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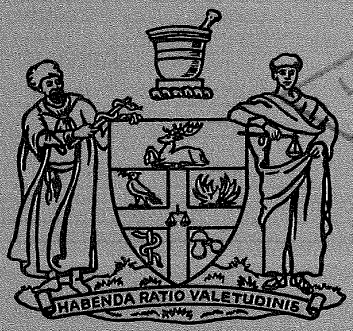

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Physicochemical characterization of the human nail: permeation pattern for water and the homologous alcohols and differences with respect to the stratum corneum*

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In order to develop a basic concept of the permeability of the human nail plate and thus create a better understanding of the toxic potentials and therapeutic possibilities of substances applied to the nail, avulsed cadaver nails have been placed in specially constructed diffusion chambers and their permeation by water and the n-alkanols through dodecanol, all in high aqueous dilution, has been investigated. The permeability coefficient of water is $16{\cdot}5 \times 10^{-3}$ cm h^{-1} and that for methanol is $5{\cdot}6 \times 10^{-3}$ cm h^{-1}. Ethanol's permeability coefficient measured $5{\cdot}8 \times 10^{-3}$ cm h^{-1}. Permeability coefficients decreased systematically thereafter to a low value of $0{\cdot}27 \times 10^{-3}$ cm h^{-1} at n-octanol. The middle chain length alkanols, n-pentanol through n-octanol, have similar permeability coefficients but n-decanol and n-dodecanol show higher rates of permeation. The data suggest that, as a membrane, the hydrated human nail plate behaves like a hydrogel of high ionic strength to the polar and semipolar alcohols. Declining permeability rates appear linked to decreased partitioning into the complex matrix of the plate as the compounds become hydrophobic. The results for n-decanol and n-dodecanol introduce the possibility that a parallel lipid pathway exists which favours the permeation of these exceedingly hydrophobic species.

Apparently, no evidence exists concerning fundamental permeation mechanisms and possible influences of chemical structure on transport across the nail plate. To an extent its permeability properties have been inferred without foundation from the behaviour of other horny tissues. In order to make *a priori* judgements concerning toxic risk and therapeutic benefit of substances brought in contact with the nail, some baseline information on this tissue is needed.

We have shown it possible to determine nail plate permeability coefficients using standard diffusion cell techniques (Walters et al 1981). Results obtained for water agreed well with literature data on water transpiration through the nail plate (Burch & Winsor 1946; Spruit 1971; Baden et al 1973). In pursuant studies the techniques have been extended to the permeation of some n-alkanols. These are useful prototype compounds with systematically varying oil/water (o/w) distribution coefficients and diffusion coefficients. Such structural influences on physicochemical properties, when considered together with relative permeabilities, have helped decipher the barrier mechanisms of several membranes (Blank 1964; Scheuplein 1965; Hwang et al 1976; Ho et al 1977: Behl et al 1980; Durrheim et al 1980; Flynn et al 1981). Previous studies of the alkanol's permeation of skin are especially notable as these provide evidence that the stratum corneum acts to some extent as a hydrophobic continuum (barrier) (Blank 1964; Scheuplein 1965; Behl et al 1980; Durrheim et al 1980; Flynn et al 1981). Similar studies on the human nail plate presented here are comparably revealing as, unlike the stratum corneum, the nail becomes less permeable to the n-alkanols as their hydrophobicity is increased. At extreme hydrophobicity there is increased permeability. The mechanistic significance of these general observations is considered.

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MATERIALS AND METHODS

Materials

Tritiated water and radiolabelled alcohols were obtained from New England Nuclear ([^{3}H]water, [^{3}H]methanol, [^{14}C]ethanol, [^{14}C]butanol), California Bionuclear ([^{14}C]propanol, [^{14}C]pentanol,

[^{14}C]heptanol, [^{14}C]dodecanol) and ICN ([^{14}C]hexanol, [^{14}C]octanol, [^{14}C]decanol). All radiolabelled compounds were diluted with saline (0·9% NaCl Irrigation Solution, Abbott Labs) before use. The alkanols were diluted to trace concentrations, 10^{-4} molar or less.

