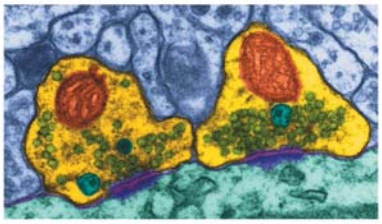
Lecture 8, 04 Feb 2008

Vertebrate Physiology
ECOL 437 (MCB/VetSci 437)
Univ. of Arizona, spring 2008

Kevin Bonine & Kevin Oh



1. Neurons & Synapses (Ch11&12)
   (finish slides posted for 30 Jan 2008)

http://eebweb.arizona.edu/eeb_course_websites.htm

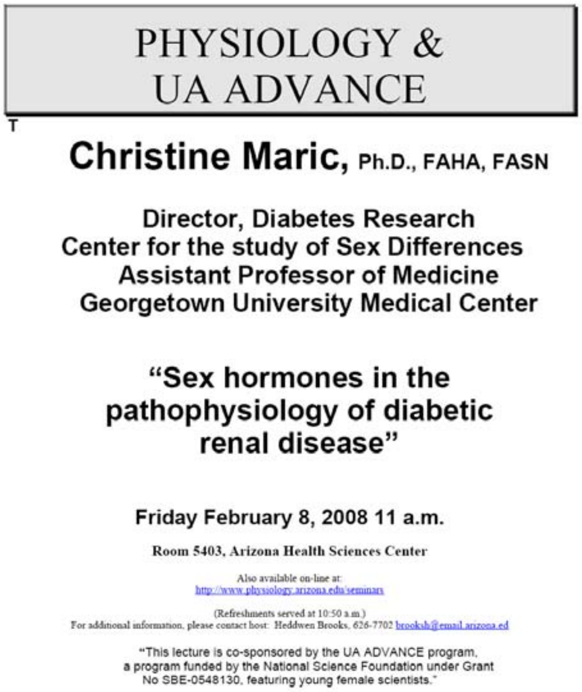
Housekeeping, 04 February 2008

Upcoming Readings
today: Ch 11, 12, Slowinski article
Wed 06 Feb: Ch13
LAB Wed 06 Feb: Catania 2002, Barinaga 1999, Malakoff 1999
(see website for links to papers; "worksheet" via email)
Fri 08 Feb: Ch13
Mon 11 Feb: Ch13
Wed 13 Feb: Ch13
LAB Wed 13 Feb: none
Fri 15 Feb: Exam 1, through Ch13

Lab discussion leaders: 20 Feb
1pm – Virsheena, Mathew S. Arturo
3pm – Kat, Clif, Amber

Lab discussion leaders: 06 Feb
1pm – Rittner, Whitney
3pm – Roxanne, Maria

Upcoming Physiology Seminar



PHYSIOLOGY & UA ADVANCE

T

Christine Maric, Ph.D., FAHA, FASN

Director, Diabetes Research
Center for the study of Sex Differences
Assistant Professor of Medicine
Georgetown University Medical Center

"Sex hormones in the pathophysiology of diabetic renal disease"

Friday February 8, 2008 11 a.m.

Room 5403, Arizona Health Sciences Center

Also available on-line at:
http://www.physiology.arizona.edu/seminars

(Refreshments served at 10:50 a.m.)
For additional information, please contact host: Heddwen Brooks, 626-7702 brooksh@email.arizona.ed

"This lecture is co-sponsored by the UA ADVANCE program,
a program funded by the National Science Foundation under Grant
No SBE-0548130, featuring young female scientists."

The Edges of Life

Wednesday, February 6
Life's Final Edge? The Origin and Extinction of Species in a Human-Dominated Earth
Michael Rosenzweig, Professor, Ecology and Evolutionary Biology

Today, Earth's treasury of species, its biodiversity, faces an existential challenge and its outcome depends on man. Science now knows we've taken away enough land from nature to precipitate a mass extinction like the one that exterminated the dinosaurs 65 million years ago. Using reconciliation ecology, we can prevent this - and preserve life.

Wednesday, February 13
Life's Cognitive Edge: The Role of the Mind and What it Means to be Human
Anna Dornhaus, Assistant Professor, Ecology and Evolutionary Biology

Our human mind distinguishes us from other animal life-or does it? Recent research has revealed culture and social learning, tool use, complex communication, self-recognition, and planning for the future are not unique to the human experience. With these new findings, science is finally getting closer to understanding exactly what makes us human.

Wednesday, February 20
Life's Human Edge: Changing Perspectives on the End of Life
Michael Gill, Associate Professor, Philosophy

Nothing looms with more certainty than the final edge of one's own life. But in fact, the edge between life and death is anything but clear. This lecture will address the attempts that have been made to define the line between life and death and will explore the biological, legal, ethical, and spiritual debates that have raged around that line.

Wednesday, March 5
Life's Technological Edge: The Singularity is Near: When Humans Transcend Biology
Ray Kurzweil, *via Teleportec Teleporter*
Founder, Chairman and Chief Executive Officer, Kurzweil Technologies

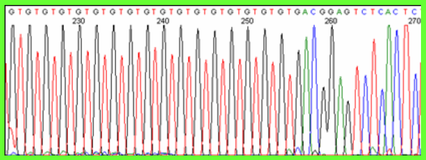
Humanity is on the edge of a vast transformation, when what it means to be human will be both enriched and challenged. Inventor and futurist Ray Kurzweil will introduce this radically optimistic singularity, an era when we break our genetic shackles to create a nonbiological intelligence trillions of times more powerful than today. In this new world, humans will transcend biological limitations to achieve entirely new levels of progress and longevity.

This lecture co-sponsored by: UA College of Engineering and UA College of Science

These do not count as physiology lectures.

- Want to work in an exciting **genetics research** lab on campus?
- Want to get a fancy biometric catcard and use your fingerprint to get into buildings?
- Want to learn how to do PCR? How about real-time PCR?
- Want to study amphibian declines and chytrid fungus?

We are looking for an outstanding, motivated, interesting person with good people, motor, and learning skills who could plan to invest a couple of years in the lab.



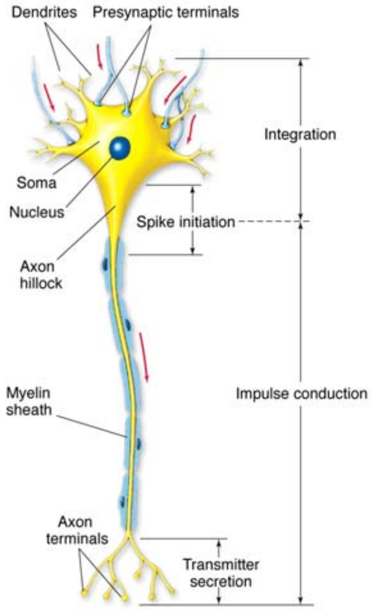
Will train!

Contact Kevin Bonine or Kim Baker:
kebonine@u.arizona.edu
KimDBaker@Juno.com

Vertebrate Physiology 437

Chapter 11

1. Action Potentials



5-2 Randall et al. 2002

In conjunction with 2 or 3 students around you,
explain how a change in the
postsynaptic membrane potential
from -70 to -65
could actually be inhibitory.

(Assume that -70 is resting and that -50 is threshold for an AP.)

