Journal of Integrative Neuroscience, Vol. 3, No. 2 (2004) 115–124

Imperial College Press
www.icpress.co.uk

Short Communication

ON THE CONDUCTION VELOCITY OF NONMYELINATED NERVE FIBERS

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Received 24 December 2003
Accepted 27 March 2004

Nerve impulse conduction in nonmyelinated nerve fibers is analyzed by considering this process as a direct consequence of the coexistence of two structurally distinct regions, active and resting. Assuming that the active (i.e. swollen) region of the fiber is in direct contact with the resting (i.e. shrunken) region, a simple procedure for deriving the conduction velocity equation is described. The physico-chemical significance of the quantities in this velocity equation is briefly discussed.

Keywords: Nerve conduction; nonmyelinated nerve fiber; conduction velocity; cable equation.

1. Introduction

In 1977, Dr. Gen Matsumoto and I closely examined the cable properties of squid giant nerve fibers under internal perfusion and derived the following simple equation relating the conduction velocity to the electric parameters of the fibers [8]:

$$v = \sqrt{\frac{d}{8\rho C^2 R^*}} \tag{1}$$

where v is the conduction velocity, d the diameter, ρ the resistivity of the fiber interior, C the membrane capacitance per unit area, and R^* the unit area resistance of the membrane in its excited state. We were gratified to find that the velocity calculated by means of this equation is in good agreement with the values observed under various experimental conditions. Furthermore, by varying the salt concentration in the internal perfusion solution, we examined the dependence of the velocity on the resistivity of the fiber interior, ρ, and found that the results obtained are quite consistent with those expected from the above relationship. The well-known dependence of the velocity on the fiber diameter (d) [13] is correctly described by the equation.

In the present paper, dedicated to the memory of Dr. Matsumoto, it will be demonstrated that this conduction velocity equation can be readily derived from the distribution of the *local current* which links the resting region of the nerve fiber with its active (excited) region. We deal in this paper primarily with normal nerve fibers of which the membrane resistance falls during excitation far below its value at rest. Under these circumstances, a graphic representation of the cable property of the fiber is quite revealing and the derivation of the velocity equation is very simple. In this connection, the physical basis of the present approach to problems of nerve impulse conduction will be briefly discussed.

In the theory of propagation of the rising phase and peak of the action potential formulated by Hodgkin and Huxley [6], the conduction velocity is given by $v = [Kd/(4\rho C)]^{1/2}$, where the quantity K depends on the conductance $g_{Na}(V,t)$ in their theory, in an intricate fashion (see [6], pp. 524, 528). When the quantity K is replaced simply with $1/(2R^*C)$, their velocity equation is converted to Eq. (1). In general it seems difficult to obtain relationship between the membrane conductances and the conduction velocity explicitly from the Hodgkin-Huxley equations. A more recent approach to approximate the relationship between the membrane conductances and conduction velocity explicitly from the Hodgkin-Huxley equations was undertaken by Muratov [10].

2. Cable Properties of Nonmyelinated Nerve Fibers

The microscopic structure of the cortical gel layer ("axolemma-ectoplasm complex" [9, 14]) of a living nonmyelinated nerve fiber is extremely complicated and highly vulnerable to various chemical and mechanical disturbances. It is to be noted, however, that a simple, quantitative description of the process of nerve impulse conduction is possible solely in terms of *course-grained variables*, such as membrane capacitance, resistance, emf, etc., without reference to the details of the microscopic structure of the fiber. The present treatment of the process of nerve conduction may be considered as being comparable to the familiar theory of sound wave in which the propagation velocity is discussed without reference to complex structures and movements of individual air or water molecules in the medium. In other words, we do not assume an explicit representation for the ionic conductances (see [10] for a discussion based on a variety of simplified assumptions).

