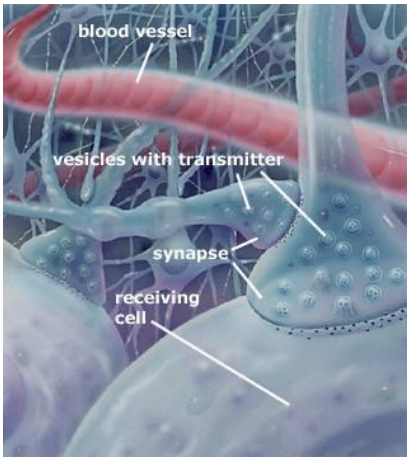
CSB 332
Neurobiology of the Synapse

Melanie A. Woodin
January 2012

Lecture 1
Chpts 4 & 5



Dr. Melanie A Woodin

- You can read a little about my research here: *http://www.csb.utoronto.ca/faculty/woodin-melanie*
- Who am I? What is my background?
- Why is Neurobiology exciting to me?

Syllabus

Date	Lecture	Readings	Title
9-Jan	1	Chpts 4 & 5	Introduction; Ion Channels
11-Jan	2	Chpt 6	Resting Membrane Potential
16-Jan	3	Chpt 7	Action Potentials
18-Jan	4	Chpts 11 & 12	Synaptic Transmission
23-Jan	5	Chpts 11 & 12	Synaptic Transmission
25-Jan	6	Chpt 13	Synaptic Transmission
30-Jan	7	Chpt 14	Synaptic Transmission
1-Feb			***Quiz***
6-Feb	8	p. 550-557	Axon Guidance
8-Feb	9	p. 558-562	Synapse Formation
13-Feb	10	Chpt 27	Denervation & Regeneration
15-Feb	11	Chpt 16	Synaptic Plasticity
27-Feb	12	Chpt 16	Synaptic Plasticity
29-Feb			***Mid-Term Test***
5-Mar	13	Chpt 16	Synaptic Plasticity
7-Mar	14		Learning & Memory
12-Mar	15		Learning & Memory
14-Mar	16	Chpt 24	Motor Control
19-Mar	17	Chpt 17	Autonomic Nervous System
21-Mar	18	Chpt 19	Sensory Systems
26-Mar	19	Chpt 19	Sensory Systems
28-Mar	20	Chpts 2 & 20	Sensory Systems
2-Apr	21	Chpts 2 & 20	Sensory Systems
4-Apr	22	Chpt 26	Sensory Systems

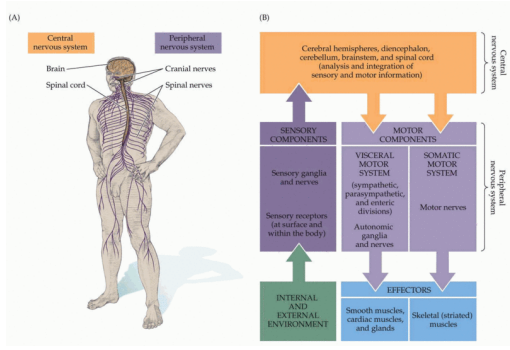
From Neuron to Brain *5th Edition*
Note: Additional readings from peer-reviewed manuscripts will be assigned in lecture throughout the course.

Marking Scheme

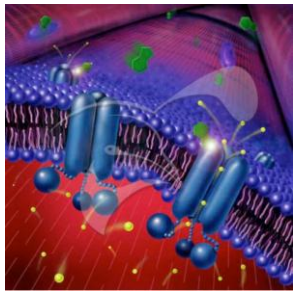
Date	Weight	Assignment	Notes
Feb 1st	20%	Quiz	• Short Answer • Material covered: Lectures 1 – 7 including readings • If you miss the quiz you must submit a medical note to Peggy Salmon. Please see the Missed Test Policy for details.
Feb 27th	30%	Mid-term test	• Combination of short answer, labeling and drawing diagrams. • Material covered: Lectures 1-12 including readings • If you miss the mid-term you must submit a medical note to Peggy Salmon. Please see the Missed Test Policy for details.
Final Exam Period	50%	Final Exam	• Cumulative • Multiple Choice, Diagrams and Long Answer

Course Details:

- Dr. Woodin's Office Hours Mondays 10-11am RW 303; you can also ask questions before or after class; please don't send emails asking about course content
- All course information will be posted on Blackboard; the Discussion board has been enabled (so that you can discuss amongst yourselves)
- Course Administrator: Peggy Salmon
  - **Work Phone** 416-978-8608
  - **Office Location** RW424E
  - **Office Hours** Tuesdays 9-11am, Wednesdays 2-3pm Thursdays 2-4pm



How do these membrane potentials arise?