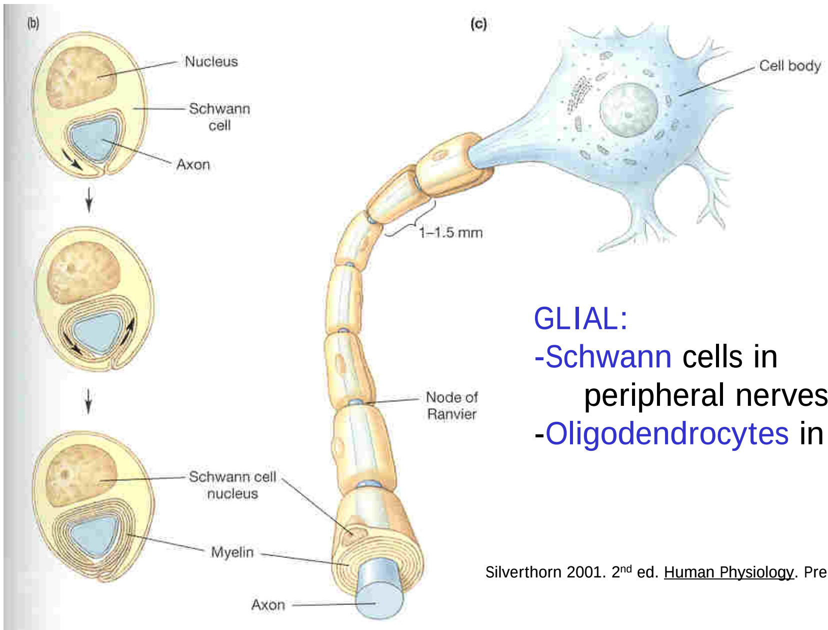


Figure 8-6 **Formation of myelin** (a) In the CNS, oligodendrocytes form myelin around portions of several interneuron axons. Astrocytes contact both neurons and blood vessels, but do not form myelin. (b) During myelin formation in the peripheral nervous system, the Schwann cell wraps around the axon many times while its nucleus is pushed to outside of the myelin sheath. (c) A Schwann cell forms myelin around a small segment of one axon.

GLIAL:
-Schwann cells in
peripheral nerves
-Oligodendrocytes in CNS

Silverthorn 2001. 2nd ed. Human Physiology. Prentice Hall

-How increase conduction velocity?

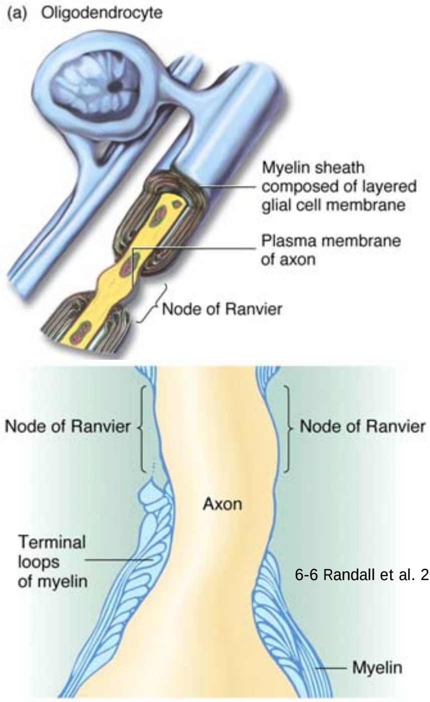
1 –Diameter

2 -Insulation

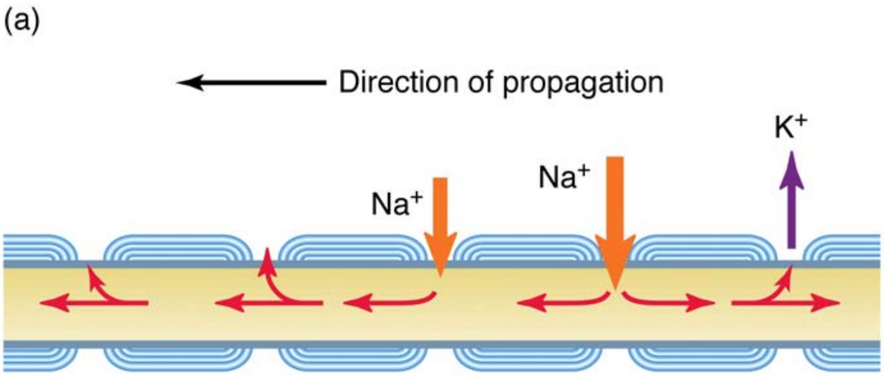
-Long axons require insulation (support cells)

-glial cells for myelination (fatty tissue) aka:

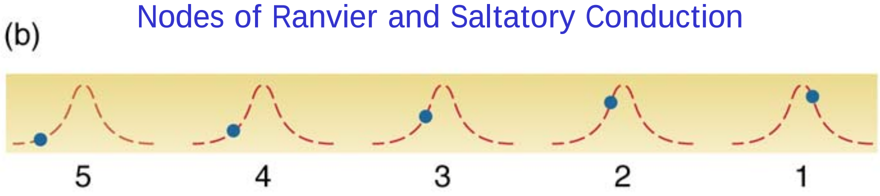
-Schwann cells in peripheral nerves
-Oligodendrocytes in CNS



6-6 Randall et al. 2002



Nodes of Ranvier and Saltatory Conduction



6-7 Randall et al. 2002

longitudinal current
vs. cross membrane

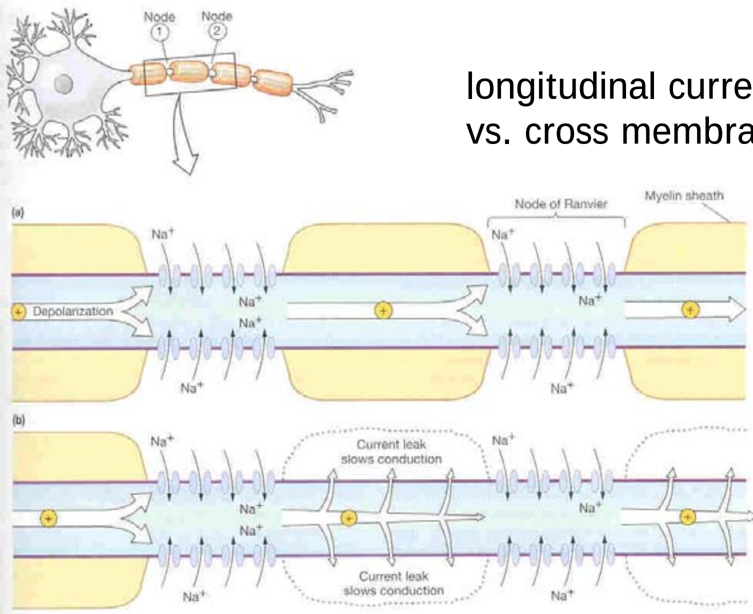


Figure 8-17 **Saltatory conduction** (a) Action potentials appear to jump from one node of Ranvier to the next when local current flow moves rapidly through the myelinated sections between the nodes. Voltage-gated Na^+ channels are scarce between the nodes. (b) In demyelinating diseases, conduction slows down as current leaks out of the previously insulated regions between the nodes. Since there are few Na^+ channels in those regions, the action potentials are not conducted as strongly between the nodes.

