النادي الطبي

PHYSIOLOGY
HAYAT BATCH

done by : Scientific Team

lecture no: Lec 11 (full material)

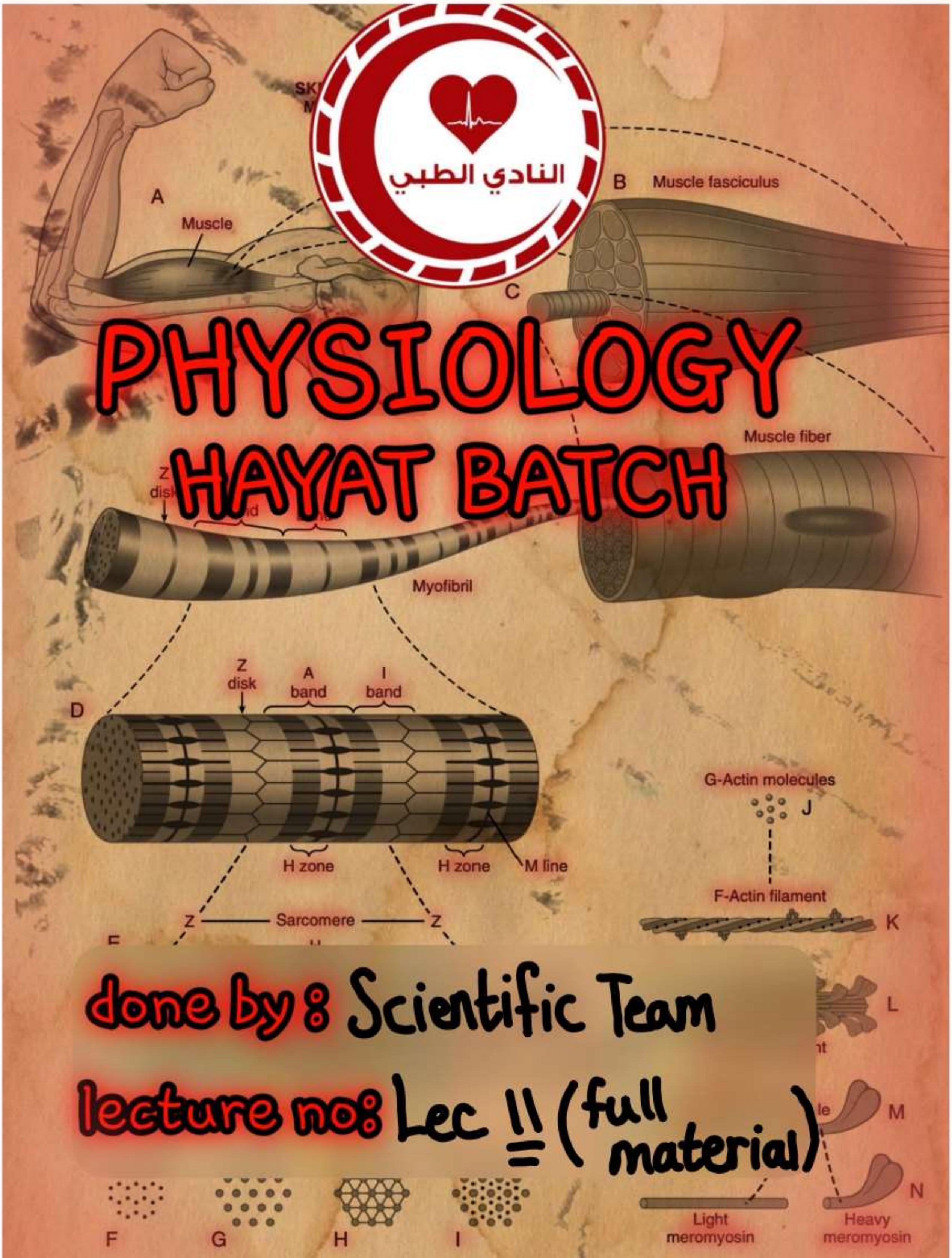

Figure 6-1. Organization of skeletal muscle, from the gross to the molecular level. F, G, H, and I are cross sections at the levels indica

General physiology
Lecture 11
Resting membrane potential

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Lecture objectives

- Define the resting membrane
- Review the different types of ionic channels in the cell membrane
- Understand ionic basis of resting potential by applying the concept of diffusion potential
- Describe the relation between the resting membrane potentials and K and Na equilibrium potentials
- Apply the Nerst equation and GHK equation and to estimation of resting potential
- Describe the contribution of NaK ATPase pump to the resting potential
- Know the resting membrane of different cell types including neurons, muscle cells and other cell types of the body

في هاي المحاضرة رح نحكي عن الخلايا الحية مثل :

