

Functional map and age-related differences in the human face: nonimmunologic contact urticaria induced by hexyl nicotinate

SLAHEDDINE MARRAKCHI* AND HOWARD I. MAIBACH

Department of Dermatology, School of Medicine, University of California, San Francisco, CA, USA

Variation in human skin reactivity to various irritants in association with age and body region has been reported. Hexyl nicotinate (HN), a lipophilic nicotinate ester, was used to induce nonimmunologic contact urticaria in human volunteers of 2 age groups: 10 young subjects [24–34 years, mean $\pm$ standard deviation (SD) 29.8 ± 3.9 years] and 10 older volunteers (66–83 years, mean $\pm$ SD 73.6 ± 17.4 years); and to define skin function and potential age-related differences in various facial areas. About 5 mM of HN in ethanol was applied to 8 locations on the face, neck, and volar forearm. A laser Doppler flowmeter was used to determine baseline blood flow and to monitor the skin blood flow changes after HN application. In the contralateral areas, stratum corneum turnover was determined using 5% dansyl chloride in petrolatum. In the young group, the perioral area exhibited the strongest reaction to HN. In the older group, the chin was the most sensitive site. In both the groups, the forearm was the least responsive. The older group demonstrated a stronger reaction than the younger group in 3 sites (forehead, cheek, and nasolabial area). Stratum corneum turnover was slower in the nasolabial area and in the forearm in both age groups, whereas the fastest was in the perioral area and the chin in the younger group and in the chin and the forehead in the older group. Compared to the older group, the younger group showed a slower stratum corneum turnover in the nose and the neck. This study demonstrates the regional and the age-related variability of the stratum corneum turnover and the skin reactions to HN. These observations may help explain some aspects of the cutaneous intolerance in skin care of the face.

Key words: age-related differences; contact urticaria; hexyl nicotinate; human face; regional variation. © 2006 The Authors. Journal compilation © 2006 Blackwell Munksgaard

Accepted for publication 4 September 2005

Age-related and regional variation studies of the human skin reactivity to various irritants have been reported (1–5). Marked variation of the various areas of the face in reactivity to benzoic acid has been documented by Shriner and Maibach (6).

In the present study, hexyl nicotinate (HN), a more lipophilic compound than benzoic acid, was used to induce nonimmunologic contact urticaria (NICU) in the same sites as documented by Shriner and Maibach (6). Blood flow changes were recorded to determine potential regional and age-related differences in cutaneous vascular reactivity to HN.

Subjects and Methods

Subjects

2 age groups were studied: 10 healthy volunteers in the young group, aged 29.8 ± 3.9 years, ranging from 24 to 34 years, and 10 in the older group, aged 73.6 ± 17.4 years, ranging from 66 to 83 years.

Exclusion criteria were a history of atopy and current antihistaminic drug use.

All the volunteers gave written consent, and the study was approved by the local ethical committee.

Methods

8 regions (forehead, nose, cheek, nasolabial and perioral areas, chin, neck, and volar forearm) were studied in terms of stratum corneum turnover (dansyl chloride test) and pharmacodynamic response to HN.

*Now with the Department of Dermatology, H Chaker Hospital, Sfax, Tunisia

5 per cent dansyl chloride in petrolatum was applied for 16 hr on the 8 locations of the skin using 8-mm Finn Chamber[®] aluminium discs (Epitest Ltd Oy, Tuusula, Finland) (7).

After dansyl chloride patch removal, the subjects were allowed to acclimate to the examination room for 15 min and then the baseline measurements were taken on the contralateral locations.

Baseline measurements of the cutaneous blood flow laser doppler flowmetry (LDF) were taken using a laser Doppler flowmeter (Laser blood flow monitor MBF3D; Moor Instruments, Axminster, UK) (8). Blood flow measurements were not taken on the upper eyelid because of the potential effect of the laser beam on the retina. Blood flow was monitored at 1 measurement per second for 30 seconds, and the values were averaged.

