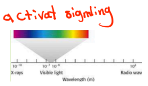
Biochemstrey

lecture 1 vesion.

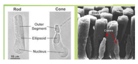
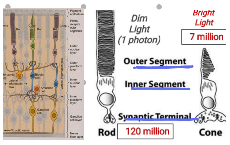
* Basic Human Vesion

- see only very narrow range of this spectrum "visible light"
- This narrow rang activat signaling pathways in humans.



* RODS and CONES

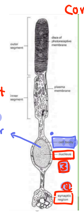
- C cells responsible for vesion
- Conist in rtina
- inter mixed and connected with other cell eg: bipolar cells, amacrine cells, ganglions cells
- These cell regulat transduction process

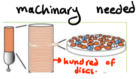
RoD	Cones
→ 120 million rod cells	→ 7 milio.
→ vesion in dim light (faint)	→ bright light
→ black, white, gray color	→ see in colors (Red, green blue...)
→ More Sensitive	→ less Sensitive.
→ Most study done on it.	
→ Rodopsin	→ photop sin.
→ Same chromophore	→ Same chromophore.
→ only 1 type of cells.	3 type of cone cells
WL → peack 500 nm	peack 100 nm (narrower)
→ present all over retina	→ concentrated in the back of retina [Fovea]
→ multiple rods connected to single nerve [unclear fuzzy image]	→ one cone cell → one nerve [sharp clear image]

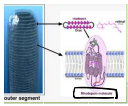
* Rod cells.

Consist of 4 regions:



1. outer sigment: contain biochemical machinary needed for visual transduction.
2. inner sigment
   - cell body
   - Contain cellular orgenells





- The components of Photo transduction enzyme cascade are backed into stacks of membrane vesicles.
- Each disc has molecular machinery responsible for signal transduction.
- Signal is transmitted from outer sigment & inner sigment causing release of glutamate.

* The dark current

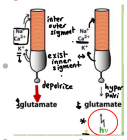
Rods and cones work "backwards"
at rest Rods and cones are depolarized to -35 to -45 mV.

1. At dark, Na+ and, to a lesser amount, Ca^{2+} enter through cyclic nucleotide-gated channels in the outer segment membrane.
2. K^+ is released through voltage-gated channels in the inner segment.
3. Rod cells are depolarized.
4. The neurotransmitter glutamate is released continuously.

- No light (No excites)
- channel open.
- Ca+ enter cell
- glutamat releas.

bright light, rods will be
When excited:
1. Channels in the outer segment membrane close.
2. Rod cells hyperpolarize, and
3. Glutamate release decreases.

- excites cell
- channel close
- hy perpolarization
- reduce glutamate release.

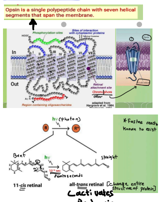


* Generation Of Vesion Signals.

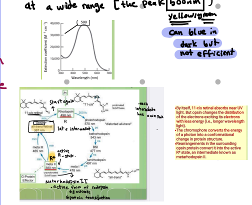
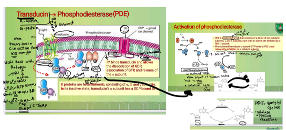
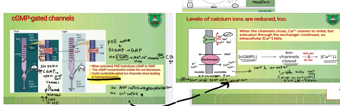
The players:

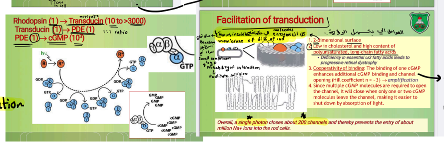
- Rodopsin (opsin + pigment molecule)
  - (holo protein)
  - 11-cis retinal
  - responsible for absorbing photons
- Transducin (G-protein)
- phosphodiastrase (cGMP)
- Na+ gated channels. closer of channel
- Regulatory proteins. Terminate reactivation.

