Chemical communication

CODE

PSY 511

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- Fun
- Neural communication
  - What triggers the action potential?
  - Synaptic transmission
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    - Synapse Types & Locations
    - Steps in chemical transmission
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      - Transporters/exchangers
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      - Metabotropic receptors (receptor only)
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      - Melatonin
  - Thinking about neurochemical influences
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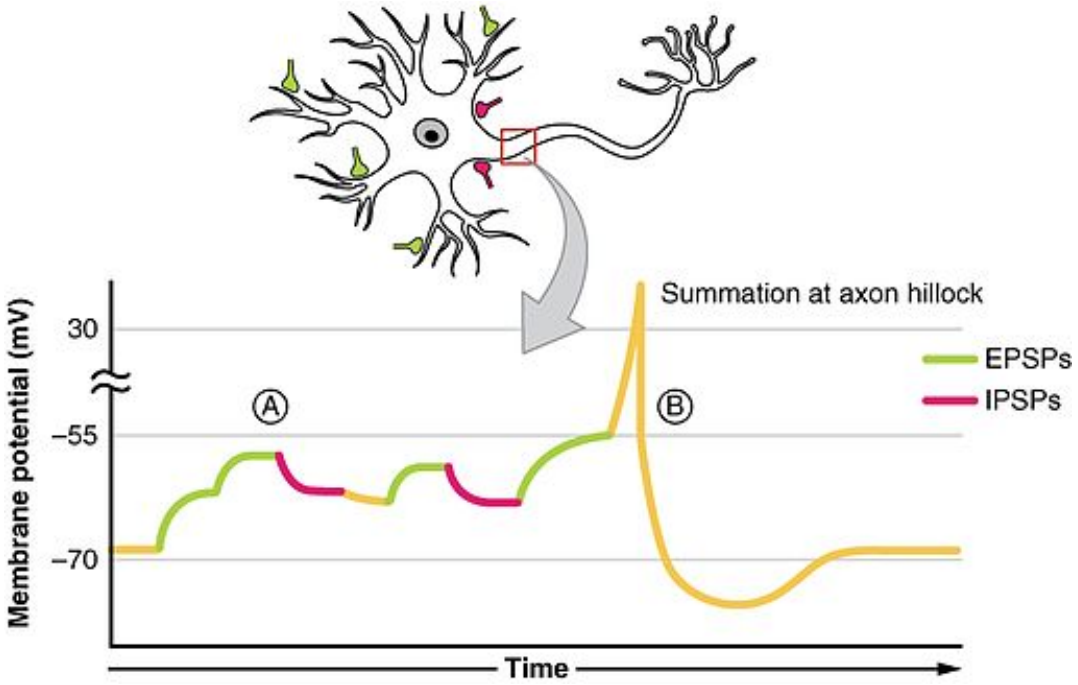
- References

Fun

Neural communication

What triggers the action potential?

- Soma receives input from dendrites (and on soma directly)
- Axon hillock sums/integrates
- If sum > threshold, action potential “fires”
- Action potential propagates along the axon



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- Action potential's rapid change in voltage triggers neurotransmitter (NT) release

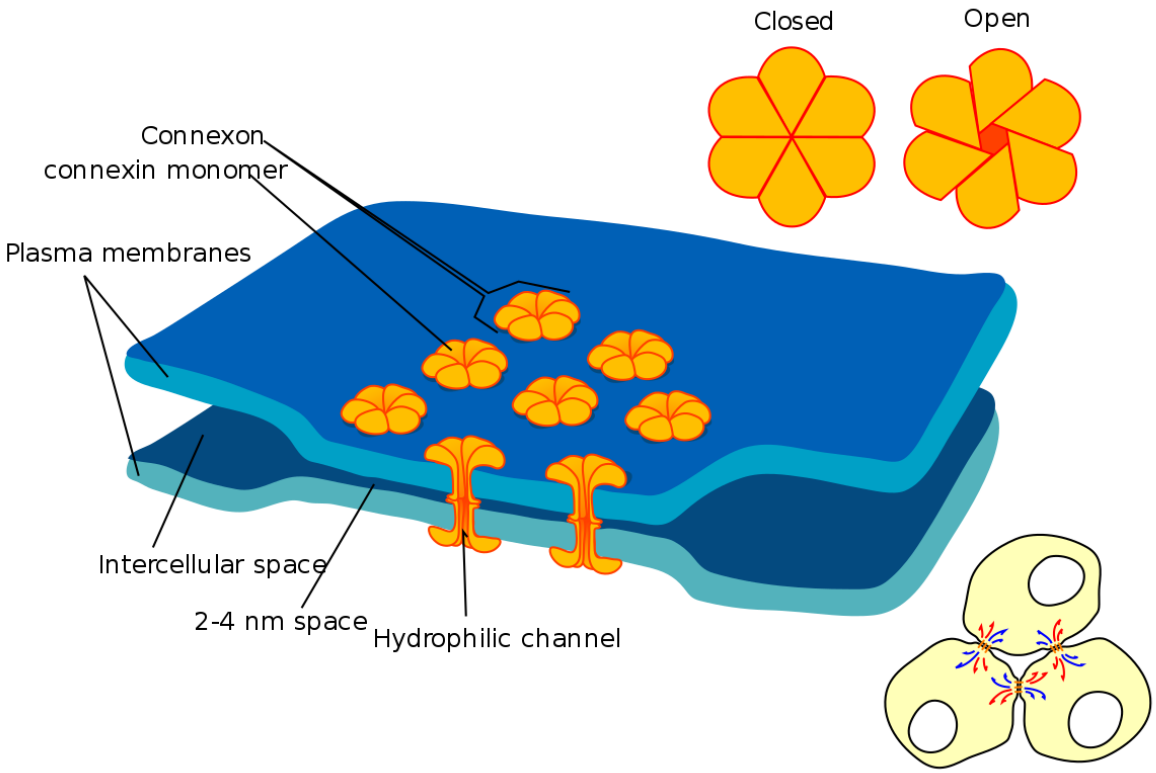
Synaptic transmission

Synapse permits neuron to pass electrical or chemical messages to another neuron or target cell (muscle, gland, etc.)

Synapse locations

Synapse Types & Locations

- Chemical
- Electrical
  - Gap junctions
  - *Cytosol* (and ionic current) flows through adjacent neurons



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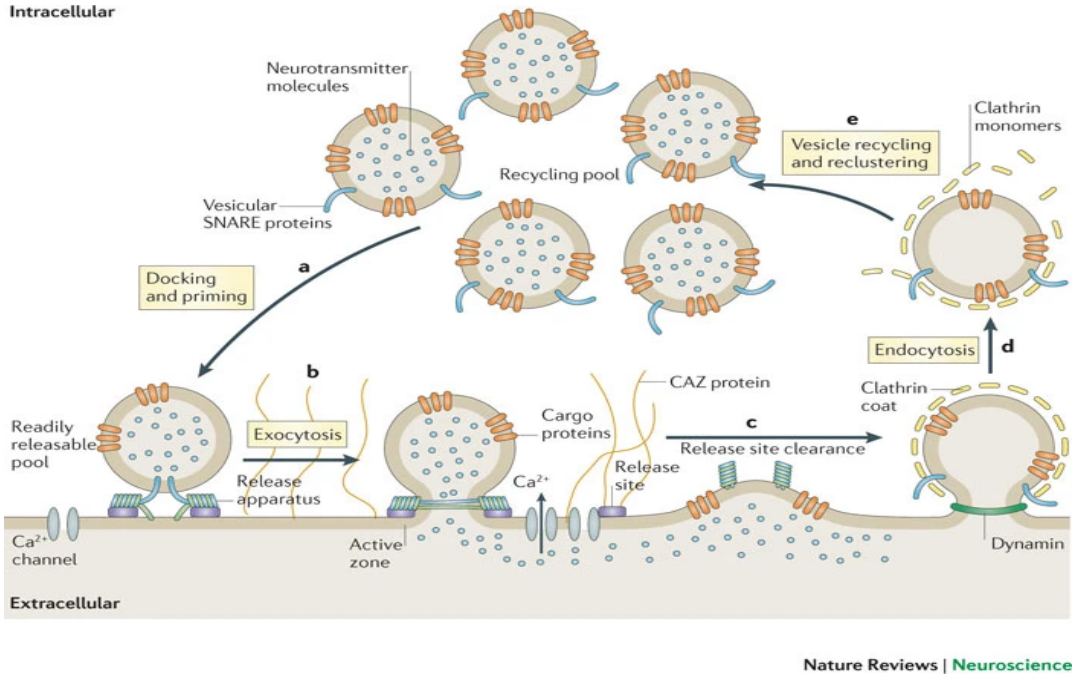
By Mariana Ruiz LadyofHats - the diagram i made myself using the information on this websites as source: (http://academic.brooklyn.cuny.edu/biology/bio4fv/page/gap-junctions.html%22%3E);[1] , (http://www-biology.ucsd.edu/classes/bipn140.FA05/10_2.jpg%22%3E);[2], (http://www.colorado.edu/MCDB/MCDB1150/ohd/gapjunctionmodel.JPG%22%3E);[3] , and (http://www.lrz-muenchen.de/~jmd/gap%20junction2.gif%22%3E);[4]. Made with Adobe Illustrator. Image renamed from File:Gap (File:Gap) cell junction.svg, Public Domain, Link (https://commons.wikimedia.org/w/index.php?curid=6027074)

