CHAPTER 5
ION CHANNEL
Molecules are diffused into the cell

1. Lipid soluble molecules
2. Through channels
**FIGURE 3-15  DIFFUSION ACROSS THE PLASMA MEMBRANE**

*EXTRACELLULAR FLUID*

- Lipid-soluble molecules diffuse through the plasma membrane.
- Channel protein.
- Small water-soluble molecules and ions diffuse through membrane channels.
- Large molecules that cannot diffuse through lipids cannot cross the plasma membrane unless they are transported by a carrier mechanism.
Molecules are actively transported into the cell

What means ‘actively’?
FIGURE 3-19 THE SODIUM-POTASSIUM EXCHANGE PUMP

extracellular fluid

sodium-potassium exchange pump

2 $K^+$

ATP

ADP

cytoplasm
Endocytosis: getting molecules inside

vs.

Exocytosis: spitting molecules outside
THE PERMEABILITY OF THE CELL MEMBRANE

Cell membrane

Permeable?
Membrane potential (also transmembrane potential or membrane voltage) is the difference in electric potential between the interior and the exterior of a biological cell. With respect to the exterior of the cell, typical values of membrane potential range from $-40$ mV to $-80$ mV.

If a channel opens?
HOW TO DETECT THE CURRENT?
CHARACTERISTICS OF THE CURRENT

---

**GRAPH 5.2**  단일 이온채널을 통한 전류의 특성. 이 그림은 인공지질이중으로 분리된 응액과 그레이미신 A (gramicidin A) 분자들 모델에서 채널을 형성했을 때 얻어진 결과이다.

A. 그레이미신 A 채널은 두 개의 그레이미신 펄타이드가 결합하여 형성한 이동체를 형성하여 기능적인 채널이 될 것으로 생각된다. (Sawyer, Koepppe and Andersen 1989에서 인용)

B. 채널의 개폐는 실험을 통해, 이로 인해 세포막을 통해 전류의 체계의 전류가 생성된다. 세포막을 촉매로 전위(V)가 변화해되면 이로 인해 세포막의 채널을 통한 전류도 변화하게 된다. V,은 밀리볼트(mV)로 측정되었으나, V,는 밀리아포시(pA)로 측정되었다.

C. 채널을 통한 전류를 세포막 스테로드 질점에 대해 그래프로 그렸을 때 전류는 전압에 함수로 바뀌었다. 달리 표현하면 주기의 오름은 법칙 = V/R 또는 I = γ × V를 따르는 지점과 같이 작용했다. (Olef Andersen and Lyndon Providence에서 인용)
CURRENT-VOLTAGE

Ohmic channel

Rectifying channel

Linear
Non-linear

Characters of channels
The Nobel Prize in Chemistry 2003 was awarded "for discoveries concerning channels in cell membranes" jointly with one half to Peter Agre "for the discovery of water channels" and with one half to Roderick MacKinnon "for structural and mechanistic studies of ion channels".
THE NOBEL PRIZE IN CHEMISTRY 2003
MACKINNON PAPERS

POTASSIUM CHANNELS AND THE ATOMIC BASIS OF SELECTIVE ION CONDUCTION

Nobel Lecture, December 8, 2003

by

Roderick MacKinnon

Howard Hughes Medical Institute, Laboratory of Molecular Neurobiology and Biophysics, Rockefeller University, 1230 York Avenue, New York, NY10021, USA.

RESEARCH ARTICLES

The Structure of the Potassium Channel: Molecular Basis of $K^+$ Conduction and Selectivity

Declan A. Doyle, João Morais Cabral, Richard A. Pfuetzner, Anling Kuo, Jacqueline M. Gulbis, Steven L. Cohen, Brian T. Chait, Roderick MacKinnon*
Passage of water molecules through the aquaporin AQP1. Because of the positive charge at the center of the channel, positively charged ions such as $\text{H}_3\text{O}^+$, are deflected. This prevents proton leakage through the channel.
The ion channel permits passage of potassium ions but not sodium ions. The oxygen atoms of the ion filter form an environment very similar to the water environment outside the filter. The cell may also control opening and closing of the channel.
THREE PHYSICAL MODELS OF CHANNEL

