Biochimica et Biophysica Acta, 642 (1981) 67—78

BBA 79141

PERMEABILITY OF NOVIKOFF HEPATOMA CELLS TO WATER AND MONOHYDRIC ALCOHOLS

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(Received August 21st, 1980)

Key words: Membrane permeability; Diffusion coefficient; Aqueous lipophilic pathway; Lipid phase; (Novikoff cell)

Summary

The permeability coefficients of Novikoff hepatoma ascites cell membranes for tritiated water (^{3}HHO) and for a homologous series of monohydric alcohols (methanol through hexanol) were deduced from linear diffusion coefficients by means of a series-parallel pathway model (Redwood et al. (1974) J. Gen. Physiol. 64, 706—729). Membrane permeability coefficients for ^{3}HHO at 20, 30 and 37°C were (all $\times 10^{-5}$) 97, 125, and 163 cm $\cdot$ s^{-1}, respectively, and were significantly smaller than the corresponding values for the alcohols tested. In the alcohol series, ethanol had the lowest permeability coefficient 198 $\cdot$ 10^{-5} cm $\cdot$ s^{-1} at 20°C. The apparent activation energy for water permeation was 6.7 $\pm$ 1.9 S.E. kcal $\cdot$ mol^{-1}. The apparent membrane diffusion coefficients for the alcohols were a complex function of molecular properties with less diffusional membrane resistance to the alcohols in the middle of the homologous series than would have been expected on the basis of oil-water partitioning or molar volume considerations. The conventional parallel aqueous lipophilic pathway model is not consistent with the present data which can be interpreted by consideration of parallel lipophilic pathways through the Novikoff hepatoma cell membrane.

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Introduction

Significant advances in our current understanding of the passive permeability properties of biological membranes have resulted from studies of erythrocyte and model membrane systems. Solomon and co-workers [1—4] have investigated the red-cell barrier and concluded that permeation of solutes occurs via parallel aqueous lipophilic pathways. According to their model, small hydrophilic solutes cross the membrane by an aqueous route whereas larger and more lipophilic solutes diffuse through the lipid matrix. Furthermore, study of the latter pathway [5—10] has shown that, for a given solute, the rate of permeation is a function of the physical properties and chemical composition of the lipid membrane.

Although a wealth of information has been provided by these studies, they may have not reflected fully the diversity possible in plasma membranes from different cell types. To date, there have been only limited data on other isolated mammalian cells [11—15]. The present study characterizes the passive permeability properties of the Novikoff hepatoma cell membrane. The diffusional and osmotic permeability coefficients are described here and in the accompanying paper [16], respectively. We compare our data with the red-cell studies and evaluate the usefulness of the parallel aqueous lipophilic pathway model in interpreting our data.

In this report, the diffusional permeability properties of the Novikoff cell membrane to tritiated water and a series of monohydric alcohols are described. The monohydric alcohols were chosen for this study because their hydrophobic properties permit selective probing of the membrane lipid environment. We interpret our data to indicate that the Novikoff membrane is a heterogeneous barrier with parallel lipophilic permeation pathways.

Materials and Methods

^{125}I-labeled human serum albumin was purchased from Mallinckrodt and purified by centrifugation through a CF-25 Centriflo membrane cone (Amicon). Bovine serum albumin (Fraction V) was obtained from Sigma. [^{14}C]Pentanol was obtained from California Bionuclear. Other radioisotopes were purchased from New England Nuclear.

Novikoff hepatoma ascites cells were maintained in female Sprague-Dawley rats for a period of 7—8 days. The cells were removed from the peritoneal cavity and centrifuged at $600 \times g$ for 10 min at 4°C. Erythrocytes were removed by repeated washes and centrifugations in 0.166 M NH_4Cl (pH 7.4) until microscopic examination revealed few intact red cells * [17]. The Novikoff cell preparation was washed two additional times with Na^+/K^+ Ringer's buffer (pH 7.4, 290 mosM/kg) [13].

