511-2018-09-26-neurochemistry-II

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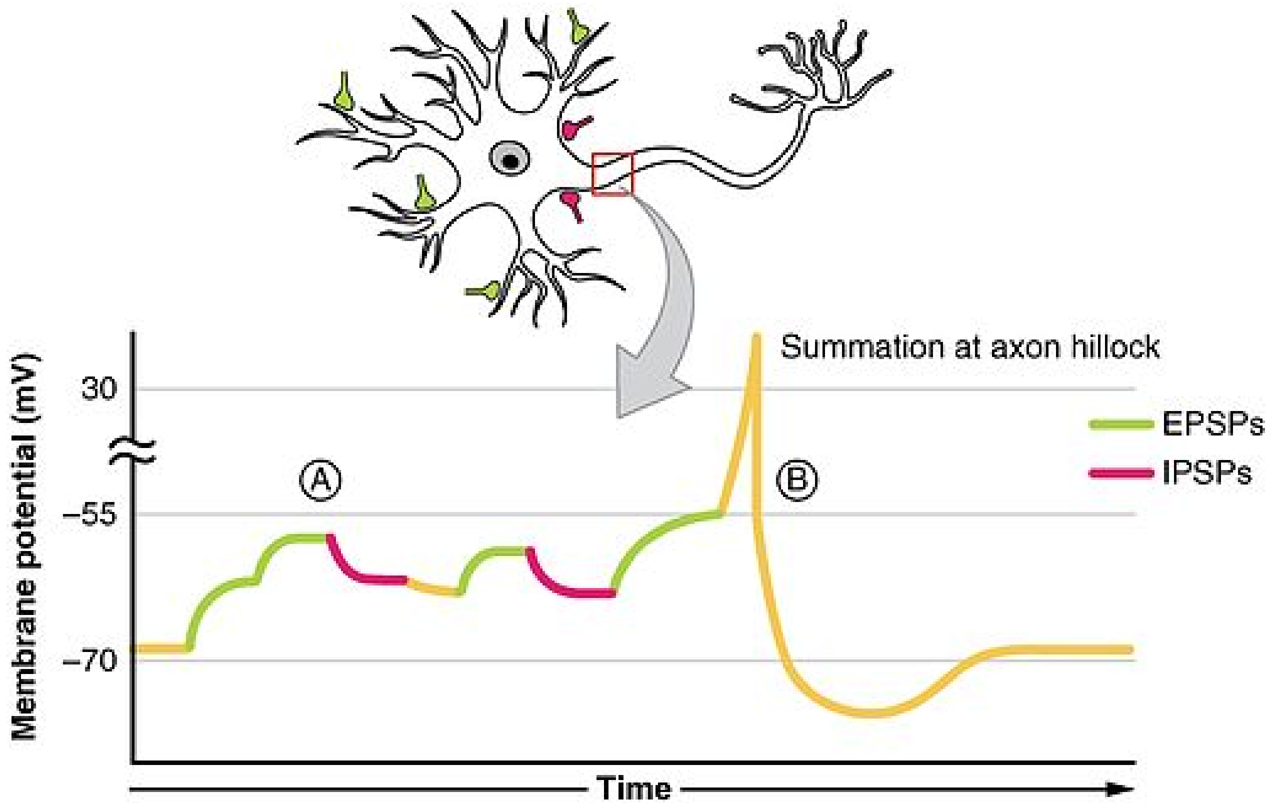
Today's Topics

- Neurochemistry
  - How neurons talk to one another
- Synaptic communication
- Neurotransmitters

In the beginning

- Soma receives input from dendrites
- Axon hillock sums/integrates
- If sum > threshold, AP "fires"