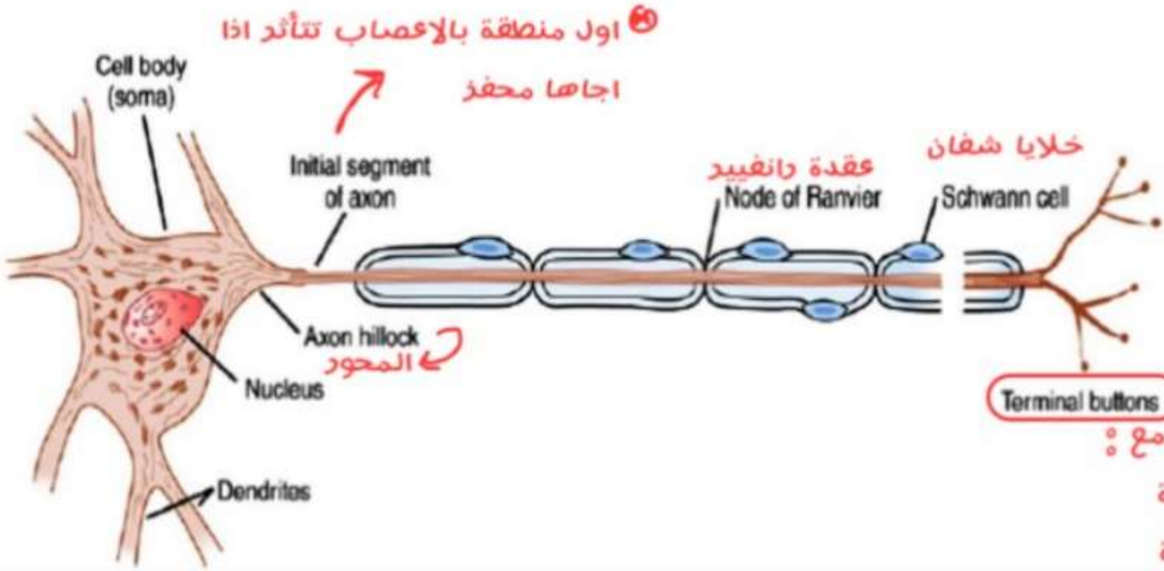
الخلايا العصبية

الخلايا العضلية

و رح نعرف اليوم انه مو كل الخلايا الها نفس ال membrane

potential يعني العصبية غير عن العضلية

Schematic diagram of a neurons



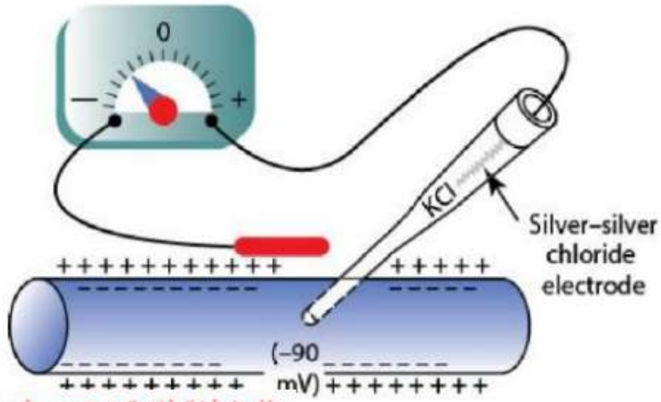
الخلايا العصبية عليها phospholipid material و تسمى ب(myelin) وظيفتها انشاء peripheral nerves اسمها خلايا شفان ، طبعا موجود في control nervous system

هس الي اخذناه بمحاضرة 10 رح يتم تطبيقه في ال cell membrane و خاصة في الخلايا العصبية و العضلية

هسا في شغلة بدنا نكون حريصين عليها و هو اختلاف ال action potential بين الخلايا (مثل الخلية العصبية تختلف عن العضلية) و يعود ذلك إلى اختلاف ال properties للخلايا

Measurement of Resting membrane potential

RMP is a potential difference across biological membranes, and it reflects the separation of charges across the membrane.
There are a few excess negative charges (about 1 pmol/cm2) on the inner surface and the same number of excess positive charges on the outer surface
The resting membrane potential measured when the cell is at rest—that is, not active
Different cells have different resting potentials.



شغلة ثانية : هس في ال ICF و ال ECF ما عندهم difference in potential ، ليش ؟
لانه ال difference in potential يكون قريب من ال cell membrane

Resting Membrane Potential of Different cell

الأرقام هون مو للحفظ

Cell types	Resting potential
Skeletal muscle fibers	-85 to 95 mV
Smooth muscle fibers	-50 to -60 mV
Astrocytes	-80 to -90 mV
Neurons	-60 to -70 mV
Erythrocytes	-8 to -12 mV
Photoreceptor cells	-40 mV (dark) to -70 mV (light)

هس في عنا خلايا عبارة عن non-existing cells يعني انه عندها resting potential و مهمة كثير في عملية ال volume regulation، و ذكر الدكتور أمثلة منهم :

