Lecture 2. The nervous system, the neuron; genesis of the membrane potential

I. The nervous system (sensory detection, information processing, behavior)
   A. Central nervous system (CNS) (neurons and glia cells)
      1. Brain
      2. Spinal cord
   B. Peripheral nervous system (PNS)
      1. Afferent - signals from tissues and organs to the CNS
      2. Efferent - signals to effector cells and ganglia
         a. Somatic NS - to skeletal muscles; voluntary
         b. Autonomic NS - to smooth and cardiac muscles and glands, involuntary.
            Sympathetic, parasympathetic and enteric

II. Neurons (nerve cells) - general structure (Fig. 1B)

A. Cell body (soma) - Contains nucleus and most other organelles
B. Dendrites - Receive incoming signals via synapses with other neurons - main organelles are microfilaments and microtubules
   Sensory neurons such as photoreceptors in the eye, or mechanoreceptors in the skin don't have dendrites with neurotransmitter receptors, they have receptors for physical stimuli in specialized regions (e.g. the outer segments in photoreceptors transduce light to neural signals).
C. Axon - carries outgoing neural signals, and also transport proteins and polypeptides made in the cell body to terminal (orthograde), and neurotrophins such as nerve growth factor from
terminal where they are taken up, to cell body (retrograde). The axon generally does not have rough ER, Golgi bodies, or ribosomes – however, it contains smooth ER and prominent microtubules involved in axonal transport. Transport can be as fast as 400 mm/day.

III. Genesis of membrane potentials

A. The membrane potential is the voltage difference that exists across the plasma membrane of a cell (see Fig. 2). When the cell is at rest, and at the resting (membrane) potential, the inside of the cell is always negatively charged with respect to the outside (-5 to -90 mV). Membrane potentials can be measured directly by placing very fine-tipped “sharp” recording electrodes inside cells and referencing to a point outside the cell, or by using a patch pipette sealed to a membrane and referenced to a point outside the cell.

B. Changes in the membrane potential (See Fig. 2c above)

Changes in the membrane potential are named in reference to the resting potential.

1. Hyperpolarizing - more negative than the resting potential
2. Depolarizing - more positive than the resting potential.
3. Repolarizing - a change toward the resting potential, from more positive or more negative.

C. The resting potential is determined by:

1. The difference in ion concentrations [ion] of the intra- and extracellular fluid. Recall that [K⁺] is very high inside the cell, [Na⁺] is high outside the cell, due to the Na⁺-K⁺ ATPase pump. This difference in intra- and extracellular ion concentrations can be used to determine the equilibrium potential, or diffusion potential, for each ion:

   a. The equilibrium potential for a given ion is the membrane potential for which the electrical force is equal and opposite to the concentration force. Thus the given ion is at electrochemical equilibrium.
b. The equilibrium potential in millivolts (mV) can be calculated with the Nernst equation:

$$E_{\text{ion}} \text{ (mV)} = \frac{-60 \text{ (mV)} \times \log ([\text{ion conc}]_{\text{in}}/ [\text{ion conc}]_{\text{out}}) (2.3RT/zF)}{1 + 60 (+ \text{ ion})^+ + 60 (- \text{ ion})^-} = \frac{-60 \log (120/4)}{1 + 60 (+ \text{ ion})^+ + 60 (- \text{ ion})^-} = -90 \text{ mV}$$

$$E_{\text{Na}^+} = \frac{-60 \log (14/140)}{1 + 60 (+ \text{ ion})^+ + 60 (- \text{ ion})^-} = +60 \text{ mV} \ (\text{often reported as } -65)$$

$$E_{\text{Cl}^-} = \frac{+60 \log (10/105)}{1 + 60 (+ \text{ ion})^+ + 60 (- \text{ ion})^-} = -61.2 \text{ mV}$$

-60 is a constant that depends on the gas constant, the Faraday number (F), the valence (z), and the absolute temperature (T). At room temperature the constant is 58; at body-temperature for warm-blooded animals, it is 61 (about 60).

Note that if the concentrations were equal inside and outside the cell for an ion, then $E_{\text{ion}}$ would be zero (the log of 1 = 0).