Measurement of linear diffusion coefficients

The Novikoff cells were used for diffusion studies as described previously for

* Comparison of diffusion coefficients in control and in NH_4Cl-treated cells revealed no significant difference.

lung cells [11]. To the cell suspension, 6 μl ^{125}I-labeled human serum albumin (1 μCi/μl in 4 g/100 ml carrier albumin) and 6 μl of either [^{14}C]- or [^{3}H]sucrose (1 μCi/μl in 0.27 M carrier sucrose) were added to each 0.1 ml packed cells, to serve as extracellular markers. The cell suspension was drawn into polyethylene tubing (Intramedic, P.E.-90) with a syringe, and the tubing cut into appropriate lengths. One end of each tube was plugged with Sealease and fitted inside a glass 100-μl micropipet for support. Cells were packed by a 45 min centrifugation at 13 500 × g at 4° C in a microhematocrit centrifuge (IEC). Following centrifugation, a sample was taken to determine cellular damage by trypan blue exclusion (95% of the cell population excluded dye). The supernatant layer was sliced off and used to determine extracellular volume [18].

The packed-cell columns were taped to Plexiglass platforms and pulsed individually for 2 min with either 25 μCi tritiated water (^{3}HHO) or 1 μCi ^{14}C-labeled alcohol. Diffusion was allowed to proceed in insulated chambers at a constant temperature for 2—3 h. After incubation, 95% of the cells remained viable. The columns of packed cells were frozen rapidly with solid CO_2 and cut into sections (0.5—1.0 mm) with a Mickel gel slicer. The sections were placed into individual vials and counted for radioactivity.

The experimental conditions are assumed to correspond to one-dimensional semi-infinite diffusion through a homogeneous medium, with the initial impulse deposition of tracer amount m_0 (cpm/cm^2) at $x = 0$, $t = 0$. The theoretical solution for such diffusion is given by Crank [19].

$$c(x,t) = m_0 \ (\pi Dt)^{-1/2} \exp(-x^2/4Dt) \qquad (1)$$

Radioactivity, c (cpm), plotted semilogarithmically against x^2 (x, distance from pulsing point) is a straight line of slope $1/4Dt$ which yields D, since t is known.

Diffusion coefficients for extracellular and intracellular diffusion were measured by the same method. The supernatant from the final cell wash was used as diffusion medium to determine the extracellular diffusion coefficients. Intracellular diffusion coefficients were measured in a packed-cell preparation in which the cells were lysed by rapidly mixing (Vortex) them with 5-mm diameter glass beads (Ace Scientific) in a polycarbonate centrifuge tube for 20 min at 4°C. Phase-contrast microscopy showed that this procedure disrupted 99% of the original cell population.

Light microscopy

In order to determine the packing geometry in the diffusion tubes the cells were packed into Teflon tubing under conditions identical to those used in the diffusion studies. The packed cell column was cut into slices of 0.7 mm thickness. These slices were fixed for 2 h at 4°C in 2.5% glutaraldehyde/phosphate buffer and 1.5 h in 1% osmium tetroxide/phosphate buffer. The slices were then dehydrated in graded alcohol solutions and embedded in Epon 812. Thick sections (1 μm) were cut with a MT-II ultramicrotome and a glass knife. Sections were fixed to glass slides with gentle heating and stained with 4% toluidine blue.

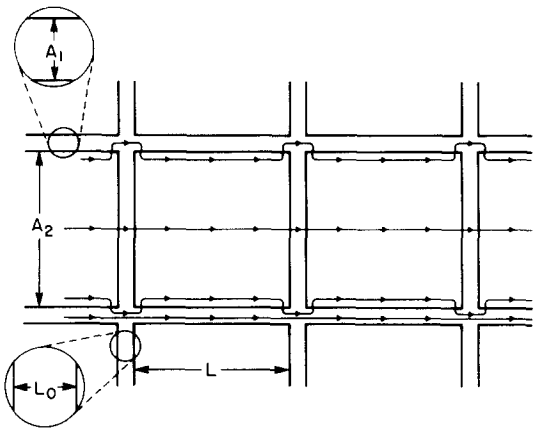

Fig. 1. Local steady-state one-dimensional model idealized for packed Novikoff cells: schematic cells; geometry and flux lines. (Reproduced from Ref. 11 by permission of Am. J. Physiol.)