Illustration of summation



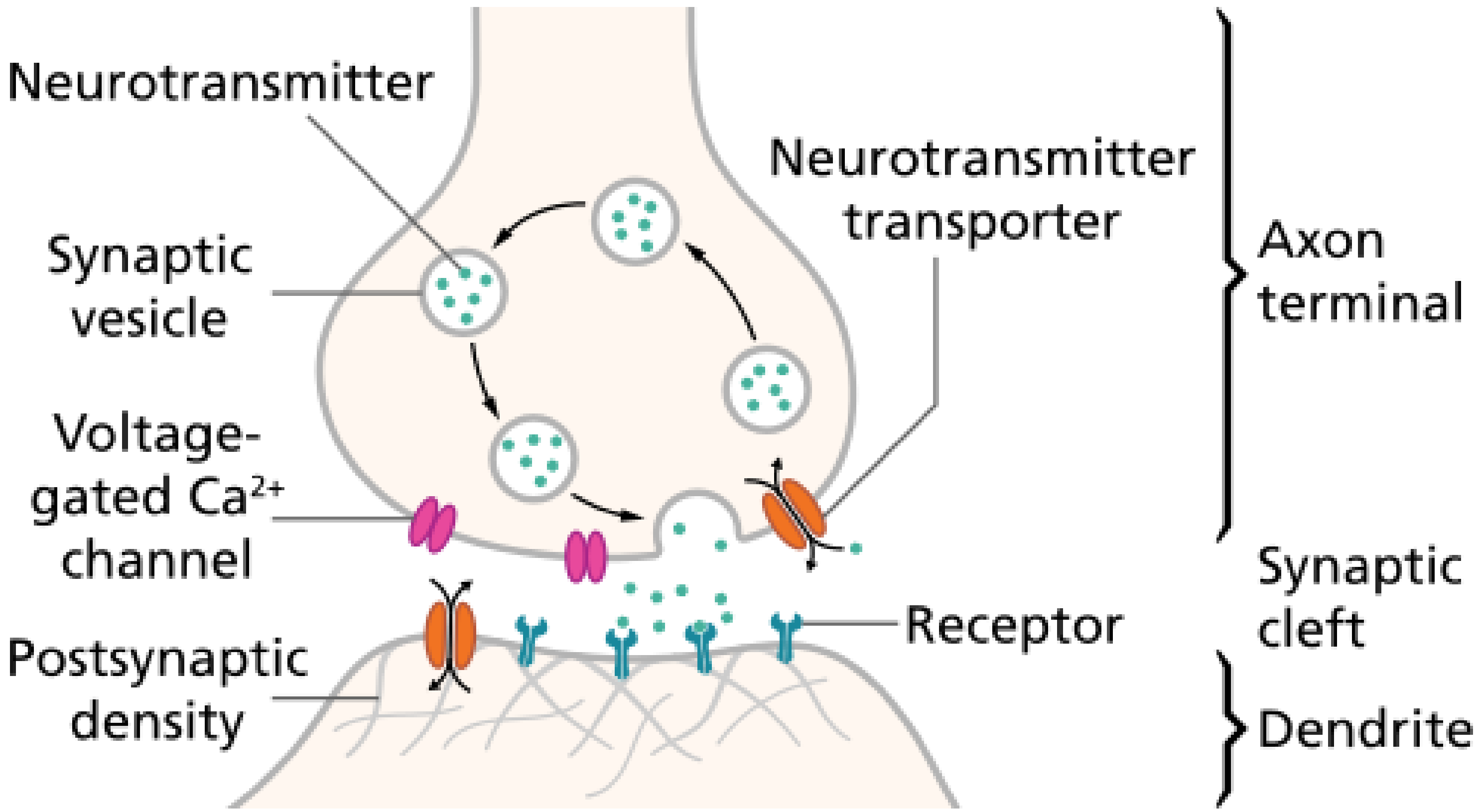
Steps in synaptic transmission

- Rapid change in voltage triggers neurotransmitter (NT) release
- *Voltage-gated calcium Ca++ channels* open
- Ca++ causes *synaptic vesicles* to bind with presynaptic membrane, merge, *exocytosis*

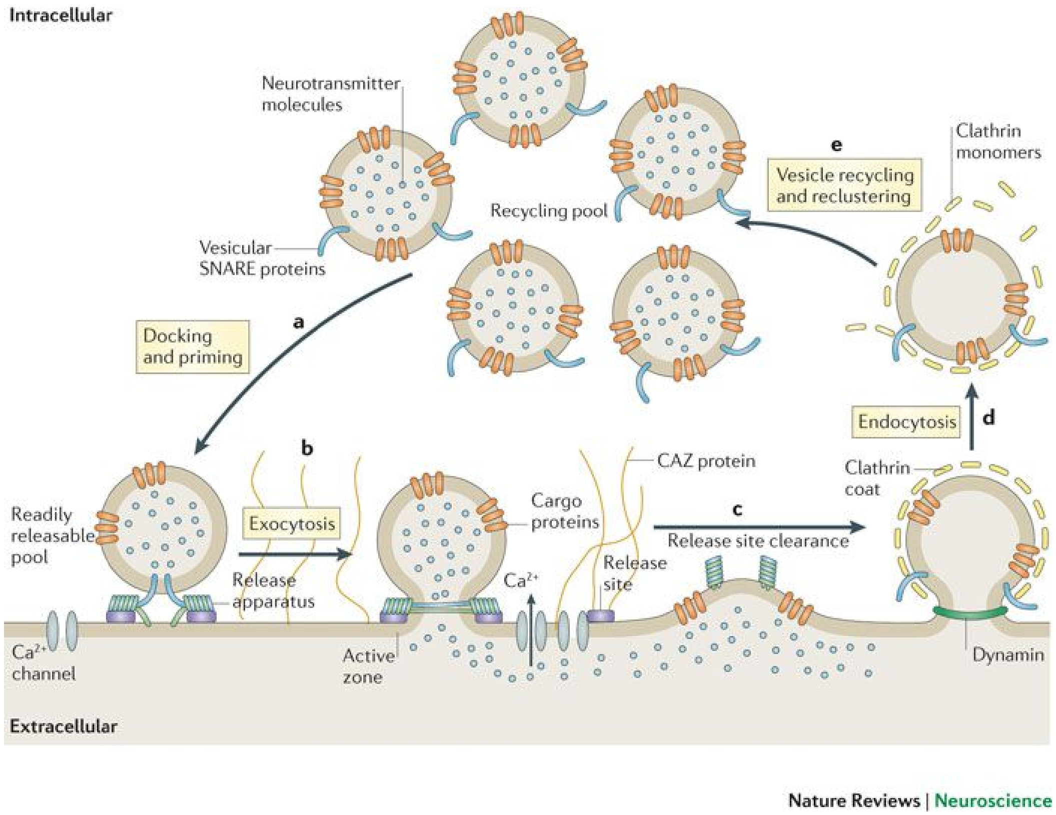
Steps in synaptic transmission

- NTs diffuse across *synaptic cleft*
- NTs bind with *receptors* on *postsynaptic membrane*
- Receptors respond
- NTs unbind, are inactivated

Synaptic transmission



Excocytosis



http://dx.doi.org/doi:10.1038/nrn2948

Why do NTs move from presynaptic terminal toward postsynaptic cell?

