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TRANSITION TEMPERATURES OF THE ELECTRICAL ACTIVITY OF ION CHANNELS IN THE NERVE MEMBRANE

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Summary

The temperature dependence of some of the electrical characteristics of neuronal membranes from *Aplysia* giant neurons and crustacean and cuttlefish giant axons has been analyzed. Arrhenius plots for the maximum rate of depolarization of ($\mathring{V}^{+}_{max}$) or repolarization ($\mathring{V}^{-}_{max}$) of the action potential, for the resting membrane conductance, and for the speed of propagation of the action potential, exhibited clear breaks at characteristic temperatures between 17 and 20°C.

Lobster giant axons and frog nodes of Ranvier were voltage-clamped at different temperatures between 5 and 30°C. Arrhenius plots for relaxation times related to the opening and closing processes affecting the Na^+ and K^+ channels were linear. No 'transition' temperature was detected. However, clear-cut changes in $\overline{I_{Na}}$ and $\overline{I_K}$, the maximum Na^+ and K^+ currents, were consistantly observed around 18°C. Values for $\overline{I_{Na}}$ and $\overline{I_K}$ plateaued above 18°C, then decreased gradually as a function of reduced temperature.

Variations in temperature between 1 and 30°C did not alter the binding properties of [^{3}H]tetrodotoxin to a purified crab axonal membrane.

Pharmacological properties of the Na^+ channel are sensitive to temperature. The temperature-dependent effect of veratridine has been studied and indicates a change in properties of the Na^+ channel below 20°C.

These results support the possibility that the fluidity of membrane lipids in the ionic channel microenvironment may influence the degree to which the channel can open.

Introduction

Evidence accumulated in the last few years shows that the Na^+ channel involved in the generation of action potentials is a protein [1—4]. This channel

protein must evidently span the lipid bilayer of the membrane. It is known that the functioning of the Na^+ channel can be altered from both sides of the membrane. Receptors for toxins like tetrodotoxin, saxitoxin, scorpion or sea anemone toxins are situated on the external side of the channel [5—7] but the channel protein is also accessible from the internal side of the membrane, since the inactivation system in the squid giant axon can be destroyed by a perfusion of pronase [1]. Much less is known of the molecular properties of the K^+ channel, mainly because specific and high-affinity toxic tools which are available for the Na^+ channel are not available for the K^+ channel. However, it is reasonable to assume by analogy with the Na^+ channel that the K^+ channel is also a protein which spans the membrane. Some parts of the channel proteins must therefore be associated with surrounding membrane lipids and it seems possible that the channel function is influenced by the physical state of its lipid environment [4,8,9].

In many systems, breaks in Arrhenius plots of various membrane functions have been taken as evidence for phase transitions or lateral phase separation of membrane phospholipids (see, for example, Refs. 10—14). The possibility also exists, that in some membrane functions, breaks in Arrhenius plots might reflect intrinsic changes of the proteins, independent of changes in the membrane phospholipids [15—17].

Recently, several groups have observed breaks in Arrhenius plots for conductances of channels coupled to the acetylcholine or to the glutamate receptor [18,19]. A transition temperature was also observed for the excitation-contraction coupling in frog twitch muscles fibers [20].

In this paper, we study the influence of temperature variations (i) on the electrical properties of several types of excitable membranes in relation to the functioning of Na^+ and K^+ channels, (ii) on the number of the Na^+ channels as measured with radioactively labeled tetrodotoxin.