Rodopsin



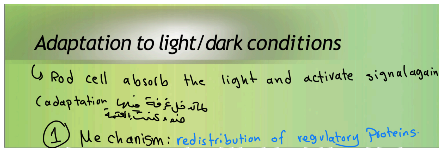
- Rodopsin can absorb light at a wide range [the peak 500nm]
  - yellow - can blue in dark but not efficient

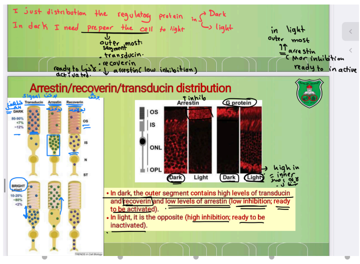


Signal amplification

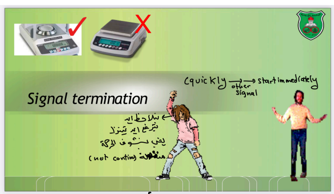
release one cGMP make easier for next one

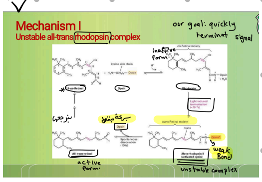


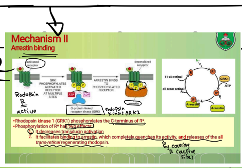
Rod cell absorb the light and activate signal again (adaptation)
1. Mechanism: redistribution of regulatory proteins.

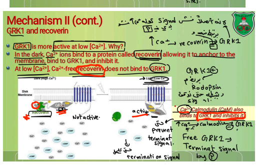


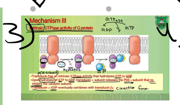
	Dark	light
Transducin	↑ in outer segment [inactive form] bind with GDP (ready to+)	↑ inner segment
Recoverin	in Both (more in inner segment)	inner segment
Arrestin.	inner segments.	outer sigment

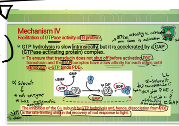


1. 

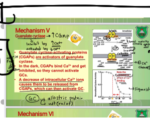
2. 

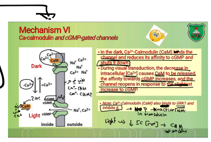


3. 

4. 

GAP
Transducin low affinity
PDE

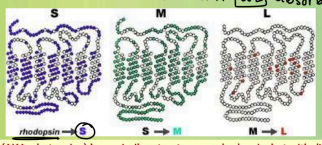
5. 

6. 

Dark Ca+ - recoverin → GRK1
light Ca+ - recoverin

Color vision

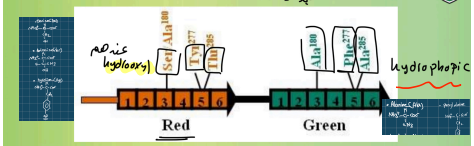
How different are they? Primary structure of AA



- Cone opsins (AKA, photopsins) have similar structures as rhodopsin, but with different amino acid residues surrounding the bound 11-cis retinal; thus, they cause the chromophore's absorption to different wavelengths.
- Each of the cone photoreceptors vs. rhodopsin = 40% identical.
- The blue photoreceptor vs. green and red photoreceptors = ~ 40% identical.
- The green vs. red photoreceptors > 95% identical.

almost identical

Three important aa residues

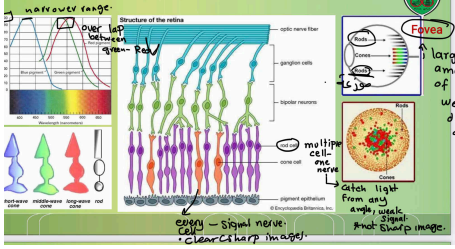


A hydroxyl group has been added to each amino acid in the red pigment causing a λ_{max} shift of about 10 nm to longer wavelengths (lower energy).

