

NICE network. Evidence and application to cosmetics

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Received: July, 2010. Presented at The IX ISCD International Multidisciplinary Congress "Wellness and Beauty Outside In: East & West working together", Rome, 21-23 October 2009.

Key words: Stress; Hormon; Neuropeptide; Barrier; Langerhans cell;

Summary

It is well known that mental stress affects the body and that the skin reflects a person's mental condition. Thus, proverbs, such as "The skin is the mirror which reflects the state of the mind", "The skin is a window to the mind." have developed and scientific evidence supporting this relationship has been accumulated. Examples of the effects of stress, their mechanisms, and modulation by cosmetics are reviewed in this article.

Riassunto

È ben noto come lo stress mentale influenzi il benessere del nostro corpo, mentre la pelle ne riflette le conseguenze.

"La pelle è lo specchio che riflette lo stato della mente" e che la pelle sia lo specchio della mente è ormai supportata da molte evidenze scientifiche.

Questo articolo riporterà alcuni esempi a dimostrazione degli effetti provocati dallo stress, dei loro meccanismi di azione e del come i prodotti cosmetici ne possano modulare l'attività.

INTRODUCTION

Effects of stress

Although the skin is located at the outer most periphery of the body and appears simple, it performs various functions that protect the whole body, including providing a barrier of water/bacteria/chemicals, shading from UV radiation, and removal of invading bacteria/chemicals/proteins. Keratinocytes, melanocytes, Langerhans cells, mast cells, endothelial cells, and nerve fibers cooperate in the maintenance of homeostasis.

Stress decreases proliferation of keratinocytes. Tsuchiya et al. counted the number of epidermal cells that were positive for proliferating cell nuclear antigens and found that the number was lower after immobilization (1). Intensive studies by Elias et al. on the barrier function of the cornified layer demonstrate that psychological stress decreases epidermal cell proliferation, impairs epidermal differentiation, and decreases the density and size of the corneodesmosomes (2). Altemus et al. found that psychological interview stress or sleep deprivation delays the recovery of skin barrier function (3). Melanocytes are also affected by stress. Inoue et al. measured the color of the skin and the number of dihydroxyphenylalanine-positive melanocytes and found that immobilization augmented pigmentation induced by ultraviolet light (4). In 2008 examination of human skin biopsies by Kleyn et al. clearly demonstrated the decrease in the number of Langerhans cells after the acute interview stress (5), suggesting that stress suppresses skin immune function. Effects of stress on contact hypersensitivity reaction were reported by Mettrop and Visser as early as 1971 (6). Since then, the effects of stress on the immune function of skin have been studied mostly using allergic contact hypersensitivity. In some reports, reactions were suppressed by stress but

stress augmented these reactions in other reports. The controversy was explained, at least partially, by Dabhbar et al (7) and Flint et al (8). The timing, intensity, and duration of stress influence the effects of stress. The recent report by Klein et al.(5) may offer one explanation.

Hair loss might be one of the symptoms of stress reaction. Studies by Paus et al. suggested a possible relationship between stress and hair loss, based on finding an increased number of hair follicles containing apoptotic cells following the application of sonic stress (9). Substance P (10), NGF (11), neurokinin 1 (12) and mast cells (13) were reported to be mediators of the interaction. Down-regulation of lipogenesis by stress was also reported. The incorporation of ¹⁴C-acetate to sebaceous glands was decreased by about 50% after immobilization (14).

Mechanisms of the effects of stress on skin functions

Nerve system, endocrine system, and immune system function in coordination to maintain homeostasis in the body. Physiological and psychological inputs are processed in the brain together with information from memory. In order to cope with these problems the brain directs each organ to initiate defensive actions, i.e. stress reaction.

The hypothalamus-pituitary-adrenal gland axis (HPA axis) is the main pathway of stress reaction. CRH secreted from the hypothalamus stimulates the secretion of ACTH from the pituitary gland. ACTH induces the secretion of glucocorticoids from the adrenal cortex. This chain reaction provides negative feed back for the suppression of CRH secretion by glucocorticoids. Those hormones are detected in the skin (15) and considered triggers of the effects of stress on the skin. Impairment of the barrier function by stress is prevented by the cortisol antagonist RU418 (2). The involvement of ACTH in the augmentation of UV-induced pigmentation has been suggested (4).