When a weak electric current of a constant strength is delivered to a squid giant nerve fiber by use of a long internal wire electrode [7], the potential difference across the cortical layer changes, as is well known, exponentially with time. The membrane capacitance and resistance of the nerve fiber are determined by this operation. To determine these quantities at the peak of an action potential, more elaborate techniques, such as the A.C. impedance method [1] or voltage clamping [5], are required (see e.g., Fig. 2 in [8]). The transient changes in the membrane emf can be determined by use of a glass micro-pipette [11] or internal wire electrode [7]. In

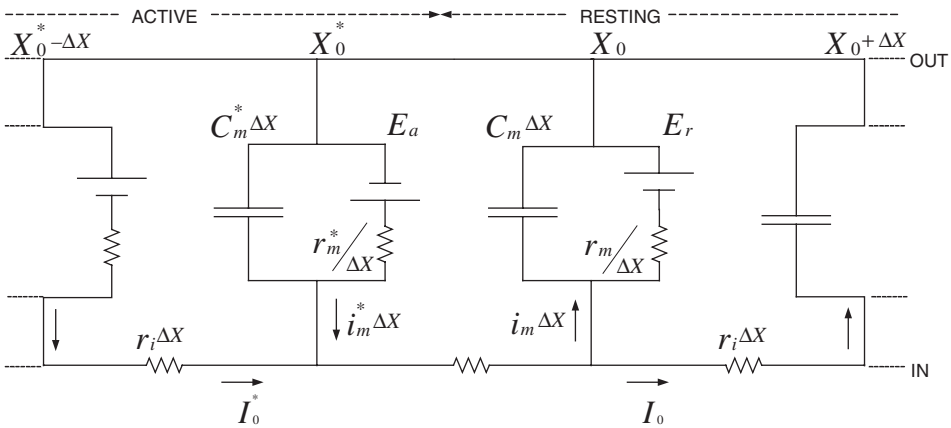

Fig. 1. Electrical network used for explaining the distribution of the local current in the vicinity of the boundary between the active and resting regions of a nonmyelinated nerve fiber carrying a nerve impulse. "OUT" indicates a large volume of the salt solution outside the fiber; "IN" represents the salt solution inside the fiber. The symbol "ΔX" signifies the length (infinitesimal) of the element of the fiber. Other symbols are explained in the text.

the present treatment of the subject, we do not care to inquire after the behavior of the microscopic components in the cortical layer involved in these measurements.

The distribution of the local current, set up by the difference between the emfs in the active and resting regions, is illustrated by the diagram shown in Fig. 1. In the diagram, the element of the fiber located between X_0^* and X_0 constitutes the boundary between the active and resting regions of the fiber. Note that variable X denotes the distance along the nerve fiber measured from the boundary which is moving at a constant velocity v (see [8, 17]). The resting region extends from X_0 formally to $+\infty$ and the active region from X_0^* toward $-\infty$.

The equation describing the distribution of the membrane potential in its resting region of the fiber is

$$V = E_r - (E_r - V_0)e^{-\xi(X - X_0)} \tag{2}$$

where E_r is the membrane emf in the resting state, V_0 denotes the membrane potential at position $X = X_0$ and $1/\xi$ is the characteristic length, termed "space parameter", of the fiber at rest. When ξ is properly chosen, Eq. (2) satisfies the following cable equation for the resting region of the fiber:

$$\frac{1}{r_i}\frac{\mathrm{d}^2 V}{\mathrm{d}X^2} = -C_m v \frac{\mathrm{d}V}{\mathrm{d}X} + \frac{1}{r_m}(V - E_r) \tag{3}$$

where $r_i (= 4\rho/\pi d^2)$ denotes the longitudinal resistance, $C_m (= \pi C d)$ the membrane capacitance and r_m the membrane resistance of a unit length of the fiber. This equation states that the *membrane current* [see the right-hand side of the Eq. (3)], consisting of the capacitive and resistive components at position X, is equal to the *derivative of the longitudinal current*, $(1/r_i)\,\mathrm{d}V/\mathrm{d}X$.

