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Cutoff effect of n-alkanols in an excitable model membrane composed of dioleyl phosphate

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Abstract

A series of n-alkanols from ethanol to tridecanol interacted with a negatively charged lipid membrane composed of dioleyl phosphate, which exhibited a self-sustained oscillation of the membrane potential. A cutoff effect was observed in the electrical characteristics of the membrane; e.g., alkanols with carbon atoms less than 11 decreased the membrane resistance and alkanols with more than 12 carbon atoms increased it. n-Alkanols usually depressed the oscillation of the membrane potentials as it has been observed in biological systems. Electrochemical theory provided a quantitative explanation of the observed electrical charactersitics.

Keywords: Anesthetics; n-Alkanols; Membrane potential; Membrane resistance; Cutoff effect; Electrical oscillation

1. Introduction

The anesthetic potency of n-alkanols is enhanced by increasing the chain length of alkanols, but the potency loses suddenly at about 12 carbon atoms. This fact is known as a cutoff effect [1–3]. Historically, a general correlation between the anesthetic potency and the solubility in olive oil led to the conclusion that the site of anesthetic action has a hydrophobic nature to interact with hydrocarbon parts of lipids [4]. In an early, comprehensible lipid theory [5], the cutoff has been accounted for in terms of an abrupt decrease in adsorption into the lipid bilayer. It has been shown, however, that the adsorption of n-alkylmethyl ammonium ions to liposomes continues up to the alkanol with 18 carbon atoms [6]. Hence, it is difficult to explain the cutoff with a failure of large molecules to bind with lipids. Recently, several hypotheses on the cutoff effect have been proposed; those are based on a hydrophobic volume change [3], a lipid disorder [2], a lipid phase transition [7,8] or a lipid surface potential [9].

In previous papers [10,11], effect of local anesthetics was examined using an excitable lipid

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membrane composed of dioleyl phosphate. This lipid membrane reproduced well responses of biological nerve membranes to anesthetics [12,13] such as the decrease in the membrane resistance and the repression of nerve excitation. We have now investigated, thereby, systematically the effect of homologous series of n-alkanols on the electrical characteristics of this lipid membrane. The membrane resistance and the membrane potential showed the cutoff effect; for example, alkanols with carbon atoms less than 11 decreased the membrane resistance and those with more than 12 carbon atoms increased it. In general, n-alkanols depressed the oscillation of the membrane potential. The observed electrical characteristics were explained quantitatively using an electrochemical theory taking account of adsorption of alkanols to lipid membranes.

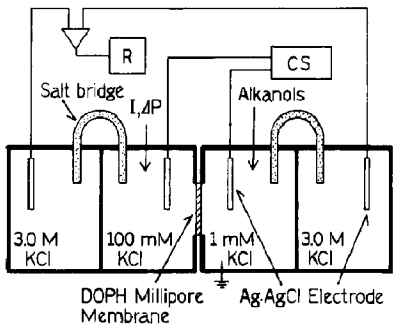

Fig. 1. Schematic illustration of experimental apparatus. A DOPH-adsorbed Millipore membrane was placed between two cells containing 1 m*M* and 100 m*M* KCl solutions. The membrane potential was measured with Ag/AgCl electrodes via salt bridges and was recorded with an XY recorder (R). The membrane resistance was measured by the potential change accompanying the application of d.c. electrical current, which was imposed with a current supply (CS). In experiments for electrical oscillations, a pressure application device was provided. The electrical oscillation of the membrane potential was induced by imposing the electrical current and the pressure difference on the membrane from the 100 m*M* KCl side to the 1 m*M* KCl side.

2. Materials and methods

The n-alkanol is abbreviated by C_n hereafter. n-Alkanols from C_2 to C_{13} except C_{10} were obtained from Kanto Chemical Co., while C_{10} was from E. Merck A.G.

