

A MATHEMATICAL MODEL FOR THE CARDIAC ACTION POTENTIAL BASED ON SLOW INACTIVATION OF SODIUM CONDUCTANCE

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Summary

A mathematical model for the action potential in Purkinje fibres is developed. It is based on voltage-clamp results which show that inactivation of sodium current in these muscles is much slower than in squid axon and that the latent rise in potassium conductance is not present. Both the sodium and the potassium conductances are represented as a sum of slow and fast components. This is incorporated in the suitably adjusted Hodgkin-Huxley model for the squid axon. It is shown that such a model can account satisfactorily for the shape of the action potentials in Purkinje fibres.

I. INTRODUCTION

Brady and Woodbury (1960) introduced the concept of a fast and a slow component of sodium conductance in cardiac membranes on theoretical grounds. The existence of such components was demonstrated by Deck and Trautwein (1964) and Deck, Kern, and Trautwein (1964) who succeeded in applying the voltage-clamp technique to short lengths of Purkinje fibre. The existence of these two components would have a significant effect on the generation of the action potential in these fibres, particularly in the plateau region. We were therefore interested to see if the Hodgkin and Huxley (1952) equations for the squid axon could be adjusted so as to incorporate the observed slow sodium component in a manner which would on the one hand be consistent with Deck and Trautwein's observations on voltage clamps and on the other would produce solutions similar to observed cardiac action potentials. Some preliminary results are given below.

II. DEFINITION OF SYMBOLS

E_m	Membrane potential (mV)
E_{Na}, E_K	Equilibrium potentials of Na^+ and K^+ (mV)
C	Membrane capacity ($\mu F/cm^2$)
t	Time (sec or msec)
g_{Na}, g_K	Total Na^+ , K^+ membrane chord conductances (m-mho/cm ²)
$(g_{Na})_H, (g_K)_H$	Total Na^+ chord conductance as used by Hodgkin and Huxley (1952)
$(g_{Na})_\infty, (g_K)_\infty$	Long time values of g_{Na} and g_K (m-mho/cm ²)
$(g_{Na})_f, (g_K)_f$	The fast components of g_{Na}, g_K (m-mho/cm ²)
$(g_{Na})_s, (g_K)_s$	The slow components of g_{Na}, g_K (m-mho/cm ²)
m, h, l, n', n	Dimensionless variables which can vary between 0 and 1
α, β	Rate constants which vary with voltage but not with time
$\bar{g}_{Na}, \bar{g}_K$	Constants
f_1, f_2, f_3	Functions of E_m and t

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III. MEMBRANE ACTION POTENTIAL THEORY

(a) Sodium Conductance

The equation for the membrane action potential is assumed to be

$$C_m(dE_m/dt) + g_K(E_m - E_K) + g_{Na}(E_m - E_{Na}) = 0. \quad (1)$$

These terms take account of the capacity, the potassium, and the sodium currents only. All other current contributions are assumed to be negligible (Hutter and Noble

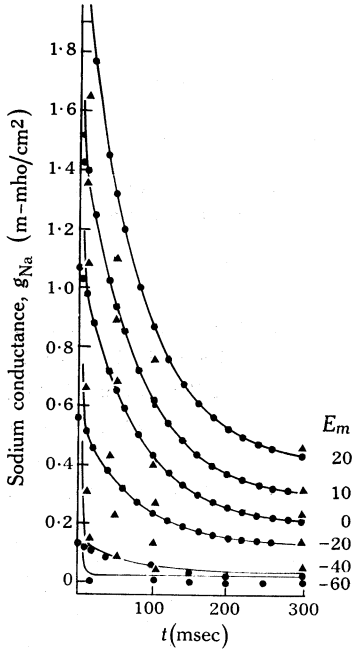


Fig. 1.—Theoretical sodium conductance, g_{Na} , for various membrane potentials, E_m , calculated from equations (2)–(6). ● Slow component of g_{Na} . ▲ Experimental results of Deck and Trautwein (1964).