- Electrostatic force pulls them
- Force of diffusion

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- Electrostatic force pulls them
- **Force of diffusion**

Postsynaptic receptor types

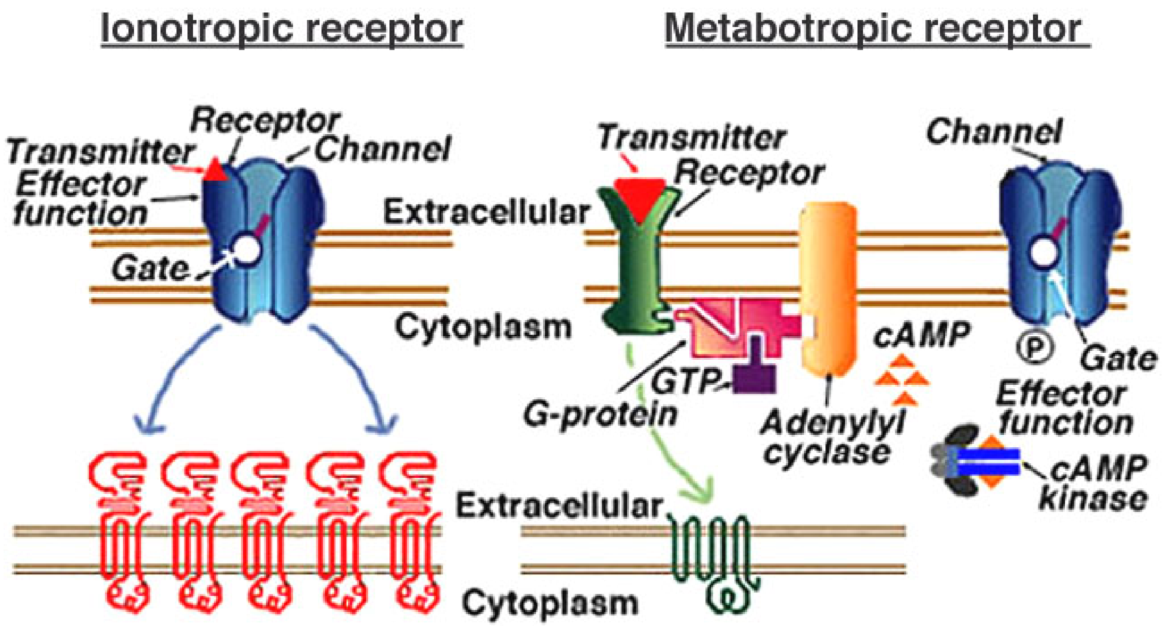


Fig. 5a. Ionotropic receptors and their associated ion channels form one complex (top). Each iGluR is formed from the co-assembly of multiple (4-5) subunits (From Kandel et al., 1991).

Fig. 5b. Metabotropic receptors are coupled to their associated ion channels by a second messenger cascade (top). Each mGluR is composed of one polypeptide, which is coupled to a G-protein (from Kandel et al., 1991).

Postsynaptic receptor types

- Ligand-gated ion channels
- *Ionotropic* (receptor + ion channel)
    - Ligand-gated
    - Open/close channel
    - Faster, but short-acting effects

Postsynaptic receptor types

- *Metabotropic* (receptor only)
    - Trigger 2nd messengers
    - G-proteins
    - Open/close adjacent channels, change metabolism
    - Slower, but longer lasting effects

Receptor types

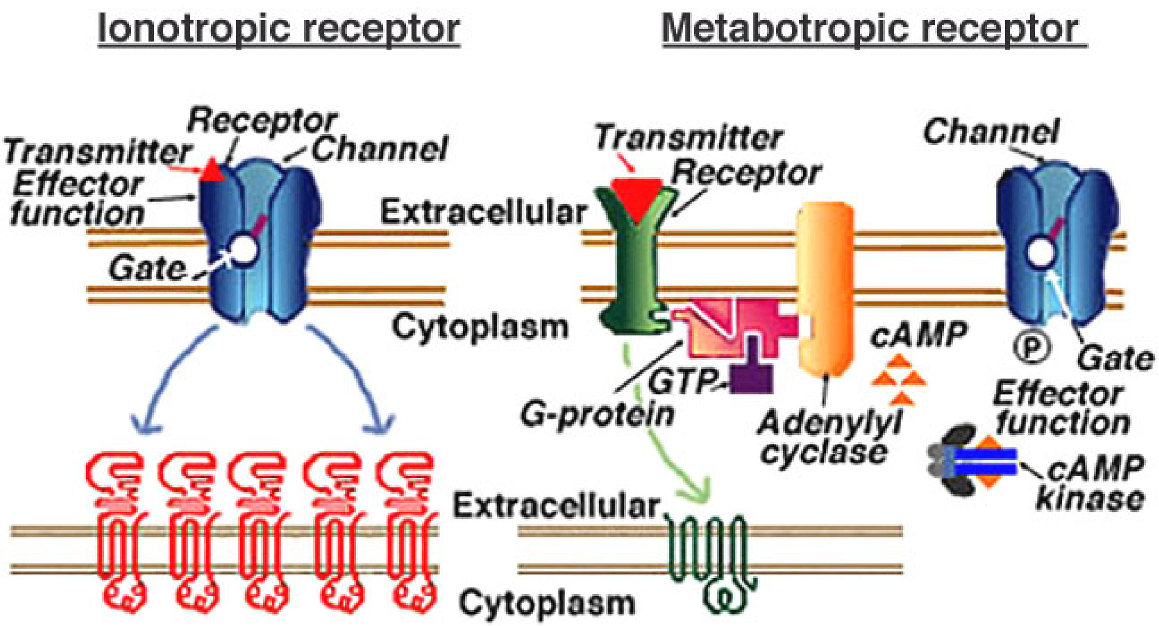


Fig. 5a. Ionotropic receptors and their associated ion channels form one complex (top). Each iGluR is formed from the co-assembly of multiple (4-5) subunits (From Kandel et al., 1991).