any difference in position → shift in wavelength of absorption

3 type of cones
1. can absorbe green range
2. blue range
3. Red range

Cone photoreceptor proteins

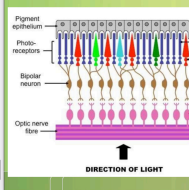


narrower range
over lap between green-Red
multiple cell- one nerve
catch light from any angle, weak signal
not sharp image
every cell – signal nerve
clear-sharp image
large amount of light
we dont need distributed all over

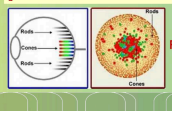
Rods vs. cones

Rod > cone
More nsive. Taksrp(width WL)

- Location, light absorption, number, structure, photoreceptors, chromophores, image sharpness, sensitivity (amplification)



Sharpness and sensitivity of viewing images depend on the brain determining the number and location of the photoreceptor cell(s) that passes an impulse to any given nerve fiber.



Color blindness

Chromosomal locations

- The "blue" opsin gene: chromosome 7
- The "red" and "green" opsin genes: X chromosome
- The X chromosome normally carries a cluster of from 2 to 9 opsin genes.
- Multiple copies of these genes are fine.

if there is a mutation in the "blue" opsin gene → males more affect

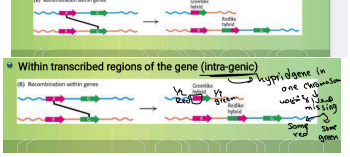
(The number of genes and the similarity in the primary structure between red and green (95%) very important because during cell devision in the chromosome line up in middle of cell and recombination process (exchange of genetic material between)

If Male 3 green opsin genes → Female → diversity → new chromosome combination

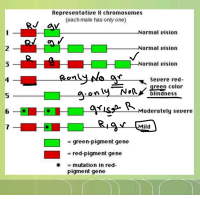
Red-green homologous recombination

The DNA sequence of genes highly similar / when chromosome line up, may unequal cut and unequal swap

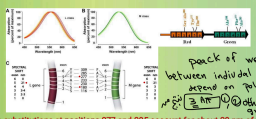
- Between transcribed regions of the gene (inter-genic)
- Within transcribed regions of the gene (intra-genic)



Genetic probabilities



Spectral fine-tuning

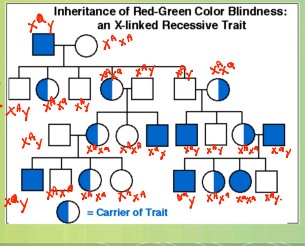


pack of wavelenght between individual different depend on polymorphism

3 AA other region in green/red opsin

- The substitutions at positions 277 and 285 account for about 20 nm of the difference in peak sensitivity.
- Serine (S) vs. alanine (A) at position 180 produces a considerable shift in the spectrum.

Pedigree



Examples

Red blindness

Green blindness

Biochemistry of neurotransmitters

Chemical substance that synthesized in neuron, released at synaps following depolarization of nerve terminal [dependant on influx ca++]
&
bind to receptor on the Post synaptic cell (M)
→ presynaptic terminal.
&
elect specific response.
&
removed (inactivated) from synaptic cleft

have different structuers.

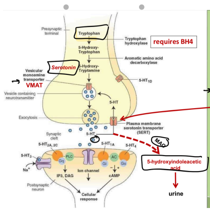
Type.

- *Small molecule
  - → usually synthesized from amino acids.
  - Biogenic amines: [Epinphrin] [dopamine] [histamine] [serotonin]
  - Acetylcholin
  - Purines (ATP)
  - Amino acid: [GABA] [glutamate] [aspartate] [glycine].
- *Neuropeptides
- *Gases.
  - NO, CO [exceptions]

*Neuropeptides	*Small-molecular neurotransmitters
Short chain peptide	endogenous chemical
↑ Mw	↓ Mw
slow → acting, slow response	rapid acting & short term response.
act on several receptors	Act on specific receptor.
can change metabolism	Most do can change metabolism.
synthesized in ER, golgi apparatus	synthesized in cytosol of presynaptic nerves.
synthesized in low concentration	synthe sized in ↑ high concentration.
found all over neuron	found in the axon terminals of presynaptic neurons.
stored in large dense core vesicles.	stored in small secretry vesicles.
Released to the synaptic cleft along with another NT	Released individually
Released at low cytosolic ca++ concentration.	released at high cytosolic ca++ concentration.
different site of actions than their origen.	act in direct apposition of the releasing cell.
Not retaken up and reused.	can retaken up, reused.
Relatively more potent	Relatively less potent.
Terminated when proteolytically degraded or diffused.	Terminated by: reuptake, taken up by glial cells, diffused, enzyme degradation.