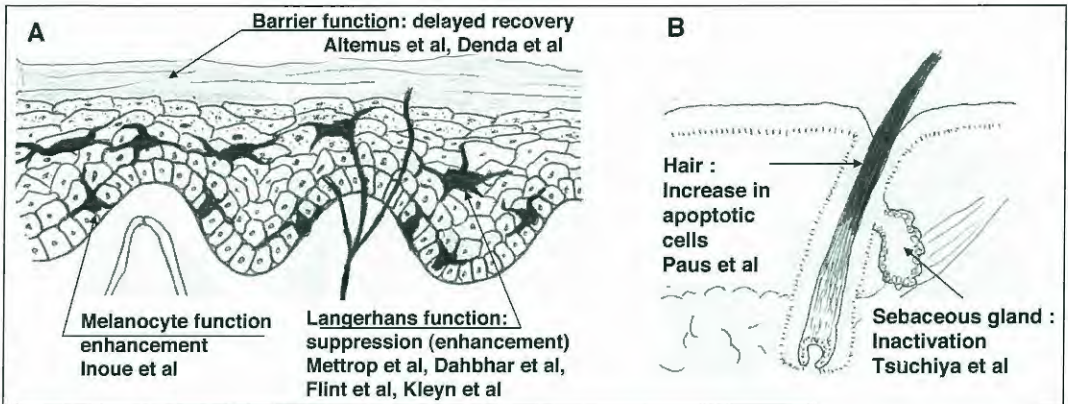


Fig. 1 Effects of stress on various skin functions.

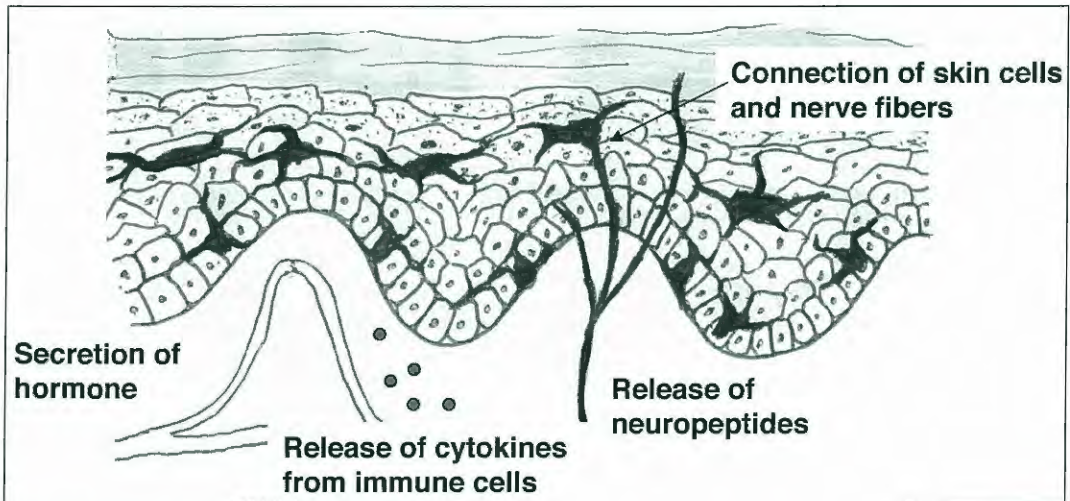


Fig. 2 Mediators of the effects of stress on the skin.

Involvement of nerve-related factors has also been suggested. The skin is a heavily innervated organ. It was previously thought that nerve fibers end at the bottom of the epidermis following observation of silver staining of the skin sections, but the advances in the methods and equipment used for immunohistochemistry and electron microscopy have demonstrated that free nerve endings enter the epidermis and even

extend into the cornified layer. Several neuropeptides are released from nerve fibers in the skin, such as CGRP and substance P. We demonstrated an intimate association between epidermal Langerhans cells and nerve fibers (Fig.3A, 16). The antigen-presenting function of Langerhans cells was suppressed by CGRP (Fig.3B, 16).