1961; Dudel, Peper, Trautwein 1966). We find that the experimental voltage-clamp observations are fitted by the following expressions:

$$g_{Na} = (g_{Na})_f + (g_{Na})_s, \quad (2)$$

where

$$(g_{Na})_f = \bar{g}_{Na} m^3 h l. \quad (3)$$

(Here m and h have their usual Hodgkin–Huxley significance and l is an additional inactivation term similar to h but with a time constant of about 2 msec.)

$$(g_{Na})_s = f_1(E_m, t) + f_2(E_m), \quad (4)$$

where

$$f_1(E_m, t) = \frac{0.9 \exp(E_m/29 - t/75)}{\exp\{\frac{1}{5}(-E_m - 40)\} + 1}, \quad (5)$$

$$f_2(E_m) = \frac{0.14 \exp\{(E_m + 10)/64 \cdot 9\}}{2.6 \exp\{\frac{1}{2}(-E_m - 40)\} + 1} \left(\frac{0.8 \exp\{(E_m - 20)/20\}}{100 \exp(E_m + 10) + 1} + 1 \right). \quad (6)$$

A family of curves calculated from equations (2)–(6) are shown in Figure 1, where a comparison is made with experimental results of Deck and Trautwein (1964).

(b) Potassium Conductance

These latter authors found that, for $t = 12.5$ msec following a large depolarization ($E_m = +20$ mV), g_K is still a little above its resting value and falls asymptotically with time to its final value $(g_K)_\infty$. This is only possible if g_K rises rapidly immediately after depolarization and then decays slowly. We therefore took

$$g_K = (g_K)_f + (g_K)_s, \quad (7)$$

where

$$(g_K)_f = n' f_3(E_m), \quad (8)$$

$$(g_K)_s = \bar{g}_K n, \quad (9)$$

$$f_3(E_m) = 0.3 \exp \{(E_m - 20)/30\}. \quad (10)$$

n' is an inactivation term similar to l in equation (3). $(g_K)_f$ decays with a time constant of the order of 20 msec. For E_m negative $(g_K)_f$ is negligible at all times.

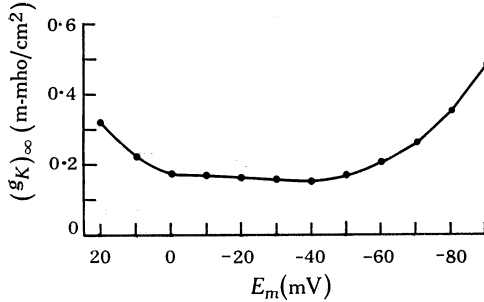


Fig. 2.—Potassium conductance at infinite time, $(g_K)_\infty$, for various membrane potentials.

In equation (9) $\bar{g}_K$ is a constant and n is a term of the Hodgkin-Huxley type. n , n' , $\bar{g}_K$, and $\bar{g}_{Na}$ are specified in the Appendix. $(g_K)_s$ is responsible for the slow decay of g_K and the value $(g_K)_\infty$ is the value it attains at long times. As can be seen in Figure 2, equation (7) correctly gives the minimum in $(g_K)_\infty$ found at $E_m = -40$. A family of curves for g_K is shown in Figure 3. The reason for showing few points on the curves for $E_m = -60$ and -70 is to facilitate the identification of the lines. All the curves in Figure 3 were drawn from a much larger number of calculated values. The variations of g_K with time as observed by Deck and Trautwein (1964) are replotted in Figure 4 in a way that makes direct comparison with our results easier. The values for the resting value and potassium conductances given by this model are 0.035 and 0.48 m-mho/cm² respectively.

(c) Membrane Action Potential

The membrane action potential given by the solution to equation (1) with $C_m = 12 \mu\text{F/cm}^2$ and g_K and g_{Na} as specified in equations (2)–(10) is shown in

Figure 5. The plateau duration is a little short. The possibility of improving the action potential shape by minor adjustments to the constants in equations (2)–(10) is now under investigation.

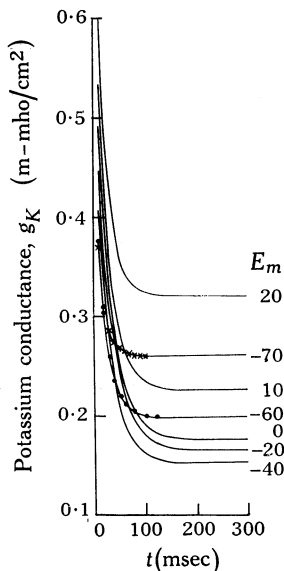


Fig. 3

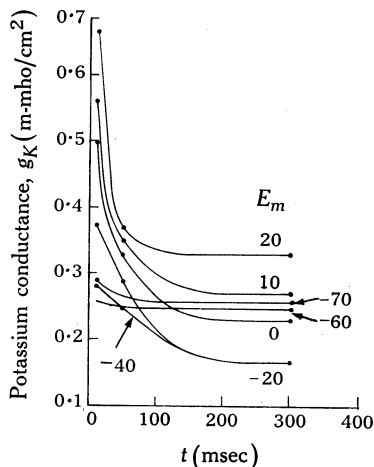


Fig. 4

Fig. 3.—Theoretical potassium conductance, g_K , for various membrane potentials.

