Chain reaction – skin enzymes and enzyme defects

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The human metabolism is a finely tuned system operated and maintained in balance by various chemical reactions. Enzymes are the facilitators that catalyse the individual reactions. Defects and mutations cause dysregulations which also have consequences for the skin.

Enzymes can be visualised as pitfalls into which precisely fitting substrates in the form of molecules or molecule parts disappear; they are retained, chemically changed and then again released. Unlike conventional chemical reactions, the whole process happens with minimal energy input. This is why we speak of biochemical reactions and biocatalysts.
Some enzymes are highly specialised and content themselves with the conversion of a particular substance only, while others are occupied with a whole substance class. The number of enzymes probably runs into thousands. In addition, there are the enzymes of the dermal microbiome on the skin surface which is dominated by staphylococci and propioni bacteria and contributes to the formation of the acid mantle of the skin.

The specialists

Enzyme performances are increased or reduced by activating, multiplying, degrading or inhibiting the enzymes depending on the available material. This occurs via endogenic or exogenous, physical or chemical influences. The enzyme tyrosinase which is responsible for the formation of the protective melanin for instance is activated by UV radiation of the sun and can be inhibited by the ascorbyl phosphate (vitamin C ester) of a topically applied serum.

Enzymes, linguistically identifiable by their suffix "…ase", mainly consist of protein structures; active hubs with possibly metallic elements which can induce particular reactions. Depending on the type of biochemical reaction it is differentiated into various enzyme classes:

- **Oxidoreductases** are responsible for oxidations and reductions. Example: catalase reduces hydrogen peroxide to water.
- **Transferases** transfer functional groups of a substance to another. Example: acyltransferases transfer fatty acid residues by means of coenzyme A. They participate in the degradation of fatty acids via ß-oxidation.
- **Hydrolases** decompose molecules by means of water, as for instance esters into alcohols and acids (esterases) or urea into ammonia and carbon dioxide (urease).
- **Lyases** cleave bonds or entire molecules. Example: fumarase in the natural citric acid cycle of the body transfers fumaric acid into malic acid.
- **Isomerases** change the steric structure of molecules. Example: epimerase transfers galactose (mucus sugar) into glucose.
- **Ligases** link two molecules together, as for instance aspartic acid reacts with ammonia to asparagine.

Among the enzymes are all-rounders which can catalyse several reactions and hence cannot be categorised into a single enzyme class. On the other hand there are specialists such as for instance the hydrolases that split off a single amino acid of a protein, or also fragments consisting of 2, 3 or more amino acids. These enzymes, also called proteases alias proteinases or peptidases, play a significant role in the healthy but also in disordered skin. In this context it should be realised that the homeostasis, or in other words, the balance of all processes occurring in the skin is not a static but a continuously changing process.

Out of step

Whenever there is a delay between formation and degradation, the homeostasis is disturbed. In the case of **rosacea,** the synthesis of antimicrobial peptides (AMP) and particularly of the cathelicidines is stimulated. However, since the endogenic proteases degrade peptides still at a faster pace, the antimicrobial defence of the skin is insufficient. Consequently, facultative pathogenic germs are out of control and continue to do damage with their own prote-

ases. The consequence is an inflammatory reaction.
Similar conditions are found in **neurodermitic skin**. Infections and activities of exogenous proteases are facilitated by the fact that both the filaggrin balance and the skin barrier are disturbed which still is accelerated due to itching and obsessive scratching.
In both the cases, rosacea and atopic skin, exogenous protease inhibitors as for instance the boswellic acids of frankincense can be beneficial in the form of aqueous nanodispersions. Disorders of the skin barrier also result from overdone hygiene and can be the main cause for foot mycoses. Facultative pathogenic yeast fungi such as candida albicans, assisted by proteases, erode the horny layer of the skin.

