PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

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Phil. Trans. R. Soc. Lond. B 1975 **270**, 297-300
doi: 10.1098/rstb.1975.0010

Phil. Trans. R. Soc. Lond. B. **270**, 297–300 (1975) [297]
Printed in Great Britain

The optimum density of sodium channels in an unmyelinated nerve

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In introducing this meeting I wish to refer to a theoretical development which may be relevant to some of our discussion. Present estimates suggest that the density of sodium channels varies between 2.5/μm^2 in the 0.2 μm diameter axons of the olfactory nerve of the garfish (Colquhoun, Henderson & Ritchie 1972) to about 500/μm^2 in the giant nerve fibres of the squid (Keynes & Rojas 1974). Since giant nerve fibres are considered to be an adaptation to rapid movement it is of interest to consider whether there is an optimum density of sodium channels at which conduction velocity is maximal. If this can be established it is then important to develop methods for calculating the optimum density on different sets of assumptions.

As Huxley and I (1952) argued, movement of the charged particles or dipoles which open and close ionic channels should be accompanied by electric currents that would now be called gating currents. Thus, if three m particles have to move across the membrane in order to open one sodium gate, the outward current density is $3N|Z|e\,\mathrm{d}m/\mathrm{d}t$, where N is the density of sodium gates, Z is the valency of the particle and e is the charge on the proton. At low frequencies the effect of this displacement of charge would be to increase the capacity of the membrane by NC^*_{Na} where C^*_{Na} is the capacity associated with each gate; the asterisk denotes that a single channel is considered. C^*_{Na} is potential and frequency dependent but for the purpose of the present calculations it will be assumed constant and the total membrane capacity C_{M} will be taken as

$$C_{\mathrm{M}} = C_0 + NC^*_{\mathrm{Na}}, \tag{1}$$

where C_0 is the capacity of the membrane without channels.

The maximum sodium conductance $\bar{g}_{\mathrm{Na}}$ is

$$\bar{g}_{\mathrm{Na}} = Ng^*_{\mathrm{Na}}, \tag{2}$$

where $\bar{g}^*_{\mathrm{Na}}$ is the maximum conductance of a single sodium channel. From the estimates of Keynes & Rojas (1974) $\bar{g}^*_{\mathrm{Na}} = 2.5$ pS ($= 2.5\times10^{-12}\ \Omega^{-1}$) and $C^*_{\mathrm{Na}} = 8$ aF ($= 8\times10^{-18}$ F) at low frequencies and at the optimum voltage.

It is intuitively obvious that increasing the sodium conductance will increase conduction velocity and that increasing membrane capacity will decrease it. However, in order to see whether there is an optimum value of N, and to calculate its magnitude, we need to know the dependence of the conduction velocity, θ, on C_{M} and g_{Na}. For this we consider the cable equation in the form

$$\frac{a}{2R}\frac{\partial^2 V}{\partial x^2} = C_{\mathrm{M}}\frac{\partial V}{\partial t} + I_{\mathrm{i}}, \tag{3}$$

where a is the axon radius, R is the resistivity of axoplasm, V is the internal potential, x is distance, t is time and I_{i} is the ionic current density through the membrane.

Many years ago A. F. Huxley proved that if the ionic current density is an instantaneous function of the form

$$I_{\mathrm{i}} = \frac{G}{V_{\mathrm{A}}^2}V^2(V-V_{\mathrm{A}}), \tag{4}$$

in which G and V_A are constants, the cable equation (3) has a non-infinite solution representing a wave-front propagating at a constant velocity θ, where

$$\theta = \tfrac{1}{2}a^{\frac{1}{2}}R^{-\frac{1}{2}}G^{\frac{1}{2}}C_M^{-1}. \tag{5}$$

Later, I extended his treatment to a model in which the rate of increase of sodium conductance during the rising phase is an instantaneous function of voltage.

