Membrane Properties and Neurotransmitter Actions

Shepherd (2004) Chapter 2 by David A. McCormick

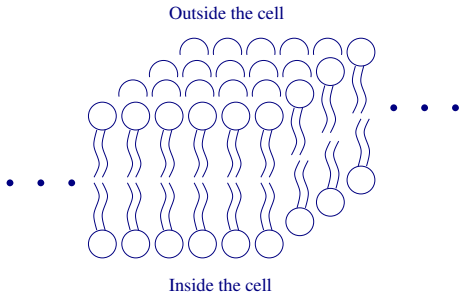
- Cell membrane.
- Ionic concentration.
- Ion channels and currents.
- Action potential.
- Neurotransmitter actions.

Instructor: Yoonsuck Choe; CPSC 644 Cortical Networks

Introduction

- Neurons with very similar morphology may act differently depending on the cell's **intrinsic properties**.
- Electrochemical and pharmacological properties become important.
- Electrochemical behavior may change due to ionic currents into and out of the cell and neurotransmitters that modulate such currents.

Lipid Bilayer



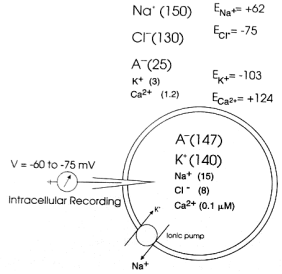
- Cell membrane is made up of lipid (i.e., fat) bilayer.
- Each lipid molecule consists of the polar head (round, hydrophilic) and non-polar tails (wiggly, hydrophobic).
- A very effective barrier of non-fatty stuff: ions, fluids, etc.

Ion Channels

Ion channels are large proteins embedded in the cell membrane, and they allow passage of specific ions.

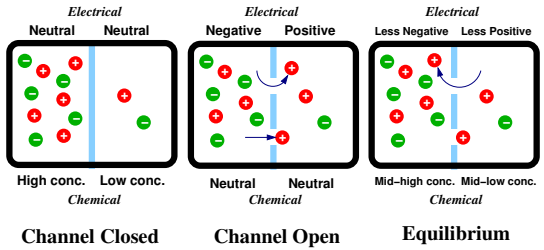
- Pores: allows ions to pass through.
- Specificity: only a certain ion species can pass.
- Voltage- or neurotransmitter sensitive (or both).
- Can be modified by intracellular mechanisms.

Ionic Concentration Difference



- Ions are differentially concentrated inside vs. outside the cellular membrane.
- For example, Na^+ ions are 10 times more abundant in the extracellular space than inside the cell.
- So, if an opening (ion channel) is made on the membrane, the Na^+ ions outside will flow inside to reach balance in the concentration.

Chemical and Electrical Equilibrium



- Ions will move from compartments of higher concentration to lower concentration.
- However, the ions are not electrically neutral, so the two compartments will become positively/negatively charged.
- Such charge will hinder the movement of ions that are trying to achieve chemical balance.
- This will lead to a potential difference across the membrane.

Calculating the Equilibrium Potential

- The Nernst equation for ion X:

$$E_X = \frac{RT}{zF} \ln \frac{[X]_\mathrm{o}}{[X]_\mathrm{i}},$$

where: R = gas const., T = abs. temp. z = valence, F = Faraday const., and $[X]_n$ = concentration of X in compartment n (o: outside, i: inside).

- It is more conveniently written as:

$$E_X = \frac{58.2}{z} \log \frac{[X]_\mathrm{o}}{[X]_\mathrm{i}},$$

assuming $T = 20^\circ\mathrm{C}$ (room temperature).

- Note: compartment o is the reference point. Voltage is determined as voltage of compartment i relative to compartment o.

Equilibrium Potential: Squid Giant Axon

- In compartment 1, 10 mM of Na^+.
- In compartment 2 (reference), 1 mM of Na^+.
- Na^+ has valence 1 ($z = 1$).

$$E_X = \frac{58.2}{z} \log \frac{[X]_2}{[X]_1}.$$

$$E_{\mathrm{Na}^+} = \frac{58.2}{1} \log \frac{1}{10} = -58.2\mathrm{mV}$$

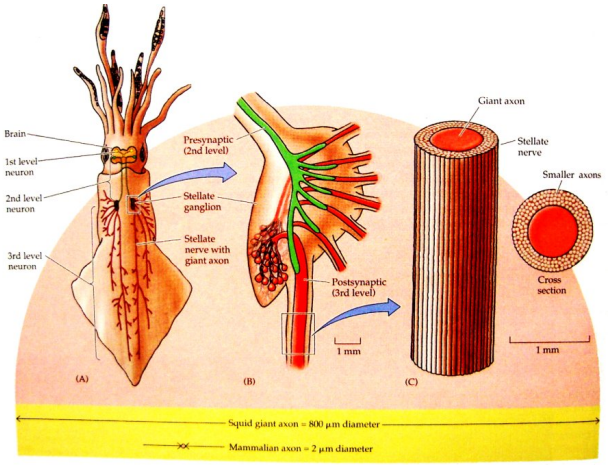
- At the equilibrium potential, ions will not flow.
- If current is applied to move the membrane potential away from the equilibrium potential, ions will start to flow: i.e., conductance will increase (conductance = 1/resistance).

Permeability

Permeability: The ease with which an ion diffuses across the membrane.

- Increased permeability lead to increased electrical conductance, and will bring the membrane potential closer to that ion's equilibrium potential.
- Higher permeability tends to keep the membrane potential near that ion's equilibrium potential.
- Lower permeability allows other kinds of ions to change the membrane potential away from that ion's equilibrium potential.

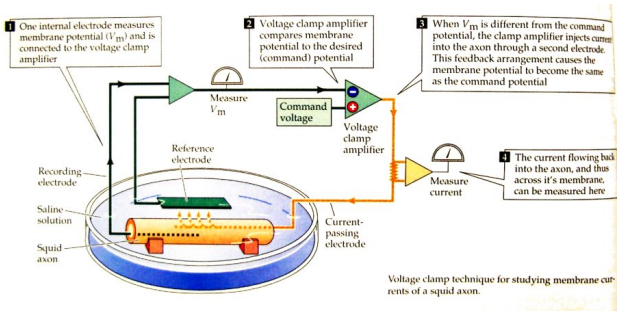
The Squid Giant Axon



Adapted from Purves et al. (1997)

- Squid giant axons are very thick, so it was easy to experiment with it to study membrane properties.

Voltage Clamp



Adapted from Purves et al. (1997)

- Dynamic controller kept the membrane potential at a fixed voltage, by adjusting the current injection level.
- Hodgkin and Huxley used this on the squid giant axon to study membrane properties.

Goldman-Hodgkin-Katz Equation: Resting Membrane Potential

For the squid giant axon:

- Weighted mixture of all ionic currents considered:

$$V_{\mathrm{m}} = \frac{RT}{F} \cdot \ln \left[\frac{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathrm{o}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathrm{o}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathrm{i}}}{P_{\mathrm{K}}[\mathrm{K}^+]_{\mathrm{i}} + P_{\mathrm{Na}}[\mathrm{Na}^+]_{\mathrm{i}} + P_{\mathrm{Cl}}[\mathrm{Cl}^-]_{\mathrm{o}}} \right],$$

  where P_X is the weight (relative permeability), which is

$$P_{\mathrm{K}} : P_{\mathrm{Na}} : P_{\mathrm{Cl}} = 1 : 0.04 : 0.45.$$

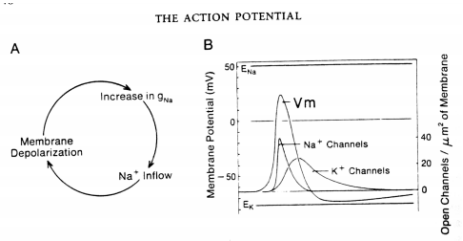
- Plugging in the actual values:

$$V_{\mathrm{m}} = 58.2 \log \left[\frac{1 \cdot 20 + 0.04 \cdot 440 + 0.45 \cdot 40}{1 \cdot 400 + 0.04 \cdot 50 + 0.45 \cdot 560} \right] = -62\mathrm{mV}.$$

Depolarization and Hyperpolarization

- The resting membrane potential is negative (e.g., -62 mV), thus it is “polar”.
- Increasing membrane potential is called “depolarization”.
- Decreasing membrane potential is called “hyperpolarization”.

Action Potential (or Spike)



- Na^+ channels open, triggered by depolarization.
- The increase in membrane voltage due to depolarization triggers a more Na^+ channels to open, thus further depolarizing the membrane (transient sodium current $I_{Na,t}$).
- Such depolarization will trigger deploarization in neighboring membranes.
- Since $I_{Na,t}$ is transient, it will quickly inactivate, and further more, voltage-gated K^+ channels will open, thus “repolarizing” (potassium current I_K). I_K is slower.