The membrane was processed as reported previously [14–16]. Lipid analogue, dioleyl phosphate (DOPH), was synthesized by hydrolysis of the reaction product of oleyl alcohol and phosphorus oxychloride. It has two hydrophobic hydrocarbon chains and one hydrophilic group of phosphoric acid. A DOPH-adsorbed membrane was prepared by immersing a filter (Millipore Corp., pore size 5 μm) into a solution of DOPH in benzene and then drying it in air. The adsorbed DOPH quantity was adjusted to about 3 mg/cm^2. The membrane was preconditioned in 100 mM KCl solution over 12 h.

The DOPH membrane was placed between two cells, as shown in Fig. 1. One cell was filled with 100 m*M* KCl and the other with 1 m*M* KCl. The membrane potential was detected with Ag/AgCl electrodes via salt bridges and was recorded with an XY recorder (Riken Denshi F-42CP) through a high-impedance transfer with a gain of unity. The 1 m*M* KCl side was grounded. The membrane resistance was measured by the potential change accompanying the application of 0.01 μA d.c. electrical current from 100 m*M* KCl side.

The d.c. component of the membrane potential is not important in studying the electrical oscillation. Thus, the salt bridges were removed, and a pressure application device was provided on the cell as usual [11,14–16]. Electrical oscillations were induced by imposing an electrical current and a pressure difference on the membrane from the 100 m*M* KCl side to the 1 m*M* KCl side. Although some fluctuations or oscillations appeared even when the electrical current was imposed from 1 m*M* side, the stable regular oscillation continuing for over one hour was obtained only under the above condition.

n-Alkanols were added to the 1 m*M* KCl side, which was stirred throughout experiments. In most of experiments, alkanols without dilution were used. Sometimes alkanols were diluted with the same volume of ethanol. A significant difference between two methods was not found, because ethanol had little effect on the membrane characteristics up to 100 m*M*. The temperature was usually maintained at 25 ± 1°C. In experi-

ments with C_{12} and C_{13}, the temperatures were kept at 26 ± 1°C and 33 ± 1°C, because the melting points are 24°C and 31°C, respectively. The concentration of each alkanol was increased stepwise at 15-min intervals. The membrane potential was recorded continuously, and the membrane resistance was determined at the end of each treatment.

3. Results

3.1 Effect of n-alkanols on the membrane potential

The electrical potential of the DOPH Millipore membrane was measured for a series of n-alkanols from C_2 to C_{13}. Experiments were carried out about five times for each alkanol. Figure 2 shows one example of the transient response of the membrane potential to nonanol (C_9).

The electrical potential of the untreated membrane was ca. −118 mV, although the value differed between −110 and −125 mV for each membrane preparation. The negative value for the potential indicates that the membrane has a fine permeability to cations due to the negatively charged phosphate group in the lipid DOPH. Vigorous stirring of the solution of 1 m*M* KCl decreased the potential by ca. 5 mV, compared with no stirring. The potential was fairly stable under constant stirring.

Alkanols of two to eleven carbon atoms decreased the magnitude of the membrane potential; i.e., they resulted in depolarization. As shown in Fig. 2, the membrane potential was depolarized slowly with addition of alkanol; the rate of depolarization is about 1 mV/min.

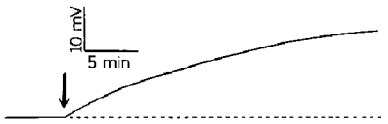

Fig. 2. Transient profile of the electrical potential. The time of addition of 7.0 m*M* nonanol is shown by the arrow. The upward change in the potential indicates the depolarization, because the potential was originally negative.

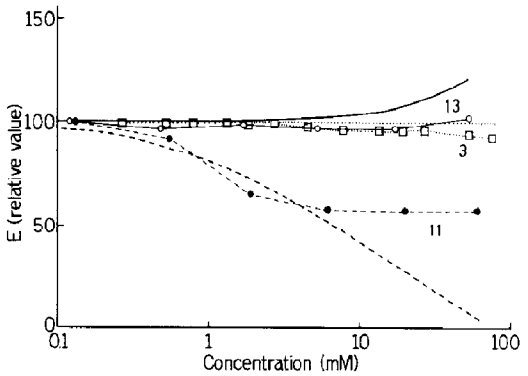

Fig. 3. Alteration of the membrane potential caused by n-alkanols. The membrane potential (E) of the untreated membrane slightly differed for each membrane, and the values were normalized to a relative value of 100 as the initial value. (□) Propanol, (●) undecanol, and (○) tridecanol. Lines without symbols indicate theoretical results. The numerical figure of n is attached to each curve.