Fig. 5b. Metabotropic receptors are coupled to their associated ion channels by a second messenger cascade (top). Each mGluR is composed of one polypeptide, which is coupled to a G-protein (from Kandel et al., 1991).

Receptors generate postsynaptic potentials (PSPs)

- Small voltage changes
- Amplitude scales with # of receptors activated
  - Dendrites usually lack voltage gated Na+ channels
- Excitatory PSPs (EPSPs)
  - Depolarize neuron (make more +)
- Inhibitory (IPSPs)
  - Hyperpolarize neuron (make more -)

NTs inactivated

- Buffering
  - e.g., glutamate into astrocytes (Anderson & Swanson, 2000)
- Reuptake via *transporters*
  - molecules in membrane that move NTs inside
  - e.g., serotonin via serotonin transporter (SERT)
- Enzymatic degradation
  - e.g., acetylcholinesterase (AChE) degrades acetylcholine (ACh)

Questions to ponder

- Why must NTs be inactivated?

Questions to ponder

- Why must NTs be inactivated?
  - Keeps messages discrete, localized in time and space
  - Maximizes concentration gradient

What sort of PSP would opening a Na+ channel produce?

- Excitatory PSP, Na+ flows in
- Excitatory PSP, Na+ flows out
- Inhibitory PSP, Na+ flows in
- Inhibitory PSP, Na+ flows out

What sort of PSP would opening a Na+ channel produce?

- **Excitatory PSP, Na+ flows in**
- Excitatory PSP, Na+ flows out
- Inhibitory PSP, Na+ flows in
- Inhibitory PSP, Na+ flows out

What sort of PSP would opening a Cl- channel produce?

Remember [Cl-out]>>[Cl-in]

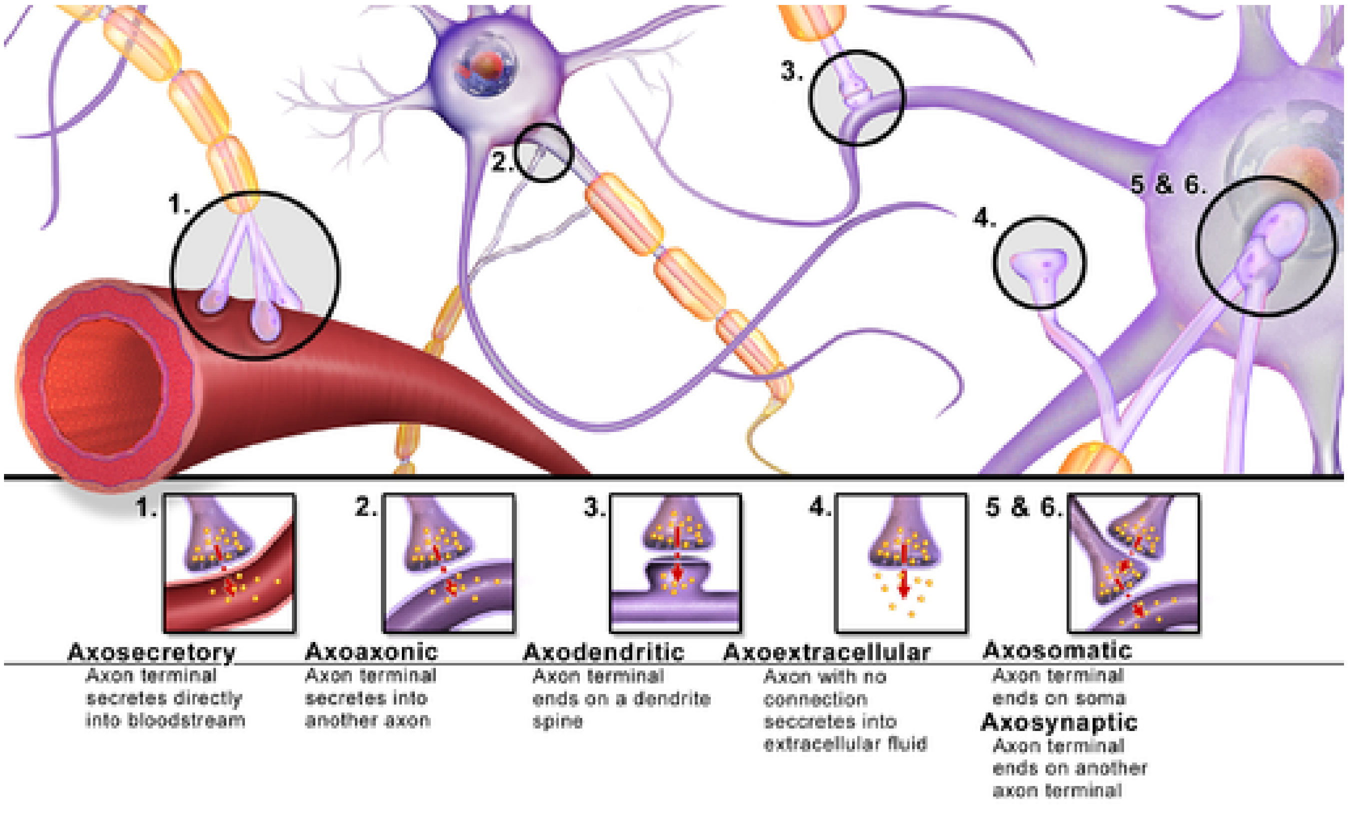
- Excitatory PSP, Cl- flows in
- Excitatory PSP, Cl- flows out
- Inhibitory PSP, Cl- flows in
- Inhibitory PSP, Cl- flows out

What sort of PSP would opening a Cl- channel produce?

