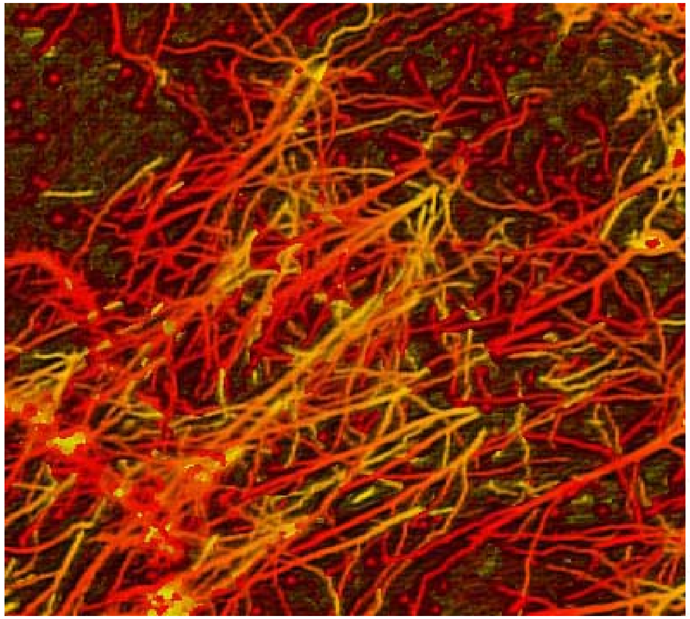
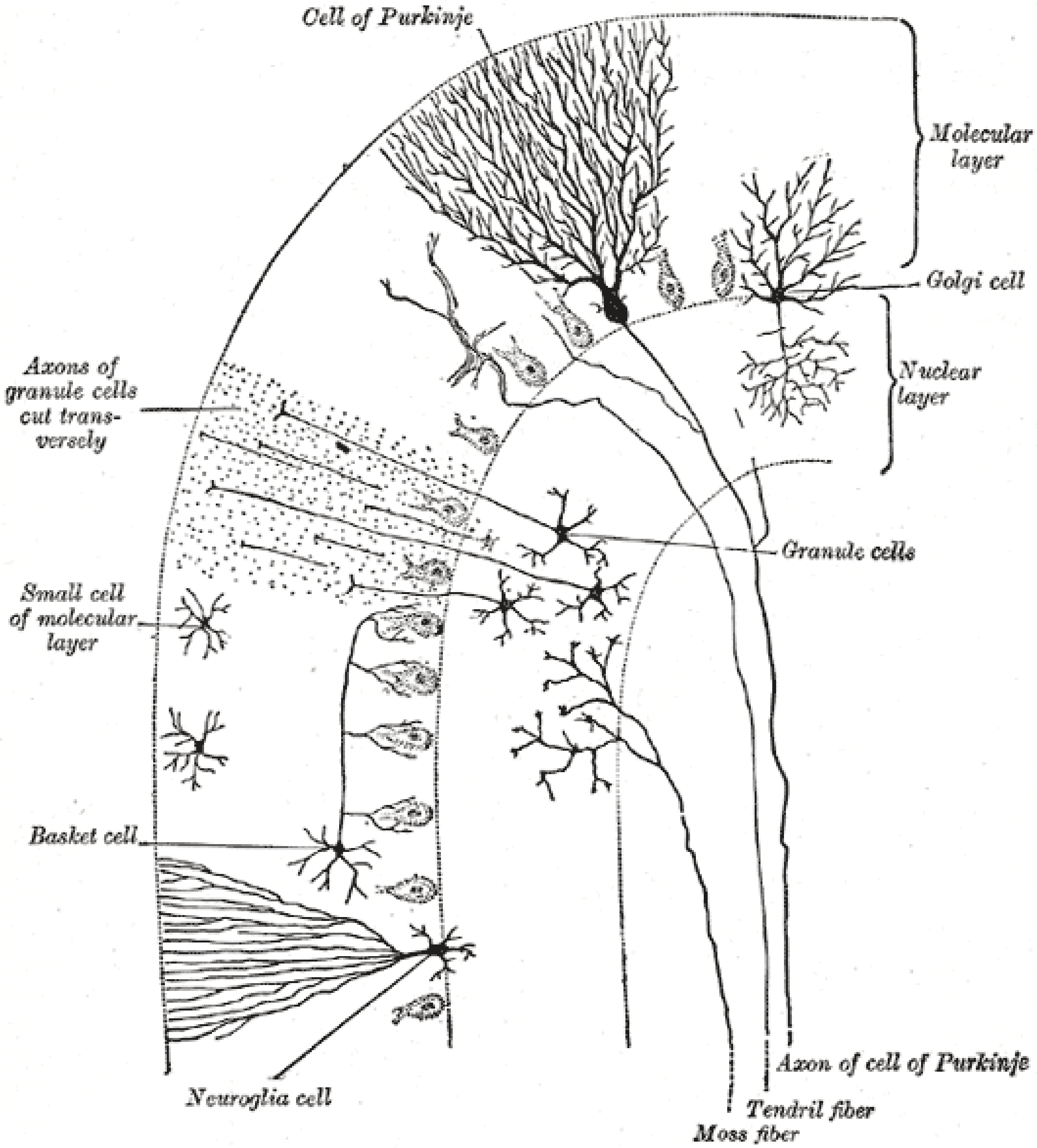
2. The neuron





Transverse section of a cerebellar folium.
http://en.wikipedia.org/wiki/Purkinje_cell

Brain cells: neurons and glial cells

Neurons: the functional cells of the nervous system. See below.

Glial cells (neuroglia): make up 90% of the brain cells

a) **astrocytes -** these cells anchor neurons to blood vessels, regulate the micro-environment of neurons, and regulate transport of nutrients and wastes to and from neurons.

b) **microglia -** these cells are phagocytic to defend against pathogens. They may also monitor the condition of neurons.

c) **ependymal** cells - these cells line the fluid-filled cavities of the brain and spinal cord. They play a role in production, transport, and circulation of the cerebrospinal fluid.

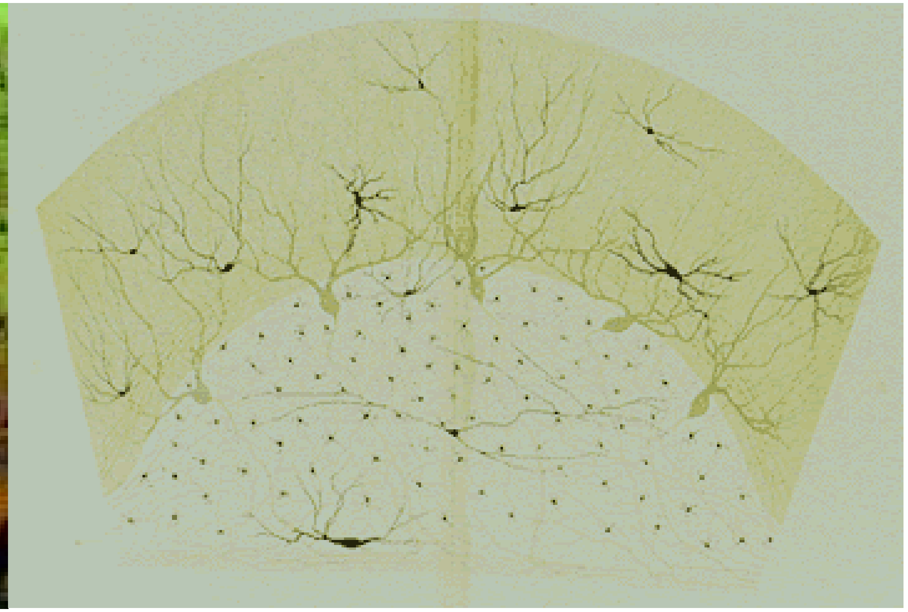
d) **oligodendrocyte -** produce the myelin sheath in the CNS which insulates and protects axons**.**

e) **Schwann cells -** produce the myelin sheath in the PNS. The myelin sheath protects and insulates axons, maintains their micro-environment, and enables them to regenerate and re-establish connection with receptors or effectors.

