in the mammalian liver, but there is no net synthesis of arginine by the liver (Wu and Morris 1998). There are no reports on the urea cycle in skin. In humans, arginine is synthesized from glutamine, glutamate and proline via the intestinal-renal axis. Arg is a conditionally essential amino acid in children and possibly in adults (Wu et al. 2009). Arg is one of the highly recommended amino acids to accelerate the wound healing of injured skin (Stechmiller et al. 2005) due to the production of nitric oxide (NO). In addition, poly-Arg has been recommended for topical application for treatment of frostbite injuries in frozen skin (Auerbach et al. 2014), although the role of this polypeptide in Arg storage in vivo has not been demonstrated.

NO is involved in the inflammatory and proliferative mechanisms of wound healing and has been proposed as an inducer of collagen synthesis in fibroblasts (Childress and Stechmiller 2002; Kim et al. 2012; Alexander and Supp 2014). However, other data indicate that Arg is not a key amino acid for skin-repairing processes. First, Arg is not contained in Vulnamin (Gly, Lys, Pro and Leu), one of the most efficient creams for skin ulcers treatment (Corsetti et al. 2010). Second, protein hydrolysates of some mollusks, such as mussels (*Mytilus galloprovincialis)* and hard-shell clam (*Rapana venosa)* are really effective in wound healing. *R. venosa* extracts contain higher amounts of Leu, Pro, Thr and Lys but not Arg than those of mussels, but are more efficient to reduce the time of wound (Badiu et al. 2010).

11.9.2 Glycine (Gly) and Proline (Pro)

Gly and Pro are by far the two most abundant amino acids in collagen, and therefore it is not surprising that they play an important role in the production of this protein (Albaugh et al. 2017). These amino acids are not only abundant constituents of collagens but also regulators of collagen synthesis (Wu et al. 2011). As collagen turnover is perhaps the most important factor to keep skin health, there is a huge amount of nutritional and dermatological studies around it. There are even some collagen-containing-creams used for topical application, although this approach is unfortunately useless as collagen cannot penetrate the skin due to its high molecular mass. Compared with meat (Wu et al. 2016), the content of both glycine and proline in plant-source foods for humans and animals is relatively low (Hou et al. 2019; Li and Wu 2020). The mean molecular mass of the tropocollagen unit is around 130 kDa, much higher than the 0.5 kDa limit for possible skin penetration (Bos and Meinardi 2000). It is much more effective for topical application mixtures of free amino acids containing Gly and Pro than collagen (Corsetti et al. 2010).

Pro, similarly to Lys, undergoes significant post-translational modifications during collagen maturation. A variable number of Pro residues in preprocollagen should be hydroxylated to 4-hydroxyproline (OHPro) by vitamin-C dependent intracellular prolyl hydroxylases (Wu et al. 2019). The HOPro residues are essential for tropocollagen stability due to the formation of hydrogen bonds inside trimers. Degradation of collagen generates OHPro, which is effectively used for glycine synthesis in mammals (including humans) (Wu et al. 2019) and is a potent antioxidant (Ji et al. 2018). Quantitative determination of collagen is difficult, but some methods have been developed for diagnosis of skin disorders based on acidic hydrolysis of a tissue sample and determination of a specific marker (Stoilov et al. 2018). Pyrrole-2-carboxylic acid derived from OH-Pro is used as a biomarker for collagen.

Due to the requirements for HOPro, the mostly used collagen-related products for skincare are short collagen-peptides obtained from partial

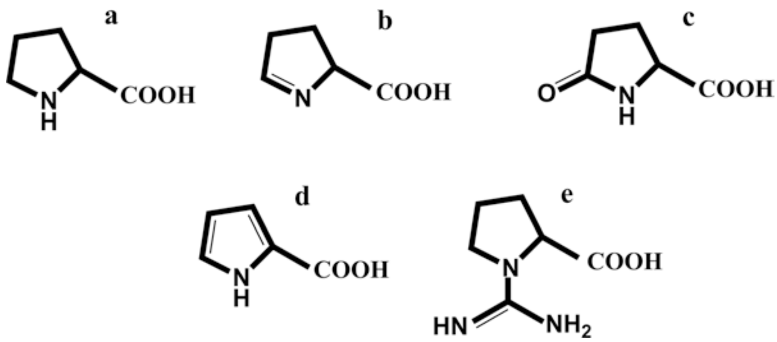

Fig. 11.5 Chemical structure of Proline and derived molecules with relevance in the skin. (**a**) Proline; (**b**) Pyrroline-5-carboxylic acid; (**c**) Pyroglutamic acid (or 5-oxo-Proline); (**d**) Pyrrole-2-carboxylic acid; (**e**) 1-Carbamimidoyl-Proline

hydrolysis. They are mixtures of low-molecular-weight short-peptides obtained from gelatins of several animal sources (Gomez-Guillen et al. 2011). These peptides are most studied than the free amino acids concerning their skin effects. Their beneficial action on human fibroblasts was described 40 years ago (Postlethwaite et al. 1978) and they are currently the most important nutrient to retard skin aging (Sibilla et al. 2015). Identification, traceability, half-life and skin effects of those peptides in human blood have been studied (Iwai et al. 2005; Zague 2008; Draelos 2010). The most effective peptides are Gln-Gly-Ala-Arg (Li et al. 2007), Gly-Pro-HOPro (Watanabe-Kamiyama et al. 2010) and Pro-HOPro (Shigemura et al. 2009). They are absorbed across intestinal brush-border membrane through peptide transporter 1 (Aito-Inoue et al. 2007) and then distributed in the human body. After oral ingestion, Pro-HOPro has a long half-life in human blood until reaching the skin. Inside fibroblasts, this dipeptide is easily hydrolyzed by intracellular prolidase to release the constituent amino acids. This enzyme plays an essential regulatory role in collagen turnover, recycling peptides derived from endogenous or exogenous collagen-degradation products. Several lines of evidence suggest that prolidase activity may be a step-limiting factor of this process during wound healing (Surazynski et al. 2008).