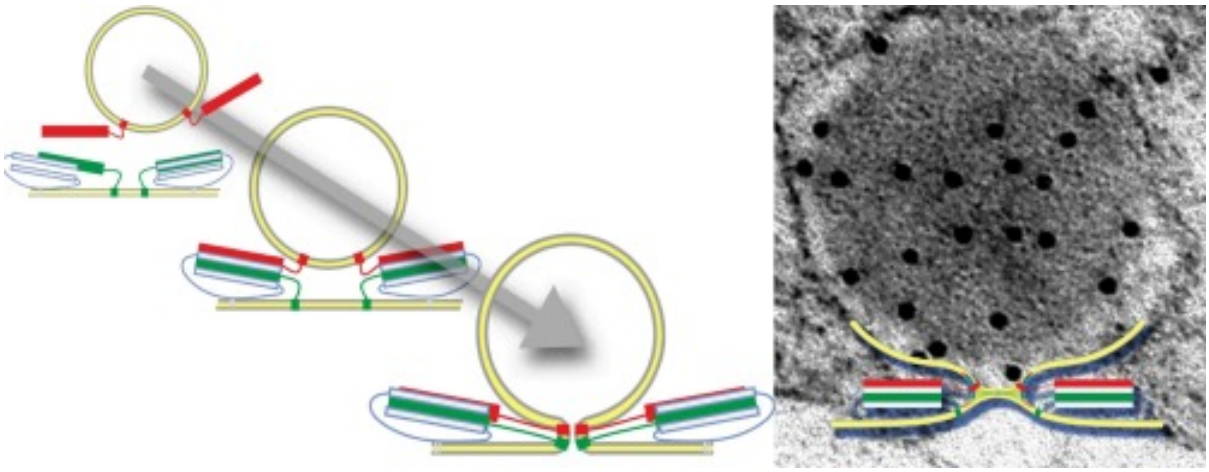
Steps in chemical transmission

- *Voltage-gated calcium Ca++ channels* open

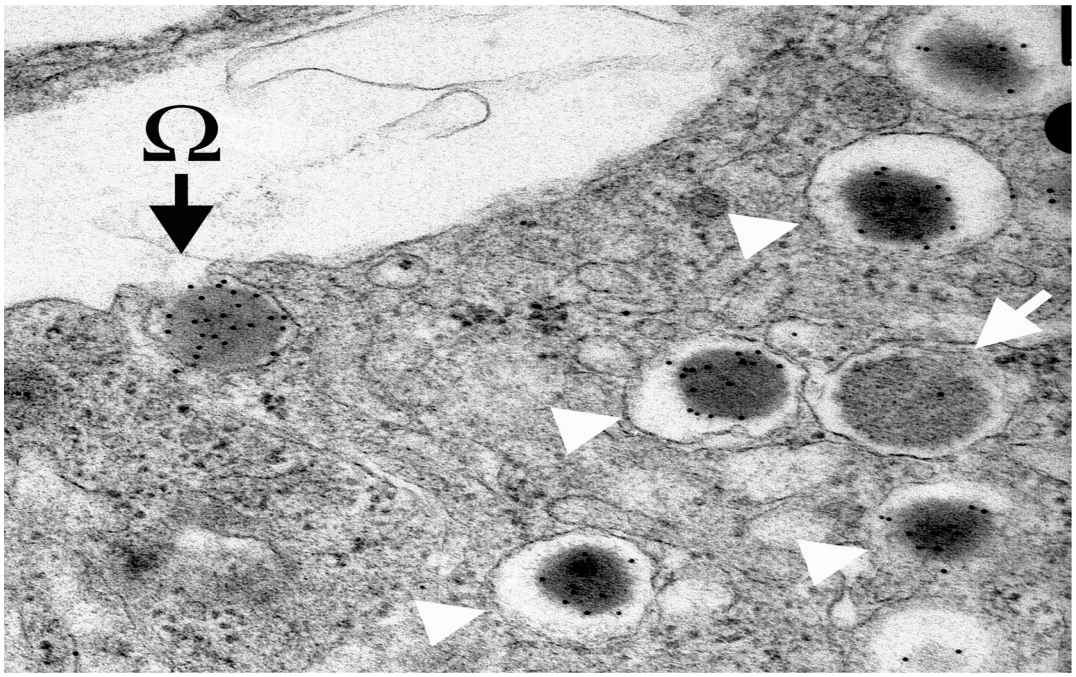
- Ca++ influx causes *synaptic vesicles* to bind with presynaptic membrane, fuse with membrane, spill contents via *exocytosis*



(Haucke, Neher, & Sigrist, 2011) (http://dx.doi.org/10.1038/nrn2948)

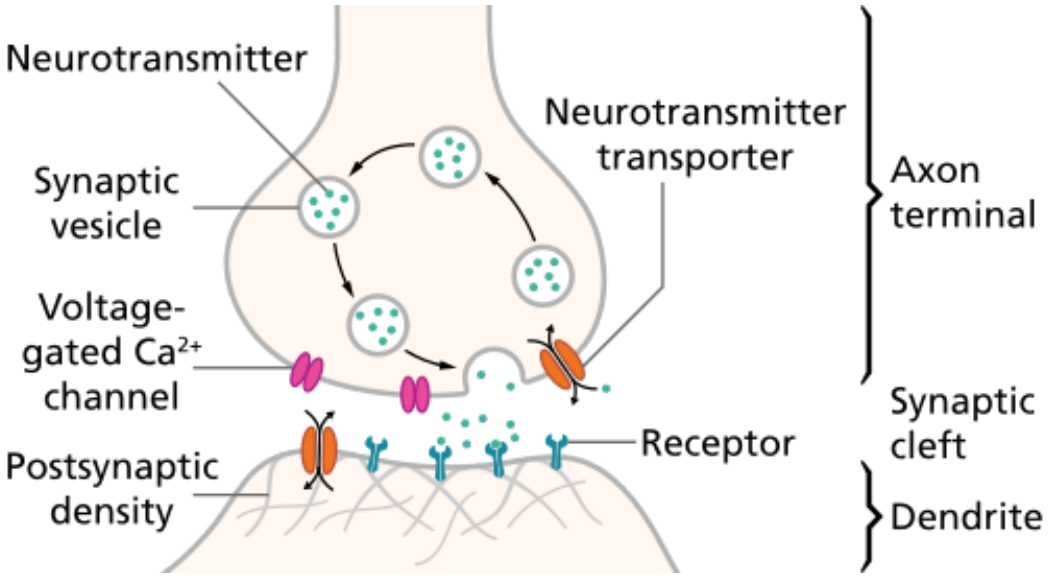


(Hastoy, Clark, Rorsman, & Lang, 2017) (https://doi.org/10.1016/j.ceca.2017.10.005)



(Hastoy, Clark, Rorsman, & Lang, 2017) (https://doi.org/10.1016/j.ceca.2017.10.005)

- NTs diffuse across *synaptic cleft*
- NTs bind with *receptors* on *postsynaptic membrane*
  - Cause some post-synaptic effect
- NTs unbind from receptor
- NTs inactivated
- NTs diffuse along concentration gradient



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Relative sizes

- Neural membrane ~8 nm
- Synaptic vesicles ~40-60 or ~90-120 nm
- Synaptic cleft ~20-50 nm
- Cleft small relative to vesicles

Receptor/channel types

Leak/passive

- Vary in selectivity, permeability

Transporters/exchangers

- Ionic
  - Na^+/K^+ ATP-ase/pump
- Chemical
  - e.g., Dopamine transporter (DAT)

Ionotropic receptors (receptor + ion channel)

- Ligand-gated
- Open/close channel
- Ions flow in/out depending on membrane voltage and ion type
- Fast-responding (< 2 ms), but short-duration effects (< 100 ms)

Metabotropic receptors (receptor only)

- G-proteins ->
- Trigger 2nd messengers
- Open/close adjacent channels, change metabolism

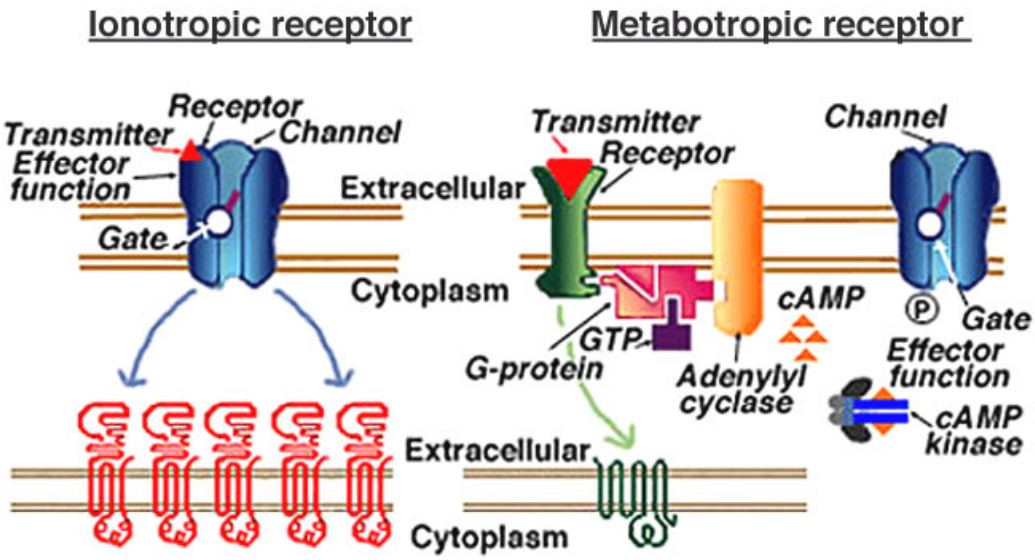


Fig. 5a. Ionotropic receptors and their associated ion channels form one complex (top). Each iGluR is formed from the co-assembly of multiple (4-5) subunits (From Kandel et al., 1991).

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
- *Excitatory PSPs (EPSPs)*
  - Depolarize neuron (make more +)
- *Inhibitory (IPSPs)*
  - Hyperpolarize neuron (make more -)

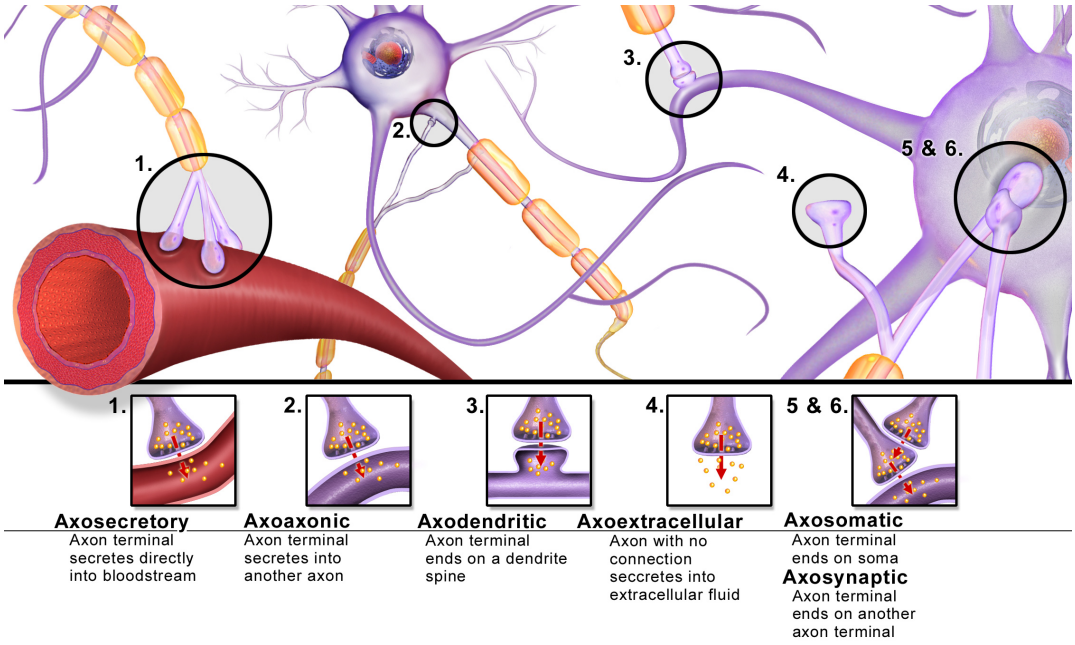
NTs inactivated

- Buffering
  - e.g., glutamate into astrocytes (Anderson & Swanson, 2000)
- *Reuptake* via *transporters (https://en.wikipedia.org/wiki/Neurotransmitter_transporter)*
  - e.g., serotonin via serotonin transporter (SERT)
- Enzymatic degradation
  - e.g., acetylcholine esterase (AChE) degrades acetylcholine (ACh)

Questions to ponder

- Why do NTs diffuse from pre- to post-synaptic membrane?
- Why must NTs be inactivated?
- What sort of PSP would *opening* a Na+ channel produce?
- What sort of PSP would *opening* a Cl- channel produce?
- What sort of PSP would *closing* a K+ produce?