١. Erythrocytes
٢. Epithelial cells
٣. الخلايا في الأمعاء الدقيقة

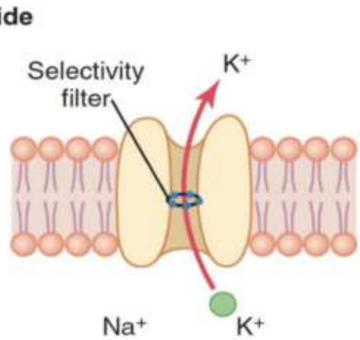
Ionic channels in nerve cells

هس هون احفظوا ال leak channels

→ **Leak Channels**

- Predominately for K Ions
- Some Na Leak channels
- cell membranes of Neurons and muscle cell in resting state are highly permeable to K ions than Na Ions ((100X)

3. Thus the resting membrane potential is mainly determined by the concentration gradients of K ion



K^+ "leak" channels

هس لو حسبنا ال equilibrium potential for k+ ions رح يطلع الجواب أعلى من - ٩٠ او اقل منها لذلك بتطلع بنتيجة انه ال resting potential قريب من ال equilibrium potential for k+ ions

و حسب النقطة الي فوق بنقدر نحكي انه السبب هو السماحية العالية للبوتاسيوم لوجود ال leak channels

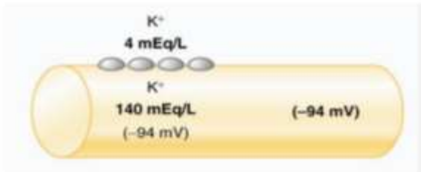
Origin of Resting Membrane Potential of Neurons

RMP =−90 mV

Contribution of K Diffusion Through the Nerve Membrane

Concentration difference 35 : 1 → K+ Nernst potential =-94 mV

If K+ ion concentration and permeability were the only factors causing RMP → RMP inside the fibber would be equal to −94 millivolts and will be equal to the Nerst potential of K ions



هس هون نرجع لحديث شابتر ١٠

The observed membrane potential as a function of the external K+ concentration

هس لما يتساوى تركيز ال k+ في داخل و خارج الخلية اعرفوا انه ال (Nernst potential = zero)

The solid line is the theoretical prediction for a membrane that is permeable only to K+. Notice the logarithmic concentration scale.

Effects Of hyo and hyperkalemia

⬇️k+ / ⬆️ negativity

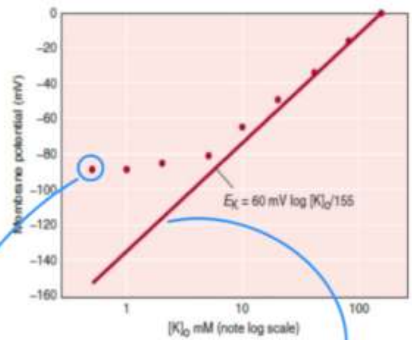
Hypokalemia the resting potential moves closer to the threshold for eliciting an action potential and the neuron becomes more excitable.

⬆️k+ / ⬇️ negativity ➡️ Depolarized

Hyperkalemia If the extracellular level of K+ is decreased (hypokalemia), the membrane potential is reduced and the neuron is hyperpolarized

Effects of Ca ions

A decrease in extracellular Ca2+ concentration increases the excitability of nerve and muscle cells(membrane destabilization)



If you calculate the RMP usually the will be the same

هذا الخط يمثل ال membrane potential في حالة ال nernst equation و في ذات الوقت تم القياس انه ال nernst potential ≠ exact membrane potential و السبب هو اختلاف بين measured potential و ال calculated potential

هس هون رح بحكي عن ال hypokalemia رح تتأثر بما يلي :

١. تفيد في تركيب ال voltage gate for +Na بالتالي رح يسمح بدخول ال +Na بشكل اسرع
٢. بتصير الخلية more excitable لانه يدخل +Na بسرعة فبزيد من ال excitability و تسميها في هاي الحالة heperexcitability و يسبب تقلص شديد في العضلات و بسميها hypocalcemic tetany ⬅️ حالة مرضية

هس في حالة ال hyperkalemia رح يصيد دفع في ال resting potential حتى يوصل جهد العتبة threshold و بالتالي صارت الخلية excitable و بسبب ال action potential صارت اكثر exciting
بالنسبة لل hypokalemia اعكس الي حكيته

هس احنا في عنا 3 types of diffusion potential :
١. Na+ ions
٢. K+ ions
٣. Na-K pump

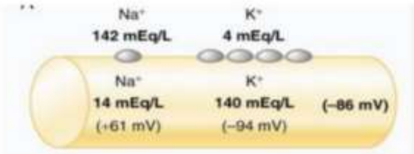
Origin of Resting Membrane Potential of Neurons

RMP =−90 mV

Contribution of Na Diffusion Through the Nerve Membrane

Concentration difference 10 : 1 → Na+ Nernst potential =+61 mV

Slight permeability of the nerve membrane to Na+→ minute diffusion of Na Therefore , According to **Goldman equation** → RMP = −86 mV→ close to K potential but not equal to the equilibrium



ذكر الدكتور زهير انه ليش عنا ٣ أنواع من ال diffusion potential:
١. لو كان عنا Na+ لحاله او K+ لحاله رح يكون ال equilibrium potential closer to resting potential لذلك في عنا gap بالخلايا بيحتوي على K+ و Na+
٢. هس The Na+ contribute to resting membrane potential because of its positivity لذلك رح يقلل من ال membrane potential و رح يكون ال RMP= -86 الي هو قريب من k potential فقط و لا يساوي ال equilibrium potential
٣. بسبب النقطة الثانية ال Na+-k+ pump رح تضيف القليل من ال negativity

Origin of Resting Membrane Potential of Neurons

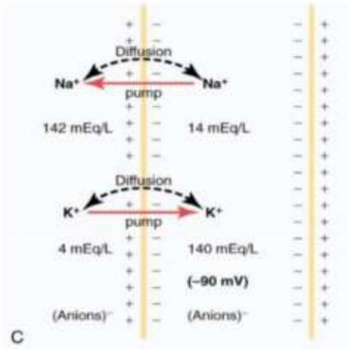
RMP =−90 mV

Contribution of the Na+-K+ Pump

Creating additional degree of negativity (about −4 millivolts additional)→ -86+-4=-90 mV

هذا مقدار مساهمة ال K / Na+ مع بعض في ال Resting potential

مقدار مساهمة المضخة في ال resting potential



و هيك بنكون قطعنا شوط كبير و ممتاز و ذكر الدكتور في نهاية شرح السلايد الي فوق مثال :

If we have a resting muscle cells that is permeable mainly to k+ , slightly permeable to Na+ diffusion potential will contribute about -86 mv and Na+-k+ pump contribute about -4mv so according to these factors

The resting potential = -90mv

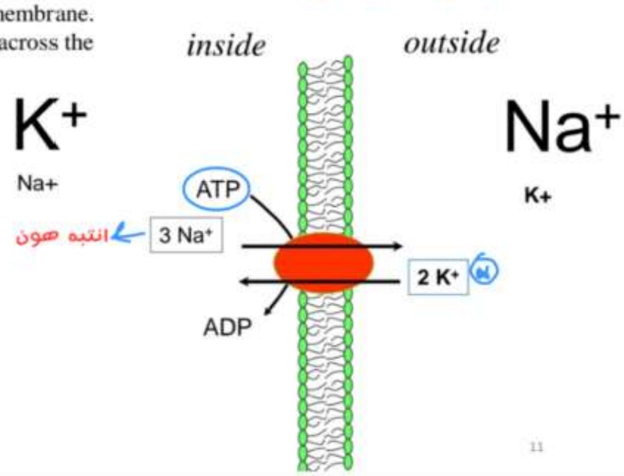
Active Transport of Na^+ and K^+

Electrogenic pump

More positive charges are pumped to the outside than to the inside→ causing **negative** potential inside the cell membrane. Causes **large concentration gradients** for Na & K across the resting nerve membrane.

ال Na+ بده يدخل لجوا لانه تركيزه قليل و ال k+ بده يطلع برا لانه تركيزه عالي

الدكتور عمل اله سكيب لانه واضح من دون شرح



18/03/2023 ١٧/١١ 11

The Resting Membrane Potential Summary

ملخص لكل السلايدات الي فوق و برضو عمل اله سكيب

Membrane potentials are generated mainly by diffusion of ions and are determined by

- the ionic concentration differences across the membrane, and
- the membrane's relative permeabilities to different ions.

Plasma-membrane Na,K-ATPase pumps maintain intracellular sodium concentration low and potassium high.

- In almost all resting cells, the plasma membrane is much more permeable to potassium than to sodium, so the membrane potential is close to the potassium equilibrium potential—that is, the inside is negative relative to the outside.
- The Na,K-ATPase pumps also contribute directly a small component of the potential because they are electrogenic.

الخلية في الحالة الطبيعية ما فيها اتزان ، ليش ؟ لانه pump شغال طول الوقت

معلومة إضافية

قلنا المضخات شغالة تمام ؟ تمام

و بردنو يكون شغال قنوات تسرب الايونات و بعكس اتجاه ال pump

Net Driving Force on Ions across the cell membrane

- When multiple ions contribute to membrane potential (Vm) of a cell→ membrane potential would **not** be at the equilibrium potential (Veq.) for any of the contributing ions. Thus, no ion would be at its equilibrium (i.e., Veq. ≠ Vm).

- i.e. chemical and electrical forces acting on K^+, Na^+, and Cl^- are not equal→ electrochemical driving force (VDF) acts on the ion, causing the net movement of the ion across the membrane down its own electrochemical gradient.

