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Local inflammation, local stress and skin aging. Status and interventions

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Local inflammation, local stress and skin aging. Status and interventions

Paolo U. Giacomoni [a], Vincenzo P.M. Rialdi [b]

[a] Insight Analysis Consulting, Brownsboro, AL, U.S.A
[b] Vevy Europe, Genova, Italy

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ABSTRACT

This paper reports the connection between cutis and the immune and nervous systems, related to local inflammation and stress conditions, occurring at the skin level and leading to early aging. Some intervention strategies to control the skin aging rate will be discussed.

Inflammatory skin condition: an issue that deserves a deepening

Inflammation is a protective response of our body which is established as the result of a tissue damage. It is a typical mechanism of innate immunity.

The inflammatory reaction allows the cause of the damage to be eliminated, repairing the injuries caused to the tissues and restoring their normal function, through regeneration of damaged cells that can proliferate. If the agent causing inflammation cannot be eliminated, or if there is some interference with the healing process, an acute inflammatory response may occur, and this can also lead to a chronic inflammation.

In the case of the skin, the repairing process also involves the skin immune system, even at the epidermal level.

Skin can undergo a state of inflammation even without being heavily damaged: physical trauma, contact with irritating materials or substances as in the case of an aggressive or repeated chemical peeling, heat and cold burns and radiation from solar and artificial light are some of the possible causes. Manifestations of an inflammatory skin condition may be itching, pain, redness, heat and edema.

Not only the inflammatory response but also the repair process can cause damages to skin structures: the normal tissue architecture not adequately regenerated leads to altered functionality of that area. Fibrous scars forming in the healing process of a wound are an example of this.

At the epidermal level, the consequence is an impaired cell turnover, with hyperproliferation and presence of undifferentiated corneocytes which can also result in parakeratosis. These conditions lead the epidermis to lose part of its functions, the first of which is protection from external agents.

It is well known that any systemic anti-inflammatory intervention is not of cosmetic competence but there are applications that remain in the cosmetic field that can promote healing by modulating the inflammatory skin response acting at the epidermal level.

An effective local anti-inflammatory action that remains of cosmetic relevance must therefore take into account the modulation of the inflammatory response by supporting the natural return to normality of the epidermal structures and their functions.

The best approach is to restore proper cell turnover and adequate hydration, and to counteract lipoperoxidation due to the oxidative cascade caused precisely by inflammatory reaction.

It is good to remember that epidermal hydration is an important marker of the correct cell turnover as well as being necessary for the proper functioning of the epidermis itself.

The micro-inflammatory hypothesis of skin aging

The single most effective pathway to skin aging is the micro-inflammatory process. The micro-inflammatory mechanism of skin aging[1] can be represented as a cyclic phenomenon as outlined below.

1. A cell is damaged by an environmental or an endogenous factor.
2. The damaged cell releases pro-inflammatory signals (prostaglandins, leukotrienes etc)

3. Inflammatory signals bind to resident mast cells and induce the release of histamine and TNF-α that diffuse to blood vessels lined by endothelial cells
4. Stimulated by histamine and TNF-α, endothelial cells synthesize and mobilize I-CAM 1.
5. Circulating immune cells bind to I-CAM 1, roll over, release hydrogen peroxide to cross the *epithelium* (i.e. perform diapedesis). This is the first step in the inflammatory oxidative cascade.
6. In the presence of chemotactic signals from damaged cell, immune cells fray a path across the dermis by releasing Matrix Metallo-proteinases that damage the extracellular matrix as well as singlet Oxygen that triggers the second inflammatory oxidative cascade. In the absence of chemotactic signals, immune cells damage the connective tissue surrounding the blood vessels, thus provoking for instance, the onset of varicose veins.
7. When the damaged cell is reached, immune cells release an oxidative burst that constitutes the third inflammatory oxidative cascade. This burst is meant to destroy the damaged cell and to allow the immune cells to engulf the debris and proceed to the lymphatic system.
8. In steps 6 and 7, "innocent" bystander cells can be damaged, thus triggering another round of release of pro-inflammatory signals (steps 1 and 2) and the cycle is repeated.

Skin stress condition: what's behind it

Stress is a non-specific and adaptive biological-behavioral response of the organism to a negative *stimulus*, as evidenced by Hans Selye, pioneer of the studies on stress. It involves different mechanisms in the body, in particular the three adaptive biological systems: neurovegetative, neuroendocrine and immune.

When stress occurs, specific hormones, so-called «stress hormones» (catecholamines and cortisol), produced by the central nervous system and by the adrenal glands, are released. These hormones prepare the body to be efficient and reactive but if they are continuously present, they cause a lowering of the immune system response and therefore make the organism more vulnerable.

Until the beginning of this century it was thought that stress hormones reached the skin only by blood through the network of local microcirculation. Thanks to basic experimental acquisitions we know today that keratinocytes react to stressor stimuli by producing noradrenaline, adrenaline and dopamine themselves. Hence, a new state of stress, the idiopathic one which develops locally, has to be considered. Specifically, the production of stress hormones takes place from the less differentiated keratinocytes and therefore mainly in the *stratum germinativum* and the *stratum spinosum*.

The main drawbacks occurring in this condition are: vasodilation, hyperhidrosis, *pruritus*, capillary fragility, dysmorphia assimilated to skin aging. It is worth mentioning that oxidative phenomena, which involve the formation of free radicals, are also induced by the presence of catecholamines.

In addition, the presence of stress hormones in the skin also modulates the trigger of immunological adverse phenomena: the presence of adrenergic receptors has been demonstrated in the immunocompetent Langerhans skin cells of (LC) which play an important role in the presentation of antigens in the immune system. This could be one of the root causes of induced skin allergopathies. Skin Langerhans cells are dendritic cells, localized in the supra-basal layers, mainly in the spinous layer. After engulfing foreign bodies, they migrate through the dermis to secondary lymphoid organs to present the antigens. Langerhans cells are connected with nervous fibers that cross the epidermis and are endowed with adrenergic receptors, thus constituting a link between the immune system and the nervous system. One could therefore suggest that stress hormones can modulate the immune response in the skin.

Apart from genetic and pathological factors and mechanical and accidental injuries, the main causes of induction of stressogenic stimuli affecting the skin are to be found among inappropriate substances applied on the skin, environmental factors such as sunlight and artificial light, unusual variations of temperature and humidity, and other inflammatory processes induced by events not always foreseeable.

The inhibition of the adaptive response of the organism is not a cosmetic competence. Instead, it is possible to modulate successfully the production of stress hormones by using targeted cosmetic actives, thus avoiding the connected drawbacks and allowing the skin to repair adequately without alteration of its functions.

Interventions to reduce the rate of skin aging

Aging has been defined as accumulation of damage[1]. In this frame of reasoning, it appears that I-CAM 1 synthesis is central to aging because it controls the triggering of the inflammatory process and therefore the three oxidative cascades and the damage to the extracellular matrix (i.e. the dermis) that in the long run will lose its elasticity, resilience, and water retention capability. This process can be stimulated by UV,

stretching, anoxia, glycated proteins, hormonal imbalance, cigarette smoke, wounds, infections, nutritional status, cold, ethanol consumption or other signals not originating from damaged cells, which can therefore be considered factors of skin aging.

It has also been shown that, as much as peripheral organs release neurological molecules to signal the Central Nervous System when the body is under attack, neuropeptides are released by the Central Nervous System under stress. These neuropeptides have the capability of inducing the synthesis and mobilization of ICAM-1[2,3] thus providing evidence supporting the old postulate that psychological stress accelerates skin aging.

Stress hormones like catecholamines (adrenaline and nor-adrenaline) are secreted in conditions of stress and trigger for instance the fight-or-flight response. Their mechanisms of action have been elucidated: they bind to different types of receptors to control different types of response. When they bind to the so-called α-receptors they induce the synthesis of ICAM-1[4]. On the other hand, when they bind to the so-called β-receptors, they can affect the expression of ICAM-1[5]. Dopamine binding to a β receptor hinders the chemoattractant role of IL-8[6].

Catecholamines and Dopamine are synthesized by human keratinocytes and this allows one to envision the topical applications of specific inhibitors. Inhibitors of catecholamine synthesis and therefore of the undesired consequences of their overexpression can play an anti-aging effect by intervening on the inflammatory pathway. One of these inhibitors is a fractional organic phyto-derivative from *Krameria Triandra* Root, called ACS-Anticytostressor (Vevy codex 13.4566) that has been shown to inhibit by 20% the synthesis of Noradrenaline and by 30% the synthesis of Dopamine[7].

Another modulator of the synthesis of ICAM-1 is Salycuminol (Vevy codex 18.3726), a calibrated blend of two long-chain esters of salicylic acid (Isopropylbenzyl Salicylate and Isodecyl Salicylate) that has been shown to inhibit the accumulation of ICAM-1 in keratinocytes stimulated with γ-interferon[8]. Salycuminol, being able to improve cell turnover until normal, is an effective moisturizer[9], therefore it helps maintain the biochemical activity occurring in the stratum corneum and facilitates its own penetration in the epidermis where it can exert its positive activity.

Salycuminol owns specific peculiarities that make it particularly effective and unique:

- Its specific long-chain lipid nature meets the requirements for the correct interaction with the lipid composition of the cytomembrane;
- It has a direct action on the enzymatic activities connected to the topical inflammation (ornithine decarboxylase and cyclooxygenase), physiologically modulating the inflammatory response;
- The related studies include all the successful results on the other activities it exerts (antilipoperoxidation, keratoplastic, UV protecting as it is a salicylic derivative).

ACS-Anticytostressor promotes an overall bio-regulation by reducing the alterations caused by stress hormones, with respect of the cutaneous physiological mechanisms:

- It supports reparative and reconstitutive processes in case of stress due to improper substances applied on the skin, environmental factors, professional mechanical agents, clothes, solar and artificial light, genetic factors, infective factors;
- It is effective in protective and preventive interventions for the local stress caused by skin lesions, modulating the healing process in order to avoid the formation of keloids.

CONCLUSION

The micro-inflammatory hypothesis of skin aging provides a self-consistent frame of thought that allows one to take advantage of the criteria set forward to identify new factors of aging as well as to select xenobiotics to tackle the presence or the undesirable effects of specific factors of aging. In this review, we have pointed out that two ingredients, ACS-Anticytostressor and Salycuminol are indeed endowed with the properties required for being identified as anti-aging factors.

BIBLIOGRAPHY

1. Giacomoni PU, D'Alessio P. *Skin Aging, the relevance of antioxidants.* Suresh I.S. Rattan and Olivier Toussaint (Eds) *Molecular Gerontology, Research Status and Strategies*. Plenum Press, New York-London 1996: 177-192.
2. Giacomoni PU, Rein G. *Factors of Skin Aging share common mechanisms.* Biogerontology 2001, 2(4): 219-229.
3. Giacomoni PU, Rein G. *Skin Aging: A Generalization of the Micro-inflammatory Hypothesis.* https://doi.org/10.1007/978-3-642-27814-3_76-2 Farage MA, Miller KW, Maibach HI (Eds) *Textbook of Aging Skin*. Springer, Berlin-Heidelberg 2017: 1289-1298.
4. Flierl MA, Rittirsch D, Nadeau BA, Sarma JV, Day DE, Lentsch AB, Huber-Lang MS, Ward PA. *Upregulation of phagocyte-derived catecholamines augments the acute inflammatory response.* https://doi.org/10.1371/journal.pone.0004414 PLoS One 2009, 4(2): e4414.
5. Tamura R, Takahashi HK, Iwagaki H, Yagi T, Mori S, Yoshino T, Nishibori M, Tanaka N. *Effect of β2-adrenergic receptor agonists on intercellular adhesion molecule (ICAM)-1, B7, and CD40 expression in mixed lymphocyte reaction.* https://doi.org/10.1097/01.TP.0000101517.48541.7B Transplantation 2004, 77(2): 293-301.
6. Sookhai S, Wang JH, Winter D, Power C, Kirwan W, Redmond PH. *Dopamine attenuates the chemoattractant effect of IL-8: a novel role in the systemic inflammatory response syndrome*. https://doi.org/10.1097/00024382-200014030-00009 Shock 2000, 14 (3): 295-299.
7. Brenci S, Rialdi VPM, Rialdi G. *Neuroimmunological Activities of Keratinocytes*. Cosmetics & Toiletries 2002, 117: 63-72.
8. Brenci S, Indiveri F. *Expression of ICAM-1 Antigen and FAS Antigen on Keratinocytes after Salycuminol Treatment.* Relata Technica 1995, 1: 5-8.
9. Donetti M. *Salycuminol and Skin Moisturization.* Relata Technica 1998, 1: 1-2.
10. Rialdi V.P.M., Giacomoni P.U. *Diabetic skin: targeted soothing and support.* Relata Technica 2018:1-8