Various Ionic Currents

Table 2.1. Neuronal Ionic Currents

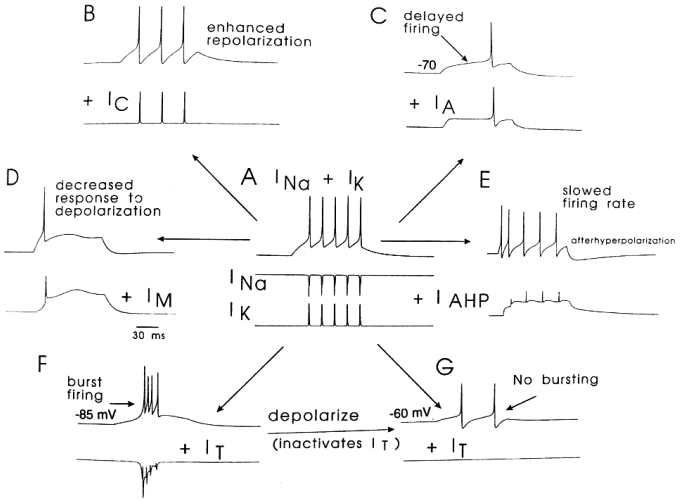
Current	Description	Function
Na^+		
$I_{Na,t}$	Transient; rapidly activating and inactivating	Action potentials
$I_{Na,p}$	Persistent; noninactivating	Enhances depolarization; contributes to steady state firing
Ca^{2+}		
I_T, low threshold	“Transient”; rapidly inactivating; threshold negative to −65 mV	Underlies rhythmic burst firing
I_L, high threshold	“Long-lasting”; slowly inactivating; threshold around −20 mV	Underlies Ca^{2+} spikes that are prominent in dendrites; involved in synaptic transmission
I_N	“Neither”; rapidly inactivating; threshold around −20 mV	Underlies Ca^{2+} spikes that are prominent in dendrites; involved in synaptic transmission
I_P	“Purkinje”; threshold around −50 mV	
K^+		
I_K	Activated by strong depolarization	Repolarization of action potential
I_C	Activated by increases in $[Ca^{2+}]_i$	Action potential repolarization and interspike interval
I_{AHP}	Slow afterhyperpolarization; sensitive to increases in $[Ca^{2+}]_i$	Slow adaptation of action potential discharge; the block of this current by neuromodulators enhances neuronal excitability
I_A	Transient; inactivating	Delayed onset of firing; lengthens interspike interval; action potential repolarization
I_M	“Muscarine” sensitive; activated by depolarization; noninactivating	Contributes to spike frequency adaptation; the block of this current by neuromodulators enhances neuronal excitability
I_h	Depolarizing (mixed cation) current that is activated by hyperpolarization	Contributes to rhythmic burst firing and other rhythmic activities
$I_{K,leak}$	Contributes to neuronal resting membrane potential	The block of this current by neuromodulators can result in a sustained change in membrane potential

Lesson: There are many currents related to diverse functions.

Some Notable Ionic Currents

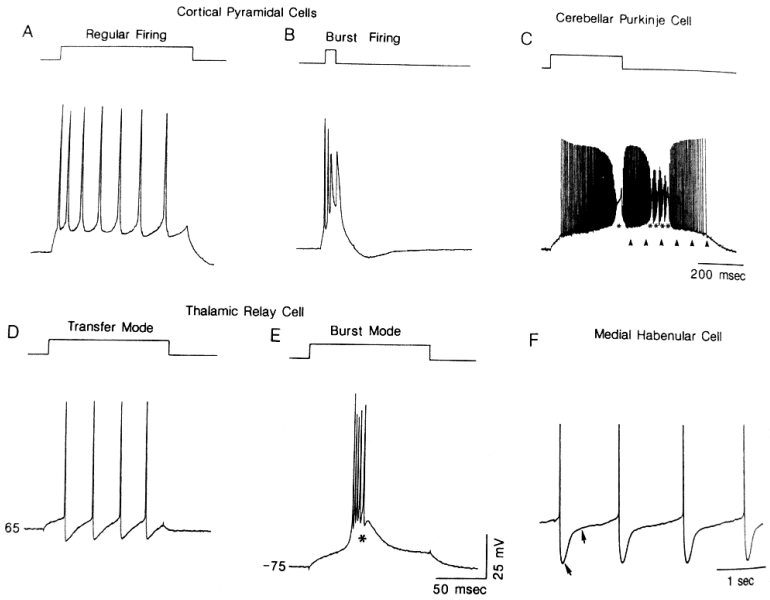
- $I_{Na,t}$: Transient Na^+ current – action potential.
- I_K: activated by strong depolarization – repolarization.
- I_T: Transient Ca^{2+} current – low threshold burst firing.
- I_h: activated by hyperpolarization – depolarizing current related to burst firing.
- Ca^{2+} currents in general: Involved in diverse functions such as neurotransmitter release, synaptic plasticity, neurite outgrowth during development, and even gene expression.