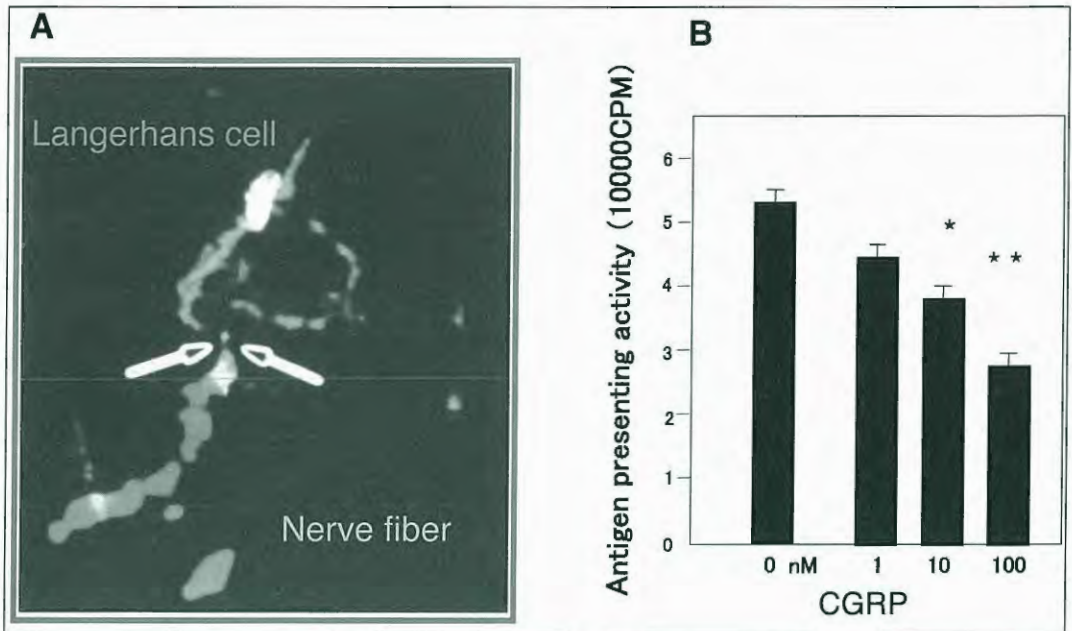


Fig. 3 A, Intimate association of nerve fibers with a Langerhans cells. B, Suppression of Langerhans cell function by the neuropeptide, CGRP. (Hosoi et al Nature 1993).

The most peripheral organ is connected with central nerve system. Kleyn et al. took biopsies before and after acute social stress and demonstrated that Langerhans cells were decreased and that the CGRP level was increased after stress (5). Catecholamines have been reported to regulate Langerhans cell function (17). Another neuropeptide, substance P, is increased in response to immobilization stress (18). Paus et al. hypothesized that substance P is a regulator of stress reactions affecting the hair cycle (13). In a previous report we summarized various effects of neuropeptides on the skin (19).

The nervous system, endocrine system, and cutaneous immune system cooperate to maintain homeostasis of the skin. Nerve-related factors regulate skin immune cells (20), and immune

factors stimulate the extension of nerve fibers (21). Hormones are well known to regulate immune functions. Those 3 systems interact with each other and regulate the skin functions. Based on these data, a group of Harvard scientists called this system the "NICE network" or neuro-immuno-cutaneous endocrine network (Fig. 4; 22, 23).

Regulation of the skin condition by cosmetics via the NICE system

The data presented above suggest that a systemic approach could be as effective as topical treatment. Some basic studies support the idea of the use of odorants for the protection of the skin from the stress.

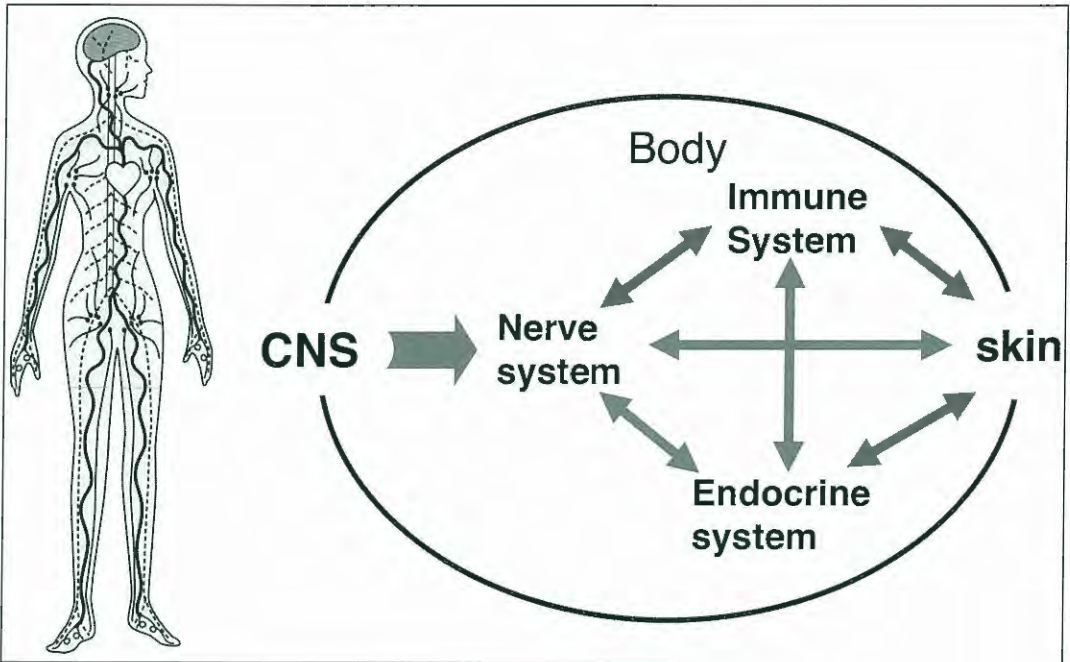


Fig. 4 NICE network.

The allergic contact hypersensitivity reaction suppressed by stress was prevented by inhalation of certain types of odorants (24). Interestingly, other types of odorants upregulate the reaction (25). The barrier function of the skin was also influenced by odorant inhalation (26). These findings support the utilization of odorants for skin care.

First, the effect of mental stress on skin was examined. When volunteers inhaled the odorant (dimethoxymethylbenzen) chosen for suppression of the induction of serum cortisol (Fig.5), impairment of barrier recovery was blocked (Fig 6). In this experiment, the stress reaction was induced by color word Stroop test.

Utilizing the odorant and other ingredients, we developed a system of cosmetics. The effects of daily use of skin care products were examined. Subjects were asked to use their own cosmetics or the newly developed skincare system on their face for one month.

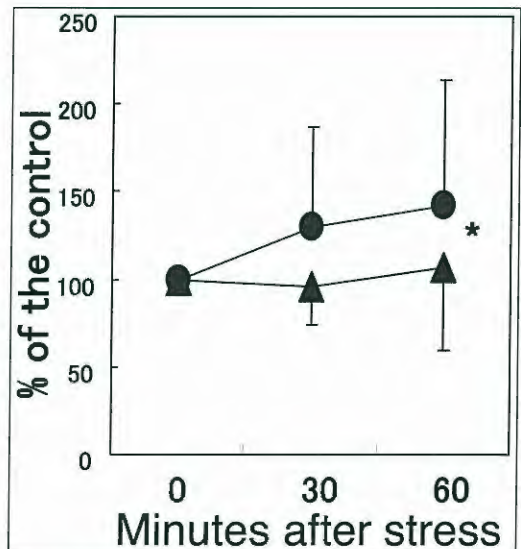


Fig. 5 Suppression of stress-induced serum cortisol. Twenty volunteers underwent the color word Stroop test with (5) or without (1) odorant inhalation.

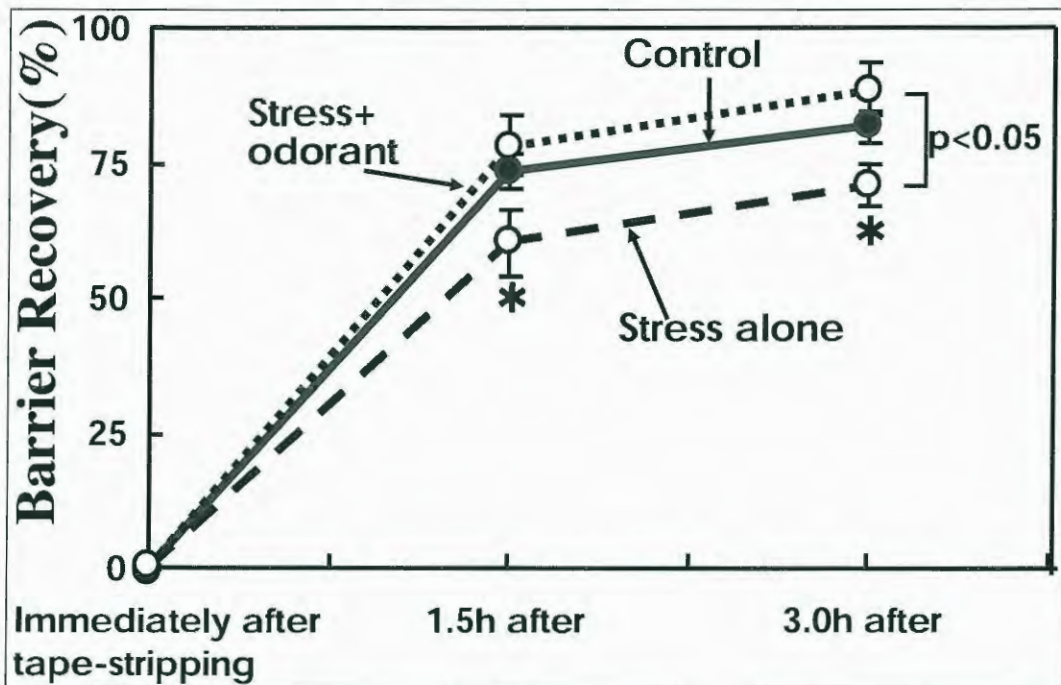


Fig. 6 Stress-induced impairment of the barrier function was blocked by inhalation of odorant. Transepidermal water loss was measured before and after tape stripping and the recovery rate was calculated. $n=20$.

They were also told not to use skin care cream on their arms. The moisture content of skin was measured by conductance and was increased in the subjects who used the novel skin care system, but decreased in the group using conventional cosmetics (Fig 7). From the data obtained after repeated use of the novel cosmetics (Fig. 8), the usefulness of applying the NICE approach to cosmetics was confirmed.

We then extended further the idea of applying NICE approach. The human body has a potent ability to manage stress reactions. Our next aim was to facilitate the self-defense system, rather than simply block mal-function. Dehydroepiandrosterone (DHEA) is secreted from adrenergic tissue. DHEA is known to decrease as people age. Various functions of DHEA have been reviewed by Oberbeck et al.

(27), including regulation of metabolism, cardiovascular function, and immune function. DHEA was increased after acute and chronic stress and is supposed to contribute to the protection of the body (28). Following is the summary of the work taking advantage of the protective effect of DHEA (29).

We developed a fragrance and examined its effect by measurement of contingent negative variation (CNV) on electroencephalogram. CNV is considered an index of psychological tension. The fragrance, containing mimosa, rose, and violet leaf, appeared to be beneficial (Fig. 9). Then, the usefulness of the fragrance in cosmetic products for daily use was examined with 90 young women. Changes in DHEA levels in saliva were measured by radioimmunoassay and the values are shown in Fig 10.

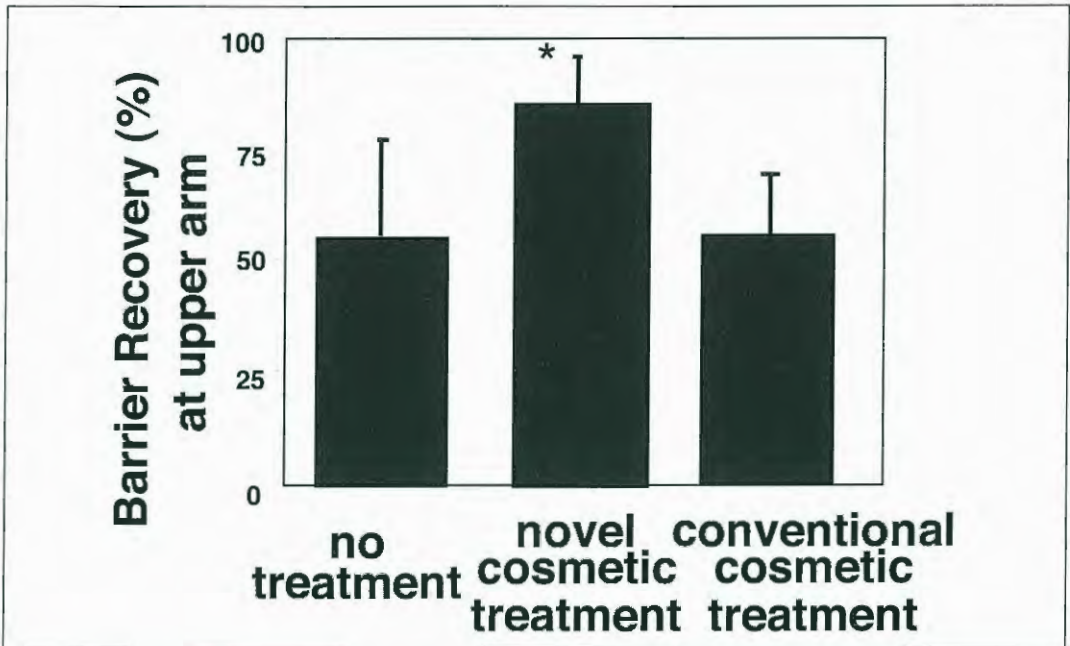


Fig. 7 Improvement of the barrier function at upper arm by a novel cosmetic treatment. n=20, *p<0.05.

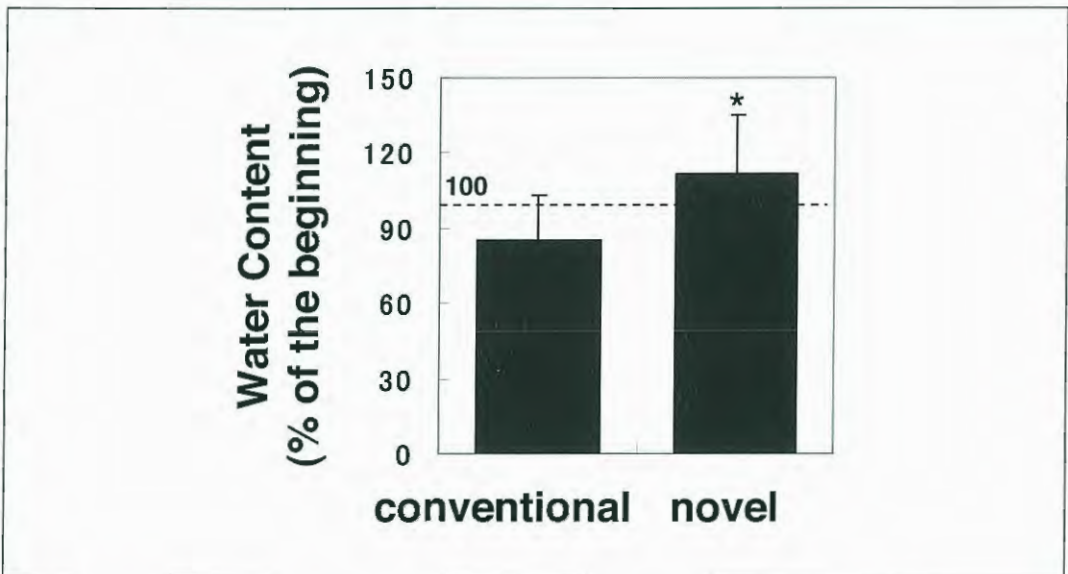


Fig. 8 Changes in the moisture content of the skin measured by skin conductance on the arm n=20, *p<0.05.

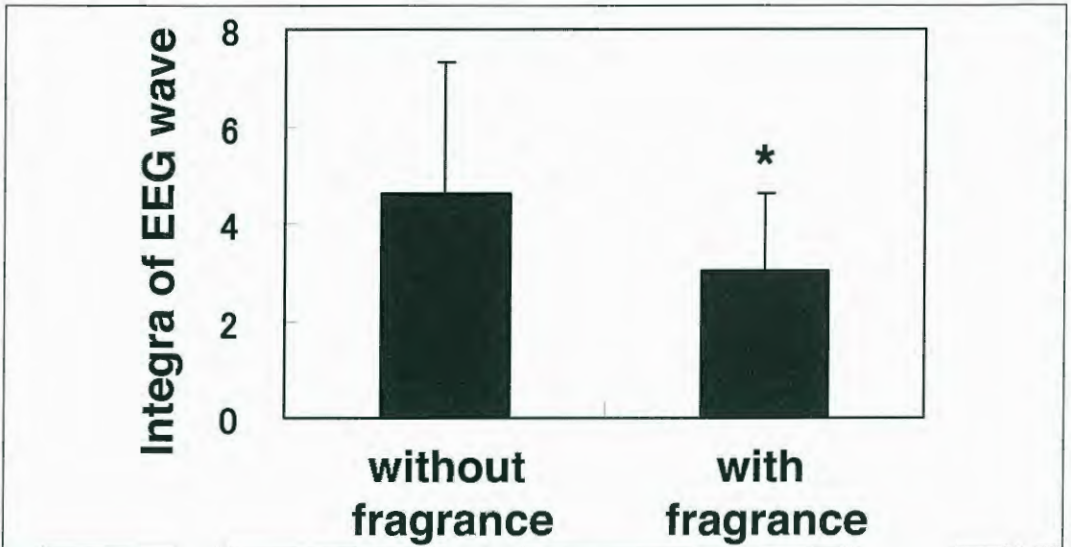


Fig. 9 Suppression of Contingent negative variation measured on an electroencephalogram. $n=8$, $*p<0.05$.

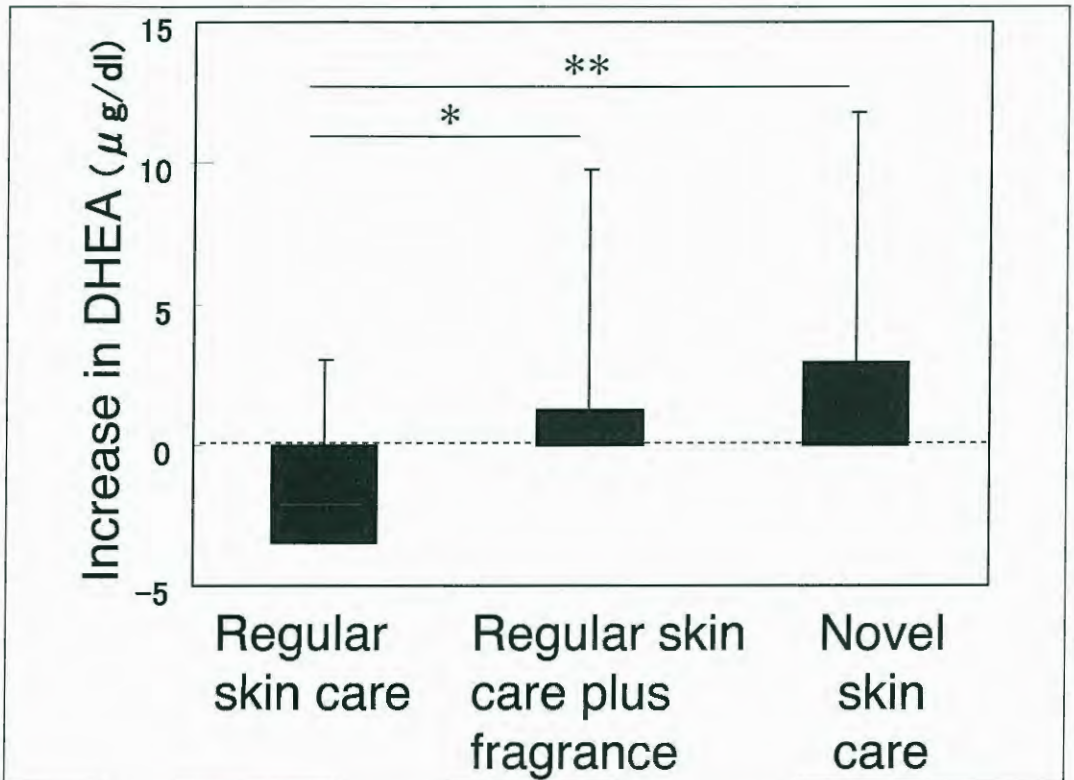


Fig. 10 Increase in salivary DHEA by specially designed fragrance or skin care. $n=30$, $*p<0.05$, $**p<0.01$.

Compared to the decrease in Group 1 who continued to apply their own skin care products on their face, a slight but significant increase was detected in Group 2 who used the fragrance we developed as an environmental scent and in Group 3 who used the specially designed skin care system. These findings demonstrate that daily use of certain cosmetics or exposure to an ambient fragrance effectively enhances the circulation of DHEA.