لا اله الا الله، بردنو عمل سكيب
بس الحلو انه صار يقرأ فيه يعني ما
في اشي جديد

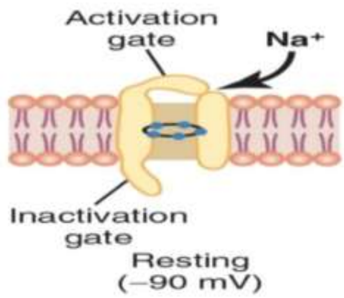
- $VDF = Vm - Veq.$

الزبدة يا اخوان كل اشي بعد سلايد ١٠ صار يكرر بعضه بس اكمن نقطة بدنا ننتبه الها

Voltage-Gated Na Channel in neuronal cell membranes
Activation and Inactivation of the Voltage-Gated Na Channel

This channel has two gates:
1- activation gate → near the outside of the channel
2- inactivation gate → near the inside of the channel

هس الدكتور ذكر انه فتح القنوات
او تسكيرها يعتمد على ال
membrane potential لذلك
سميت ب voltage gate

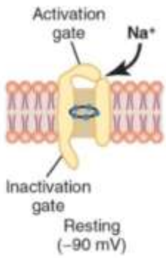


هسا هون تقريبا اهم جزء من بعد سلايد ١٠ ، هس هو كله مهم بس هذا اهم للأمانة

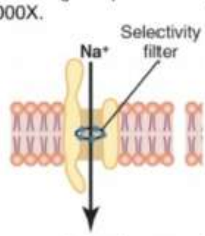
Activation and Inactivation of the Voltage-Gated Na Channel

state of two gates in:

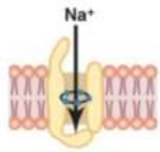
A- RMP=−90 mV.
activation gate is closed → prevents Na entry to the interior

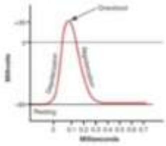


B- **Activation of the Na Channel**
activation gate → open position
inactivation gate → open→ Na pour inward, increasing Na permeability of membrane 500-5000X.



C-**Inactivation of the Na Channel.**
activation gate → open
Inactivation gate→ closed
No Na ions entry





- Occurs a few 10,000ths of a second after **activation** gate opens.
- Conformational change that closes **inactivation** gate is a **slower** process than conformational change that opens the **activation** gate
- The inactivation gate will not reopen until the membrane potential returns to or near the original RMP

18/03/2023 15

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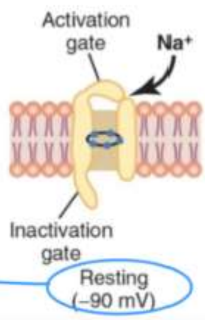
state of two gates in:

A- RMP=−90 mV.
activation gate is closed → prevents Na entry to the interior

هس هون لما يكون ال
resting potential = -90
كل القنوات بتكون مسكرة



مرحلة جهد الراحة

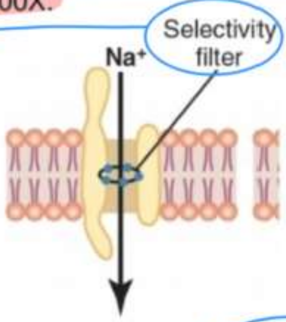
استبدلها الدكتور ب net inward movement of Na^+ او net inflex (of Na^+)

بصير يدخل لجوا Na^+

B- **Activation of the Na Channel**
activation gate → open position
inactivation gate → open→ Na pour inward,
increasing Na permeability of membrane 500-5000X.

ننتبه هون لنقطة مهمة انه في هذه الحالة بس Na^+ بفوت ال k^+ و ال Ca^+ و ال Cl^- و غيرها ممنوع يدخلوا

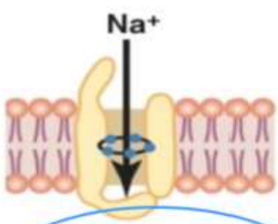
هسا لما تفتح هاي البوابة بتزيد نفاذية الصوديوم بمقدار ٥٠٠ - ٥٠٠٠ مرة عن الوضع الطبيعي



Activated
(−90 to +35 mV)

بضل الصوديوم يفوت لحتى يدفع جهد الخلية إلى 35+

C-**Inactivation of the Na Channel.**
activation gate → open
Inactivation gate→ closed
No Na ions entry



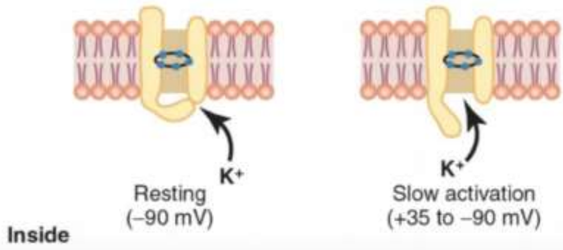
Inactivated
(+35 to −90 mV, delayed)

عند ٣٥+ بتسكر القناة بيجي دور قناة k^+ لحد ما يرجع الجهد إلى 90-

Voltage-Gated K Channel and Its Activation

two states:
A- during the resting state→ Closed
B-Activation state → opened→ K diffusion **outward**

Opens just at the same time that the Na channels are beginning to **close** → ↓ Na entry & ↑ K exit→ recovery of RMP within another few 10,000ths of a second.



