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Advan in Physiol Edu 28:139-142, 2004. ;

doi: 10.1152/advan.00029.2004

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REFRESHER COURSE | Cellular Homeostasis

Generation of resting membrane potential

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Received 2 July 2004; accepted in final form 13 September 2004

Wright, Stephen H. Generation of resting membrane potential. *Adv Physiol Educ* 28: 139–142, 2004; doi:10.1152/advan.00029.2004.—This brief review is intended to serve as a refresher on the ideas associated with teaching students the physiological basis of the resting membrane potential. The presentation is targeted toward first-year medical students, first-year graduate students, or senior undergraduates. The emphasis is on general concepts associated with generation of the electrical potential difference that exists across the plasma membrane of every animal cell. The intention is to provide students a general view of the quantitative relationship that exists between 1) transmembrane gradients for K^+ and Na^+ and 2) the relative channel-mediated permeability of the membrane to these ions.

Nernst equation; Goldman equation; electrical potential difference

IT WOULD BE DIFFICULT TO EXAGGERATE the physiological significance of the transmembrane electrical potential difference (PD). This gradient of electrical energy that exists across the plasma membrane of every cell in the body influences the transport of a vast array of nutrients into and out of cells, is a key driving force in the movement of salt (and therefore water) across cell membranes and between organ-based compartments, is an essential element in the signaling processes associated with coordinated movements of cells and organisms, and is ultimately the basis of all cognitive processes. For those reasons (and many more), it is critical that all students of physiology have a clear understanding of the basis of the *resting membrane potential* (so called to distinguish the steady-state electrical condition of all cells from the electrical transients that are the “action potentials” of excitable cells: i.e., neurons and muscle cells).¹

How, then, does this electrical gradient arise? It is the consequence of the influence of two physiological parameters: 1) the presence of large gradients for K^+ and Na^+ across the plasma membrane; and 2) the relative permeability of the membrane to those ions. The gradients for K^+ and Na^+ are the product of the activity of the $Na^+-K^+-ATPase$, a primary active ion pump that is ubiquitously expressed in the plasma membrane of (for all intents and purposes) all animal cells. This process develops and then maintains the large outwardly directed K^+ gradient, and the large inwardly directed Na^+ gradient, that are hallmarks of animal cells. For the purpose of this discussion, we will assume that the requisite gradients are

in place (acknowledging that the mechanism of ion transport is beyond the scope of this presentation).

The second parameter, the relative permeability of the plasma membrane to Na^+ and K^+ , reflects the open versus closed status of ion-selective membrane channels. Importantly, cell membranes display different degrees of permeability to different ions (i.e., “permselectivity”), owing 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 voltage differences. This idea can be developed by considering the hypothetical situation of two solutions separated by a membrane permselective to a single ionic species. 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. In other words, there is an “outwardly directed” K^+ gradient, and inwardly directed Na^+ gradient, and no transmembrane gradient for Cl^- . For the purpose of this discussion, this ideal permselective membrane is permeable only to K^+ .

Let the experiment begin! The outwardly directed K^+ gradient supports a net diffusive flux from inside to outside. As K^+ diffuses from the cell it leaves behind “residual” negative charge, in this case, its counter anion, Cl^- (recall that, in our hypothetical scenario, neither Cl^- nor Na^+ can cross the membrane). The resulting local imbalance of negative charge at the inside face of the membrane represents a force that can draw mobile positive charge at the external face of the membrane back into the cell; in this case, the only mobile ion capable of crossing the membrane is K^+ . Significantly, this electrical force can draw K^+ from the low chemical concentration found outside the cell into the higher $[K^+]$ inside the cell. As long as the *chemical force* of the outwardly directed K^+ chemical gradient is larger than the oppositely oriented *electrical force*, there will be a net efflux of K^+ from the cell. However, as more and more K^+ leaves, the residual negative charge within the cell, i.e., the attractive electrical force that

¹The PowerPoint lecture on the Generation of the Resting Potential, presented in the Cell Refresher Course at the 2003 Experimental Biology Meeting in Washington, DC, can be found at <http://www.the-aps.org/education/refresher/CellRefresherCourse.htm>.

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draws K^+ into the cell, gradually increases to a level that exactly balances the chemical force, resulting in an “equilibrium” condition. Whereas there may continue to be large *unidirectional* fluxes into and out of the cell, the *net* flux under this equilibrium condition is zero. The equation that describes this balance of electrical and chemical forces is called the *Nernst equation*:

$$V_K = - \frac{RT}{zF} \ln \frac{[K]_{in}}{[K]_{out}}$$

where V_K is the equilibrium electrical PD, which exactly opposes the chemical energy of the chemical gradient, the intracellular-to-extracellular K^+ concentration ratio ($[K]_{in}/[K]_{out}$). R is the gas constant with units of 8.31 J/(Kmol), T is absolute temperature in Kelvin ($37^\circ C = 310 K$), F is Faraday’s constant at 96,500 coulombs/mol, and z is the valance of the ion question; +1 for K^+ . It is instructive to insert the relevant values for R , T , F , and z , and to convert from the natural log to the common (base 10) log by multiplying by 2.303. The Nernst equation then becomes (at $37^\circ C$)

$$V_K = \frac{-0.0615 \text{ Volts}}{z} \log_{10} \frac{[K]_{in}}{[K]_{out}}$$

It is convenient to simplify this equation to an adequate (and useful) approximation

$$V_K \cong -60 \text{ mV} \log_{10} \frac{[K]_{in}}{[K]_{out}}$$

When we consider the K^+ gradient of our example (100 mM inside, 10 mM outside) we find that this outwardly directed 10-fold gradient of a monovalent cation is balanced by a 60 mV electrical PD (in this case, inside negative). This introduces an additional valuable concept evident in another term synonymous with equilibrium potential, i.e., the reversal potential. In our example, the direction of net K^+ flux was from inside to out until the equilibrium PD of -60 mV was reached. If the potential were, by some means, to become even more negative (say, -70 mV), then the direction of net K^+ flux would *reverse*, i.e., a net flux from the low chemical concentration of K^+ outside the cell into the higher K^+ concentration inside, with this “uphill” flux driven by the imposed electrical force.

At this point, it reasonable to ask, “If we started with 100 mM K^+ inside and there was a net efflux of K^+ from the cell, shouldn’t the intracellular K^+ concentration now be lower?” This is an important issue. As it turns out, the amount of K^+ that leaves the cell to produce the equilibrium potential is sufficiently small that it cannot be measured chemically, despite the substantial electrical effect it has (see *Sidebar 1*). Therefore, to a first approximation you can assume that $[K]_{in}$ (and Na^+) remain effectively constant during the shifts in transmembrane electrical potential of the type discussed here.

So, in our hypothetical “cell,” with the constraint that the membrane is permeable only to K^+ , the membrane potential is precisely defined by the K^+ chemical gradient. Although it was emphasized above that 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

Table 1. *Cytoplasmic and extracellular K^+ , Na^+ , Cl^- concentrations*

Ion	[Cytoplasm], mM	[Extracellular], mM	V_{eq} , mV	P_i , cm/s
K^+	135	4	-92	1×10^{-7}
Na^+	12	140	+64	1×10^{-9}
Cl^-	4	116	-88	1×10^{-8}

These values are meant to represent only hypothetical values for a mammalian cell. V_{eq} , calculated Nernstian equilibrium potentials for each ion gradient; P_i , “typical” permeability values for mammalian neurons. The listed concentrations of Cl^- in the cytoplasm and extracellular fluid do not add up to the total concentration of K^+ and Na^+ . However, macroscopic electroneutrality is maintained in each compartment through the combined contribution of a diverse array of additional charged solutes (both anionic and cationic).

of changes in $[K]_{out}$, can be extremely important, both physiologically and clinically; see *Sidebar 1*. So, go ahead, grab a calculator and determine the new equilibrium potential that would arise if $[K^+]_{out}$ were suddenly increased to 20 mM or if the internal $[K^+]$ fell to 50 mM (be advised, these macroscopic changes in K^+ concentration would be associated with parallel changes in the concentration of one or more anions). Here is the rule of thumb: any manipulation that reduces the K^+ gradient (i.e., either decreasing intracellular K^+ or increasing extracellular K^+), will decrease the equilibrium potential for K^+ (i.e., a voltage value closer to zero). In other words, if there is less energy in the chemical gradient, it will take less energy in an electrical gradient to “balance” it (go ahead, do the math. . .).

You will not be surprised to learn that 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” (in terms of concentration): 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, more typically, the “*Goldman equation*”

$$V_m \cong -60 \text{ mV} \log_{10} \frac{P_K[K]_{in} + P_{Na}[Na]_{in} + P_{Cl}[Cl]_{out}}{P_K[K]_{out} + P_{Na}[Na]_{out} + P_{Cl}[Cl]_{in}}$$

where V_m is the actual PD across the membrane, and P_i is the membrane permeability (in cm/s) for the indicated ion. Close inspection reveals that 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^+ .² Note that to account for the differences in valence, the anionic Cl^- concentrations are presented as “out over in,” rather than as the “in over out” convention used here for cations.

It is worthwhile to consider the transmembrane ion gradients and ion-specific membrane permeabilities of a “typical” neuron

²The Goldman equation can also be viewed as a weighted sum of the reversal potentials for each of the three ion gradients, with the individual ion permeabilities serving as weighting factors that define the relative influence of each gradient on the overall membrane potential.

(Table 1). The calculated Nernstian equilibrium potential for K^+ , Na^+ , and Cl^- establish the “boundary conditions” for the electrical PD across the cell membrane; i.e., our cell cannot be more negative than -92 mV or more positive than $+64$ mV (Fig. 1) because there are no relevant chemical gradients sufficiently large to produce larger PDs. At rest, importantly, the membrane permeability of most cells, including neurons, is greatest for K^+ due to the activity of several distinct populations of K^+ channels that share the general characteristic of being constitutively active under normal resting conditions. The relative contribution to the resting potential played by these channels varies with cell type, but 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 (the product of Na-K-ATPase activity) and a high resting permeability to K^+ makes the interior of animal cells electrically negative with respect to the external solution. However, the finite permeability of the membrane to Na^+ (and to Cl^- ; see *Sidebar 2*) prevents the membrane potential from ever actually reaching the Nernstian K^+ potential. The extent to which each ion gradient influences the PD is defined by the permeability of the membrane to each ion, as is evident from inspection of the Goldman equation. Even very large concentrations exert little influence if the associated P_i value is small. However, if the membrane were suddenly to become permeable only to Na^+ , the result would be a Nernstian condition for Na^+ , with a concomitant change in membrane potential.

Although under normal physiological conditions the concentration terms of the Goldman equation remain relatively constant, the permeability terms do not. Indeed, large, rapid changes in the ratios of permeability for different ions represent the basis for the control of bioelectric phenomena. On a molecular level, membrane permeability to ions is defined by the activity of membrane channels (the molecular basis of which, like so many other things, is outside the scope of this review). Indeed, a large increase in P_{Na} (owing to activation of

a population of voltage-gated Na^+ channels) is the basis of the transient depolarization of membrane potential that is associated with the neuronal action potential.

In summary, the combination of an outwardly directed K gradient (the product of Na-K-ATPase activity) and a high resting permeability to K^+ makes the interior of animal cells electrically negative with respect to the external solution. Changes in either of these controlling parameters, i.e., transmembrane ion gradients or channel-based ion permeability, can have large, and immediate consequences. Although the “stability” of ion gradients has been emphasized here, in fact, changes in these gradients can occur, generally with pathological consequences (see *Sidebar 2*). The $[K^+]_{out}$ is particularly susceptible to such changes. Because in absolute terms it is comparatively “small” (i.e., ~ 4 mM), increases in $[K^+]_{out}$ of only a few millimoles per liter can have large effects on resting membrane potential (prove this to yourself using the Goldman equation and the permeability parameters listed in Table 1). Such changes can occur as a consequence of, for example, 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). Alternatively, failure of the Na-K-ATPase during ischemia can result in local increases in the $[K^+]_{out}$, a problem exacerbated by both the low starting concentration of K^+ and the low volume of fluid in the restricted extracellular volume of “densely packed” tissues (e.g., in the heart or brain). The “other side of the coin,” i.e., alteration in membrane permeability to ions, can arise as a consequence of an extraordinary number 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 mentioned previously. Mutations in these channels, and the consequent changes in resting membrane potential, have been linked to persistent hyperinsulinemic hypoglycemia of infancy, a disorder affecting the function of pancreatic beta cells; Bartter’s syndrome, characterized by hypokalemic alkalosis, hypercalciuria, increased serum aldosterone, and plasma renin activity; and to several polygenic central nervous system diseases, including white matter disease, epilepsy, and Parkinson’s disease.

Sidebar 1

How many ions cross the membrane during bioelectric activity? Although the PD at equilibrium is the result of the physical separation by the membrane of cations from anions, the actual number of ions separated to produce this PD is very small. At time zero in our example, there were equal concentrations of cations and anions on both Side 1 and Side 2 (i.e., 0.11 M each). On a *macroscopic* scale, this is always the case and is the basis for the presumption that “*electroneutrality*” must be maintained in any system; you can’t have a jar that contains only cations! However, as K^+ diffuses from Side 2 to Side 1, there will be a net increase in positive charge along the Side 2 (outside) surface of the membrane, producing a *microscopic* imbalance in charge with respect to the residual negative charge (i.e., Cl^-) left behind along the inside surface of the membrane. The net movement of K^+ produces a current, and the storage of charge on the membrane surface is analogous to the action of a capacitor. When the net movement of K^+ is zero (i.e., at equilibrium), the current flow will be zero and maxi-

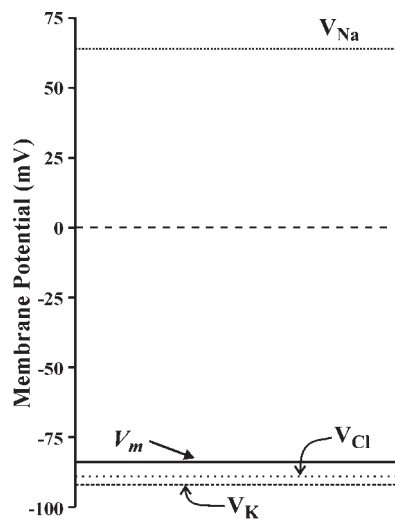


Fig. 1. Graphical representation of the Nernstian equilibrium potentials (V_i) for Na^+ (V_{Na}), K^+ (V_K), and Cl^- (V_{Cl}); and the resting membrane potential (V_m) calculated by using the Goldman equation. The relevant ion concentrations and permeabilities are listed in Table 1.

num storage of charge in the “capacitor” has occurred. The amount of charge stored is proportional to the net movement of K^+ and is given by

$$q = cV$$

where q is charge (coulombs), c is the capacitance of the membrane (in farads), and V is the applied voltage (the PD). For the purpose of this discussion, we will use the capacitance of a “generic” biological membrane, 1×10^{-6} F/cm². As shown previously, the equilibrium voltage for a 10-fold gradient of a monovalent ion ~ 0.060 V. Thus

$$q = (1 \times 10^{-6} \text{ F/cm}^2)(0.060\text{V}) = 6.0 \times 10^{-8} \text{ coulombs/cm}^2$$

There are about 1×10^{-5} mol of monovalent ion per coulomb (recall the Faraday constant). Thus if we consider the specific instance of our example, i.e., K^+ efflux across a K^+ permselective membrane, this charge separation corresponds to

$$(6.0 \times 10^{-8} \text{ coulombs/cm}^2)(1 \times 10^{-5} \text{ mol } K^+/\text{coulomb}) \\ = 6.0 \times 10^{-13} \text{ moles of } K^+/\text{cm}^2$$

So, to move the membrane potential from zero to a PD of -60 mV, the necessary efflux of K^+ amounts to a minimum of 6×10^{-13} mol/cm² of membrane, leaving behind its negatively charged counter ion (in this case, Cl^-).

