

PSYC301: Neurotransmitters and drugs

Jay Hosking, PhD



Overview

Small molecule neurotransmitters

Amino acids

Amines

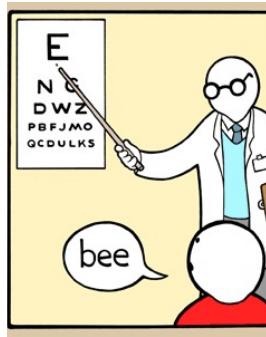
Other

Large molecule neurotransmitters



FALSEKNEES ©2021

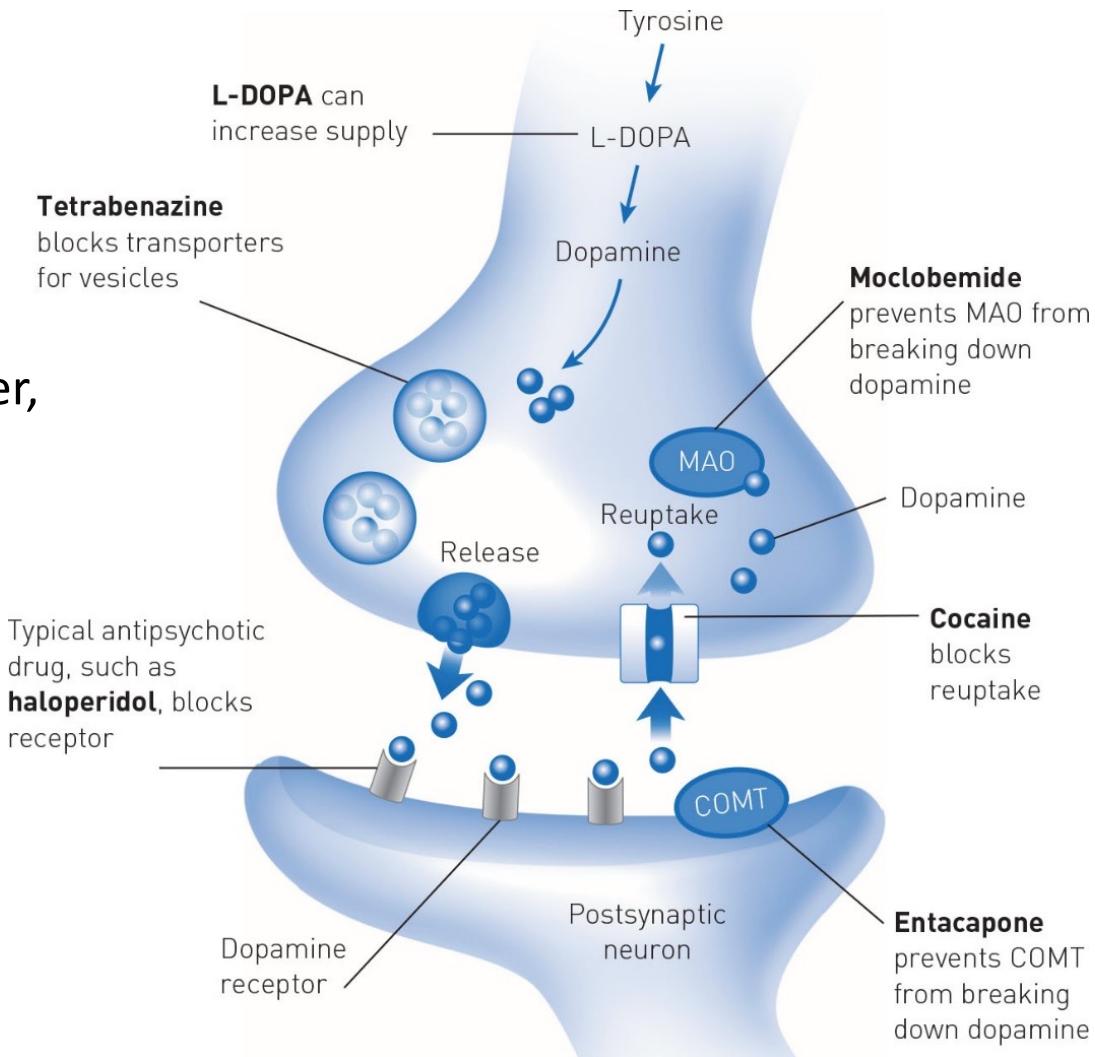
Learning objectives



1. Identify the two main effects of drugs, including why it can be complicated (e.g. GABA).
2. Take a tour of the most famous neurotransmitter systems, including commonly used drugs, for the following: glutamate, GABA, dopamine, norepinephrine, serotonin, acetylcholine, endocannabinoids, adenosine, and opioids.
3. Is dopamine the “pleasure molecule”? Justify your answer with evidence.
4. Is norepinephrine the “memory molecule”? Justify your answer with evidence.
5. Is serotonin the “mood molecule”? Justify your answer with evidence.
6. (Optional.) Read chapter 4 of Pinel & Barnes for some extra help on the material.

