Simulation analysis of intermodal sodium channel function

Shangyou Zeng
Department of Physics, Xiangtan University, Hunan Province, 411105, People's Republic of China

Peter Jung
Department of Physics and Astronomy, Ohio University, Athens, Ohio 45701, USA

(Received 6 September 2008; published 17 December 2008)

Although most sodium ion channels clustered in nodes of Ranvier provide the physiological basis for saltatory conduction, sodium ion channels cannot be excluded from internodal regions completely. The density of internodal sodium ion channels is of the order of $10/\mu m^2$. The function of internodal sodium ion channels has been neglected for a long time; however, experimental and theoretical results show that internodal sodium ion channels play an important role in action potential propagation. In this paper, based on the compartment model, we investigate the function of internodal sodium ion channels. We find that internodal sodium ion channels can promote action potential propagation, enlarge the maximal internodal distance guaranteeing stable action potential propagation, and increase the propagation speed of action potentials. In this paper, we find an optimal conductance of internodal sodium ion channels ($4-5$ mS/cm^2), which accords with the active internodal sodium ion conductance in a real myelinated axon. With the optimal conductance, the average sodium ion channel conductance of the axon is minimal, and the metabolic energy consumption due to ion channels is also minimal.

DOI: 10.1103/PhysRevE.78.061916 PACS number(s): 87.16.Uv

I. INTRODUCTION

The stable, efficient, and fast propagation of action potentials across the long axon of the peripheral nervous system is the important requirement for the successful evolution of large body sizes of organisms. The development of the myelinated axon is the elegant solution to this problem. In a myelinated axon, sodium ion channels are concentrated at the nodes of Ranvier, separated by segments sheathed with myelin. The myelin sheath's resistance is high, capacitance is low, and it provides the basis for fast propagation of action potentials. The myelin is interrupted at distance ranging from 50 μm to 2000 μm, and nodes of Ranvier are distributed at the interrupted regions. These axonal domains differ dramatically from the internodal regions. The density of sodium ion channels in the nodes of Ranvier is approximately as high as $2000/\mu m^2$ [1]; however, the density of sodium ion channels at internodal regions is of the order of $10/\mu m^2$ [2–8].

Although most sodium ion channels clustered in nodes of Ranvier provide the physiological basis for saltatory conduction, sodium ion channels cannot be excluded from internodal regions completely. The function of internodal sodium ion channels has been neglected for a long time; however, experimental and theoretical results [7,9] show that internodal sodium ion channels with low density can promote action potential propagation. In this paper, based on the compartmental model, we investigate the function of internodal sodium ion channels. Our results show that internodal sodium ion channels can promote action potential propagation dramatically, enlarge the maximal internodal distance guaranteeing stable action potential propagation, and increase the propagation speed of action potentials. We find an optimal conductance of internodal sodium ion channels ($4-5$ mS/cm^2). With the optimal conductance, the average sodium ion channel conductance of the axon is minimal, and the energy consumption due to ion channels is also minimal. Because the pumping action of ion channels will consume a large quantity of energy, and 50% energy in human brains is consumed by the pumping action of sodium and potassium ion channels [10–15], internodal sodium ion channels with low conductance ($4-5$ mS/cm^2) can optimize metabolic activities and save metabolic energy up to 50%. Due to the myelin sheath, the activation of internodal sodium ion channels will be reduced 80% [1,16], and the density of internodal sodium ion channels is of the order of $10/\mu m^2$, so the active conductance of internodal sodium ion channels is approximately 4 mS/cm^2 (conductance of each sodium ion channel is 20 pS), which accords with the optimal internodal sodium ion conductance we get in this paper. So the real myelinated axon has the optimal sodium ion channel distribution to guarantee the minimal metabolic energy consumption of ion channels.