Part of structural change

Overall structural change

Blocking particle
HOW IT WORKS? – REGULATION OF ACTIVITY
SEVERAL TYPES OF STIMULI CONTROL THE OPENING AND CLOSING

- Ligand
- Phosphorylation
- Voltage-gated
- Stress-gated
HOW IT WORKS? - INACTIVATION
VOLTAGE-GATED CHANNELS:  
TWO MECHANISMS

Ion binding (ex) Calcium binding

Refraction
EXOGENOUS LIGANDS CAN BIAS AN ION CHANNEL TOWARD AN OPEN OR CLOSED STATE.
STRUCTURE OF CHANNEL

Transmembrane domain

Property of membrane?
THE SECONDARY STRUCTURE OF MEMBRANE-SPANNING PROTEINS

Acetylcholine receptor

Type I & II?
THREE SUPERFAMILIES

A. Ligand-opening

B. Gap channel

C. Voltage gated
The more external (i.e., more extracellular) portion of the pore is formed by the "P-loops" (the region between S5 and S6) of the four domains. This region is the most narrow part of the pore and is responsible for its ion selectivity.
FOUR RELATED FAMILIES OF ION CHANNELS WITH P-REGIONS

- Voltage gated K+ channel
- Inward rectifying K+ channel
- Glutamate opening channel
- K+ channel With two p regions
FOUR RELATED FAMILIES OF ION CHANNELS WITH P-REGIONS

(Sandoz & Levitz, 2013)
FOUR RELATED FAMILIES OF ION CHANNELS WITH P-REGIONS
GENE EXPRESSION IN DEVELOPMENT

- Cassette Exon
- Mutually Exclusive Exons
- Intron Retention
- Alternative 5' or 3' Splice Sites
- Alternative Promoters
- Alternative Splicing and Polyadenylation
Different types of L+ channels are expressed in the different brain regions...

Functional differences
X-RAY CRYSTAL STRUCTURE
GATING OF BACTERIAL POTASSIUM CHANNELS

Close state

Open state

Glycine
CIC FAMILY OF CHLORIDE CHANNELS AND TRANSPORTERS

Can you see some difference?

Link between function and structure…
Figure 5-17 The vertebrate CIC family of chloride channels and transporters are double-barrel channels with two identical pores.

A. Recordings of current through a single vertebrate Cl⁻ channel show three levels of current: both pores closed (0), one pore open (1), and both pores open (2). (Reproduced, with permission, from Miller 1982.)

B. The CIC channels are dimers composed of two identical subunits, each forming a Cl⁻-selective pore. The channel is shown from the side (left) and looking down on the membrane from outside the cell (right). Each subunit contains its own ion transport pathway and gate. In addition, the dimer has a gate shared by both subunits (not shown). The drawing illustrates the functional properties of the channel.

C. The X-ray crystal structure of the Escherichia coli CIC Cl⁻/H⁺ exchanger in a side view (left) and top-down view (right). The ribbon diagram shows that each subunit is composed of a large number of α-helices. Two Cl⁻ ions (green spheres) are shown bound to each subunit: one ion is bound to the selectivity filter and a second is bound to an internal site closer to the cytoplasmic side of the membrane. (Reproduced, with permission, from Dutzler et al. 2002; Dutzler 2004.)

D. Left: The linear arrangement of the two cytoplasmic helices (A and B) and 16-membrane helices (B–Q) in a single subunit of the E. coli CIC transporter. The helices from the N-terminal half of a subunit are shown in green, while the helices from the C-terminal half are shown in cyan. (Reproduced, with permission, from Dutzler et al. 2002.) Right: The three-dimensional arrangement of the helices in a single E. coli CIC subunit. The regions in red help form the Cl⁻ permeation path. The Cl⁻ ions at the selectivity filter (top) and an internal site (bottom) are illustrated as green spheres. A negative charge on the channel wall that may serve as the channel's gate is illustrated as a red sphere. (Reproduced, with permission, from Jentsch 2002.)
COMPARISON OF GENERAL ARCHITECTURE

Parallel

Anti-parallel

K+ channel

Cl- channel
SPECIFICITY
HOW TO GET THE SPECIFICITY?

https://www.youtube.com/watch?v=4zms9bXM2FA
POTASSIUM CHANNELS AND THE ATOMIC BASIS OF SELECTIVE ION CONDUCTION

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Signal conduction
CHAPTER 06.