Calculation of permeability coefficients

Permeability coefficients were calculated from the diffusion coefficients with the series parallel pathway model and the assumption of a local steady-state flux pattern [18]. This model is shown schematically in Fig. 1. 'Unstirred layer' effects are corrected in the model and include measured diffusion coefficients through appropriate solutions. An analysis of the model is given in Redwood et al. [18]. Some of the parameters required for this analysis and referred to are below:

D = 'packed cell' diffusion coefficient ($cm^2 \cdot s^{-1}$)
D_1 = extracellular diffusion coefficient ($cm^2 \cdot s^{-1}$)
D_2 = intracellular diffusion coefficient ($cm^2 \cdot s^{-1}$)
L = end-to-end distance of cell in diffusion direction (cm)
L_0 = intercellular distance in diffusion direction (cm)
P_0 = membrane permeability coefficient ($cm \cdot s^{-1}$)
V = total column volume
V_1 = extracellular volume
V_1/V = relative extracellular volume

Numerical values of P_0 L were obtained from experimental values of D, D_1, D_2, and V_1/V with calculated values for tortuosity (L_1/L_2) and exchange area (S/A_2) [11].

Results and Discussion

Packing geometry

The packing geometry of the Novikoff cells in Teflon tubing following centrifugation was examined by light microscopy and is illustrated in Fig. 2. No specific orientation or polarity is exhibited by the cells in either the cross-section (Fig. 2a) or longitudinal-section (Fig. 2b). The diameter of the Novikoff cell was determined from Fig. 2 by means of a Poisson distribution analysis. A mean diameter of 14.4 ± 0.4 (S.D.) μm was obtained and is in good agreement with that of 13.5 μm reported by Wohlheuter et al. [20].

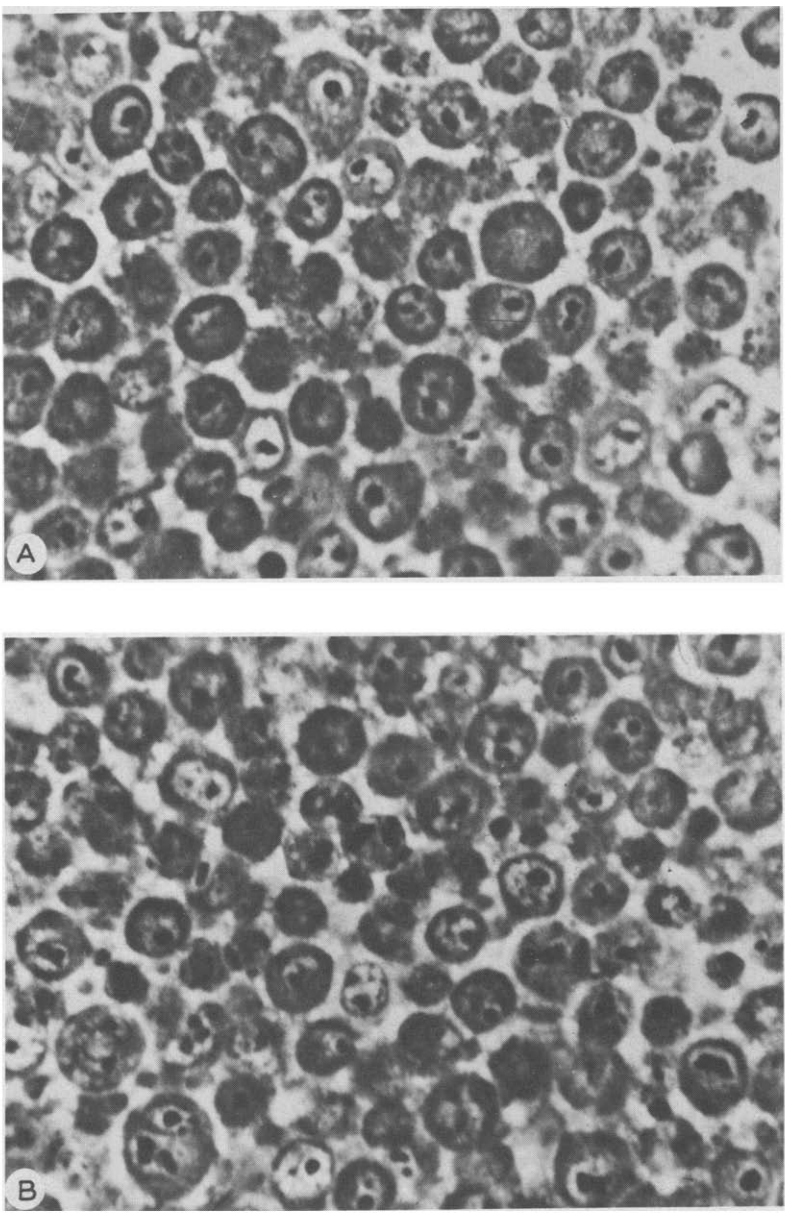

Fig. 2. Packing geometry of Novikoff cells in diffusion tubes following centrifugation. Specimens were prepared as described in the methods: A, cross section; B, longitudinal section (magnification: 400X).

