Continuing from last time

-if we prevent uptake of drugs in the synapse what does that do to synaptic transmission? more nt in synapse thus larger PSP change (how low ligand is bound, how much binds, type of receptor, number of receptor)
-when we have these transport reuptake blockers, we keep nt in synapse for longer time, if we allow for more post synaptic receptors to be bound we can increase post synaptic response
-can also activate these receptors for longer period of time
-so can have a bigger PS change or a longer PS change
-don't need to memorize specific drugs
-1 hour for midterm then group exam, bring calculator

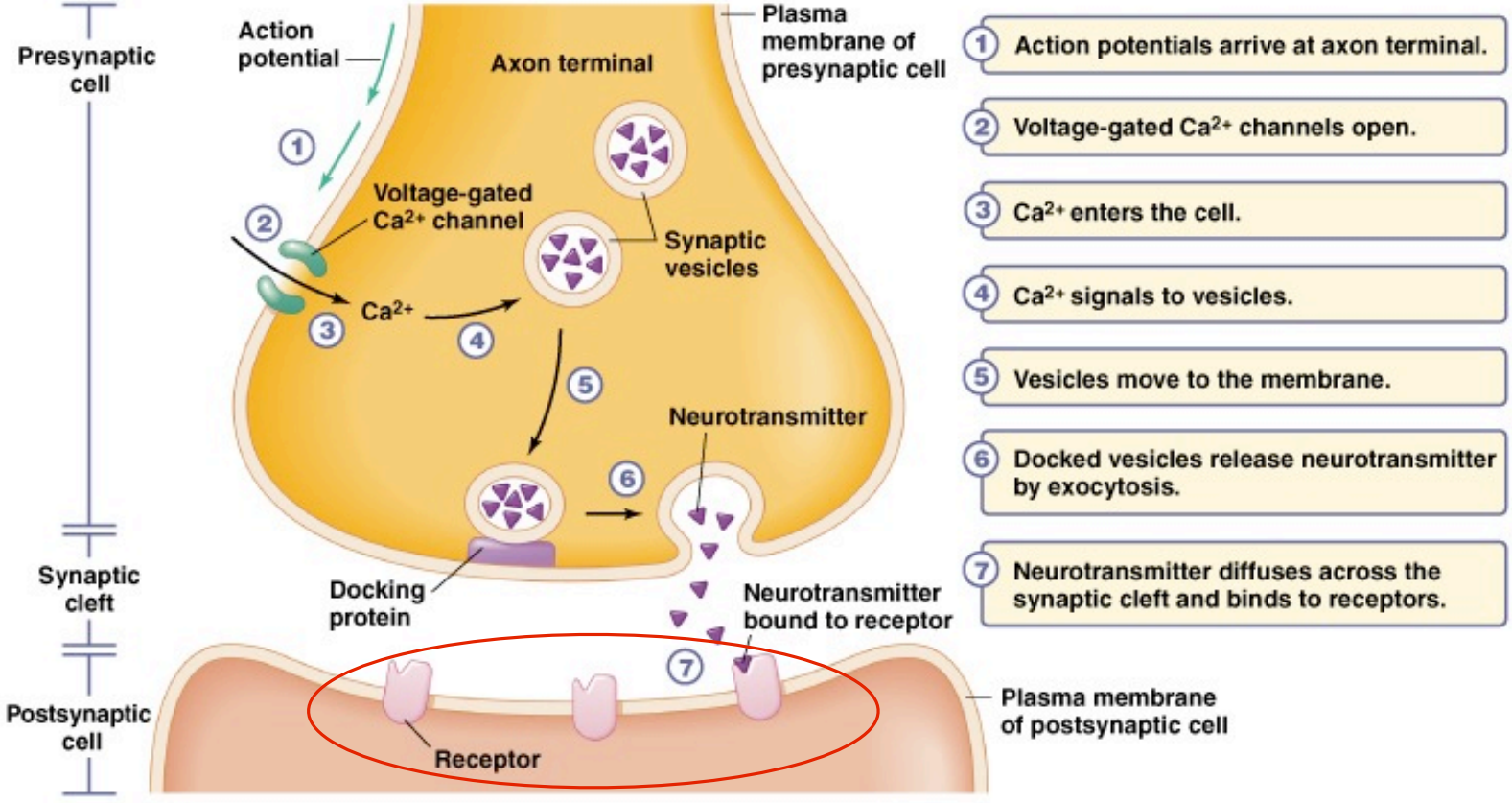
Synaptic Transmission

- Define the parts of synapse.
- Explain how Ca^{2+} regulates neurotransmitter release
- Determine how neurotransmitters causes distinct changes in postsynaptic cells.
- Distinguish between the major types of receptors (iono vs. metabotropic)
- Explain how neurotransmitter concentration is regulated in the synaptic cleft.
- Describe the role of membrane receptors in cell to cell communication
- Describe the long-term effects of agonists and antagonists on receptor concentration
- Predict the relative number of receptors based on a saturation curve
- Predict the receptor sensitivity based on a saturation curve
- Predict the effects of modifications to any of the steps of a given signal transduction pathway

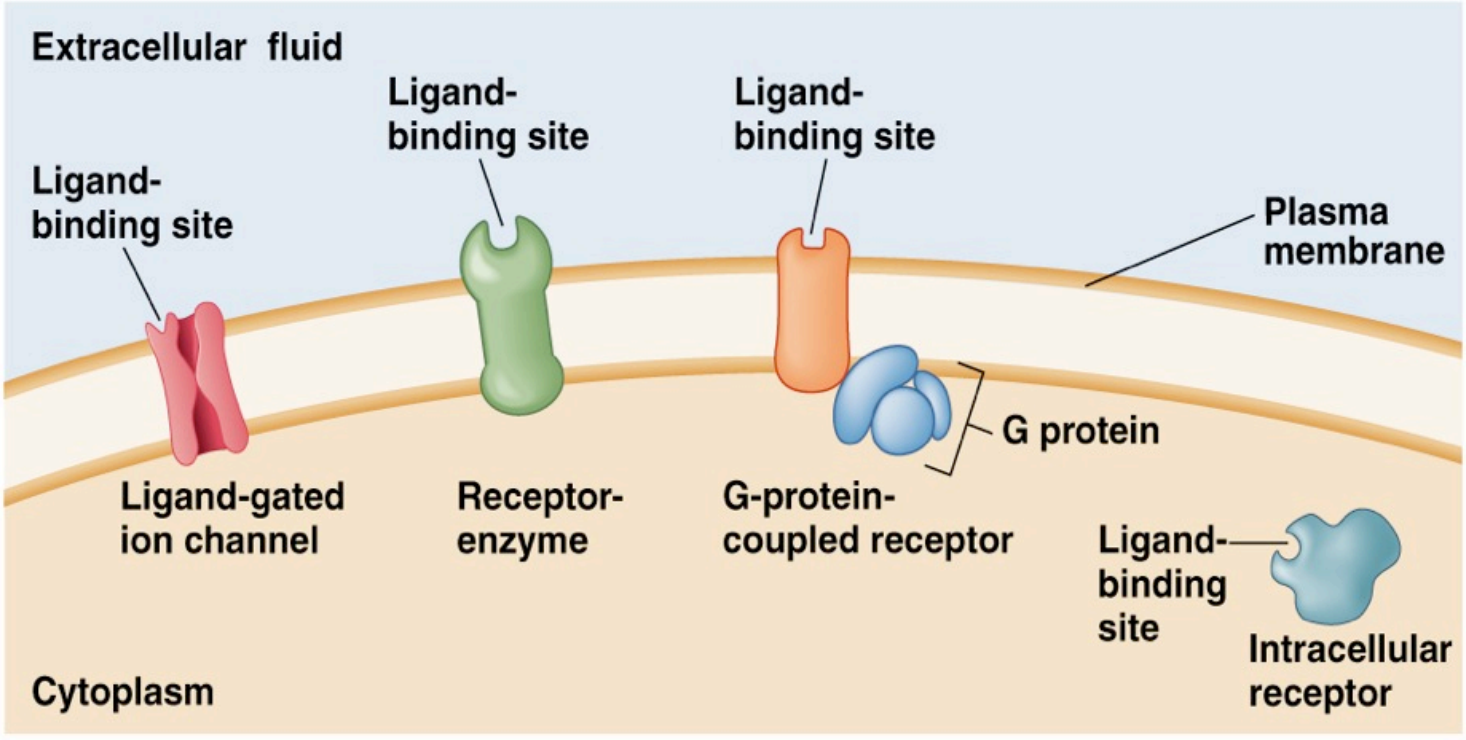
Many drugs prolong the action of neurotransmitter in the synapse. Any ideas?

- MAOIs: Monoamine oxidase inhibitors (MAs: dopamine, epinephrine, serotonin). for depression, anxiety, etc.
- SSRIs: selective serotonin re-uptake inhibitors: for depression, anxiety.
- Cocaine: inhibitor of dopamine transporter. (this is also a very effective local anesthetic!)
- **What effect do these have on the functioning of the synapse?**

Synaptic Transmission Overview



What happens when neurotransmitter binds to receptors on the other side of the cleft?



Receptor binding:

- The binding of the ligand to the receptor induces a change in receptor conformation, which acts as a signal within the cell.

Receptors are characterized by:

1. specificity
2. saturation
3. sensitivity

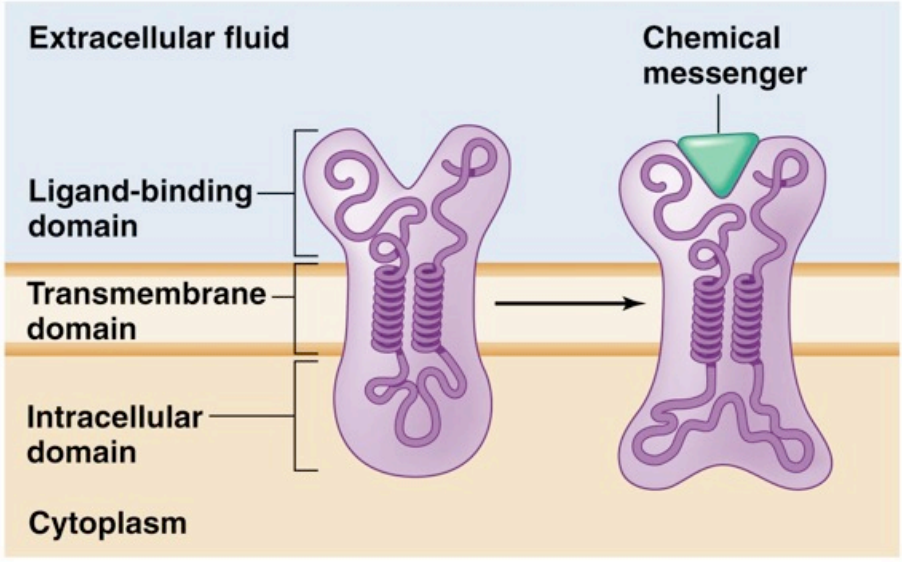
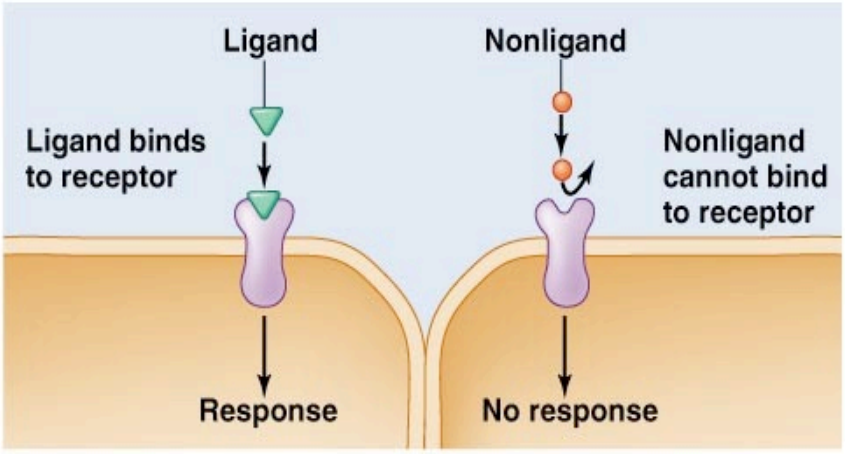


Figure 3.6

1. Receptor Specificity:

receptor only sensitive to specific ligand

- Receptors have a ligand binding domain. Only molecules with an appropriate structure will 'fit' and activate the receptor.

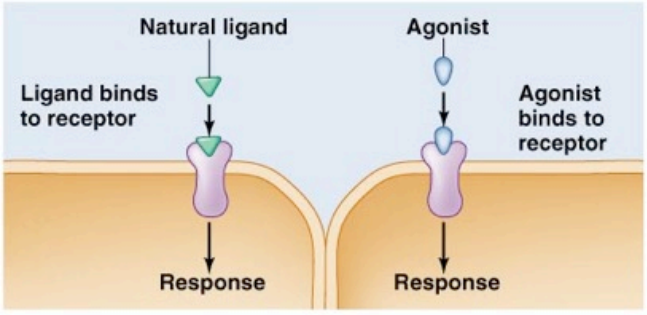


(a) Ligand binding causes a response

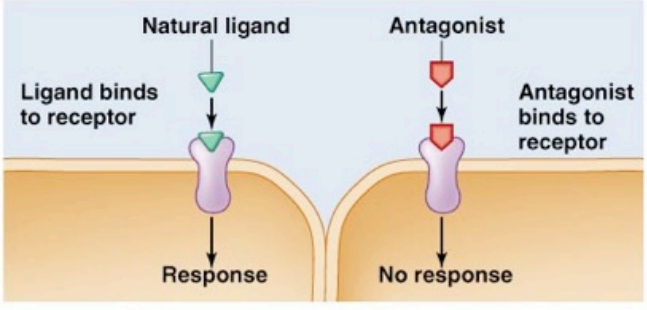
1. Receptor Specificity:

agonist molecules bind to receptor and mimic response of endogenous ligand
-antagonist prevents the response

- Agonists v. Antagonists



(b) Agonist binding causes a response



(c) Antagonist binding does not cause a response

muscimol: $GABA_A$

curare: nAChR

GABAa receptors usually inhibit neurons by opening up to allow Cl to flow across the membrane

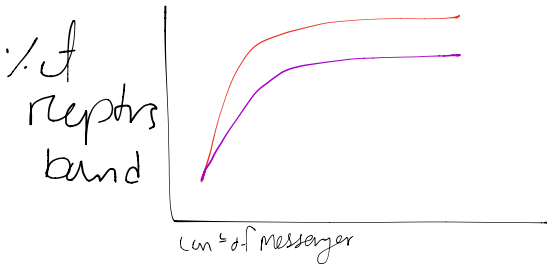
(1) which direction is Cl flowing if its movement inhibits neurons?
(2) if a molecule activates GABA receptors is it an agonist or antagonist?
(3) Are GABA agonists excitatory or inhibitory?
(4) Muscimol is an agonist of GABA receptors what effect will it have on neuron if one accidentally ingests Amanita?