II. METHODS

A. Deterministic Hodgkin-Huxley equations

Hodgkin and Huxley (HH) first presented quantitatively the electrical potential of nerve membranes in terms of a mathematical model [17]. The following equation expresses the time evolution of the electrical potential across the membrane:

$$c_m \frac{dV}{dt} = -g_L(V - V_L) - g_K(V - V_K) - g_{Na}(V - V_{Na}) + I, \tag{1}$$

where c_m denotes the capacitance of the nerve membrane; g_{Na}, g_K, and g_L denote, respectively, the conductances of the sodium ion channels, potassium ion channels, and leakage system; the voltages V_{Na}, V_K, and V_L denote the sodium, potassium, and leakage reversal potentials; and I is injected

current. The sodium and potassium ion channel conductances, g_{Na} and g_{K}, are voltage (V) dependent; however, the leakage conductance g_L is a constant,

$$g_{\mathrm{Na}}(V,t) = \bar{g}_{\mathrm{Na}} m^3 h,$$

$$g_{\mathrm{K}}(V,t) = \bar{g}_{\mathrm{K}} n^4, \tag{2}$$

where $\bar{g}_{\mathrm{Na}}$ denotes the maximal sodium ion channel conductance (all sodium ion channels open), and $\bar{g}_{\mathrm{K}}$ denotes the maximal potassium conductance (all potassium ion channels open). The gating variables m, n, and h, with $0 < m,n,h < 1$ are voltage dependent, and governed by the set of linear equations

$$\frac{dn}{dt} = -[\alpha_n(V) + \beta_n(V)]n + \alpha_n(V),$$

$$\frac{dm}{dt} = -[\alpha_m(V) + \beta_m(V)]m + \alpha_m(V),$$

$$\frac{dh}{dt} = -[\alpha_h(V) + \beta_h(V)]h + \alpha_h(V) \tag{3}$$

with the rates

$$\alpha_n(V) = \frac{0.0462(V+83.2)}{1-e^{-(V+83.2)/1.1}},$$

$$\beta_n(V) = \frac{-0.0824(V+66)}{1-e^{(V+66)/10.5}},$$

$$\alpha_m(V) = \frac{6.57(V+20.4)}{1-e^{-(V+20.4)/10.3}},$$

$$\beta_m(V) = \frac{-0.304(V+25.7)}{1-e^{(V+25.7)/9.16}},$$

$$\alpha_h(V) = \frac{-0.34(V+114)}{1-e^{(V+114)/11}},$$

$$\beta_h(V) = \frac{12.6}{1+e^{-(V+31.8)/13.4}}. \tag{4}$$

The voltages V in Eq. (4) are measured in millivolts.

B. Compartmental model for the axon

In order to describe the spatial and temporal evolution of the action potential along the heterogeneous axon, a spatially explicit model of the cable—the compartmental model—is needed. The main assumption of the compartmental model is that small pieces of an axon can be treated approximately as isopotential elements [18]. If the continuous cable system is divided into sufficiently small compartments, it is reasonable to assume that each compartment is isopotential and spatially uniform in properties.

We show a chain of three cylindrical dendritic compartments in Fig. 1(a). The three compartments are sufficiently small to be considered isopotential, and the equivalent circuit of the three compartments is plotted in Fig. 1(b). We can express mathematically the compartment model of neurons as a set of ordinary differential equations. Each equation is derived from Kirchhoff's current law. In the jth compartment, the net current i_{m_j} through the membrane equals the longitudinal current that enters the compartment minus the longitudinal current that leaves the compartment. Then the membrane current through the jth compartment is

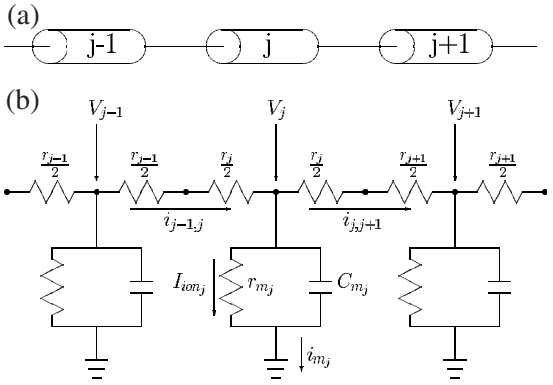

FIG. 1. (a) A chain of three cylindrical segments that are sufficiently short to be considered isopotential. (b) The equivalent circuit for the compartmental model of a chain of three successive small cylindrical segments of a passive dendritic membrane.

$$i_{m_j} = i_{j-1,j} - i_{j,j+1}, \tag{5}$$

where $i_{j-1,j}$ is the longitudinal current that flows from the $(j-1)$th to the jth compartments and $i_{j,j+1}$ is the longitudinal current that flows from the jth to the $(j+1)$th compartments.