The relative extracellular volume (V_1/V) in the packed cell column was measured with ^{125}I-labeled human serum albumin and with either [^{14}C]- or [^{3}H]-sucrose as markers. The relative extracellular volume for ^{125}I-labeled human serum albumin was 0.103 ± 0.018 (S.D.), whereas for sucrose a larger value of 0.156 ± 0.024 (S.D.) was obtained. Since carrier solutes were present with radioactively labeled extracellular markers, we believe that nonspecific adsorp-

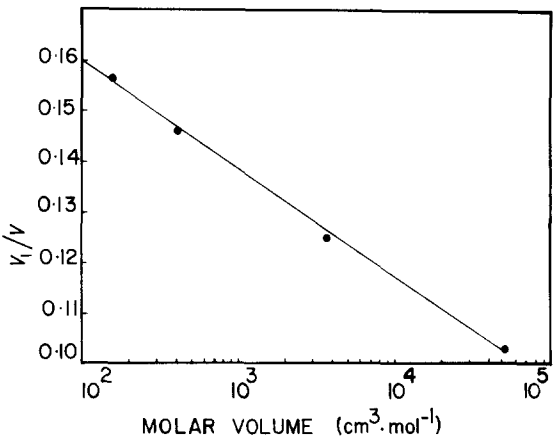

Fig. 3. Relative extracellular volume (V_1/V) of packed Novikoff cells as a function of test solute molar volume. Cells were packed by a 45 min centrifugation at 13 500 × g.

tion was not responsible for the discrepancy and that the solutes occupied two different extracellular spaces. Two additional markers, [^{14}C]inulin and [^{3}H]-raffinose, yielded the relative extracellular volumes listed in Table I. In Fig. 3, the relative extracellular volumes are plotted as a function of the marker molar volume. The linear semilogarithmic relationship between extracellular volume and molar volume of radioactively labeled markers observed in the packed cell system is analogous to the relationship between solute partition coefficients and molecular size in analytical gel chromatography [21,22].

A relative extracellular volume (V_1/V) necessary for the calculation of permeability coefficients was obtained by extrapolation of the line in Fig. 3 to 100 $cm^3 \cdot mol^{-1}$. This volume was used since it is approximately the mean molar volume of the larger alcohols employed in this study. Based on the relative extracellular volume of $V_1/V = 0.16$ and a cell length of $L = 14.4$ μm, a mean intercellular distance in the diffusion direction (L_0) was calculated to be 0.91 μm.

Numerical solution of the experimental data is based on the steady-state diffusional model which depends on defined average values of the dimension-

TABLE I

RELATIVE EXTRACELLULAR VOLUME (V_1/V) OF PACKED NOVIKOFF CELL PREPARATION

The values reported for V_1/V are mean ± S.D., with the number of determination given in parenthesis.

Solute	Molar volume ($cm^3 \cdot mol^{-1}$)	V_1/V
Albumin	50 370	0.10 ± 0.02 (91)
Inulin	3 852	0.13 ± 0.01 (36)
Raffinose	407	0.15 ± 0.01 (24)
Sucrose	157	0.16 ± 0.02 (91)

less geometric parameters L_1/L_2 and S/A_2. The dependence of the calculated permeability coefficients on L_1/L_2 and S/A_2 has been evaluated; it is relatively small. (A similar dependence was noted previously in the study of isolated lung cells, and was illustrated in Fig. 4 of Ref. 11.) The ratio of the extracellular diffusion length to the intracellular diffusion length (L_1/L_2) is a measure of the tortuosity of the extracellular diffusion pathway. For cells packed as shown in Fig. 1, L_1/L_2 is 1.0, while for less regular packing, as found for the Novikoff cells, this value is greater than unity. The tortuosity factor for the Novikoff cells was estimated as in Garrick and Redwood [11]. Independent estimates of the tortuosity factor were obtained from diffusion studies with [^{14}C]sucrose and [^{3}H]raffinose as test solutes. With the values for the total cross-sectional area [11] and the relative extracellular volume V_1/V of sucrose and raffinose (Table I), the tortuosity factors calculated for Novikoff cells were 1.20 ± 0.03 (S.E.) and 1.27 ± 0.04 (S.E.) for sucrose and raffinose, respectively.

