Neurobiology – resting potential and chloride channels

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- **Ionic concentrations** are determined and maintained by the activity of ionic pumps, including the Na^+–K^+ ATPase (pumping 3 Na^+ out and 2 K^+ in), the K^+/Cl^- cotransporter (using the K^+ gradient to extrude Cl^-), the active Ca^+ pump (extruding Ca^+ and using ATP) and the Na^+/Ca^{2+} exchanger (using the Na^+ gradient to extrude Ca^+, 3 Na^+ in to 1 Ca^{2+} out). Action potentials involve the transfer of too few ions to affect the ionic concentration significantly (a drop in the ocean) so we can ignore their effects.
- **Actual ionic concentrations** in mammalian neurons:

Ion	Internal concentration	External concentration	Valence (z)	Equilibrium potential
Na^+	15 mM	150 mM	+1	+62 mV
K^+	150 mM	5.5 mM	+1	–89 mV
Cl^-	9 mM	125 mM	–1	–71 mV
Ca^{2+}	10^{-4} mM	1 mM	+2	+124 mV

- **Equilibrium potential** for each ion is determined solely by the concentration gradient and valence, by the Nernst equation: $E = (RT/zF) \ln(conc_{out}/conc_{in})$. R is the gas constant (8.314 J deg^{-1} mol^{-1}); T is the absolute temperature (37°C = 310 K); z is the valence for the ion; F is Faraday's constant (96500 C mol^{-1}); E is in volts.
- **Remember** that an ion will not flow across a membrane if the potential gradient equals that ion's equilibrium potential (by definition).
- **The resting potential** is determined by the equilibrium potentials for every ion to which the membrane is permeable, weighted by the permeability (p), via th Goldman equation: $E = (RT/F) \ln[(p_K[K^+]_{out} + p_{Na}[Na^+]_{out} + p_{Cl}[Cl^-]_{in}) / (p_K[K^+]_{in} + p_{Na}[Na^+]_{in} + p_{Cl}[Cl^-]_{out})]$.
- **Neurons are permeable predominantly to K^+,** so the membrane potential at rest V_R at rest is close to E_K. However, there is a small permeability to Na^+ and to Cl^- at rest, so $V_R > E_K$.

- **Electrogenic effects of the pumps.** The Na^+/K^+ pump is electrogenic as it extrudes 3 Na^+ for each 2 K^+ that come in. Therefore steady state is reached when there is a net inward current through the ion channels that exactly matches the active outward pump current. This pump makes the resting potential slightly more negative (because the current is outwards) than you'd expect from pure passive diffusion.
- **Chloride in the steady state.** In neurons with no Cl^- pump, the chloride ions move (because the membrane is slightly permeable to them) until $E_{Cl} = V_R$. That is, the other ions set the resting potential and the chloride concentrations change until the new Nernst potential for chloride is the same as that resting potential. In neurons that have a Cl^- pump, chloride is pumped outwards, so $[Cl^-]_o/[Cl^-]_i$ increases, so E_{Cl} decreases *below* V_R.[1]

- While muscle cells have a resting potential of about –90 mV, **most neurons have a resting potential of about –65 mV** (range –60 to –70 mV).
- The **threshold for AP intiation is about –55 mV.**

- **The EPSP reversal potential** (E_{EPSP}) is about 0 mV (because glutamate non-NMDA receptors gate Na^+ and K^+). The size of the EPSP depends upon the current it injects: $V_{EPSP} = I_{EPSP} / g_m$ where g_m is the membrane conductance. It also depends upon how far it is from its reversal potential, obviously, because when it's at the reversal potential no current will flow: $I_{EPSP} = g_{EPSP} \times (V_m - E_{EPSP})$.
- **The IPSP reversal potential** is about –70 mV (because they're chloride channels). In neurons where $V_R = E_{Cl}$, therefore, opening chloride channels does not change the membrane potential. If V_m was below E_{IPSP}, the IPSP would be *depolarizing but still inhibitory* (mechanisms 2 & 3 below).
- **Mechanisms of inhibition:** (1) The IPSP can hyperpolarize the membrane, taking it away from threshold. (2) Opening chloride channels holds the membrane potential at E_{Cl}, which is below the threshold. (3) Opening chloride channels increases g_m, reducing V_{EPSP}. This is *short-circuiting* or *shunting*. Another way to look at it is to see that when more excitatory channels open, causing an influx of Na^+, this increases the driving force for Cl^- to enter, which is an outward current that opposes the Na^+ inward current. The bigger the sodium current, the bigger the opposing chloride current.

- **Confusion.** The GABA channel's reversal potential is apparently –60 mV; one would expect –71 mV. If this is true (suggesting it lets something other than Cl^- through) then one would realistically expect to see depolarizing IPSPs in real neurons (from –65 to –60 mV, for example). Is there any other way, other than by artificial techniques, you might see $V_R < E_{Cl}$? Certainly possible in the short term; for example if $[K^+]_o/[K^+]_i$ decreased then V_R would be lower than E_{Cl} until the chloride redistributed itself.

Sources

Ionic concentrations: this year's NST 1B handout from H.R. Matthews.

Neuron resting potentials and thresholds: Kandel, Schwartz & Jessel (1991), *Principles of Neural Science*, pp. 82 & 156. Neural versus glial resting permeabilities, p85. IPSP reversal potential, p161. GABA channel reversal potential, p163. Electrogenic pump effects, p88.

More maths and discussion of KCl transients: Aidley (1989), *The physiology of excitable cells*, pp26–29. More on GABA and other channels, pp206–7.

[1] This contradicts what I told you. Sorry.