Fig. 4.—Variation of potassium conductance, g_K , with time. Observed values of Deck and Trautwein (1964) have been replotted to enable easier comparison with theoretical values (see text).

IV. DISCUSSION

We have attempted to fit the experimental observations of Deck and Trautwein whilst retaining functions of the Hodgkin–Huxley type, and in so doing have had to introduce some 20 parameters and functions whose values have been adjusted to fit 49 experimental findings. Questions therefore may be raised as to the accuracy of the parameter adjustment and as to the uniqueness of the functions employed. As to the latter, it must be admitted that functions different from those employed here could be found, containing a similar number of fitted parameters, which would give an equally good fit to the experimental findings. It was not our purpose to explore the whole range of potential models but to show that models, unique or otherwise, based on Deck and Trautwein experimental results and formulated within Hodgkin and Huxley's framework give an adequate description of events. As to the accuracy of setting the adjustable parameters, this was found to vary considerably with time following the establishment of a voltage clamp. For example, in Figure 1, the values of g_{Na} for small times were found to be insensitive to the time constant $\tau = 75$ [equation (5)], but for $t > 5$ msec the results were highly sensitive to this parameter

which is set to an accuracy corresponding to the small percentage error of the observations.

It has been demonstrated that equation (3) adequately predicts the behaviour of the sodium conductance during the depolarizing phase of the cardiac action potential. During this phase the value of the inactivation constant l is approximately equal to 1 and equation (3) reduces to the expression used by Hodgkin and Huxley for the sodium conductance in the squid axon. The only difference is the value used for $\bar{g}_{Na}$. Like Noble (1962) we have found that $\bar{g}_{Na}$ has to be increased to about 400 before the spike of the action potential is obtained. Unlike Noble, however, we did not find it necessary to alter in any way the equations for the variables m and h . The expressions used by us for the rate constants α_m , β_m , α_h , and β_h [equations (6)–(9). Appendix] are as given by Hodgkin and Huxley (1952).

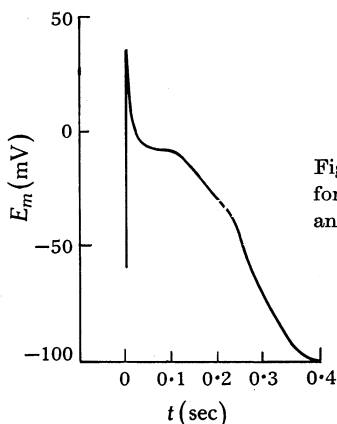


Fig. 5.—Variation of membrane action potential with time for specified membrane capacity ($12 \mu\text{F}/\text{cm}^2$) and with g_K and g_{Na} as specified in equations (2)–(10).

At longer times the Hodgkin and Huxley equations were unable to account for the behaviour of the sodium conductance. It was necessary to make a second slowly decaying sodium component predominant during this period. This was done by reducing $(g_{Na})_{H-H}$ by multiplying it by the inactivation constant l which decays on depolarization rendering $(g_{Na})_f$ negligible for $t > c. 5 \text{ msec}$. Thus for $t > 5 \text{ msec}$ g_{Na} is in fact equal to $(g_{Na})_s$ except for $E_m < -70 \text{ mV}$. For E_m in this range, $(g_{Na})_f$ is sufficiently slow in decaying that it can account for the value of g_{Na} even at longer times. Therefore for $E_m < -70$ $(g_{Na})_s$ is made small.

The predominant term in g_K for all t is $(g_K)_s$. We chose to express it as $\bar{g}_K n$ as this was the simplest expression we could use. It is possible to express it as $\bar{g}_K n^4$ as done by Hodgkin and Huxley, by suitably adjusting α_n and β_n . However since n must necessarily be different from n_{H-H} , to account for the difference in the behaviour of potassium conductance in cardiac muscle, there was nothing to be gained by making our expression conform with that used by Hodgkin and Huxley. The simpler equation was therefore thought to be preferable.