The dependence of the potential change on the concentration of alkanols is shown in Fig. 3, where some typical data are shown by lines with symbols, while theoretical results mentioned afterwards are shown by the same kinds of lines without symbols. The potential is presented as a relative value by taking the initial value without alkanols as 100%.

Propanol (C_3) had little effect, although it tended to decrease the magnitude of the membrane potential, i.e., depolarized the potential. Undecanol (C_{11}) significantly decreased the magnitude of the membrane potential even at the low concentrations. On the contrary, tridecanol (C_{13}) increased slightly the magnitude of the potential at higher concentrations, i.e., hyperpolarized the potential.

Effects of all alkanols on the membrane potential are summarized in Fig. 4. The potential change at 3 m*M* of each alkanol is plotted against the number of carbon atoms, although the extent of changes caused by alkanols depends on their concentrations. The depolarization increased with the number of carbon atoms up to 11. Alkanols of more than 12 carbon atoms abruptly lost their actions. It resembles the cutoff effect.

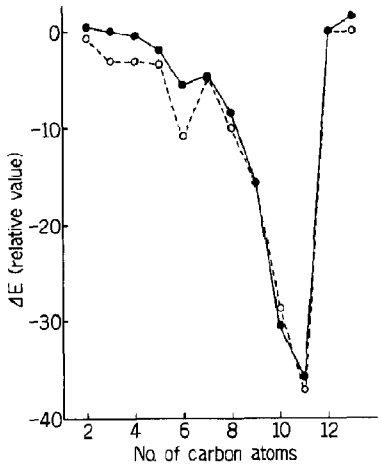

Fig. 4. Effect of n-alkanols on the membrane potential. Relative potential change (ΔE) at 3 mM of each alkanol is plotted against the number of carbon atoms, dashed and solid lines indicating experimental and theoretical results, respectively. Whereas all the experiments were not made at 3 mM, the values were determined by interpolating the neighboring measured two points (e.g., 2 mM and 5 mM).

3.2 Effect of n-alkanols on the membrane resistance

Figure 5 shows effects of several alkanols on the membrane resistance. The untreated resistance value was 4 to 6 MΩ, depending on the membrane preparation; hence the membrane resistance is displayed as a relative value. Propanol (C_3) increased the resistance above about 0.5

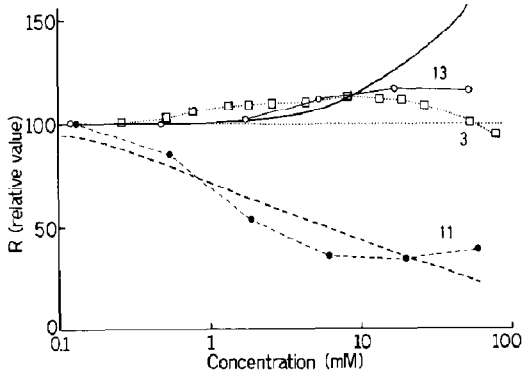

Fig. 5. Alteration of the membrane resistance caused by n-alkanols. The membrane resistance (R) was normalized in the same manner as that in Fig. 3. (□) Propanol, (●) undecanol, and (○) tridecanol. Lines without symbols indicate theoretical results.