Synapse location and function



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

Neurotransmitters

What are they?

- Chemicals produced by neurons
- Released by neurons
- Bound by neurons and other cells
- Send messages (have physiological effect on target cells)
- Inactivated after release

Things to know

- Neurotransmitter
- Where released from/to
- What receptor(s) bind it

Types

Family	Neurotansmitter

Family	Neurotansmitter
Amino acids	Glutamate (https://en.wikipedia.org/wiki/Glutamate_(neurotransmitter))
	γ aminobutyric acid (GABA) (https://en.wikipedia.org/wiki/Gamma-Aminobutyric_acid)
	Glycine
	Aspartate

Glutamate

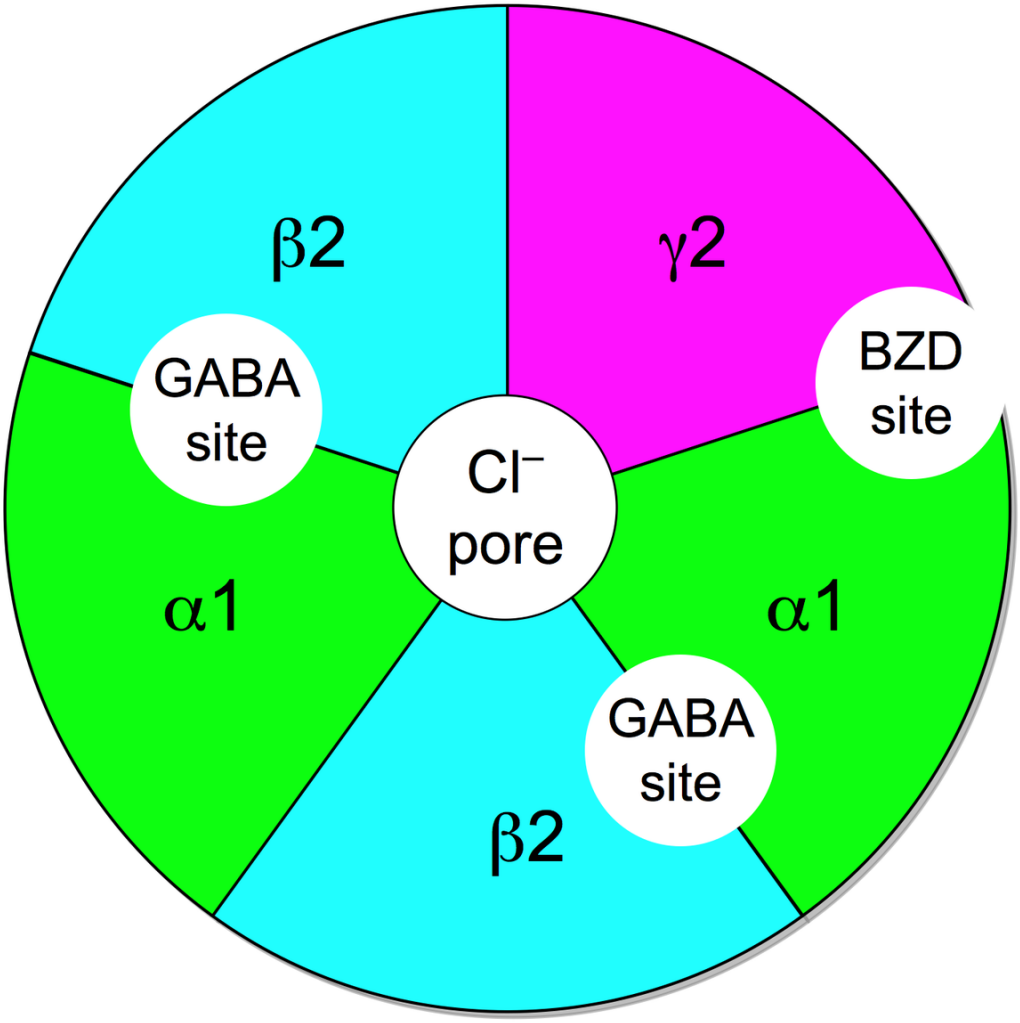
- Primary excitatory NT in CNS (~ 1/2 all synapses)
- Role in learning (via NMDA receptor)
- Receptors on neurons and glia (astrocytes and oligodendrocytes)
- Linked to umami (savory) taste sensation (think monosodium glutamate or MSG)
- Dysregulation in schizophrenia (McCutcheon, Krystal, & Howes, 2020) (https://doi.org/10.1002/wps.20693), mood disorders (Małgorzata, Paweł, Iwona, Brzostek, & Andrzej, 2020) (http://dx.doi.org/10.1080/14728222.2020.1836160)

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 (BZD; e.g., Valium), barbiturates, ethanol, etc.
  - BZD affect subset of GABA-A receptors
  - Increase total Cl- influx

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



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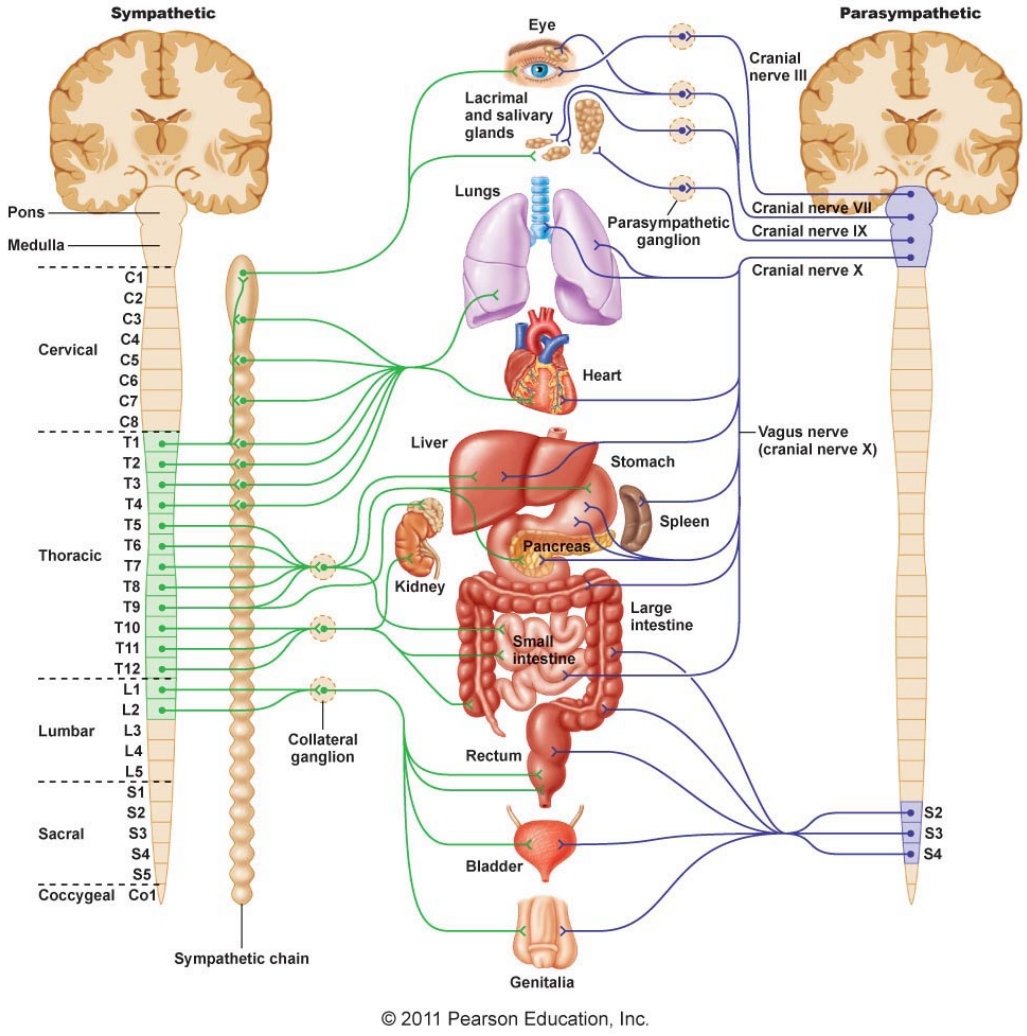
Other amino acid NTs

- *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 (ANS)
  - Sympathetic branch: preganglionic neuron
  - Parasympathetic branch: pre/postganglionic



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

Curare

Atropine

- aka, nightshade or belladonna
- inhibits (acts as an antagonist for) muscarinic ACh receptor