In normal squid nerve fibers, the membrane resistance (r_m) is relatively high. Hence, in discussing the nerve conduction process, the last term Eq. (3) may be neglected. Then, this equation becomes

$$\frac{1}{r_i}\frac{\mathrm{d}V}{\mathrm{d}X} + C_m v(V - E_r) = 0 \tag{4}$$

Substituting Eq. (2) in this equation, we then have

$$\xi = vC_m r_i \tag{5}$$

Note that ξ/v is the time-constant for the process of charging the membrane capacitance (C_m) by way of the longitudinal resistance (r_i).

Analogously, the potential distribution in the active region is given by

$$V = E_a - (E_a - V_0^*)e^{-\eta(X_0^* - X)} \tag{6}$$

where E_a is the emf of the membrane in the active state, V_0^* is the membrane potential at the advancing end of the active region (located at $X = X_0^*$), and $1/\eta$ is the space parameter of the active region. The cable equation which Eq. (6) has to satisfy can be obtained simply by replacing E_r and r_m in Eq. (3) with E_a and r_m^*, respectively.

3. The Case in which the Transitional Region is Extremely Short

It is known that the cortical layer of the nerve fiber undergoes a discrete structural transformation in association with the process of nerve excitation (see [14]). The results of our recent model experiments using cross-linked polyacrylate gels (see [15, 16]) strongly suggest that this structural transformation, involving redistribution of water molecules in and around the layer, proceeds with great rapidity. It appears likely, therefore, that the transition from the resting to active region of the fiber is wholly abrupt. It is possible that the transitional region between the active and resting region is extremely short.

Since the potential inside the fiber, V, and its derivative, $\mathrm{d}V/\mathrm{d}X$, are continuous functions of X, let us suppose that

$$V_0^* = V_0 \tag{7}$$

and

$$\left.\frac{\mathrm{d}V}{\mathrm{d}X}\right|_{X_0^*} = \left.\frac{\mathrm{d}V}{\mathrm{d}X}\right|_{X_0} \tag{8}$$

Let us now examine the distribution of the electric current in the vicinity of the boundary between the active and resting regions under these circumstances.

From Eq. (8), it follows immediately that the capacitive current, $C_m v(\mathrm{d}V/\mathrm{d}X)\Delta X$, at position X_0 is equal to that at X_0^* (see Fig. 1). [Note that the boundary is moving at a constant velocity, v.] Since we are assuming additionally that V_0 is equal to V_0^*, the inwardly-directed current generated by the membrane emf of the element located at X_0^*, is divided into two equal portions passing

through the two capacitive pathways. Consequently, the (net) inwardly-directed current, $-i_m^*$ in the figure, through the membrane element at X_0^* is equal to that of the outwardly-directed current, i_m, through the element at X_0:

$$i_m = -i_m^* \tag{9}$$

We now proceed to relate these membrane currents with the potential (V) inside the nerve fiber. According to the cable equation mentioned above (see Eq. 3), the spatial distribution of the membrane currents along the fiber can be given by $(1/r_i)\mathrm{d}^2V/\mathrm{d}X^2$ in the resting region of the fiber as well as in the active region. Thus, from Eq. (9), we have

$$i_m = \lim_{x\to x_0} \frac{1}{r_i}\frac{\mathrm{d}^2V}{\mathrm{d}X^2} = -i_m^* = \lim_{x\to x_0^*} \frac{-1}{r_i}\frac{\mathrm{d}^2V}{\mathrm{d}X^2} \tag{10}$$

From this, we obtain

$$\left.\frac{\mathrm{d}^2V}{\mathrm{d}X^2}\right|_{X_0^*} = -\left.\frac{\mathrm{d}^2V}{\mathrm{d}X^2}\right|_{X_0} \tag{11}$$

By combining Eqs. (2) and (6) with Eq. (11), we finally arrive at the relation:

$$\xi = \eta \tag{12}$$

expressing the symmetric distribution of the local current with respect to the boundary between the active and resting regions (see p. 1073 in [17] for experimental verification of this relation).