MEMBRANE POTENTIAL AND THE PASSIVE ELECTRICAL PROPERTIES OF THE NEURON
Neuronal condition

Membrane Potential, $V_m$

$V_m = V_{in} - V_{out}$

Figure 6-1 The cell membrane potential results from the separation of net positive and net negative charges on either side of the membrane. The excess of positive ions outside the membrane and negative ions inside the membrane represents a small fraction of the total number of ions inside and outside the cell at rest.
THREE METHODS TO RECORD NEURON

- Patch-clamp
- Extracellular (action potentials)
- Intracellular (transmembrane potential)
- Planare Microelectrodearray (MEA) (extracellular fieldpotential)
PATCH CLAMP RECORDING
Figure 6–2A The recording setup.
EXTRACELLULAR RECORDING

Good for in vivo recording…
INTRA VS. EXTRACELLULAR RECORDING
Let’s talk about the intracellular recording!

Concept of Depolarization & Hyperpolarization.
Imagine…

Resting potential: -60 ~ -70 mV
Figure 6–2B  Oscilloscope display.
Figure 6–2C  Depolarization.
Figure 6–2D  Hyperpolarization.
How do they send information through the long neurites?
How do they send information through the long neurites?

Ion influx occurs and then??

Input here?!
How do they send information through the long neurites?
Action potential

(Cole & Curtis, 1939)
Action potential

Fig. 4. Double exposure of the 2 per cent maximum bridge unbalance at 20 kc. and the monophasic action potential at one of the impedance electrodes. The time marks at the bottom are 1 millisecond apart.
THE ACTION POTENTIAL IS A RAPID CHANGE IN MEMBRANE POTENTIAL

1. Depolarization phase
2. Repolarization phase
3. Hyperpolarization phase

- Resting potential
- Threshold potential
VOLTAGe-GATED CHANNELS

Two important types:
1.) Na+ voltage gated channels
2.) K+ voltage gated channels

How voltage-gated channels work

At the resting potential, voltage-gated Na⁺ channels are closed.
Conformational changes open voltage-gated channels when the membrane is depolarized.
Resting Potential - Both voltage gated Na+ and K+ channels are closed.
Initial Depolarization - Some Na⁺ channels open. If enough Na⁺ channels open, then the threshold is surpassed and an action potential is initiated.
Na\textsuperscript{+} channels open quickly. K\textsuperscript{+} channels are still closed.

\[ P_{Na^+} > P_{K^+} \]
\( \text{Na}^+ \) channels self-inactivate, \( \text{K}^+ \) channels are open.

\[ P_{K^+} \gg P_{\text{Na}^+} \]
$E_{membrane} \approx E_{K^+}$

$P_{K^+} > P_{K^+}$ at resting state
**Resting Potential** - Both Na+ and K+ channels are closed.
Action potential

https://www.youtube.com/watch?v=ifD1YG07fB8
https://www.youtube.com/watch?v=OZG8M_IdAIM
How to travel the long, long way through axon?
The capsaicin receptor: a heat-activated ion channel in the pain pathway

Michael J. Caterina*, Mark A. Schumacher†‖, Makoto Tominaga*‖, Tobias A. Rosen*, Jon D. Levine† & David Julius*

Departments of *Cellular and Molecular Pharmacology, †Anesthesia, and ‡Medicine, University of California, San Francisco, California 94143-0450, USA
‖These authors contributed equally to this study.

Capsaicin, the main pungent ingredient in ‘hot’ chilli peppers, elicits a sensation of burning pain by selectively activating sensory neurons that convey information about noxious stimuli to the central nervous system. We have used an expression cloning strategy based on calcium influx to isolate a functional cDNA encoding a capsaicin receptor from sensory neurons. This receptor is a non-selective cation channel that is structurally related to members of the TRP family of ion channels. The cloned capsaicin receptor is also activated by increases in temperature in the noxious range, suggesting that it functions as a transducer of painful thermal stimuli in vivo.
ACTION POTENTIALS AND CONDUCTION
Axons carry information from the cell body to the axon terminals.