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Monoamine NTs

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

- DA -> NE/NAd -> Epi/Ad

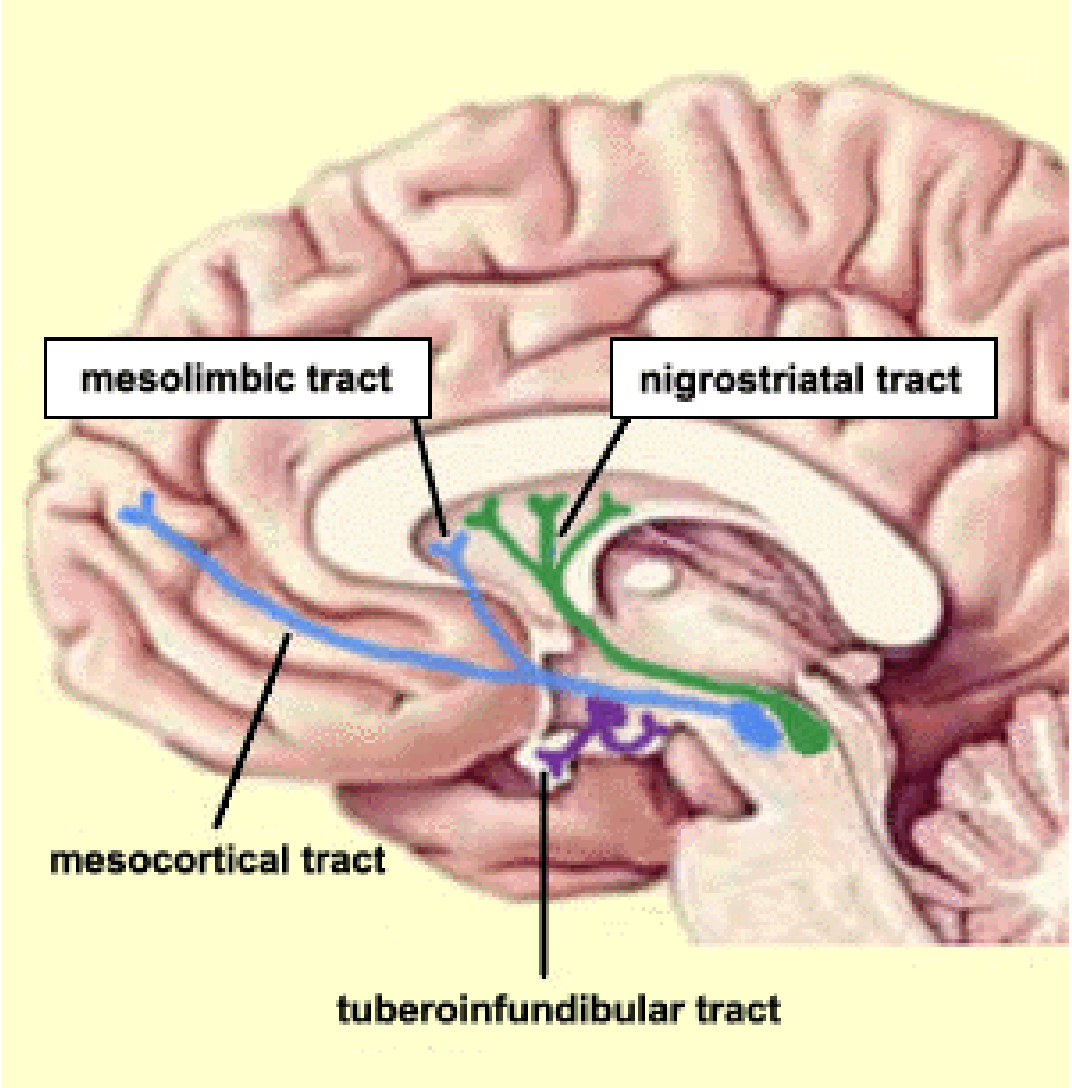
Information processing

- 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*



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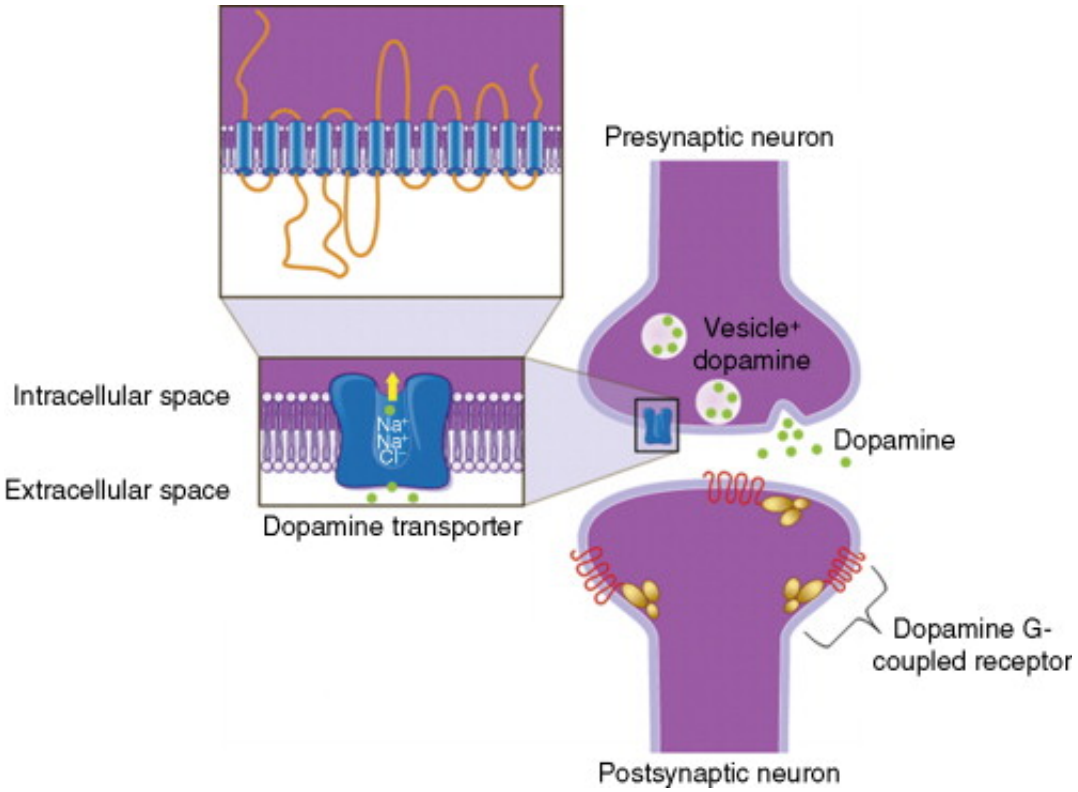
Clinical relevance for

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

Inactivated via

- Chemical breakdown (e.g., via monoamine oxidase), http://www.scholarpedia.org/article/Dopamine_anatomy#Dopamine_receptors (http://www.scholarpedia.org/article/Dopamine_anatomy#Dopamine_receptors)
- Dopamine transporter (DAT)

- Psychostimulants (e.g., cocaine, methylphenidate) act upon. (“Dopamine transporter,” n.d.) (https://www.sciencedirect.com/topics/neuroscience/dopamine-transporter)
- DAT also transports norepinephrine (NE)



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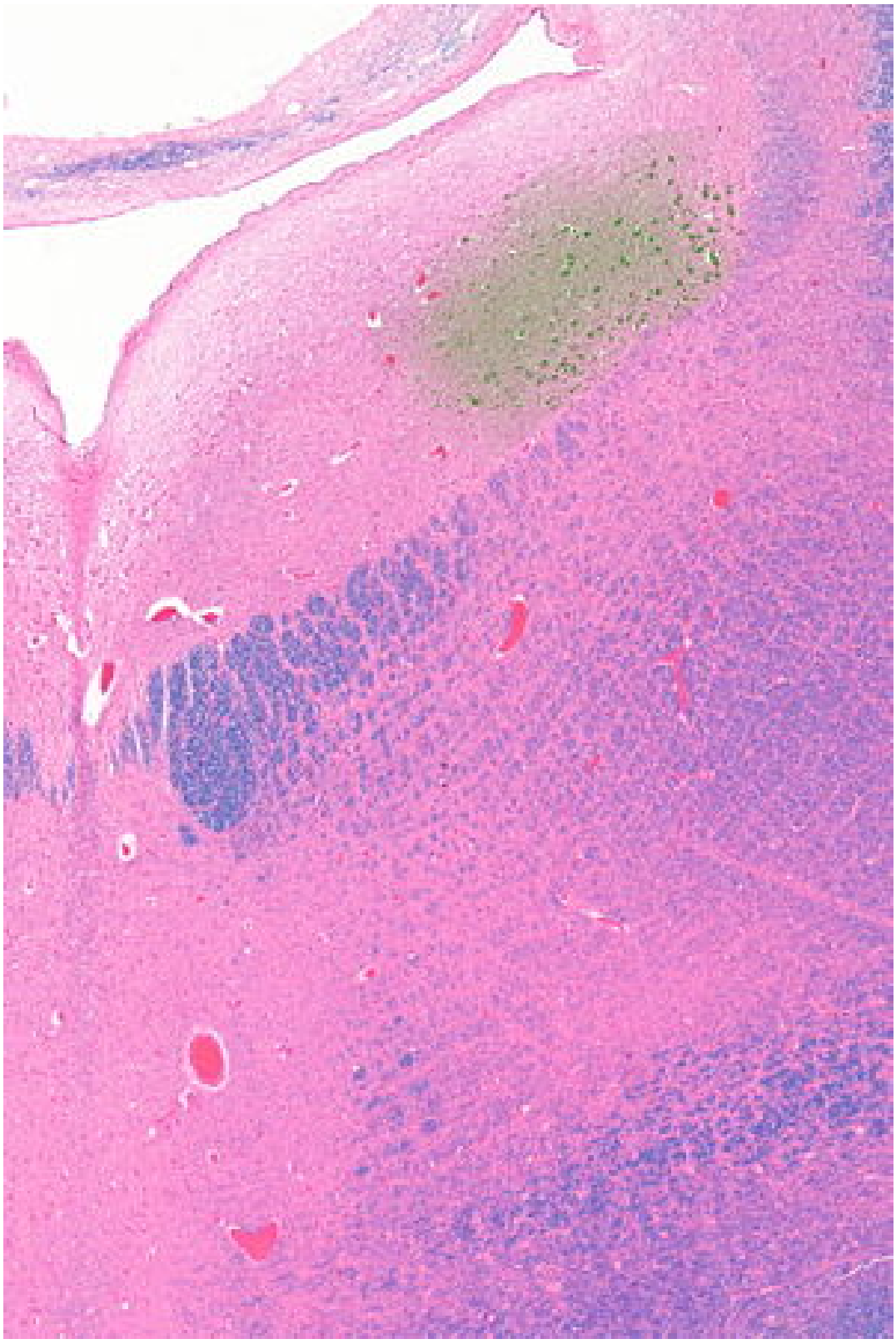
Type	Receptor	Comments
Metabotropic	D1-like (D1 and D5)	more prevalent
	D2-like (D2, D3, D4)	target of many antipsychotics

Norepinephrine

- Released by
  - *locus coeruleus (http://www.scholarpedia.org/article/Locus_coeruleus)* in pons/caudal tegmentum
  - postganglionic sympathetic neurons onto target tissues