(1) inside because it will move membrane further from threshold: hyperpolarizing it, also reduces membrane resistance

(2) Agonist

(3) inhibitory

(4) inhibit them
what would you expect would happen to the NS as a whole?
may be physically slower since harder to move motor neurons
-slower cognitively: fatigue, dizziness, dissociative hypnotic effect (dissociate from reality)



which cell has more receptors? if you see a plateau like this: as we go up in concentration you can't get a bigger response because receptors are occupied; as you go up in nt concentration, you don't get bigger response then all receptors occupied
-thus y axis should be number receptors bound

*higher one

2. Receptor saturation

- The more receptors that are bound to ligand, the larger the magnitude of the response.

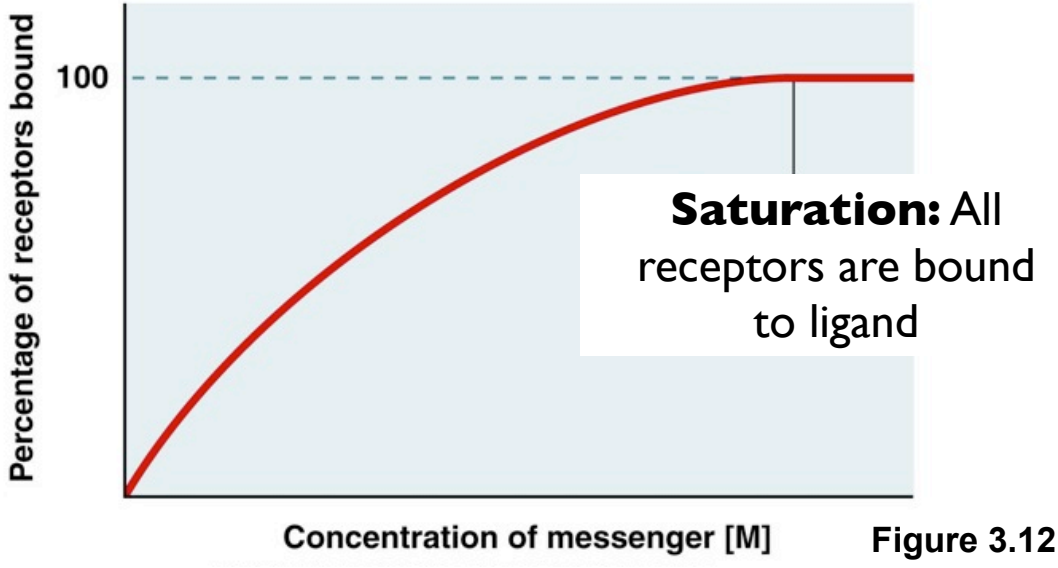


Figure 3.12

Dave is heroin addict eg some of his synapses are saturated with agonist of M-opioid receptors.

(1) What will his neurons do in response to these consistently high levels of ligand?
(2) What will happen to him if he stops taking heroin?
(3) What will happen in the long term if he continues to stop taking heroin?

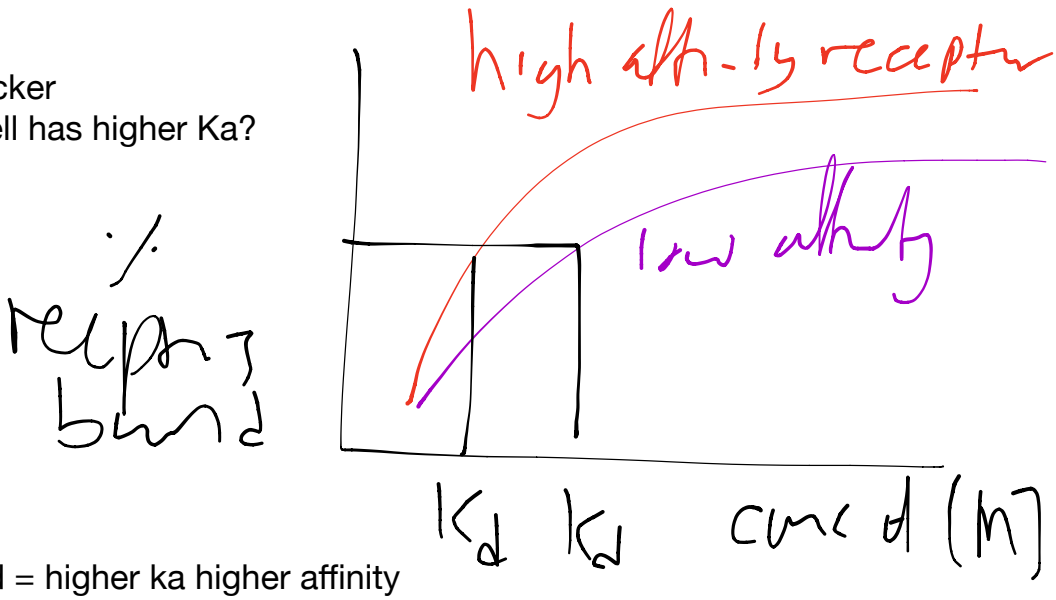
(1) body will down-regulate them, body is trying to maintain homeostasis to maintain our level of excitement
-reduce number of receptors to compensate for high consumption of ligands

(2) body won't respond to the normal amount of endogenous ligand

(3) receptors return to maintain homeostasis

endogenous = naturally occuring ligand for the receptor eg endorphins
-this is up-regulation

Next iClicker
Which cell has higher Ka?



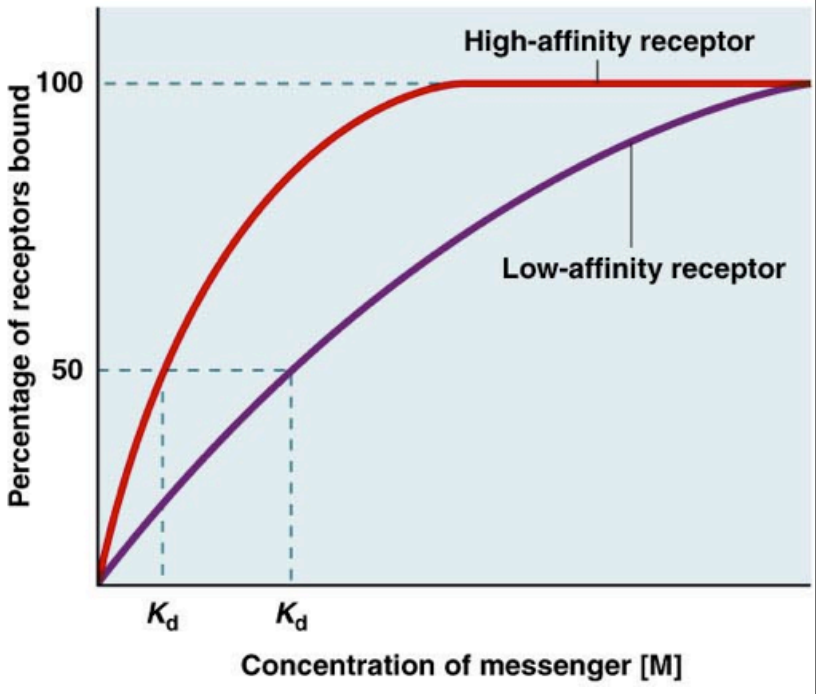
-lower kd = higher ka higher affinity
RED

3. Receptor sensitivity

- The affinity of a receptor for a ligand.
- **Dissociation constant** (K_d): ligand concentration at which half of receptors are bound.
- **Affinity constant** (K_a):

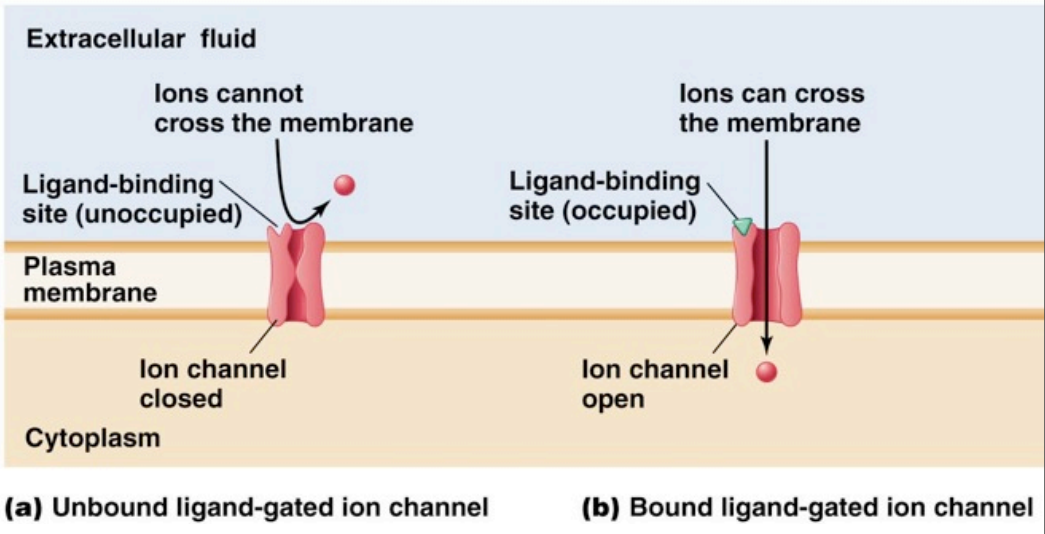
$$1 / K_d$$

- As K_a increase, response increases

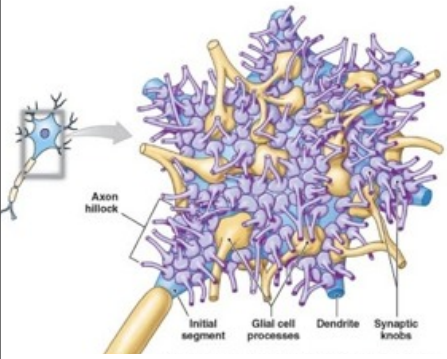


Ionotropic receptors

- aka: Ligand-gated ion channels.
- The receptor itself is an ion channel.
- Usually very fast.
- eg: nicotinic acetylcholine receptors, γ-aminobutyric acid (GABA) receptors, etc.

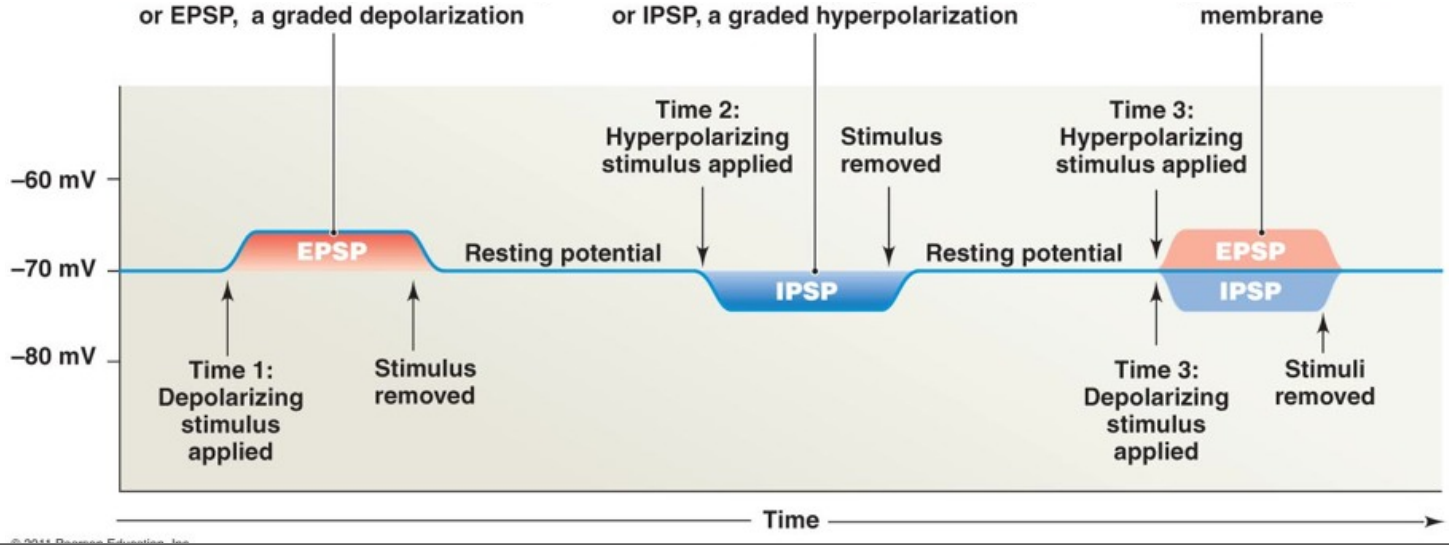


Release of transmitter onto post-synaptic membrane:

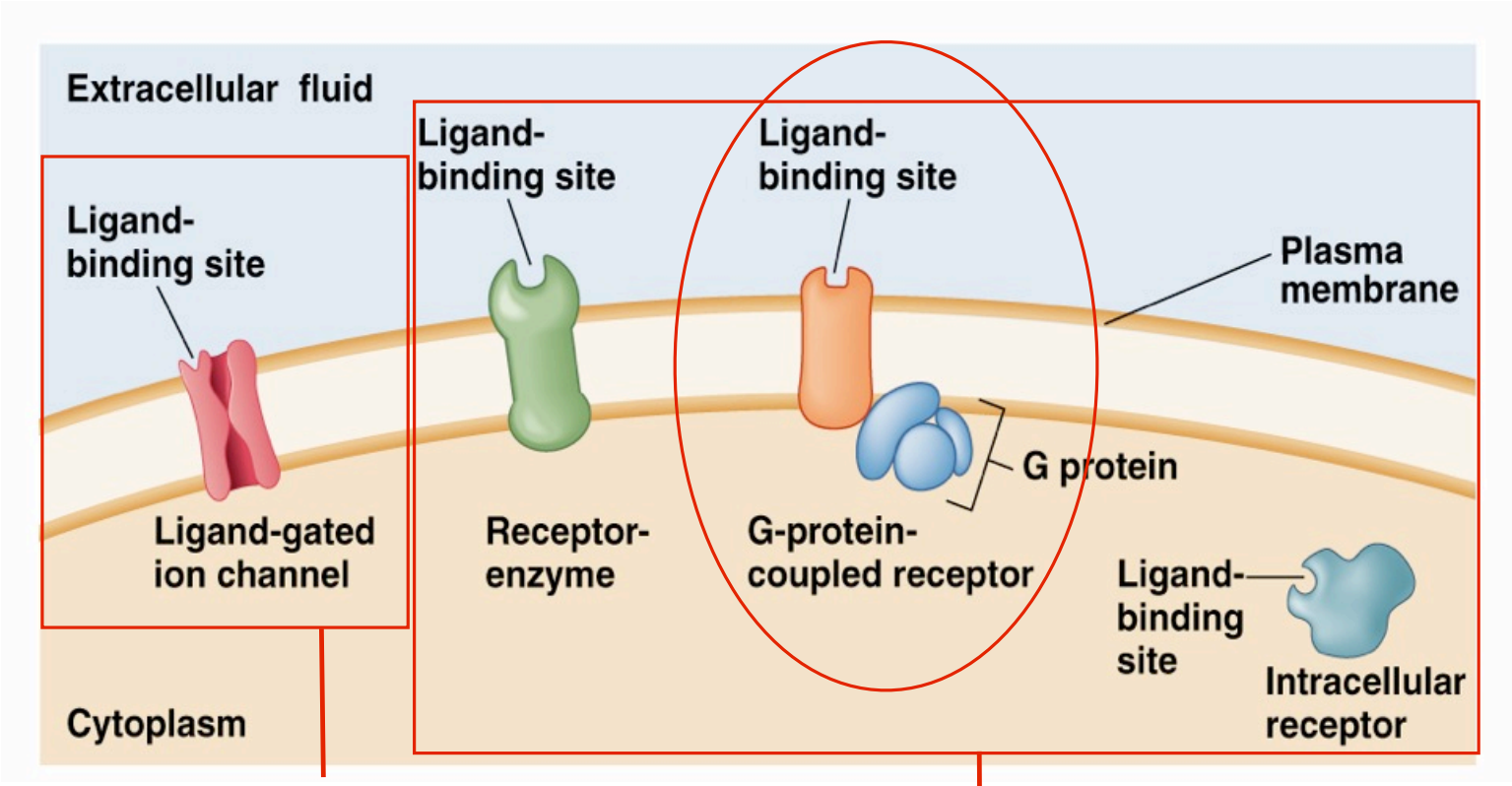


Inhibitory post-synaptic potential (IPSP): hyperpolarization

Excitatory post-synaptic potential (EPSP): depolarization



What happens when neurotransmitter binds to receptors on the other side of the cleft?