Remember [Cl-out]>>[Cl-in]

- Excitatory PSP, Cl- flows in
- Excitatory PSP, Cl- flows out
- **Inhibitory PSP, Cl- flows in**
- Inhibitory PSP, Cl- flows out

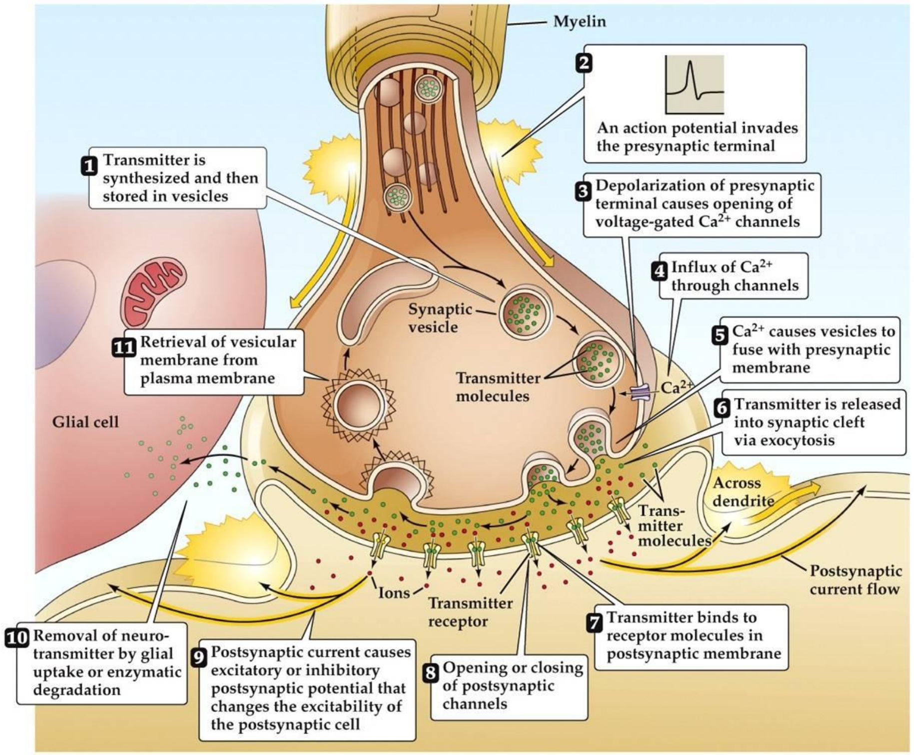
Types of synapses



Synapses on

- dendrites
  - usually excitatory
- cell bodies
  - usually inhibitory
- axons
  - usually modulatory (change p(fire))

Summary of chemical transmission



***NEUROSCIENCE 5e*, Figure 5.3**

Neurotransmiters

Family	Neurotansmitter
Amino acids	Glutamate
	γ aminobutyric acid (GABA)
	Glycine
	Aspartate

Glutamate

- Primary excitatory NT in CNS
- Role in learning (via NMDA)
- Receptors on neurons and glia (astrocytes and oligodendrocytes)
- Linked to umami (savory) taste sensation (think monosodium glutamate or MSG)
- Dysregulation in schizophrenia? (Javitt, 2010)

Glutamate

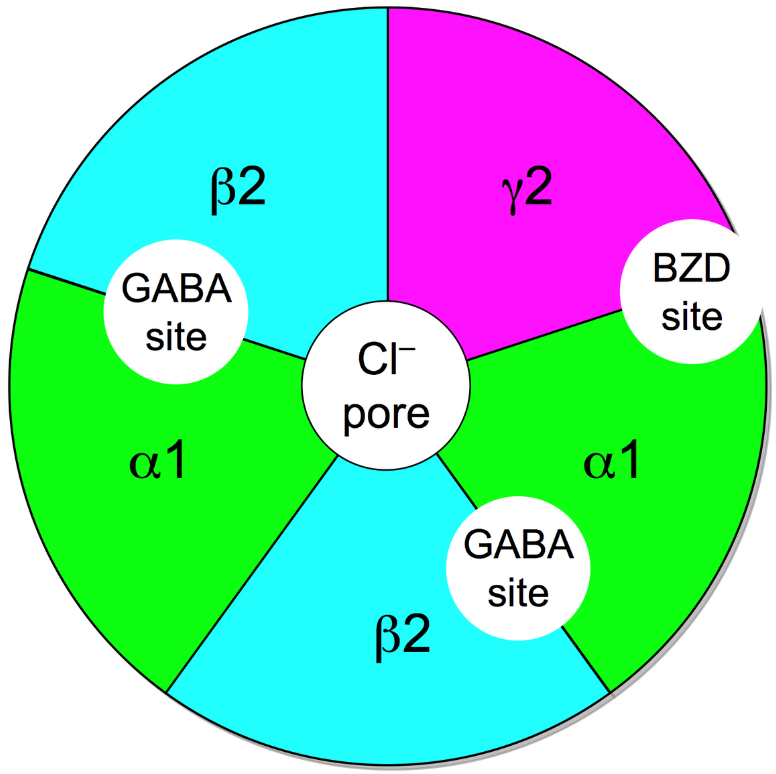
Type	Receptor	Esp Permeable to
Ionotropic	AMPA	Na+, K+
	Kainate	
	NMDA	Ca+
Metabotropic	mGlu	

γ aminobutyric acid (GABA)

- Primary inhibitory NT in CNS
- Excitatory in developing CNS, [Cl-] in >> [Cl-] out
- Binding sites for benzodiazepines (e.g., Valium), barbiturates, ethanol, etc.