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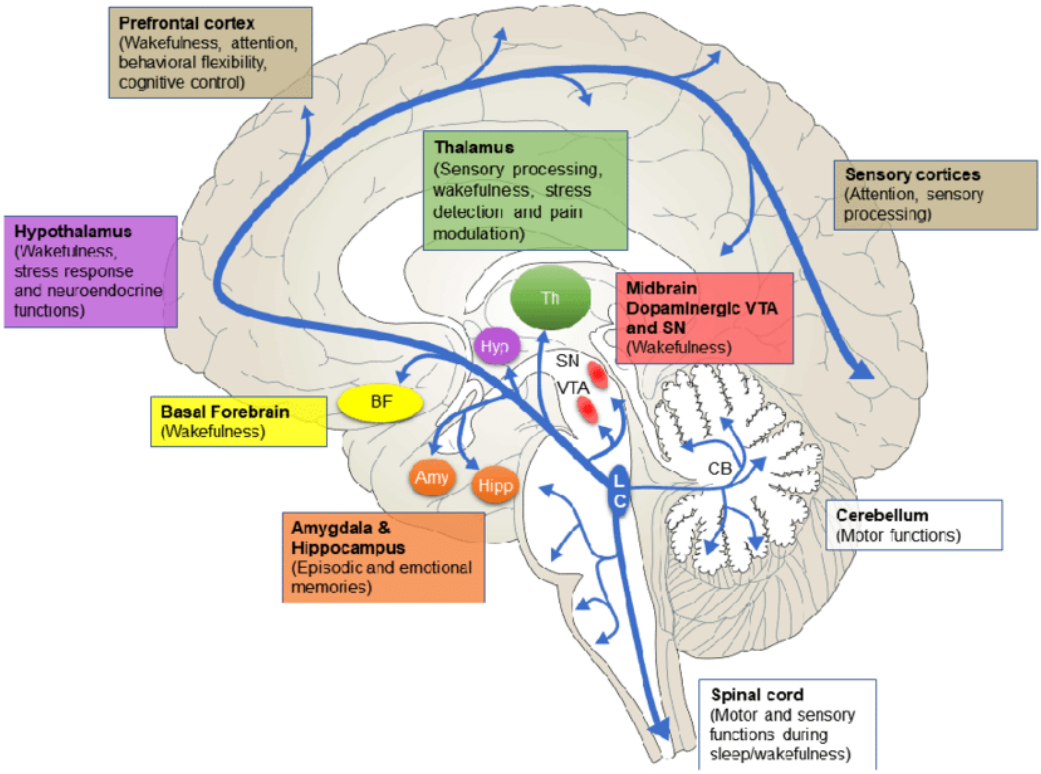

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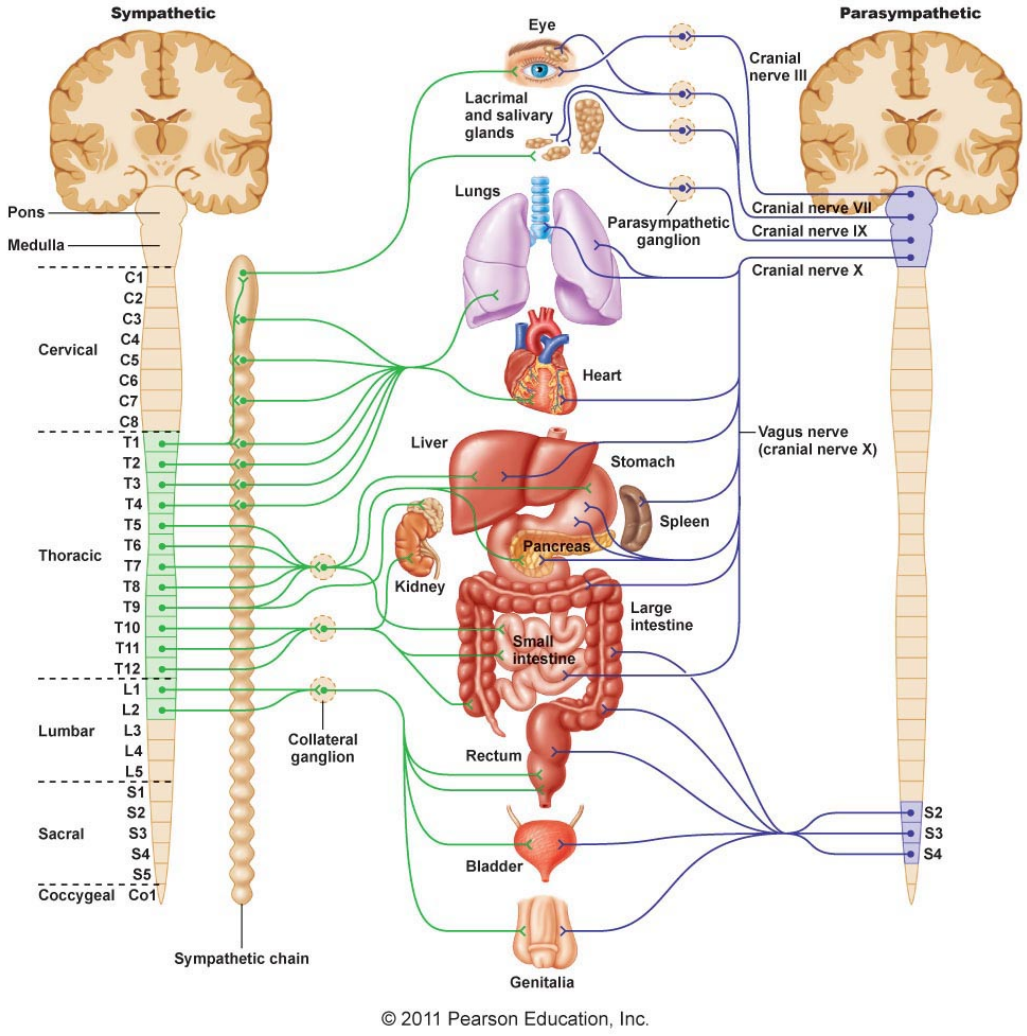

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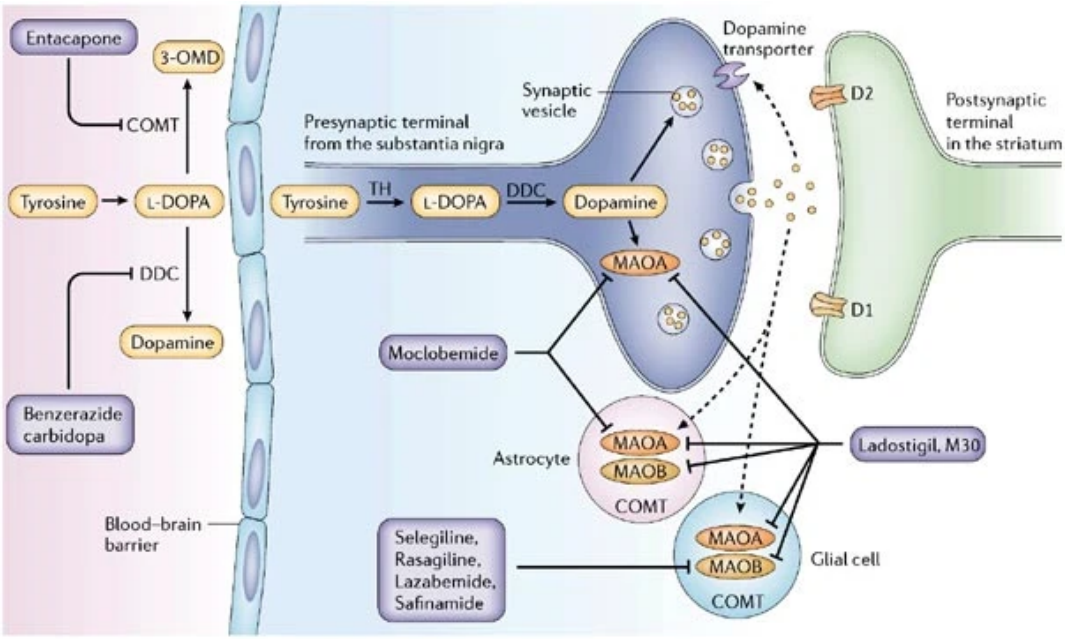
- Role in arousal, mood, eating, sexual behavior
- Clinical relevance for ADHD, Alzheimer's, Parkinson's, depression
- Inactivated by norepinephrine transporter (NET), aka noradrenaline transporter (NAT)
  - Contributes to DA uptake, too.
- Also monoamine oxidase inhibitors (MAOIs)
  - inactivate monoamines in neurons, astrocytes
  - MAOIs increase NE, DA
  - Treatment for depression



(Youdim, Edmondson, & Tipton, 2006) (http://dx.doi.org/10.1038/nrn1883)

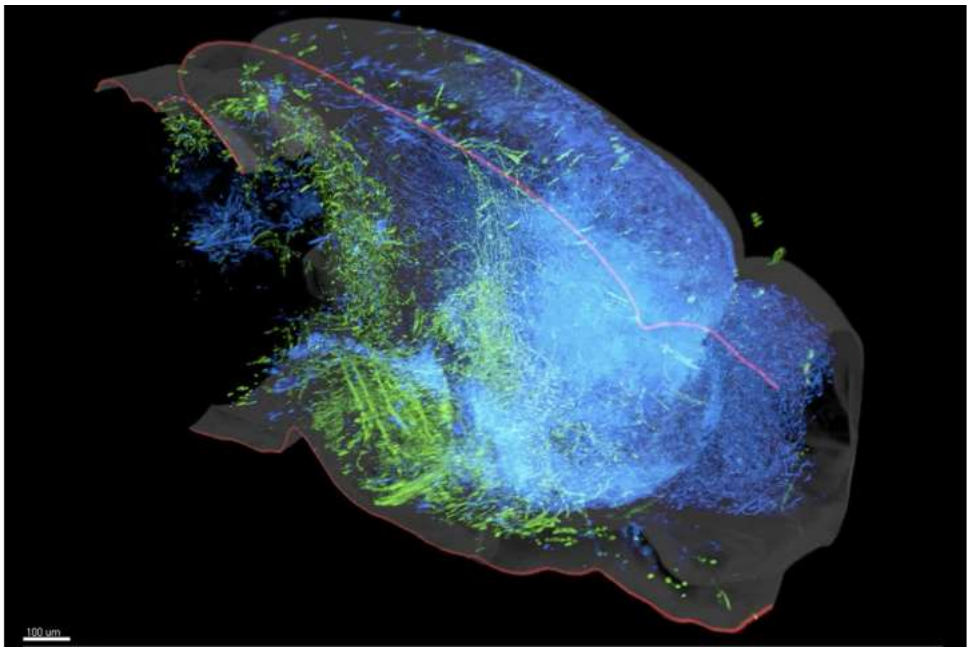
Type	Receptor	Comments
Metabotropic	α (1,2)	antagonists treat anxiety, panic
	β (1,2,3)	'beta blockers' in cardiac disease

Adrenaline/Epinephrine

- Synthesized from norepinephrine
- As NT: Released in small amounts by medulla oblongata
- As hormone: Released by adrenal medulla
- Binds to ($\alpha_{1,2}, \beta_{1,2,3}$ receptors in blood vessels, cardiac muscle, lungs, eye muscles controlling pupil dilation, liver, pancreas, etc.
- Release enhanced by cortisol from adrenal cortex
- Unusual in NOT being part of negative feedback system controlling its own release

Serotonin (5-HT)

- Released by *raphe nuclei* in brainstem
- Role in mood, sleep, eating, pain, nausea, cognition, memory
- Modulates release of other NTs
- Most (90%; (De Ponti, 2004) (http://dx.doi.org/10.1136/gut.2003.035568)) of body's 5-HT regulates digestion
- Separate cortical, subcortical 5-HT projection pathways?