Using a saturated absorbent filter paper disc (0.8-cm diameter) (Finn Chamber[®]; Epitest Ltd Oy), 5 mM HN in ethanol was applied on the 8 skin areas for 15 seconds to elicit NICU. Then, the blood flow measurements were taken every 10 min for 1 hr in order to detect the maximum vascular response of the skin to HN.

Stratum corneum turnover was determined by detecting fluorescence on each skin site everyday using an ultraviolet (UV) lamp. The period for the fluorescence to disappear was considered as the stratum corneum turnover.

Room temperature and relative humidity were recorded each time when a subject was studied. Room temperature during the study of young group (20.3 ± 2.3 centigrade) was significantly

($P = 0.042$) lower than that during the study of older group (22.1 ± 2.3 centigrade).

Relative humidity during the study of young group (52.6 ± 3.8) was significantly higher ($P = 0.009$) than that during the study of older group (46.5 ± 5.5).

Statistical analysis

To compare the measurements in the various skin sites within each group, the analysis of variance test was used. The two-tailed Student's *t*-test for unpaired data was used to compare the differences between the 2 age groups.

Results

Baseline to peak changes

Cutaneous reactivity to HN was assessed by the baseline to peak changes (peak = maximum LDF-baseline LDF). In some investigations, area under the curve was also considered to assess these changes (6, 9, 10), but as it was correlated to peak values (6), only the baseline to peak changes (peak) were considered in our study.

Comparison between regions. In the young group, the perioral area, followed by the neck, was most sensitive to HN (Fig. 1). The perioral and nasolabial areas, the nose, the forehead, and the neck were more sensitive than the forearm ($P < 0.05$). The perioral area ($P = 0.012$) and the neck ($P = 0.009$) were more sensitive than the cheek.

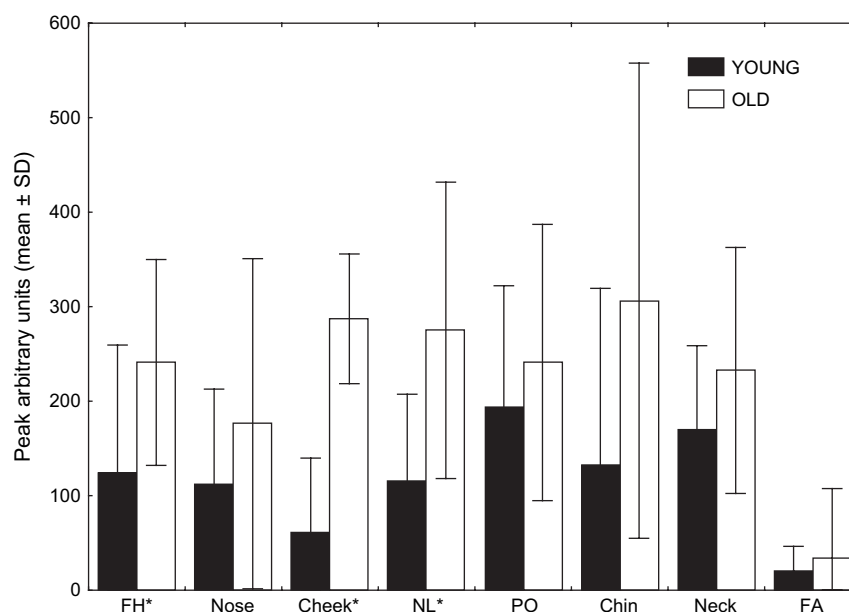


Fig. 1. Baseline LDF to peak changes. Regional variation in the young and old groups and age-related differences. *The regions where the difference between the 2 age groups was significant ($P < 0.05$). FA, forearm; FH, forehead; PO, perioral area; NL, nasolabial area; SD, standard deviation.

In the older group, all the areas of the face were more sensitive, except the forearm. The chin, followed by the cheek and the nasolabial area, was the most sensitive. However, no difference in reactivity to HN was found between the various areas of the face.