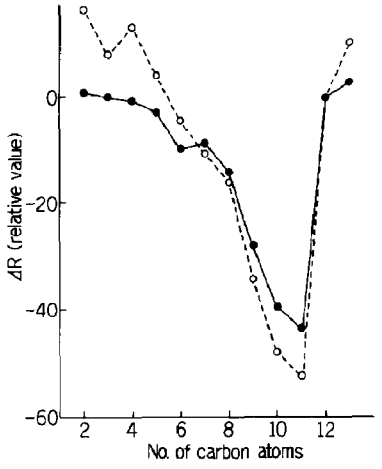

Fig. 6. Effect of n-alkanols on the membrane resistance. The relative resistance change (ΔR) at 3 mM of each alkanol is plotted against the number of carbon atoms, dashed and solid lines indicating experimental and theoretical results, respectively.

mM and then decreased it at higher concentrations, i.e., showed a biphasic behavior. Undecanol (C_{11}) markedly decreased the resistance with its threshold value about 0.2 mM. At higher concentrations, the resistance increased a little. Tridecanol (C_{13}) increased the resistance about 1 mM, but later decreased it above about 20 mM. The changes of membrane resistance were generally larger than those of membrane electrical potential.

Changes of the membrane resistance plotted against the number of carbon atoms are shown in Fig. 6 for each alkanol at 3 mM. The membrane resistance was scarcely affected by alkanols from C_2 to C_4, whereas it decreased with the increase in the number of carbon atoms up to 10 or 11. Alkanols of more than 12 carbon atoms had no effect, or increased slightly the resistance. Thus, a series of n-alkanols also displayed a cutoff-like action on the membrane resistance as well as the membrane potential.

3.3 Effect of n-alkanols on the electrical oscillation of the membrane

The DOPH-adsorbed Millipore membrane exhibits a self-sustained oscillation of the membrane potential [14–19]. The frequency is usually

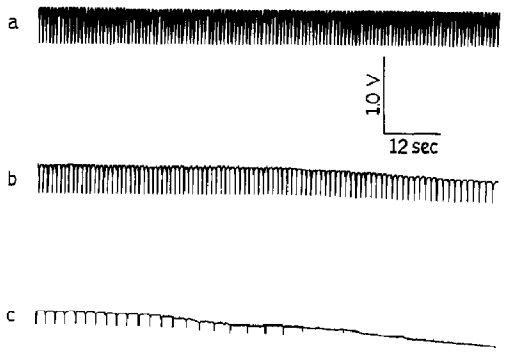

Fig. 7. Depression of the oscillation by nonanol in (a) 0.6 mM, (b) 7.0 mM, and (c) 23.0 mM.

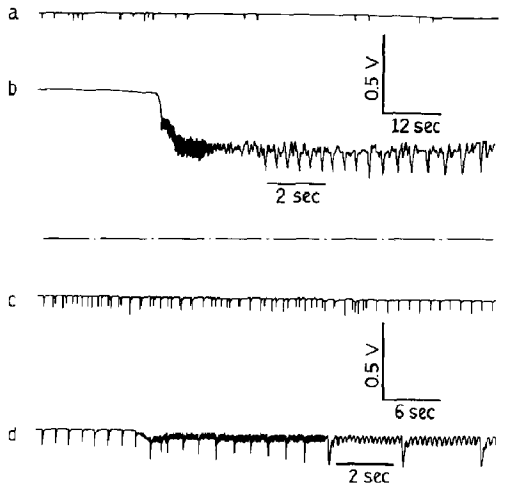

Fig. 8. Induction of the burst by (a) 2.1 mM decanol, (b) 21.6 mM decanol, (c) 2.0 mM undecanol, and (d) 6.2 mM undecanol.

0.3 ~ 2.0 Hz with an amplitude of 100 ~ 300 mV under the condition of a pressure difference of about 30 cm H_2O and an electrical current of 0.05 ~ 0.5 μA imposed on the membrane from the 100 mM to the 1 mM KCl side. The membrane can be considered as a model of the excitable nerve membrane. In the biological system, anesthetics depress the nerve excitation [12,13].

In some cases, alkanols depressed the oscillation (Fig. 7), whereas other times they disturbed the wave form, causing a sudden, nearly ten-fold increase in the frequency (Fig. 8). This fast, aperiodic oscillation has been also observed when treated with some chemicals such as bitter substances and local anesthetics; it has been referred to as a burst [11,16]. Further increase in alkanol concentration stopped even the burst.

Table 1 summarizes the effect of alkanols on the oscillation of the membrane potential. While alkanols with carbon atoms less than eight tended to cease the oscillation, alkanols with carbon atoms more than nine often induced the burst. The increase of frequency, however, in short-chain alkanols was small.

