In computational models, action potential propagation in ultrathin axons is resilient despite considerable intracellular Na^+ accumulation

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Function of neuronal circuitry requires precisely timed cellular interactions, which, in turn, depend on stable action potential (AP) propagation in myelinated and unmyelinated axons. The elegant computational analysis of Zang and Marder (1) in PNAS describes the complex relationship between the temporal and spatial dynamics of Na^+ influx, Na^+/K^+ pumping, intracellular Na^+ accumulation and resultant changes in electromotive force (emf), and the influence of these factors on the resilience of AP generation and propagation in axons of varying diameters. They note that, because of surface-to-volume considerations, high-frequency firing in ultrathin, nonmyelinated axons may result in a rapid

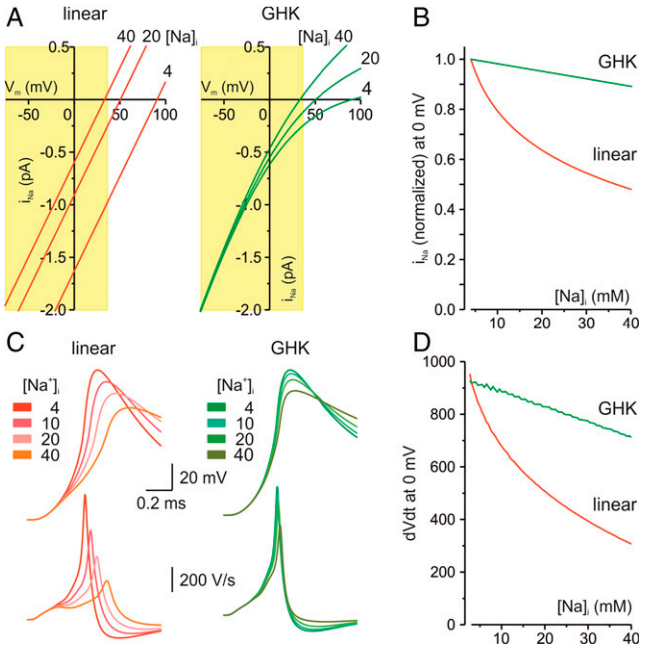

Fig. 1. Linear and GHK equation-based models differ in their predictions of the effect of changes in axoplasmic Na^+ concentration on Na^+ current and excitability. (*A*) Single Na^+ channel current–voltage relationship calculated using linear (red) and GHK current (green) equation for intracellular Na^+ concentrations of 4, 20, and 40 mmol/L. The yellow boxes indicate the functionally relevant range of voltages at which AP occurs. (*B*) Plot of the single Na^+ channel current amplitude at 0 mV as a function of $[Na^+]_i$, calculated using the linear conductance model (red) and GHK current (green) equation. (*C*) Axonal APs (*Top*) and the first derivative of AP voltage (*Bottom*) in the models using linear (red) and GHK current equation (green) at $[Na^+]_i$ of 4, 10, 20, and 40 mmol/L, as indicated. (*D*) Plot of the first derivative of AP voltage at 0 mV as a function of $[Na^+]_i$ in the models using linear (red) and GHK current (green) equation.

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rise in $[Na^+]_i$. What is not clear is the extent to which the consequent decrease in emf might impede continued generation and propagation of APs. This will largely depend on the altering relationship between Na^+ current and membrane voltage as the Na^+ equilibrium potential changes. The Hodgkin–Huxley formalism, $I = g_{max} * m^3 h (V - E)$, which is used by Zang and Marder (1) and is widely used in computational neuroscience, gives a linear estimation of the *I–V* relationship. However, as first shown by Goldman (2) and formalized in the Goldman–Hodgkin–Katz (GHK) current equation (3), the actual relationship is nonlinear when the transmembrane Na^+ concentration gradient is asymmetrical,

$$I = P_{max} * m^3 h * zF\frac{zFV}{RT}\left(\frac{[X]_{in} - [X]_{out}e^{-\frac{zFV}{RT}}}{1 - e^{-\frac{zFV}{RT}}}\right).$$

As shown in Fig. 1*A*, when a linear equation (Ohm's law) is used to compute the *I–V* relationship for an open Na^+ channel, changes in $[Na^+]_i$ greatly influence the current at all voltages. However, with the nonlinear, GHK current equation, even the effect of a 10-fold increase in $[Na^+]_i$ is minimal at voltages that are relevant for AP generation and propagation. Fig. 1*B* shows that the Na^+ current predicted by the linear expression is very sensitive to decreases in gradient as compared to the actual relationship revealed by GHK. Moreover, at the depolarized voltages where the effect of the decreased gradient is greater, Na^+ current during the AP is rapidly inactivating. Indeed, Fig. 1*C* shows that the amplitudes and rates of rise of APs generated by the linear model (using the same parameters as Zang and Marder) are very sensitive to intracellular Na^+ accumulation. However, when the Hodgkin–Huxley formalism is amended to use the GHK current equation, the effect on the AP is comparatively small. Finally, Fig. 1*D* shows dV/dt at 0 mV, as a function of $[Na^+]_i$.

In summary, application of the GHK current equation reveals that AP generation in extremely thin axons is very resilient, even under conditions of considerable intracellular Na^+ accumulation. Of course, increased $[Na^+]_i$ may affect excitability through various other mechanisms, such as electrogenic pump activation, Na^+-dependent ionic conductances, etc. However, we contend that, with regard to AP generation, this distinction between the predictions of the original Hodgkin–Huxley equations and the GHK current equation is particularly important because the limited experimental accessibility of ultrathin axons makes computational models extremely significant tools for understanding their function.

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