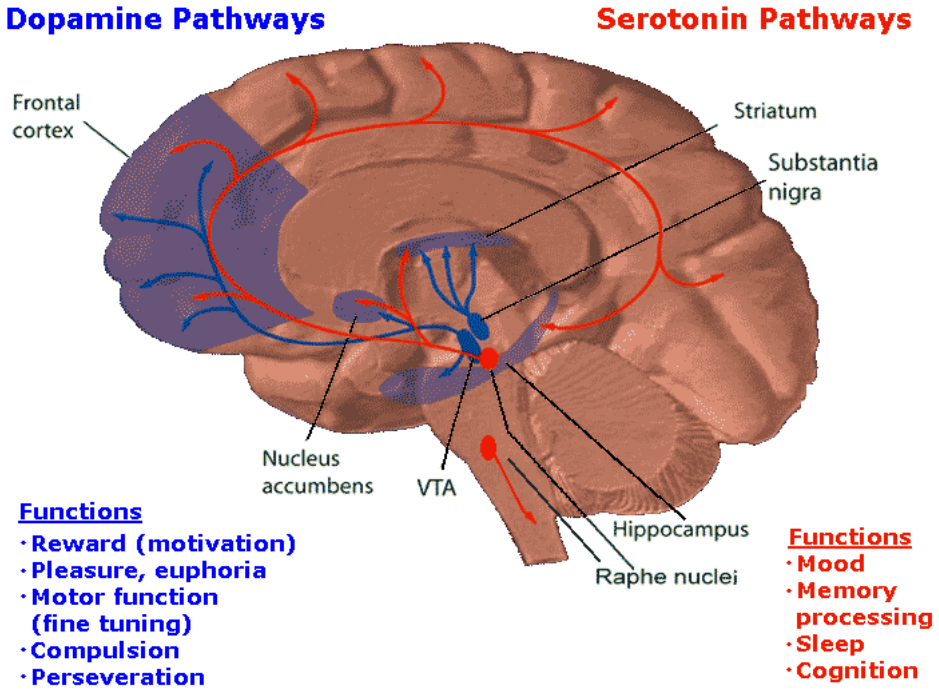


(Ren et al., 2018) (http://dx.doi.org/10.1016/j.cell.2018.07.043)

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

Clinically significant because

- 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



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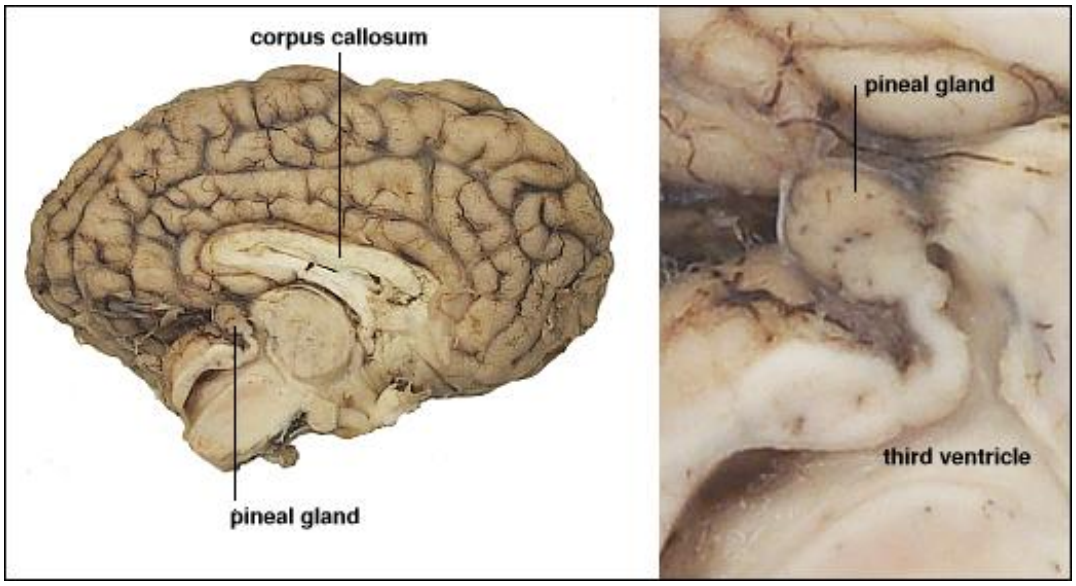
- Different psychological roles (passive vs. active coping) associated with different 5-HT receptor subtypes? (Carhart-Harris & Nutt, 2017) (http://dx.doi.org/10.1177/0269881117725915)

Melatonin

- Released by pineal gland (pine cone-like appearance)



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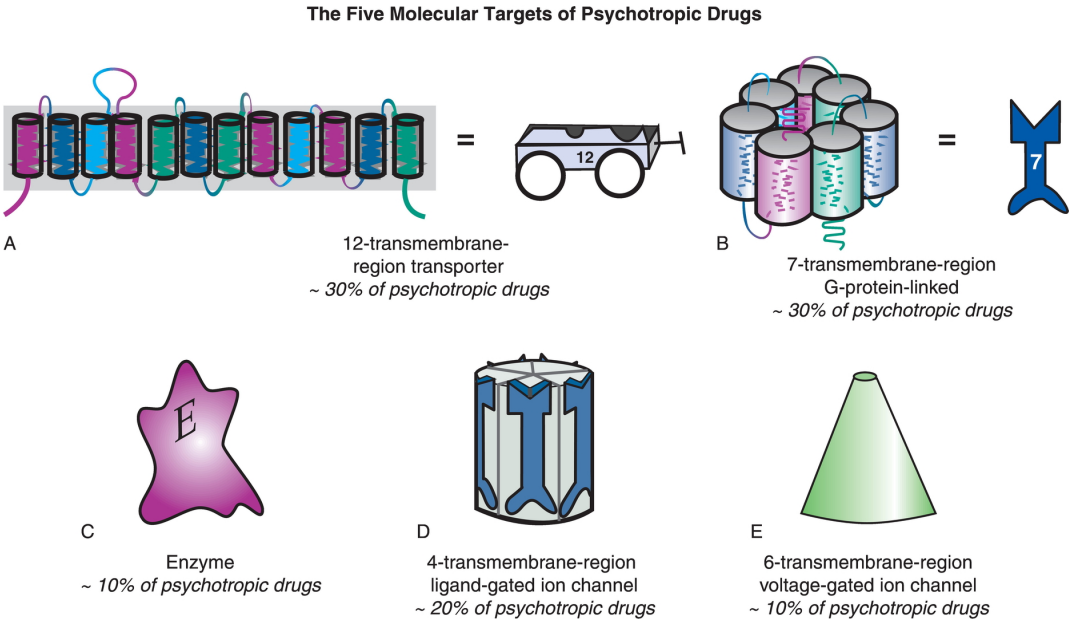
Histamine

- Released by hypothalamus, projects to whole brain

- H_1-H_4 Metabotropic receptors, one ionotropic type in thalamus/hypothalamus
- Role in arousal/sleep regulation
- In body, part of immune/inflammatory response

Targets of psychotropic drugs



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Other NTs

- 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)

Hormonal communication

- Chemicals secreted into blood
- Act on specific target tissues via receptors
- Produce specific effects

Examples of substances that are both hormones and NTs

- Melatonin
- Epinephrine/adrenaline
- Oxytocin
- Vasopressin

Behaviors under hormonal influence

Ingestive (eating/ drinking)

- Fluid levels
- Na, K, Ca levels
- Digestion
- Blood glucose levels

Reproduction-related

- Sexual Maturation
- Mating
- Birth
- Care giving

To threat/challenge

- Metabolism
- Heart rate, blood pressure
- Digestion
- Arousal

Common factors

- Biological imperatives
- Proscribed in space and time
- Foraging/hunting
  - Find targets distributed in space, evaluate, act upon
- Often involve others

Principles of hormonal action

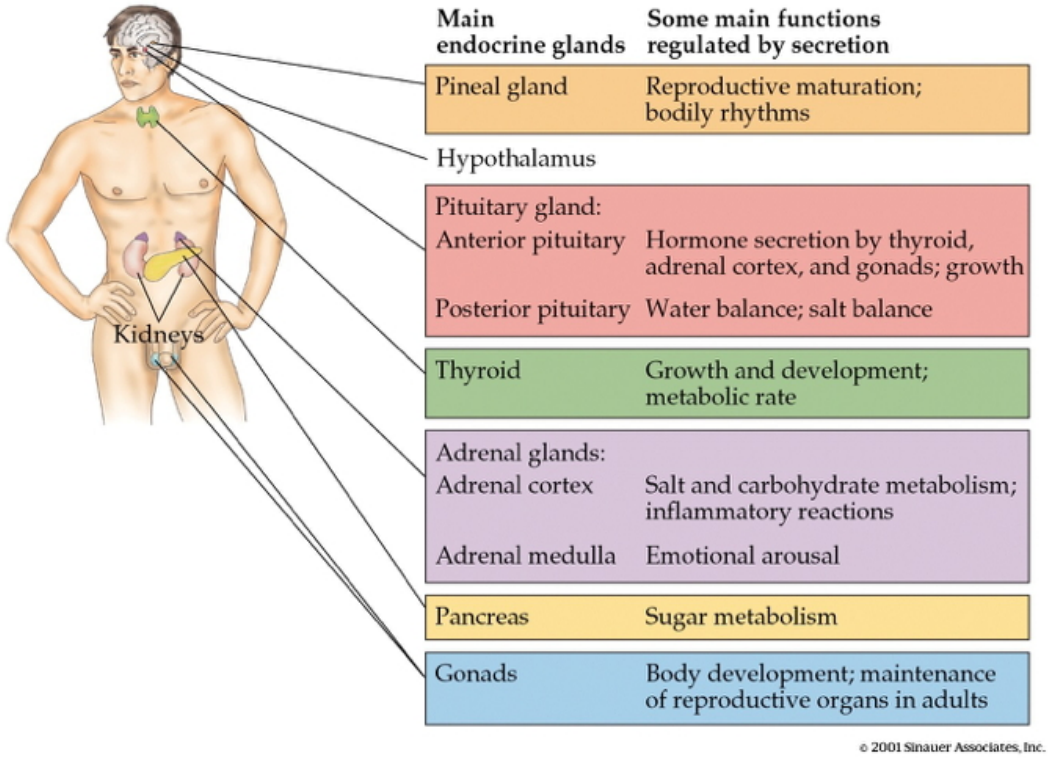
- Gradual action
- Change intensity or probability of behavior
- Behavior influences/influenced by hormones
  - +/- Feedback
- Multiple effects on different tissues
- Produced in small amounts; released in bursts
- Levels vary daily, seasonally