Drug types

- **Agonist**
- **Antagonist**
- Other
 - e.g. transporter blocker, reuptake inhibitor, enzyme inhibitor



*you don't need to know all the types in this image; I simply wanted to portray that there are many ways for drugs to affect the synapse

Small-Molecule Neurotransmitters

Amino acids		Glutamate GABA
Monoamines	Catecholamines	Dopamine Epinephrine Norepinephrine
	Indolamines	Serotonin
Acetylcholine		Acetylcholine
Unconventional neurotransmitters		

>100 identified neurotransmitters

Neurons named for NTs

“Co-occurrence” is the norm

Psychoactive drugs act here

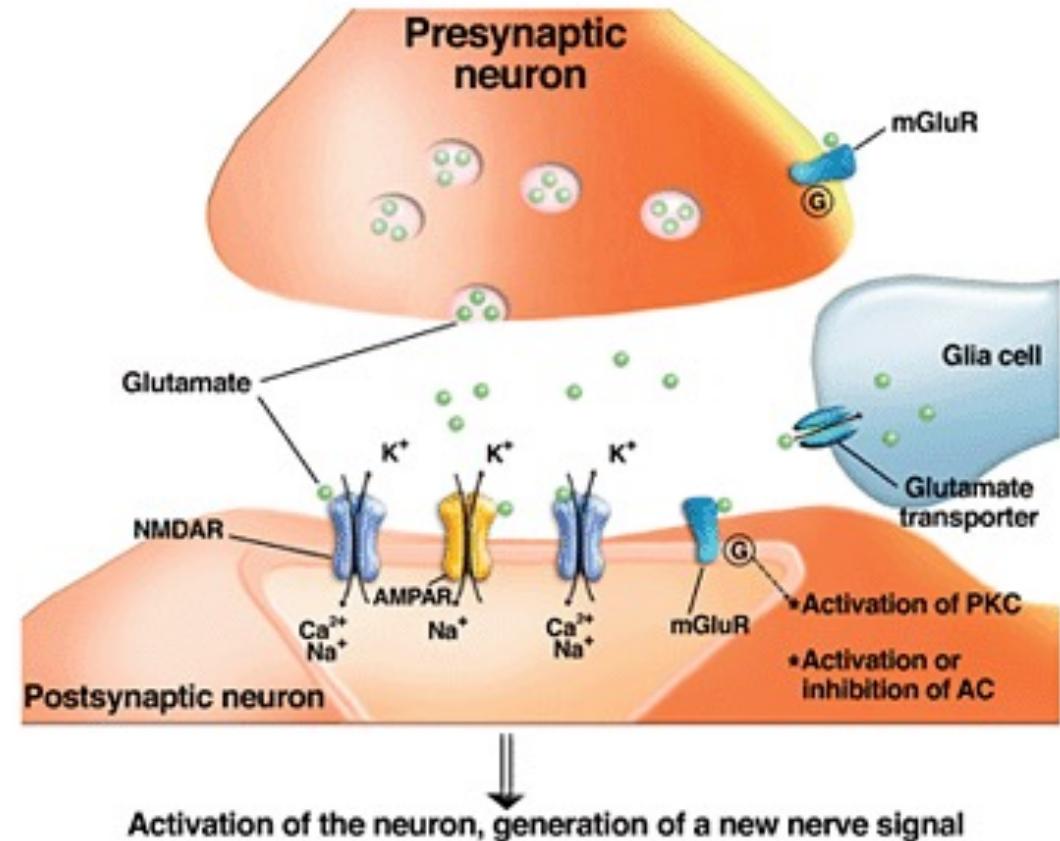
Large-Molecule Neurotransmitters

Neuropeptides	Opioid peptides
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Types of neurotransmitters

Glutamate

- Primary excitatory neurotransmitter
- Used throughout the brain
- Ionotropic receptors
 - AMPAR
 - NMDAR
 - Kainate receptor
- Metabotropic receptors
 - mGluR 1-8
- Often not a great target for drugs—why?