Axon terminals communicate with their target cells at synapses.
• Difference in ion concentration between compartments gives rise to the resting membrane potential (RMP). Membrane permeability to these ions also influences the RMP.

• **Transient changes** from the RMP produce electrical signals which transmit information in nerve cells.

### Changes in the Membrane Potential Produce Electric Signals in Nerve Cells

<table>
<thead>
<tr>
<th>Ion</th>
<th>Intracellular</th>
<th>Extracellular</th>
<th>Normal Plasma Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>K⁺</td>
<td>150</td>
<td>5</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Na⁺</td>
<td>12</td>
<td>140</td>
<td>135-145</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>10</td>
<td>105</td>
<td>100-108</td>
</tr>
<tr>
<td>Organic Anions</td>
<td>65</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
• **Depolarization** - a decrease in the potential difference between the inside and outside of the cell.

• **Hyperpolarization** - an increase in the potential difference between the inside and outside of the cell.

• **Repolarization** - returning to the RMP from either direction.

• **Overshoot** - when the inside of the cell becomes +ve due to the reversal of the membrane potential polarity.
• In the nervous system, different channel types are responsible for transmitting electrical signals over long and short distances:

• A) **Graded potentials** travel over **short distances** and are activated by the opening of mechanically or chemically gated channels.

• B) **Action potentials** travel over **long distances** and they are generated by the opening of voltage-gated channels.
Graded potentials are depolarizations or hyperpolarizations whose strength is proportional to the strength of the triggering event.

Graded potentials lose their strength as they move through the cell due to the leakage of charge across the membrane (e.g., leaky water hose).
Frequency of Action Potential Firing is Proportional to the Size of the Graded Potential

The amount of neurotransmitter released from the axon terminal is proportional to the frequency of action potentials.
A graded potential depolarization is called **excitatory postsynaptic potential (EPSP)**. A graded potential hyperpolarization is called an **inhibitory postsynaptic potentials (IPSP)**.

They occur in the cell body and dendrites of the neuron.

The wave of depolarization or hyperpolarization which moves through the cell with a graded potential is known as **local current flow**.

**Question:** EPSP or IPSP?
Question: See through the AP!!!
Graded potentials travel through the neuron until they reach the trigger zone. If they depolarize the membrane above threshold voltage (about -55 mV in mammals), an action potential is triggered and it travels down the axon.
What happens?
Graded potential summation
= Information summation
A neuron may receive greater than 10,000 inputs from presynaptic neurons.

The initiation of an action potential from several simultaneous subthreshold graded potentials, originating from different locations, is known as **spatial summation**.
Temporal Summation

- When summation occurs from graded potentials overlapping in time, it is called temporal summation.

- Summation of graded potentials demonstrates a key property of neurons: postsynaptic integration.
Then Action potential occurs!
Action Potential (AP)