Silverthorn 2001. 2nd ed. Human Physiology. Prentice Hall

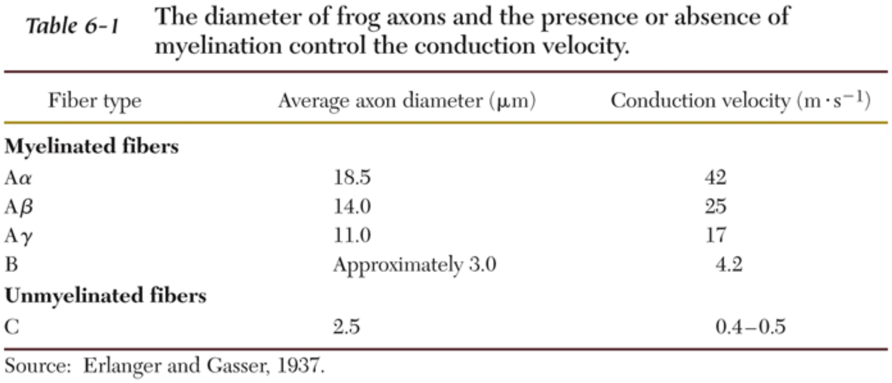


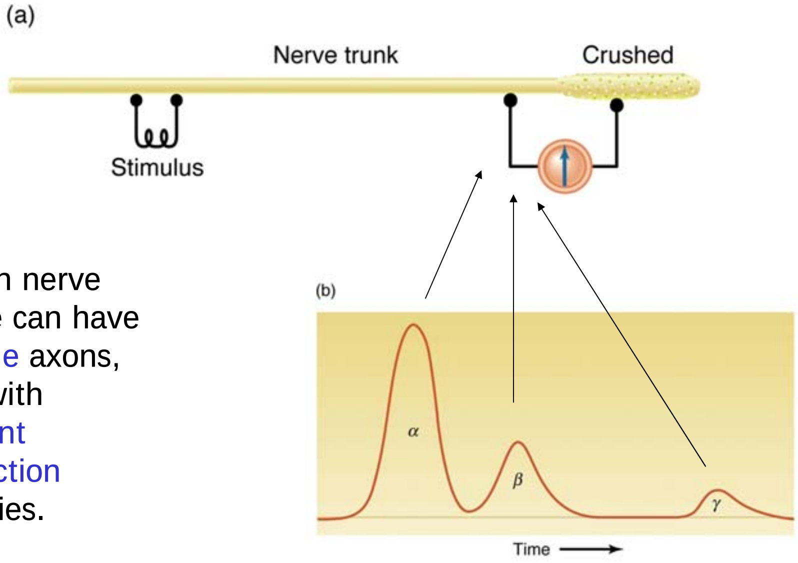
Table 6-1 **The diameter of frog axons and the presence or absence of myelination control the conduction velocity.**

Fiber type	Average axon diameter (μm)	Conduction velocity ($m \cdot s^{-1}$)
Myelinated fibers		
Aα	18.5	42
Aβ	14.0	25
Aγ	11.0	17
B	Approximately 3.0	4.2
Unmyelinated fibers		
C	2.5	0.4–0.5

Source: Erlanger and Gasser, 1937.

Randall et al. 2002

Multiple sclerosis caused
by demyelination

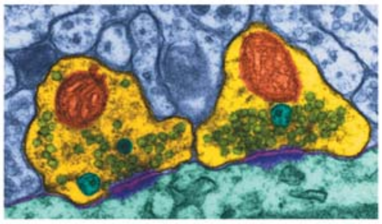


A given nerve bundle can have multiple axons, each with different conduction velocities.

6-8 Randall et al. 2002

Synapses

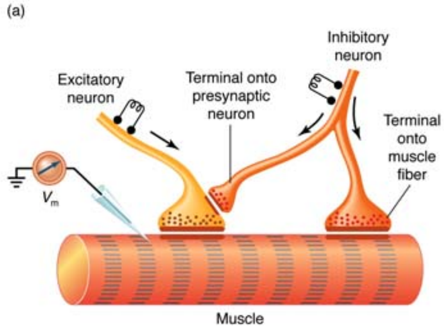
Ch13 in your text



SYNAPSES

-communication between neurons
 or between neuron and effector organ

1-electrical (rapid)
2-chemical(‘fast’ or slow)



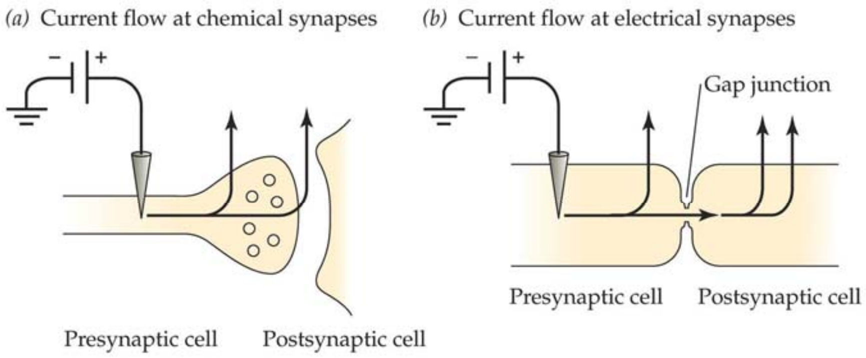
6-22 Randall et al. 2002

In postsynaptic neuron:

1. De- or hyper-polarize
2. Change # ion channels in membrane
3. Alter rate of ion channel activity
4. Modify sensitivity to activation signals

Chemical

Electrical



Hill et al. 2004, Fig 12.1

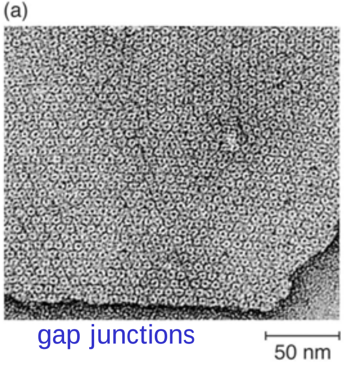
ANIMAL PHYSIOLOGY, Figure 12.1 (Part 1) © 2004 Sinauer Associates, Inc.

Electrical Synapse (rapid)

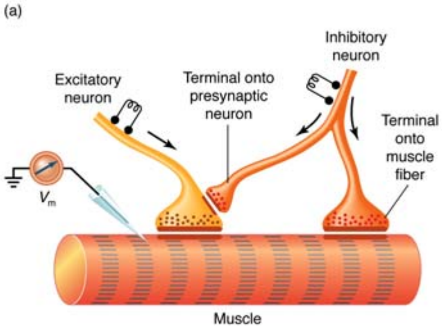
- direct ionic coupling via gap junctions

-examples in retina, CNS, smooth muscle, cardiac muscle, etc.