Amino acid neurotransmitters

Drugs: Glutamate (all antagonists)

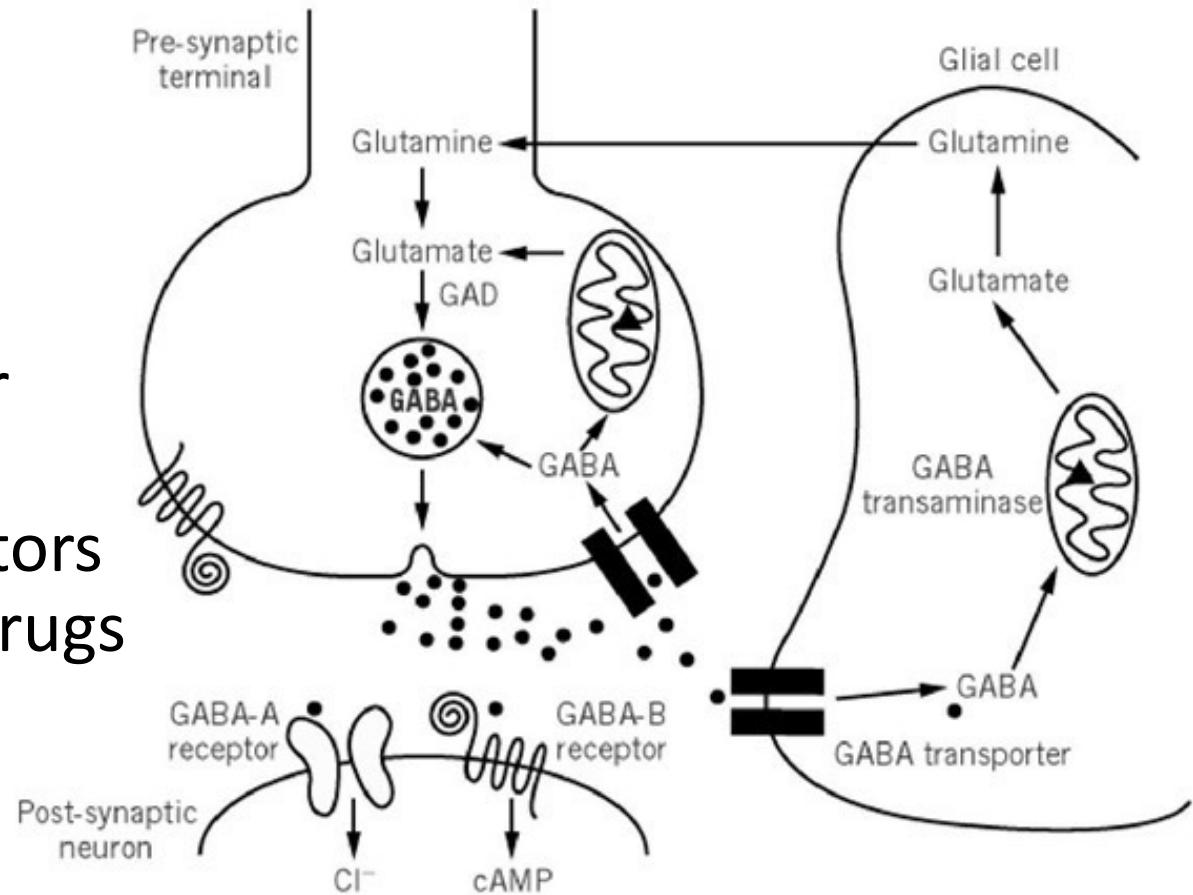
- Barbiturates
- Nitrous oxide
- Ketamine
- Ethanol



- Pattern?
- Agonists?

GABA

- aka gamma-Aminobutyric acid
- Primary inhibitory neurotransmitter
- Used throughout brain
- Ionotropic and metabotropic receptors
- Again, often not a great target for drugs



Amino acid neurotransmitters

Drugs: GABA (all agonists)