Thus if
$$I_i = g(V-V_A) \tag{6}$$
and
$$\frac{\mathrm{d}g}{\mathrm{d}t} = \frac{\alpha G}{V_A^3}V^2(V_A-V), \tag{7}$$

where α is a rate constant, g is a variable conductance per unit area and G a constant conductance per unit area, then the conduction velocity is

$$\theta = \tfrac{1}{2}a^{\frac{1}{2}}R^{-\frac{1}{2}}\alpha^{\frac{1}{4}}G^{\frac{1}{4}}C_M^{-\frac{3}{4}}. \tag{8}$$

In both cases the time course of the wave front is

$$V = \tfrac{1}{2}V_A(1+\tanh\gamma t),$$

where $\gamma = \frac{1}{4}G/C_M$ in the first case (equation (5)) and $\gamma = \frac{1}{4}\surd(\alpha G/C_M)$ in the second (equation (8)).

If equations (1) and (2) are used in conjunction with equation (5) it is found that the maximum velocity occurs when $NC^*_{Na} = C_0$ whereas equation (8) gives $NC^*_{Na} = \frac{1}{2}C_0$. The second estimate, which I consider to be more realistic, may be summarized in words by saying that the conduction velocity is maximal when the additional capacitance associated with the sodium channels is half the basic capacitance C_0.

A more general approach is to use the dimensional equations developed by Huxley (1959) in an article where he proves in his equation (22) a relation that is equivalent to

$$\frac{\partial \ln\theta}{\partial \ln C_M} = -\frac{1}{2} - \frac{\partial \ln\theta}{\partial \ln \bar{g}_{Na}} \tag{9}$$

and gives a graph derived from solutions of our equations which allows $\partial \ln\theta/\partial \ln \bar{g}_{Na}$ to be calculated under different conditions, for example at different temperatures. To apply his results, first note that

$$\frac{\mathrm{d}\ln\theta}{\mathrm{d}\ln N} = \frac{\mathrm{d}\ln \bar{g}_{Na}}{\mathrm{d}\ln N}\,\frac{\partial \ln\theta}{\partial \ln \bar{g}_{Na}} + \frac{\mathrm{d}\ln C_M}{\mathrm{d}\ln N}\,\frac{\partial \ln\theta}{\partial \ln C_M}. \tag{10}$$

From equation (2) $\partial \ln \bar{g}_{Na}/\partial \ln N = 1$ and from equation (1)

$$\partial \ln C_M/\partial \ln N = C^*_{Na}N/(C_0+C^*_{Na}N);$$

on inserting these values, eliminating $\partial \ln\theta/\partial \ln C_M$ by equation (9), and equating

$$\mathrm{d}\ln\theta/\mathrm{d}\ln N$$

to zero to find the maximum, we obtain

$$C^*_{Na}N = 2C_0\frac{\partial \ln\theta}{\partial \ln \bar{g}_{Na}}. \tag{11}$$

From figure 20 of Huxley (1959) and the last equation on his page 244, $\partial \ln\theta/\partial \ln \bar{g}_{Na}$, which is equivalent to his $\partial \ln\theta/\partial \ln\eta$, is found to be 0.32 at 25 °C, 0.23 at 18.5 °C and 0.14 at 6 °C.

Taking the 18.5 °C value and assuming C_0 to be 1.0 μF/cm² the optimum value of the extra capacity due to gating currents is found to be 0.46 μF/cm². Keynes & Rojas (1974) obtained 0.4 μF/cm² for the low-frequency capacity due to gating currents at the transition potential where the capacity is maximal. My guess is that at 18.5 °C this might correspond to an effective capacity during the rising phase of about 0.15 μF/cm². A different way of presenting the result of this calculation is to say that equation (11) predicts that the optimum value of N is 575/μm² if we take C^{*}_{Na} at its maximum, low frequency value of 8 aF, and 1500/μm² if we take it as 3 aF; the mean value of N obtained by Keynes & Rojas was 480/μm².