Materials and Methods

Electrophysiology. The different preparations used in the electrophysiological experiments include: (i) giant neurons of the visceral ganglion of the marine mollusc, *Aplysia depilans;* (ii) giant axons of crustacea, i.e., from the crabs, *Carcinus maenas* and *Cancer pagurus*, and from the lobster, *Homarus gammarus*, and giant axons of a cephalopod, the cuttle-fish, *Sepia officinalis;* (iii) myelinated fibers from the sciatic nerve of the frog, *Rana esculenta.* Intracellular glass microelectrodes filled with 3 M KCl (resistance ranging between 5 and 10 MΩ) were used to record the resting potential and action potential from *Aplysia* giant neurons and from giant axons. The double sucrose gap method used in voltage-clamp experiments on giant axons of lobster have been previously described [6]. Voltage-clamp experiments on the node of Ranvier were carried out according to the method of Nonner [21]. In all experiments, electrical data were digitized on line, stored, and treated by a digital computer (Intertechnique-Plurimat S). The temperature of the different preparations was changed from 5 to 30°C by varying the intensity of the current flowing across Peltier elements (Figraton) in close contact with a heat exchanger through which the physiological solution flowed. Temperature

was measured by a micro-thermocouple (BLH thermocouples) electrically isolated and placed near the preparation.

Axonal membranes. Axonal membranes were prepared from walking-leg axon bundles of *C. pagurus* as previously described [22]. Fraction II was used in this study.

Preparation of [^{3}H]tetrodotoxin and binding assays. Tetrodotoxin, obtained citrate-free from Sankyo Chemicals Co. (Tokyo, Japan), was tritiated as previously described [22]. A further purification of radioactive toxin was achieved by electrophoresis on paper with a pyridine/acetate buffer as described by Colquhoun et al. [23]. The specific radioactivity of [^{3}H]tetrodotoxin was determined by measurement of the toxin concentration in three different ways. The first used the fluorescence technique described by Nuñez et al. [24]. The second method was a bioassay on nerve fibers which has been previously described [25]. The third method involved the determination of the concentration of the labeled toxin which remained active, using the displacement curve obtained by displacing the [^{3}H]tetrodotoxin from its receptor with precisely known amounts of the corresponding unlabeled toxin [3]. The specific radioactivity found for [^{3}H]tetrodotoxin was 0.6 Ci/mmol. Binding measurements were performed by equilibrium dialysis as already described [22].

Results

Electrophysiological analysis of the temperature effects on various excitable membranes

Fig. 1 shows the temperature dependence of characteristic parameters of the electrical activity in different nervous preparations.

Aplysia giant neuron. The spike amplitude (115 mV) remains constant between 5 and 20°C. Above 20°C, it decreases slightly (96 mV at 25°C). The maximum rate of depolarization ($\mathring{V}^+_{max}$) and of repolarization ($\mathring{V}^-_{max}$) of the action potential are temperature dependent. At 5°C, the mean $\mathring{V}^+_{max}$ and $\mathring{V}^-_{max}$ values are, respectively, 15 and 3.5 V/s; at 15°C, their values are, respectively, 50 and 15 V/s. The relationship between log $\mathring{V}^+_{max}$ (or log $\mathring{V}^-_{max}$) and $1/T$ (Arrhenius plot) can be approximated by two straight lines intersecting at about 17°C (Fig. 1A). In Fig. 1B, the resting membrane conductance (G_M) is measured at different temperatures. G_M is the ratio between the intensity of a hyperpolarizing current and the resulting membrane potential change. It is a measure of the 'leakage' conductance including all ionic non-voltage and non-time-dependent conductances. The Arrhenius plot of G_M shows a change in slope at about 18°C.

Lobster giant axon. Fig. 1C and D shows Arrhenius plots relating $\mathring{V}^+_{max}$, $\mathring{V}^-_{max}$ and the speed of propagation of the action potential (v) to temperature variations. As in *Aplysia* neurons, a break in slope is observed in the same range of temperature at about 18°C. For $\mathring{V}^+_{max}$ and v, another break in slope is apparent for a temperature of about 7°C. Arrhenius plots of action potential parameters in other nervous preparations show, in all cases, a characteristic temperature in the 15–20°C range. Table I summarizes these experiments.