TRYPTOPHAN-DERIVED NEUROTRANSMITTERS

Serotonin and melatonin



enzyme transport to nerve terminals to produce serotonin which then packaged into vesicle by VMAT [proton exchanger] and ATP

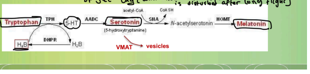
Antidepressants, called selective serotonin reuptake inhibitors (SSRIs) like Prozac® inhibit the reuptake process resulting in prolonged serotonin presence in the synaptic cleft.

Serotonin is packaged into vesicles by VMAT.

Melatonin

- Serotonin is synthesized in the pineal gland and serves as a precursor for the synthesis of melatonin, which is a neurohormone involved in regulating:
  - sleep patterns
  - seasonal and circadian (daily) rhythms
  - dark-light cycle

(melatonin is used to get rid of Jet lag (when normal sleep pattern is disturbed after long flight)



AMINO ACID-BASED NEUROTRANSMITTERS

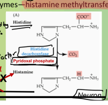
Histamine (synthesize by decarboxylation of Histidine

- It does not penetrate the blood-brain barrier and, hence, must be synthesized in the brain.
- Histamine is inactivated by two enzymes—(1) histamine methyltransferase and (2) diamine oxidase (histaminase).

No reuptake mechanism so removed by neighboring astrocyte or by enzymes.

Histamine is packaged into secretry vesicles by VMAT.

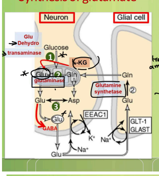
→ *No recycling*



Glutamate and aspartate

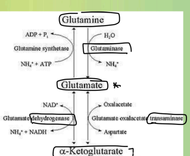
- Nonessential amino acids
- Do not cross BBB
  - must be synthesized in neurons
- Main synthetic compartments
  - neurons
  - glial cells
- Both are excitatory neurotransmitters.

Synthesis of glutamate



- Sources:
  1. Glycolysis → Krebs cycle → dehydrogenation of α-ketoglutarate (transamination)
  2. Glutamine (deamination)
  3. Aspartate (transamination)
- Removal
  - Uptake and re-uptake by high affinity transport systems in the nerve
  - terminal and glial cells.

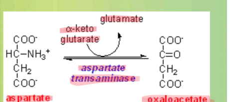
Sources of glutamate *(supplementary)*



Aspartate

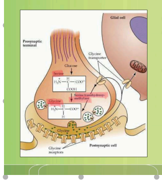
Note: Similar to glutamate

Precursor: oxaloacetate (transamination)

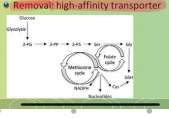


Glu..inhibit

Glycine



- A major inhibitory neurotransmitter
- It is synthesized from serine by serine hydroxymethyltransferase through 3-phosphoglycerate.
- Removal: high-affinity transporter



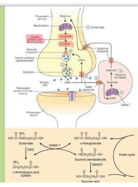
Gamma-aminobutyric acid (GABA)

- GABA is present in high concentrations (millimolar) in many brain regions.
  - These concentrations are about 1,000 times higher than concentrations of the classical monoamine neurotransmitters in the same regions.
- The GABA shunt is a closed-loop process with the dual purpose of producing and conserving the supply of GABA. synthesized from glutamate and degradation by

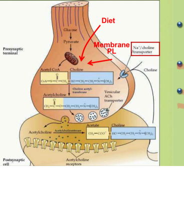
GABA shunt

A conservation mechanisms of glutamate and GABA

- Gln → Glu by glutaminase.
- Glu → GABA by glutamate decarboxylase (GAD), which requires pyridoxal phosphate (vitamin B6).
- GABA is stored in vesicles until released.
- GABA is either
  - taken up into the presynaptic terminal and repackaged
  - goes into the GABA Shunt where it is taken up into the glia and converted to Glu.
    - Glu is converted into Gln, which is transported into the neighboring nerve terminals to synthesize Glu.