6-9 Randall et al. 2002

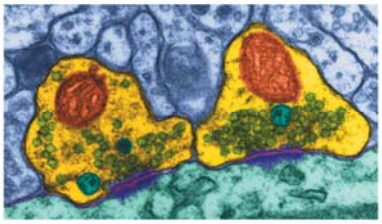


gap junctions



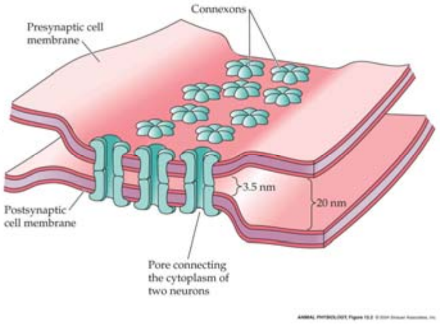
6-22 Randall et al. 2002

Chemical (neurotransmitter)
20-30nm apart



1 amplify
2 excitatory or inhibitory
3 ~one-way
4 modifiable

Electrical
(gap junction, connexons)
3nm apart



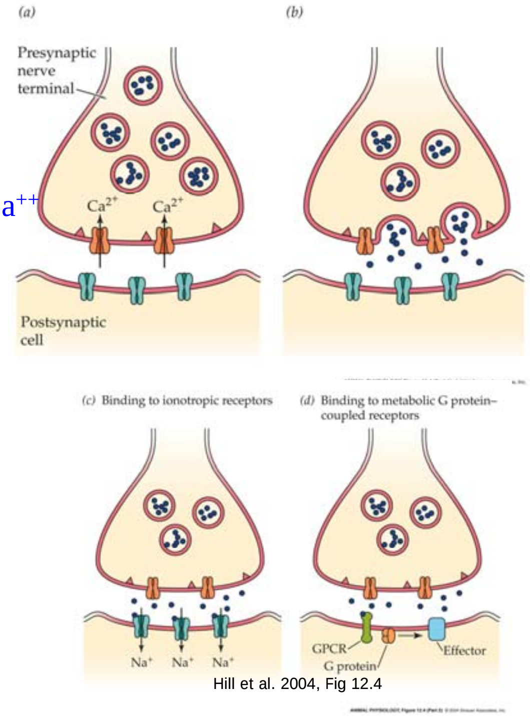
Hill et al. 2004, Fig 12.2,3

Chemical synapses

Role of Ca^{++}

ionotropic

metabotropic

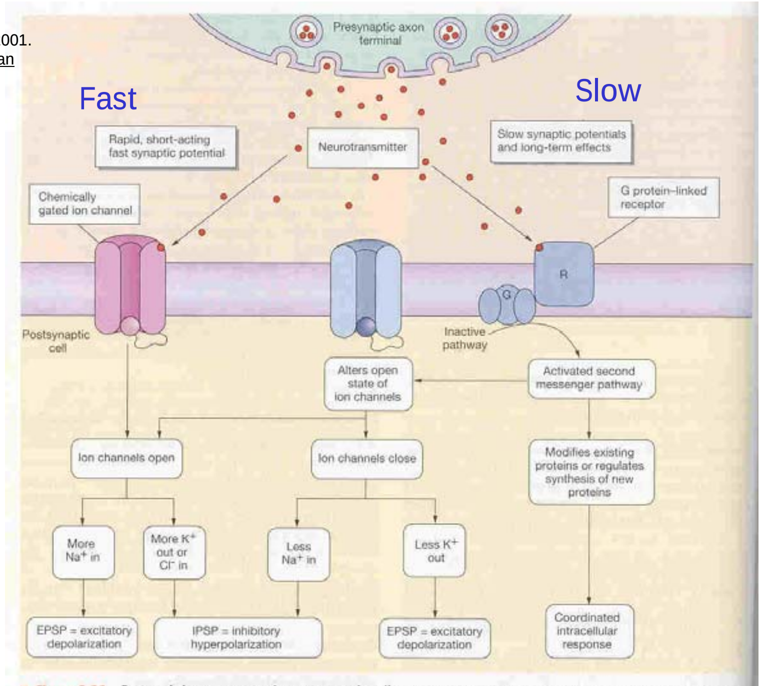


Hill et al. 2004, Fig 12.4

Silverthorn 2001. 2nd ed. Human Physiology. Prentice Hall

Fast

Slow



■ Figure 8-22 **Fast and slow responses in postsynaptic cells** Many neurotransmitters create rapid, short-acting responses opening ion channels. Some neurotransmitters create slower, longer-lasting responses by activating second messenger systems.

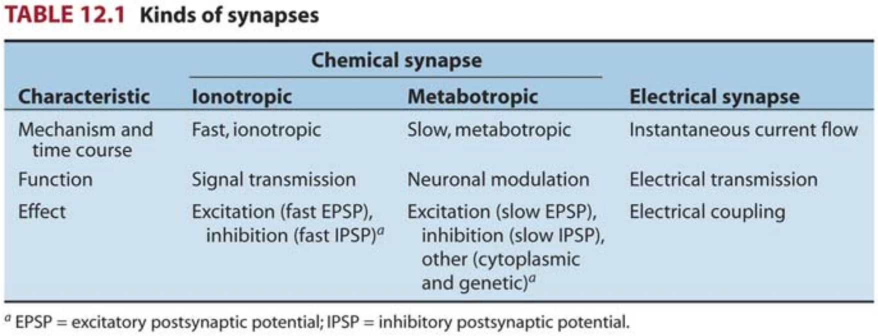


TABLE 12.1 Kinds of synapses

	Chemical synapse		
Characteristic	Ionotropic	Metabotropic	Electrical synapse
Mechanism and time course	Fast, ionotropic	Slow, metabotropic	Instantaneous current flow
Function	Signal transmission	Neuronal modulation	Electrical transmission
Effect	Excitation (fast EPSP), inhibition (fast IPSP)[a]	Excitation (slow EPSP), inhibition (slow IPSP), other (cytoplasmic and genetic)[a]	Electrical coupling

[a] EPSP = excitatory postsynaptic potential; IPSP = inhibitory postsynaptic potential.

Hill et al. 2004

ANIMAL PHYSIOLOGY, Table 12.1

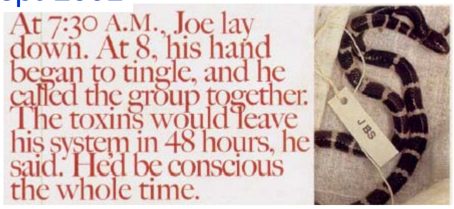
Postsynaptic Neurotransmitter Effects

NT role depends primarily on receptor characteristics on postsynaptic neuron

e.g., ACh receptors

1. Fast and direct	1. Nicotinic (muscles, autonomic/sympathetic NS)
2. Slow and indirect	2. Muscarinic (parasympathetic, indirect)

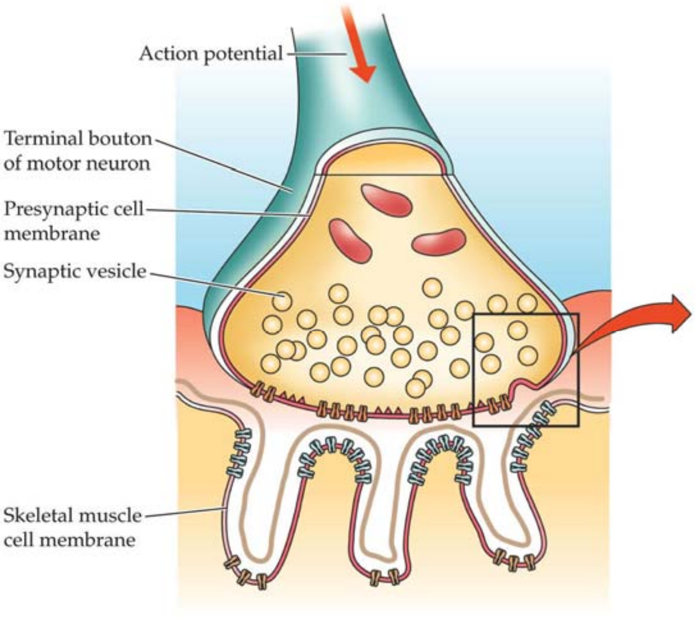
Bitten 11 Sept 2001, died 12 Sept 2001


At 7:30 A.M., Joe lay down. At 8, his hand began to tingle, and he called the group together. The toxins would leave his system in 48 hours, he said. He'd be conscious the whole time.


ENTWINED FATES: SLOWINSKI IN BURMA IN MAY 1999; OPPOSITE, THE FATAL KRAIT

Joe Slowinski
Myanmar/Burma
Bungarus multicinctus
Multibanded Krait
alpha bungarotoxin

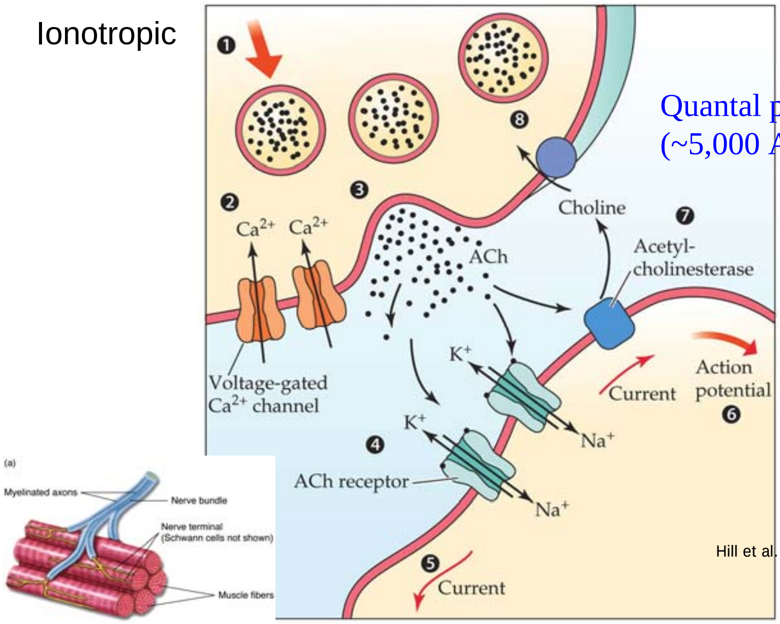
nicotinic ACh receptor
antagonist



ANIMAL PHYSIOLOGY, Figure12.7 (Part 1) © 2004 Sina

Neuromuscular Junction

Ionotropic



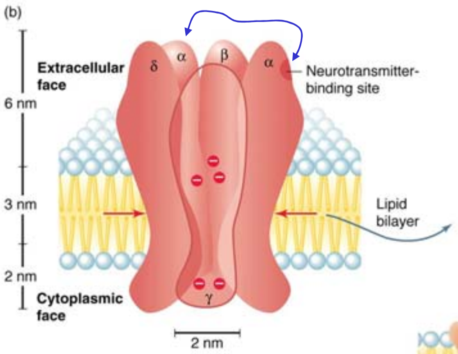
Quantal packets (~5,000 Ach/vesicle)

Hill et al. 2004, Fig 12.7

ANIMAL PHYSIOLOGY, Figure12.7 (Part 2) © 2004 Sinauer Associates, Inc.

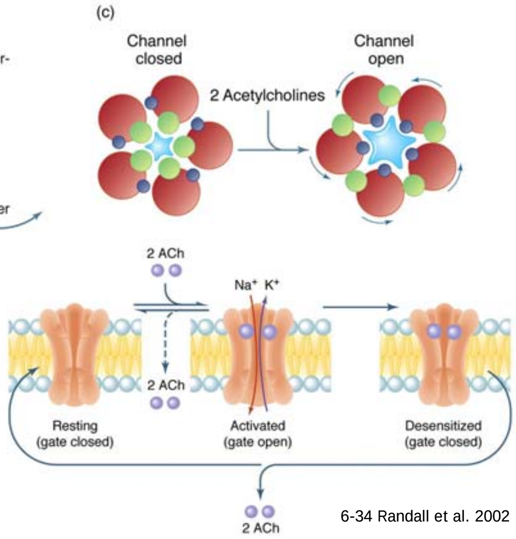
Postsynaptic Neurotransmitter Effects

1. Fast and direct e.g., fast nicotinic ACh receptors



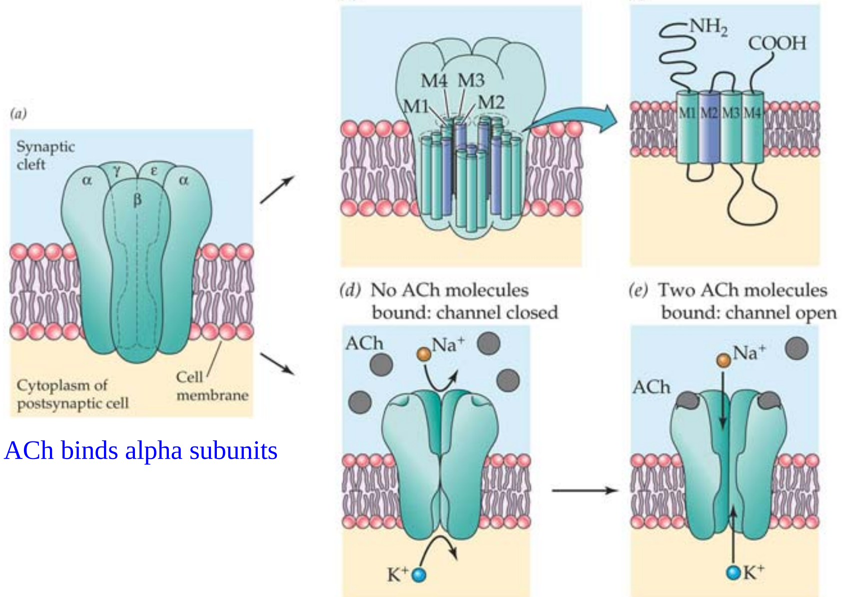
6-32 Randall et al. 2002

ACh binds alpha subunits



6-34 Randall et al. 2002

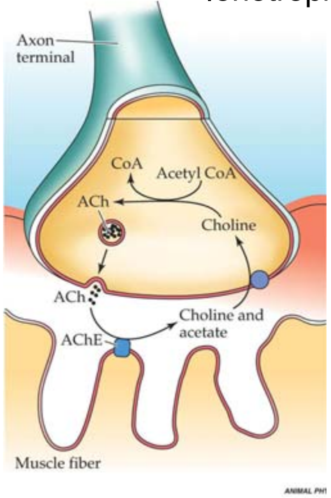
Nicotinic ACh receptor

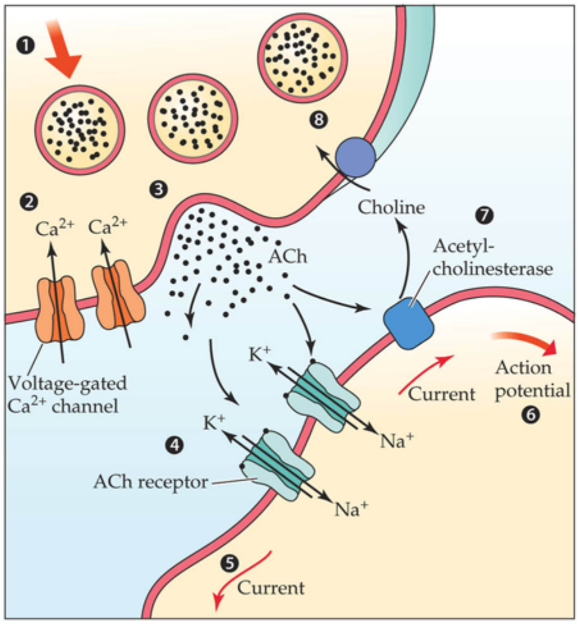


ACh binds alpha subunits

Hill et al. 2004, Fig 12.16

Ionotropic





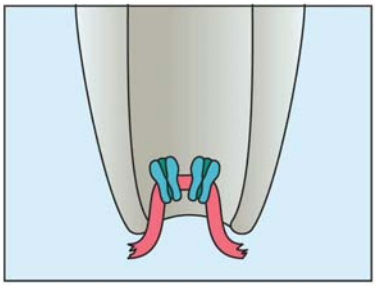
ANIMAL PHYSIOLOGY, Figure12.7 (Par

Acetylcholinesterase

Hill et al. 2004, Fig 12.10, 12.7

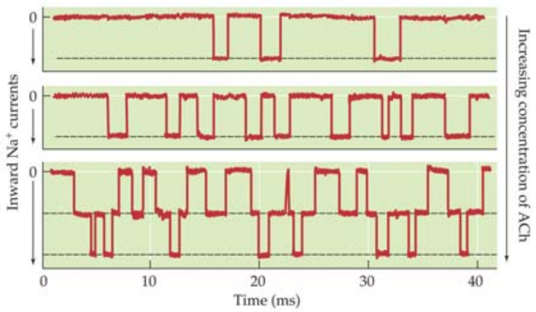
How do we study these receptors?
Patch-clamp technique