For the jth compartment, the membrane current is the sum of the capacitative current and the net ionic current that flows through the transmembrane, and can be expressed as

$$i_{m_j} = c_{m_j}\frac{dV_j}{dt} + I_{\mathrm{ion}_j}, \tag{6}$$

where V_j is the membrane potential. The longitudinal current can be expressed as the voltage difference between two nearby compartments divided by the axial resistance between the two compartments. Combining Eq. (5) and Eq. (6), we can obtain the following equation:

$$c_{m_j}\frac{dV_j}{dt} + I_{\mathrm{ion}_j} = \frac{V_{j-1}-V_j}{r_{j-1,j}} - \frac{V_j - V_{j+1}}{r_{j,j+1}}, \tag{7}$$

where $r_{j,j+1}$ is the axial resistance between the jth and the $(j+1)$th compartments. If using d to denote the diameter of the axon, l_j to denote the length of the jth compartment, C_{m_j} to denote the specific membrane capacitance of the jth compartment, and ρ_j to denote the specific axoplasmic resistivity of the jth compartment, we can obtain the following relationship:

$$c_{m_j} = \pi d l_j C_{m_j},$$

$$r_{j-1,j} = \frac{r_{j-1}}{2} + \frac{r_j}{2} = \frac{2\rho_{j-1}l_{j-1} + 2\rho_j l_j}{\pi d^2},$$

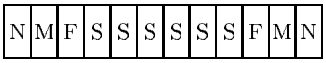

FIG. 2. The cable model with 10 internodal compartments. Each internodal section of the model consists of two myelin attachment compartments (MYSA, M in the figure), two paranode main compartments (FLUT, F in the figure), and six internodal compartments (STIN, S in the figure). N denotes the nodal compartment.

$$r_{j,j+1} = \frac{r_j}{2} + \frac{r_{j+1}}{2} = \frac{2\rho_j l_j + 2\rho_{j+1} l_{j+1}}{\pi d^2}, \quad (8)$$

where r_{j-1}, r_j, and r_{j+1} are resistances of the $(j-1)$th, jth, and $(j+1)$th compartments, respectively.

In this paper, I_{ion_j} can embody the leakage current, the sodium current, and the potassium current; then the term can be expressed as

$$I_{\text{ion}_j} = \pi d l_i [g_L(V - V_L) + g_K(V - V_K) + g_{Na}(V - V_{Na})]. \quad (9)$$

We consider 21 nodes of Ranvier connected by an axon. The 21 nodes are separated by 20 internodes. There are 10 compartments between two successive nodes [19,20]. The present model provides an explicit representation of the nodes of Ranvier, the myelin attachment compartments (MYSA), the paranode main compartments (FLUT), and the internode compartments (STIN). The geometric structure of the cable model is shown in Fig. 2. Sodium ion channels exist in a high density in the nodes of Ranvier, and a very low density in the internodal region. Potassium ion channels only exist in the paranode main compartment (FLUT) [5,21,22]. The nodes consist of a parallel combination of the nonlinear sodium ion channel conductance, the leakage conductance, and the membrane capacitance. The internodal region consists of a parallel combination of the nonlinear sodium ion channel conductance, nonlinear potassium ion channel conductance, the leakage conductance, and the membrane capacitance. The parameters of the cable model are listed in Table I.

TABLE I. Axonal parameters.

Axon diameter	2–10 μm
Axoplasmic resistivity	70 Ω cm
Na^+ reversal potential	50 mV
K^+ reversal potential	−90 mV
Leakage reversal potential	−80 mV
Nodal membrane capacitance	2 μF/cm^2
Na^+ conductance in nodal region	4000 mS/cm^2
Nodal leakage current conductance	8 mS/cm^2
Nodal length	1 μm
Internodal membrane capacitance	0.005 μF/cm^2
Internodal Na^+ conductance	0–10 mS/cm^2
Internodal leakage current conductance	0.1 mS/cm^2
MYSA, STIN K^+ conductance	0 mS/cm^2
FLUT K^+ conductance	80 mS/cm^2
MYSA length	3 μm
FLUT length	20 μm
STIN length	10–300 μm

III. RESULTS

A. Internodal sodium ion channels promoting action potential propagation

We inject external current in node 1 to evoke an action potential, and measure whether the action potential can propagate successfully from node 1 to node 21. We set the diameter of the axon as 5 μm, change the conductance of internodal sodium channels from 0 to 10 mS/cm^2, define 99% action potential successful propagation as stable action potential propagation, and measure the maximal internodal length guaranteeing stable action potential propagation. In the measuring process, we change the internodal length through varying the STIN compartment length. The maximal internodal length guaranteeing stable action potential propagation versus different internodal sodium ion channel conductance is plotted in Fig. 3.