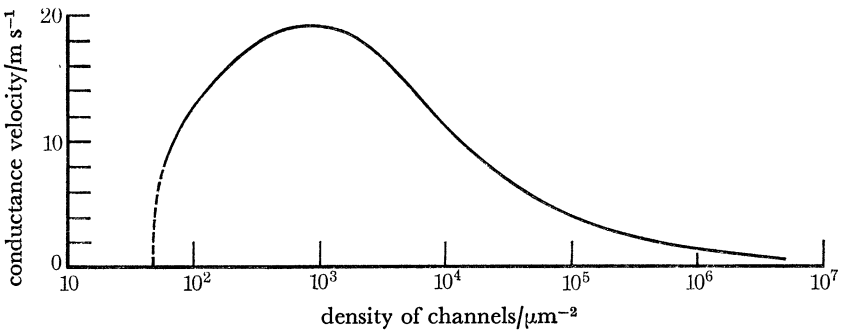

FIGURE 1. Variation of conduction velocity with density of sodium channels calculated from equations of Hodgkin & Huxley (1952) by extension of the method of Huxley (1959). The standard Hodgkin–Huxley axon at 18.5 °C is assumed to have 500 Na channels, $C_0 = 0.8$ μF/cm²; $NC^{*}_{\mathrm{Na}} = 0.2$ μF/cm² and $\bar{g}_{\mathrm{Na}} = 120$ mS/cm²; the velocity is calculated for a radius of 238 μm and an internal resistivity of 35.4 Ω cm. The curve was calculated from equations (19), (20) and Fig. 20 of Huxley (1959) with $\eta = N/500$ and

$$\gamma = (C_0 + NC^{*}_{\mathrm{Na}})/C_0.$$

The broken portion of the curve depends on an uncertain extrapolation of figure 20 of Huxley (1959). The abscissa gives the number of channels/μm² on a logarithmic scale.

The curve in figure 1 shows the conduction velocity calculated as a function of channel density at 18.5 °C. The detailed assumptions and method of calculation are given in the figure legend. It can be seen that conduction fails below a density of about 50 channels/μm², and that the relation has a flat maximum so that little is lost if the actual number of sites is somewhat less than the optimum number. Thus the velocity is only 8 % below the maximum when the density of sites is one-third of the optimum.

The weak point in the theory described in this note is the assumption that the gating mechanism is equivalent to a fixed capacity. In order to put the argument on a firm basis it would be desirable to recalculate propagated action potentials from Hodgkin–Huxley equations modified by the addition of a term $3N|Z|e\,\mathrm{d}m/\mathrm{d}t$ to represent gating currents. It might also be advisable to allow for the presence of the small series resistance which has been ignored in previous calculations of propagated action potentials.

The calculations outlined here indicate that the garfish olfactory nerve with only 2.5 channels/μm² in its 0.2 μm diameter axons must be a long way from the optimum density, and indeed if the characteristics of its gating mechanism were identical with those in the squid giant axon it would be unable to propagate action potentials at all (figure 1). The reason for failure would be the same as the reason that the squid axon fails at temperatures above 33 °C, i.e. that the processes leading to repolarization, inactivation of sodium conductance and increase in potassium conductance, set in before the rising phase is complete. This difficulty is avoided by the adaptation that in very small nerve fibres the processes leading to repolarization are greatly prolonged and the total duration of the single axon spike in a garfish nerve is probably of the order of 0.1 s (Howarth 1974; see also Paintal 1967, who has shown that spike duration varies inversely with axon diameter). Conduction of impulses can thus take place with a good margin of safety but at the expense of a slower maximum frequency as well as a slow velocity.

It is not hard to see why the density of sites might have to be much less in small nerve fibres. In the squid axon at 18 °C the entry of sodium and loss of potassium per impulse are 3 or 4 times the theoretical minimum of $C_M V_A / F \approx 1$ pmol (V_A is spike amplitude, F is the Faraday constant). This does not matter because the expenditure of energy needed to keep pace with 1 or 2 impulses per second is not high compared to the resting metabolism. However, in a fibre of 0.1 μm diameter the surface/volume ratio is 5000 times greater than in the squid axon and it is probably important to reduce the ionic exchange during each impulse to the absolute minimum. This, together with the absence of a requirement for fast conduction of olfactory information, may help to explain why the density of channels in garfish nerve is so much less than in the squid axon. Another possibility which needs quantitative exploration is that spontaneous initiation of impulses might be a frequent event if there were 500 channels/μm^2 in an 0.1 μm diameter axon with a resistance of about $10^{10}\,\Omega$ between inside and outside.

Note added in proof, 23 *January* 1975. Adrian (1975) has obtained numerical solutions of modified Hodgkin–Huxley equations which confirm the existence of a maximum conduction velocity at a channel density between 500 and 1000 μm^{-2}.

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