At present there is some controversy as to the existence of a delayed rectification of potassium conductance (Noble 1962; Deck and Trautwein 1964; Trautwein, Dudd, and Peper 1965; McAllister and Noble 1966). Noble's (1962)

mathematical model for the cardiac action potential is based on the opinion that this delayed rectification is present in cardiac muscle. This is not in agreement with the interpretation given by Deck, Kern, and Trautwein (1964) and Trautwein, Dudel, and Peper (1965) to their voltage-clamp observations. Like Noble's model the present treatment is based on the balance between sodium and potassium currents. It is apparent now that this balance can be achieved in the plateau region of the action potential even if there is no delayed rectification. However, for this to be possible $(g_{\text{Na}})_{\infty}$ must be made to fall continuously with E_m (Fig. 4). This is consistent with Deck and Trautwein's observations. Noble obtains this balance by using equations for g_{Na} where $(g_{\text{Na}})_{\infty}$ exhibits a maximum at $E_m = -10$ mV. This again cannot be reconciled with the voltage clamp results of Deck and Trautwein. Our model in its present form cannot predict the pacemaker potential or the hysteresis effect (Dudel, Peper, and Trautwein 1966). It is possible that, with minor adjustments now under consideration, the model could be made to give the pacemaker potential. It is unlikely that the mechanism of this model could be made to account for the hysteresis.

V. CONCLUSIONS

From the work reported in this paper the following conclusions can be drawn:

- (1) An adequate mathematical representation can be made of the Deck and Trautwein voltage-clamp observations on Purkinje fibres [equations (2)–(10)].
- (2) This model requires both g_{Na} and g_{K} to consist of separate fast and low components, the fast sodium component being very similar to that given for the squid axon by Hodgkin and Huxley.
- (3) Solution of the dynamic equation incorporating the slow and fast components of both the sodium and the potassium conductance give cardiac-like membrane action potentials.

VI. REFERENCES

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APPENDIX

$\bar{g}_{Na}$ and $\bar{g}_K$ are constants with dimensions of conductance (m-mho/cm²). Their values are 400 and 1.067 respectively. The variables m , h , l , n' , and n are defined as follows:

$$dm/dt = \alpha_m(1-m) - \beta_m m, \quad (1A)$$

$$dh/dt = \alpha_h(1-h) - \beta_h h, \quad (2A)$$

$$dl/dt = \alpha_l(1-l) - \beta_l l, \quad (3A)$$

$$dn'/dt = \alpha_{n'}(1-n') - \beta_{n'} n', \quad (4A)$$

$$dn/dt = \alpha_n(1-n) - \beta_n n, \quad (5A)$$

$$\alpha_m = \frac{1}{10}(-E_m - 65)/\exp\{\frac{1}{10}(-E_m - 65)\} - 1, \quad (6A)$$

$$\beta_m = 4 \exp\{(-E_m - 90)/18\}, \quad (7A)$$

$$\alpha_h = 0.07 \exp\{(-E_m - 90)/20\}, \quad (8A)$$

$$\beta_h = [\exp\{\frac{1}{10}(-E_m - 60)\} + 1]^{-1}, \quad (9A)$$

$$\alpha_l = 0.008 \exp\{(-E_m - 90)/40\}, \quad (10A)$$

$$\beta_l = 0.5/[3 \exp(-E_m - 80) + 1], \quad (11A)$$

$$\alpha_{n'} = 0.05 \exp\{(-E_m - 90)/13\}, \quad (12A)$$

$$\beta_{n'} = 0.05/[\exp\{\frac{1}{5}(-E_m - 60)\} + 1], \quad (13A)$$

$$\alpha_n = A/[0.8BC \exp\{(E_m - 20)/80\}], \quad (14A)$$

$$\beta_n = A'/[0.8B' \exp\{(E_m - 20)/80\}]. \quad (15A)$$

The contents A , B , C , A' , B' may be evaluated as follows:

$$A = 0.0036 \exp[8.66\{(E_m + 40)/100\}^2].$$

$$B = 0.43 \exp\{(E_m + 40)/35.93\} + 1.5.$$

$$C = \frac{0.95 \exp\{(E_m - 20)/101.23\}}{1.9 \exp\{(-E_m - 10)/4.44\} + 1} + 1.$$

$$A' = 0.0093 \exp[2.65 \exp\{(m + 40)/100\}^2].$$

$$B' = 0.393 \exp\{(E_m - 40)/137.93\} + 0.6.$$