From Fig. 3, we can find that internodal sodium ion channels promote action potential propagation dramatically. If without internodal sodium ion channels, the maximal internodal length guaranteeing stable action potential propagation is just 210 μm. If the internodal sodium ion channel conductance is 4 mS/cm^2, the maximal internodal length guaranteeing stable action potential propagation reaches to 1000 μm.

B. Optimal internodal sodium ion channel conductance for minimal metabolic energy consumption

Based on the data of Fig. 3, we calculate the average minimal sodium ion channel conductance guaranteeing stable action potential propagation. We add the sodium ion channel conductance of one node of Ranvier and that of one internode (two MYSA compartments, two FLUT compartments, and six STIN compartments) together, divide the total area of one node of Ranvier and one internode, and then get the average minimal sodium ion channel conductance guaranteeing stable action potential propagation. We plot the av-

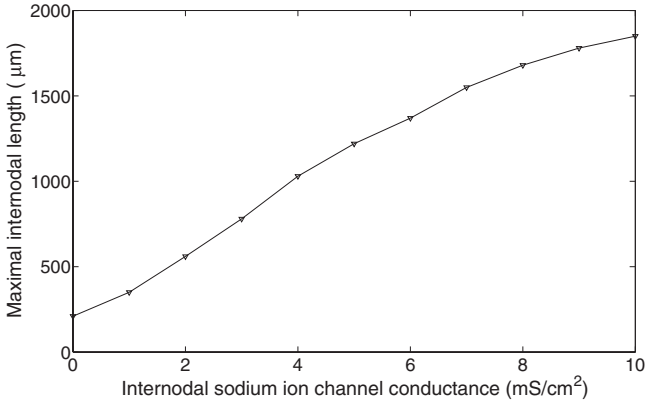

FIG. 3. The maximal internodal length guaranteeing stable action potential propagation versus different internodal sodium ion channel conductance.

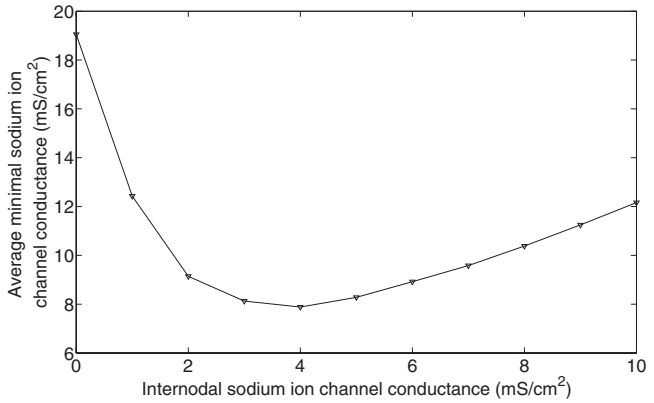

FIG. 4. The average minimal sodium ion channel conductance guaranteeing stable action potential propagation versus different internodal sodium ion channel conductance.

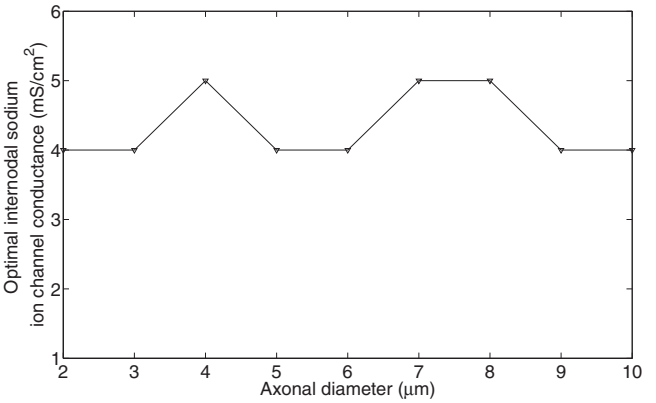

FIG. 5. The optimal internodal sodium ion channel conductance for minimal metabolic energy consumption versus different axonal diameters.

erage minimal sodium ion channel conductance guaranteeing stable action potential propagation versus different internodal sodium ion channel conductance in Fig. 4.