- They are initiated in an all-or-none manner when the summed graded potential exceed threshold voltage. “0 or 1”
- They remain the same size as they travel along the axon over long distances.
- They are identical to one another.
- Occurs upon alteration of the permeability of $\text{Na}^+$ and $\text{K}^+$ ions through voltage-gated channels.
```markdown
<table>
<thead>
<tr>
<th></th>
<th>Graded Potential</th>
<th>Action Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of signal</strong></td>
<td>Input signal</td>
<td>Conduction signal</td>
</tr>
<tr>
<td><strong>Where occurs</strong></td>
<td>Usually dendrites and cell body</td>
<td>Trigger zone through axon</td>
</tr>
<tr>
<td><strong>Types of gated ion channels involved</strong></td>
<td>Mechanically or chemically gated channels</td>
<td>Voltage-gated channels</td>
</tr>
<tr>
<td><strong>Ions involved</strong></td>
<td>Usually Na⁺ and Cl⁻</td>
<td>Na⁺ and K⁺</td>
</tr>
<tr>
<td><strong>Type of signal</strong></td>
<td>Depolarizing (e.g., Na⁺) or hyperpolarizing (e.g., Cl⁻)</td>
<td>Depolarizing</td>
</tr>
<tr>
<td><strong>Strength of signal</strong></td>
<td>Depends on initial stimulus; can be summed.</td>
<td>Is always the same as long as graded potential is above threshold (all-or-none); cannot be summed</td>
</tr>
<tr>
<td><strong>What initiates the signal</strong></td>
<td>Entry of ions through chemically or mechanically gated ion channels</td>
<td>Above-threshold graded potential arrives at the integration zone</td>
</tr>
<tr>
<td><strong>Unique characteristics</strong></td>
<td>No minimum level required to initiate a graded potential</td>
<td>Threshold stimulus required to initiate action potential</td>
</tr>
<tr>
<td></td>
<td>Two-signal coming close together in time will sum</td>
<td>Refractory period: two signals too close together in time cannot sum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initial stimulus strength is indicated by frequency of a series of action potentials</td>
</tr>
</tbody>
</table>
```
Timecourse of the Action Potential
Na⁺ Channels Have Two Gates

(a) At the resting membrane potential, the activation gate closes the channel.

(b) Depolarizing stimulus arrives at the channel.

(c) With activation gate open, Na⁺ enters the cell.

(d) Inactivation gate closes and Na⁺ entry stops.

(e) During repolarization caused by K⁺ leaving the cell, the two gates reset to their original positions.
• The movement of the inactivation gate is coupled to the movement of the activation gate, but its response time is slower.

• When the activation gate is open, the signal passes along the channel protein to the inactivation gate.

• Na⁺/K⁺-ATPase Has No Direct Role to Play in the Action Potential.
<table>
<thead>
<tr>
<th>Name of Chemical</th>
<th>Channel Blocked</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrodotoxin (TTX)</td>
<td>Voltage-gated Na⁺</td>
<td>Made in ovaries and liver of Japanese puffer fish</td>
</tr>
<tr>
<td>Saritoxin</td>
<td>Voltage-gated Na⁺</td>
<td>Made by marine organism that causes “red tide”</td>
</tr>
<tr>
<td>Procaine</td>
<td>Voltage-gated Na⁺</td>
<td>Local anesthetic</td>
</tr>
<tr>
<td>Tetraethylammonium chloride (TEA)</td>
<td>Voltage-gated K⁺</td>
<td>Amine derivative</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Ca²⁺ and assorted receptor-operated channels</td>
<td>Depresses action potentials and depolarizes the membrane; inhibitory in higher doses and excitatory in low doses</td>
</tr>
</tbody>
</table>
**Tetrodotoxin (TTX) as a Therapeutic Agent for Pain**

![Figure 1. Schematic representation of voltage-gated sodium channel α-subunits and Tetrodotoxin (TTX) binding site. Voltage-gated sodium channel α-subunits are formed by four homologous domains (DI-IV), each consisting of 6 α-helical transmembrane segments (1–6). Segment 4 (dark red) corresponds to the voltage sensors. Sites of phosphorylation by protein kinase A (PKA) and protein kinase C (PKC) are represented by yellow circles and brown squares, respectively. The fast inactivation gate (IFM motif) is located in the intracellular loop between domains 3 and 4 and is represented by h (in pink oval); pink circles show the sites involved in forming the inactivation gate receptor. P-loops are located between helices 5 and 6 (in blue), which are the pore-lining segments (as shown in the lower figure). Outer (EEDD motif) and inner (DEKA motif) rings, represented by a green and purple band, respectively (in both the upper and lower figures), are formed by the amino acids indicated by circles of the same color. The TTX molecule interacts with the amino acid residues of these two rings in the pore of the channel, as detailed in the lower figure.](image-url)
The more external (i.e., more extracellular) portion of the pore is formed by the "P-loops" (the region between S5 and S6) of the four domains. This region is the most narrow part of the pore and is responsible for its ion selectivity.
• Absolutely refractory period - a second AP will not occur until the first is over. The gates on the Na\(^+\) channel have not reset.

