ELEC ENG 3BB3:

Cellular Bioelectricity

Notes for Lecture 12

Thursday, January 30, 2014

Temperature effects:

The temperature of an excitable cell affects:

1. the Nernst equilibrium potentials, e.g.,

$$E_{\mathrm{K}} = \frac{-R\mathbf{T}}{F} \ln \frac{[K]_{\mathrm{in}}}{[K]_{\mathrm{out}}}, \qquad (5.63)$$

2. and the rate constants (® and ¯) of the gating particles.

In the latter case, a temperature-dependent scaling constant Q (or Q_{10}) is utilized.

Temperature effects (cont.):

For example, the rate constants for the HH model were obtained at a temperature of 6.3°C. In order to correctly scale the rate constants for other temperatures T (in units of °C), the Q value is calculated according to:

$$Q = 3^P, \tag{5.64}$$

where:

$$P = \frac{T - 6.3}{10}. \tag{5.65}$$

Temperature effects (cont.):

The differential equations describing the gating particle kinetics then become:

$$\frac{\mathrm{d}n}{\mathrm{d}t} = Q\alpha_n(1-n) - Q\beta_n n, \qquad (5.66)$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = Q\alpha_m(1-m) - Q\beta_m m, \qquad (5.67)$$

$$\frac{\mathrm{d}h}{\mathrm{d}t} = Q\alpha_h(1-h) - Q\beta_h h. \qquad (5.68)$$

Active transport:

When the membrane is at rest, there is a steady influx of sodium and a steady efflux of potassium.

During an action potential these fluxes grow very large (see the sodium and potassium currents in Fig. 5.16 of Plonsey and Barr).

Without the action of ion pumps and exchangers, the intra- and extra-cellular concentrations would become identical over time, such that a *Donnan equilibrium* is reached, i.e., the Nernst equilibrium potentials are identical for all ion species. Note that it is impossible to generate action potentials when at a Donnan equilibrium.

Active transport (cont.):

In an experiment by Hodgkin and Keynes, efflux of radioactively-labelled sodium was linear on a log-linear scale. This indicates a constant pump rate, i.e., the efflux is proportional to the intracellular concentration [$^{24}Na^{+}$]:

$$-\frac{\mathrm{d}\left[^{24}\mathrm{Na}^{+}\right]_i}{\mathrm{d}t} = k\left[^{24}\mathrm{Na}^{+}\right]_i \qquad (5.70)$$

$$\Rightarrow \left[^{24}\mathrm{Na}^{+}\right]_i = A\exp\left(-kt\right). \qquad (5.71)$$

Application of the metabolic inhibitor DNP greatly reduced sodium efflux, indicating inhibition of an active sodium pump.