An example of the cessation of the oscillation caused by nonanol (C_9) is shown in Fig. 7, where the membrane displayed the electrical oscillation of 1.3 Hz before the treatment. The alkanol did not affect the oscillation between 0.2 and 0.6 mM, whereas it prolonged the oscillation period between 2.2 and 7.0 mM; it finally stopped the oscillation at 23 mM. Subsequently, the concentration of nonanol was raised to 71 and 231 mM; however, the oscillation did not reappear.

All treatments with hexanol (C_6) depressed the oscillation and finally stopped it (Table 1), six examples being shown in Fig. 9, where the frequency is presented relative to that in the untreated membrane (control). Whereas the con-

Table 1

Effect of n-alkanols on the oscillation of the membrane potential. Occasionally the burst appeared after at temporary cessation of the oscillation; this case was counted in "burst". The frequency increase in C_4 and C_5 was much smaller than that in C_9 ~ C_{12}. Further addition of alkanols on the membrane showing the burst often stopped it.

Effect	Alkanol										
	C_2	C_3	C_4	C_5	C_6	C_7	C_8	C_9	C_{10}	C_{11}	C_{12}
Cessation	4	6	3	5	6	6	6	4	2	2	2
Burst	0	0	2	1	0	0	0	2	4	4	3

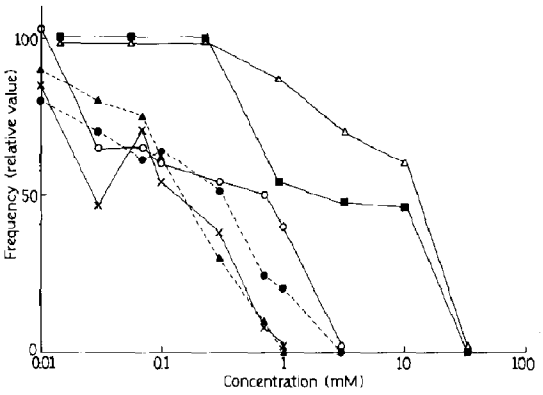

Fig. 9. Depression of the oscillation by hexanol (six experiments). The frequencies of the oscillation of the untreated membrane were normalized to a relative value of 100.

centrations which stopped the oscillation were not constant, the frequency decreased with the increased concentration of hexanol.

The upper half of Fig. 8 shows an example of the burst induced after the cessation of the oscillation. When decanol (C_{10}) was added to the membrane showing the oscillation with 0.7 Hz, the oscillation was gradually suppressed and stopped at 2.1 m*M*. Successive addition of 6.6 m*M* decanol did not cause any change. Treatment with 21.6 m*M* decanol, however, decreased the base line of the membrane potential and subsequently evoked the burst.

The burst without cessation of the oscillation is shown in the lower half of Fig. 8, concerned with the undecanol (C_{11}) treatment. The successive addition of 0.1 to 2.0 m*M* undecanol gradually decreased the frequency from 2.0 Hz to 1.0 Hz, and then 6.2 m*M* undecanol abruptly induced the burst.

4. Theory

We shall analyze the experimental results of the membrane potential and resistance in Figs. 3–6. Since n-alkanols have no electrical charge, they do not directly affect the membrane characteristics even if they are adsorbed to the lipid membrane, but may indirectly affect the membrane permeability to ions as K^+ by change in order of lipids. According to the previous theory for local anesthetics based on a constant-field theory [10], the membrane potential is given by

$$V_m = -\frac{RT}{F}\ln\frac{D_K P_K^I C_K^I + D_{Cl} P_{Cl}^{II} C_{Cl}^{II}}{D_K P_K^{II} C_K^{II} + D_{Cl} P_{Cl}^I C_{Cl}^I} \qquad (1)$$

where R, T and F denote the gas constant, absolute temperature and Faraday constant, respectively. The potential is measured at the higher-salt-concentration side (I) from the lower-salt-concentration side (II) as the reference. The diffusion constants of K^+ ions and Cl^- ions within the DOPH membrane are designated D_K and D_{Cl}, respectively. The partition coefficients of both ions between the lipids and water are denoted by P_K^i and P_{Cl}^i for $i = I, II$ due to the penetration of ions from the aqueous phase to the membrane phase. The K^+ and Cl^- concentrations in the aqueous solution of ith side are denoted as C_K^i and C_{Cl}^i, respectively. Because noncharged n-alkanols do not contribute to the electrical current, their concentrations disappeared in eq. (1) contrary to the case of local anesthetics [10].