The forearm was the less sensitive area in both groups.

Comparison between the 2 age groups. Peak values were higher in the older group in 3 areas: forehead ($P = 0.047$), cheek ($P < 0.001$), and nasolabial area ($P = 0.012$) (Fig. 1).

Stratum corneum turnover

Comparison between regions. The stratum corneum turnover was slower in the nasolabial area and the forearm in both age groups (Fig. 2).

The fastest stratum corneum turnover was shown in the perioral area and the chin in the young group and in the chin and the forehead in the older group.

In the young group, stratum corneum turnover in the nasolabial area and the forearm was significantly slower ($P < 0.05$) than in the forehead, the cheek, the perioral area, and the chin. The stratum corneum turnover was slower in the nose when compared to that in the forehead ($P = 0.028$), the perioral area ($P = 0.016$), and the chin ($P = 0.015$). The stratum corneum turnover was slower in the neck than in the perioral area ($P = 0.004$) and in the chin ($P = 0.029$).

In the older group, the forearm and the nasolabial area demonstrated a significantly slower

stratum corneum turnover than the forehead ($P < 0.001$ and $P = 0.008$, respectively), the nose ($P < 0.001$; $P = 0.025$), the cheek ($P < 0.001$; $P = 0.011$), the perioral area ($P < 0.001$; $P = 0.023$), the chin ($P < 0.001$; $P = 0.001$), and the neck ($P < 0.001$; $P = 0.013$).

Comparison between the 2 age groups. In the nose and the neck, the stratum corneum turnover was significantly ($P < 0.05$) slower in the young group than in the older group (Fig. 2).

Discussion

Vascular response to HN (peak)

In the young group, the highest vascular responses to HN were by the perioral area and the neck. In the older group, the chin, the cheek, and the nasolabial area showed the highest skin reactivity to HN.

This difference between the 2 age groups might be partly explained by the enlargement of the sebaceous glands in the elderly (11). The ultra violet A (UVA) has been reported to induce sebaceous gland hyperplasia (12) that might lead to the enlargement of the sebaceous glands in the face when compared to other areas (13, 14) and in the elderly when compared to the younger subjects (11, 15).

Appendages may be an important factor in HN absorption because the areas in the older group where peak values were significantly higher than those in the young group are known to have a high appendage density (16), and the enlargement of the sebaceous glands in the elderly (11) might explain that in the older group, the absorption

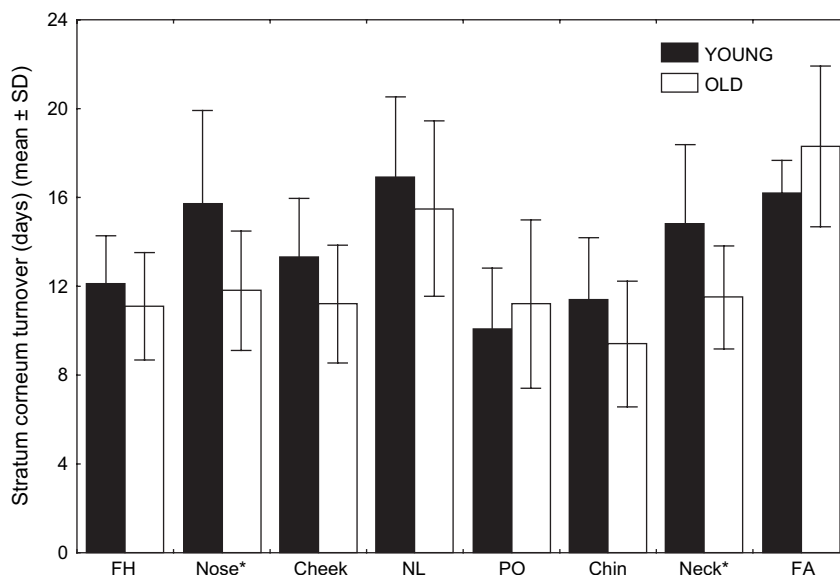


Fig. 2. Stratum corneum turnover. Regional variation in the young and old groups and age-related differences. *The regions where the difference between the 2 age groups was significant ($P < 0.05$). FA, forearm; FH, forehead; PO, perioral area; NL, nasolabial area; SD, standard deviation.

of HN seems to be higher where the appendage density increases.

