

SHORT REPORTS

Acetylation Phenotype and Skin Complexion

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The relationship of acetylation phenotype to skin complexion was studied in 155 healthy Caucasians. Individuals received 500 mg sulphadimidine at 11.00 p.m.; urine was collected eight hours later. The percentage of acetylated sulphadimidine in urine was measured with high performance liquid chromatography. There was a slight but insignificant preponderance of slow acetylators in the dark skin types. It is concluded that slow acetylation phenotype is not correlated with light skin complexion. Therefore, it is unlikely that acetylation of xenobiotic carcinogens plays a dominant role in melanoma risk. *Key words:* Acetylation; Melanoma risk. (Received February 25, 1986.)

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Light skin complexion represents a key factor in the etiology of melanoma. Sunlight or sunburn may form the principal inducing factor (1-3). However, there are many inconsistencies in the epidemiology of melanoma. Since the relationship between skin type, solar exposure and melanoma risk is by no means overwhelming, it is pertinent to search for other risk factors. For instance, environmental xenobiotics may be involved as (co)carcinogens. Acetylation of xenobiotics is an important detoxification mechanism. Acetylation phenotype influences the risk for some types of cancer, e.g. urinary bladder carcinoma (4). Acetylation phenotype varies with ethnic background (5). The same applies to cutaneous melanoma. In 1983 Leperchey et al. found a statistically significant excess of slow acetylators in Caucasians with a light skin complexion as compared to those with a dark complexion (6). Since this report may hold the key to the chemical (co)carcinogenesis of melanoma, we repeated this study to see whether there is a genuine association between N-acetyltransferase phenotype and skin complexion.

MATERIALS AND METHODS

We studied 155 healthy adult Caucasians, 85% of which were <30 years of age (mean 26 years). There were 89 males and 66 females. Skin type was established according to the burning-tanning histories after Fitzpatrick, ranging from type I (always burn—never tan) to type IV (never burn—always tan) (7). Since self-reported tendency to burn and tan are rather subjective, we also used a scoring system with burning-tanning ability, eye and hair color and freckling tendency as the four ingredients. Thus, a scoring index was obtained from 4-8 points.

Sulphadimidine (500 mg) was administered per os at 11.00 p.m. Urine samples were collected at 07.00 a.m. The percentage of acetylated sulphadimidine was measured in the urine with high performance liquid chromatography (8). Correlations between skin type and skin complexion and acetylation phenotype were studied using a multifactorial regression model.

RESULTS

The rate of acetylation showed a bimodal distribution pattern. There were 83 persons with the slow acetylation phenotype (53.5%) and 72 with the fast acetylation phenotype

(46.5%). The cut-off point between the slow and fast acetylators was 87% acetylated sulphadimidine. The percentages of slow and fast acetylators in the various subgroups according to skin type and skin complexion showed no substantial differences (Table I). Contrary to expectation, there was even a slight preponderance of slow acetylators in the groups with a dark skin type: 48.3% of the subjects with skin type I or II exhibited the slow acetylation phenotype versus 56.8% of those with skin type III or IV. This difference did not reach statistical significance. If the "intermediate" group (85–90% acetylated sulphadimidine) was excluded from analysis (8 cases), the findings remained essentially the same.

DISCUSSION

This study failed to reveal a correlation between slow acetylation phenotype and skin complexion. Our findings are in sharp contrast to those of Leperchey et al. who found a statistically significant excess of slow acetylators in the light complexion categories (6). It is difficult to track down the reason for this discrepancy. It is unlikely that the methods used were of great importance. In the study of Leperchey et al. a "pigmentation index" was established with skin, eye and hair colour as substituents. Freckling of the skin was not considered. We used two scoring systems (the classical Fitzpatrick scheme (7) and a modified pigmentation index with four complexion characteristics). Both methods showed basically the same findings. The fact that we used sulphadimidine whereas Lepershey et al. used isoniazid as the test drug is probably not relevant since acetylation metabolism involves a myriad of acetyltable compounds in a similar way. Finally, we assessed urine levels of sulphadimidine. Plasma concentrations were not measured. Although plasma and urine findings may occasionally diverge, there exists a very strong correlation between the two parameters (9, 10).