Firing Pattern Dependent on Ionic Currents



- The presence or absence of different ionic currents drastically alter the spike behavior of neurons.

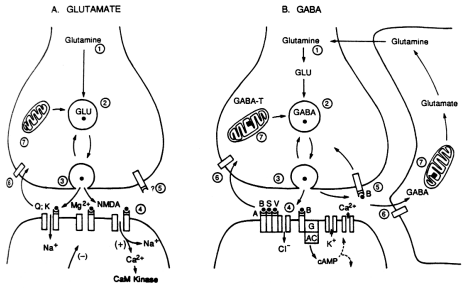
Firing Modes of Typical Neurons



Neuronal Communication

- Gap junctions: Direct flow of current across cells.
- Ephaptic interactions: Electrical field effect.
- Chemical synapses: Neurotransmitter action.

Chemical Synapses



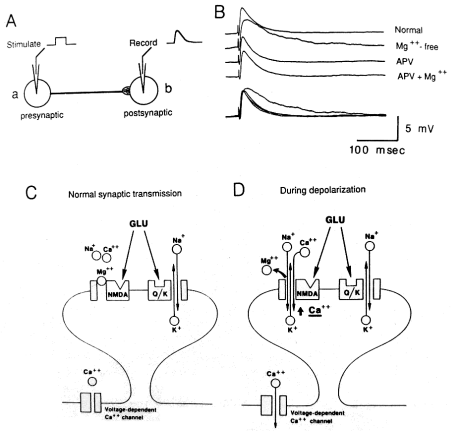
- Neurotransmitter release and binding.
- Channel opening or secondary effects (G-protein).
- Re-uptake of neurotransmitter by presynaptic terminal (GLU) or glia (GABA).
- GLU induces excitatory post synaptic potential (EPSP).
- GABA induces inhibitory post synaptic potential (IPSP).

Neurotransmitter and Ionic Currents

Table 2.2. Common Neurotransmitter Responses in the Central Nervous System

Response	Neurotransmitter	Receptor
$\uparrow I_{Na}$, $\uparrow I_K$	Glutamate	Quisqualate/kainate
$\uparrow I_{Na}$, $\uparrow I_K$, $\uparrow I_{Ca}$	Glutamate	*N*-Methyl-D-aspartate (NMDA)
	Acetylcholine	Nicotinic
$\uparrow I_{Cl}$	γ-Aminobutryic acid	$GABA_A$
	Glycine	
$\uparrow I_{K,IR}$	Acetylcholine	M_2
	Norepinephrine	α_2
	Serotonin (5-hydroxytryptamine [5-HT])	5-HT_1
	GABA	$GABA_B$
	Dopamine	D_2
	Adenosine	A_1
	Somatostatin	SST_5
	Enkephalins	μ, δ
$\downarrow I_{AHP}$	Acetylcholine	Muscarinic
	Norepinephrine	β_1
	Serotonin	5-HT_7
	Histamine	H_2
	Glutamate	Glutamate metabotropic
$\downarrow I_{K,leak}$	Acetylcholine	Muscarinic
	Norepinephrine	α_1
	Serotonin	5-HT_2
	Glutamate	Glutamate metabotropic
$\downarrow I_{Ca}$	Multiple transmitters	

Action of NMDA



- At high-frequency activation, Mg^+ will be unblocked, leading to long term potentiation (LTP), which is believed to play an important role in memory.

Neurotoxins and Drugs

- Agonist: Binds and turns on ion channel; Antagonist: Binds and blocks ion channel; Allosteric modulator: Binds and up- or down-modulate channel activity.
- Tetrodotoxin (TTX): Binds to the pores of voltage-gated Na^+ channels, thus blocking action potentials (found in puffer fish, toads, etc.).
- Benzodiazepine, Barbiturate: Binds to GABA-A receptors to up-modulate GABA binding.
- Bicuculine: Occupies GABA-A receptors, preventing GABA from activating the receptor. Overdose can lead to epilepsy.