Reviews and investigative studies have been published discussing the contribution of the various structures of the skin in the drug diffusion. Some note that the contribution of the appendages in the skin permeability to chemicals should not be overlooked, especially during the early phase of absorption (17–19). The appendageal route was reported to contribute to methyl nicotinate transport in the skin (5). Using normal and artificially damaged skin (without follicles and sebaceous glands), Hueber et al. (20) demonstrated that the appendageal route accounts for the transport of hydrocortisone and testosterone, but it is more important for latter, the more lipophilic compound. Illel et al. (21), studying rat skin, found that appendageal diffusion is a major pathway in the absorption of hydrocortisone, caffeine, niflumic acid, and p-aminobenzoic acid. Other studies (22, 23) suggest that intercellular lipids composition is a major factor in barrier function.

However, one should keep in mind that skin reactivity to HN is probably not only the expression of the sole transcutaneous penetration of the molecule but also the manifestation of individual variability in the vascular response to HN.

Stratum corneum turnover

The stratum corneum turnover was slower in the nasolabial area and the forearm in both age groups.

Kawai et al. (24) reported a longer transit time in the volar forearm than in the face in women. In previous studies reviewed by Grove and Kligman (25), the stratum corneum turnover of the forearm was reported to decrease in the elderly. In our study, the same trend was found, although not statistically significant in all the areas, probably because of the shorter application time of dansyl chloride (16 hr). Kawai et al. (24) did not find changes in the stratum corneum turnover in the face in the elderly.

So, in the volar forearm, a photoprotected area, mainly the ageing process is responsible for the differences in stratum corneum turnover between the age groups. The face is the most exposed area to the UV radiations. This could account for the reverse trend in the stratum corneum turnover, although endogenous factors could also intervene. The stratum corneum transit time was shorter in the face than in the protected area (the forearm) and in the older subjects who have received much UV radiation during their life than the young group. So, it seems that the photoageing process probably decreases the stratum corneum transit time.

Conclusions

Many factors certainly account for the percutaneous absorption of the drugs. Besides the various physical parameters used in our study, non-invasive methods for the study of the appendageal density (26) and the stratum corneum lipids composition (27) should be considered to evaluate the influence of these 2 parameters on percutaneous absorption of chemicals.