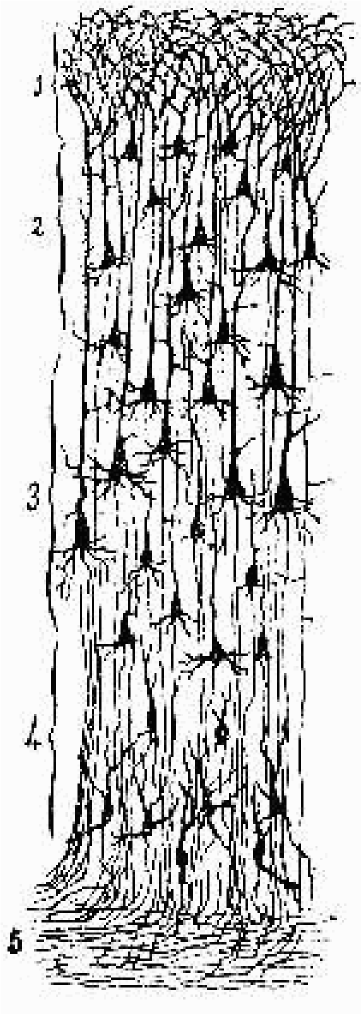
f) **satellite cells -** surround cell bodies of neurons in ganglia. Their role is to maintain the micro-environment and provide insulation for the ganglion cells.

http://webanatomy.net/anatomy/neuro_notes.htm

Camillo Golgi (1843-1926)



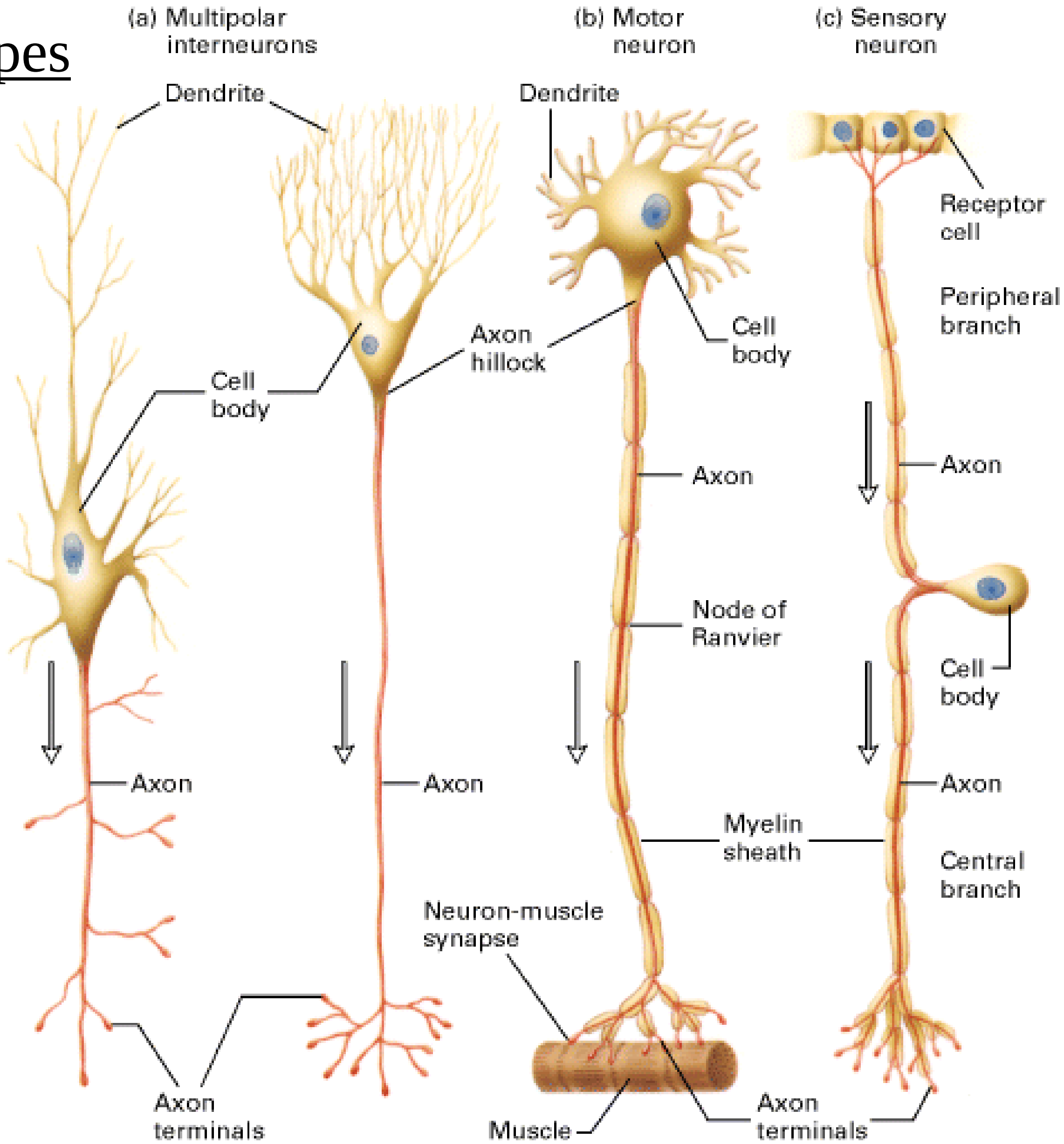
Santiago Ramón y Cajal (1852-1934)



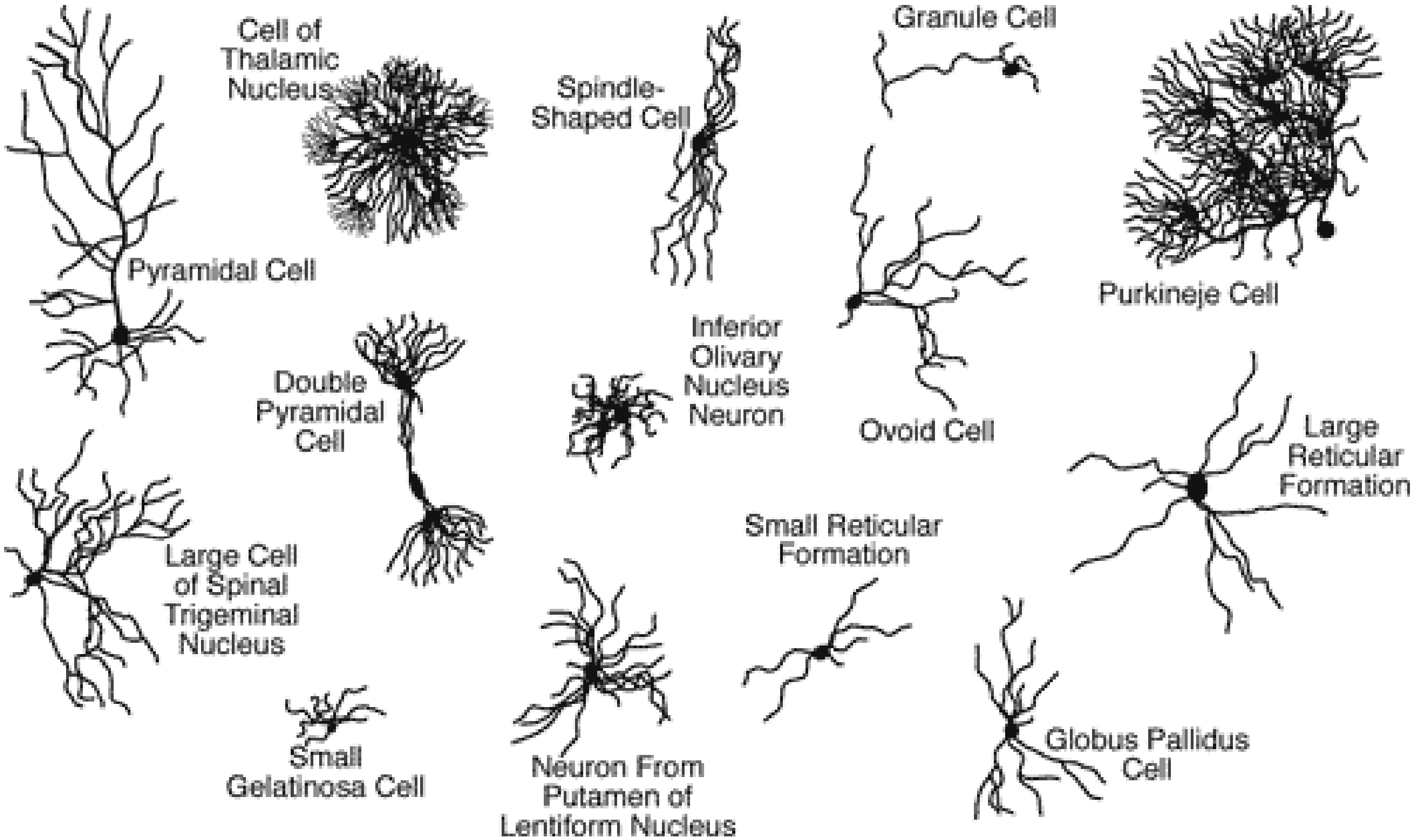
independent neurons, or nerve cells, are the building blocks of the central nervous system

Neurons: 3 basic types

Interneuron
Motor neuron
Sensory neuron

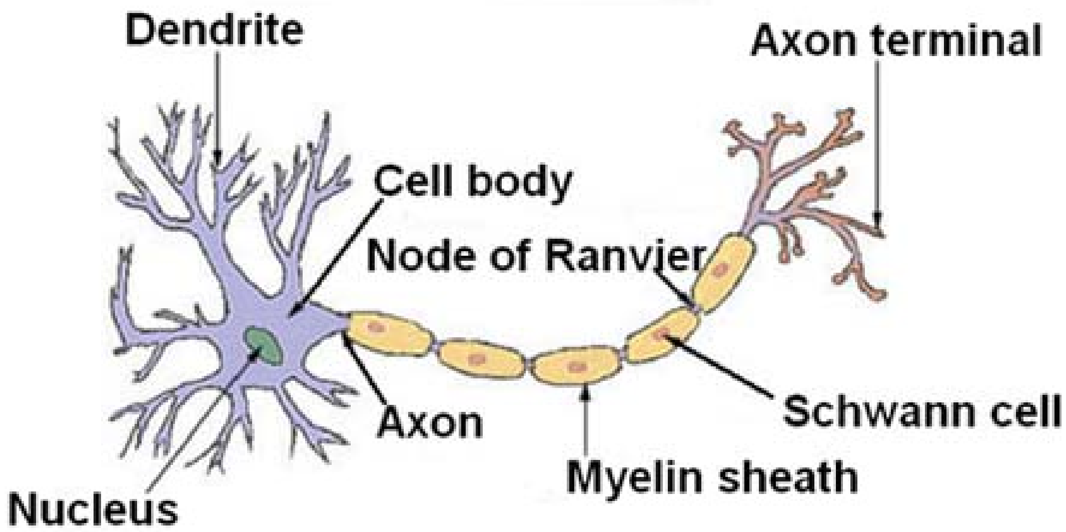


10,000 specific types of neurons in the human CNS
various shapes and sizes
100-200 billion neurons in a brain