From Fig. 4, we find when the internodal sodium ion channel conductance is 4 mS/cm^2, the average sodium ion channel conductance guaranteeing stable action potential is minimal. Because the pumping action of ion channels will consume a large quality of energy, and 50% energy in human brains is consumed by the pumping action of sodium and potassium ion channels [10–15], internodal sodium ion channels with low conductance (4 mS/cm^2) can optimize metabolic activities and save metabolic energy up to 50%. If without internodal sodium ion channels, the maximal internodal length guaranteeing stable action potential propagation is very short, so the average minimal sodium ion channel conductance is high due to the very high sodium ion channel conductance of the nodes of Ranvier. As increasing the conductance of the internodal sodium ion channels gradually, the maximal internodal length guaranteeing stable action potential propagation will enlarge dramatically, and then the average minimal sodium ion channel conductance will decrease. After reaching a specific minimal value, the average minimal sodium ion channel conductance will increase due to increasing internodal sodium ion channel conductance. So there exists a minimal value for the average minimal sodium ion channel conductance guaranteeing stable action potential propagation. We further calculate the optimal internodal sodium ion channel conductance for minimal metabolic energy consumption versus different axonal diameters, and demonstrate the result in Fig. 5. From Fig. 5, we can find that the optimal internodal sodium ion channel conductance is almost constant (4–5 mS/cm^2). Because we calculate the maximal internodal length guaranteeing stable action potential propagation with discrete internodal sodium ion channel conductance, the optimal internodal sodium ion channel conductance for minimal metabolic energy consumption versus different axonal diameters is also discrete.

C. Internodal sodium ion channels speeding up action potential propagation

In this section, we investigate the function of internodal sodium ion channels increasing action potential propagation. We set the axonal diameter as 5 μm. The propagation speed of action potential versus different internodal sodium ion channel conductance is plotted in Fig. 6. From Fig. 6, we can find that internodal sodium channels can speed up the propagation speed of action potentials up to 30%.

IV. CONCLUSION

Although sodium ion channels clustered at the nodes of Ranvier provide the physiological basis for saltatory conduction, sodium ion channels cannot be excluded totally from internode. The function of internodal sodium ion channels has been neglected for a long time; however, experimental and theoretical results [7,9] show that internodal sodium ion channels with low density can promote action potential propagation. In this paper, based on HH equations and the compartmental model, we investigate the function of internodal sodium ion channels. Our research results show that internodal sodium ion channels can promote action potential propagation, enlarge the maximal internodal length guaranteeing stable action potential propagation, and increase propagation speed of action potentials up to 30%. If without internodal sodium ion channels, the maximal internodal length guaranteeing stable action potential propagation is as

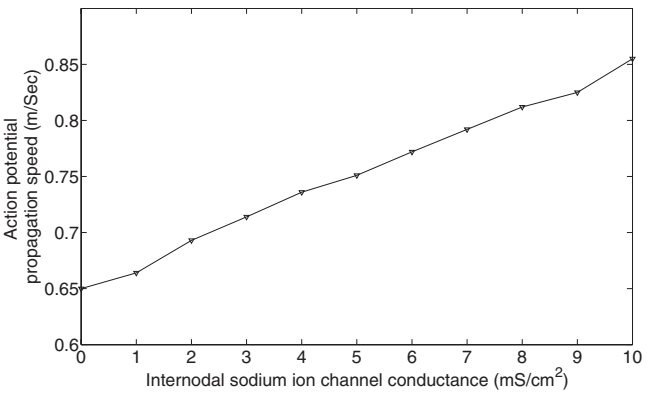

FIG. 6. The propagation speed of action potential versus internodal sodium ion channel conductance.