The geometric parameter S/A_2 is the ratio of the cellular side-face exchange area to the intracellular cross-sectional area. If the cells are assumed to be cuboidal, the model used here to idealize spherical Novikoff cells, the side-face exchange area is 4-times the end-face area.

Linear diffusion coefficients

The linear diffusion coefficients for tritiated water and the alcohol series at 20 and 37°C are listed in Table II. It is evident that the diffusion coefficients through the packed cells (D) are considerably lower than the corresponding intracellular (D_2) or extracellular (D_1) diffusion coefficients at each temperature. This feature is illustrated in Fig. 4, where the various diffusion coeffi-

TABLE II

LINEAR DIFFUSION COEFFICIENTS

The diffusion coefficients reported are mean ± S.E., with the number of determinations in parenthesis. D is the 'packed cell' diffusion coefficient; D_1, the extracellular diffusion coefficient; and D_2, the intracellular diffusion coefficient. The temperature for the first set of measurements was 20 ± 0.5°C and for the second 37 ± 0.1°C.

Solute	Molar volume ($cm^3 \cdot mol^{-1}$)	D	D_1 ($\times 10^{-5}$) ($cm \cdot s^{-1}$)	D_2	$(D_2-D)/D$
^{3}HHO	20.0	0.329 ± 0.010 (15)	1.915 ± 0.058 (16)	1.356 ± 0.069 (11)	3.121
Methanol	40.5	0.427 ± 0.013 (12)	1.454 ± 0.039 (12)	1.036 ± 0.038 (12)	1.426
Ethanol	59.3	0.312 ± 0.012 (11)	1.221 ± 0.042 (11)	0.840 ± 0.024 (18)	1.692
Propanol	74.5	0.418 ± 0.010 (10)	1.055 ± 0.050 (9)	0.716 ± 0.032 (11)	0.713
Butanol	91.0	0.377 ± 0.011 (11)	0.900 ± 0.057 (11)	0.610 ± 0.016 (14)	0.618
Pentanol	108.0	0.351 ± 0.008 (8)	0.775 ± 0.018 (8)	0.512 ± 0.009 (8)	0.456
Hexanol	126.2	0.275 ± 0.020 (12)	0.649 ± 0.029 (13)	0.404 ± 0.021 (13)	0.469
^{3}HHO	20.0	0.433 ± 0.021 (15)	2.435 ± 0.048 (8)	1.531 ± 0.033 (8)	2.536
Methanol	40.5	0.561 ± 0.016 (8)	2.048 ± 0.059 (8)	1.169 ± 0.044 (8)	1.084
Ethanol	59.3	0.458 ± 0.013 (8)	1.636 ± 0.069 (8)	0.935 ± 0.035 (8)	1.041
Propanol	74.5	0.546 ± 0.028 (9)	1.456 ± 0.066 (8)	0.834 ± 0.042 (8)	0.527
Butanol	91.0	0.655 ± 0.022 (11)	1.169 ± 0.072 (8)	0.746 ± 0.034 (8)	0.139
Pentanol	108.0	0.553 ± 0.009 (8)	1.082 ± 0.035 (8)	0.638 ± 0.007 (8)	0.154
Hexanol	126.2	0.401 ± 0.015 (8)	0.966 ± 0.029 (8)	0.610 ± 0.027 (8)	0.521

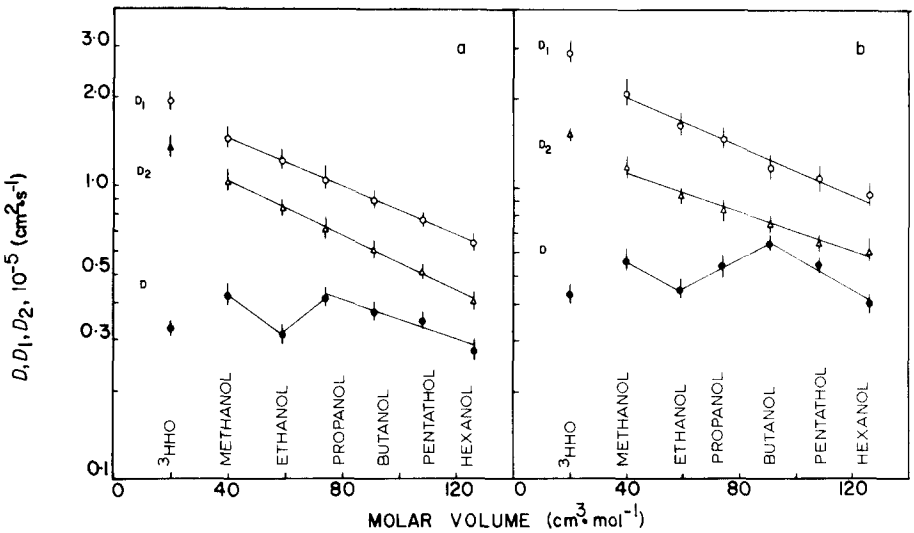

Fig. 4. Variation of linear diffusion coefficients (mean ± S.E.) with molar volume of the diffusing solute at 20°C (a) and 37°C (b) Diffusion medium: ●, packed Novikoff cells; △, intracellular material; ○, extracellular fluid.

cients are plotted against solute molar volume. For the alcohols there is a linear semilogarithmic decrease in the diffusion coefficients with increasing molar volume for both intracellular (D_2) and extracellular (D_1) diffusion. The intracellular diffusion coefficient for ^{3}HHO at 20°C ($1.36 \cdot 10^{-5}$ cm$^2 \cdot$ s^{-1}) is comparable to the upper limit of the literature values measured in a variety of cells types which range from $0.68 \cdot 10^{-5}$ to $1.4 \cdot 10^{-5}$ cm$^2 \cdot$ s^{-1} [23]. The relatively large intracellular diffusion coefficient for the Novikoff hepatoma cell may be attributable to its relatively large intracellular water content, which we measured by wet weight/dry weight analysis to be 85 ± 2.1% (S.E.) [16]. It is noteworthy that the nuclear magnetic resonance spin lattice relaxation time (T_1) of water protons in tissues increases in proportion to the water content [24]. For example, Hollis et al. [25] have reported that the T_1 value for a poorly differentiated hepatoma is significantly larger than for normal lines, in direct correlation with the increased cellular water content of the hepatoma cell.

The rate of diffusion of the solutes through packed cells (D), does not show a linear semilogarithmic dependence with respect to molar volume. That the (total) cellular diffusion coefficient is less than the intracellular diffusion coefficient is taken as an indication of the resistance due to the plasma membrane. An estimate of the relative resistance provided by the plasma membrane with respect to the cytoplasm is given by the term $(D_2 - D)/D$ and is listed in Table II. The values for ^{3}HHO, methanol, and ethanol are significantly larger than for the other solutes.

Novikoff membrane permeability coefficients

In this report we present the diffusional permeability coefficients for water

TABLE III

THE PERMEABILITY COEFFICIENTS TO ^{3}HHO FOR NOVIKOFF CELLS AT 20, 30 AND 37°C

The values reported are means ± S.E. with the number of determinations of D given in parenthesis. P_0 was determined from individual values of D and means of D_1 and D_2.

Temperature (°C)	P_0 ($\times 10^{-5}$) (cm · s^{-1})
20	97 ± 10 (18)
30	125 ± 9 (6)
37	163 ± 26 (10)

and an alcohol series through a tumor cell membrane. The membrane permeability coefficients for ^{3}HHO and the alcohols are listed in Tables III and IV, respectively. These values were calculated from the measured linear diffusion coefficients by means of the series-parallel pathway model [18] and were corrected for intercellular aqueous spacing [11]. At 20, 30, and 37°C, the permeability coefficients for ^{3}HHO are (all $\times 10^{-5}$) 97, 125, and 163 cm · s^{-1}, respectively. The $P_{3_{HHO}}$ at 20°C is approximately 1/3 the permeability coefficient observed in isolated lung cells [11], and 1/6 the ^{3}HHO permeability in dog erythrocytes [18]. The $P_{3_{HHO}}$ for the Novikoff cell membrane is similar to the corresponding value for planar lipid bilayer membranes lacking aqueous channels [26].