Permeation procedures

Details of the diffusion cell and permeation procedures have been given previously (Walters et al 1981). Briefly, trimmed human nail plate sections* were placed between two halves of a diffusion cell. A known amount of a radiolabelled permeant was placed in the donor chamber and samples were taken at predetermined intervals from the receptor chamber. Isotope activity was monitored using a Beckman LS 9000 liquid scintillation counter.

The permeation behaviours of [^{3}H]water and [^{3}H]methanol and [^{14}C]alkanols in dilute solution were followed as a function of time at 37 °C. In all cases two permeants were applied with different radiolabels. Generally methanol was run as a tritiated compound along with a ^{14}C-labelled copermeant. Methanol thus served as a reference and it is important to note that the increased values for the permeability coefficient of decanol and dodecanol were obtained concurrently with normal methanol data.

Permeability coefficients (P) were calculated from:

$$P = \frac{V(dC/dt)}{A.\Delta C} \qquad (1)$$

where V is the volume of the receiver half cell, dC/dt is the rate of change in concentration in the pseudo-steady state portion of the receiver concentration versus time plot, A is the diffusional area and ΔC is the concentration differential of permeant across the membrane. V(dC/dt) gives the diffusional flux in mass per unit time. The diffusion cells with nail plate membranes in place were scrupulously checked for intercompartmental leakage using soluble but impenetrable polyethyleneglycol markers and no leaks were evident.

Diffusivities of the permeants in the nail plate tissue were calculated from the non-stationary state periods using:

$$D_{eff} = \frac{h^2}{6t_L} \qquad (2)$$

Where D_{eff} is the effective diffusivity for a given compound, h is the nail plate thickness and t_L is the diffusional lag time obtained by linear regression of the steady state slope of uptake versus time plots. The nail plates used in these studies were measured with a micrometer and averaged 0·54 mm in thickness.

* Fresh cadaver nails generously supplied by Dr T. M. Oelrich, University of Michigan, School of Medicine.

RESULTS AND DISCUSSION

Permeability coefficients of water and the saline diluted n-alkanols are given along with diffusion lag times in Table 1. Fig. 1 shows the relationship between the logarithms of the permeability coefficients and the alkyl chain lengths of the alcohols. An unusual pattern is observed with minimum permeability coefficient values at intermediate alkyl chain length.

Table 1. Nail plate permeability data for water and n-alkanols.

Permeant	Permeability[a] coefficient (cm h^{-1} × 10^3)	Lag. time (t_L) (s)	Effective diffusion[b] constant (D_{eff}) cm^2 s^{-1} × 10^7
Water	16·5 ± 5·9 (6)	900 ± 100	5·4
Methanol	5·6 ± 1·2 (26)	1790 ± 200	2·7
Ethanol	5·8 ± 3·1 (8)	2730 ± 200	1·3
n-Propanol	0·83 ± 0·15 (4)	4020 ± 350	1·2
n-Butanol	0·61 ± 0·27 (4)	3470 ± 350	1·4
n-Pentanol	0·35 ± 0·07 (6)	2700 ± 250	1·8
n-Hexanol	0·36 ± 0·23 (5)	3540 ± 300	1·4
n-Heptanol	0·42 ± 0·12 (4)	2520 ± 300	1·9
n-Octanol	0·27 ± 0·03 (4)	2120 ± 150	2·2
n-Decanol	2·5 ± 1·7 (10)	2090 ± 150	2·1
n-Dodecanol	4·1 ± 2·7 (8)	2300 ± 150	2·1

a. Data include standard deviation and ( ) number of experiments.

b. From $t_L = \frac{h^2}{6D}$ (Mean value for h = 0·54 mm)

Fig. 2 shows the effective diffusivities of the permeants in the nail plate tissue as a function of alkyl chain length.

Theoretical considerations

The nail plate's barrier properties are governed by its anatomical construction and its physicochemical properties and a proposed model must be supportable in terms of both. The model developed here, although speculative, fulfills these requirements. The plate consists of a laminate of sheets of keratinized cells (Caputo & Dadati 1968; Forslind 1970; Forslind & Thyresson 1975). Like the stratum

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