Voltage-clamp studies on lobster giant axons and on the frog node of Ran-

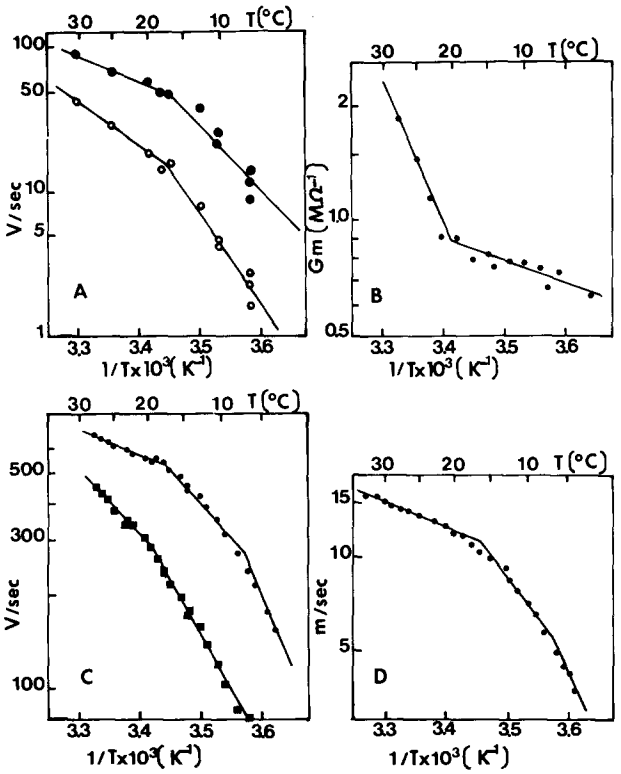

Fig. 1. Arrhenius plots. (A) The maximum rate of depolarization $\overset{\circ}{V}^{+}_{max}$ (•) and of repolarization $\overset{\circ}{V}^{-}_{max}$ (○) of the action potential in the *Aplysia* giant neuron. (B) The resting membrane conductance (G_m) of the somatic membrane of the *Aplysia* giant neuron. (C) The maximum rate of depolarization $\overset{\circ}{V}^{+}_{max}$ (•) and of repolarization $\overset{\circ}{V}^{-}_{max}$ (■) in the lobster giant axon. (D) The speed of propagation of the action potential (v) in the lobster giant axon. Note, in all cases, the change in slope between 17 and 20°C.

vier. The effects of temperature on the kinetics of the Na^+ and K^+ conductances were analyzed separately by using specific inhibitors, i.e., tetraethylammonium (10 mM) to block the K^+ channel and tetrodotoxin (10 nM) to block the Na^+ channel. For each temperature, the 'leakage' current, i.e., the current unable to be activated by the voltage, was assumed to be a linear function of the membrane potential as is generally accepted [26,27]. It is measured from a hyperpolarizing pulse and used in the correction of the subsequent current measurements. In response to a voltage jump, the Na^+ and K^+ currents were assumed to follow the Hodgkin-Huxley theory as previously shown for both preparations [27,28].

The Na^+ current is described by Eqn. 1:

$$I_{Na} = \overline{I_{Na}} \cdot [1 - \exp(-t/\zeta_m]^k \cdot \exp(-t/\zeta_h) \quad (1)$$

where $\overline{I_{Na}}$ is the maximum possible Na^+ current; ζ_m and ζ_h are, respectively, the time constant of activation and inactivation of the Na^+ current, k is taken as equal to 3 in lobster axons, as in squid axons [26], and as equal to 2 in the

TABLE I

TEMPERATURE DEPENDENCE OF CHARACTERISTIC PARAMETERS OF THE ELECTRICAL ACTIVITY IN DIFFERENT NERVOUS PREPARATIONS

$\overset{\circ}{V}^{+}_{max}$ and $\overset{\circ}{V}^{-}_{max}$ are, respectively, the maximum rate of depolarization and of repolarization of the action potential. v is the speed of propagation of the action potential. G_m is the membrane conductance.