The drawings made by Cajal

Structure of a Typical Neuron



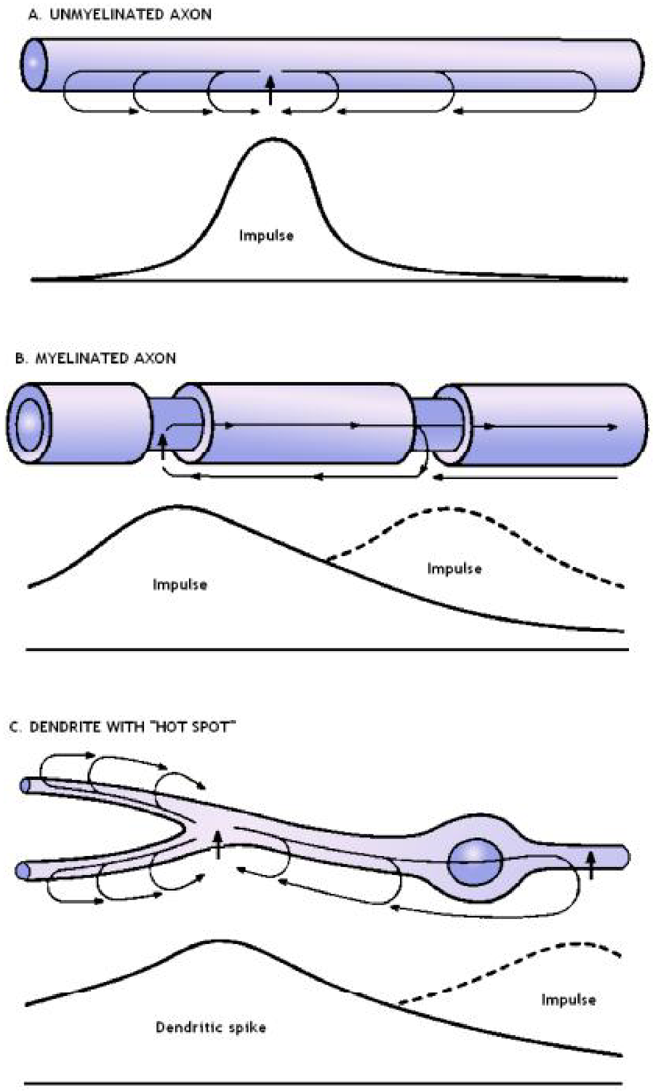
Diameter: 4 – 100 um
Length: an inch to several feet

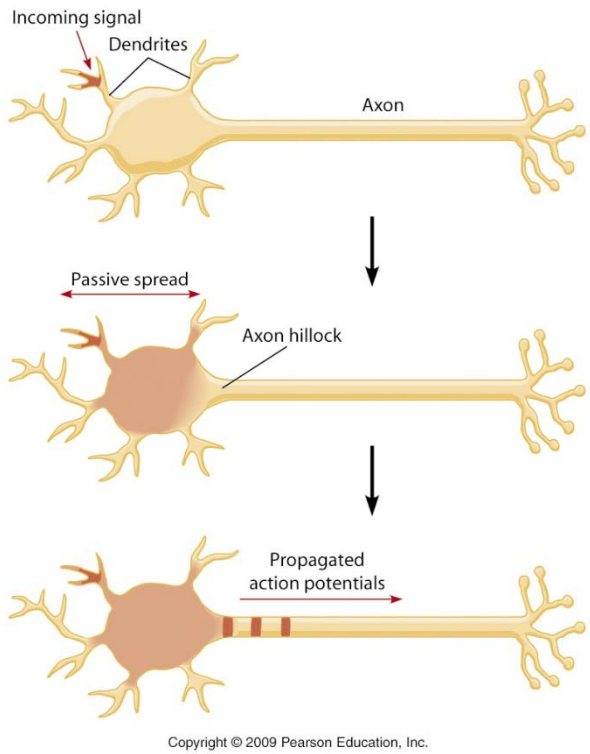
Active Conduction

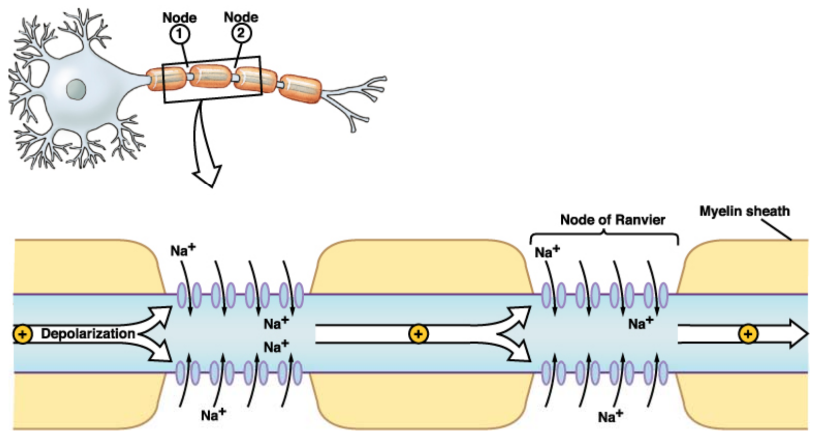
Unmyelinated Axons
Many voltage gated Na^+ channels in proximity
Action potential and passive conduction of the depolarizing current
Opening of the nearby Na^+ channels to generate another action potential
Repeated until the action potential reaches the terminal

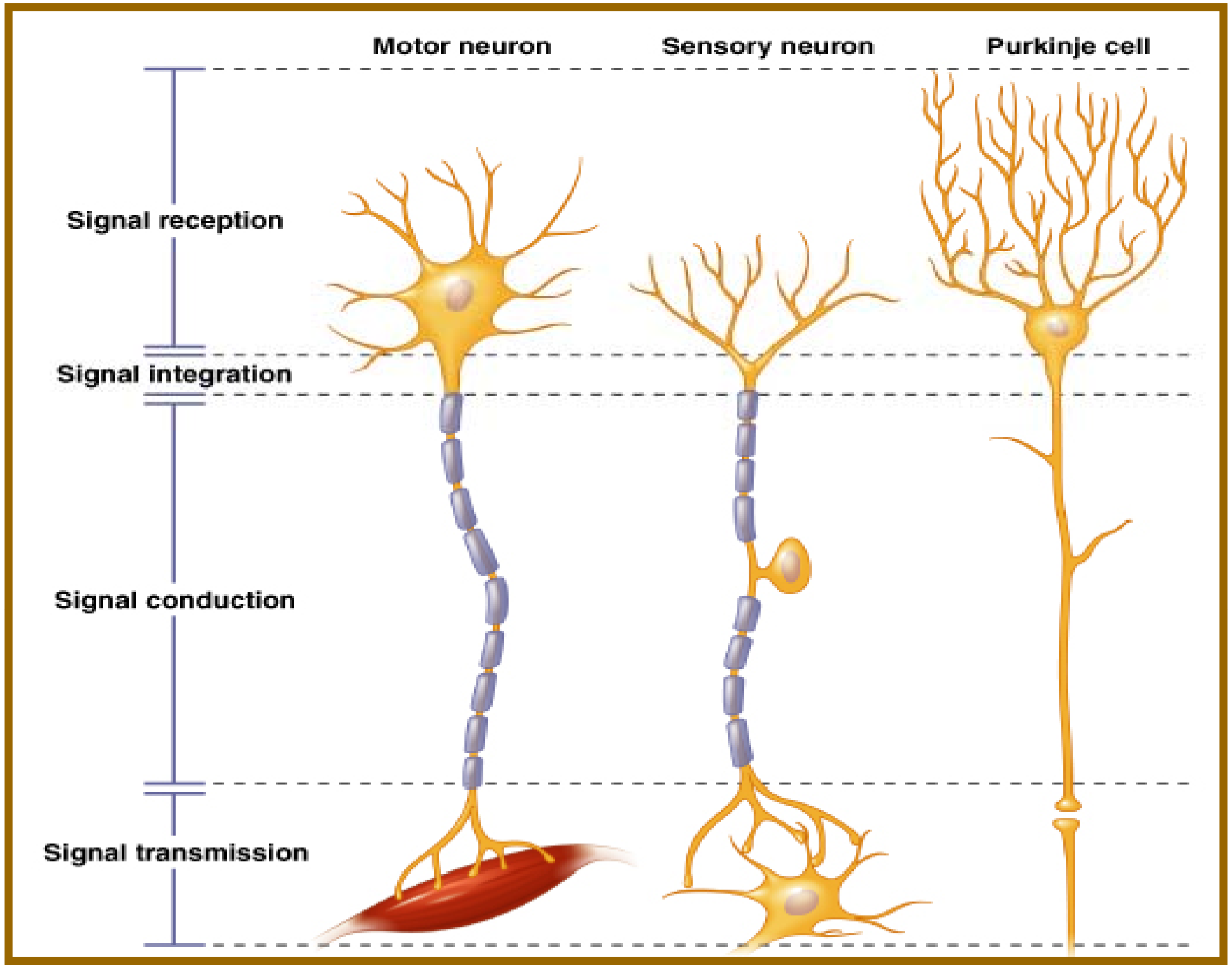
Myelinated Axons
Jumping of action potentials from node to node called saltatory conduction
axons covered with myelin sheath
(in the form of Schwann cells in the PNS or oligodendrocytes in the CNS)
Myelin prevents current leakage by increasing resistance in the axon
Passive current to the gaps between the myelin sheaths (Nodes of Ranvier)
The Nodes of Ranvier contains Na^+ channels, which fire another action potential upon depolarization from the passive current

Passive & Saltatory conduction





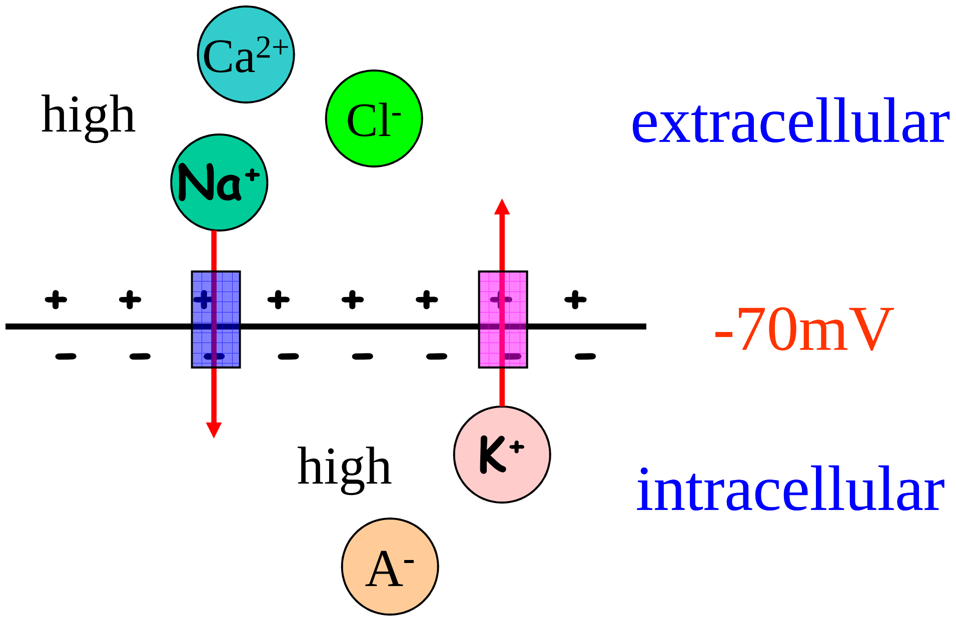


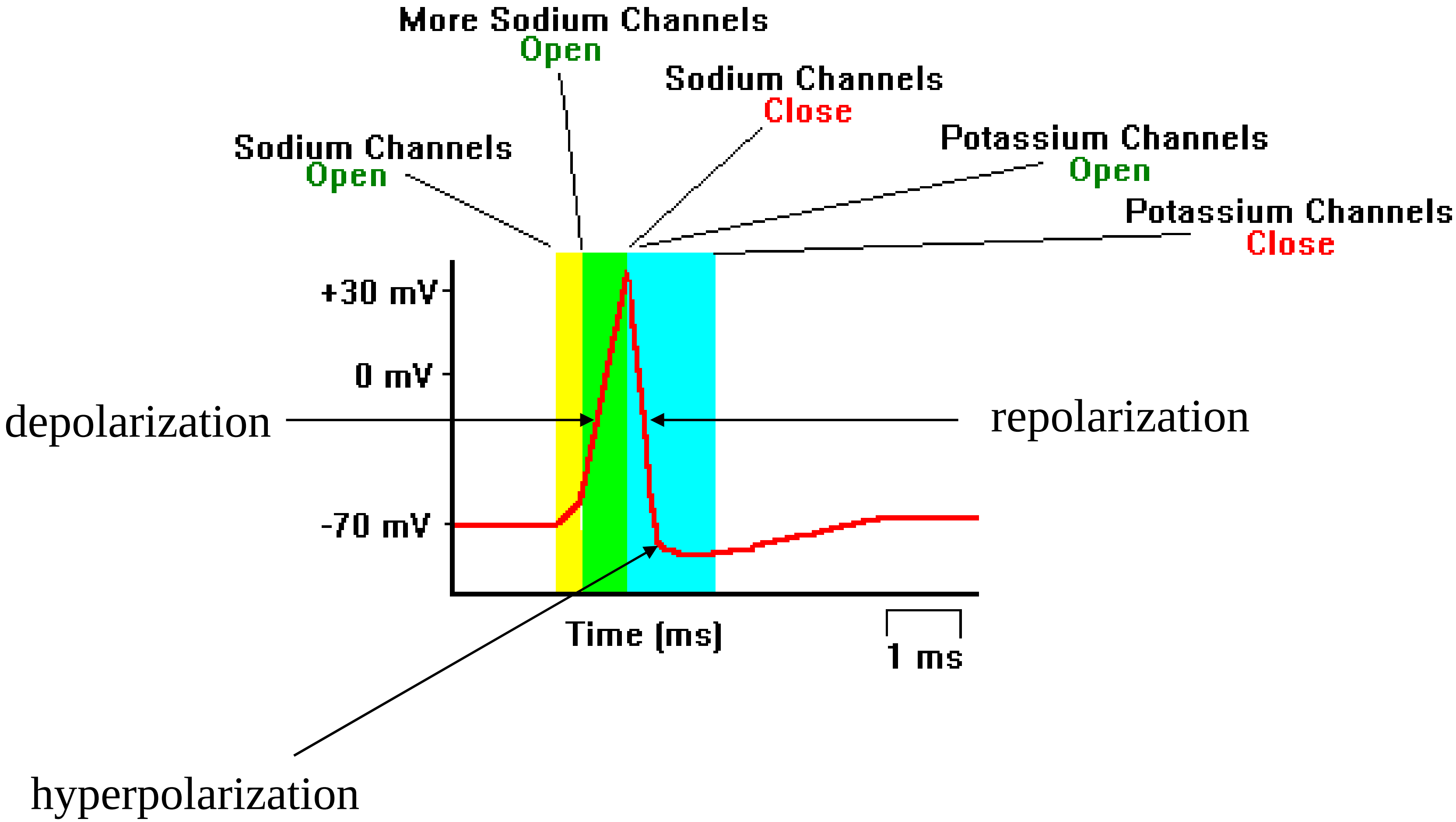


Motor neuron
Sensory neuron
Purkinje cell
Signal reception
Signal integration
Signal conduction
Signal transmission

Action potential

http://faculty.washington.edu/chudler/ap.html




More Sodium Channels
Open
Sodium Channels
Close
Sodium Channels
Open
Potassium Channels
Open
Potassium Channels
Close
+30 mV
0 mV
depolarization
repolarization
-70 mV
Time (ms)
1 ms
hyperpolarization

Signal intensity

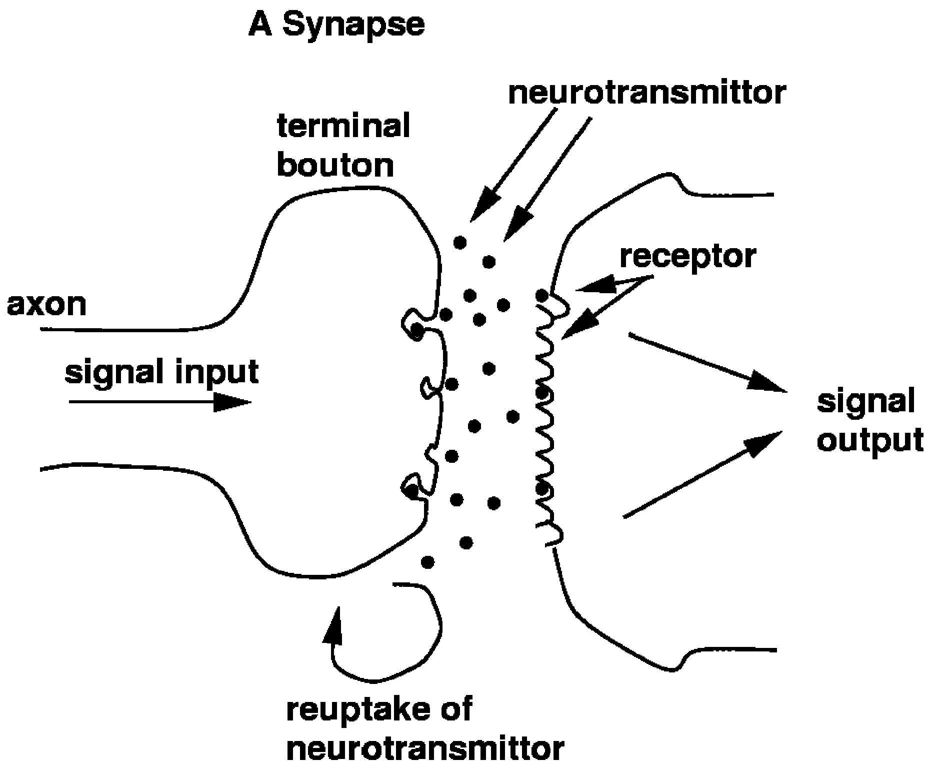
Repeated action potential: normally 30-100 Hertz or up to 500

Signal speed

axon diameter
myelin sheath
up to 220 miles/h

Synapse

A gap between neurons (axon terminal and dendrite)
Suggested by Cajal
Demonstrated by EM in 1950s
How the signal is transmitted?
    translation of electrical signal to chemical signal



Chemical Synapses Can Be Excitatory or Inhibitory

Excitatory neurotransmitters

Open cation channels

Cause an influx of Na^+ that depolarizes the postsynaptic membrane for firing an action potential

Acetylcholine, *glutamate*, and *serotonin* are used as excitatory transmitters:

Glutamate mediates most of the excitatory signaling in the vertebrate brain

Inhibitory neurotransmitters

Open either Cl^- channels or K^+ channels

Suppresses firing by making it harder for excitatory influences to depolarize the postsynaptic membrane

γ-aminobutyric acid (GABA) and *glycine* are used as inhibitory transmitters.