Type	Receptor	Esp Permeable to
Ionotropic	GABA-A	Cl^-
Metabotropic	GABA-B	K^+

GABA



"GABAA-receptor-protein-example" by Chemgirl131 at English Wikipedia - Transferred from en.wikipedia to Commons by Sreejithk2000 using CommonsHelper.. Licensed under Public Domain via Commons.

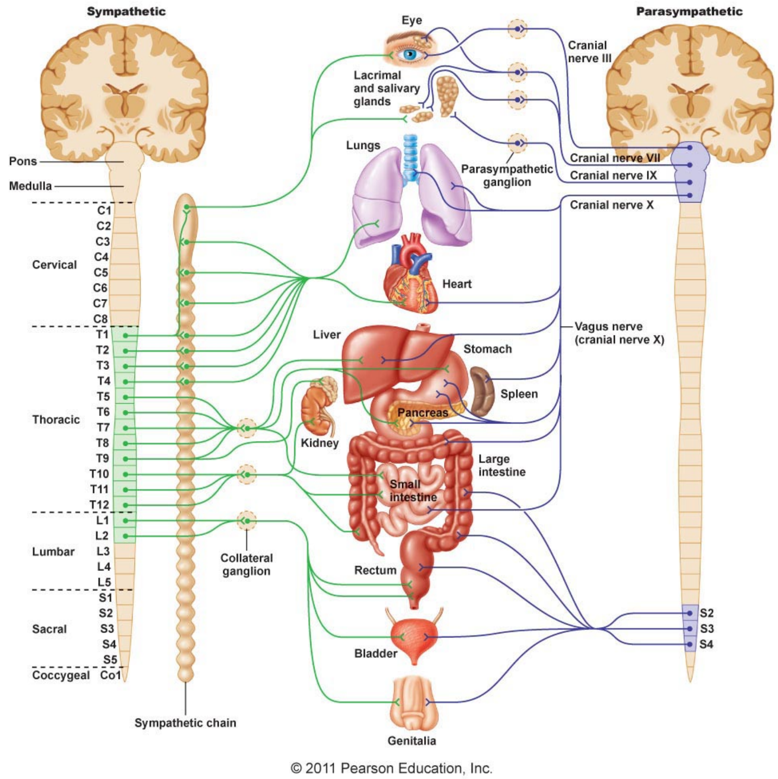
Other amino acid NTs

- *Aspartate*
    - Like Glu, stimulates NMDA receptor
- *Glycine*
    - Spinal cord interneurons

Acetylcholine (ACh)

- Primary excitatory NT of CNS output
- Somatic nervous system (motor neuron -> neuromuscular junction)
- Autonomic nervous system
  - Sympathetic branch: preganglionic neuron
  - Parasympathetic branch: pre/postganglionic

ACh anatomy



http://myzone.hrvfitltd.netdna-cdn.com/wp-content/uploads/2014/09/Image-1.jpg

Acetylcholine

Type	Receptor	Esp Permeable to	Blocked by
Ionotropic	Nicotinic (nAChR)	Na+, K+	e.g., Curare
Metabotropic	Muscarinic (mAChR)	K+	e.g., Atropine

Curare

http://www.general-anaesthesia.com/images/indian-curare.jpg

Atropine

- aka, nightshade or belladonna

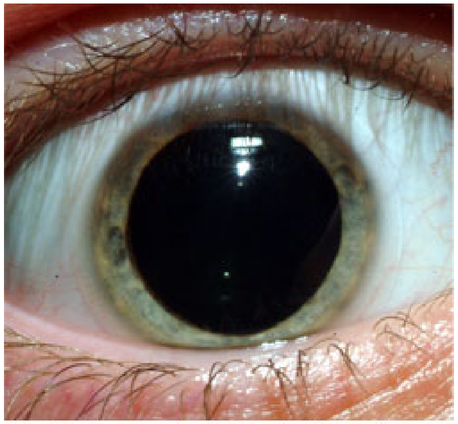


Fig. 2 Pharmacologically dilated pupil.

http://www.aapos.org/client_data/files/2011/_138_dilatingeyedrops2.jpg

Monoamine NTs

Family	Neurotansmitter
Monoamines	Dopamine (DA)
	Norepinephrine (NE)/Noradrenaline (NAd)
	Epinephrine (Epi)/Adrenaline (Ad)
	Serotonin (5-HT)
	Melatonin
	Histamine