Crustacean perioesophagial giant axons of:		Break-point temperature in the Arrhenius plot (T_B) (°C)	Q_{10} ($T < T_B$)	Q_{10} ($T > T_B$)
Carcinus maenas	$\overset{\circ}{V}^{+}_{max}$	19	1.6	1.2
	$\overset{\circ}{V}^{-}_{max}$	18	3	2.3
Cancer pagurus	$\overset{\circ}{V}^{+}_{max}$	20	1.8	1.3
	$\overset{\circ}{V}^{-}_{max}$	18	3.6	2
Lobster	$\overset{\circ}{V}^{+}_{max}$	18	4	1.3
	$\overset{\circ}{V}^{-}_{max}$	18	3.2	1.7
	v	17	2.2	1.3
Cuttle-fish giant axon	$\overset{\circ}{V}^{+}_{max}$	15	1.7	1.5
	$\overset{\circ}{V}^{-}_{max}$	16	4	2.6
Aplysia giant cell	$\overset{\circ}{V}^{+}_{max}$	17	3.8	1.5
	$\overset{\circ}{V}^{-}_{max}$	17	4.2	2.5
	G_m	18	1.2	2.5

frog node of Ranvier [27]. The K^+ current is described for the two preparations by Eqn. 2:

$$I_K = \overline{I_K} \cdot [1 - \exp(-t/\zeta_n)]^4 \qquad (2)$$

where $\overline{I_K}$ is the maximum possible K^+ current and ζ_n is the time constant of activation of the K^+ current.

For each preparation, both the holding potential and the amplitude of the voltage jump have been chosen to activate the Na^+ channel or the K^+ channel to their maximum permeability.

For each temperature, fits between the experimental results and Eqns. 1 and 2 were found by using a least-squares method. This method has given the best approximations for the parameters characterizing the Na^+ current, i.e., $\overline{I_{Na}}$, ζ_m and ζ_h and those characterizing the K^+ current, $\overline{I_K}$ and ζ_n.

The effect of temperature on the kinetics of the Na^+ and K^+ currents is shown in Fig. 2A for the lobster giant axon and in Fig. 2B for the frog node of Ranvier. Arrhenius plots for the reciprocal time constants are linear. Values of activation energies are calculated from the data by a linear-regression analysis using the equation: $\ln(1/\zeta) = A - E_{act}/RT$ where A is a constant, E_{act} the activation energy, R the gas constant and T the absolute temperature. The values of the activation energies for $1/\zeta_m$, $1/\zeta_h$ and $1/\zeta_n$ are, respectively, 14, 12.4 and 17.3 kcal/mol in the case of the lobster axon and 8.8, 16.5 and 13 kcal/mol in the case of the frog node of Ranvier. The influence of temperature between 5 and 30°C on the peak amplitude of the Na^+ current and on values of $\overline{I_{Na}}$ and $\overline{I_K}$ is shown in Fig. 3A and B for the lobster axon and in