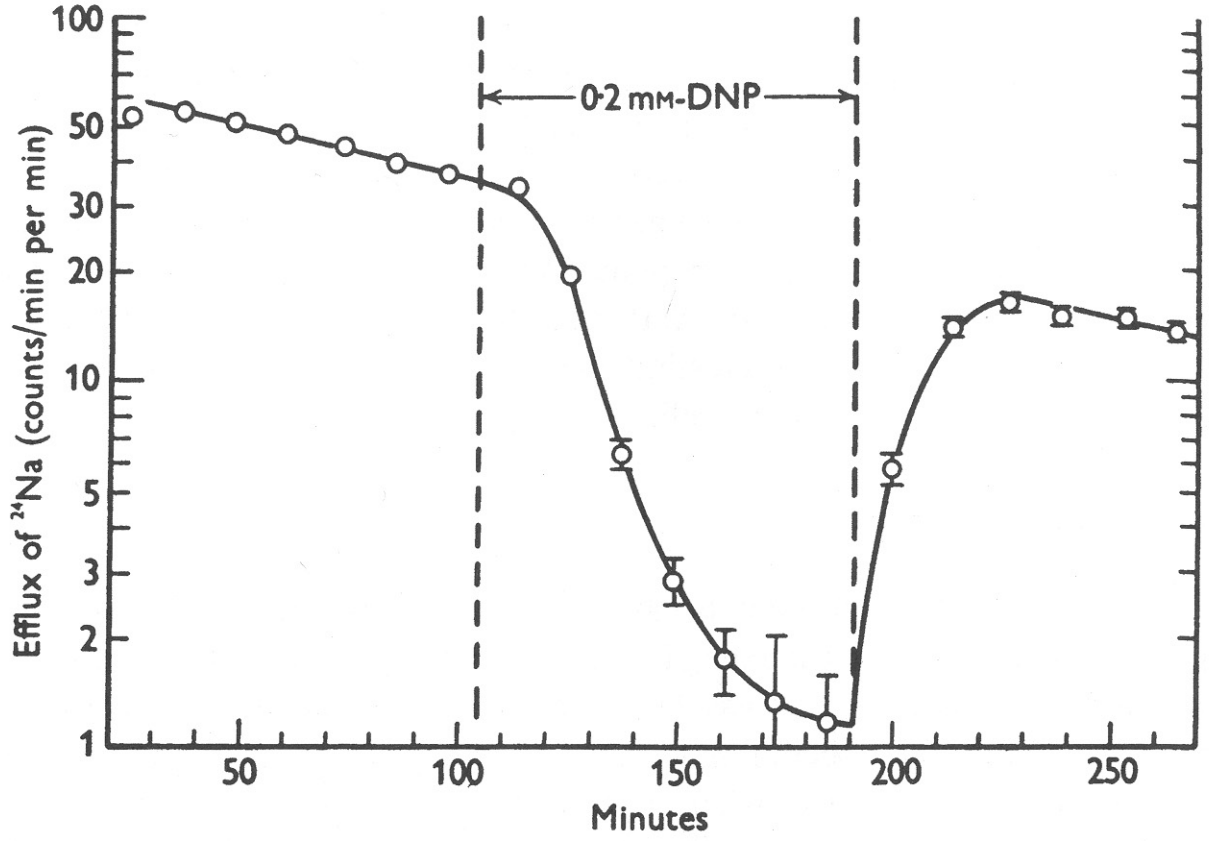

Figure 5.20. The effect of the metabolic inhibitor 2:4-dinitrophenol (DNP) on the efflux of radioactive sodium from a *Sepia* giant axon. From Hodgkin AL, Keynes RD. 1955. Active transport of cations in giant axons from *Sepia* and *Loligo*. *J Physiol* **128**:28–60.

Pump stoichiometry:

The sodium pump stoichiometry is:

$$\mathrm{ATP} + x\,[\mathrm{Na}]_i + y\,[\mathrm{K}]_o \longrightarrow$$
$$\mathrm{ADP} + \mathrm{P}_i + x\,[\mathrm{Na}]_o + y\,[\mathrm{K}]_i\,, \quad (5.72)$$

where the best fit of the experimental data is obtained with x = 3 and y = 2.

That is, one mole of ATP is reduced to ADP + P_i to drive the process of three moles of sodium ions being pumped out and two moles of potassium being pumped in) A net efflux of one mole of cations, i.e., a positive transmembrane current I_p.

Including pump in steady-state model:

The total steady-state transmembrane current is now:

$$I_m = I_{\mathsf{K}} + I_{\mathsf{Na}} + I_{\mathsf{Cl}} + I_p = 0, \qquad (5.73)$$

and Eqn. (3.30) becomes:

$$g_{\mathsf{K}}\,(V_m - E_{\mathsf{K}}) + g_{\mathsf{Na}}\,(V_m - E_{\mathsf{Na}}) + g_{\mathsf{Cl}}\,(V_m - E_{\mathsf{Cl}}) = -I_p, \qquad (5.74)$$

and Eqn. (3.31) becomes:

$$V_{\mathsf{rest}} = \frac{g_{\mathsf{K}}E_{\mathsf{K}} + g_{\mathsf{Na}}E_{\mathsf{Na}} + g_{\mathsf{Cl}}E_{\mathsf{Cl}} - I_p}{g_{\mathsf{K}} + g_{\mathsf{Na}} + g_{\mathsf{Cl}}}. \qquad (5.75)$$

Calcium channels and "other" membrane models:

The Hodgkin–Huxley equations only incorporate sodium and potassium channels that have linear conductances when open.

However:

- some excitable cells have other significant ionic channels, especially calcium channels, and
- some channels exhibit non-linear conductances when open.