Many transmitters can be either excitatory and inhibitory,

depending on where they are released,

what receptors they bind to,

and the ionic conditions that they encounter.

Acetylcholine can either excite or inhibit, depending on the type of acetylcholine receptors it binds to.

Chemical provides nerve communication

Curare: nerve toxin suggested by Claud Barnard

acetylcholine receptor blocker

muscle contraction is inhibited

Discovery of the first neurotransmitter by Otto Loewi in 1929

http://faculty.washington.edu/chudler/chnt1.html

acetylcholine

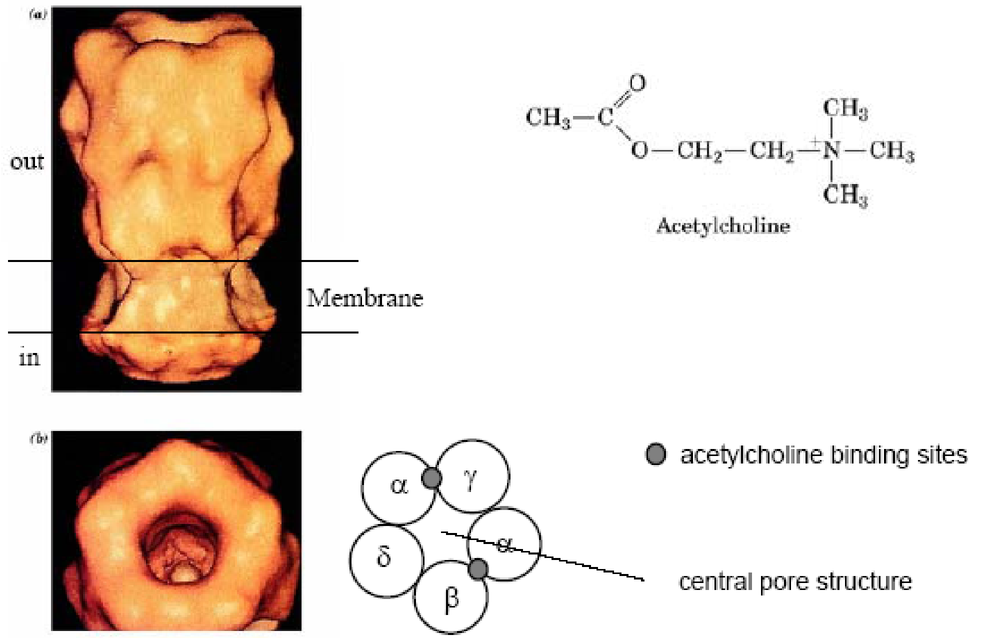
Release of acetylcholine into the synapse

the higher the signal the more acetylcholine released

Specific receptor molecules

Opening of ion channel

Image reconstruction from electron micrographs at low resolution of skeletal muscle nicotinic Acetylcholine Receptor



Voet&Voet, Biochemistry, 2nd ed., chapter 34, figure 117

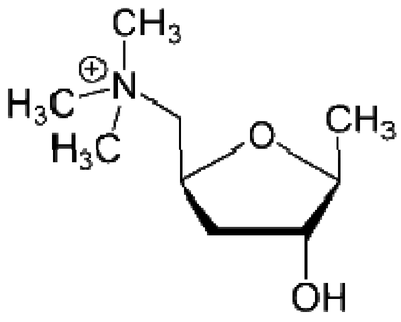
Nicotinic acetylcholine receptor (nAChR)

Ligand-gated ion channels
Found at the edges of junctional folds at the neuromuscular junction on the postsynaptic side
Activated by acetylcholine
Diffusion of Na^+ and K^+ across the receptor causes depolarization
Opening voltage-gated sodium channels
Firing of the action potential
Muscular contraction

Muscarinic acetylchoine receptor (mAChR)

G-protein-coupled receptors
Activate other ionic channels via a second messenger cascade

Muscarine: a natural product in mushrooms



Ionotropic receptor & Metabotropic receptors

Ionotropic: ion channels

- Ligand-gated ion channels
- Voltage-gated ion channels
- Stretch-activated ion channels

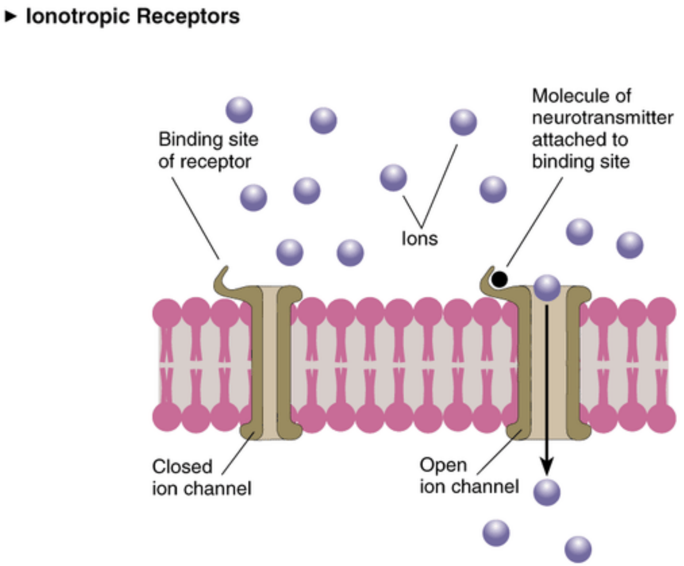
Metabotropic: indirectly linked with ion channels through signal transduction

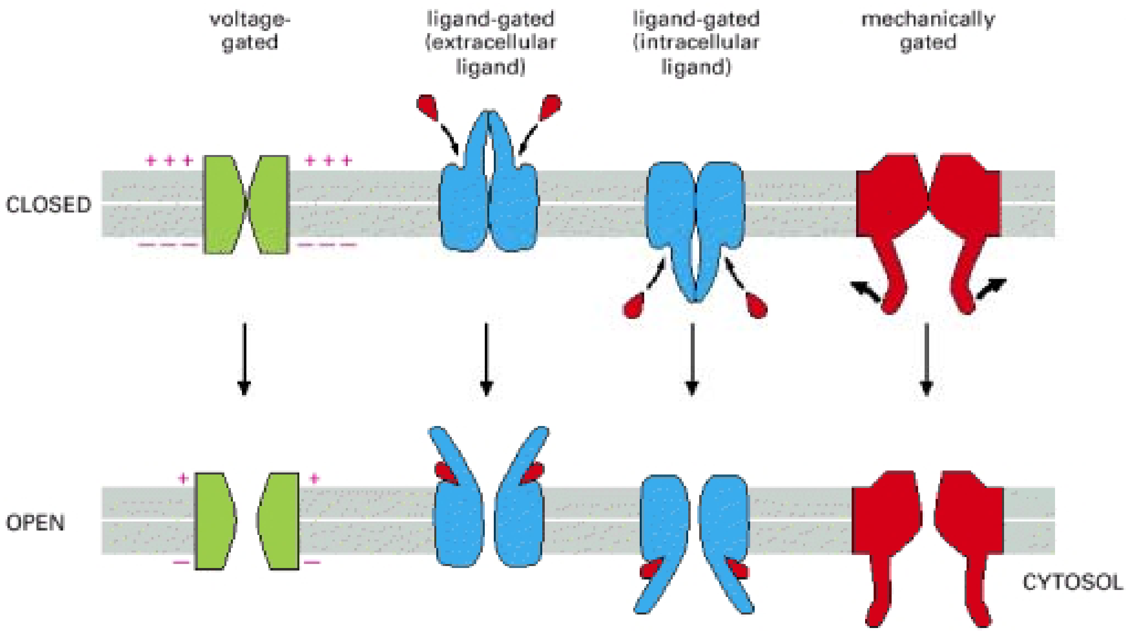
- G protein-coupled receptors
- Tyrosine kinases
- Guanylyl cyclase receptors

Signaling mediated by ion channels is generally immediate, simple, and brief

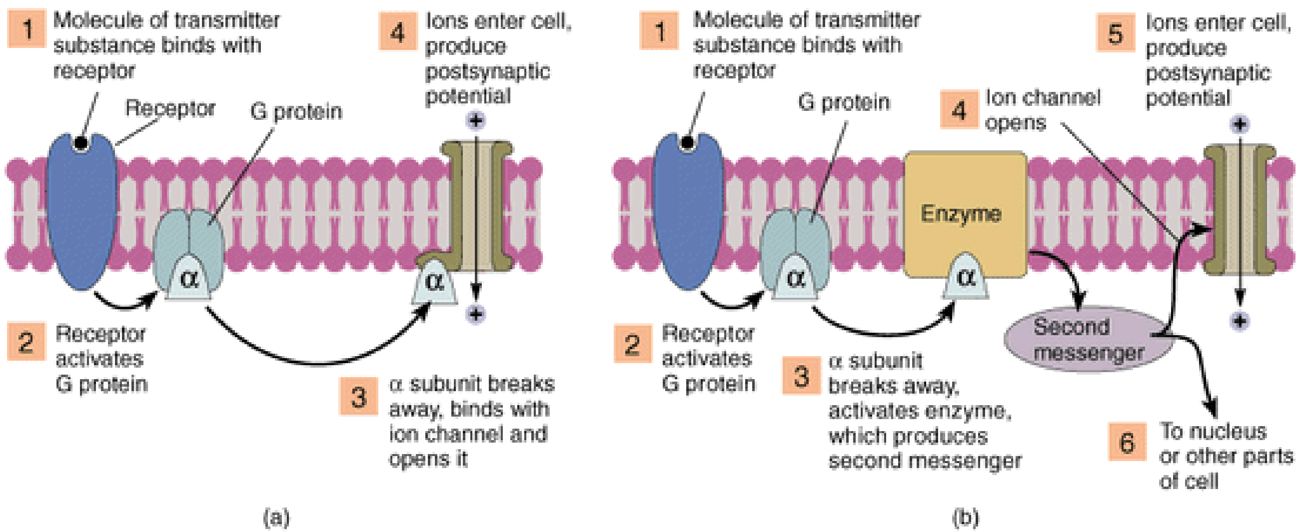
Signaling mediated by metabotropic receptors tends to be far slower and more complex, and longer lasting in its consequences.

Ion channels





► Metabotropic Receptors



How many synapses?

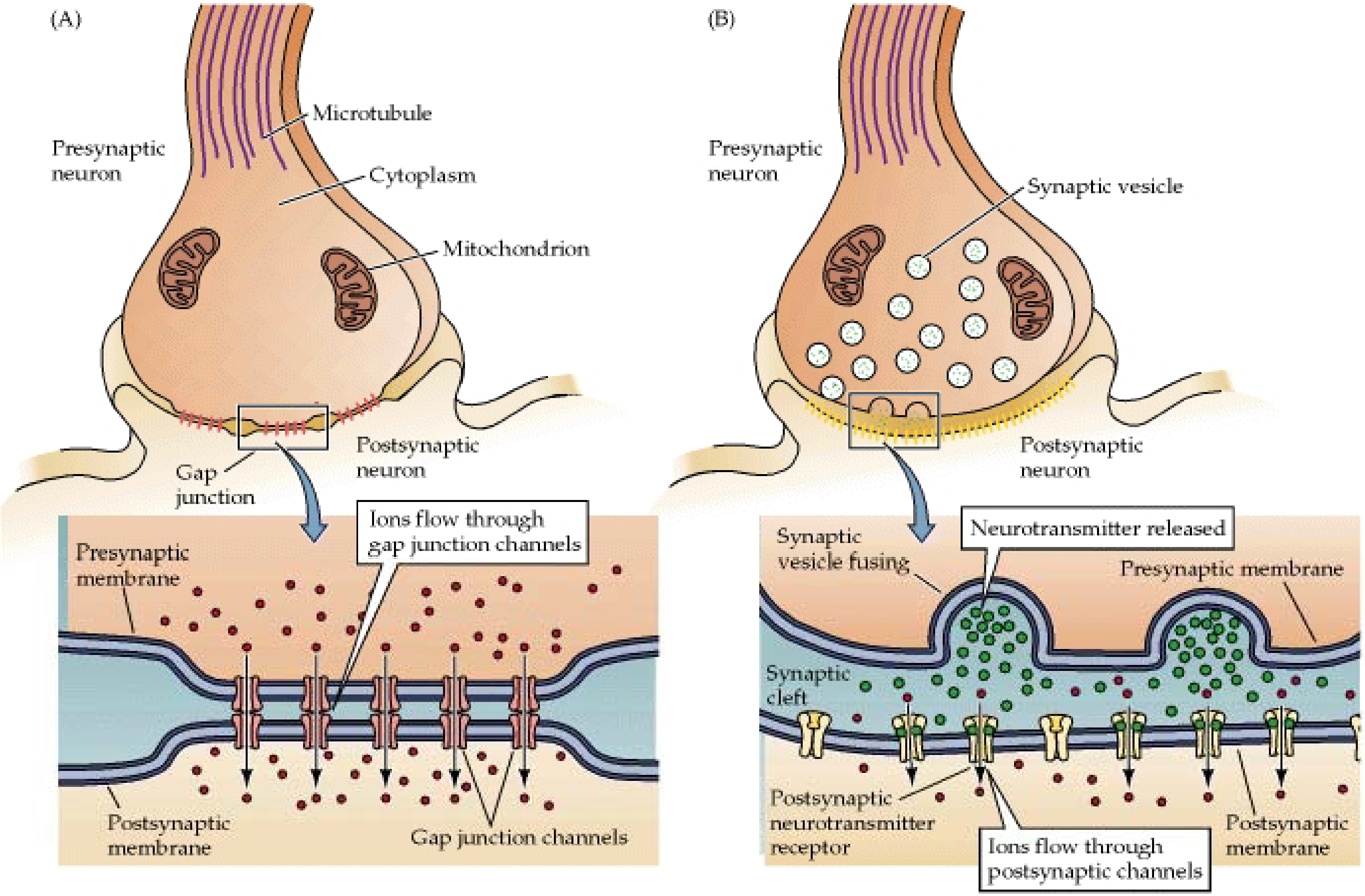
- 100-200 billion neurons in a brain
- Each connected to 5000 and 200000 other neurons
- (trees in the Amazon jungle and leaves in the trees)

Rapid removal of released neurotransmitters

- transporters and degrading enzymes

Chemical synapse & electrical synapse

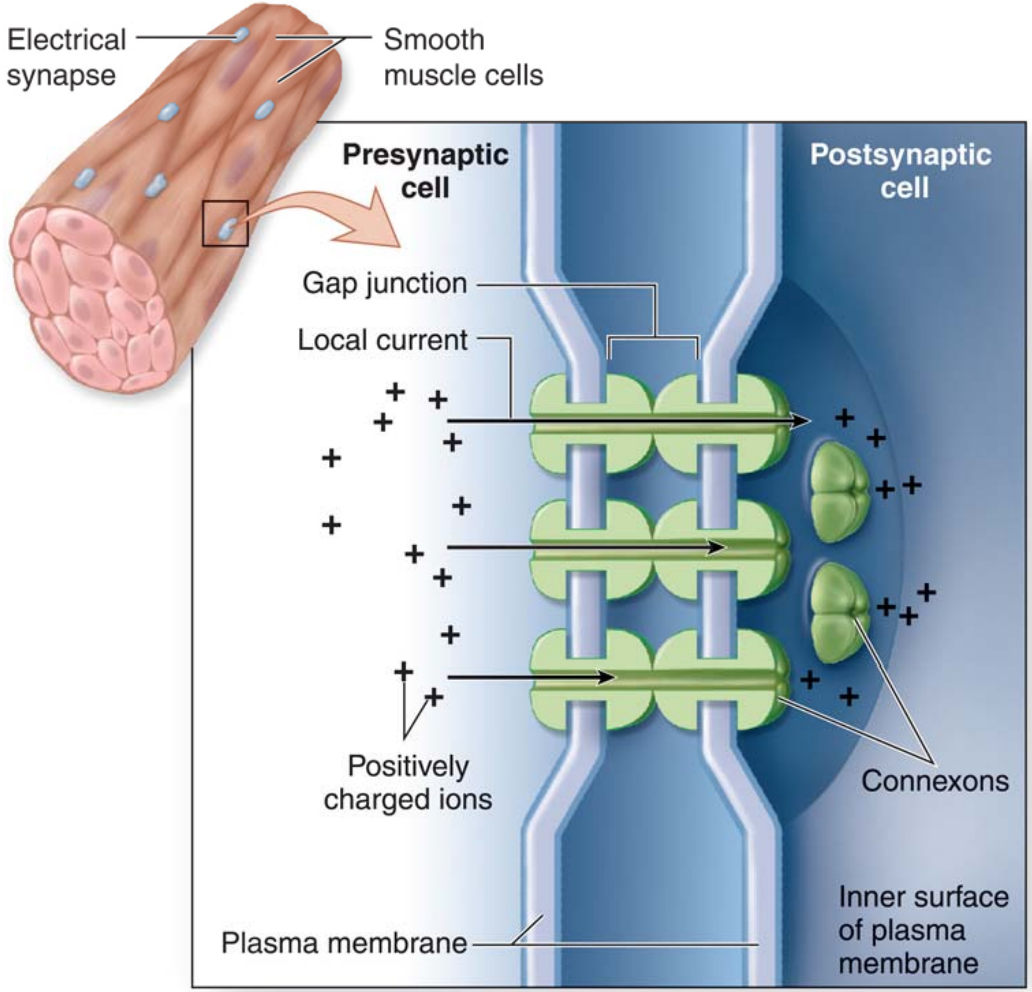
- electrical synapse has an advantage of time and energy
- but the majority are chemical synapse