• Relatively refractory period - the period shortly after the firing of a nerve fiber when partial repolarization has occurred and a greater than normal stimulus can stimulate a second response.
• Movement of the AP along the axon at high speed is called conduction.

• A wave of action potentials travel down the axon. GP => AP => GP =>…

• Each section of the axon is experiencing a different phase of the AP (see figure).
If you stimulated here...
If you stimulated here…

Which way?
If you stimulated here…

Which way?
• Absolute refractory periods prevent back propagation of APs into the cell body.

• Refractory periods limit the rate at which signals can be transmitted down a neuron. Limit is around 100 impulses/s.
Let’s see the steps of action potential again!
Graded potential triggers AP. Opens voltage-gated Na⁺ channels.
• The Na\(^+\) spreads **in all directions** attracted by the -ve ions in adjacent regions (3,4). Opens Na\(^+\) channels and initiates AP in the adjacent region along the axon (4), but not in the cell body where there are **no voltage-gated Na\(^+\)** channels (3).
•K⁺ channels have opened in the initial segment (5) and the Na⁺ (6) ions cannot trigger an AP in that region since its absolutely refractory. Na⁺ ions initiate action potentials in segment (7).
• K⁺ channels have opened in the initial segment (5) and the Na⁺ (6) ions cannot trigger an AP in that region since its absolutely refractory. Na⁺ ions initiate action potentials in segment (7).
Factors Influencing Conduction Speed of APs

- The resistance of the membrane to current leak out of the cell and the diameter of the axon determine the speed of AP conduction.

- Large diameter axons provide a low resistance to current flow within the axon and this in turn, speeds up conduction.

Myelin sheath which wraps around vertebrate axons prevents current leak out of the cells. Acts like an insulator, for example, plastic coating surrounding electric wires.

However, portions of the axons lack the myelin sheath and these are called Nodes of Ranvier. High concentration of Na⁺ channels are found at these nodes.
Saltatory Conduction

from the Latin saltare, to hop or leap

- When depolarization reaches a node, Na\(^+\) enters the axon through open channels.
- At the nodes, Na\(^+\) entry reinforces the depolarization to keep the amplitude of the AP constant, but slows the current flow due to a loss of charge to the extracellular fluid.

F8-22

- However, it speeds up again when the depolarization encounters the next node.
- The apparent leapfrogging of APs from node to node along the axon is called saltatory conduction.
Which one is faster?
Jacqueline du Pré died of Multiple Sclerosis

- In demyelinating diseases, such as multiple sclerosis, the loss of myelin in the nervous system slows down the conduction of APs. Multiple sclerosis patients complain of muscle weakness, fatigue, difficulty with walking and a loss of vision.
Membrane potential and its property...
The capsaicin receptor: a heat-activated ion channel in the pain pathway

Michael J. Caterina*, Mark A. Schumacher†, Makoto Tominaga*, Tobias A. Rosen*, Jon D. Levine† & David Julius‡

Departments of *Cellular and Molecular Pharmacology, †Anesthesia, and ‡Medicine, University of California, San Francisco, California 94143-0430, USA

Capsaicin, the main pungent ingredient in ‘hot’ chilli peppers, elicits a sensation of burning pain by selectively activating sensory neurons that convey information about noxious stimuli to the central nervous system. We have used an expression cloning strategy based on calcium influx to isolate a functional cDNA encoding a capsaicin receptor from sensory neurons. This receptor is a non-selective cation channel that is structurally related to members of the TRP family of ion channels. The cloned capsaicin receptor is also activated by increases in temperature in the noxious range, suggesting that it functions as a transducer of painful thermal stimuli in vivo.

The action potential in mammalian central neurons

Bruce P. Bean

Abstract | The action potential of the squid giant axon is formed by just two voltage-dependent conductances in the cell membrane, yet mammalian central neurons typically express more than a dozen different types of voltage-dependent ion channels. This rich repertoire of channels allows neurons to encode information by generating action potentials with a wide range of shapes, frequencies and patterns. Recent work offers an increasingly detailed understanding of how the expression of particular channel types underlies the remarkably diverse firing behaviour of various types of neurons.