Impacts on the skin barrier

The Natural Moisturizing Factor (NMF) is the result of endogenous proteases. When degrading proteins they leave a mixture of amino acids which regulate skin hydration and osmotic balance but also are responsible for the defence mechanisms against exogenous radicals. NMF and skin barrier deficiencies cause dry skin and an increased transepidermal water loss (TEWL). A high TEWL means an increased permeability of the skin barrier which in its turn then facilitates the penetration of germs from the outside.
Since all the enzymes work hand in hand and continually exchange various substances, one deficient enzyme in a reaction chain already has effects on the whole metabolism and the skin. In a multitude of neurodermitic cases, the fatty acid metabolism of the essential omega-6 acids is disturbed due to a malfunction of delta-6-desaturase. The enzyme transfers linoleic acid into gamma linolenic acid. In the case of malfunction the missing gamma-linolenic acid can be replaced topically in the form of evening prim rose or borage oil.
In the liver, delta-6- and delta-5-desaturases and the elongase which is responsible for an extension of the carbon chain in carboxylic acids by 2-C atoms, form arachidonic acid (omega 6 sequence) from linoleic acid, respectively eicosapentaenoic acid (omega-3 sequence) from herbal alpha-linolenic acid; both of them are buffered in phospholipids (membrane lipids). Released through phospholipase A_2, a hydrolase enzyme, the acids form metabolites in a cascade-like process, which then in minor concentrations in the form of local hormones control clotting factors, blood pressure, blood fats (triglycerides), inflammations, fever, pain, vascular muscles, course of pregnancy and immune responses (allergies, asthma etc.). By the way, phospholipase A_2 is inhibited by glucocorticoids. That is one of the reasons why these pharmaceuticals have anti-inflammatory effects.
Triglycerides in the form of herbal oils absorbed via skin are degraded by esterases (alias lipases, belonging to hydrolases). In this process fatty acids are eliminated and diglycerides, monoglycerides and finally glycerin are formed. This is the reason why triglycerides are adequate biodegradable, physiological substances for the care of the lipid and acid mantle of the skin. A practical illustration for the degradation process of glycerides of the skin's lipid mantle through esterases is the example of grating fresh potatoes without wearing kitchen gloves. The hands are getting rougher and rougher in the process.

Oxidation and reduction

If the fatty acids of the topically applied herbal oils are linoleic acid, alpha- and gamma linolenic acid, the epidermal 15-lipoxygenase (15-LOX), belonging to the oxidoreductases, oxidises them into unsaturated hydroxy fatty acids with anti-inflammatory features.
Just to amplify the process: 13-hydroxy-9,11-octadecadienoic acid (13-HODE) is formed from linoleic acid, 13-hydroxy-6,9,11-octadecatrienoic acid (13-HOTrEg) from gamma linolenic acid and 13-hydroxy-9,11,15-octadecatrienoic acid (13-HOTrE) from alpha-linolenic acid. The latter mentioned is responsible for the excellent anti-inflammatory effect of linseed oil which formerly used to be a frequent component of burn bandages. Kiwi seed oil still has a higher content of alpha-linolenic acid, hence it has similar effects. Today both the oils are applied in the form of aqueous nanodispersions for the follow-up skin care of sun erythema. Essential fatty acids in general can be used for the skin care of inflammatory skin disorders – due to their sensitivity to atmospheric oxygen they should preferably be applied in the evening.
The above-mentioned copper-containing and melanin-forming tyrosinase also is an oxidoreductase with sensitive reaction to various reducing agents. Besides by vitamin-C derivatives the enzyme also is inhibited by polyphenols, hence flavonoids and isoflavonoids (phytohormones) which occur in herbal extracts, thus, the pigmentation of the skin is impeded.
Increased hydrogen peroxide concentrations are found in the skin of vitiligo patients (white spot skin disease). One of the suspected triggers is an insufficient function of the skin's natural catalase (reductase) which reduces hydrogen peroxide to water. Hydrogen peroxide impedes melanin formation.

Anti-aging

Elasticity and firmness of the skin respectively of the skin's connective tissue gradually decrease with increasing age. Since enzymes regulate the formation and degradation of collagen, it is essential that formation processes are activated and that degrading proteases alias matrix-metalloproteinases (collagenases) are inhibited.
Various studies on adequate active agents are available in the media. Most of them are based on in-vitro examinations and short-term observations though. Questions regarding solid in-vivo results, long-term effects and their significance are permitted. **It is important to realise that matrix-metalloproteinases are activated with high UV stress of the skin. Avoiding sun overexposure is an effective anti-aging measure.**
Protease inhibitors such as boswellic acids are suitable active agents to treat sun erythema. An important co-factor for the collagen formation is ascorbic acid which in skin care products is preferably used in the form of its ester (see above) as it can pass through the skin barrier.
Other significant enzyme co-factors are:

- vitamin B_2 (riboflavin),
- nicotinamide (niacin),
- pantothenic acid (coenzyme A component),
- biotin and
- folic acid

D-panthenol, the pre-stage of pantothenic acid is used against erythema and for improved skin hydration. Niacin has regenerative and anti-inflammatory effects. Coenzyme Q_{10} (ubiquinone-10) plays a role in the formation of adenosine triphosphate (ATP) which provides the energy for all cell activities.

Endocrine disruptors

Endocrine disruptors can be of synthetic or natural origin; they bind to hormone receptors and influence hormone synthesis or the transformation of hormones. Enzymes such as aromatase and 5-alpha-reductase participate, among others, in biochemical reactions.
Up to now only a few causalities have been known which are significant for the human body. WHO maintains a list of substances that are presumably associated with the mentioned criteria. Endocrine disruptors are associated with unwanted adverse effects. However this cannot be generalised. Phytohormones alias isoflavones should be mentioned in this context as they are considered to be safe and offer various interesting features in nutrition and skin care.

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