- or are triggered by specific external/internal events
- Effect cellular metabolism
- Influence only cells with receptors
- Point to point vs.“broadcast”
  - Wider broadcast than neuromodulators
- Fast vs. slow-acting
- Short-acting vs. long-acting
- Digital (yes-no) vs. analog (graded)
- Voluntary control vs. involuntary

Similarities between neural and hormonal communication

- Chemical messengers stored for later release
- Release follows stimulation
- Action depends on specific receptors
- 2nd messenger systems common

Hormonal release sites



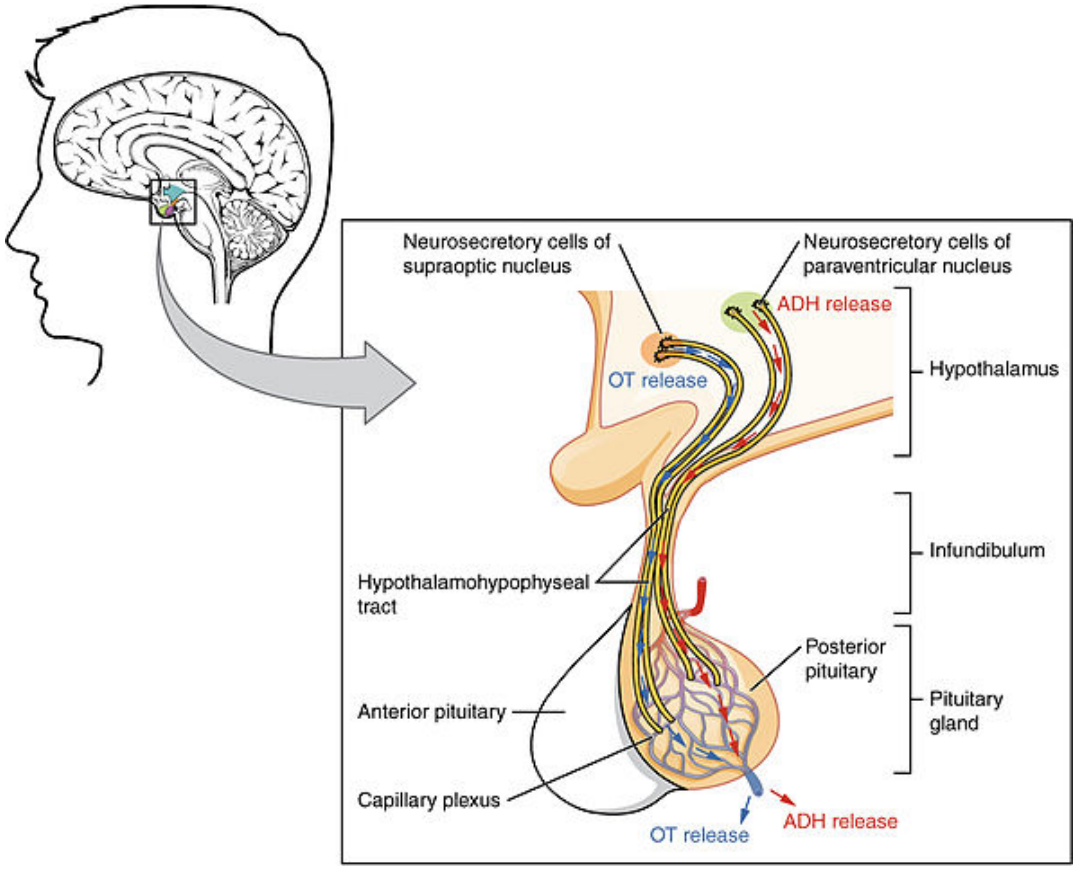
- CNS
  - Hypothalamus
  - *Pituitary*
    - *Anterior*
    - *Posterior*
  - Pineal gland
- Rest of body
  - *Thyroid*
  - *Adrenal (ad=adjacent, renal=kidney) gland*

    - *Adrenal cortex*
    - *Adrenal medulla*
  - *Gonads* (testes/ovaries)

Two release systems from hypothalamus

Direct release

- Hypothalamus (paraventricular, supraoptic nucleus) to
- Posterior pituitary
  - *Oxytocin*
  - *Arginine Vasopressin (AVP, vasopressin)*



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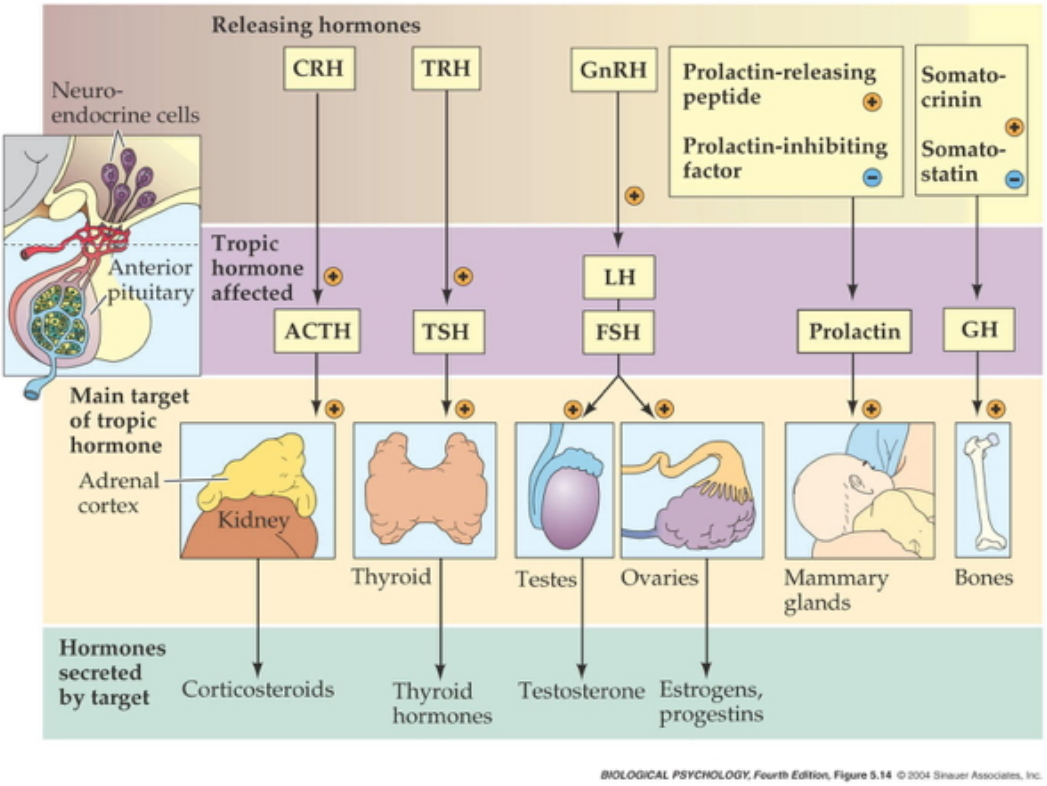
Indirect release

- Hypothalamus -> *releasing hormones*
- Anterior pituitary -> *tropic hormones*
- End organs



Case studies

Responses to threat or challenge

- Neural response
  - *Sympathetic Adrenal Medulla (SAM) response*
  - Sympathetic NS activation of adrenal medulla, other organs
  - Releases NE and Epi into bloodstream

    [[@ulrich-lai_neural_2009]](http://doi.org/10.1038/nrn2647)

    (Ulrich-Lai & Herman, 2009) (http://doi.org/10.1038/nrn2647)
- Endocrine response
  - *Hypothalamic Pituitary Adrenal (HPA) axis*
  - Adrenal hormones released
- Hypothalamus
  - *Corticotropin Releasing Hormone (CRH)*
- Anterior pituitary
  - *Adrenocorticotropic hormone (ACTH)*
- Adrenal cortex
  - *Glucocorticoids (e.g., cortisol)*
  - *Mineralocorticoids (e.g. aldosterone)*

    [[@ulrich-lai_neural_2009]](http://doi.org/10.1038/nrn2647)

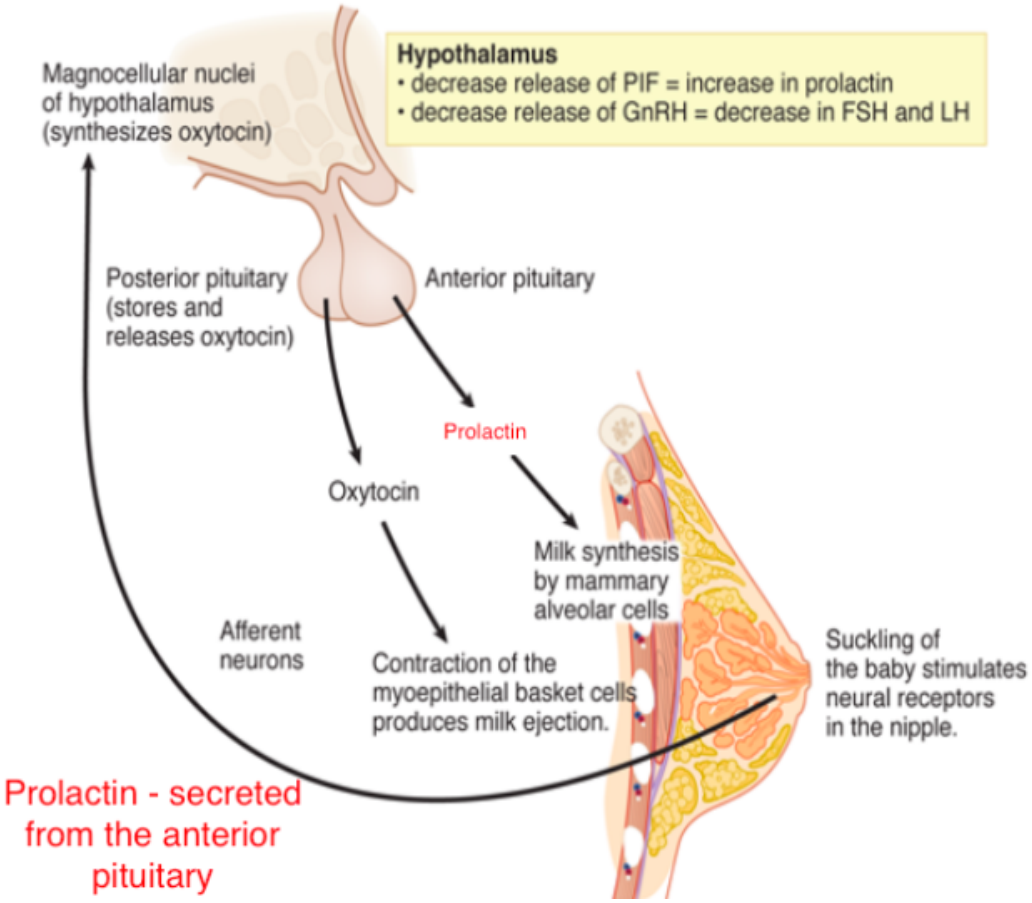
    (Ulrich-Lai & Herman, 2009) (http://doi.org/10.1038/nrn2647)