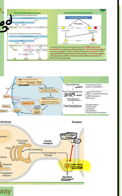
Synthesis of acetylcholine



- Choline + acetyl coenzyme-A by choline acetyltransferase in the cytoplasm.
- Transported into and stored in vesicles.
- Removal: hydrolysis by acetylcholinesterase

* Neuropeptides.

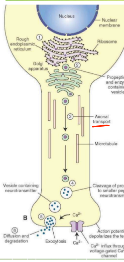
- More than 50 neuropeptides have been described affecting:
  - Behavior, pain perception, memory, appetite, thirst, temperature, homeostasis, and sleep
- They can be considered neurotransmitters (release in cell) or neurohormones (releas in Blood).
- They are synthesized just like proteins are.
  - They are subject to alternative splicing and protein processing.
  - They can be tissue-specific.
  - Examples: substance P, neurokinin A and proopiomelanocortin



→ Roles of ca++

- Vesicles are located further away from the presynaptic membrane and away from the area of Ca^{2+} ions influx
- Ca^{2+} ion influx can be from external of internal sources and at lower concentrations than required for small-molecule neurotransmitters.

Stages of action

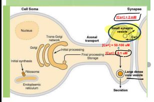


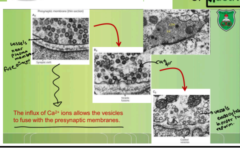
1. Synthesize in surface ER as pre-pro petides then propeptides
2. Golgi apparatus: packaged into large dense core vesicles with modifying enzymes.
3. Fast axonal transport into nerve terminal.
4. (during transport protease cleave precursor neuropeptide into final mature form)
5. released. + Prolonged action [survive long time] GPCR
   - gradual over time in response to general ↑ of IC-ca++
6. Termination by
   - → diffusion (small amount)
   - → degradation.

*small molecule neurotransmitters.

Role ca++ ions

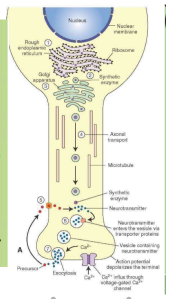
- Vesicles are located near the presynaptic membrane and the area of Ca^{2+} ions influx.





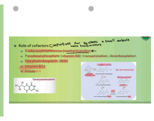
The influx of Ca^{2+} ions allows the vesicles to fuse with the presynaptic membranes.

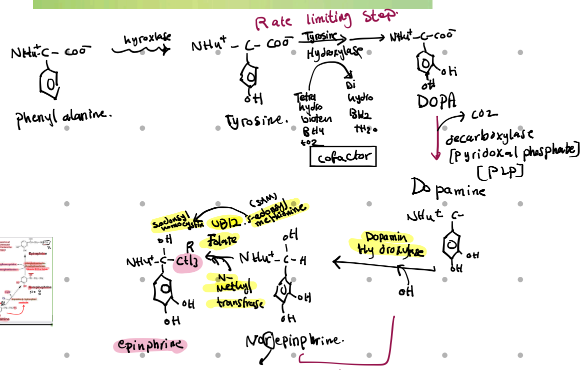
- Synthesis of the enzymes in ER (1) and Golgi apparatus (2) where they are modified (3).
- Transport of soluble enzymes via slow axonal transport (4)
- Neurotransmitter precursors are taken up into the cells via transporter proteins located in the plasma membrane of the nerve terminal (5), and the neurotransmitter is synthesized in the presynaptic nerve terminal and then packaged in small synaptic vesicles (6).
- Release is stimulated by brief pulses each time an action potential triggers the influx of calcium (7).
- Action (short)
- Termination by diffusion, re-uptake, glial cell uptake, or inactivation