2. The second important factor for the resting potential is the permeability (p) or conductance (g) of the plasma membrane to the different ions. If channels are open so that the ion can flow down the chemical concentration gradient created by a pump, then the membrane potential can approach the $E_{\text{ion}}$. For the neuron at rest, its membrane potential is generally much nearer the $E_{\text{K}^+}$ than $E_{\text{Na}^+}$ because more $K^+$ channels are open and $K^+$ can flow out of the cell and cause the cell to approach $E_{\text{K}^+}$ which is -90 mV (calculated from Table 1). $E_{\text{Na}^+}$ is +60 mV. If the conductance for Na$^+$ were to increase, Na$^+$ would flow into the cell and the inside of the cell would become more positive. Thus, altering the relative conductances will move the membrane potential between the limits set by $E_{\text{Na}^+}$ and $E_{\text{K}^+}$. This relationship is described by the:

**chord conductance equation**

$$E_m = \frac{g_{\text{K}^+} E_{\text{K}^+} + g_{\text{Na}^+} E_{\text{Na}^+} + g_{\text{Cl}^-} E_{\text{Cl}^-}}{g_{\text{Na}^+} + g_{\text{K}^+} + g_{\text{Cl}^-}}$$
3. The Goldman/Hodgkin/Katz equation:

$$E_{m,K_x Na^{+}_{1-x} Cl^{-}} = \frac{RT}{F} \ln \left( \frac{P_{Na^{+}} [Na^{+}]_{out} + P_{K^{+}} [K^{+}]_{out} + P_{Cl^{-}} [Cl^{-}]_{in}}{P_{Na^{+}} [Na^{+}]_{in} + P_{K^{+}} [K^{+}]_{in} + P_{Cl^{-}} [Cl^{-}]_{out}} \right)$$

The equation predicts the membrane potential based on several ions, and their concentrations inside and outside of the cell. The equation says that when a membrane is permeable to several different ions, the resting membrane potential depends on permeability, charge, and concentrations of all of the ions. So, the resting potential is not at the equilibrium potential for any specific ion, but can be in a steady state, a standoff position between equilibrium potentials of the different ions. Note the effect of valence.

To sum up so far, the resting potential is mainly influenced by these 2 factors.

a. The difference in ion concentrations (due to the Na⁺-K⁺ ATPase pump)

b. Ion permeability: K⁺ conductance is 50 to 75 times more than Na⁺ conductance at rest, and this sets the resting membrane potential much nearer to $E_{K^+}$ than to $E_{Na^+}$

Two additional factors that contribute to the resting potential of the membrane:

c. The Na⁺-K⁺ ATPase pump contributes directly to the resting potential. Since the pump sends three Na⁺ ions outside the cell for each 2 K⁺ ions that it brings in, there is a loss of one positive charge (+) from the cell. Thus the pump it is said to be electrogenic. It contributes about -4 mV to the resting potential of a muscle cell.

d. There are negatively charged proteins (anions) in the cell that cannot move through the cell membrane (causing the Donnan Effect – see below). They contribute to the osmotic pressure of the cell as well.

IV. Gibbs - Donnan Effect

Donnan (and Gibbs)

showed that in the presence of nondiffusible (impermeant) ions, such as negatively charged proteins inside cells, the diffusible ions distribute themselves so that at equilibrium the diffusible ions are at electrochemical equilibrium): their concentration ratios are equal. Theoretically, the KCl inside and outside a cell that contains nondiffusible anions is:

$$\frac{[K^+]_o}{[K^+]_i} = \frac{[Cl^-]_i}{[Cl^-]_o} \quad \text{Or} \quad [K^+]_o \times [Cl^-]_o = [K^+]_i \times [Cl^-]_i$$

Achieving the Donnan equilibrium creates an osmotic imbalance, with more particles on the side that has the impermanent anion (see Fig. 12 on next page). This could be dangerous for cells – they would swell due to osmosis if they had more particles in intracellular fluid than extracellular fluid.
In practice in neurons, the Na\(^{+}\)-K\(^{+}\) ATPase pump maintains a concentration gradient that keeps the osmotic imbalance caused by the Donnan "Equilibrium" from prevailing. The Donnan effect is quite important when we consider colloid osmotic pressure caused by proteins in blood vessels.

**Fig. 3**

Before the Donnan equilibrium has been established: Y\(^-\) is a large nondiffuable anion (protein). K\(^+\) and Cl\(^-\) can diffuse freely.

After the Donnan equilibrium has been established so that

\[
[K^+]_o \times [Cl^-]_o = [K^+]_i \times [Cl^-]_i
\]

Total positive and negative charges in each compartment are in balance, but there are more particles in compartment A.

*Pathophysiology note:* When the Na\(^{+}\)-K\(^{+}\) ATPase pump cannot operate properly and maintain the normal ionic gradient, due for example to lack of oxygen, cell injury will occur, partially because the cells swell. Lack of oxygen (hypoxia) in tissue can occur as a consequence of lack of blood flow (ischemia), perhaps due to a blocked blood vessel. The local tissue can die if circulation is not restored; the type of cell death that occurs is called **necrosis**. This is what happens in a heart attack (myocardial infarction, MI), and a stroke (brain attack), i.e. a cerebrovascular accident (CVA).