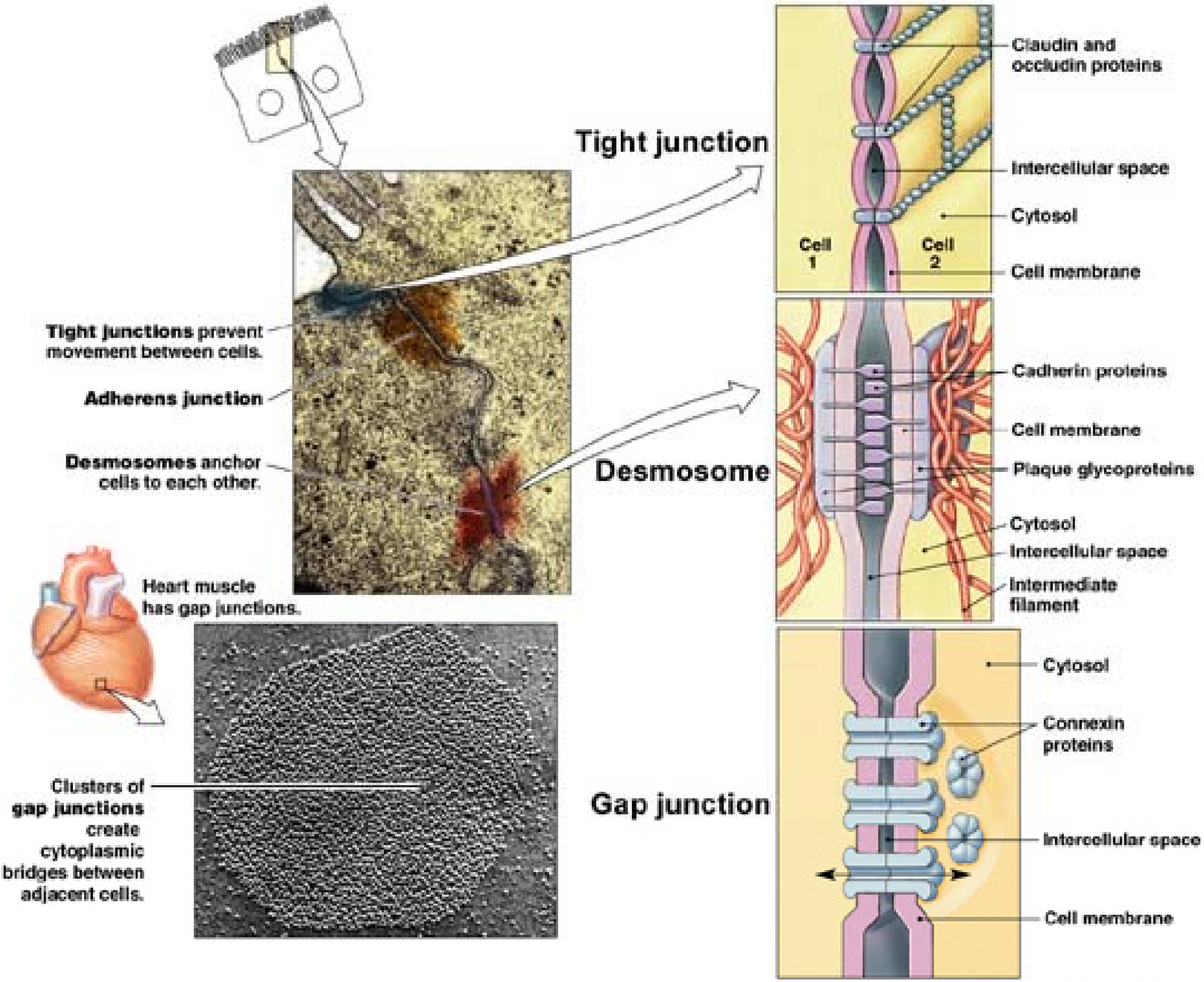
(A)
Presynaptic neuron
Microtubule
Cytoplasm
Mitochondrion
Gap junction
Postsynaptic neuron
Presynaptic membrane
Ions flow through gap junction channels
Postsynaptic membrane
Gap junction channels
(B)
Presynaptic neuron
Synaptic vesicle
Postsynaptic neuron
Synaptic vesicle fusing
Neurotransmitter released
Presynaptic membrane
Synaptic cleft
Postsynaptic neurotransmitter receptor
Ions flow through postsynaptic channels
Postsynaptic membrane

Because passive current flow across the gap junction is virtually instantaneous, communication can occur without the delay that is characteristic of chemical synapses.

A more general purpose of electrical synapses is to synchronize electrical activity among populations of neurons. For example, certain hormone-secreting neurons within the mammalian hypothalamus are connected by electrical synapses. This arrangement ensures that all cells fire action potentials at about the same time, thus facilitating a burst of hormone secretion into the circulation. The fact that gap junction pores are large enough to allow molecules such as ATP and second messengers to diffuse intercellularly also permits electrical synapses to coordinate the intracellular signaling and metabolism of coupled neurons.



(a) Electrical synapse



Tight junction
Claudin and occludin proteins
Intercellular space
Cytosol
Cell 1
Cell 2
Cell membrane
Tight junctions prevent movement between cells.
Adherens junction
Desmosomes anchor cells to each other.
Desmosome
Cadherin proteins
Cell membrane
Plaque glycoproteins
Cytosol
Intercellular space
Intermediate filament
Heart muscle has gap junctions.
Gap junction
Cytosol
Connexin proteins
Intercellular space
Cell membrane
Clusters of gap junctions create cytoplasmic bridges between adjacent cells.

Fig. 3-21

Any advantage of chemical synapse?

Variable and diverse inputs

- different concentrations (different extents)
- different chemicals (different actions)
- different times
- even more subtle role in communication
  - neuromodulation: excitatory or inhibitory

http://serendip.brynmawr.edu/bb/neuro/neuro98/202s98-paper2/Casasanto2.html

Neuromodulatory transmitters secreted by a small group of neurons diffuse through large areas of the nervous system, having an effect on multiple neurons. Examples of neuromodulators include dopamine, serotonin, acetylcholine, histamine and others (wikipedia).

Enormous flexibility and versatility in the brain

- using different combinations of transmitter chemicals

Volume transmission (extrasynaptic transmission): diffuse modulatory neurotransmitter systems

Cells of the central nervous system are able to communicate via a host of chemical signals that flow through the extracellular space. Volume transmission (VT) constitutes a novel and complementary communication system to classical synaptic transmission.

The new modality, which does not require specific connections between cells, leads to a reconsideration of the spatial relationships of neurons and glia, brings a new dimension to network modelling and is relevant to both short term interactions and long term tonic states of the brain.

Wiring and volume transmission (WT and VT)

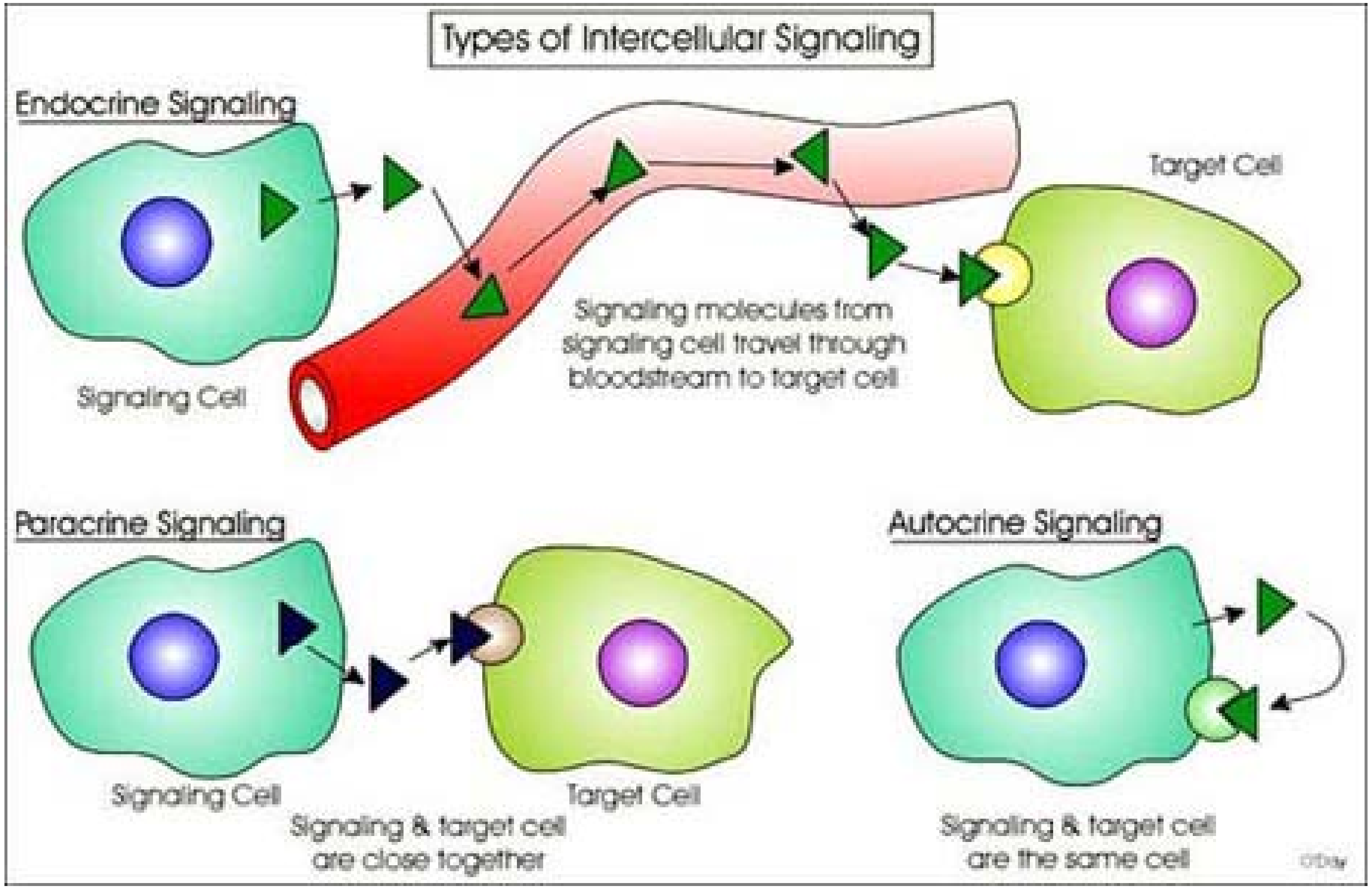
WT is one-to-one transmission and includes classical synapses, gap junctions and membrane juxtapositions

VT is a one-to-many transmission and includes paracrine and endocrine-like transmissions in the brain extracellular space and cerebrospinal fluids.