ionotropic receptors are ligand gated channels
they open up and ions flow across membrane causing either EPSP or IPSP
IPSP move membrane away from threshold and vise versa

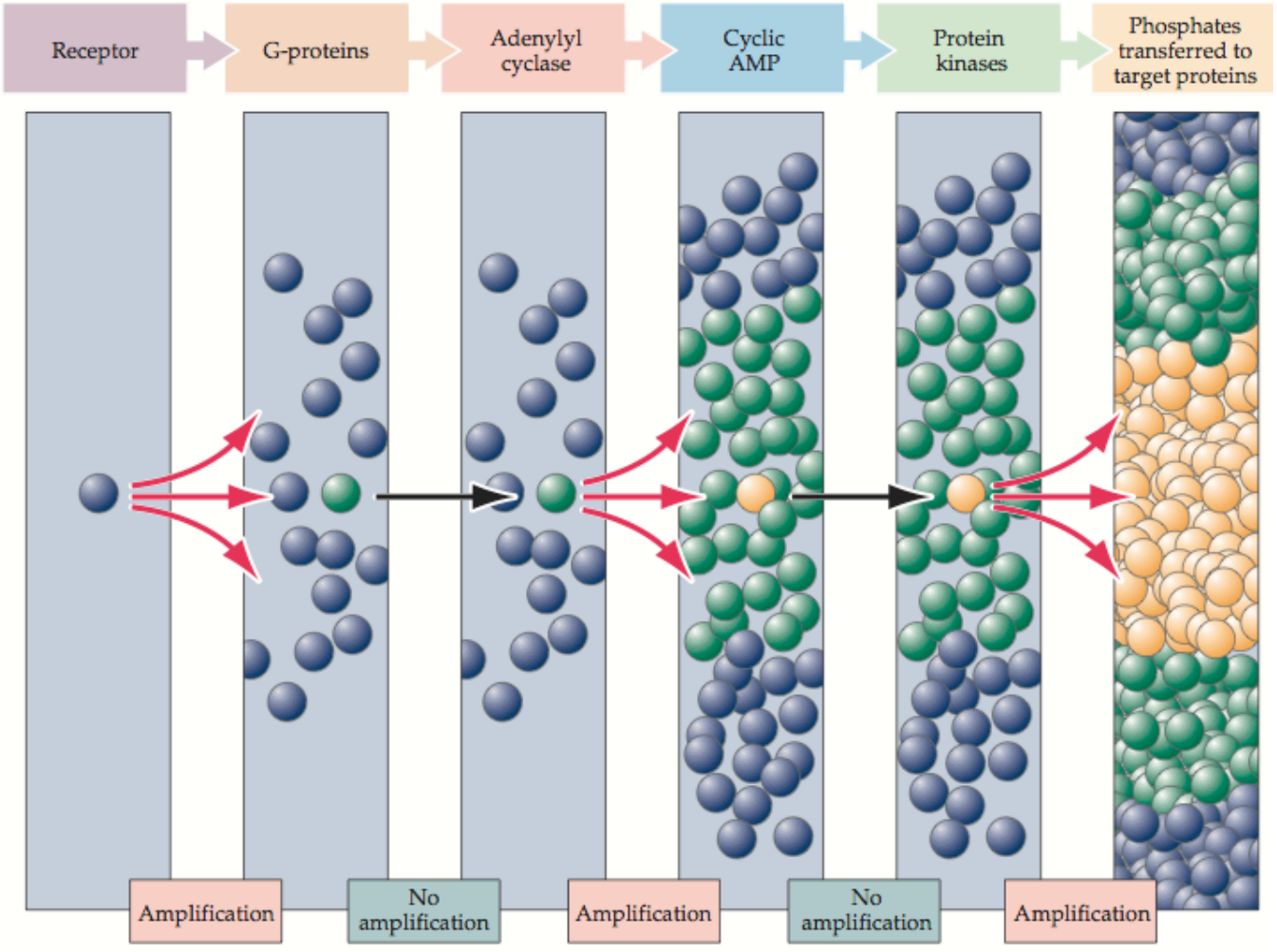
Iclicker:

In adult humans GABA is inhibitory neurotransmitter. GABAa receptors are ionotropic receptors that permit passage of Cl ions but during early development the activation of GABAa receptors by GABA is excitatory, how?

-what makes something inhibitory to begin with? allows Cl ions to enter cell which hyperpolarizes cell
-how can it be excitatory? do the opposite, Cl flowing out will excite your cell
-change Cl concentrations inside and outside the cell, switch them
-how? how are any ion gradients formed? pumps Na/Cl or K/Cl or just Cl ATPase
-so in adults GABA is released onto GABAa receptor Cl goes in hyperpolarizes the neuron, going away from threshold
normally lots of KCC2 and little NKCC1 so pump lot of Cl into the cell and bringing in just a little bit
-in embryonic development: we have small amount of KCC2 expressed and lots of NKCC1 (not tested on these names just cool example), lots Cl pumped in little pumped out
So when GABAa comes and binds, electrochemical gradient favors Cl leaving the cell so net depolarization

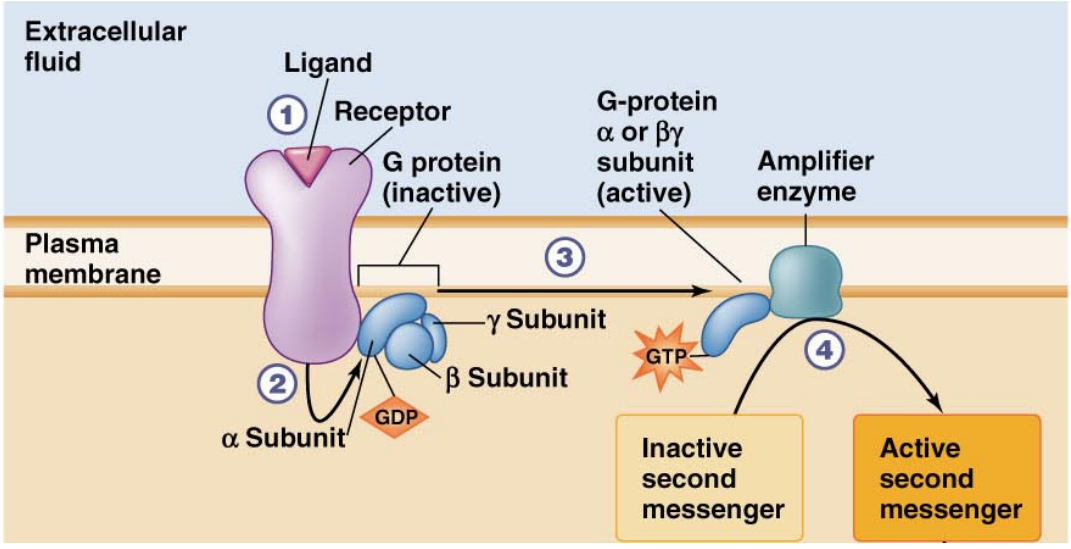
-metabotropic receptors are anything that's not ionotropic; they include signal transduction cascade
-ligand binds intracellular receptors, we go onto phosphorylating things
-GPCR allow for amplification, single receptor bound can single ligand can activate multiple G proteins, amplifier proteins because can stimulate all sorts of molecules
-alpha subunit of G protein goes off in one direction when G protein activated and b-g goes on other direction
-alpha dissociates and stimulates/activates amplifier protein which activates second messenger

GPCRs: Amplification



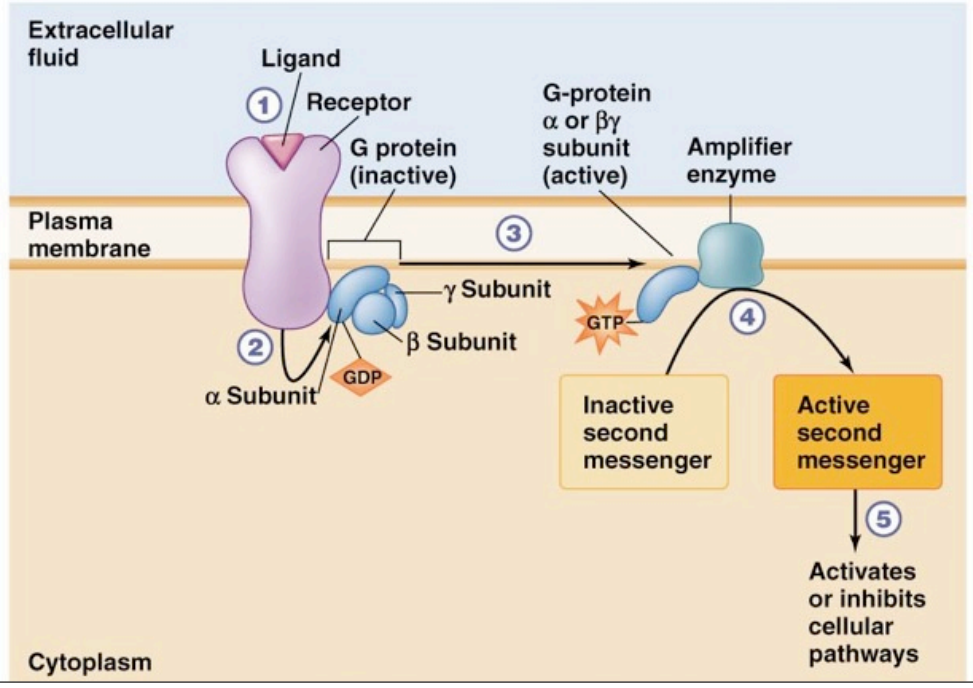
Metabotropic receptors (G-protein coupled receptors)

- Receptor is a transmembrane protein that activates intracellular "G-proteins"
- Relatively slow: many steps involved.



Metabotropic receptors (G-protein coupled receptors)

- The α and β/γ subunits can interact with **ion channels** or **amplifier enzymes**.



1. Ligand binds to a G-protein-coupled receptor, causing a conformational change.
2. The activated receptor signals to an associated G protein, causing the α subunit to release GDP and bind GTP.
3. The activated α or βγ subunits move through the membrane and interacts with an amplifier enzyme.
4. The activated amplifier enzyme converts an inactive second messenger into its active form.
5. The activated second messenger activates or inhibits cellular pathways.

the G proteins themselves can open/close different ion channels
-so can start amplifier processes or open/close ion channels themselves

Metabotropic receptors: norepinephrine can both activate and inactivate Ca channels, how does same ligand NE have opposing actions on same channel?

-depends on the receptor
-glutamate is good example of excitatory nt and acts in inhibitory fashion on some neurons
-depends on the G proteins
-eg one type of G protein stimulates turns them on amplification
-another type of G protein called inhibitory G protein Gi that shut them down
-eg same ligand binds to Gi receptor which inhibits adenylate cyclase whereas it binds to Gs and stimulates adenylate cyclase
-metabotropic receptors don't just do amplification they can also shut them down

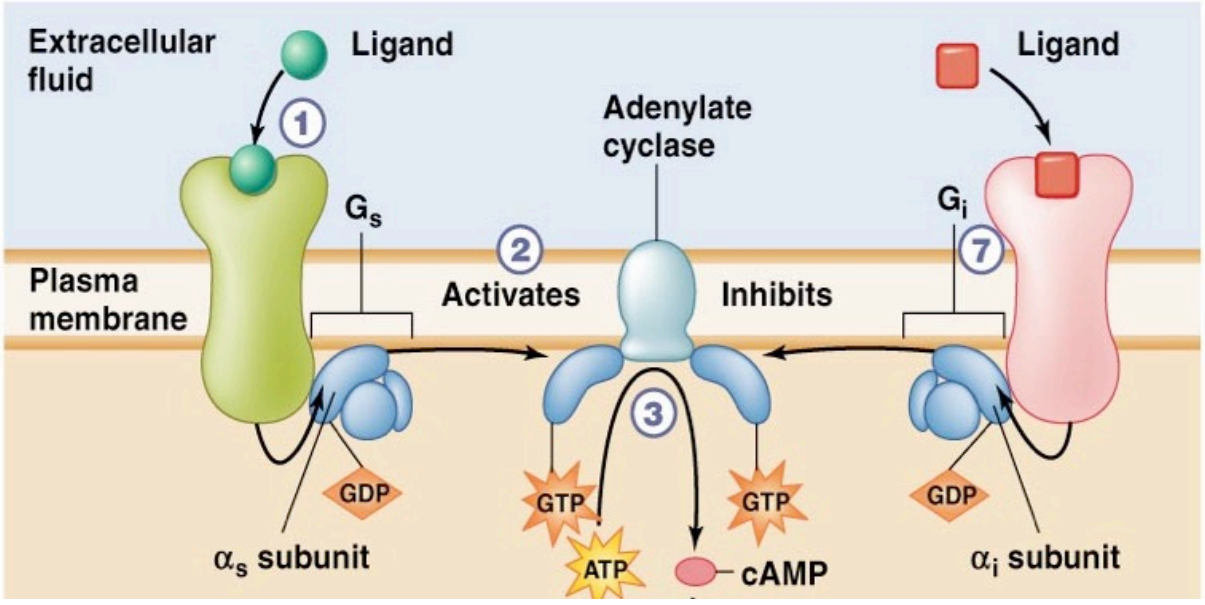
-the G proteins can act on ion channels so you can actually increase or reduce expression of genes