Recently, a double-blind, randomized clinical trial using collagen peptides demonstrated a significant increase in human skin elasticity after daily oral consumption of these products (Genovese et al. 2017). The measured indicators include human skin moisture and surface roughness Proksch et al. (2014). The skin elasticity is regulated, at least in part, by maintaining the hydration degree of the stratum corneum, presumably with the contribution of several amino acids. Another clinical trial (Kawashima et al. 2013) showed that topical treatment with a proline-derivative (1-carbamimidoyl-L-proline, Fig. 11.5) also improved skin elasticity in a number of Japanese women who had crow's feet lines on their faces. 1-Carbamimidoyl-L-proline would stabilize Pro due to the carbamimidoyl group, likely increasing the absorption of this derivative through the skin.

11.9.3 Other Amino Acids

Serine (Ser) and alanine (Ala) are moisturizing agents added to some skincare products. As for free amino acids, Ser and Ala play a general role in water retention in the stratum corneum. Ser is one of the most abundant amino acids in filaggrin, the main skin protein that helps to maintain pH and hydration at the stratum corneum (see above). Therefore, dietary sericin, a Ser-rich silk protein, has been proposed for improving skin hydration in atopic dermatitis (Kim et al. 2012).

Glutamine (Gln) has been proposed as a stimulator of collagen biosynthesis (Karna et al. 2001). Thus, this amino acid is another usual ingredient of diet supplements frequently proposed for improving wound healing because it inhibits protein breakdown (Williams et al. 2002; Morfino et al. 2013; Xi et al. 2012). High levels of Gln are needed for regulation of the acid-base balance via renal ammonia genesis in the human body. When the intake of Gln decreases, this amino acid is obtained from muscle proteins hydrolysis, but also collagen and elastin, therefore decreasing the amount of those proteins. The mechanism for Gln to stimulate collagen synthesis remains unknown. It may be related to its interconversion in glutamate (Glu) and pyrroline-5-carboxylate (P5C) or pyroglutamic acid (Fig. 11.5) that allows the interconversion of Glu into Pro. Some of these molecules show higher stimulation of collagen biosynthesis than Gln (Karna et al. 2001). P5C induces the expression of prolidase, an enzyme involved in collagen metabolism. Thus, the most likely mechanism for Gln to enhance collagen biosynthesis could involve its conversion into Pro through the intermediate P5C. In most mammals (including humans), the conversion of Gln into P5C occurs exclusively in the enterocytes of the small intestine (Wu and Morris 1998), indicating a close link between gut and skin health.

Aspartic acid (Asp) and asparagine (Asn) are not considered important amino acids for skin health. However, as excitatory neurotransmitters, excessive Asp and Glu may contribute to nociception and inflammatory pain in peripheral tissues including the skin (Omote et al. 1998). On the other hand, Asp has been proposed as an aging index. In mammals, proteins are composed of L-amino acids except for glycine which has no L or L form. However, it was observed that the skin of proteins in old adults contained some D-Asp residues that resulted from the spontaneous racemization of L-Asp residues (Ritz-Timme et al. 2003). Recently, it has been demonstrated that this is a general feature of proteins (Fujii et al. 2018). Asp racemization can be correlated with long-lived proteins, and skin proteins show a low rate of turnover. The accumulation of D-Asp residues is a feature in aging elastin, and therefore the determination of the content of this racemic mixture is useful for assessing the *in vivo* turnover and degradation of skin elastin.

Asn is needed for cell growth. Deprivation of Asn with the bacterial enzyme asparaginase is used to inhibit cell proliferation (Durden 2016). This approach has been used for malignant cells and it might be also applied to the treatment of cell hyperproliferation of keratinocytes, as occurring in psoriasis.

11.10 Non-protein Amino Acids: Mycosporine-Like Amino Acids

These are natural products of the secondary metabolism in organisms living in marine and sunlight environments. The mycosporine family of amino acids consists of several members, but they are not alpha-amino acids. The most studied mycosporine is palythine (Fig. 11.6), extracted from corals and sea hares (Carignan et al. 2009; Kicklighter et al. 2011). These molecules are photostable and show strong UVR-absorbing properties that have evolved for protection against the chronic sunlight exposure, although they can also play other roles as chemical cues. However, the mechanisms behind the UV absorption and its photostability are largely unknown.

Concerning these ecologic photoprotectors, recent data indicate that very low concentrations of palythine can provide a significant protection to human keratinocytes exposed to UVA irradiation (Lawrence et al. 2018). In addition, when palythine is added after UV light exposure, it behaves as a potent antioxidant, reducing oxidative stress by scavenging ROS species. Those results suggest that they have an interesting potential as natural and biocompatible alternatives to currently UVR filters to protect human epidermis.

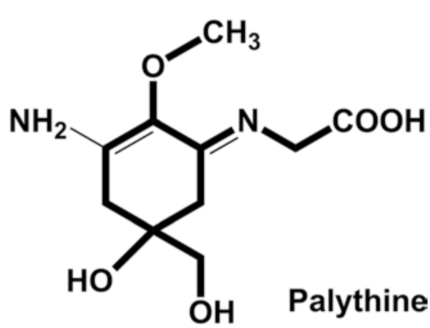

Fig. 11.6 Chemical structure of Palythine, one of the Mycosporine-like amino acids found in marine organisms

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