Whereas n-alkanols themselves do not contribute to the electrical conductivity within the membrane, they can change physical characteristics as the packing density of DOPH molecules within pores. Therefore the permeability of K^+ ions to membrane (i.e., the partition coefficient) can be changed. Chloride ions are not participated in the membrane because of the negative charge of DOPH, as understood from the negative membrane potential. Therefore we can put $P_{Cl}^i = 0$. We express the indirect effect of n-alkanols on K^+ permeability as a simple linear function of the concentration of n-alkanol C_A by

$$P_K^{II}/P_K^I = 1 + KC_A, \qquad (2)$$

where K is a constant characteristic to each n-alkanol, which will be determined so as to fit the experimental data in Figs. 3–6, In usual cases of alkanols with less than 11 carbons, we can expect that the partition coefficient P_K^{II} of K^+ at the side II, to which n-alkanols are added, is increased because the lipid membrane becomes disordered by adsorption of n-alkanols to lipid

assemblies. Equation (2) expresses such an intuitive situation if K is positive.

The membrane resistance is given by [10]

$$R_m = \left\{ \exp(FV_s(\mathrm{I})/RT) - \frac{P_K^{\mathrm{I}} C_K^{\mathrm{I}}}{P_K^{\mathrm{II}} C_K^{\mathrm{II}}} \exp\left[(V_s(\mathrm{II}) - V_a)F/RT\right] \right\} \times \left[1 - \exp(-FV_a/RT)\right]^{-1} \times \left[1 + (V_m - V_s(\mathrm{II}) + V_s(\mathrm{I}))/V_a\right]^{-1}. \quad (3)$$

We omitted the constant coefficient because we are interested only in the ratio of the membrane resistance, as shown in Fig. 5. In eq. (3), $V_s(\mathrm{i})$ refers to the surface potential of the membrane at the ith, V_a implying the increase in potential brought about by the applied current (= 0.01 μA) for measuring R_m. The term, $V_m - V_s(\mathrm{II}) + V_s(\mathrm{I})$, corresponds to the diffusion potential inside the membrane, denoted by V_d [10]. For this weak electrical current, V_a takes about 50 mV. Whereas the change in the membrane resistance causes the change in V_a, we assume V_a as constant (= 50 mV) as a first approximation.

The surface potential can be considered as almost constant with addition of n-alkanols, because they have no electrical charge. The expression for R_m, therefore, can be rewritten after omission of the trivial constant coefficient as

$$R_m = \left\{ 1 - \frac{P_K^{\mathrm{I}} C_K^{\mathrm{I}}}{P_K^{\mathrm{II}} C_K^{\mathrm{II}}} \exp\left[(V_s(\mathrm{II}) - V_s(\mathrm{I}) - V_a)F/RT\right] \right\} \times \left[1 + (V_m - V_s(\mathrm{II}) + V_s(\mathrm{I}))/V_a\right]^{-1}. \quad (4)$$

The surface potential difference $V_s(\mathrm{II}) - V_s(\mathrm{I})$ can be regarded as equal to V_m without application of n-alkanols, because the diffusion potential within the membrane may be zero, as understood from the following facts: (i) the membrane potential is changed by ca. 59 mV logarithmic slope with increasing KCl or NaCl concentration while the membrane resistance is as high as several MΩ, the permeability of ^{22}Na being nearly zero [18,24–26]; (ii) the membrane potential is changed rapidly by application of NaCl, which implies the direct effect of NaCl on the surface potential [25,26]; (iii) a recent electrochemical theory for liquid membranes shows the diffusion potential is nearly zero by taking account of both possibilities of changes in electrical charge density of membrane and diffusion of ions within the lipid assemblies [27]. Thus, $V_s(\mathrm{II}) - V_s(\mathrm{I})$ can be regarded as -118 mV, which is the membrane potential observed under 1 mM KCl/100 mM KCl difference.