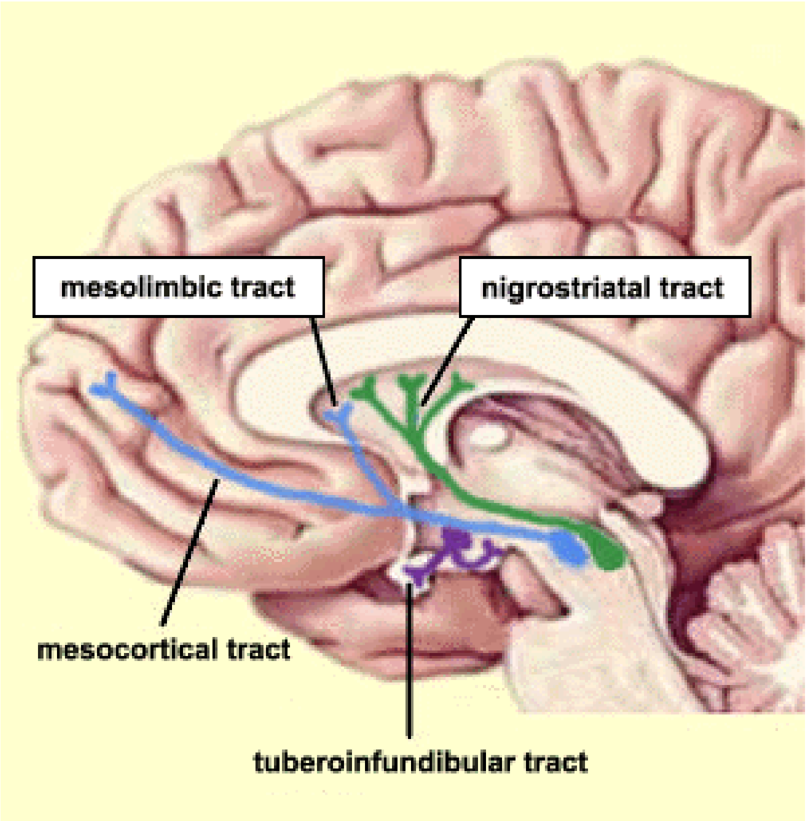
Information processing

- Point-to-point
  - One sender, small number of recipients
  - Glu, GABA
- Broadcast
  - One sender, widespread recipients
  - DA, NE, 5-HT, melatonin, histamine
- Need to know
  - NT, where projecting, type of receptor to predict function

Dopamine

- Released by
  - Substantia nigra -> striatum, *meso-striatal projection*
  - Ventral tegmental area (VTA) -> nucleus accumbens, ventral striatum, hippocampus, amygdala, cortex; *meso-limbo-cortical projection*

Dopamine Anatomy



http://thebrain.mcgill.ca/flash/a/a_03/a_03_cl/a_03_cl_que/a_03_cl_que_1a.

DA Disruption linked to

- Parkinson's Disease (mesostriatal)
    - DA agonists treat (agonists facilitate/increase transmission)
- ADHD (mesolimbocortical)
- Schizophrenia (mesolimbocortical)
    - DA antagonists treat
- Addiction (mesolimbocortical)

DA Inactivated by

- Dopamine transporter (DAT) and chemical breakdown

http://www.scholarpedia.org/article/Dopamine_anatomy#Dopamine_recep

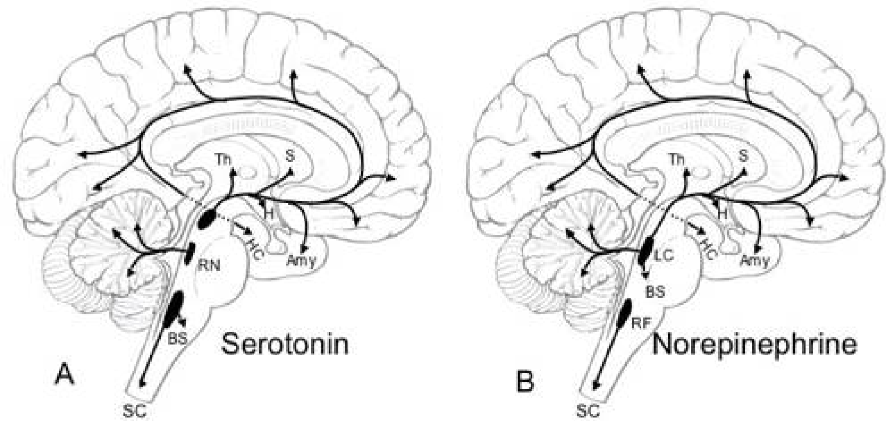
Dopamine receptors

Type	Receptor	Comments
Metabotropic	D1-like (D1 and D5)	more prevalent
	D2-like (D2, D3, D4)	target of many antipsychotics

Norepinephrine

- Released by
  - *locus coeruleus* in pons
  - postganglionic sympathetic neurons onto target tissues
- Role in arousal, mood, eating, sexual behavior
- Monoamine oxidase inhibitors (MAOIs)
  - inactivate monoamines in neurons, astrocytes
  - MAOIs increase NE, DA
  - Treatment for depression

NE Anatomy



https://www.dartmouth.edu/~rswenson/NeuroSci/figures/Figure_9_files/im

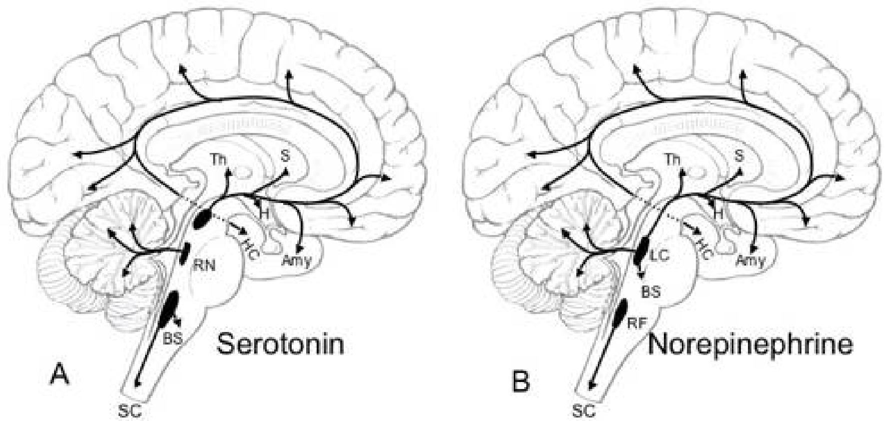
NE receptors

Type	Receptor	Comments
Metabotropic	α (1,2)	antagonists treat anxiety, panic
	β (1,2,3)	'beta blockers' in cardiac disease

Serotonin (5-HT)

- Released by *raphe nuclei* in brainstem
- Role in mood, sleep, eating, pain, nausea, cognition, memory
- Modulates release of other NTs
- Most of body's 5-HT regulates digestion

5-HT anatomy



https://www.dartmouth.edu/~rswenson/NeuroSci/figures/Figure_9_files/im

5-HT receptors

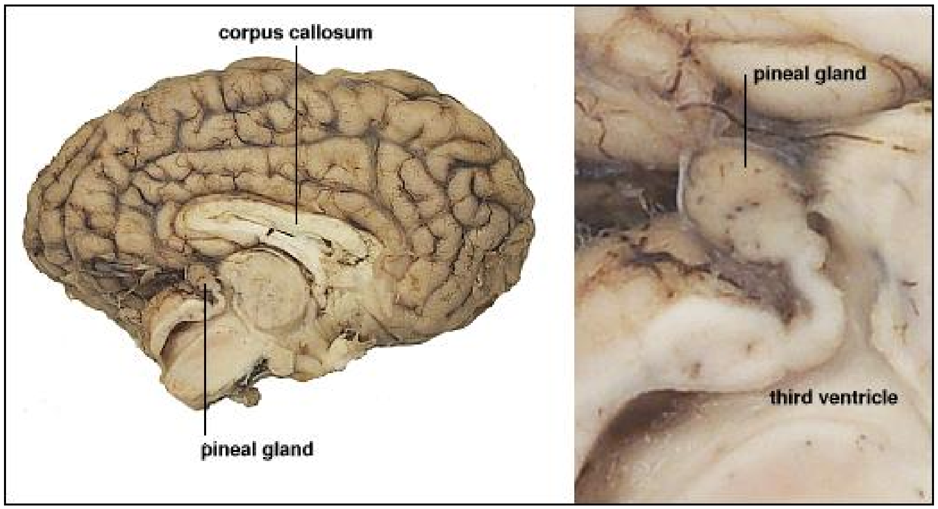
- Seven families (5-HT 1-7) with 14 types
- All but one metabotropic

5-HT clinical significance

- Ecstasy (MDMA) disturbs serotonin
- So does LSD
- Fluoxetine (Prozac)
  - *Selective Serotonin Reuptake Inhibitor (SSRI)*
  - Treats depression, panic, eating disorders, others
- 5-HT3 receptor antagonists are anti-mimetics used in treating nausea

Melatonin

- Released by pineal gland

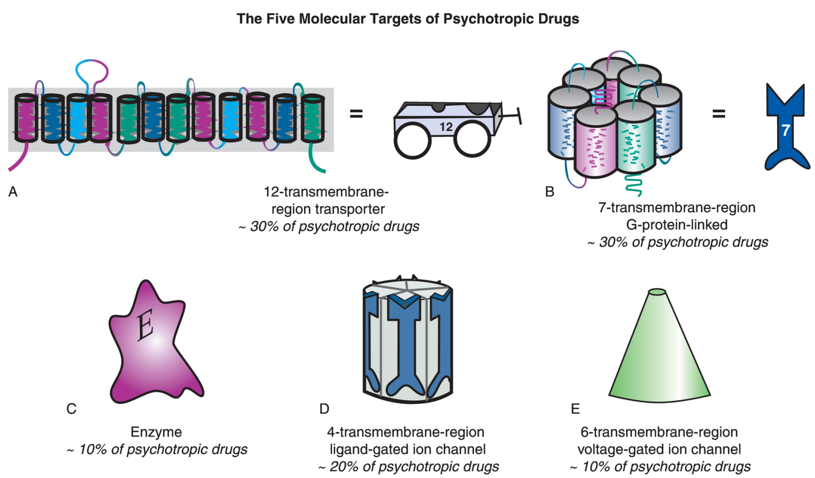


http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/otherendo/pin

Histamine

- Released by hypothalamus, project to whole brain
- Metabotropic receptors
- Role in arousal/sleep regulation
- In body, part of immune response

Targets of psychotropic drugs



https://stahlonline.cambridge.org/essential_4th_chapter.jsf?page=chapter2_summary.htm&name=Chapter%202&title=Summary

Monoamine Song

https://en.wikipedia.org/wiki/Mah_Nà_Mah_Nà

Monoamine Song

Monoamines, do-do do do-do
Monoamines, do do do-do
Monoamines, do do do do-do do do-do do do-do do do do do-do do

Monoamine Song

Monoamines, do-pa-mine is one
Monoamines, norepi, too
Monoamines, sero-tonin e-pinephrine, dop-a- mine, nor-epinephrine, melatonin, whoo!

Monoamine Song

Monoamines, mod-u-late neurons
Monoamines, throughout the brain
Monoamines, keep people happy, brains snappy, not sleepy, not sappy, do-do do-do do-do do

Others

- Gases
  - *Nitric Oxide (NO)*, *carbon monoxide (CO)*
- Neuropeptides
  - *Substance P* and *endorphins* (endogenous morphine-like compounds) have role in pain
  - *Orexin/hypocretin*, project from lateral hypothalamus across brain, regulates appetite, arousal
  - *Cholecystokinin (CCK)* stimulates digestion
- Purines
  - *Adenosine* (inhibited by caffeine)
- Others
  - *Anandamide* (activates endogenous cannabinoid receptors)

References

Anderson, C. M., & Swanson, R. A. (2000). Astrocyte glutamate transport: Review of properties, regulation, and physiological functions. *Glia*, *32*(1), 1–14. https://doi.org/10.1002/1098-1136(200010)32:1<1::AID-GLIA10>3.0.CO;2-W

Javitt, D. C. (2010). Glutamatergic theories of schizophrenia. *Israel Journal of Psychiatry and Related Sciences*, *47*(1), 4.