- Electrical signals form the basis of information transfer in the nervous system.
- Electrical signals are generated by the action of ion channels.

most common form of electrical signalling is AP
->for AP membrane potential is required by electrical charge inside + outside the cell, by a buildup of electrical charge across the membrane using proteins

neuronal membrane

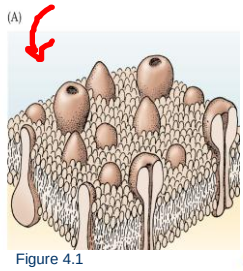
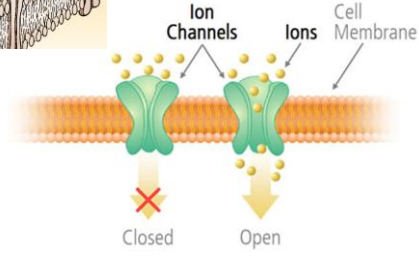


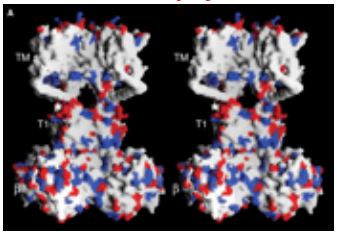
Figure 4.1



ions can't pass directly through lipid bilayer, use of diff. proteins
-> ion channels -> in general ions going through go down electrochemical gradient -> passive, not using ATP

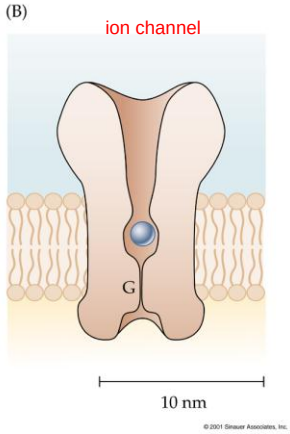
-> ion transporters ->use direct energy source of ATP, doing the work to establish the ionic gradient
-Na+/K+ ATPase
-these use ATPs to transport ions against their gradients

1st demonstration of ion channel structure, physical structure -> people knew the a.a. structure, but didn't know the physical structure until recently

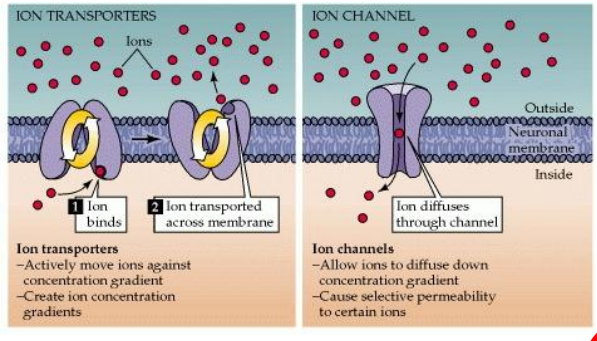


Science 5 August 2005:
Vol. 309. no. 5736, pp. 897 - 903

The Nobel Prize in Chemistry 2003
Roderick MacKinnon **K+ ion channel**
"for structural and mechanistic studies of ion channels"
http://nobelprize.org/chemistry/laureates/2003/mackinnon-autobio.html



less than 10nm in length-> packed tightly into the neuronal membrane
-they are either highly selective for one ion type or non-selective channels
->depends on the a.a. that are lining the selectivity pore
-if there's a cation -a.a. lining the selectivity pore will be -vely charged
-there are very few channels that are continuously open, most are going to open + close



large gradient

Concentrations of ions inside and outside freshly isolated axons of squid

Ion	Concentration (m*M*)		
	Axoplasm	Blood	Seawater
Potassium	400	20	10
Sodium	50	440	460
Chloride	60	560	540
Calcium	0.1 μ*M*[a]	10	10

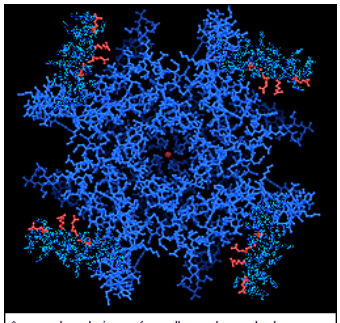
Source: After Hodgkin, 1964.
[a] Ionized intracellular calcium from Baker, Hodgkin, and Ridgeway, 1971.