Adrenal hormones

- *Steroids*
  - Derived from cholesterol
- *Cortisol*
  - increases blood glucose, anti-inflammatory effects
  - negative consequences of prolonged exposure
- *Aldosterone*
  - Regulates Na (and water)

Reproductive behavior – the milk letdown reflex

- Supraoptic & Paraventricular nucleus (PVN) of hypothalamus releases oxytocin
  - Into bloodstream via posterior pituitary (endocrine)
  - Onto neurons in nucleus accumbens (neurocrine), amygdala, brainstem
- Oxytocin stimulates milk ducts to secrete



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Oxytocin's role…

- Sexual arousal
- Released in bursts during orgasm
- Stimulates uterine, vaginal contraction during labor

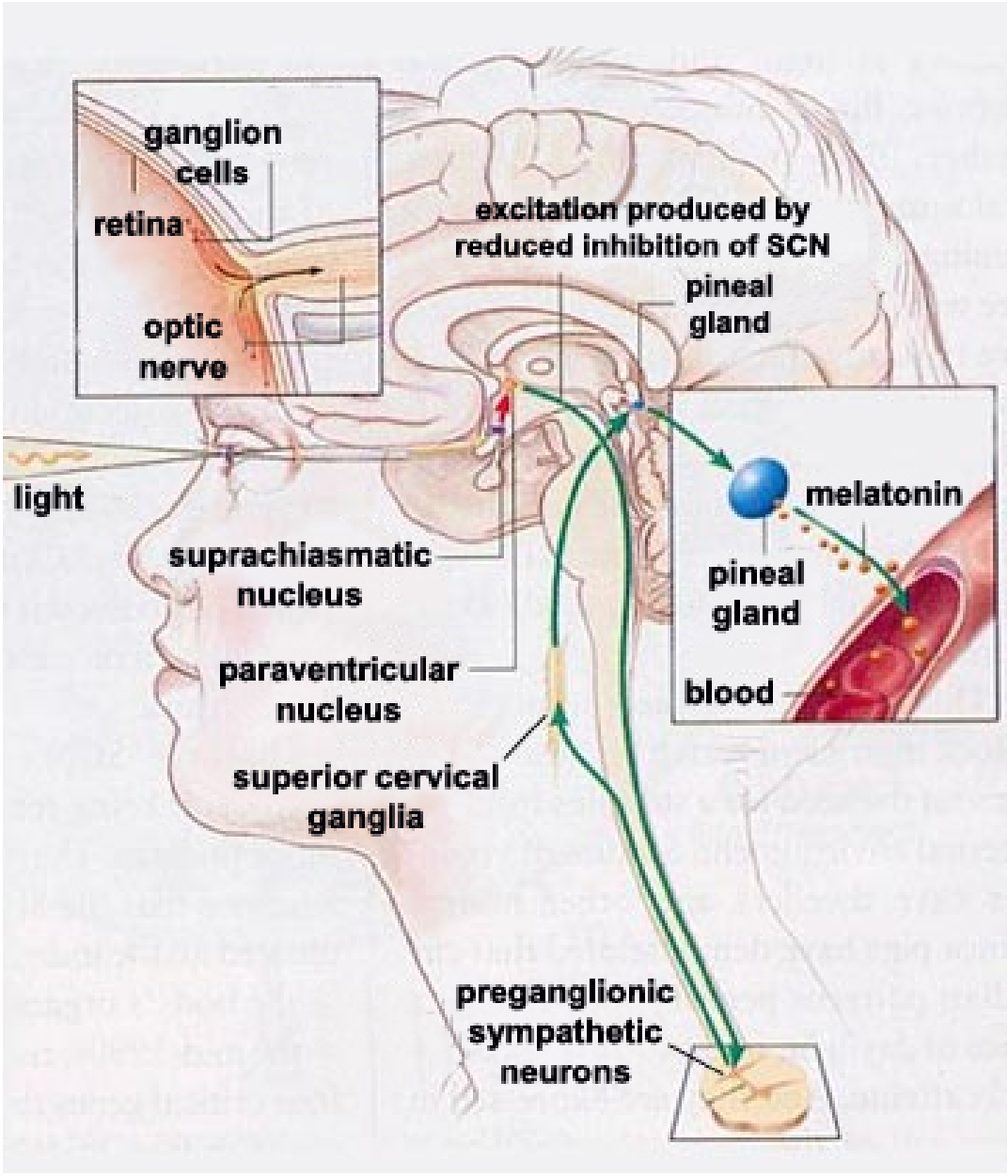
    - But mouse OXY knock-out model still engages in reproductive behavior and gives birth without incident.
- Oxytocin cells in ovarian corpus luteum, testicles, retina, adrenal medulla, pancreas
- Links to social interaction, bonding (Weisman & Feldman, 2013) (http://dx.doi.org/10.1016/j.biopsych.2013.05.026)
- Alters face processing in autism (Domes et al., 2013) (http://dx.doi.org/10.1016/j.biopsych.2013.02.007)
- May inhibit fear/anxiety-related behaviors by gating amygdala (Viviani et al., 2011) (http://doi.org/10.1126/science.1201043)

(http://columbusfreepress.com/sites/default/files/keep-calm-and-release-oxytocin-2(1).png)

Circadian rhythms

Melatonin

- Diurnal rhythm
- Night time peak, early morning low
- Secretion suppressed by short wavelength or “blue” light (< 460-480 nm)
- Rhythm irregular until ~3 mos post-natal (Ardura, Gutierrez, Andres, & Agapito, 2003) (http://dx.doi.org/68571)
- Peak weakens, broadens with age

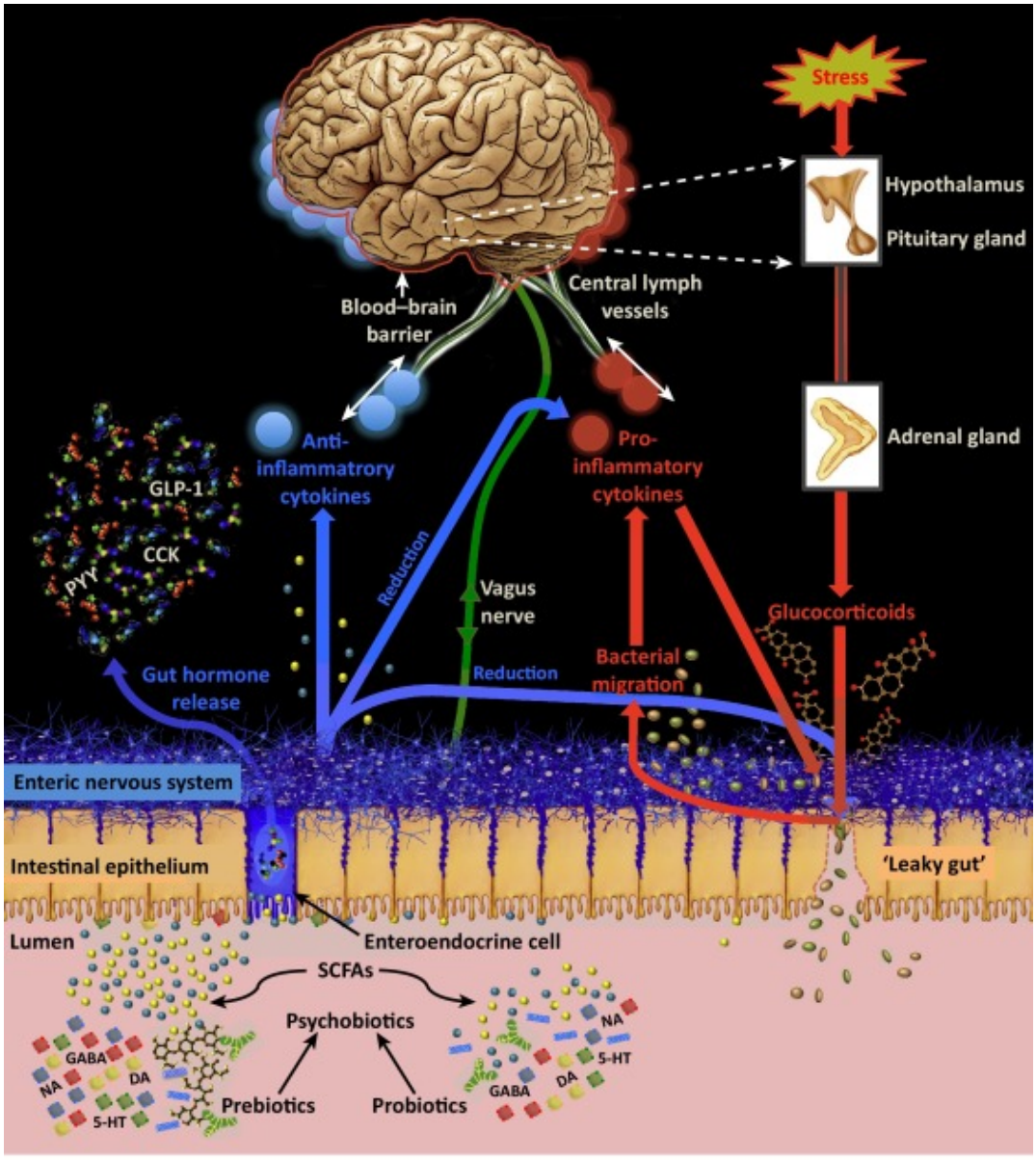


- Suprachiasmatic nucleus (SCN) of the hypothalamus
- Paraventricular nucleus of the hypothalamus
- Spinal cord
- Superior cervical ganglion
- Pineal gland

Thinking about neurochemical influences

- Measure hormones in blood, saliva; can't effectively measure NTs
- Multivariate, nonlinear, mutually interacting
- Varied time scales
  - Phasic (e.g., cortisol in response to challenge)
  - Periodic (e.g., melatonin; diurnal cortisol)
- Peripheral effects + neural feedback
- State variables and behavior
  - Are your participants sleepy, hungry, horny, distressed…
  - Endogenous & exogenous influences
  - Systems interact; need better, broader, and denser measurement

Gut/brain connection



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