الفرق الوحيد بينه و بين بوابة
K+ انه ال Na+ بيمتلك بوابتين
و k+ بيمتلك بوابة وحدة

From Guyton Textbook

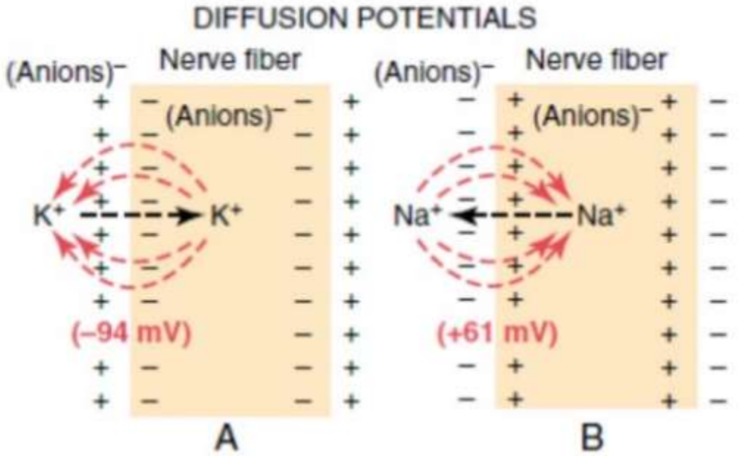
Membrane Potentials Caused by Diffusion

- **Diffusion Potential (Caused by an Ion Concentration Difference on the Two Sides of the Membrane)**

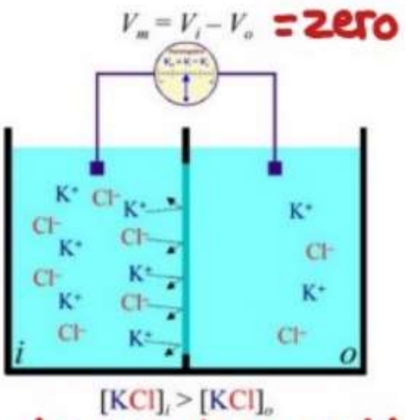
  - Figure *A,* the potassium concentration is great *inside* a nerve fiber membrane but very low *outside* the membrane. Let us assume that the membrane in this instance is permeable to the potassium ions but not to any other ions. Because of the large potassium concentration gradient from inside toward outside, there is a strong tendency for extra numbers of potassium ions to diffuse outward through the membrane. As they do so, they carry positive electrical charges to the outside, thus creating electropositivity outside the membrane and electronegativity inside because of negative anions that remain behind and do not diffuse outward with the potassium. Within a millisecond or so, the potential difference between the inside and outside, called the *diffusion potential,* becomes great enough to block further net potassium diffusion to the exterior, despite the high potassium ion concentration gradient. In the normal mammalian nerve fiber, *the potential difference required is about 94 millivolts, with negativity inside the fiber membrane.*

- **Figure B shows the same phenomenon as in Figure 5-1A, but this time with high concentration of sodium ions outside the membrane and low sodium inside. These ions are also positively charged. This time, the membrane is highly permeable to the sodium ions but impermeable to all other ions. Diffusion of the positively charged sodium ions to the inside creates a membrane potential of opposite polarity to that in Figure 5-1A, with negativity outside and positivity inside. Again, the membrane potential rises high enough within milliseconds to block further net diffusion of sodium ions to the inside; however, this time, in the mammalian nerve fiber, the potential is about 61 millivolts positive inside the fiber.**

Figure 5-1 *A*, Establishment of a "diffusion" potential across a nerve fiber membrane, caused by diffusion of potassium ions from inside the cell to outside through a membrane that is selectively permeable only to potassium. *B*, Establishment of a "diffusion potential" when the nerve fiber membrane is permeable only to sodium ions. Note that the internal membrane potential is negative when potassium ions diffuse and positive when sodium ions diffuse because of opposite concentration gradients of these two ions