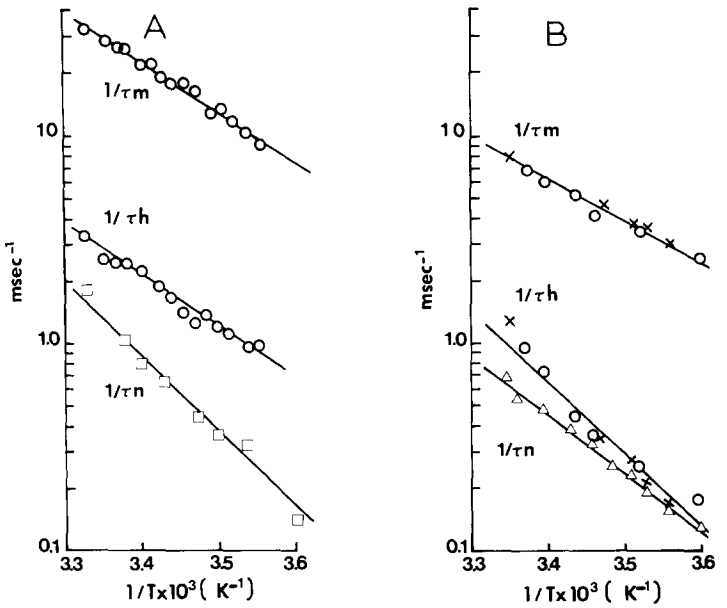

Fig. 2. Arrhenius plots of the reciprocal time constants of activation ($1/\zeta_m$) and inactivation ($1/\zeta_h$) of the Na^+ conductance and of activation ($1/\zeta_n$) of the K^+ conductance. (A) Lobster giant axon. (○) the K^+ current is blocked with 10 mM tetraethylammonium. The membrane potential (V) is clamped at −10 mV after a voltage jump from a holding potential (V_H) of −80 mV. (□) the Na^+ current is blocked with 10 nM tetrodotoxin; $V = 0$ mV, $V_H = -80$ mV. (B) Frog node of Ranvier. (○, X) tetraethylammonium (10 mM) treated fibers; depolarizing voltage jump of 60 mV. (△) tetrodotoxin (10 nM) treated fibers; depolarizing voltage jump of 100 mV. A hyperpolarizing pre-pulse of −30 mV, lasting 50 ms, always precedes the test voltage jump in order to remove completely the Na^+ inactivation. Note in A and B the absence of break in slope over the studied temperature range.

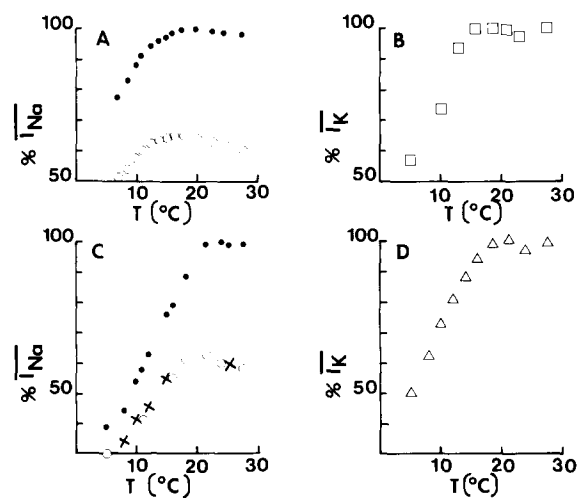

Fig. 3. The peak Na^+ current and the maximum possible $\overline{I_{Na}}$ and $\overline{I_K}$ currents vs. the temperature. Same experiments as in Fig. 2. (●) $\overline{I_{Na}}$; (○, X) peak Na^+ currents; (□, △) $\overline{I_K}$. A and B: lobster giant axon. C and D: frog node of Ranvier. Each point represents a percent value of the maximum possible $\overline{I_{Na}}$ (20° C) and $\overline{I_K}$ (20° C) currents. Note the decrease in both Na^+ and K^+ currents below 20° C.

Fig. 3C and D for the frog node of Ranvier. The maximum Na^+ and K^+ currents remain approximately constant above 18°C. $\overline{I_{Na}}$ and $\overline{I_K}$ decrease gradually from 20 to 5°C. For the lobster axon, $\overline{I_K}$ (5°C) is 50% of its maximum value, $\overline{I_K}$ (20°C). $\overline{I_{Na}}$ is less sensitive to temperature; $\overline{I_{Na}}$ (5°C) still represents 80% of its maximum value, $\overline{I_{Na}}$ (20°C). For the frog node of Ranvier, $\overline{I_K}$ (5°C) is 50% of $\overline{I_K}$ (20°C) and $\overline{I_{Na}}$ (5°C) reaches only 40% of its maximum value, $\overline{I_{Na}}$ (20°C).