An Arrhenius plot of $P_{3_{HHO}}$ is presented in Fig. 5. Linearity of the regression was tested by analysis of variance and the slope of the regression line was used to calculate an apparent activation energy for ^{3}HHO permeation of 6.7 ± 1.9 (S.E.) kcal · mol^{-1}.

Permeability coefficients reflect solute membrane interactions [27] and thus may be used to study the molecular organization of membranes. The monohydric alcohols were chosen as solutes since they would selectively probe the membrane hydrophobic region. It was observed that all alcohols tested permeated the membrane significantly faster than did ^{3}HHO (Table IV). This is illustrated in Fig. 6, where the permeability coefficients are plotted against

TABLE IV

PERMEABILITY COEFFICIENTS FOR NOVIKOFF CELLS AT 20 ± 0.5°C AND 37 ± 0.1°C

The values reported are mean ± S.E. with number of determinations of D given in parenthesis. P was determined from individual values of D and the means of D_1 and D_2.

Solute	($\times 10^{-5}$) (cm · s^{-1}) P_0		$K_{oil/water}$ *
	20°C	37°C	
^{3}HHO	97 ± 10 (15)	163 ± 26 (10)	0.0019
Methanol	311 ± 20 (12)	393 ± 29 (8)	0.013
Ethanol	198 ± 20 (11)	321 ± 19 (8)	0.074
Propanol	484 ± 34 (10)	628 ± 82 (8)	0.226
Butanol	494 ± 40 (11)	1586 ± 123 (11)	0.700
Pentanol	553 ± 41 (8)	1164 ± 77 (8)	2.55
Hexanol	320 ± 33 (12)	563 ± 62 (8)	10.9

* Ref. 23.

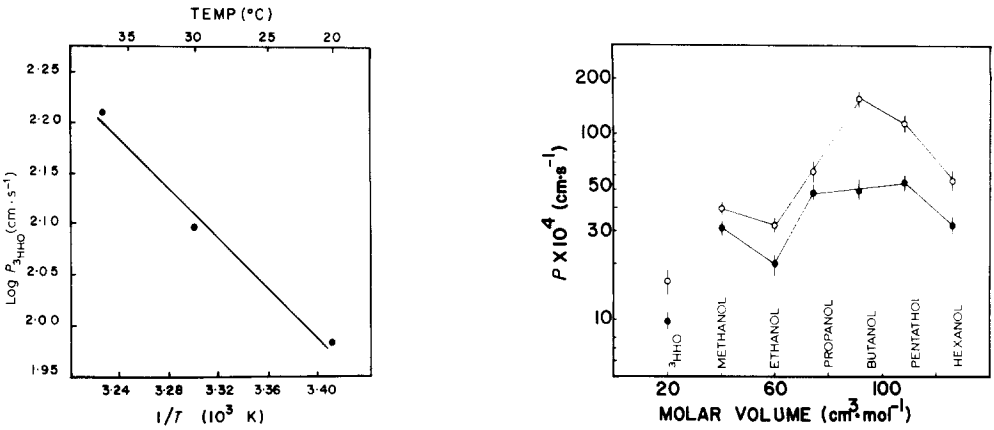

Fig. 5. Arrhenius plot of logarithm of $P_{^3HHO}$ as a function of the reciprocal of the absolute temperature. Data from Table III. E_a, 6.7 kcal · mol^{-1}!

Fig. 6. Permeability coefficients (mean ± S.E.) as a function of molar volume of test substance at 20°C (●) and 37°C (○). Permeability coefficients were calculated from individual values of D and the means of D_1 and D_2.

solute molar volume. At 20°C, the permeability coefficients decrease from methanol to ethanol and then increase at propanol. From propanol to pentanol the permeability remains relatively constant but decreases at hexanol. A similar pattern is observed for methanol, ethanol, and propanol for 37°C. The increased permeability coefficient for butanol and pentanol at 37°C suggests a permeation process for this solute with a greater temperature sensitivity than the other alcohols. A feature common to the studies at the two temperatures is the minimum in the permeability coefficients observed at ethanol.

The pattern of permeability coefficients observed for the Novikoff cell membrane to the alcohol series (Fig. 6) reveals similarities to the erythrocyte [28] and isolated lung cell system [11]. The minimum permeability at ethanol has been found with all three systems, but only in the present work is the minimum statistically significant ($P < 0.05$).