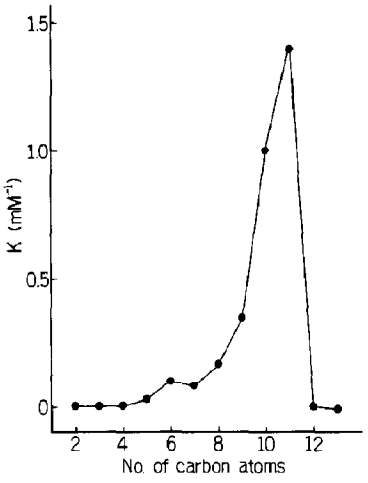

Fig. 10. Dependence of K on the number of carbon atoms to fit the theoretical results to the experimental data in Figs. 3 and 5.

Comparisons of eqs. (1) and (4) with the experimental data are made in Figs. 3–6. The adopted values of K are shown in Fig. 10. The agreement is fairly good for both V_m and R_m in their dependences on the alkanol concentrations (Figs. 3 and 5) and also on the number of carbon atoms (Figs. 4 and 6).

5. Discussion

n-Alkanols with carbon atoms from five to eleven decreased the membrane resistance and the magnitude of the membrane potential. The concentrations which affected both of the membrane potential and resistance were nearly the same for each alkanol. The velocity of the change of the membrane potential was about 1 mV/min, which is very slow compared with 100 mV/min

obtained for quinine [16]. Since quinine is positively charged, it reacts directly with the negatively charged head groups of lipids on the surface of the membrane. The slow change in the membrane potential caused by alkanols indicates their penetration into the membrane as suggested [10,16].

While the short-chain n-alkanols decreased the membrane resistance with increasing number of carbon atoms, those with more than 12 carbon atoms had no effect or slightly increased it. This result is similar to the cutoff effect. On the other hand, the solubilities of n-alkanols continue to increase up to hexadecanol (C_{16}) [2]. Hence, the abrupt change in the effect of n-alkanols on the DOPH Millipore membrane suggests that the packing efficiency of alkanol in a matrix of hydrocarbon chains is changed as the length of the alkanol alkyl chain [13].

Alkanols whose alkyl moiety differs from that of membrane lipids are likely to disorder the membrane, whereas alkanols similar to that of membrane lipids may order it. In practice, short-chain alkanols with an alkyl-chain length less than ca. 10 carbon atoms decreased the phase-transition temperature of a phospholipid membrane, whereas longer alkanols increased it [7,8,20–22]. The theoretical analysis [22] expresses this situation by treating the hydrophobic interactions between lipids and alkanols. Numerical results in Fig. 10 by use of eq. (2) implies that the penetration of K^+ ions from the aqueous phase to the lipid membrane is increased with increasing number of carbon atoms of alkanols, but is abruptly decreased above 11 carbon atoms. This result is quite reasonable because the lipid membrane becomes so disordered as to allow the penetration of ions in coexistence of short-chain alkanols. The long-chain alkanols, on the other hand, can behave similarly to the lipids themselves, to result in increasing order of lipid membrane to inhibit the ion penetration. By plotting the natural logarithm of K as a function of the carbon number of alkanols from four to eleven in Fig. 10, we obtained the slope to be approximately unity. This agrees well with the cohesive energy change, ω, transferring one mole of methylene group from a hydrocarbon environment to an aqueous medium which is approximately RT [28,29].

For alkanols C_3, C_4 and C_{13}, the biphasic behavior was observed in the membrane resistance (see Fig. 5): after the resistance increased once, it decreased at the higher concentrations. The same tendency was also obtained for local anesthetics [10]. However, this biphasic behavior did not appear for the other alkanols. On the contrary, the increase occurred after the decrease for C_{10} and C_{11}, as seen in Fig. 5. The extent of increase was not so large as to induce more increase than the initial value without alkanols. The initial-phase increase of the membrane resistance for C_3 and C_4 may be due to the decrease in ion permeability accompanied with the tight adsorption of alkanols to the surface of the membrane: at the phase, the lipid order is not disturbed so much as at the main later phase, as mentioned above in short-chain alkanols. The later-phase decrease for the long-chain alkanol C_{13} with high concentrations may originate from disturbance of the tightly packed structure due to over-adsorption, to result in the slightly disordered state. For C_{10} and C_{11}, the disordered structure due to adsorption of alkanols may be condensed with the further adsorption at high concentrations, to prevent the ion penetration to result in increasing membrane resistance.

Therefore the cutoff effect is also evident from the biphasic behavior. The reversed biphasic behavior for C_{11} is suddenly changed to the biphasic behavior for C_{13}. The present theory does not express this situation because the assumption of eq. (2) is very simple, but can reproduce the abrupt changes in membrane resistance (and membrane potential) from the largely decreased value to almost the initial value without alkanols at the threshold around C_{11}.

The changes in V_m and R_m are caused by the change due to ion permeability to the membrane, which are reflected by the diffusion potential V_d. We can rewrite V_m in eq. (1) using eq. (2) as follows:

$$V_m = 59 \log_{10}(1 + KC_A) - 118. \quad (5)$$

The first and second terms are the diffusion

potential V_d and the surface-potential difference $V_s(II) - V_s(I)$ in mV units, respectively.

Equation (5) states that the observed decrease in $|V_m|$ for short-chain alkanols originates from the increase in the diffusion potential due to ion penetration, which results from the increasing disorder of lipid membrane. The increase in V_d causes the decrease in R_m, as can be understood from eq. (3) (note $V_d = V_m - V_s(II) + V_s(I)$).

Alkanols with about 10 carbon atoms affected the electrical charactersitics of the DOPH membrane above ca. 0.1 m*M*. Lee [7] also found that alkanols were effective on the phase transition of lipid membranes at about 1 m*M*. These threshold values are larger by about one to two orders than those obtained in biological systems [2]. The clinical concentration of alkanols did not significantly affect lipids [23]. Proteins which exist in the biological membrane might amplify the action of alkanols on lipids.

The hyperpolarization occurred for C_{13}, as seen in Fig. 3. Equation (5) shows that this phenomenon originates in the negative value of K (see also Fig. 10). Whereas the present theory assumed $P_{Cl} = 0$, the increase in P_{Cl} may be possible when the membrane resistance is largely decreased because DOPH assemblies take the disordered phase.

The alkanols suppressed the oscillation of the membrane potential or induced an aperiodic, rapid one. The first effect implies that this model membrane is capable of reproducing the characteristic property of the nerve membrane; i.e., the excitability is inhibited by alkanols. In fact, $1/f$ fluctuations are observed in the DOPH membrane in a similar way to nerve membranes [30]. While several kinds of excitable model membranes have been proposed so far [31–33], study of anesthetics using these membranes is important. Study with plant materials eliciting action potentials or oscillations [34,35] is also necessary.

Both the cessation of oscillation and the burst originated from the decrease in the membrane resistance except for C_{13}, which showed the increase in membrane resistance when the oscillation stopped. In the previous study on local anesthetics [11], the membrane resistance did not decrease at the cessation of oscillation. This contradiction may arise because n-alkanols have no electrical charge while local anesthetics have a plus charge. The cessation was mainly induced by the change in surface charge density of the DOPH membrane with local anesthetics [11]. The detailed mechanism of the decreased membrane resistance to cause both the cessation and the burst is not clear at present. Nevertheless, only a slight change of some external parameter shifted a chaotic state to an entrained state of the DOPH membrane [36], and hence the above phenomenon very sensitive to the membrane resistance and other internal factors may be possible to occur. The oscillation, however, seems not to reflect the cutoff effect, as also seen from Table 1. It only appears in the following fact: the cessation was caused by the increase in membrane resistance for C_{13} and the decrease for the other alkanols.

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