->in general 4 ions
->giant axon of the squid (invertebrate axons used in early research, because dendritic axons are much larger than they are in mammalian due to lack of axon)
-they were available
-accessible as they were larger
-simpler -> could identify ind. neurons underlay behaviour

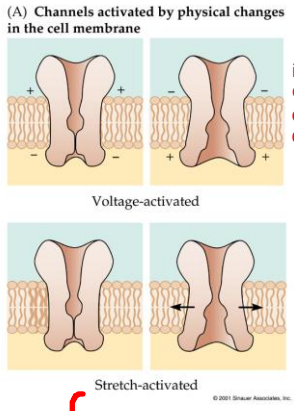
*Know where each ion is more concentrated

does not contribute to resting membrane potential

increasing probability of opening or decreasing probability
- ion channel opening may depend upon the trigger that increases the probability of them opening
-acetycholine opens the acetylcholine receptor ion channel + then it closes -> most channels are not normally available to opening right away, even if the trigger comes does not increase the probability of channel opening due to:
->inactivation - when ion channels normally open by change in membrane potential
->desensitization -> ion channels opened by ligands/ neurotransmitters



An overhead view of a voltage-dependent potassium ion channel shows four red-tipped "paddles" that open and close in response to positive and negative charges. This structure, discovered by Rockefeller scientists, shows for the first time the molecular mechanism by which potassium ions are allowed in and out of living cells during a nerve or muscle impulse.



inside is more +ve than out thus channel open on the inside
eg. Na+ channels opened when depolarizing membrane

Figure 4.2

eg. in skin receptors mechanically activated ion channels

how ion channels function
->all ion channels have a mean opening time; however there's a lot of a variability around it, not known why

->when neuron is @ rest K+ channels are open, +ve ions leaving thus -ve inside the cell

Ligand refers to a chemical most often refers to a neurotransmitter either extracellularly or intracellularly. Intracellularly it could be another ion such as Ca2+ / product of the intracellular transduction pathway which could activate the channel
When an ion channel is activated by a ligand, it is called a receptor (glutamate receptor, GABA receptor, acetylcholine receptor which are ion channels activated by ligands)

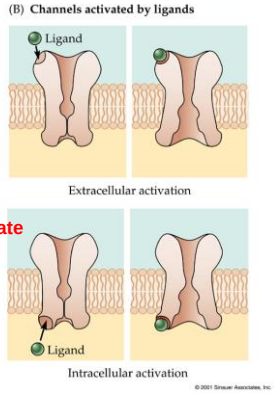


Figure 4.2

-agonist ->activate
-antagonist ->negative, inhibition

Happy Pufferfish

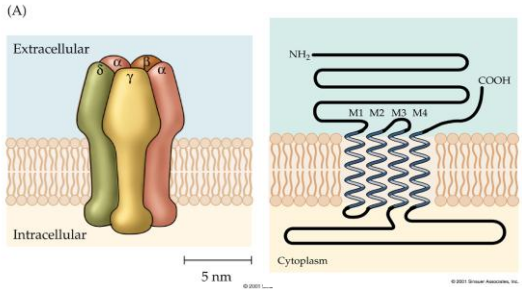
->many of the antagonists are found in biological cells

->organisms such as spiders and snails make toxins with antagonist chemicals, can be used in chemical warfare

Angry Pufferfish!

->pufferfish has this bacteria Tetrodotoxin
->TTX -> an open channel blocker generated by a bacteria
->sit on the ion selectivity pore
->prevent any AP, paralyzed
->death by respiratory paralyzes
->TTX does not cross BBB, you are awake thus completely aware of what's going on

Nicotinic acetylcholine receptor nAChR:



->if the ligand directly opens the ion channel - ionotropic
->if the ligand binds to a receptor & it initiates a signal transduction pathway which opens an ion channel -metabotropic channel
->only talking about those that are opened by direct binding of the ligand such as the nicotinic acetylcholine receptor -initially the most well studied receptor, made up of 5 subunits (2 alpha units to which acetylcholine binds to)
-called the 'nicotinic' acetylcholine receptor to distinguish itself from others such as the muscarinic acetylcholine receptor, distinguished by identifying what it binds to other than acetylcholine (nicotine) -> nicotine binding to alpha subunits can cause the acetycholine receptor to open, even though that's not how it's normally activated, other than when smoking a cigarette.
-acetylcholine receptors are densely packed
-each one the subunits it made up of long chain of a.a. & these long chains of a.a. in general have a structure, 4 transmembrane spanning domains with carboxyl and amino terminals facing ECS (M1,M2,M3 & M4) ->M2 being the most important

Proposed model of the nAChR Structure: