New Directions for Sensitive Skin Research

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ABSTRACT: *This brief review provides an insight into the current standing of sensitive skin research, including recent findings on the possible role of nerve growth factor as an underlying mechanism and predictive tool for sensitive skin.*

In recent years there has been an increase in reports of sensitive skin among men and women of various ages and ethnicities. Approximately 52% of women and 38% of men have self-diagnosed sensitive skin. Further, 10% of women and 6% of men describe themselves as having very sensitive skin.[1] Individuals who have skin with a lower tolerance threshold for cosmetic and personal care products than those with sensitive skin are described as having very sensitive skin. Thus, their adverse responses to these products occur more frequently. As a result, there has been an increase throughout the past ten years in the demand for cosmetic and personal care products formulated for individuals with sensitive skin. According to the *New York Times*, sensitive skin product sales have jumped 13% since 2000, and sales in the United States average more than US$900 million annually.[2]

Though there currently are a plethora of sensitive skin products on the market, there is no industry standard for characterizing the condition or for substantiating sensitive skin product claims.[2] This may be attributed to the lack of understanding the underlying mechanisms leading to sensitive skin.[3–6] The obscurity of the etiology may well be attributed to the lack of noticeable signs of irritation, intra- and inter-subject variability, and an unclear understanding of the effects that age, race and lifestyle play in the prevalence of sensitive skin.[6–12]

Clarification of the exact mechanisms of action in sensitive skin and the establishment of a universal, objective, reproducible and quantifiable testing method are essential for the further advancement of research in this area. Establishing these parameters will provide companies an avenue to substantiate their claims by ensuring that sensitive skin products are being tested on individuals with the condition, in turn enhancing the safety and efficacy of sensitive skin products before releasing them.

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Sensitive Skin Overview

Sensitive skin, also referred to as sensory skin irritation, chemosensory irritability, cosmetic intolerance syndrome or status cosmeticus, is a condition with varying definitions.[2,13,14] In general, the disorder is defined as a heightened intolerance to topically applied substances, mainly cosmetic or personal care products.[3,14] Neurosensory symptoms such as itching, burning, stinging, tingling and tightness are characteristics of the condition and frequently are experienced on the face. Typically, these symptoms are apparent immediately after product use; however, they can be delayed minutes to days after product use, and exacerbated by wind, sun exposure, excessive heat, humidity or cold temperatures.[1,4–6,8,12,13,15,16,20]

Individuals who suffer from sensitive skin are believed to be in good health and free of pre-existing skin disorders,[8,14] but those suffering from atopic dermatitis, eczema, allergic contact dermatitis, irritant contact dermatitis, seborrheic dermatitis, rosacea, acne and psoriasis may have a predisposition to the condition. It has not been clarified how these skin disorders are linked to sensitive skin but there is speculation that sensitive skin may be an indicator of more serious skin conditions such as rosacea and eczema.[1,6,13,16] Conversely, the link between sensitive skin and other skin conditions often categorized with it, such as irritant and allergic contact dermatitis, has been challenged.[17] Robinson et al. showed that people with self-reported sensitive skin were not more responsive to patch tests with standard irritants such as sodium dodecyl sulfate.[11] Thus, there is evidence that sensitive skin is not just a symptom that accompanies other skin disorders, but that it is a true condition and should therefore be investigated as such.[18–20]

Testing Methods

In 1977, Frosch and Kligman developed a method for diagnosing

sensitive skin. This method is known as the lactic acid sting test (LAST) and is the most widely used method for predicting sensitive skin, although many industry experts argue that it is not a true predictor of the condition.[3,5,6,15,20] The original procedure involved the induction of sweating for 15 min in a 120°F environmental chamber followed by the application of 5% lactic acid to the nasolabial fold and cheek.[21]

The LAST method came under criticism in the years following its inception.[8] Christensen and Kligman developed an improved procedure for conducting the LAST method on facial skin. The new method used 10% lactic acid instead of 5% lactic acid. The purpose of the increase of lactic acid was to allow omission of the sweat-inducing step used in the previous method. Hilltop chambers, or occlusive patch test systems used widely to assess the direct and indirect effect products have on the skin, were used on the cheek for 10 min instead of exposing the area to lactic acid with a cotton swab as done previously. The time required for stinging to occur and the peak intensity of stinging, on a scale of 0 to 3, was recorded.

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Many modified types of the LAST method are being used today. Researchers vary the use of Hilltop chambers vs. cotton swabs, the exposure time of lactic acid on the skin, and the scale that is used to measure stinging intensity.[3,9,15,18,22] The LAST method has proven to be useful and reproducible, but it does not allow easy quantification of the magnitude of stinging.[8,9] Furthermore, the role ethnicity plays in the stinging phenomenon is unclear, but it could have a profound effect on susceptibility to stinging. Aramaki et al. showed that sensitivity to stinging was higher in Japanese women as compared to German women;[22] and the effects of age, sex and product use on the stinging phenomenon is unclear.[8]

Presently, there are a number of other testing methods being used to evaluate sensitive skin such as visual scoring, blood flow measurements, ultrasound, confocal light microscopy and questionnaires.[10] Though these methods may prove promising for the future, there is still a need for extensive research in this arena.