Under these conditions moisture content of the skin (skin conductance) was measured on the

forearm where no cosmetic treatment was applied during the experiment. Fig. 11 shows the changes in moisture content from the beginning of the experiment to the end. In Group 1, the moisture content was decreased after one month, suggesting that the skin became dried without treatment. However, there was no such decrease in Group 2 and Group 3. These findings suggest that certain fragrances or skin care products potentially protect the skin by enhancing the self-protective mechanisms.

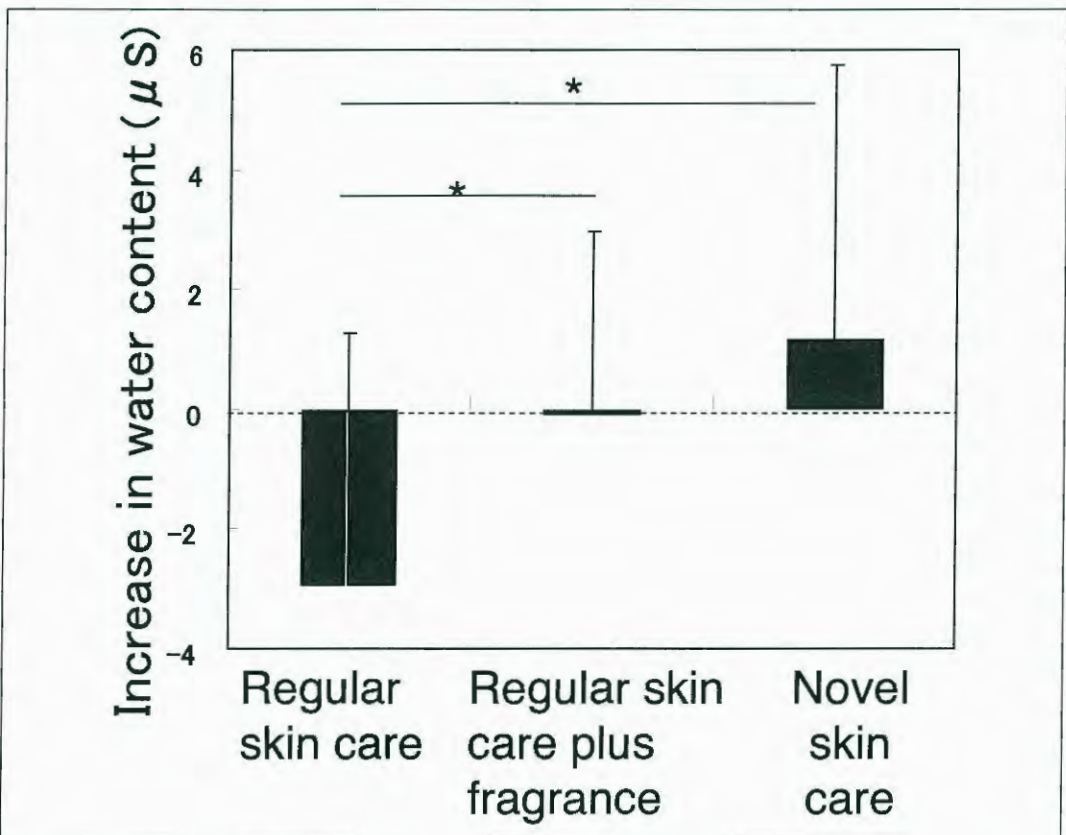


Fig. 11 Increase in moisture content of the arm in response to specially designed fragrance or skin care products. $n=30$, * $p<0.05$, ** $p<0.01$.

CONCLUSION

Intensive studies have provided evidence of the relation of the skin to the body and mind, indicating the effects of the NICE network. Skin care designed to activate the NICE network is a novel approach. Not only the topical application of cream or lotion but also the approaches to activating the internal system seem to be effective. Dermatologists in Yokohama City University demonstrated that the use of a fragrance improved the severity score of itchy atopic dermatitis (30). I hope that further information in this field is accumulated by nice network of scientists from east and west, resulting in the evolution of superior cosmetics.

ACKNOWLEDGEMENTS

The establishment of the NICE system and its application to cosmetics are described above. These works were done by a great many people and I would like to thank all of them, especially Dr. Granstein, Dr. Asahina, Dr. Tsuchiya and Dr. Haze.

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