It is instructive to consider the potential impact of moving that many ions into or out of cellular-sized compartments. Consider, for example, an axon $10 \mu\text{m}$ in diameter. Taking into account the appropriate surface-to-volume relationship, the flux associated with a 60 mV PD shift should change the axoplasmic concentration of an ion, such as K^+ by less than one part in 40,000! Moreover, the modest imbalance of charged particles arising from the net efflux of K^+ is effectively localized to the region very near the membrane, with the excess positive charge (in this case, K^+) in the extracellular compartment held electrostatically along the outer surface of the membrane by the excess negative charge (in this case, Cl^-) that is arrayed along the inner surface of the membrane. Importantly, conductive K^+ fluxes can, at least under pathophysiological conditions, produce substantial elevations in $[K^+]_{\text{out}}$, owing to 1) the low starting concentration of K^+ in the extracellular fluid; and 2) the restricted volume of the extracellular compartment of some tissues (including some neuronal tissues).

Sidebar 2

What about Cl^- ? A common question is: “What about the influence of Cl^- ? The resting PD is as close (or closer) to V_{Cl} as it is to V_K . 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* the Na-K-ATPase, in establishing the gradients for K^+ and Na^+ , not Cl^- . Indeed, to a first approximation, the observed inwardly directed Cl^- gradient, with its calculated Nernstian potential of ~ 89 mV, arises in large part through the simple passive distribution of Cl^- in response to the electrical gradient

(i.e., the resting PD) that is effectively defined by the outwardly directed K^+ gradient. In other words, 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 PD toward the equilibrium (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 intracellular Cl^- . Importantly, this is the case even in those cells (e.g., some skeletal muscle cells) in which the channel-mediated permeability to Cl^- exceeds that for K^+ . The fact that the Nernstian Cl^- potential is usually not exactly equal to the resting PD of the cell means that there are one or more “active” transport processes that keep Cl^- away from an equilibrium distribution (e.g., secondary active Cl^-/HCO_3^- exchange).

Whereas in neurons Cl^- is a minor player in establishing the resting membrane potential, there are several situations in which membrane permeability to Cl^- (as influenced by the activity of Cl^- channels) is very important. An increase in Cl^- permeability 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 Cl^- permeability is modulated as one means to influence synaptic transmission. Conversely, decreases in P_{Cl} make 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 is the result of a decrease in P_{Cl} (arising from defects in the CICN1 Cl^- channel) and the concomitant decrease in the stability of the resting membrane potential.

Sidebar 3

Traps students fall into. The material presented here is aimed at first-year medical students and graduate students. Although graduate students may need selected core concepts presented in greater depth, I have found that they must first be comfortable with the interrelation that exists between ion gradients and membrane permeability. In my experience, the two largest misconceptions that students cling to are 1) that changes in PD are associated with large changes in ion concentrations (see *Sidebar 1*); and 2) that changes in ion concentration that are frequently referred to in discussions of manipulating membrane potential influence membrane potential because they represent a net addition of charge (e.g., increasing external K^+ from 4 to 10 mM results in adding positive charge to the extracellular solution *because K^+ is a cation!*). As teachers, it is easy to “feed” these misconceptions through statements like “ Na^+ rushes in” (implying to some that “a lot” of Na^+ crosses the membrane), and “add K^+ to the extracellular solution” (implying to some the addition of “only” a positively charged species). Dealing with such issues requires attention to detail in the description of these events, and substantial repetition. In the final analysis, however, the best way for students to become comfortable with the concepts associated with establishment of the membrane potential is to work with the Nernst and Goldman equations.