Question: there is some evidence that increases in cAMP affects functioning of pre frontal cortex, leading to some behavioural abnormalities. Specifically cAMP directly activations hyperpolarization-activated cation (HCN) channels, which reduces membrane resistance in distal dendrites.
(1) How would this inhibit dendrites?
(2) Could you treat this condition with drugs that inhibit
-PKA
-Adenylyl cyclase

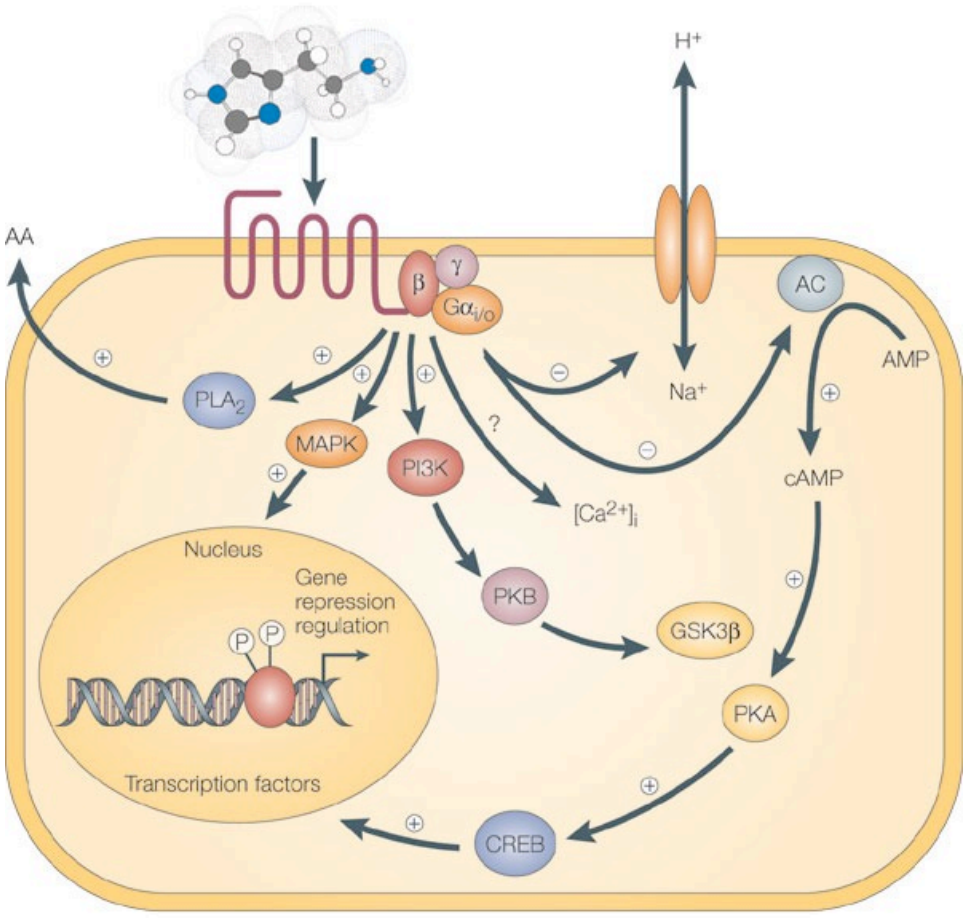
(1) hyperpolarization in the membrane opens these channels, the membrane resistance comes down reducing the length constant so it'll be harder to generate AP because membrane is more leaky
(2) PKA? no because its downstream, G protein -> AC -> cAMP -> PKA
-cAMP is still doing its thing if we inhibit PKA
AC? yes its upstream, won't make cAMP and process stops

G-protein coupled receptors: GPCRs

- GPCRs can either stimulate (G_S) or inhibit ($G_{i/o}$) amplifier enzymes



GPCR: more than just ion channel opening/closing



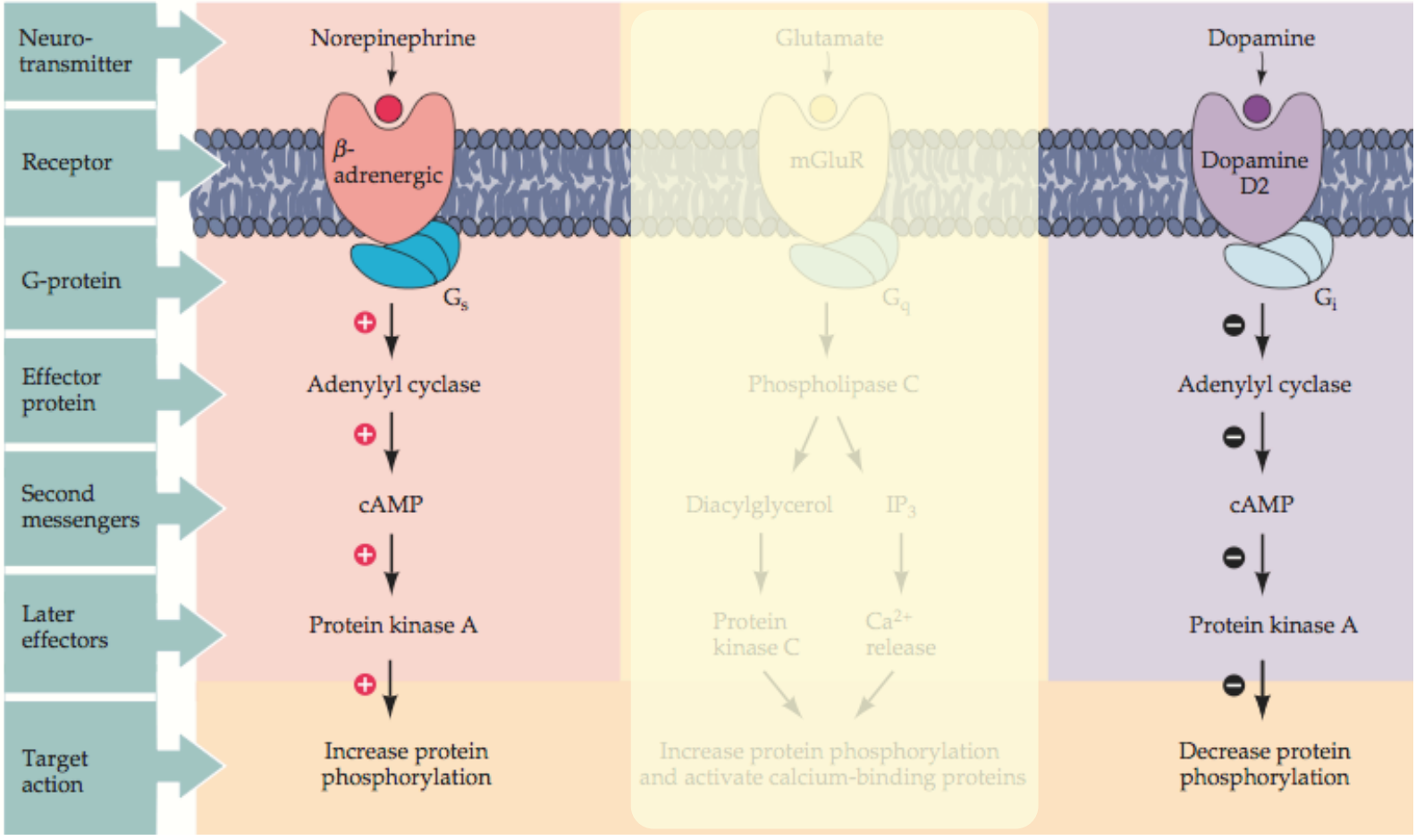
Scitable, 2014

metabotropic pathways you have to know:

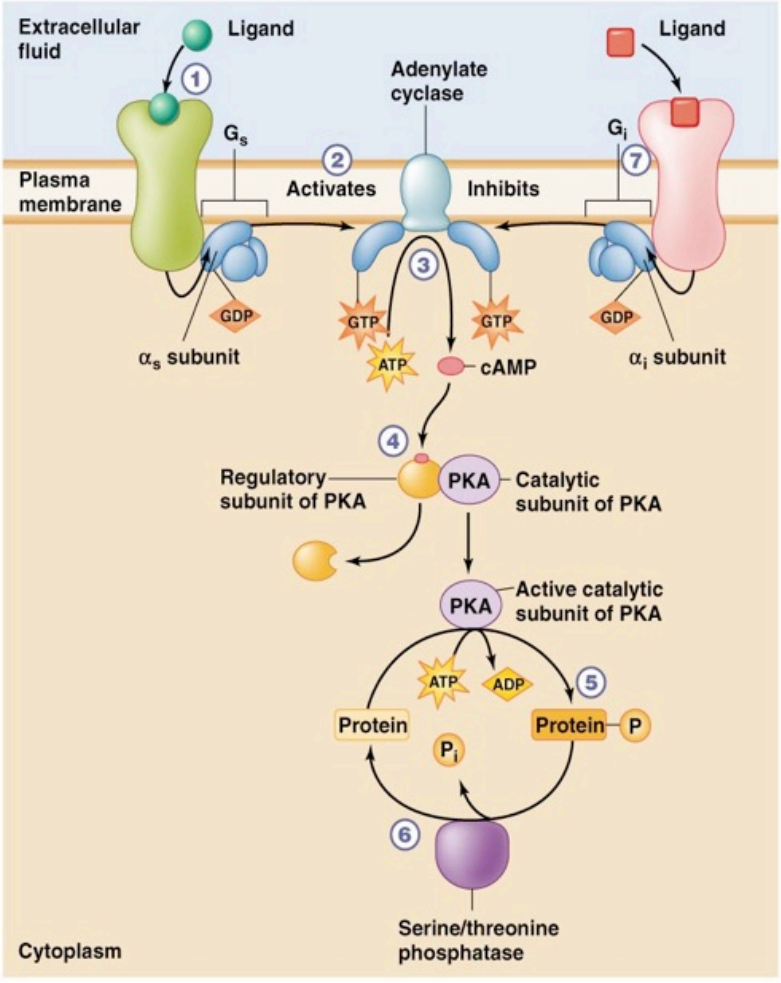
1. cAMP/PKA pathway
2. PLC/IP3 pathway
3. cGMP/PKG pathway

use abbreviations on exam eg AC, cAMP, PKA

1. cAMP / PKA pathway

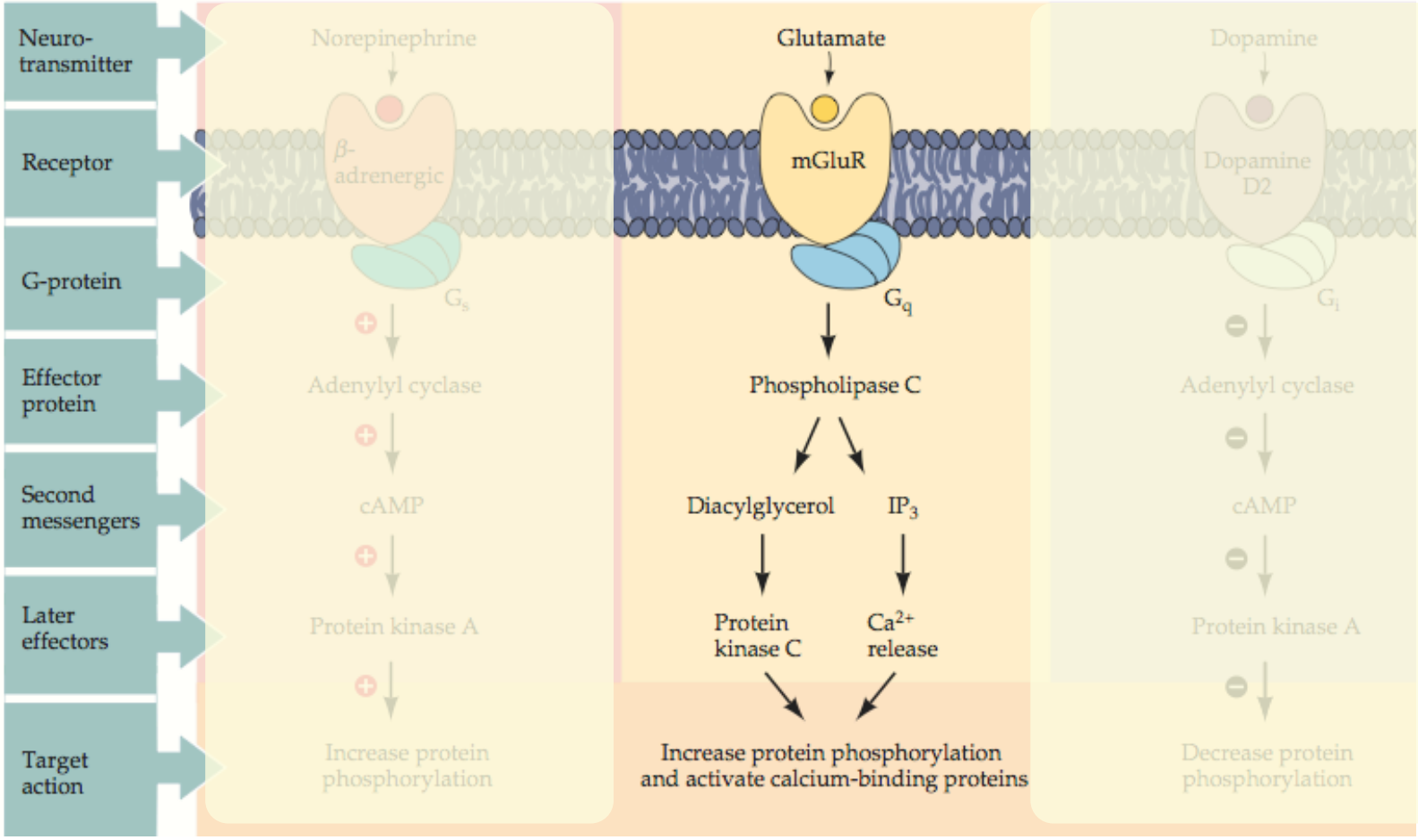


1. cAMP / PKA pathway



1. Ligand binds to a G_s-protein-coupled receptor, causing a conformational change.
2. The α_s subunit releases GDP, binds GTP, moves through the membrane, and activates adenylate cyclase.
3. Activated adenylate cyclase catalyzes the conversion of ATP to cAMP.
4. cAMP binds to the regulatory subunit of protein kinase A (PKA), which dissociates from the catalytic subunit, activating it.
5. The activated catalytic subunit phosphorylates proteins, causing a response.
6. The phosphorylated proteins are rapidly dephosphorylated by serine/threonine phosphatases, terminating the response.
7. When ligand binds to a G_i-protein-coupled receptor, the α_i subunit inhibits adenylate cyclase, inhibiting the signal transduction pathway.

2. PLC / IP3 pathway

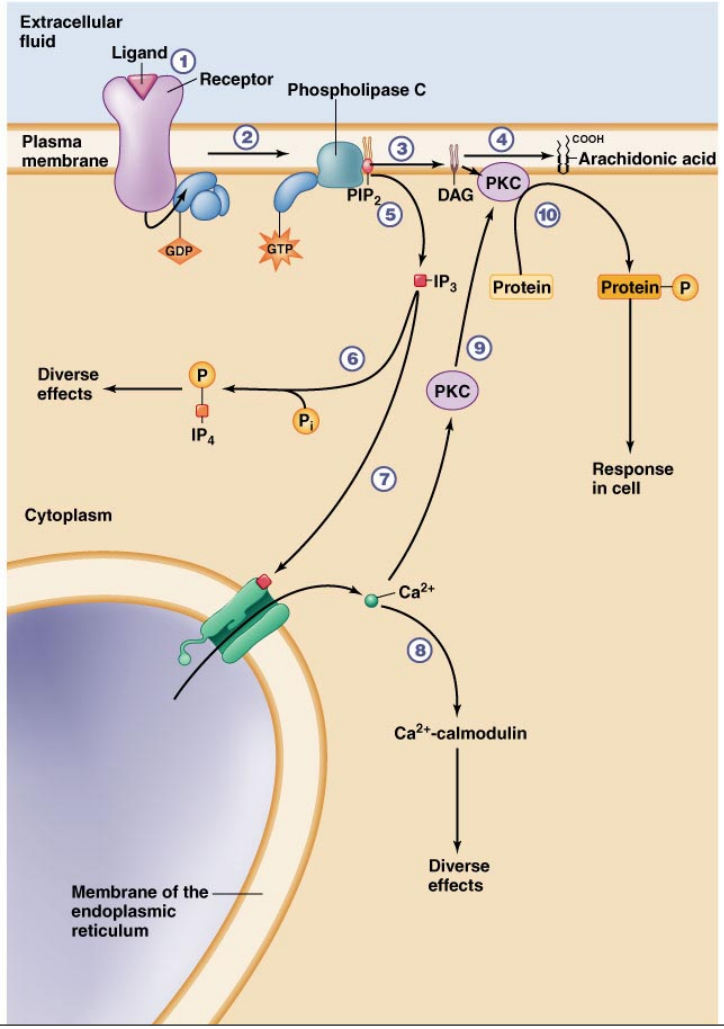


Q: Serotonin 5-HT2a receptor activation leads to production of PLC, DAG, IP3 etc
Activation of the receptor in the hypothalamus causes increases in hormonal levels of oxytocin which is known to increase contractions of smooth muscle of uterus
What do you think would happen during birthing in a female that had a disruption in her PLC pathway in the cells of her hypothalamus?

A: uterine contractions are reduced

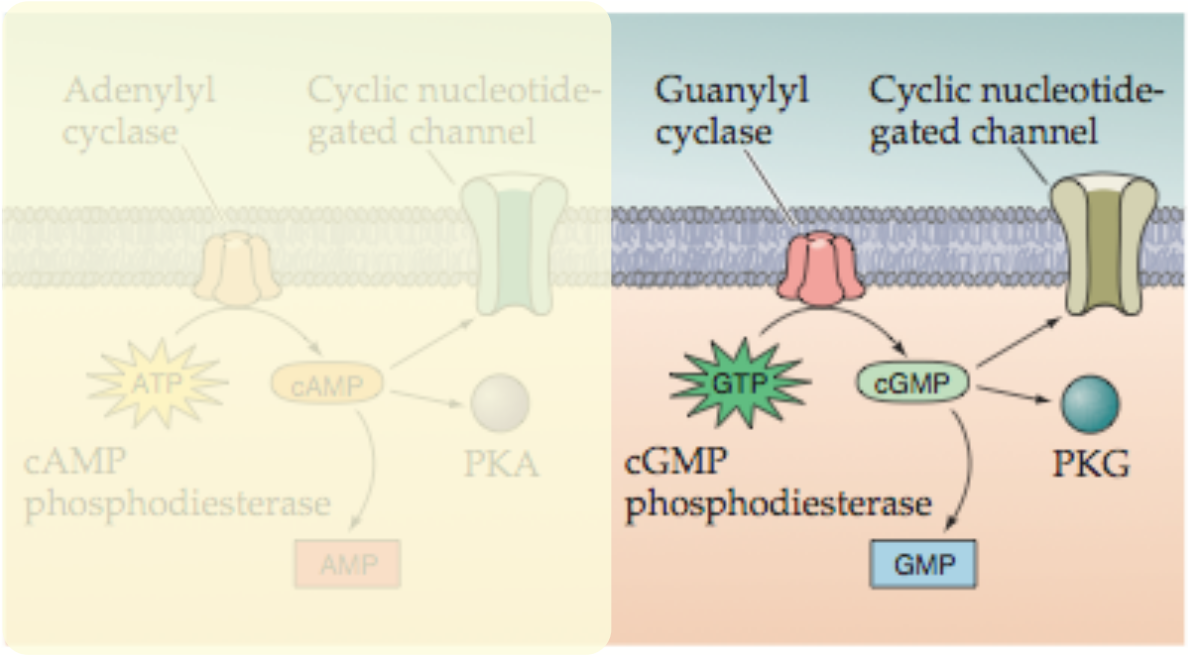
G protein -> PLC -> IP3 and DAG -> PKC

2. PLC / IP3 pathway



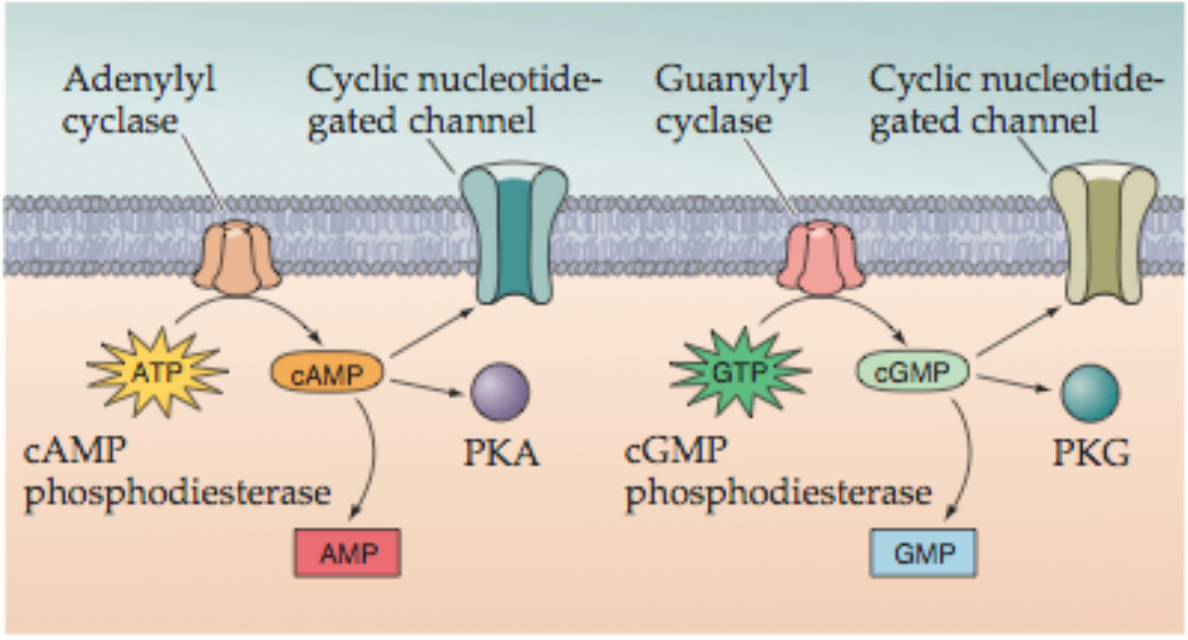
1. Ligand binds to a G-protein-coupled receptor, causing a conformational change.
2. The α subunit of the G protein releases GDP and binds GTP and moves through the membrane.
3. The activated α subunit activates phospholipase C, which cleaves PIP_2 into IP_3 and DAG.
4. DAG is cleaved in the membrane to form arachidonic acid, the substrate for the synthesis of chemical messengers called eicosanoids.
5. IP_3 is released into the cytoplasm.
6. IP_3 can be phosphorylated to IP_4, which has diverse effects.
7. IP_3 also binds to Ca^{2+} channels on the endoplasmic reticulum, releasing Ca^{2+} into the cytoplasm.
8. The Ca^{2+} binds to calmodulin, causing diverse effects within the cell.
9. The Ca^{2+} also stimulates protein kinase C (PKC) to move to the membrane where it interacts with DAG.
10. DAG activates the PKC, which then phosphorylates proteins, stimulating a phosphorylation cascade.

3. cGMP pathway



similar pathway replace A with G eg PKA or PKG

3. cGMP pathway



3. Learning and memory

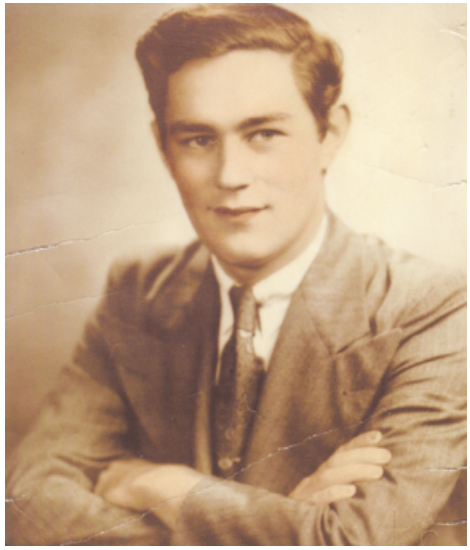
Question: think of an example when a number of someones synapses change?

- Learning is the process of acquiring new information.
- Memory is the retention and retrieval of learned information.
- Both processes are possible because the nervous systems can alter synaptic connections and functional properties of neurons - *plasticity*.

H.M., the most famous patient in neurology

- When he was 27, H.M. had a lobotomy to treat epilepsy.
  - The amygdala and a large part of the hippocampus were removed from both sides of his brain.

- Afterwards, H.M. lost the ability for long-term episodic memory.
  - He could store information — such as a sentence — for about 10 or 20 seconds. Once he stopped thinking about it, there was no way it could re-enter his short-term memory.



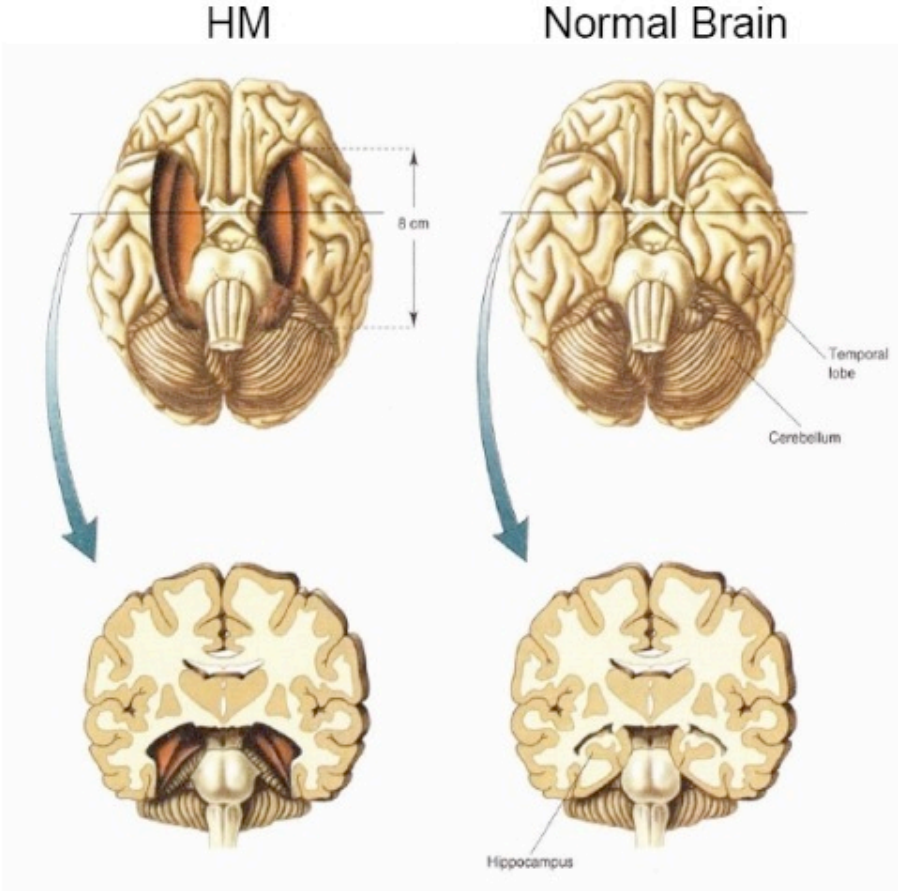
Henry Molaison on his graduation day.

- He had episodic memories from before his surgery and could form new procedural memories.

In humans and mammals

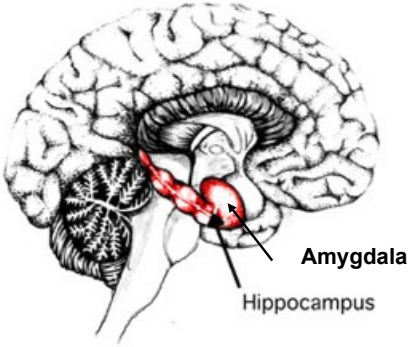
take away hippocampus and you can't form new memories

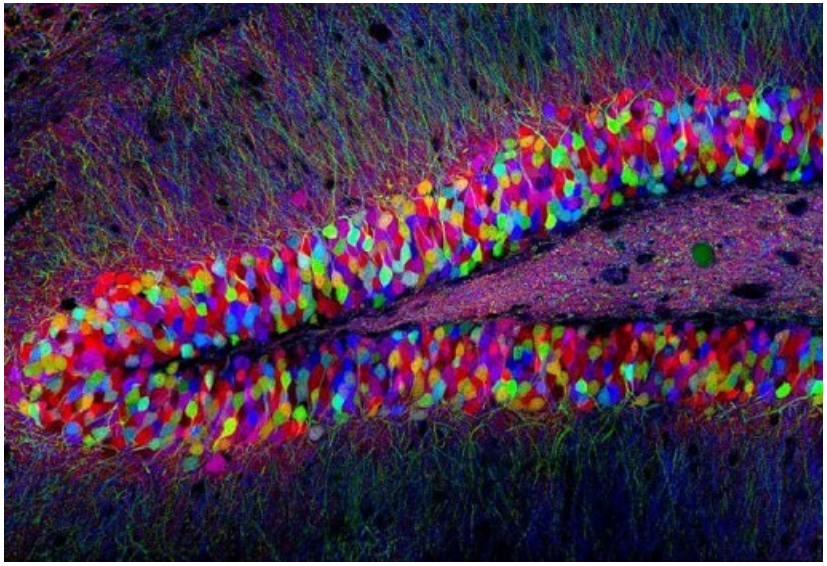
- LTP and LTD in **hippocampus**



Learning and memory in the hippocampus

long term memories get stored in the cortex
-this is the cut off for midterm content





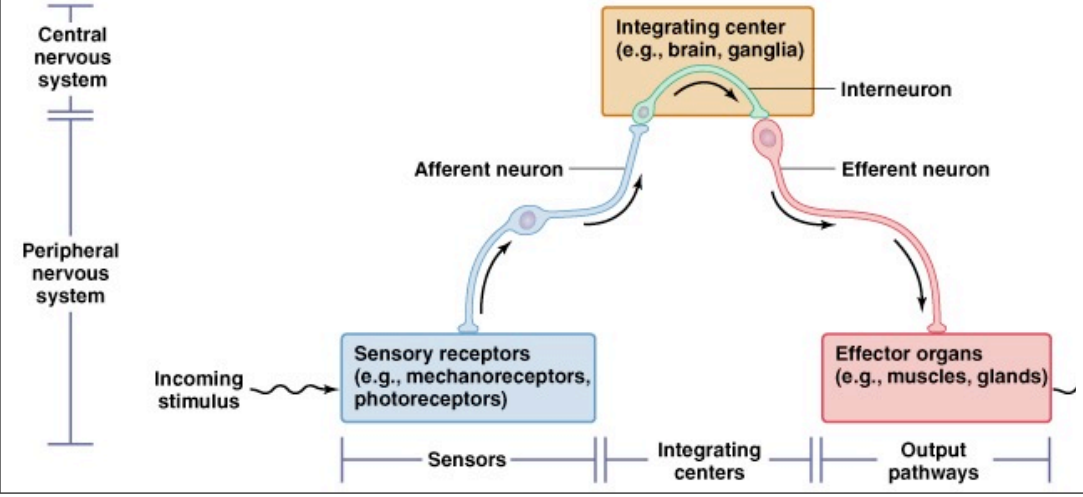
- Converts short-term memory to long-term memory
- Involved in spatial memory and navigation as well as episodic memory

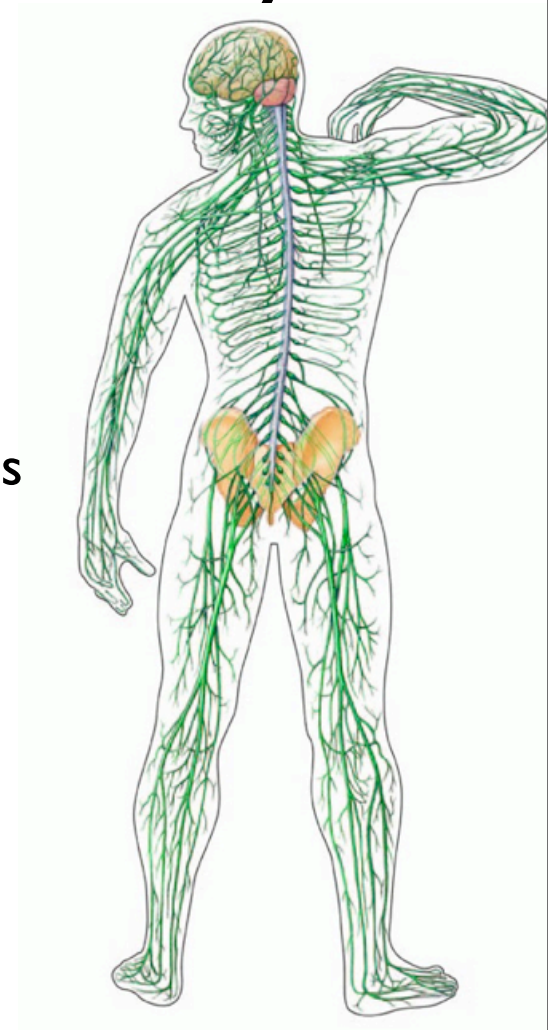
Functional Organization of the Nervous System

- Compare and contrast the form and function of different regions of the peripheral nervous system
- Predict the consequences of modifications in parasympathetic and sympathetic nervous systems in the maintenance of homeostasis
- Compare and contrast the basic organization of the central nervous system and the peripheral nervous system of vertebrates
- Differentiate the 3 subdivisions of the adult brain of vertebrate and name their principal structures and functions
- Predict the consequences of damage (such as from injury or disease) to different regions of the mammalian brain and spinal cord

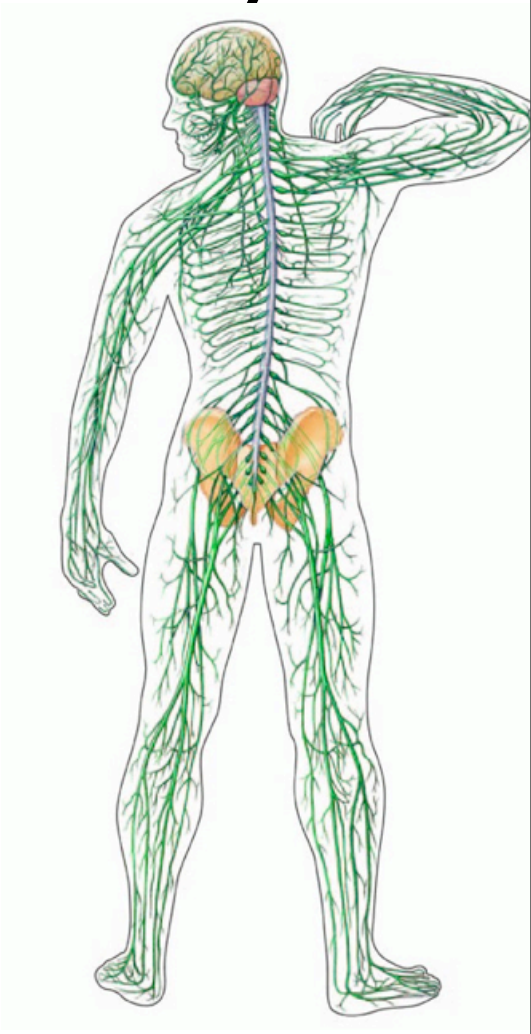
Organization of Vert. Nervous Systems

- **Central** and **peripheral** NS.
- Afferent: brings signal in to the central nervous system
  - (ie: receptor cells and their afferents)
- Efferent: brings signal from central nervous system out to body





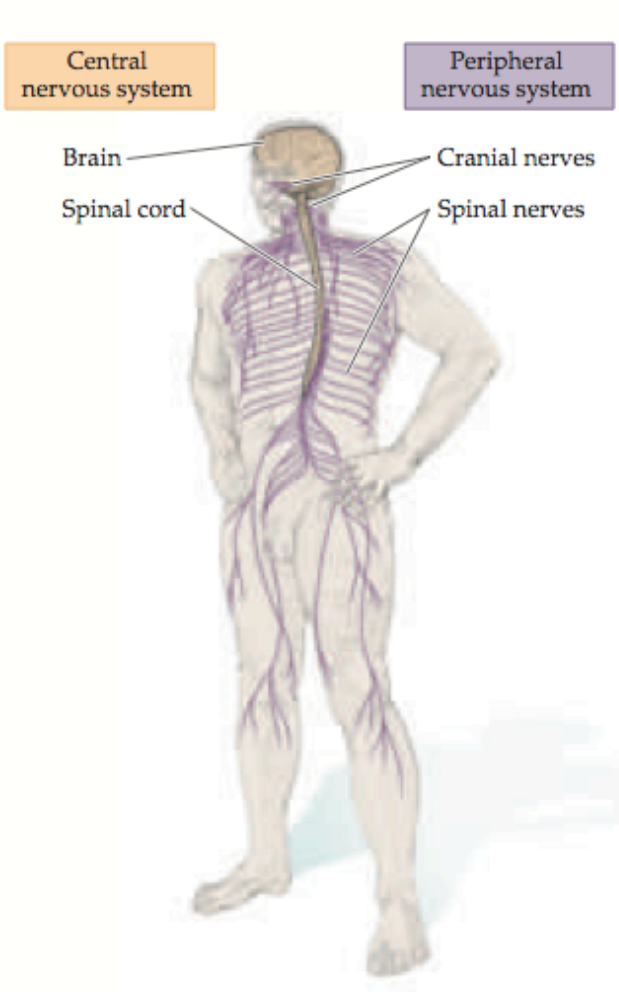
Organization of Vert. Nervous Systems

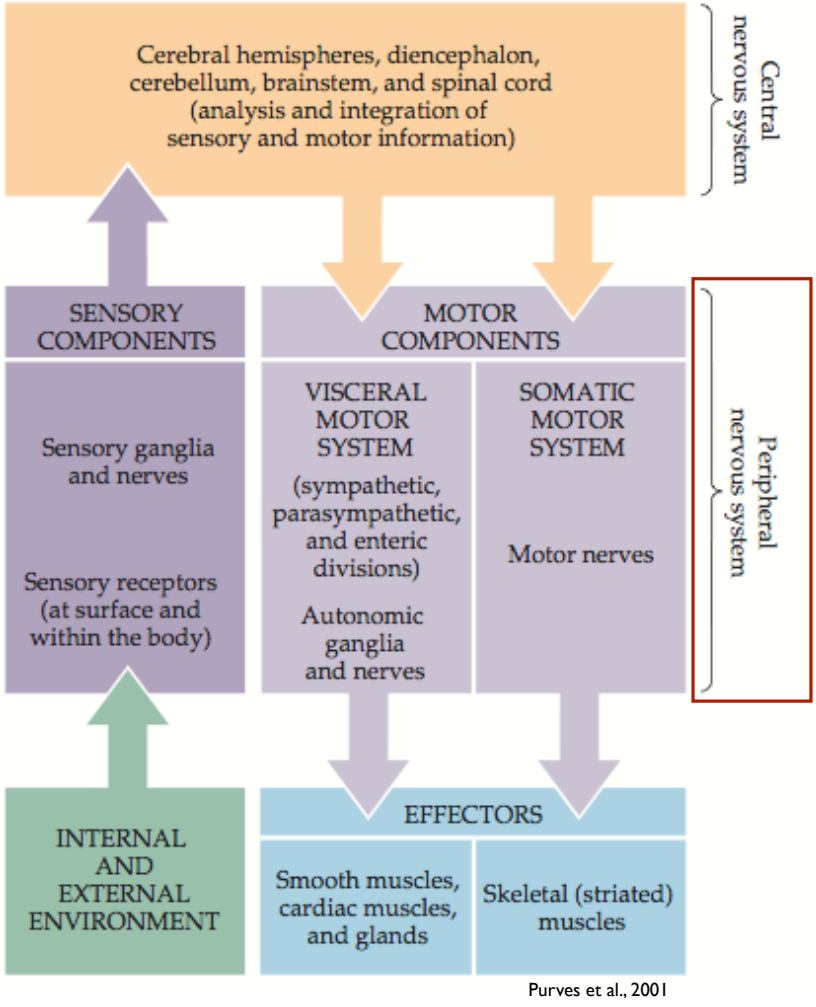


Outline:

- Peripheral nervous system:
- Central nervous system:
  - Spinal cord
  - Brain

Peripheral Nervous System

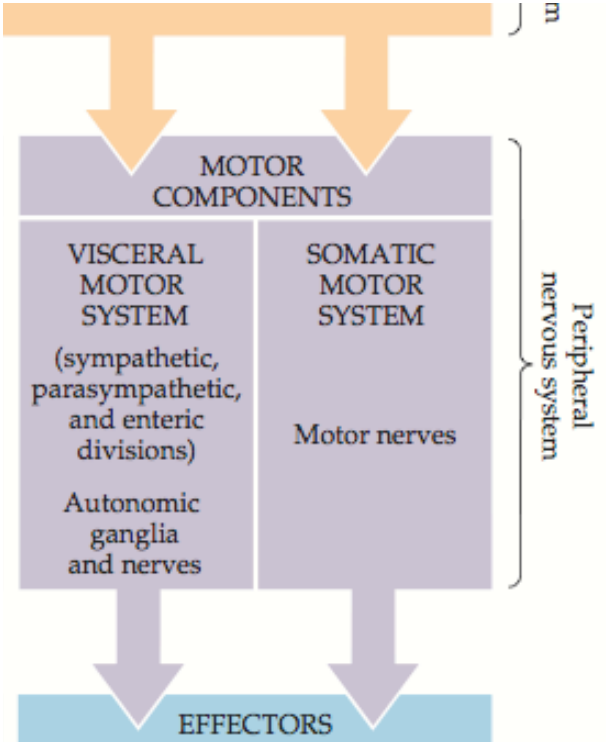




Purves et al., 2001

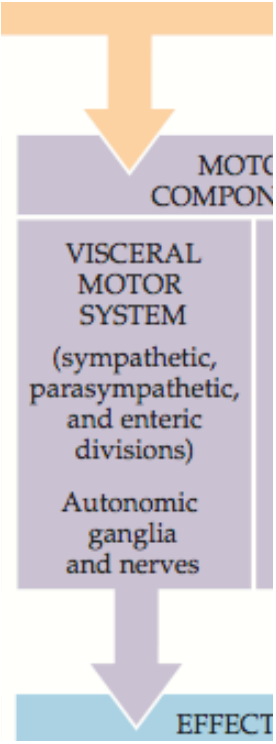
Divisions of PNS (motor components)

1. Somatic
2. Autonomic
    a) Sympathetic
    b) Parasympathetic



Autonomic Nervous System

- Smooth muscle, cardiac muscle, glands
- Usually not under conscious control
- **Sympathetic** NS:
  - "fight or flight"
- **Parasympathetic** NS:
  - "rest and digest"
- Enteric NS: independent of other 2: digestion