The condition of Eq. (12) is satisfied when a nerve fiber is carrying an impulse at a constant velocity (v). Since the boundary is moving at a constant velocity along the nerve fiber, this symmetry of the local current is expected to be directly reflected on the rate of potential rise associated with a propagated action potential. In fact, it is known that the rising phase of the action potential is nearly symmetric with respect to the half-maximum point [8, 17].

Now, it is very simple to derive the conduction velocity equation. It is to be noted in Fig. 1 that the strength of the inwardly-directed current generated by the emf of the element located at X_0^* is twice that of the outwardly-directed current passing through the element located at X_0. Thus,

$$\frac{E_a - V_0^*}{r_0^*/\Delta X} = 2v \left.\frac{\mathrm{d}V}{\mathrm{d}X}\right|_{X_0} C_m \Delta X \tag{13}$$

This equation can be rewritten in the following form:

$$\frac{1}{r_0^*} = 2C_m v\xi$$

or

$$v = \frac{1}{C_m\sqrt{2r_m^* r_i}} \tag{14}$$

[Note that $\partial/\partial t = -v\,\mathrm{d}/\mathrm{d}X, E_a - V_0^* = V_0 - E_r$, and $\xi = C_m v r_i$ under these circumstances.]

It is easy to show that Eq. (14) is nothing but an alternative form of the conduction velocity Eq. (1). When the membrane capacitance and resistance per *unit length* of the fiber, C_m, and r_m^*, are converted to the conventional quantities of per *unit area*, and the longitudinal resistance per unit length (r_i) is converted into the specific resistance of the fiber interior (ρ), then Eq. (14) is transformed into Eq. (1). This seems to be the most expedient way of deriving our conduction velocity equation.

4. Structural Changes in the Transitional Zone

In this section, we consider the most probable case in which it is assumed that there is a *gradual change* in the membrane structure from a fully active state to a fully resting state in the transitional region, $X_0^* \leq X \leq X_0$. Let us define $\alpha(X)$ as representing the fraction of the membrane in its active state. Furthermore, let us assume that this active fraction varies continuously from 1 to 0 in the transitional region.

The membrane potential V of the fiber in this region can now be described by

$$\frac{1}{r_i}\frac{\mathrm{d}^2V}{\mathrm{d}X^2} + C_m v\frac{\mathrm{d}V}{\mathrm{d}X} - \alpha\frac{(E_a - V)}{r_m^*} + (1-\alpha)\frac{(V - E_r)}{r_m} = 0 \tag{15}$$

By integrating each term of the above equation with respect to X from one end of the transitional region to the other, the following relation is obtained:

$$\frac{1}{r_i}\left[\left.\frac{\mathrm{d}V}{\mathrm{d}X}\right|_{X_0^*} - \left.\frac{\mathrm{d}V}{\mathrm{d}X}\right|_{X_0}\right] + C_m v(V_0^* - V_0) - (I_{in} - I_{out}) = 0 \tag{16}$$

where I_{in} and I_{out} represent the total inward and outward resistive currents traversing the entire surface of the transitional region, respectively. Since $r_m^* \ll r_m$, $-(I_{in} - I_{out})$ is negative. Clearly, the second term in Eq. (16) is positive (see Fig. 1). Now, it is noted that the transitional region is short and the quantity $\mathrm{d}V/\mathrm{d}X$ attains its minimum within this region. Hence, the first term, which represents the difference in the longitudinal current at the two ends of this region, is infinitesimal. From this it follows that the sum of the last two terms, representing the net membrane current in the transitional region, is also infinitesimal and can be ignored.

On these grounds, it may be concluded that this transitional region behaves like a short inert longitudinal resistance element. It is not difficult to derive Eqs. (12) and (1) under these circumstances (see [8, 17]).