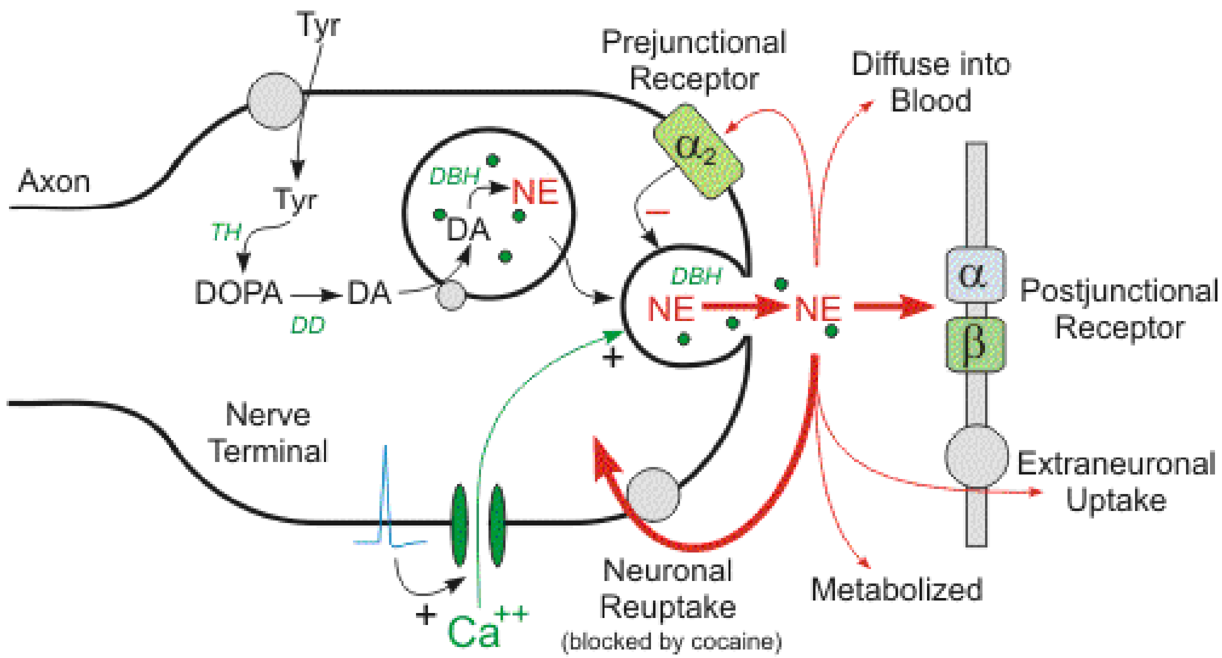
Any brain cell can participate in WT and VT and any kind of substance (e.g. ions, classical transmitters, peptides, neurosteroids) can be a signal in WT and VT.

These concepts are relevant for the pharmacokinetics and actions of neuropsychoactive drugs. These drugs can be regarded as exogenous VT signals in that they diffuse in the cerebral extracellular space and are constrained there by the same factors that influence migration of endogenous VT signals. In addition, neuropsychoactive drugs can better mimic and more effectively interact with the relatively unconstrained VT-type transmissions than with the rigidly constrained WT mechanisms, such as synaptic transmission.

Trends in Pharmacological Sciences, Volume 20, Issue 4, 142-150, 1 April 1999


Types of Intercellular Signaling
Endocrine Signaling
Target Cell
Signaling molecules from
signaling cell travel through
bloodstream to target cell
Signaling Cell
Paracrine Signaling
Autocrine Signaling
Signaling Cell
Target Cell
Signaling & target cell
are close together
Signaling & target cell
are the same cell

Neurotransmitter release



Tyr = tyrosine; TH = tyrosine hydroxylase; DD = DOPA decarboxylase;
DA = dopamine; DBH = dopamine β-hydroxylase; NE = norepinephrine

Voltage-dependent calcium channel (VDCC)

Brain & Computer

Chemical system & electrical system
Changing chemical composition & unchanging hardware
Novel response through learning to the same command
Thinking & logic (programmed)

Brain chemicals

Many brain chemicals
Highly specific targets and highly diverse ways of action

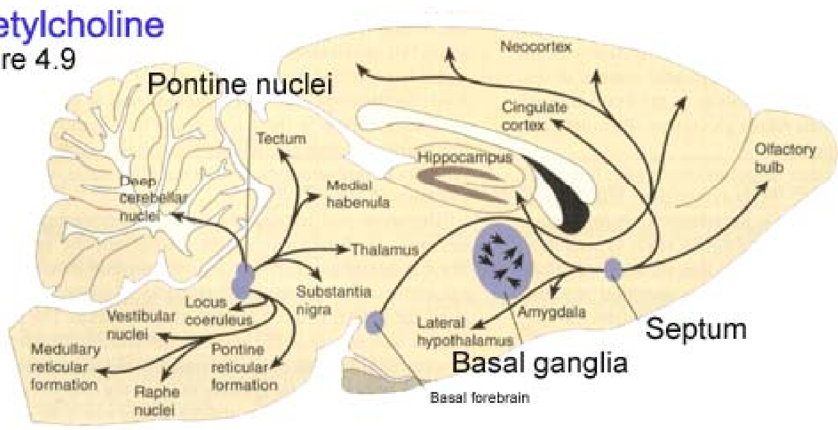
Common Neurotransmitters

Neurotransmitter	Action	Receptor Subtypes
Acetylcholine (Ach)	+/-	Nicotinic, Muscarinic
Norepinephrine (NE)	+	α_1, α_2, β_1, β_2, β_3
Dopamine (DA)	+/-	D_1, D_2 (D_3, D_4)
Serotonin (5-HT) (5 Hydroxytryptamine)	+/-	5-HT1_A, etc.
Glutamate (Glu)	+	NMDA, AMPA
GABA (Gamma-aminobutyric acid)	-	$GABA_A$, $GABA_B$
Enkephalins (Enk)	-	μ, κ, δ

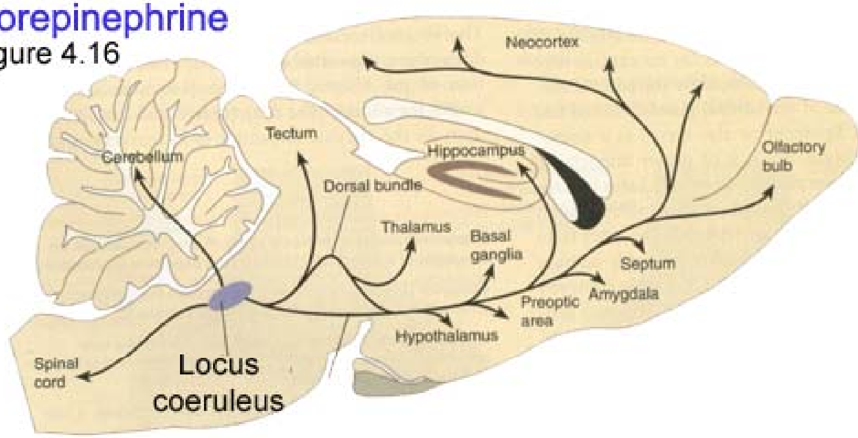
http://www.colorado.edu/intphys/Class/IPHY3730/06neurotransmitters.html

Major Brain Pathways

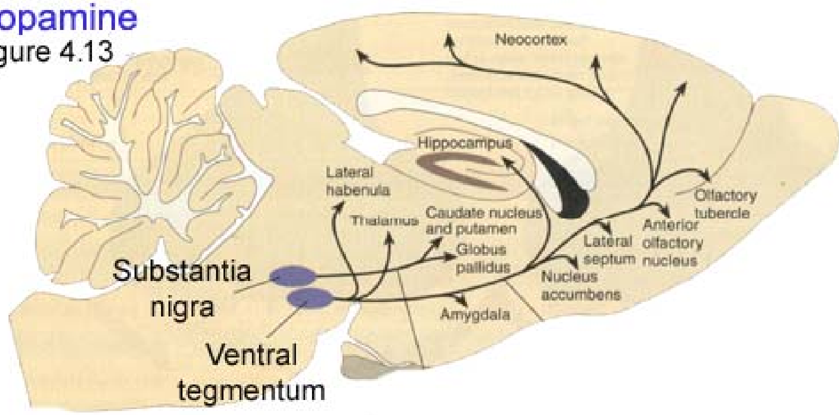
Acetylcholine
Figure 4.9



Norepinephrine
Figure 4.16



Dopamine
Figure 4.13



Serotonin
Figure 4.18