Because of the inactivation process, the peak Na^+ current is generally smaller than the maximum possible Na^+ current ($\overline{I_{Na}}$). By using Eqn. 1, it is possible to demonstrate that the ratio between the peak Na^+ current and I_{Na} is an increasing function of the ratio between the time constants of inactivation and activation (ζ_h/ζ_m). At 20°C, our experiments have shown that only 60–65% of the activable Na^+ channels are really opened at the peak Na^+ current (Fig. 3A and C).

Binding of radioactively labeled tetrodotoxin to the Na^+ channel of purified axonal membrane at different temperatures

Fig. 4 shows that the maximum binding capacity of the crab axonal membrane for [^{3}H]tetrodotoxin does not vary between 1 and 30°C. The dissociation constant of the tetrodotoxin-receptor complex is nearly the same (K_d = 2.5 nM) at 4 and 25°C.

The effect of temperature on veratridine action

Veratridine depolarizes excitable membranes by selectively increasing the Na^+ channel permeability (it opens the channel and prevents its closing) [5,29]. The effect of veratridine is known to be favored at high temperatures [29]. Fig. 5A shows a dose-response curve of the effect of veratridine on the

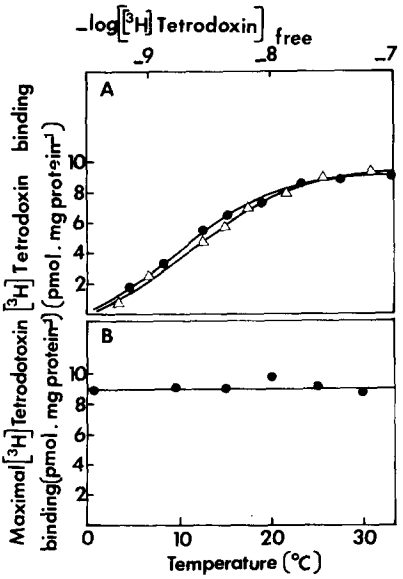

Fig. 4. (A) Titration of the tetrodotoxin receptor in crab axonal membranes at 20°C (●) and at 4°C (△). (B) Temperature independence of [^{3}H]tetrodotoxin (0.1 μM) binding to crab axonal membranes.

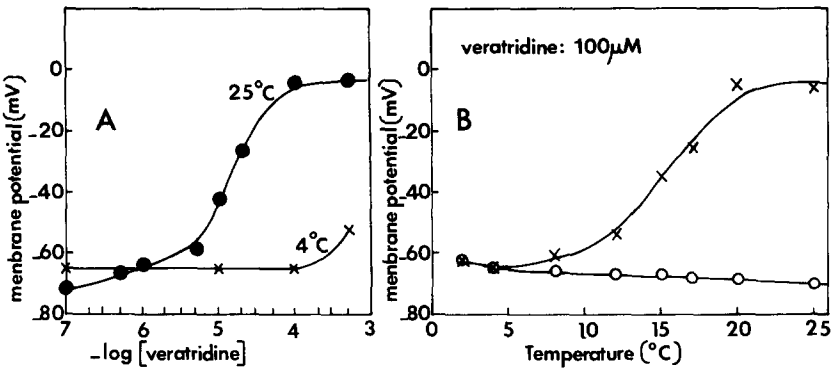

Fig. 5. (A) Veratridine concentration dependence of the membrane potential of crab giant axons at 25°C (•) and at 4°C (×). (B) Temperature dependence of the membrane potential of crab giant axons in the absence (○) and in the presence (×) of 100 μM veratridine.

membrane potential of crab axons at 25 and 4°C. The full activity of the toxin compound is observed at 0.1 mM at 25°C whereas the same concentration of veratridine gives no effect at 4°C. To see the beginning of action of the toxin at 4°C, one must reach a toxin concentration of 0.5 mM. The temperature dependence of the veratridine effect is shown in Fig. 5B. The maximal effect of 0.1 mM veratridine is attained at temperatures higher than 20°C. Below 8°C, there is hardly any effect of the toxin on the membrane potential. This representation again indicates a characteristic temperature near 20°C and another characteristic temperature near 8°C.

Discussion

The temperature dependence of the characteristic electrical parameters of the nervous membrane has been studied on different preparations, including crustacean axons, cuttle-fish axons and *Aplysia* giant axons. Arrhenius plots of action potential parameters such as the maximum rates of depolarization ($\mathring{V}^{+}_{max}$) and repolarization ($\mathring{V}^{-}_{max}$) and the speed of propagation (v) or of a subthreshold parameter like the leakage conductance (G_m) are not linear in the range of temperature between 5 and 30°C. A common feature of all these Arrhenius plots is the existence of a characteristic temperature between 17 and 20°C.

To a first approximation, the parameters $\mathring{V}^{+}_{max}$ and $\mathring{V}^{-}_{max}$ are reflecting maximum increases during the action potential of the Na^+ and K^+ conductances, respectively. In order to analyse the temperature dependence of the Na^+ and K^+ conductances in more detail, voltage-clamp analyses have been carried out with a crustacean axon, the lobster giant axon, and with the frog node of Ranvier. Although one axon is giant and the other is not, and one is myelinated and the other is not, both preparations have given similar results. Arrhenius plots for the reciprocal time constants of activation ($1/\zeta_m$) and of inactivation ($1/\zeta_h$) of the Na^+ conductance and for the activation ($1/\zeta_n$) of the K^+ conductance are linear between 5 and 30°C. The amplitudes of the peak Na^+ current, of the maximum possible Na^+ current ($\overline{I_{Na}}$) and of the

maximum possible K^+ current ($\overline{I_K}$) remain constant above 18°C. Below 18°C, these amplitudes gradually decrease when the temperature decreases. Fig. 3 clearly shows that there is a characteristic temperature at about 18°C for the peak Na^+ current, for $\overline{I_{Na}}$ and for $\overline{I_K}$ which appear both for the lobster giant axon and for the frog node of Ranvier. Interestingly enough, it has been recently reported by Kimura and Meves [30] that the maximum Na^+ permeability is decreased by a factor of 5 for the squid giant axon when passing from 15.4 to 0°C. Breaks in Arrhenius plots describing temperature effects in rates of membrane transport have generally been taken as direct evidence for phase transitions of membrane phospholipids [10—14].

Previous studies carried out in this laboratory have shown that the Arrhenius plot describing the influence of temperature on the rate of hydrolysis of ATP by the ($Na^+ + K^+$)-ATPase embedded in the crab axonal membrane also shows a break at a temperature of 19—20°C. The activation energy of the enzyme action below this critical temperature is 18 kcal/mol; it is 9 kcal/mol at temperatures between 20 and 40°C [31]. Therefore, the critical temperature observed for Na^+ and K^+ transport through the Na^+ and K^+ channels is also observed for the functioning of the Na^+ pump. The existence of this critical temperature is not observed for all enzymes present in this membrane. Acetylcholinesterase, an enzyme which conversely to the ($Na^+ + K^+$)-ATPase or to the Na^+ channel does not seem to span the lipid bilayer, displays a perfectly linear Arrhenius plot between 0 and 40°C [31].

Although a critical temperature is observed for Na^+ influx through the Na^+ channel, binding studies with [^{3}H]tetrodotoxin indicate that both the number of toxin binding sites and the affinity of the channel for tetrodotoxin remain constant between 1 and 30°C. This observation is not very surprising for two reasons: (i) the tetrodotoxin receptor only represents that part of the Na^+ channel which is situated at the external surface of the membrane and which may not be very sensitive to change in lipid fluidity in the immediate surroundings of the channel; (ii) a similar situation is found for the association of ouabain with the ($Na^+ + K^+$)-ATPase [31] embedded in the crab axonal membrane; the association of ouabain with the enzyme is not changed below the critical temperature found for the enzyme activity. Ouabain, similarly to tetrodotoxin for the Na^+ channel, binds to the part of the ($Na^+ + K^+$)-ATPase which is on the outside of the excitable membrane.