5. Numerical Evaluation

In the past, the electric parameters of the squid giant nerve fiber have been thoroughly determined and richly documented. Particularly, giant fibers of about 0.04 cm in diameter, available in Woods Hole, MA, had been extensively examined under internal perfusion with a 0.4 equiv./l KF solution and yielded highly reproducible results. In these fibers, the amplitude of the action potential, $E_a - E_r$, was roughly

110 mV at room temperature. The membrane resistance at the peak of the action potential, R^* ($= r_m^* \pi d$), was approximately $22\,\Omega \cdot \mathrm{cm}^2$. The specific resistance of the salt solution flowing inside the fiber (ρ) was $36.1\,\Omega \cdot \mathrm{cm}$, and the conduction velocity was $(2.35 \pm 0.8) \times 10^3$ cm/s (see [8]). The membrane capacitance of the fiber in its excited state was taken as being roughly equal to that in the resting state, approximately $10^{-6}\,\mathrm{F/cm}^2$ [1]. Based on this information, we now numerically evaluate some of the relationships among these quantities.

5.1. *Maximum current density*

As a consequence of the symmetry of the local current with respect to the boundary between the resting and active regions (see Eq. (12)), the minimum of the potential gradient, $\mathrm{d}V/\mathrm{d}X$, is located at the boundary. At the boundary, $V_0 - E_r = (E_a - E_r)/2$. Hence the maximum density of the inward current at the peak, $(1/2)(E_a - E_r)/R^*$, is $2.5 \times 10^{-3}\,\mathrm{A/cm}^2$.

The capacitive current $C_m \cdot \partial V/\partial t$ in the immediate vicinity of the boundary is given by $C_m \xi v(V_0 - E_r)$. By using Eqs. (5) and (12), it can be easily shown that this is equal to $(1/2)(E_a - V_0^*)/r_m^*$ which is half of the maximum inward current per unit length of the fiber. [Note that $V_0^* \approx V_0$.]

5.2. *Space parameter*

The reciprocal of the space parameter, $\xi (= \eta)$, given by Eq. (5) is

$$\xi = v \cdot C_m \cdot r_i = v \cdot C\pi d \cdot \frac{4\rho}{\pi d^2} = \frac{4\rho\nu C}{d} \tag{17}$$

Introducing the numerical values of v, C and d listed above, $1/\xi$ is found to be approximately 0.12 cm. Note that the space parameter $1/\xi$ is proportional to d.

5.3. *Conduction velocity*

We now introduce, into Eqs. (1) or (14), the aforementioned observed values of R^* (membrane resistance at the peak of excitation) and ρ (resistivity of the internal salt solution employed), together with the known value of the membrane capacitance per unit area (C) and the diameter (d). The result of the calculation, 2.5×10^3 cm/s, is in good agreement with the observed value, 2.4×10^3 cm/s (see [8]).

In their classic experiments, Cole and Hodgkin [2] and Hodgkin and Huxley [5] have established that the value of R^* in intact (i.e., internally unperfused) giant nerve fibers is in the range of $25 \sim 40\,\Omega \cdot \mathrm{cm}^2$. This classical value of R^* is not significantly different from that encountered in internally perfused fibers. Furthermore, since the dependence of the velocity on the fiber diameter [13] is correctly described by Eq. (1), it seems safe in concluding that Eq. (1) is applicable to nonmyelinated nerve fibers in general.

6. Discussion

We have known for some time that a nerve impulse propagating along a squid giant fiber is accompanied by simultaneous *swelling* of the cortical layer of the fiber [14]. It should be noted that the peak of this swelling coincides with the peak of the propagating action potential. The falling phase of the action potential is associated with shrinkage of the nerve fiber. Since these propagated mechanical changes were totally unknown in classical neurophysiology, it seems worthwhile to briefly discuss the significance of the non-electrical manifestation of the nerve impulse.