(a) Patch-clamp of ACh receptor channels



ANIMAL PHYSIOLOGY, Figur

(b) Effect on single-channel currents of increasing ACh



Hill et al. 2004, Fig 12.17

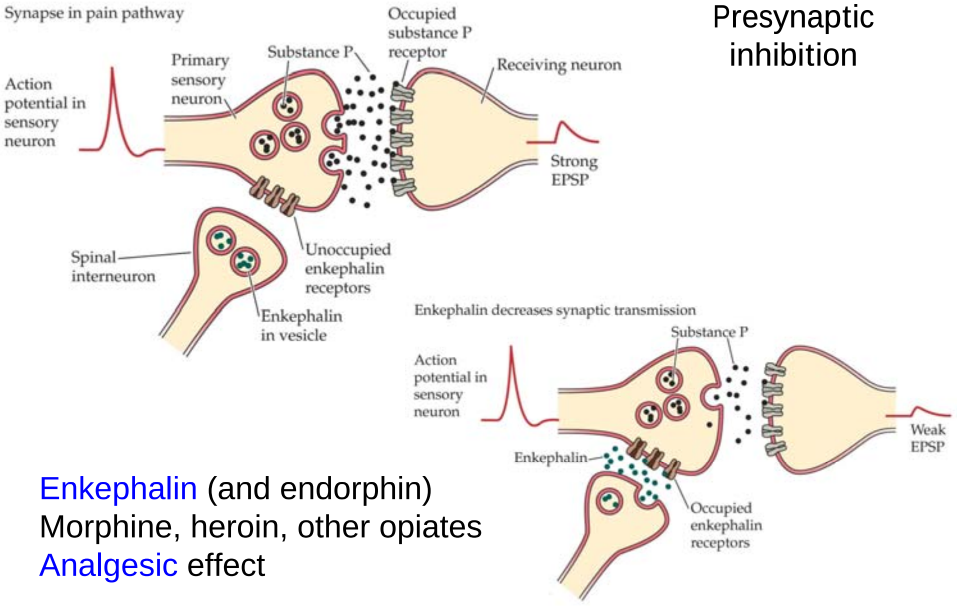
ANIMAL PHYSIOLOGY, Figure 12.17 (Part 2)

Agonist (mimics)
(e.g., heroin mimics natural opiates)

vs.

Antagonist (blocks)
(e.g., curare blocks ACh reception)

Presynaptic inhibition

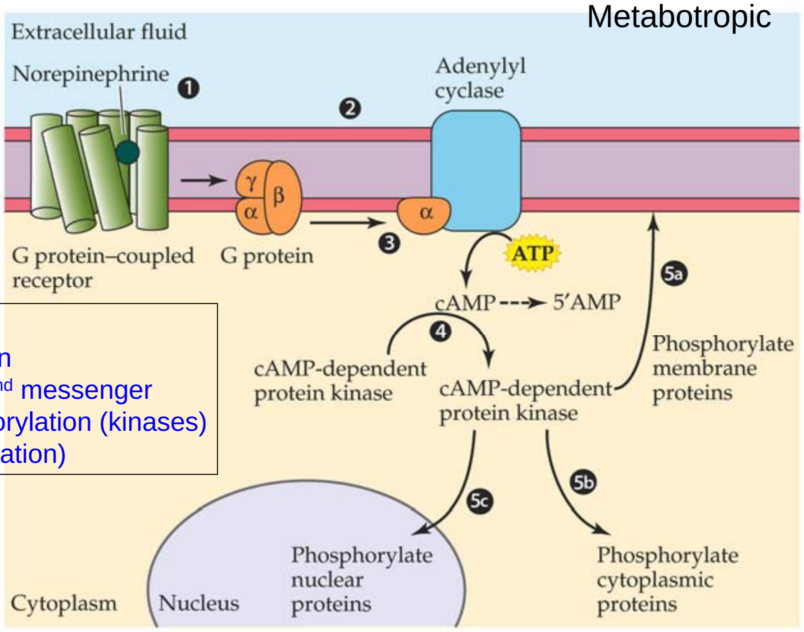


Enkephalin (and endorphin)
Morphine, heroin, other opiates
Analgesic effect

Hill et al. 2004 pg. 330

ANIMAL PHYSIOLOGY, Box 12.1 (Part 2) © 2004 Sinauer Associates, Inc.

Metabotropic

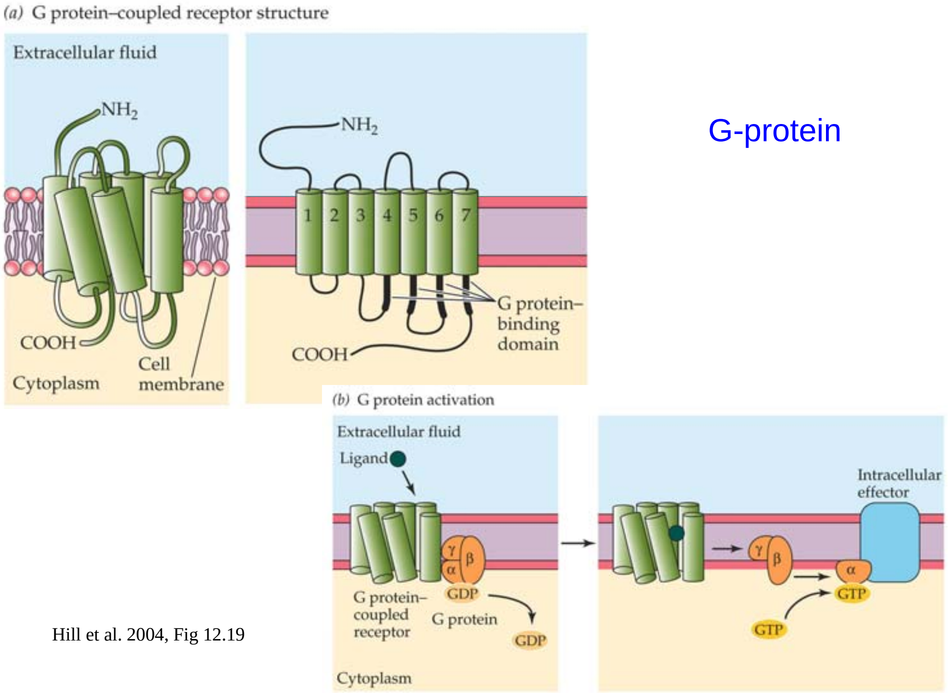


- Norepi
- G-protein
- cAMP 2nd messenger
- Phosphorylation (kinases)
- (amplification)

Hill et al. 2004, Fig 12.18

ANIMAL PHYSIOLOGY, Figure 12.18 © 2004 Sinauer Associat

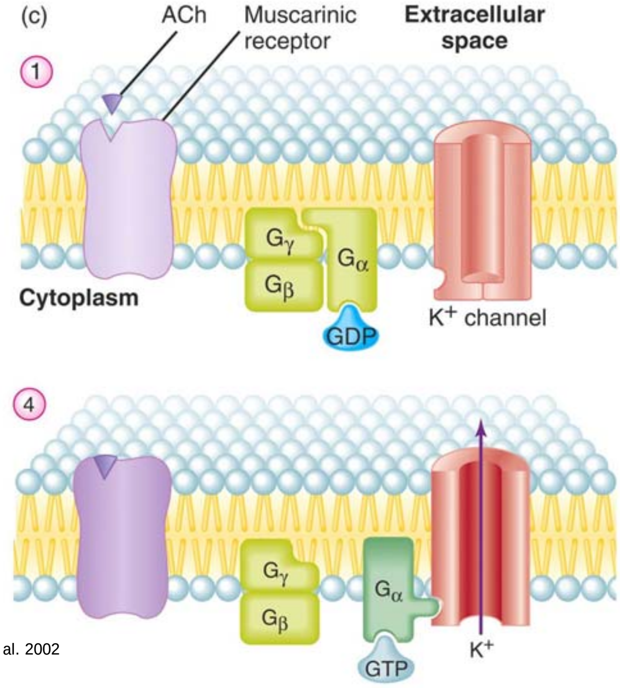
G-protein



Hill et al. 2004, Fig 12.19

Postsynaptic Neurotransmitter Effects

e.g., indirect, metabotropic muscarinic ACh receptors acting to reduce heart cell excitability