Mechanisms of Sensitive Skin

Today, the majority of the literature on sensitive skin focuses on the premise that sensitive skin is caused by an increased permeability of compounds through the skin due to a compromised stratum corneum (SC) barrier. This ideology originated in 1977 when Frosch and Kligman developed

the LAST method for diagnosing sensitive skin. Compromised barrier function has become the most accepted mechanism of sensitive skin.[3–5,21] This hypothesis was supported further when Issachar et al. found higher skin pH in those who tested positive to the LAST method due a higher lactic acid penetration of the skin and less remaining on the surface.[7] Thus, it is understandable why many would believe that a compromised SC barrier is the main culprit of sensitive skin.

On the contrary, Yokota et al. reported that a compromised SC barrier was present in some individuals with sensitive skin but not in all of them. This was shown by separating individuals with sensitive skin into subgroups according to mechanism of action. Type I had compromised SC barrier function, Type II had inflammation with normal barrier function and Type III was defined as pseudo-healthy in terms of normal barrier function and absence of inflammation.

Elevated levels of nerve growth factor (NGF) were the only commonality that researchers found among the groups. NGF levels in the SC were evaluated by tape stripping the SC and analyzing the tape strips for NGF content. Each sensitive skin group had significantly higher levels of NGF in the SC as compared to those without the condition. They also showed that individuals categorized as Type II and III had higher sensitivity to electrical stimulation than people with normal skin, which could suggest that innervation plays a role in sensitive skin.[23]

Hyperinnervation in the epidermis has been implicated as an underlying mechanism of sensitive skin.

Recently, hyperinnervation in the epidermis has been implicated as an underlying mechanism of sensitive skin.[5,13,20] It has been suggested that this phenomenon causes heightened neurosensory input that leads to the adverse sensory responses that individuals with sensitive skin often experience.[13] However, this has not been studied extensively. The paucity of research in this area is surprising since it has been established that cutaneous sensory responses are directly related to sensory nerve fibers found in the dermis and epidermis.[24] Scientists from Shiseido and investigators of the Massachusetts General Hospital/Harvard Cutaneous Biology Research Center showed the direct connection between the skin and brain by confirming the contact point between Langerhan cells in the skin and nerve cells.[25] Hence, it is essential that the connection between hyperinnervation of the epidermis and sensitive skin be studied since sensory responses are the key component of the condition.

Further research on NGF levels in the SC could prove to be useful in fully understanding sensitive skin. This

is an area that should be researched in more depth because it is has been proven that NGF plays a crucial role in a number of cutaneous processes such as the determination of the innervation density of skin, survival and differentiation of neurons during early development and sensitization of nerve fibers.[24,26] Additionally, changes in cutaneous NGF content leads to alterations in cutaneous innervation densities and abnormalities in sensory neurons in adult rats.[27] Heightened levels of NGF in the epidermis of transgenic mice resulted in increased and abnormal innervation patterns in the skin.[26,28] It is unclear whether NGF levels in the SC can be directly related to innervation or sensitive skin. Therefore, understanding what role, if any, NGF and epidermal innervation play in sensitive skin will shed light on this theory.

It is has been proven that nerve growth factor (NGF) plays a crucial role in a number of cutaneous processes.

Conclusions

Great strides have been made in the study of sensitive skin. However, more research is needed to fully explain the condition. Clarifying the mechanisms of sensitive skin would benefit industrial and clinical arenas. Clinically, it will be much easier to develop an objective and quantitative diagnosis tool if the biological basis of the condition was completely understood. In turn, this would lead to a clear-cut diagnosis of the condition, and it would be helpful in understanding the link between sensitive skin and other skin conditions.

It is well established that consumers discriminate between products based on how they feel on the skin during use; however, it is extremely difficult to measure these types of responses during clinical trials because there is no objective method for categorizing people with sensitive skin. Thus, companies are limited in their ability to predict adverse sensory responses because the products are not always being tested on those who truly have sensitive skin.[5,6,9,10,29]

If a distinct group of individuals with sensitive skin could be identified and used for product testing and claim substantiation, adverse effects could be minimized and efficacy maximized before products reach the consumer. Perhaps if it were further established that increased levels of NGF in the SC are a commonality among those with sensitive skin, then tape-strip sampling of the neurotrophin would prove to be a very reliable and objective method for predicting sensitive skin that also could be quantified. Until the underlying mechanisms of sensitive skin are explained, it will be a challenge to develop the robust testing method that is needed.

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