References

- Gollhausen R, Kligman A M. Human assay for identifying substances which induce non-allergic contact urticaria: the NICU-test. *Contact Dermatitis* 1985; 13: 98–106.
- Lotte C, Rougier A, Wilson D R, Maibach H I. In vivo relationship between transepidermal water loss and percutaneous penetration of some organic compounds in man: effect of anatomic site. *Arch Dermatol Res* 1987; 279: 351–356.
- Larmi E, Lahti A, Hannuksela M. Immediate contact reactions to benzoic acid and the sodium salt of pyrrolidone carboxylic acid: comparison of various skin sites. *Contact Dermatitis* 1989; 20: 38–40.
- Wilhelm K-P, Maibach H I. Factors predisposing to cutaneous irritation. *Dermatol Clin* 1990; 8: 17–22.
- Tur E, Maibach H I, Guy R H. Percutaneous penetration of methyl nicotinate at three anatomic sites: evidence for an appendageal contribution to transport? *Skin Pharmacol* 1991; 4: 230–234.
- Shriner D L, Maibach H I. Regional variation of nonimmunologic contact urticaria: functional map of the human face. *Skin Pharmacol* 1996; 9: 312–321.
- Johannesson A, Hammar H. Measurement of horny layer turnover after staining with dansyl chloride. Description of a new method. *Acta Derm Venereol (Stockh)* 1978; 58: 76–79.
- Bircher A, de Boer E M, Agner T, Wahlberg J E, Serup J. Guidelines for measurement of cutaneous blood flow by laser doppler flowmetry. A report from the standardization Group of the European Society of Contact Dermatitis. *Contact Dermatitis* 1994; 30: 65–72.
- Guy R H, Tur E, Bjerke S, Maibach H I. Are there age and racial differences to methyl nicotinate-induced vasodilation in human skin? *J Am Acad Dermatol* 1985; 12: 1001–1006.
- Gean C J, Tur E, Maibach H I, Guy R H. Cutaneous responses to topical methyl nicotinate in black, oriental, and caucasian subjects. *Arch Dermatol Res* 1989; 281: 95–98.
- Kligman A M, Balin A K. Aging of human skin. In: *Aging and the Skin*, Balin A K, Kligman A M (eds): New York, Raven Press, 1989; pp. 1–42.
- Lesnik R H, Kligman L H, Kligman A M. Agents that cause enlargement of sebaceous glands in hairless mice. II. Ultraviolet radiation. *Arch Dermatol Res* 1982; 284: 106–108.
- Dimond R L, Montagna W. Histology and cytochemistry of human skin: XXXVI. The nose and lips. *Arch Dermatol* 1976; 112: 1235–1244.
- Moretti G, Elis R A, Mescon H. Vascular patterns in the skin of the face. *J Invest Dermatol* 1959; 33: 103–112.
- Smith L. Histopathologic characteristics and ultrastructure of aging skin. *Cutis* 1989; 43: 419–424.
- Blume U, Ferracin I, Verschoore M, Czernielewski J M, Schaefer H. Physiology of the vellus hair follicle: hair growth and sebum excretion. *Br J Dermatol* 1991; 124: 21–28.
- Blank I H, Scheuplein R J, Macfarlane D J. Mechanism of percutaneous absorption: III. The effect of temperature on the transport of non-electrolytes across the skin. *J Invest Dermatol* 1967; 49: 582–589.
- Scheuplein R J, Blank I H. Permeability of the skin. *Physiol Rev* 1971; 51: 702–747.

19. Idson B. Percutaneous absorption. *J Pharm Sci* 1975; 64: 901–924.
20. Hueber F, Wepierre J, Schaefer H. Role of transepidermal and transfollicular routes in percutaneous absorption of hydrocortisone and testosterone: in vivo study in the hairless rat. *Skin Pharmacol* 1992; 5: 99–107.
21. Illel B, Schaefer H, Wepierre J, Doucet O. Follicles play an important role in percutaneous absorption. *J Pharm Sci* 1991; 80: 424–427.
22. Elias P M, Cooper E R, Korc A, Brown B E. Percutaneous transport in relation to stratum corneum structure and lipid composition. *J Invest Dermatol* 1981; 76: 297–301.
23. Wiechers J W. The barrier function of the skin in relation to percutaneous absorption of drugs. *Pharm Weekbl Sci* 1989; 11: 185–198.
24. Kawai M, Imokawa G., Mizoguchi. Physiological analysis of the facial skin by corneocyte morphology and stratum corneum turnover. *Jpn J Dermatol* 1989; 99: 999–1006.
25. Grove G L, Kligman A M. Age-associated changes in human epidermal cell renewal. *J Gerontol* 1983; 38: 137–142.
26. Piérard-Franchimont C, Piérard G E. Assessment of aging and actinic damages by cyanoacrylate skin surface strip-pings. *Am J Dermatopathol* 1987; 9: 500–509.
27. Wefers H, Melnik B C, Flür M, Bluhm C, Lehmann P, Plewig G. Influence of UV irradiation on the composition of human stratum corneum lipids. *J Invest Dermatol* 1991; 96: 959–962.

Address:

Dr Slaheddine Marrakchi

Department of Dermatology

Hopital H Chaker

TN-3029 Sfax

Tunisia

Tel/Fax: +21 674242627

e-mail: nadia.zeghal@cogitel.com.tn