- Maintain homeostasis

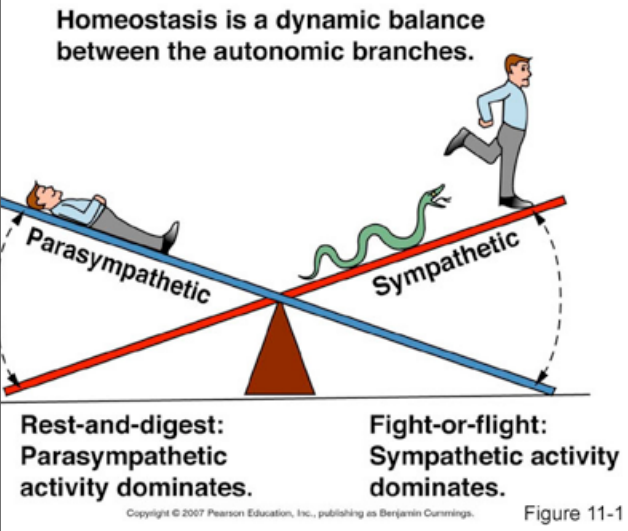
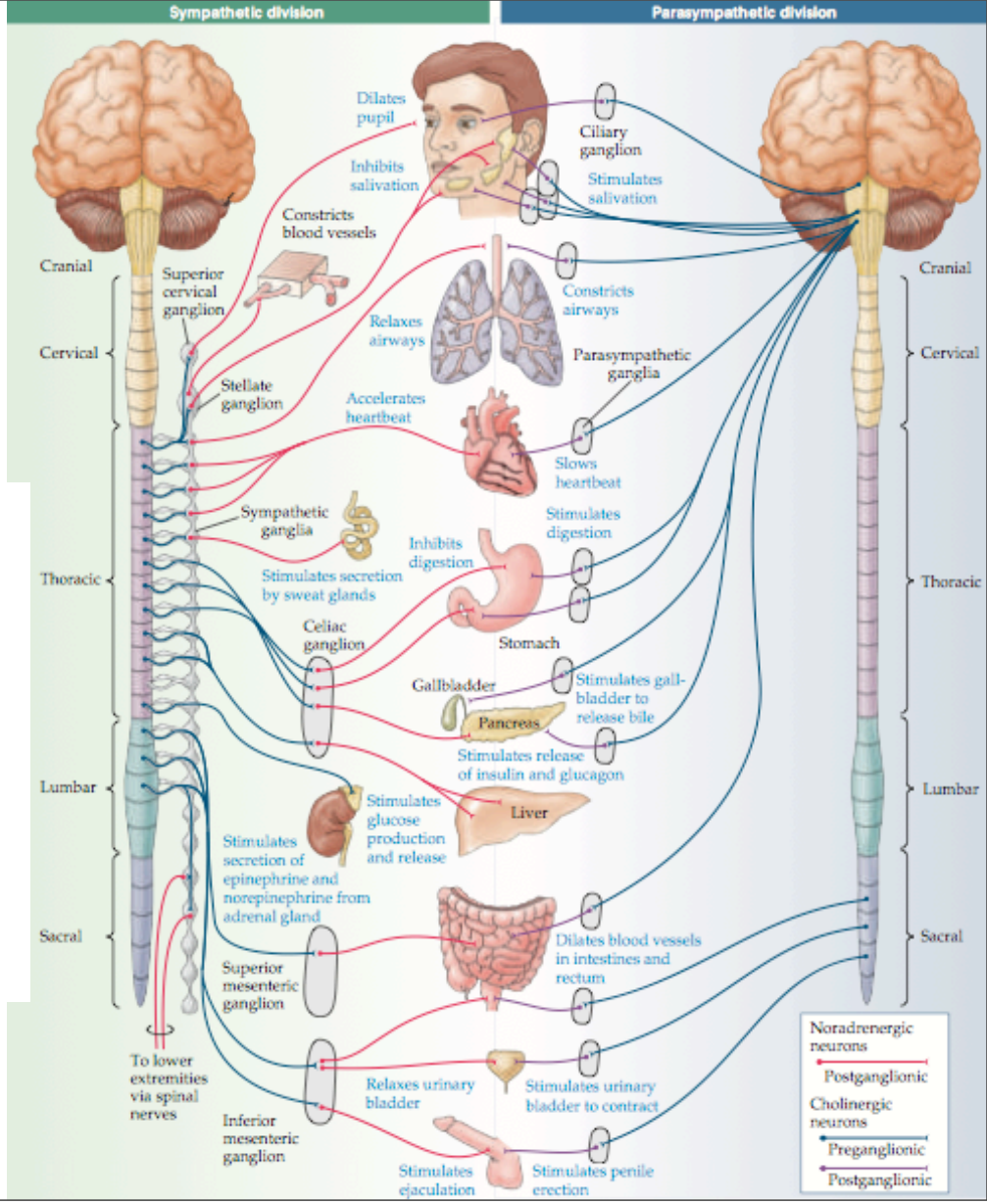


Figure 11-1



Purves et al., 2004

Antagonistic actions of Autonomic NS

Table 8.3 Actions of the sympathetic and parasympathetic nervous systems in humans.

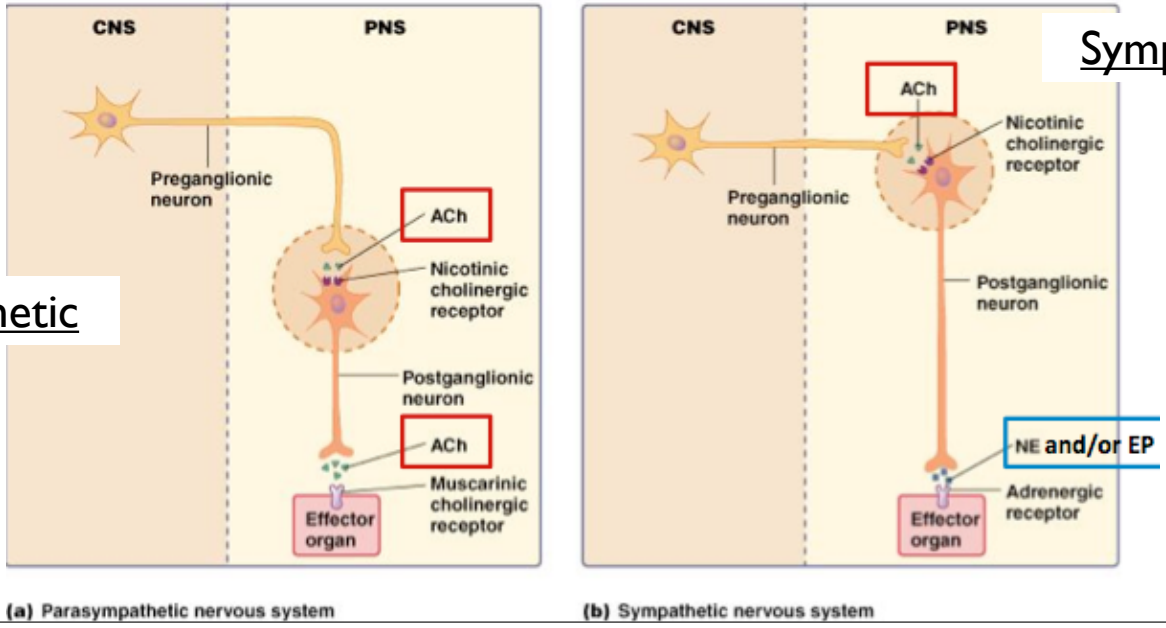
Effector organ	Parasympathetic stimulation	Sympathetic stimulation	Adrenergic receptor
Pupil of eye	Constricts	Dilates	α
Lacrimal glands of eyes	Stimulates secretion	None	None
Salivary gland	Watery secretion	Thick secretion	α, β2
Heart	Slows heart rate	Increases rate and force of contraction	β1
Arterioles	None	Constricts	α
Nasal glands	Stimulates secretion	None	None
Bronchioles of lungs	Constricts	Dilates	β2
Digestive tract	Increased motility and secretion	Decreased motility and secretion	α, β2
Exocrine pancreas	Increases enzyme secretion	Decreases enzyme secretion	α
Endocrine pancreas	Stimulates insulin secretion	Inhibits insulin secretion	α
Adrenal medulla	None	Secretes epinephrine	
Kidney	None	Increases renin secretion	β1
Bladder	Release of urine	Retention of urine	α, β2
Adipose tissue	None	Fat breakdown	β1
Sweat glands	General sweating	Localized sweating	α
Arrector pili muscles of skin	None	Contract, causing hair to stand on end	α
Male sex organs	Erection	Ejaculation	α
Uterus	Depends on stage of cycle	Depends on stage of cycle	α, β2

Autonomic innervation

- Neurons in series, synapsing in autonomic ganglia
- One pre-synaptic neuron may synapse with multiple post-synaptic neurons.

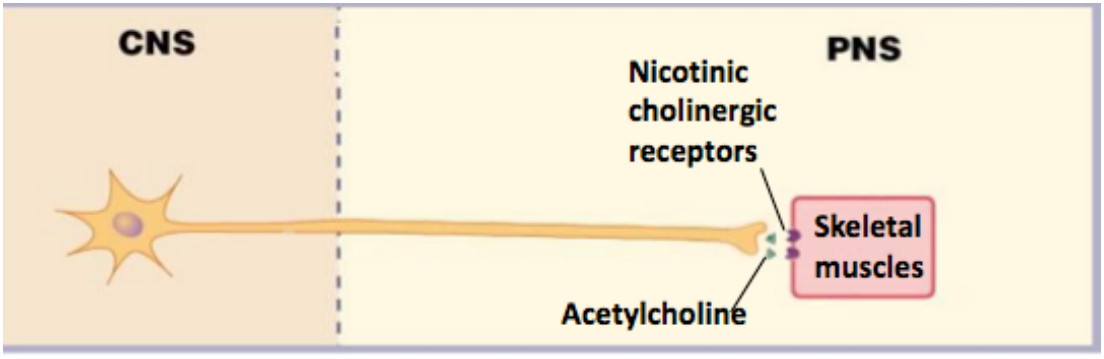
Parasympathetic

Sympathetic

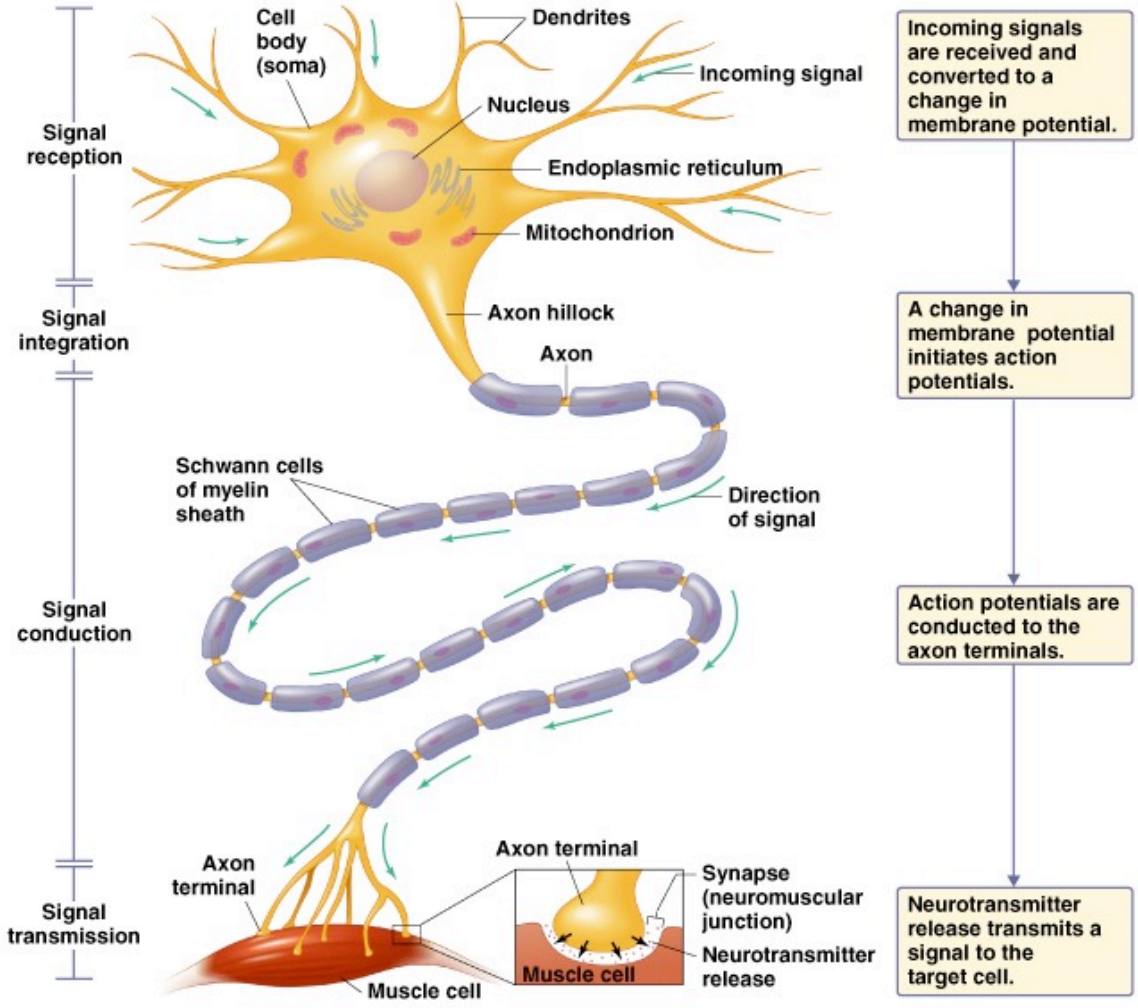


Somatic Nervous System

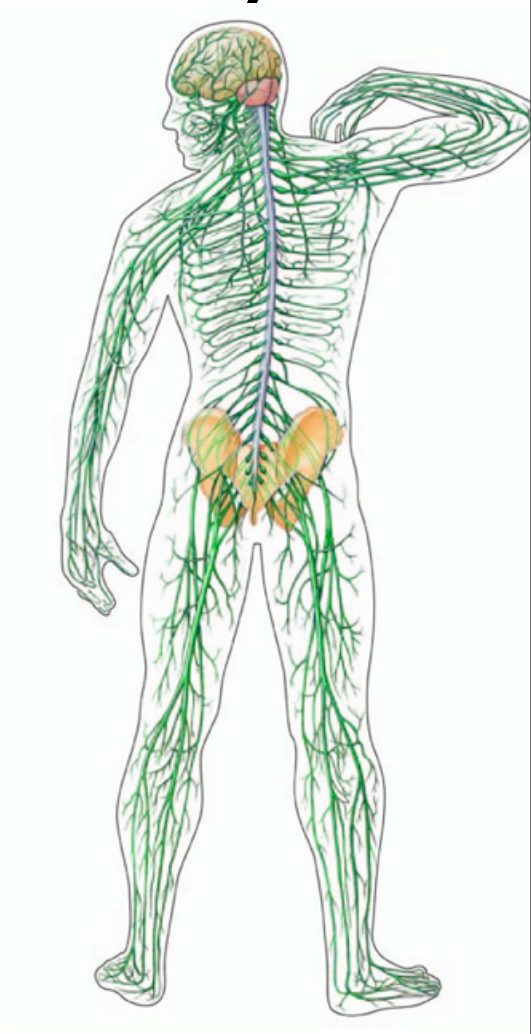
- Control skeletal muscle
- Usually under conscious control
- Only one neuron from CNS to muscle
- Acetylcholine (ACh) is released on nicotinic cholinergic receptors of muscles



Release of NT into NMJ



Organization of Vert. Nervous Systems



Outline:

- Peripheral nervous system:
- Central nervous system:
  - Spinal cord
  - Brain

Spinal cord – cross section

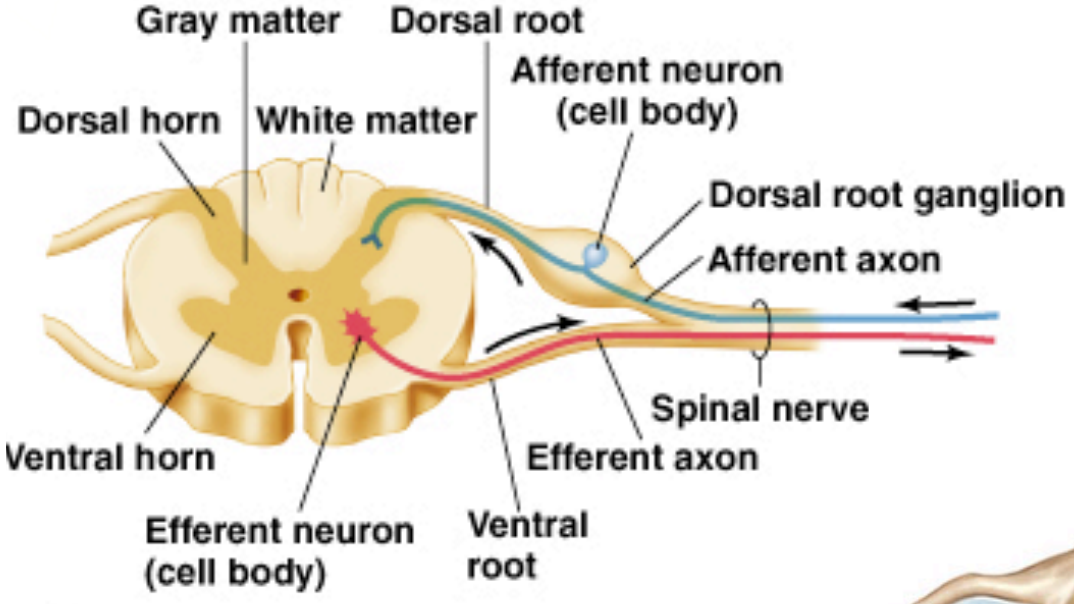
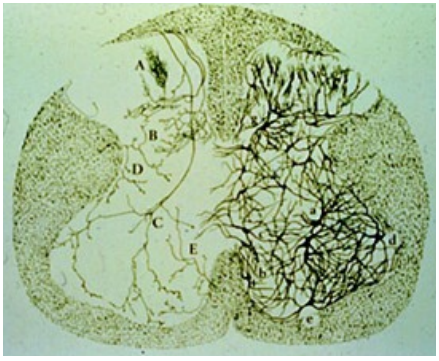
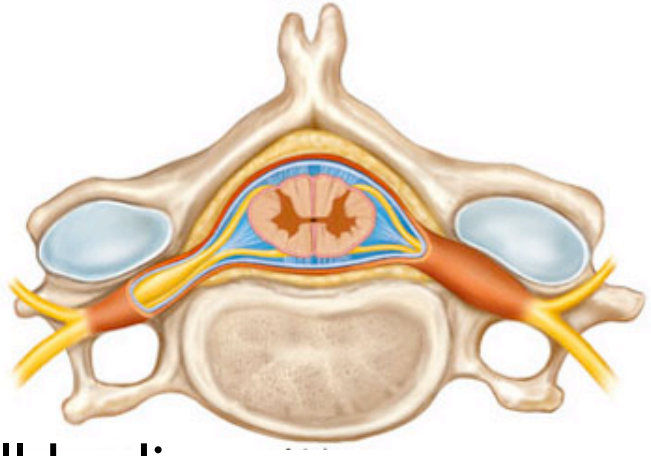


Figure 7.5b



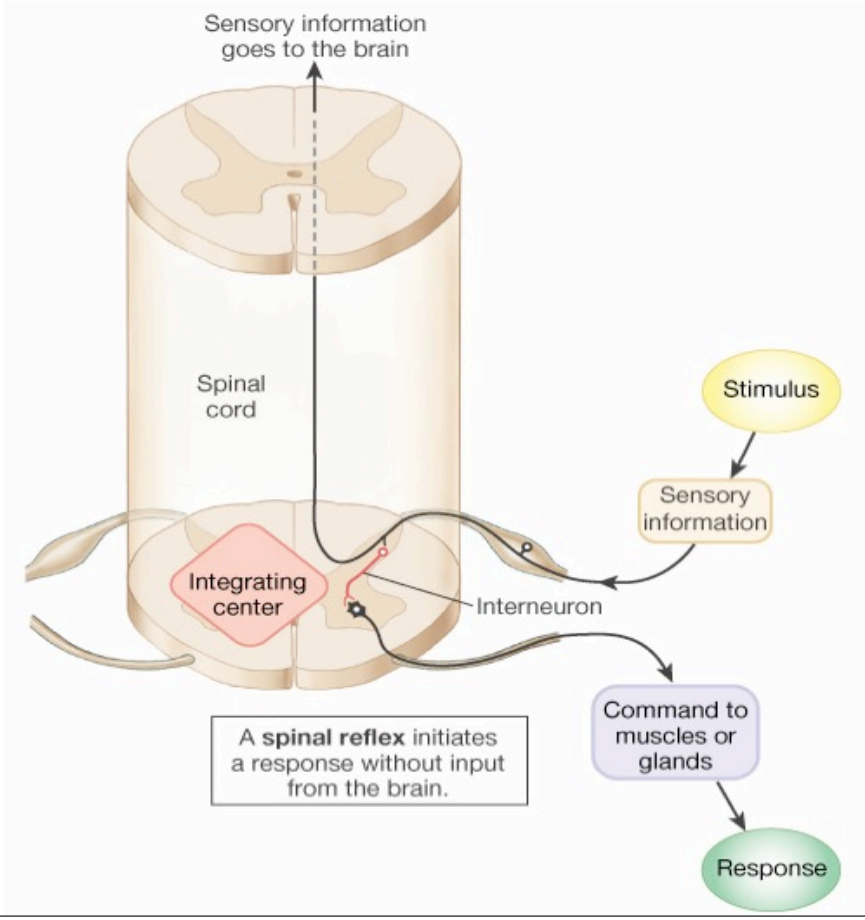


Gray matter – cell bodies

White matter – axons and their myelin sheaths

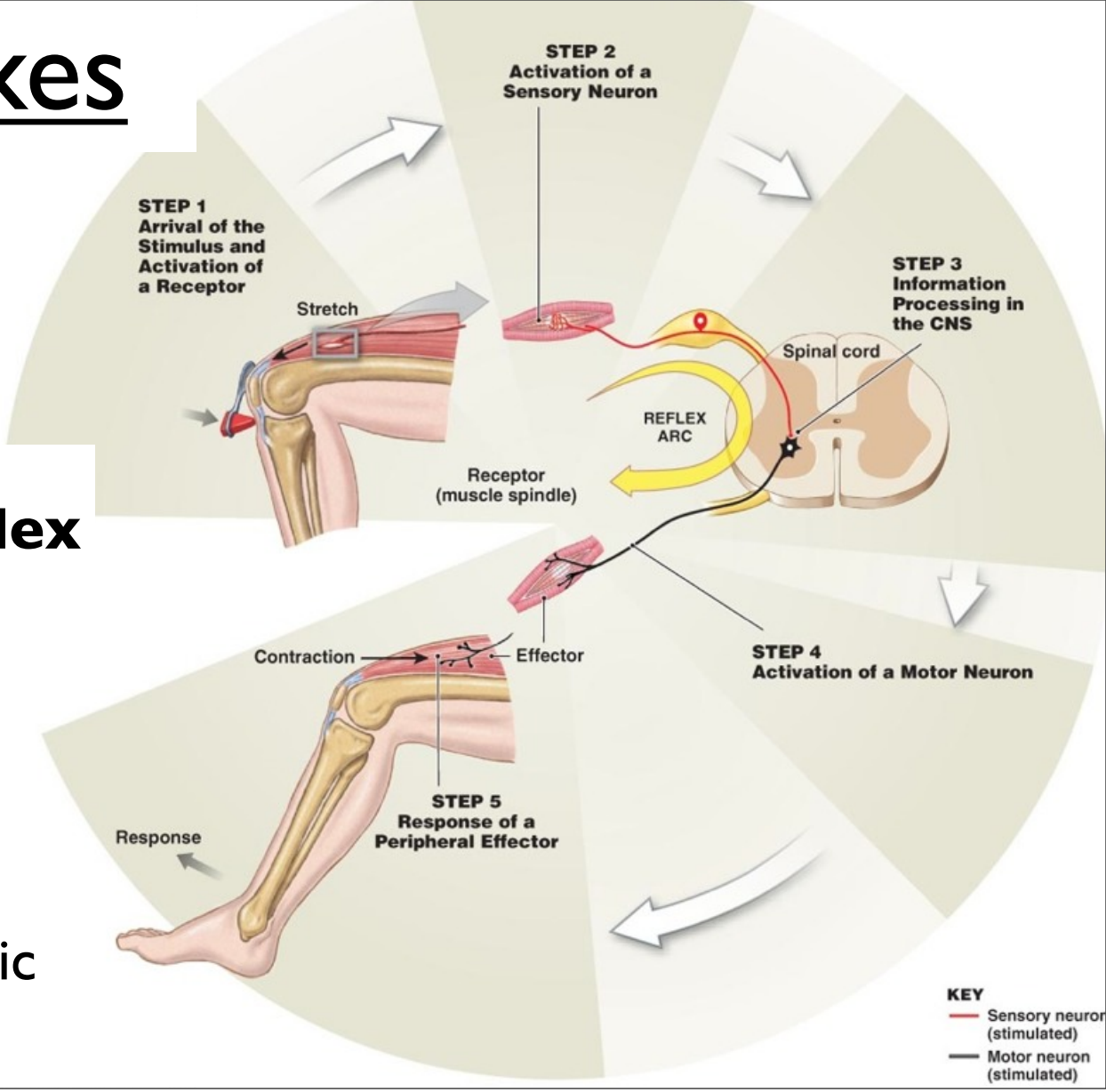
Spinal cord – an integrating centre

- Spinal reflexes are involuntary and very rapid
- The brain receives sensory information as the reflex occurs



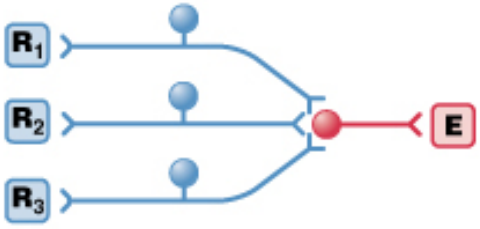
Reflexes

Stretch reflex

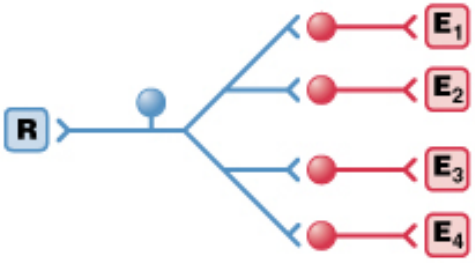


Classic monosynaptic reflex arc

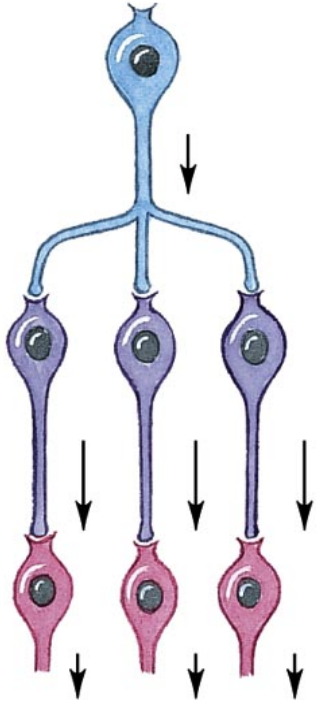
Reflex arcs



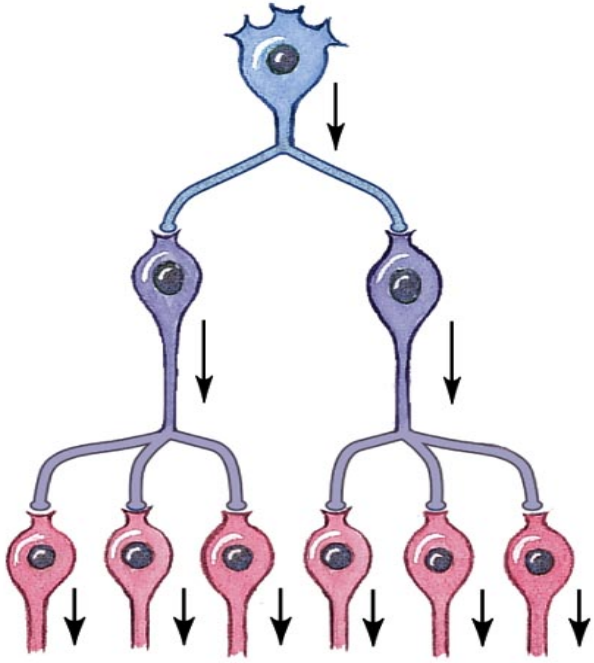
(a) Convergence



(b) Divergence



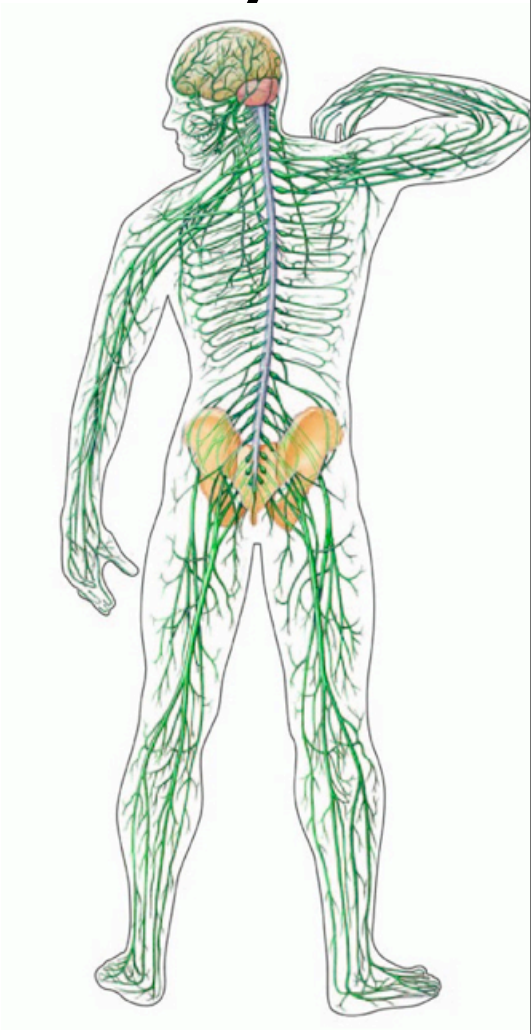
(d) Parallel processing



(a) Divergence

- Convergence: allows spatial summation
- Divergence: amplify signals; parallel processing

Organization of Vert. Nervous Systems



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