6-37 Randall et al. 2002

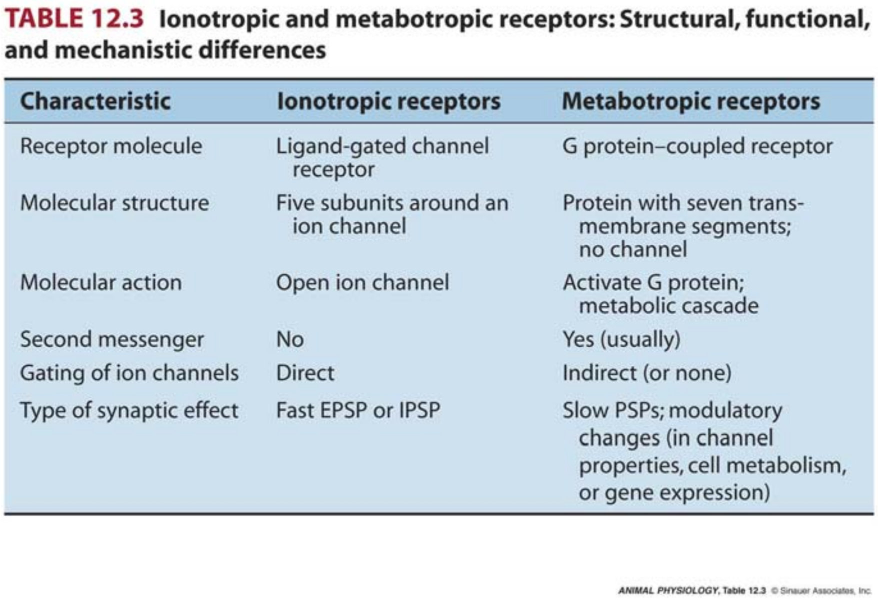
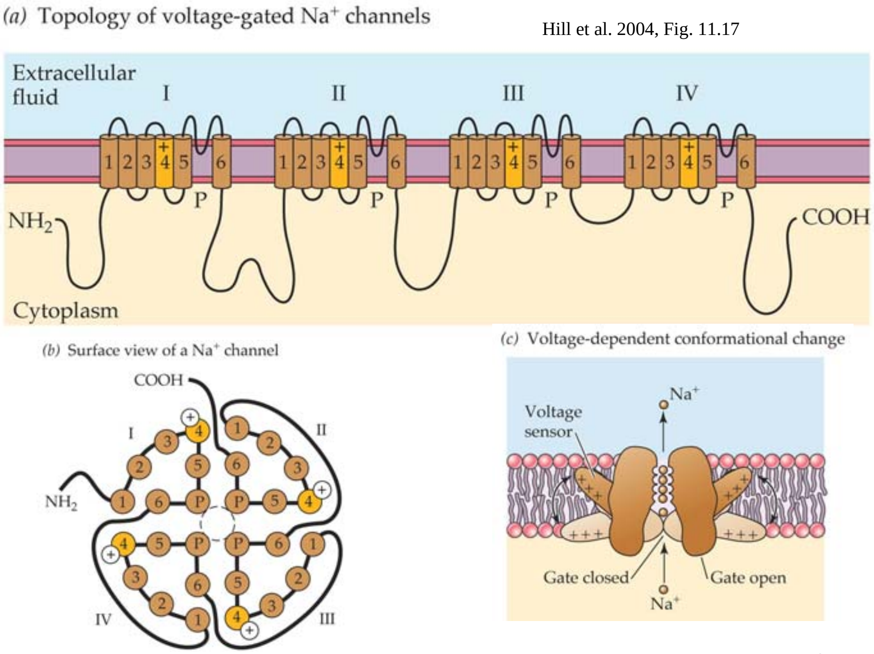


TABLE 12.3 Ionotropic and metabotropic receptors: Structural, functional, and mechanistic differences

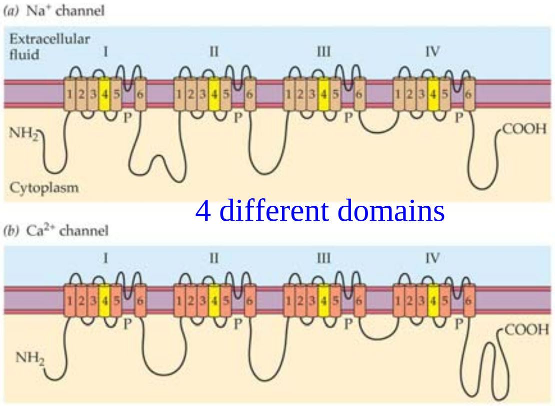
Characteristic	Ionotropic receptors	Metabotropic receptors
Receptor molecule	Ligand-gated channel receptor	G protein–coupled receptor
Molecular structure	Five subunits around an ion channel	Protein with seven trans-membrane segments; no channel
Molecular action	Open ion channel	Activate G protein; metabolic cascade
Second messenger	No	Yes (usually)
Gating of ion channels	Direct	Indirect (or none)
Type of synaptic effect	Fast EPSP or IPSP	Slow PSPs; modulatory changes (in channel properties, cell metabolism, or gene expression)

ANIMAL PHYSIOLOGY, Table 12.3 © Sinauer Associates, Inc.



Hill et al. 2004, Fig. 11.17

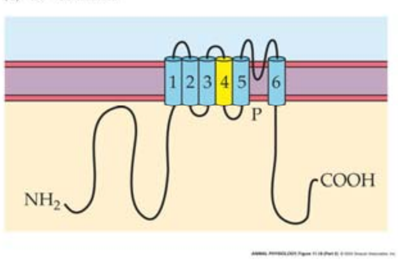
37



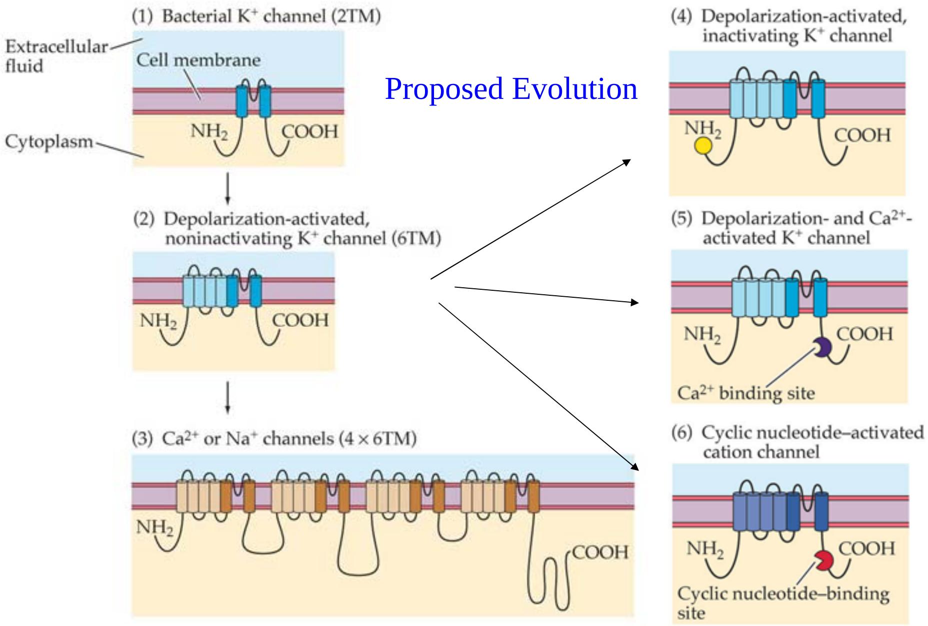
4 different domains

Hill et al. 2004, Fig. 11.18

4 identical subunits



Voltage-gated channel superfamily



Proposed Evolution

Voltage-gated Channels

Hill et al. 2004, pg. 301

Neurotransmitters:

1. small-molecule neurotransmitters
   (often made in axon terminals; common)
2. neuroactive peptides
   (often made in soma and shipped down axon)

Nematodes use a lot of the same neurotransmitters.