It is generally thought that membrane integral proteins are surrounded by an annulus of boundary phospholipids which would differ either in their conformation or in composition (or in both) from the bulk phospholipd phase of the membrane. This phospholipid micro-environment of membrane integral proteins will generally be in an immobilized, solid-like state unlike the bulk of the membrane phospholipids which will be in a fluid-like state. Boundary phospholipids which form the annuli of membrane integral proteins will only represent a small fraction of the total number of membrane phospholipids [9]. This is particularly true in a membrane like the crab axonal membrane, since it has been shown that this membrane has an unusually low protein-to-phospholipid ratio [22].

If one accepts that the critical temperatures shown in Fig. 3 correspond to changes of fluidity of the boundary lipids around the channels' structures,

one must explain why there are no breaks in the Arrhenius plots of $\log(1/\zeta_m)$, $\log(1/\zeta_h)$ or $\log(1/\zeta_n)$ vs. $1/T$ whereas a discontinuity is observed for the variation of $\overline{I_{Na}}$ and $\overline{I_K}$ with temperature. A possible explanation can be given: below 18°C, the lipid environment of the channels is gradually transformed from a fluid-like to a solid-like state. The fraction of the channels for which the environment is in the solid-state is transformed into 'silent' channels, i.e., into channels which cannot be opened by electrical stimulation (the presence of silent Na^+ channels has been detected recently [32]). Electrophysiological experiments will only reveal fractional Na^+ and K^+ channels which have their lipid annuli in the fluid state. Kinetic data will obviously only relate to the opening and closing of that fraction of channel which remains functional. With such a model, the Arrhenius plot for $1/\zeta_m$, $1/\zeta_h$ and $1/\zeta_n$ will not show any break.

Breaks, however, will be seen in the total permeabilities of Na^+ and K^+ channels which are proportional to the maximum possible Na^+ ($\overline{I_{Na}}$) or K^+ ($\overline{I_K}$) currents.

The pharmacological properties of the Na^+ channel are also very temperature dependent, pyrethroids which selectively alter the inactivation process of this channel are known to be more active at low temperature (8°C) than at high temperature (23°C) [33]. Conversely, veratridine is known to be active only at high temperature. The analysis of the temperature dependence of the veratridine effect (Fig. 5B) indicates that no effect of veratridine is found below 8°C whereas the full toxic effect appears near 20°C. These data would suggest that there may be two 'critical' temperatures at 20 and 8°C. The characteristic temperature near 18°C might only mark the beginning of a transition which would be finished near 8°C. The molecular form of the Na^+ channel which is thermodynamically stable at temperatures higher than 20°C would be sensitive to veratridine, the molecular form of the channel stable below 8°C would be insensitive to the alkaloid toxin.

Although the characteristic temperatures observed by electrophysiological techniques have been tentatively interpreted as being due to changes in fluidity in the lipid annuli around ionic channels, it cannot be excluded that the characteristic temperature near 18°C is due to temperature-induced changes in the channel protein itself. However, the second interpretation, which would not change the main conclusion of the discussion, seems unlikely since the same critical temperature was found for three different molecular components of the crustacean axonal membrane: the $(Na^+ + K^+)$-ATPase, the Na^+ channel and the K^+ channel. Another possibility which cannot be eliminated is that critical temperatures observed in this work are due to cytoskeletal proteins in contact with the membrane and which are important to the membrane organization [34].

If temperature-induced changes in electrical characteristics are indeed due to changes in lipid fluidity, one should observe large variations in the electrical activities linked to Na^+ and K^+ channels by manipulating the lipid composition of neuronal membranes.

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