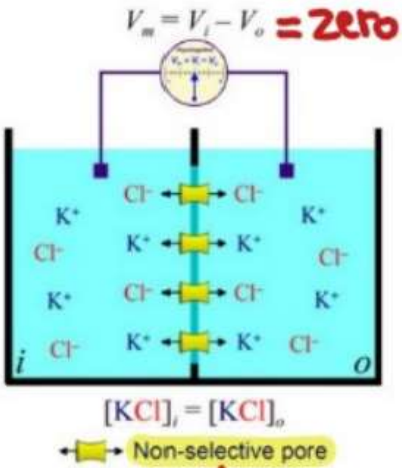
↓RMP



$V_m = V_i - V_o$ = zero

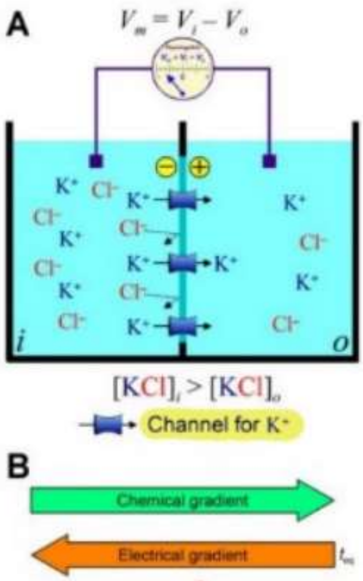
Membrane not permeable (no movement of ions)

KCl ملح
↓
يتأين إلى
K⁺/Cl⁻



$V_m = V_i - V_o$ = zero

↓
K⁺/Cl⁻ تدخل
↓
Diffusion
↓ ثم
Equilibrium



↓
selective permeability (K⁺)

* Chemical Gradient = Concentration Gradient

The Nernst Potential

- The diffusion potential level across a membrane that exactly opposes the net diffusion of a particular ion through the membrane is called the ***Nernst potential*** for that ion.
- **The magnitude** of this Nernst potential is determined by the *ratio* of the concentrations of that specific ion on the two sides of the membrane. The greater this ratio, the greater the tendency for the ion to diffuse in one direction, and therefore the greater the Nernst potential required to prevent additional net diffusion
- When using this formula, it is usually assumed that the potential in the extracellular fluid outside the membrane remains at zero potential, and the Nernst potential is the potential inside the membrane. Also, the sign of the potential is **positive (+)** if the ion diffusing from inside to outside is a negative ion, and it **is negative (–)** if the ion is positive.

$$\text{EMF (millivolts)} = \pm 61 \times \log \frac{\text{Concentration inside}}{\text{Concentration outside}}$$

Origin of the Normal Resting Membrane Potential

- **1-Contribution of the Potassium Diffusion Potential.**
- **2-Contribution of Sodium Diffusion Through the Nerve Membrane.**
- **3-Contribution of the Na+-K+ Pump.**

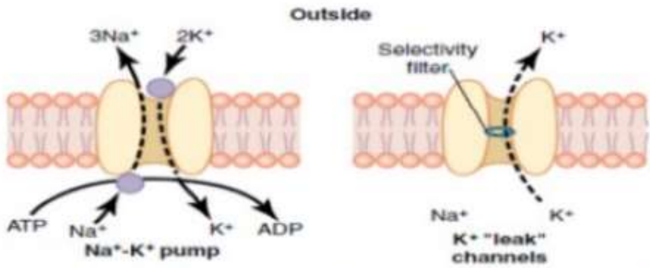


Figure 5-4 Functional characteristics of the Na^+-K^+ pump and of the K^+ "leak" channels. ADP, adenosine diphosphate; ATP, adenosine triphosphate. The K^+ "leak" channels also leak Na^+ ions into the cell slightly, but are much more permeable to K^+.

1-Contribution of the Potassium Diffusion Potential.

- In Figure 5-5*A,* we make the assumption that the only movement of ions through the membrane is diffusion of potassium ions, as demonstrated by the open channels between the potassium symbols (K+) inside and outside the membrane. Because of the high ratio of potassium ions inside to outside, 35:1, the Nernst potential corresponding to this ratio is −94 millivolts because the logarithm of 35 is 1.54, and this multiplied by −61 millivolts is −94 millivolts. Therefore, if potassium ions were the only factor causing the resting potential, the resting potential *inside the fiber* would be equal to −94 millivolts, as shown in the figure.

2-Contribution of Sodium Diffusion Through the Nerve Membrane.

- Figure 5-5*B* shows the addition of slight permeability of the nerve membrane to sodium ions, caused by the minute diffusion of sodium ions through the K+-Na+ leak channels. The ratio of sodium ions from inside to outside the membrane is 0.1, and this gives a calculated Nernst potential for the inside of the membrane of +61 millivolts. But also shown in Figure 5-5*B* is the Nernst potential for potassium diffusion of −94 millivolts. How do these interact with each other, and what will be the summated potential? This can be answered by using the Goldman equation described previously. Intuitively, one can see that if the membrane is highly permeable to potassium but only slightly permeable to sodium, it is logical that the diffusion of potassium contributes far more to the membrane potential than does the diffusion of sodium. In the normal nerve fiber, the permeability of the membrane to potassium is about 100 times as great as its permeability to sodium. Using this value in the Goldman equation gives a potential inside the membrane of −86 millivolts, which is near the potassium potential shown in the figure.

