MEDICAL UNIVERSITY – PLEVEN
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LECTURE No13

RESTING MEMBRANE POTENTIAL

Generation of resting membrane potential. The Goldman and Thomas equations. Factors contributing to the resting potential

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Physiological significance of the transmembrane electrical potential difference :

- It influences the transport of a vast array of nutrients into and out of cells;
- It is a key driving force in the movement of salt (and therefore water) across cell membranes and between organ-based compartments;
- It is an essential element in the signaling processes associated with coordinated movements of cells and organisms;
- It is ultimately the basis of all cognitive processes.

How does this electrical gradient arise?

It is the consequence of two physiological parameters:

- 1) the presence of large gradients for K and Na across the plasma membrane;
- 2) the relative permeability of the membrane to those ions.

The gradients for K^+ and Na^+ are the product of the activity of Na-K-ATPase, a primary active ion pump that is ubiquitously expressed in the plasma membrane of all animal cells.

The pump maintains
the large outwardly directed K gradient, and
the large inwardly directed Na gradient, that are hallmarks of animal cells.

The second parameter, the relative permeability of the plasma membrane to K^+ and Na^+ reflects **the open versus closed status of ion-selective membrane channels.**

Cell membranes display different degrees of permeability to different ions due to the **inherent selectivity of specific ion channels.**

The combination of

1) ***transmembrane ion gradients*, and**
2) ***differential permeability to selected ions*, is the basis for generation of transmembrane potential difference.**

Consider the hypothetical situation of two solutions separated by a membrane selective to a single ion.

Side 1 (the "inside" of our hypothetical cell) contains 100 mM KCl and 10 mM NaCl.

Side 2 (the "outside") contains 100 mM NaCl and 10 mM KCl.

Hence, there is an "outwardly directed" K^+ gradient, and inwardly directed Na^+ gradient, and no transmembrane gradient for Cl^-.

Let this ideal membrane is permeable only to K^+.

Since the membrane is permeable only to K, the membrane potential is precisely defined by the K chemical gradient. Although intracellular ion concentrations generally do not change as a consequence of the downhill fluxes associated with transmembrane voltage changes, it is instructive to consider what would happen if the K gradient were to change. In fact, changes in the K gradient, typically the result of changes in $[K]_{out}$, are extremely important, both physiologically and clinically.

The rule of thumb: any manipulation that reduces K gradient (i.e., either decreasing $[K]_{in}$ or increasing $[K]_{out}$), will decrease E_{mK}. In other words, if there is less energy in the chemical gradient, it will take less energy in an electrical gradient to balance it.

Cytoplasmic and extracellular K^+, Na^+ , Cl^- concentrations

Ion	C_{intra}, mM	C_{extra} [mM]	E_m [mV]	P [cm/s]
K^+	135	4	-92	1×10^{-7}
Na^+	12	140	+64	1×10^{-9}
Cl^-	4	116	-88	1×10^{-8}

E_m - calculated Nernstian equilibrium potentials for each ion gradient
P - typical permeability values for neurons

These values are only hypothetical for a mammalian cell. The listed concentrations of Cl in the cytoplasm and extracellular fluid do not add up to the total concentration of K and Na. However, electroneutrality is maintained in each compartment through the combined contribution of a diverse array of additional charged solutes.

Biological membranes do not show "ideal" permselectivity. Real membranes have a finite permeability to all the major inorganic ions in body fluids.

For most cells, the only ions that can exert any significant influence on bioelectrical phenomena are the "big three": K^+, Na^+, and Cl^- (Ca^{2+} also contributes to bioelectric issues in a few tissues, including the heart).

The Nernst equation, which represents an idealized situation, can be modified to represent the more physiologically realistic case in which the membrane shows a finite permeability to these three major players.

The new equation is called the "Goldman-Hodgkin-Katz Constant Field equation";or the "Goldman equation".

$$E_m = -60 \log_{10} \frac{P_K[K]_{in} + P_{Na}[Na]_{in} + P_{Cl}[Cl]_{out}}{P_K[K]_{out} + P_{Na}[Na]_{out} + P_{Cl}[Cl]_{in}}$$

"Goldman equation"

The Nernst equation is lurking within the Goldman equation:

if the membrane were to become permeable only to K^+, i.e., if P_{Na} and P_{Cl} were zero, then the equation simplifies to the Nernstian condition for K.

The calculated Nernstian potential for K, Na, and Cl establish the "boundary conditions" for the electrical potential difference across the cell membrane;
the cell cannot be more negative than 92 mV or more positive than 64 mV because there are no relevant chemical gradients sufficiently large to produce larger voltage across the membrane.

At rest, the membrane permeability of most cells **is greatest for K**, due to the activity of several distinct populations of K channels constitutively active under normal resting conditions.

The relative contribution to the resting potential played by these channels varies with cell type.

In neurons relevant players include members of the family of inwardly rectifying K channels (KIR) and the K(2P) family of K "leak" channels.

The combination of an outwardly directed K gradient and a high resting permeability to K makes the interior of animal cells electrically negative with respect to the external solution.