Solomon and co-workers [3,4] have observed a minimum permeability in erythrocyte membranes occurring at the second or third member of various homologous series of solutes, and have postulated the parallel aqueous lipophilic pathway model to explain the transport data. If functional aqueous channels existed in the Novikoff cell membrane, then one would predict that the permeability coefficient for ^{3}HHO would be higher than for methanol or ethanol, but such is not the case (Fig. 6). It is therefore not necessary to invoke the existence of functional aqueous pathways in the Novikoff cell membrane. In order to rationalize the observed permeability values, we would rather propose that the Novikoff cell membrane functions as a mosaic barrier consisting of parallel lipophilic pathways. The greater influence of temperature on the permeability coefficients for butanol and pentanol may reflect changes in the physical properties of these lipophilic domains. However, this behavior may also be related to the intrinsic physicochemical properties of the alcohols

which, for example exhibit a melting-point minimum at propanol [29].

Solute permeability has been shown previously to be a function of both molecular size and the ability of the solute to dissolve into the membrane matrix [30]. Diffusion within the membrane interior can be evaluated by normalizing the permeability coefficients for the solubility of the solutes in the membrane. Solubility coefficients for solutes in the plasma membrane are not available. However, they may be approximated by oil/water partition coefficients. In Fig. 7, the permeability coefficients, normalized with olive oil/water partition coefficients [31], are plotted as a function of solute molar volume. Linearity of regression for the ln $P/K_{oil/water}$ vs. molar volume plot was tested by an analysis of variance [32]. This statistical test indicated significant deviation from linearity ($F_{0.95,(1,73)} = 31.2$). Normalization of the permeability coefficients with diethyl ether/water or octanol/water partition coefficients did not alter the trend observed in Fig. 7.

In contrast to these data for the Novikoff cell membrane, Hung and Autian [33] have found that the diffusion coefficients for monohydric alcohols (methanol through octanol) across synthetic polyurethan membranes are a linear function of molar volume. Fig. 7 shows that the diffusion of alcohols through the Novikoff cell membrane is not a simple function of the molar volume, but there appears to be less diffusional resistance to the alcohols in the middle of the homologous series than would be expected from considerations of the solute lipid solubility and molar volume. This complex dependence on molar volume is interpreted here as evidence supporting the concept of lipid phase heterogeneity. We propose for the Novikoff cell membrane barrier a model that is characterized by parallel lipophilic permeation routes. These

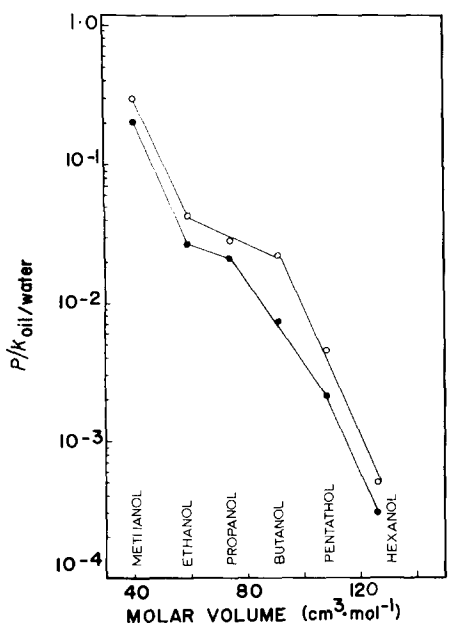

Fig. 7. Relationship of $P/K_{oil/water}$ with the molar volume of test solute at 20°C (•) and 37°C (○).

pathways are envisioned as two or more lipid phases which are affected differently by temperature changes. Interaction between these lipid domains would be dictated by their compositions, which would in turn determine their physical properties [34]. The presence of three functionally distinct domains in rat hepatocyte membranes [35] supports the concept of the mosaicism of the Novikoff hepatoma cell membrane reported here. Solute permeation proceeding by a mechanism such as Trauble's 'kink' model [36] permits solute discrimination to be attributed to the physical properties of the lipid domains.

Acknowledgements

This study was supported in part by National Institutes of Health Grant HL-12974 and in part by funds made available by the Graduate School of Biomedical Sciences.

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