The investigation of the effects of various environmental and occupational chemical substances on melanoma carcinogenesis is of urgent pursuit. The etiology of melanoma is by no means settled and claims with regard to the solar etiology are inconsistent. Xenobiotic (co)carcinogens may be involved. We studied the potential clinical significance of human acetylator polymorphism in melanoma risk. First of all because acetylation phenotype plays a role in the etiology of some other malignancies like urinary bladder carcinoma (4). Secondly, the melanocyte conceivably reacts quite differently on xenobio-

Table I. Percentages of slow and fast acetylation phenotypes according to skin type and complexion (from light to dark: I–IV and 4–8, respectively)

		Number of subjects	Acetylation phenotype (%)	
			Slow	Fast
Skin type	I	11	45.5	54.5
	II	49	49.0	51.0
	III	84	57.1	42.9
	IV	11	54.5	45.5
Skin complexion	4	14	50.0	50.0
	5	30	56.7	43.3
	6	40	50.0	50.0
	7	49	55.1	44.9
	8	22	54.5	45.5

tic challenges compared to the keratinocyte on the basis of differences in enzyme patterns. For instance, the melanocyte is the target cell of α -MSH, the activity of which peptide greatly depends on the acetylation-deacetylation equilibrium of the intracellular milieu (11). Such regulatory enzymes may also be involved in detoxification mechanisms. Finally, we were intrigued by the study of Leperchey et al. who claimed a statistically significant correlation between slow acetylation phenotype and light skin complexion which, in its turn, is a strong denominator of melanoma risk (6). Unfortunately, we were unable to confirm the results of the latter study. We conclude that it is very unlikely that acetylation phenotype is related to xenobiotic risk of melanoma. Further studies on the potential impact of xenobiotics and the corresponding enzyme mechanisms on melanoma carcinogenesis are warranted.

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REFERENCES

1. Armstrong BK. Melanoma of the skin. *Br Med Bull* 1984; 40: 346-350.
2. Kopf AW, Kripke ML, Stern RS. Sun and malignant melanoma. *J Am Acad Dermatol* 1984; 11: 674-684.
3. Swerdlow AJ. Epidemiology of cutaneous malignant melanoma. *Clin Oncol* 1984; 3: 407-437.
4. Lower GM, Nilsson T, Nelson CE, Wolf H, Gamsky TE, Bryan GT. N-acetyltransferase phenotype and risk of urinary bladder cancer: approaches in molecular epidemiology. Preliminary results in Sweden and Denmark. *Environ Health Perspect* 1979; 29: 71-79.
5. Propping P. Pharmacogenetics. *Rev Physiol Biochem Pharmacol* 1978; 83: 124-173.
6. Leperchey F, Vivien JN, Vicaut E, Gervais P. Puissance d'acétylation de l'isoniazide et pigmentation dans la population blanche. Incidences pratiques et perspectives embryologiques. *Thérapie* 1983; 38: 613-620.
7. Melsky JW, Tanenbaum L, Parrish JA, Fitzpatrick TB, Bleich HL et al. Oral methoxsalen photochemotherapy for the treatment of psoriasis: a cooperative clinical trial. *J Invest Dermatol* 1977; 68: 328-335.
8. Van der Hoeven R. De serumconcentratie van enkele sulfonamiden en hun N_4 -acetylmetabolieten: bepaling en praktische betekenis voor de kliniek. *Pharm Weekbl* 1982; 117: 845-850.
9. Viznerova A, Slavikova Z, Ellard GA. The determination of the acetylator phenotype of tuberculosis patients in Czechoslovakia using sulphadimidine. *Tubercle* 1973; 54: 67-71.
10. Ellard GA, Gammon PT. Acetylator phenotyping of tuberculosis patients using matrix isoniazid or sulphonamide and its prognostic significance for treatment with several intermittent isoniazid-containing regimens. *Br J Clin Pharmacol* 1977; 4: 5-14.
11. Tilders FJH, Parker CR, Barnea A, Porter JC. The major immunoreactive α -melanocyte-stimulating hormone (α -MSH)-like substance found in human fetal pituitary tissue is not α -MSH but may be desacetyl α -MSH (adrenocorticotropin $_{1-13}$ NH₂). *J Clin Endocrinol Metab* 1981; 52: 319-323.