40

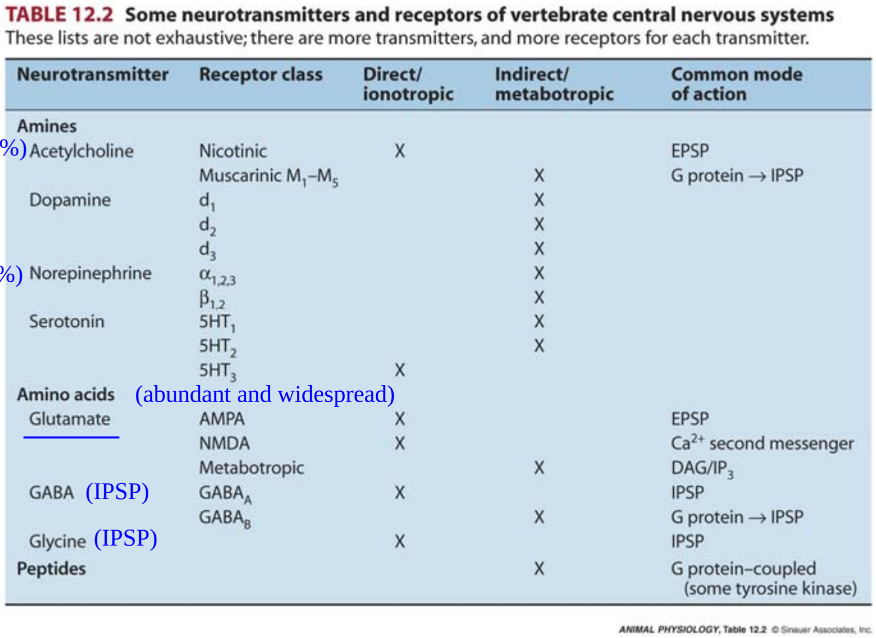


TABLE 12.2 **Some neurotransmitters and receptors of vertebrate central nervous systems**

These lists are not exhaustive; there are more transmitters, and more receptors for each transmitter.

Neurotransmitter	Receptor class	Direct/ ionotropic	Indirect/ metabotropic	Common mode of action
Amines				
(10%) Acetylcholine	Nicotinic	X		EPSP
	Muscarinic M_1–M_5		X	G protein → IPSP
Dopamine	d_1		X	
	d_2		X	
	d_3		X	
(1%) Norepinephrine	$\alpha_{1,2,3}$		X	
	$\beta_{1,2}$		X	
Serotonin	$5HT_1$		X	
	$5HT_2$		X	
	$5HT_3$	X		
Amino acids (abundant and widespread)				
Glutamate	AMPA	X		EPSP
	NMDA	X		Ca^{2+} second messenger
	Metabotropic		X	DAG/IP_3
GABA (IPSP)	$GABA_A$	X		IPSP
	$GABA_B$		X	G protein → IPSP
Glycine (IPSP)		X		IPSP
Peptides			X	G protein–coupled (some tyrosine kinase)

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Synaptic Plasticity

- Change synaptic efficacy
- Alter rate of NT production and release

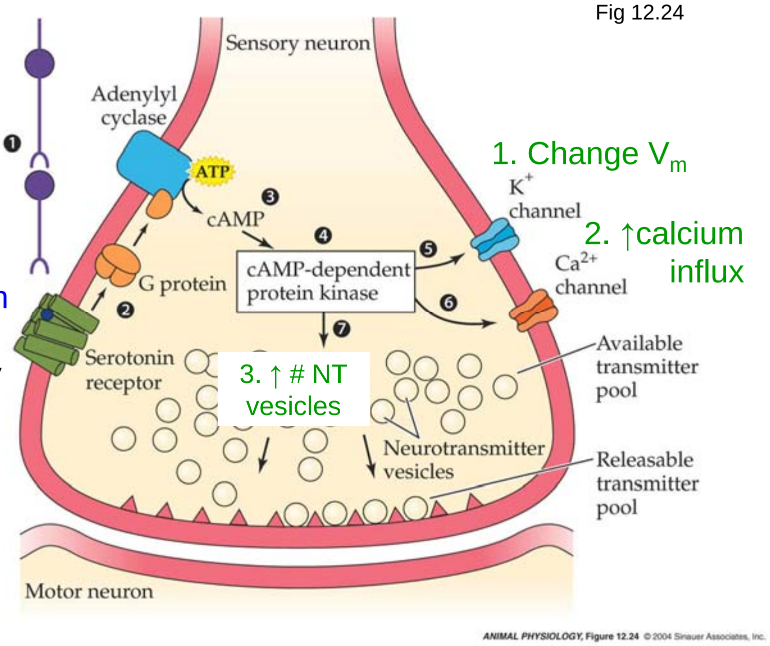
- Learning and Memory

- Facilitation vs. antifacilitation/depression

- Retrograde messengers (i.e., NO)

- Calcium-dependent
  - Research on-going

Hill et al. 2004
Fig 12.24



ANIMAL PHYSIOLOGY, Figure 12.24 © 2004 Sinauer Associates, Inc.

1. Change V_m

2. ↑calcium influx

3. ↑ # NT vesicles

Sensitization (facilitation) mediated by serotonin

Long-term Potentation

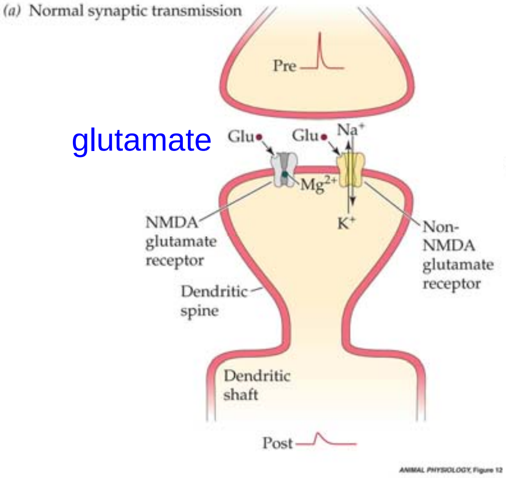
- Often in Hippocampus
  - Site of Learning and Memory
- "Neurons that fire together wire together"
- NMDA glutamate receptors…

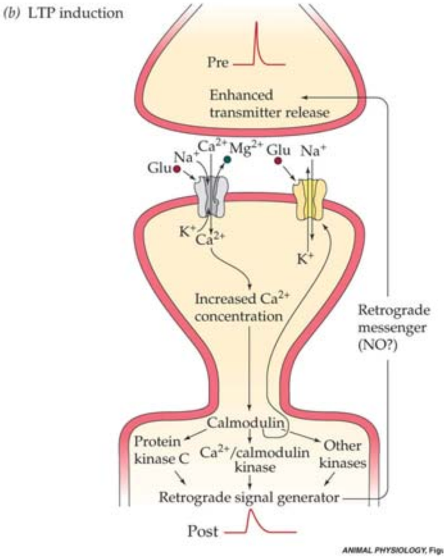
NMDA = N-methyl-D-aspartic acid

Hill et al. 2004, Fig 12.27

Long term potentiation (LTP)

glutamate





- NMDA glutamate receptors
    - role of Mg2+
    - voltage-dependent

Doogie Mice?

Genetic engineers upregulated production of juvenile subunit of NMDA receptor in adult mice (Doogie mice).

Ethical?

Should we do this in humans or other animals?

Under what conditions?