WHAT IS RELATA TECHNICA?

Starting from the beginning of the human story numberless substances have been applied on the skin to favour wound healing, for the management of skin diseases, or simply and perhaps more often for cosmetic aims. In sharp contrast, only in recent years, and with a great delay as compared with otherfields of pharmacology, the study of the effects of chemicals on the skin moved from art to science; now it is soundly based on a rational approach. Regulatory Authorities classify substances and formulations to be applied on the skin in two distinct categories: drugs and cosmetics. This in order to prevent that harmful or extremely active chemicals, contained in cosmetic preparations, are used without medical control.

Nevertheless, all pharmacologists know that in its widest meaning drug is every substance capable of modifying cell function, and it is difficult to admit that chemicals used in cosmetic preparations are devoid of any influence on biochemical mechanisms of epidermal cells, in particular in the case of long-term treatments. Thus dermopharmacology and cosmetology are at least overlapping disciplines, and there is no doubt that the same methodology should be employed in both fields.

Over the years Relata Technica has achieved a wide readership; at present its aim is to broaden the journal to make it a truly comprehensive dermopharmacology research journal in which articles in all of the most interesting and exciting areas of modern skin care have their forum. As a consequence, Relata Technica should attract manuscripts concerning the pharmacokinetic behaviour and the pharmacodynamic activity of old and new chemicals used to control skin diseases or to prevent skin aging, as well as studies providing insights on which to base rational development of new compounds for medicinal or cosmetic use.

Investigations on the various aspects of the interaction of chemicals with the skin can be analysed by the use of several experimental models: the intact animal, fragments of surviving skin, keratinocytes cultures or the more sophisticated in vitro reconstructed human skin, subcellular fractions and pure enzyme systems. The end point examined in the study may be the macroscopic appearance of the skin, its histological, histochemical or ultrastructural features, and a biochemical or molecular marker.

An important aspect of dermopharmacology, and even more of cosmetology, is safety assessment. Therefore the journal will be also very interested in publishing the results of research dealing with the local and systemic tolerability of new compounds. In this respect, one of the major goals of Relata Technica is to promote studies on the use and validation of the so called alternative assays which should have the final aim of substituting, at least for cosmetics, the use of laboratory animals in the assessment of systemic toxicity, local irritant activity and, in a broader sense, of any possible adverse effect.

Finally, Relata Tecnica should be the natural publication outlet for manuscripts concerning the formulation of dermopharmaceutical and cosmetic preparations, and in particular for those which analyse the influence of the vehicle and other ingredients on the efficacy and tolerability of the active substance.

It is essential that the quality of papers published in Relata Technica be good and, on the other hand, it is important for the journal to process and publish papers promptly. We will make every possible effort to improve and shorten the review process, and I believe that Relata Technica will become a preeminent journal in the field of dermopharmacology.

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