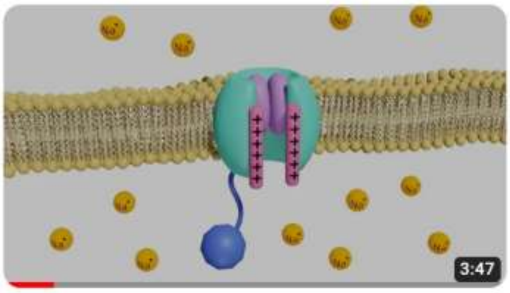
3-Contribution of the Na+-K+ Pump.

In Figure 5-5*C,* the Na+-K+ pump is shown to provide an additional contribution to the resting potential. In this figure, there is continuous pumping of three sodium ions to the outside for each two potassium ions pumped to the inside of the membrane. The fact that more sodium ions are being pumped to the outside than potassium to the inside causes continual loss of positive charges from inside the membrane; this creates an additional degree of negativity (about −4 millivolts additional) on the inside beyond that which can be accounted for by diffusion alone. Therefore, as shown in Figure 5-5*C,* the net membrane potential with all these factors operative at the same time is about −90 millivolts. In summary, the diffusion potentials alone caused by potassium and sodium diffusion would give a membrane potential of about −86 millivolts, almost all of this being determined by potassium diffusion. Then, an additional −4 millivolts is contributed to the membrane potential by the continuously acting electrogenic Na+-K+ pump, giving a net membrane potential of −90 millivolts.

Resting Membrane Potential of Nerves

- The resting membrane potential of large nerve fibers when not transmitting nerve signals is about −90 millivolts. That is, the potential *inside the fiber* is 90 millivolts more negative than the potential in the extracellular fluid on the outside of the fiber.

Another Notes from Videos



Voltage-Gated Sodium Channels in Neurons

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This video explains how **voltage-gated sodium channels** work in neurons, and how they influence the shape of an action potential ...

Full Video

Physiology Chapter 11

Sodium ions are more concentrated outside the cell whilst potassium ions are more concentrated inside the cell. Due to the concentration gradient formed, the ions will diffuse down their concentration gradients (known as the chemical gradient) across the membrane. For example, potassium will diffuse outside of the cells through potassium leak channels. However, as more potassium leaves the cell this causes the inside of the cell to become more negative, due to the presence of negatively charged molecules and ions. This means that the potassium will then diffuse back into the cell down its electrical gradient.
The potential difference needed to make the net movement of potassium equal zero is called the equilibrium potential, or Nernst potential.

An ion's Nernst potential can be calculated by the Nernst equation, and the resting membrane potential (RMP) can be calculated by the GHK equation, which is the combination of multiple Nernst equations. This is because there are many ions contributing towards the overall membrane potential, with potassium being the main contributor (90%) due to being the most permeable, which is why the RMP very close to the equilibrium potential of potassium.

Potassium's equilibrium potential is -94mV, Sodium's equilibrium potential is +61mV, and chloride's equilibrium potential is -86mV. Since each ion's contribution towards the membrane potential differs, the resting membrane potential will be related to the activity of each of these ions. Potassium contributes towards 90% of membrane permeability, chloride contributes towards 8% and sodium contributes 1%. Thus, $0.9 \times -94 + 0.01 \times 61 + 0.08 \times -86$ = approximately -86mV.
Since the sodium potassium pump actively transports 3 sodium ions out of the cell and 2 potassium ions into the cell, this further decreases the value of the RMP, making it more negative by about -4mV, giving us the final value for the RMP as -90mV.

Resting potential is thus the difference in potential across the membrane when the cell is not active (an example of an activity is action potential propagation). Different cells have different RMP's, with muscle and nerve cells having the most negative resting potential values.

Voltage-gated channels:

The voltage-gated channels for sodium has two gates, an activation gate on the outside of the membrane and an inactivation gate on the inside of the membrane. At RMP the activation gate is closed, so no sodium ions can enter. Once the membrane potential reaches threshold value due to stimulation, the activation gate opens leading to a massive influx of sodium ions. Once the sodium reaches +30mV, the inactivation gate closes, no more sodium enters the cell.

The voltage-gated potassium channels open once the sodium channels begin to close, which causes a massive efflux of potassium ions which repolarizes the membrane potential back to RMP.

Another Questions

16. The velocity of conduction of action potentials along a nerve will be increased by

(A) stimulating the Na^+–K^+ pump
(B) inhibiting the Na^+–K^+ pump
(C) decreasing the diameter of the nerve
(D) myelinating the nerve
(E) lengthening the nerve fiber

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6. If this cell were permeable only to K^+, what would be the effect of reducing the extracellular K^+ concentration from 14 to 1.4 millimolar?

A) 10 millivolts depolarization
B) 10 millivolts hyperpolarization
C) 122 millivolts depolarization
D) 122 millivolts hyperpolarization
E) 61 millivolts depolarization
F) 61 millivolts hyperpolarization

☺

بالتوفيق

#النادي__الطبي

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