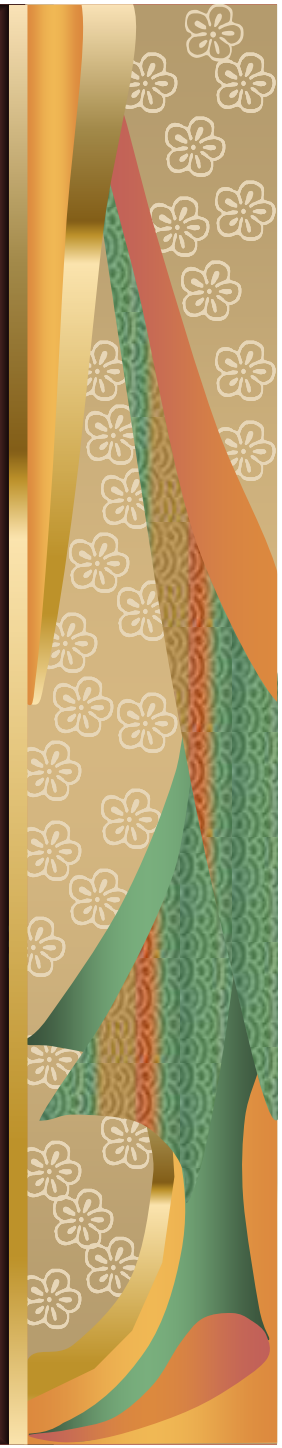
The finite permeability of the membrane to Na^+ (and to Cl) prevents the membrane potential from ever actually reaching the Nernstian K^+ potential. The extent to which each ion gradient influences the potential difference is defined by the permeability of the membrane to each ion (Goldman equation).

Even very large concentrations exert little influence if the associated *P* value is small.

If the membrane were suddenly to become permeable only to Na^+, the result would be a Nernstian potential for Na.

In summary: the combination of an outwardly directed K gradient (due to Na-K ATPase activity) and a high resting P_K makes the interior of animal cells electrically negative with respect to the extacellular space.

The $[K]_{out}$ is particularly susceptible to changes. In absolute terms it is comparatively "small" (4 mM) and increases in $[K]_{out}$ of only a few mM can have large effects on resting membrane potential. Such changes can occur as a consequence of, for e.g., crushing injuries that rapidly release into the blood stream large absolute amounts of K (from the K-rich cytoplasm in cells of the damaged tissue).



Failure of the Na-K ATPase during ischemia can result in local increases in $[K]_{out}$, a problem exacerbated by both the low starting K concentration and the low extracellular volume of "densely packed" tissues (e.g., in the heart or brain).

Alteration in membrane permeability to ions, can arise as a consequence of pathological defects in ion channel proteins (or "channelopathies").

Of particular relevance to the resting membrane potential are lesions in one or more subunits of the KIR channels.

Mutations in these channels is linked to persistent hyperinsulinemic hypoglycemia of infancy, and to several polygenic CNS diseases, including white matter disease, epilepsy and Parkinson's disease.

What about the effect of Cl^-? The resting potential is as close to E_{mCl} as it is to E_{mK}.

Why don't we conclude that Cl is the dominant ion in defining the resting membrane potential? The answer lies in the fact that the cell is spending its energy via Na-K-ATPase in establishing the gradients for K^+ and Na^+, not Cl^-.

The observed inwardly directed Cl^- gradient, with E_{mCl}= 89 mV, arises in mainly due to the simple passive distribution of Cl^- in response to the electrical gradient that is effectively defined by the outwardly directed K gradient.

1) The cell actively builds transmembrane gradients of K and Na;
2) The outward flux of K down its gradient that reflects the large P_K of the resting cell (relative to P_{Na}), shifts the potential difference toward the Nernstian potential for K;
3) Cl^-, which is high in the blood, moves into the cell in response to its chemical gradient;
4) But the inside negative potential established by K serves as a force to limit the buildup of Cl^-_i. This is the case even in skeletal muscle cells in which the channel-mediated permeability to Cl exceeds that for K.

The fact that the Nernstian Cl potential is not exactly equal to the resting PD means that there are one or more "active" transport processes that keep Cl away from an equilibrium distribution (secondary active Cl/HCO_3 exchange).

Whereas in neurons Cl is a minor player in the resting membrane potential, there are several situations in which P_{Cl} (due to the activity of Cl channels) is very important.

- An increase in P_{Cl} is an effective way to "stabilize" the resting membrane potential by opposing changes in PD that would otherwise be produced by fluxes of K or Na. Thus P_{Cl} is modulated to influence synaptic transmission.

- A decrease in P_{Cl} makes it easier for the PD to shift away from its resting value. Thus, in the disease myotonia congenita, the observed hyperexcitability of skeletal muscle cells results from a decreased P_{Cl} (arising from defects in the ClCN1 Cl channel).

Factors contributing to the resting potential:

A. Gibbs-Donnan Equilibrium contributes less than **-10 mV** to the resting membrane potential.

B. The electrogenic Na-K ATPase:

In vertebrate skeletal muscle and many vertebrate nerve cells the contribution of the electrogenic Na-K ATPase to the resting membrane potential is small, less than **5 mV** or so. In contrast, in smooth muscle and some neurons, the electrogenic pump may make a major contribution to the resting membrane potential.

C. Electrodiffusion of ions: Each permeable ion "strives" to bring the transmembrane electrical potential difference toward its equilibrium potential.