Frankenhaeuser-Huxley equations:

The *Frankenhaeuser–Huxley* (F–H) model of the vertebrate node of Ranvier incorporates non-linear instantaneous conductances. For example, the F–H potassium channel has the following current-voltage relationship based on the GHK current equation (5.90):

$$I_{\mathrm{K}} = P_{\mathrm{K}} \frac{V_m^2 F^2}{RT} \left(\frac{[\mathrm{K}]_o - [\mathrm{K}]_i \, \mathrm{e}^{V_m F/RT}}{1 - \mathrm{e}^{V_m F/RT}} \right), \quad (12.27)$$

where the potassium permeability is:

$$P_{\mathrm{K}} = \bar{P}_{\mathrm{K}} n^2. \quad (12.28)$$

Frankenhaeuser-Huxley equations (cont.):

The potassium activation dynamics described by the activation particle n are identical to the HH equations, and the rate constants are:

$$\alpha_n = 0.02\,(v_m - 35)\left(1 - e^{\frac{35 - v_m}{10}}\right)^{-1} \qquad (12.30)$$

$$\beta_n = 0.05\,(10 - v_m)\left(1 - e^{\frac{v_m - 10}{10}}\right)^{-1} \qquad (12.31)$$

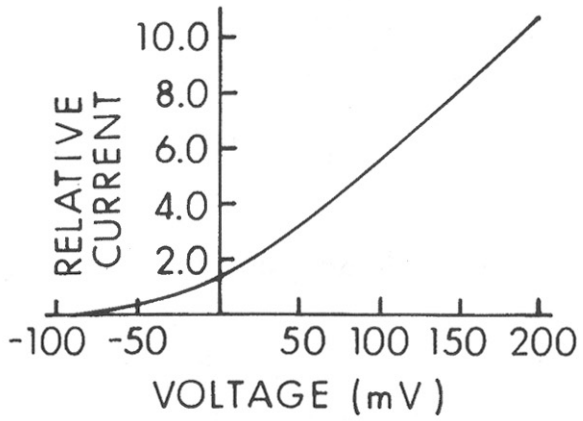

Figure 12.27. *I–V* Curve for the Potassium Channel as described by the GHK Current Equation. Parameter values are given in (12.32).

Calcium currents:

Macroscopic voltage-clamp data for a calcium channel:

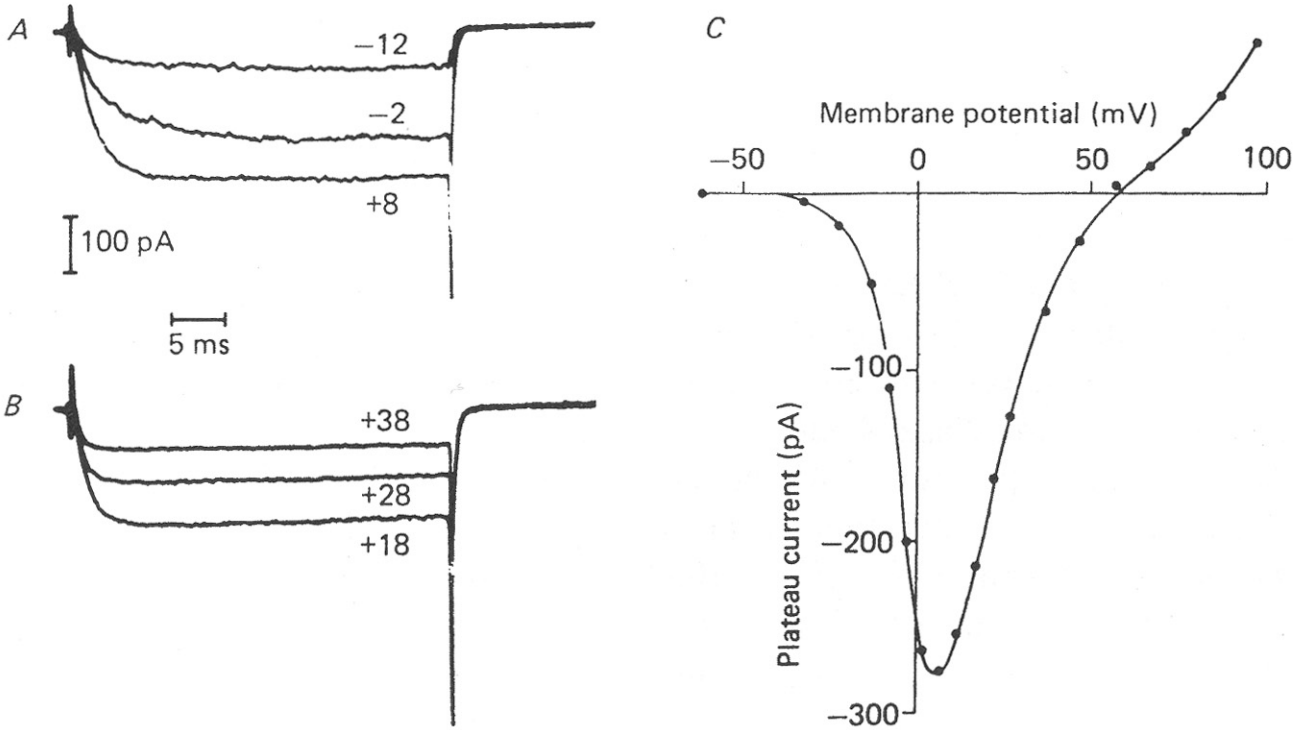

Figure 5.18. Current–Voltage Relations for plateau current amplitudes measured in bovine chromaffin cells. The cells contain CsCl, TEA, and EGTA and are bathed in a solution containing TTX and 5mM Ca. (These steps inhibit the otherwise overwhelming sodium and potassium currents.) From Fenwick EM, Marty A, Neher E. 1982. Sodium and calcium channels in bovine chromaffin cells. *J Physiol* **331**:599–635.

Calcium currents (cont.):

The following current-voltage relationship explains the macroscopic behaviour of the calcium channel shown in the previous slide:

$$I_{\mathrm{Ca}} = 4\frac{P_{\mathrm{Ca}} V_m F^2}{RT}\left(\frac{[\mathrm{Ca}]_o - [\mathrm{Ca}]_i\, \mathrm{e}^{2V_m F/RT}}{1 - \mathrm{e}^{2V_m F/RT}}\right). \quad (5.69)$$

This channel exhibits very strong inward rectification for calcium. However, this channel is also slightly permeable to potassium, which somewhat reduces the rectification and greatly reduces the reversal potential of the channel.

Calcium currents (cont.):

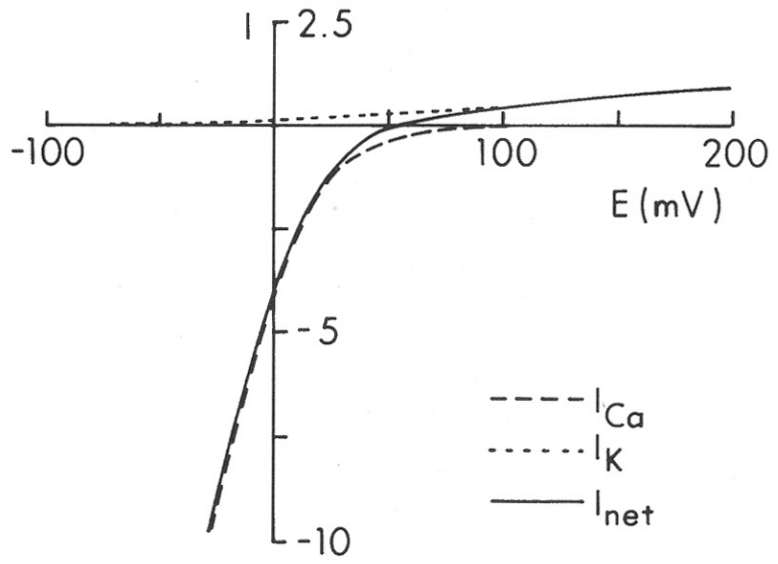

Figure 5.19. Theoretical *I–V* calcium Curve, as obtained from the GHK Eq. (5.69). The dashed line denotes the calculated values assuming $[\mathrm{Ca}]_i = 100$ nM and $[\mathrm{Ca}]_o = 2$ nM. Also plotted is the potassium current through the calcium channel based on (5.90), assuming $[\mathrm{K}]_i = 100$ nM, $[\mathrm{K}]_o = 2$ nM, and $P_{\mathrm{Ca}}/P_{\mathrm{K}} = 1000$. The solid curve is the total current. From Hille B. 1992. *Ionic currents*. Sunderland, MA: Sinauer Associates.