6.1. *The requirement of the salt of Ca^{2+} in the external medium*

Normal sea water contains about 400 mM NaCl and about 25 mM of the salts of divalent cations, Ca^{2+} and Mg^{2+}. Carefully excised squid giant nerve fibers maintain their ability to generate propagated impulses for many hours in this medium. Taking advantage of the ability of these fibers to respond to brief electric shocks repeatedly, mechanical or optical signs of swelling have been detected. The nerve fibers do *lose* their ability to respond to a brief shock with generation of a propagated impulse when the salts of divalent cations in the medium are replaced with NaCl or sucrose. These nerve fibers do not lose their excitability when the salt of Ca^{2+} is substituted for the Mg^{2+} salt completely. However, a complete substitution of Mg^{2+} for Ca^{2+} leads to a loss of excitability of the fiber. The presence of Ca^{2+} in the medium is required for the production of action potentials and associated mechanical responses.

6.2. *The discreteness of the volume change associated with Ca^{2+}–Na^{+} exchange in anionic gels and in nerve fibers: the cooperativity of the process*

A clear understanding of the mechanical changes in nerve fibers was brought about by comparing them with the structural changes associated with cation-exchange in artificial polyelectrolyte gels. The volume of a swollen polyacrylate gel (bead or rod) immersed in a Na-salt solution was shown to undergo an abrupt reduction (to about 1/10) when the amount of the Ca^{2+} salt added to the solution by gradual steps reaches a certain critical level [14–16]. This volume transition is remarkably sharp, indicating that this reversible Ca^{2+}–Na^{+} exchange process is highly cooperative. An extensive comparison of the ion-exchange process in nerve fibers with that in anionic gels suggests that this high cooperativity of the process is at the base of the all-or-none behavior of the nerve excitation and conduction.

6.3. *The relationship between the electric parameters and the swelling of nerve fibers*

In the resting state of the nerve fiber, the negatively charged sites in its cortical layer are occupied predominantly by Ca^{2+} from the external salt solution. Because

the Ca^{2+} concentration in the fiber interior is very low, a brief pulse of outwardly-directed membrane current is effective in triggering a cooperative replacement of Ca^{2+} in the layer with monovalent cations from both in- and outside of the layer. A rise in the water-content of the layer associated with this cation-exchange process brings about a marked enhancement of the mobilities of the cations in the layer. This is considered to be the mechanism by which the transition $r_m \rightarrow r_m^*$ is induced during nerve conduction. The selectivity and the mobility ratio for these cations are also expected to change in association with this transition, causing a sudden shift of the membrane emf, $E_r \rightarrow E_a$. The relaxation process which follows this transition brings about a gradual fall in the membrane potential [14].

6.4. *A problem encountered in neurophysiological studies*

In studies of the potential difference across a cation-exchanger membrane, it is known that serious difficulty is encountered in predicting the sign and magnitude of the potential when there is a mixture of divalent and univalent cations in the surrounding solutions (see e.g., [4], pp. 379 and 382). There seems little doubt that the cortical layer of the nerve fiber has properties of a cation-exchanger membrane. The situation is more complicated when the solutions surrounding the membrane cannot be stirred (see e.g., Fig. 8.14 in [4]). Furthermore, the interior of the normal nerve fiber is not an aqueous solution of simple salts, but rather a gel containing a considerable amount of filamentous macromolecules (see e.g., [9, 14]). From a strict thermodynamic point of view, the electric potential difference across the intact nerve fiber membrane may be considered as indefinable (see e.g., Overbeek [12]; and pp. 374 and 378 in Guggenheim [3]). This seems to be one of the knotty problems which neurophysiologists had to tackle in the past.

7. Conclusion

The conduction velocity equation (Eq. 1), relating the velocity to the classical parameters of the nonmyelinated nerve fiber, was derived by analyzing the distribution of the local current in the vicinity of the boundary between the resting and active regions of the fiber. In this derivation, we have employed only those quantities which are amenable to direct experimental determination, such as $(E_a - E_r), r_m^*$, etc. There seems to be only little ambiguity as to the physical significance of the quantities in this conduction velocity equation.

Acknowledgement

I express my sincere thanks to Dr. Peter Basser and Dr. Ralph Nossal of the LIMB, NIDHD, and to Dr. Matin Zatz of LCMR, NIMH for their continuous support.

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