small as 200 μm; however, the maximal length is enlarged to 1000 μm if the internodal sodium ion channel conductance is 4 mS/cm^2. We calculate the average minimal sodium ion channel conductance guaranteeing stable action potential propagation, and find when the internodal sodium ion channel conductance is 4–5 mS/cm^2, the average sodium ion channel conductance guaranteeing stable action potentials is minimal. If without internodal sodium ion channels, the maximal internodal length guaranteeing stable action potential propagation is very short, so the average minimal sodium ion channel conductance is high due to the very high sodium ion channel conductance of the nodes of Ranvier. As increasing the conductance of the internodal sodium ion channels gradually, the maximal internodal length guaranteeing stable action potential propagation will enlarge dramatically, and then the average minimal sodium ion channel conductance will decrease. After reaching a specific minimal value, the average minimal sodium ion channel conductance will increase due to increasing internodal sodium ion channel conductance. So there exists a minimal value for the average minimal sodium ion channel conductance guaranteeing stable action potential propagation. Because the pumping action of ion channels will consume a large quantity of energy, and 50% energy in human brains is consumed by the pumping action of sodium and potassium ion channels [10–15], internodal sodium ion channels with low conductance (4–5 mS/cm^2) can optimize metabolic activities and save metabolic energy up to 50%. In a real myelinated axon, the density of internodal sodium ion channels is approximately 10/μm^2 [2–8]. Due to the myelin sheath, the activation of internodal sodium ion channels will be reduced by 80% [1,16], so the active conductance of internodal sodium ion channels is approximately 4 mS/cm^2 (conductance of each sodium ion channel is 20 pS), which accords with the optimal internodal sodium ion channel conductance we get in this paper. So the real myelinated axon has the optimal sodium ion channel distribution to guarantee the minimal metabolic energy consumption due to sodium ion channels.

ACKNOWLEDGMENTS

This work was supported by the Scientific Research Fund of Hunan Provincial Education Department (07B075), the Xiangtan University Fund of Interactive Projects (061ND09), and the Xiangtan University Fund of Dr. Shangyou Zeng's initial scientific research.

[1] B. Hille, *Ion Channels of Excitable Membranes* (Sinauer Associates, Inc., Sunderland, MA, 2001).
[2] P. Shrager, J. Physiol. (London) **392**, 587 (1987).
[3] P. Shrager, J. Physiol. (London) **404**, 695 (1988).
[4] P. Shrager, Brain Res. **483**, 149 (1989).
[5] S. Y. Chiu and J. M. Ritchie, J. Physiol. (London) **313**, 415 (1981).
[6] S. G. Waxman and J. M. Ritchie, Science **228**, 1502 (1985).
[7] S. G. Waxman, J. A. Black, J. D. Kocsis, and J. M. Ritchie, Proc. Natl. Acad. Sci. U.S.A. **86**, 1406 (1989).
[8] J. M. Ritchie, J. A. Black, S. G. Waxman, and K. J. Angelides, Proc. Natl. Acad. Sci. U.S.A. **87**, 9290 (1990).
[9] A. G. Dimitrov, J. Theor. Biol. **235**, 451 (2005).
[10] S. Takahashi, B. F. Driscoll, M. J. Law, and L. Sokoloff, Proc. Natl. Acad. Sci. U.S.A. **92**, 4616 (1995).
[11] T. A. Churchill and B. J. Fuller, Transplantation **59**, 904 (1995).
[12] R. A. Edwards, P. L. Lutz, and D. G. Baden, Am. J. Physiol. Regulatory Integrative Comp. Physiol. **257**, 1354 (1989).
[13] M. Erecinska, F. Dagani, D. Nelson, J. Deas, and I. A. Silver, J. Neurosci. **11**, 2410 (1991).
[14] F. Dagani, R. Ferrari, and L. Canevari, Brain Res. **530**, 261 (1990).
[15] S. S. Kety, *Metabolism of the Nervous System* (Pergamon, London, 1957).
[16] C. Koch, *Biophysics of Computation: Information Processing in Single Neurons* (Oxford University Press, New York, 1999).
[17] A. L. Hodgkin and A. F. Huxley, J. Physiol. (London) **117**, 500 (1952).
[18] I. Segev and R. E. Burke, *Methods in Neuronal Modeling: From Ions to Networks* (MIT Press, Cambridge, MA, London, England, 1998).
[19] C. C. Mcintype, A. G. Richardson, and W. M. Grill, J. Neurophysiol. **87**, 995 (2002).
[20] S. Zeng and P. Jung, Phys. Rev. E **71**, 011910 (2005).
[21] S. Y. Chiu, J. M. Ritchie, R. B. Rogart, and D. Stagg, J. Physiol. (London) **292**, 149 (1979).
[22] H. Wang, D. D. Kunkel, T. M. Martin, P. A. Schwartzkroin, and B. L. Tempel, Nature (London) **365**, 75 (1993).