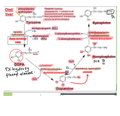


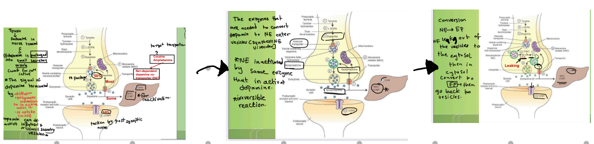
TYROSINE-DERIVED NEUROTRANSMITTERS

Dopamine, norepinephrine and epinephrine



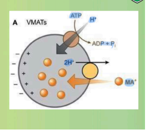




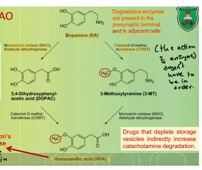


Packaging into vesicles

- The catecholamines (dopamine and epinephrine) are transported into vesicles by an ATP-dependent process linked to a proton pump.
  - Protons are pumped into the vesicles by a vesicular ATPase (V-ATPase).
  - The protons then exchange for the positively-charged catecholamine via the transporter VMAT (vesicular monoamine transporter).
  - Targeting VMATs causes depletion of the neurotransmitters.



COMT and MAO

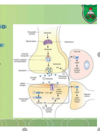


Regulation

- Tyrosine hydroxylase: rate limiting step → highly regulated
  - Short-term:
    - Inhibition by free cytosolic catecholamines, which compete with BH_4 binding to the enzyme.
    - Activation by depolarization, which activates several protein kinases including PKC, PKA, Ca^{2+}-calmodulin–dependent kinases that phosphorylate tyrosine hydroxylase. This makes the enzyme bind more tightly to BH4 and, consequently, less sensitive to end-product inhibition.
  - Long-term (plus dopamine β-hydroxylase) gene expression.
    - Prolonged sympathetic neuronal activity increases the transcription of tyrosine hydroxylase and dopamine β–hydroxylase.

Nitric oxide (NO)

- Glutamate is released (1) and acts on the N-methyl-D-aspartate (NMDA) receptors located on the post-synaptic neuron (2)
- Ca^{2+} enters the postsynaptic neuron activating nitric oxide synthase (NOS) (3), which forms NO from arginine (4).
- NO stimulates guanylate cyclase forming cGMP (5), which results in a physiological response (6)
- NO can diffuse out:
  - a) to the presynaptic terminal (retrograde messenger) (7) and
  - b) into adjacent neurons (8) and glial cells (9) stimulating guanylate cyclase.
- It has a half-life of 2-4 seconds.
- NO is inhibited by hemoglobin and other heme proteins which bind to it tightly.



Is NO a neurotransmitter?

- Yes, but:
  - It is not stored in vesicles
  - It is not released by calcium-dependent exocytosis (it diffuses)
  - Its inactivation is passive (there is no active process that terminates its action)
    - It decays spontaneously
  - It does not interact with receptors on target cells
    - Its sphere of action depends on the extent to which it diffuses, and its action is not confined to the conventional presynaptic-postsynaptic direction.
  - NO acts as a retrograde messenger and regulates the function of axon terminals presynaptic to the neuron in which it is synthesized.

NO synthase

- Isoform I (nNOS or cNOS)
  - Neurons and epithelial cells
  - activated by the influx of extracellular calcium
- isoform II (iNOS)
  - Macrophages and smooth muscle cells
  - induced by cytokines
- and isoform III (eNOS)
  - Endothelial cells lining blood vessels
  - activated by the influx of extracellular calcium
- All three isoforms require BH2 as a cofactor and nicotinamide adenine dinucleotide phosphate (NADPH) as a coenzyme.