- Benzodiazepines
- Ethanol
- Chloroform
- Ether

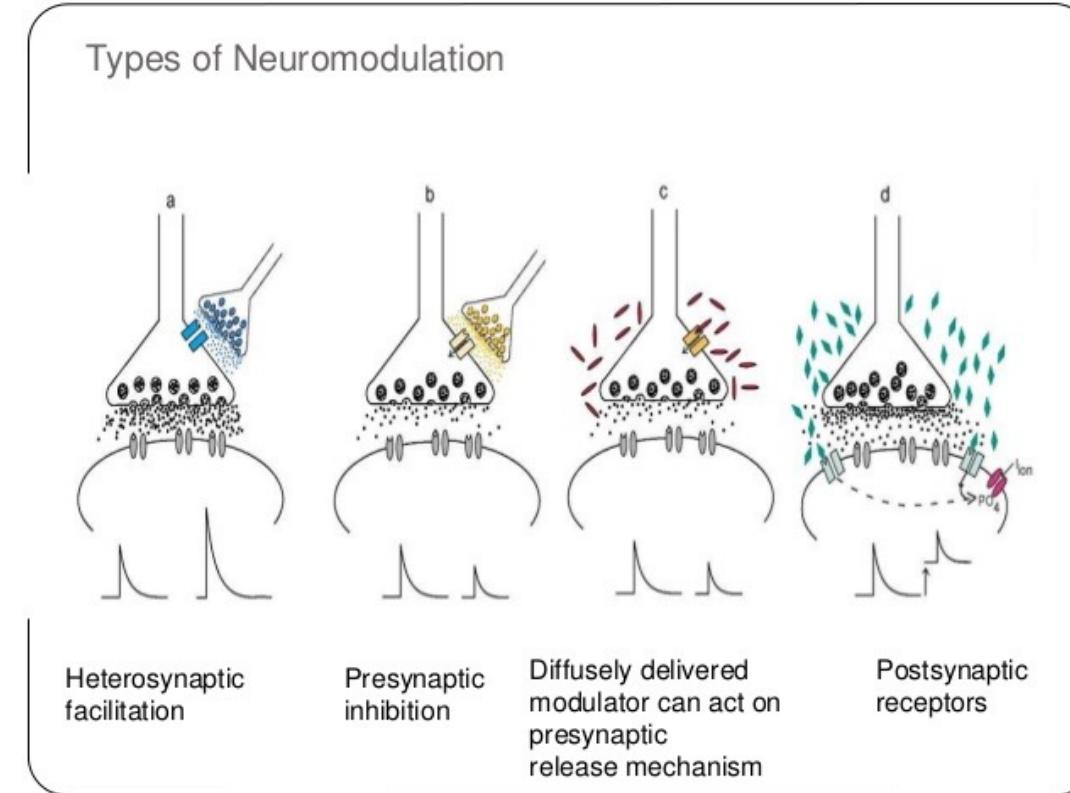


- Pattern?
- Antagonists?

Amino acid neurotransmitters

The amines

- Dopamine (DA)
- Epinephrine (aka Adrenaline)
- Norepinephrine
(NE, aka Noradrenaline)
- Histamine
- Serotonin
(5-HT)

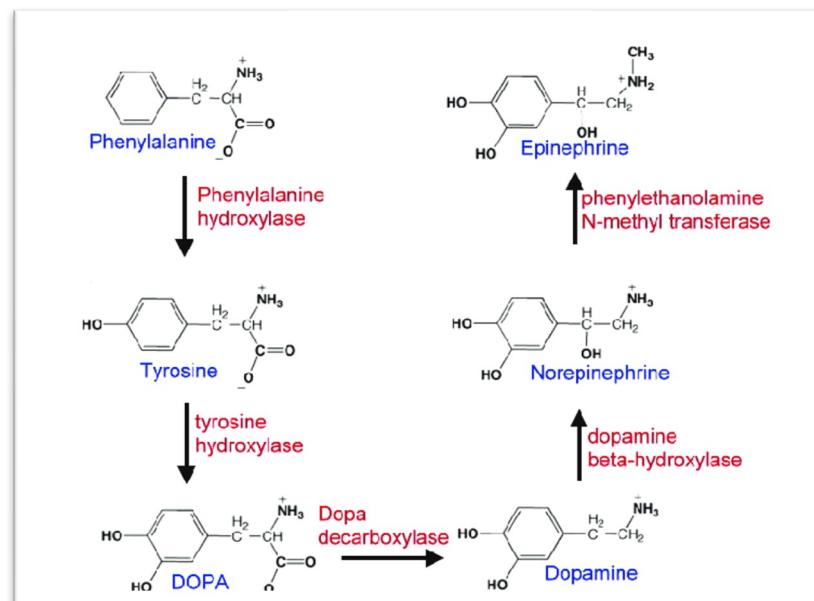
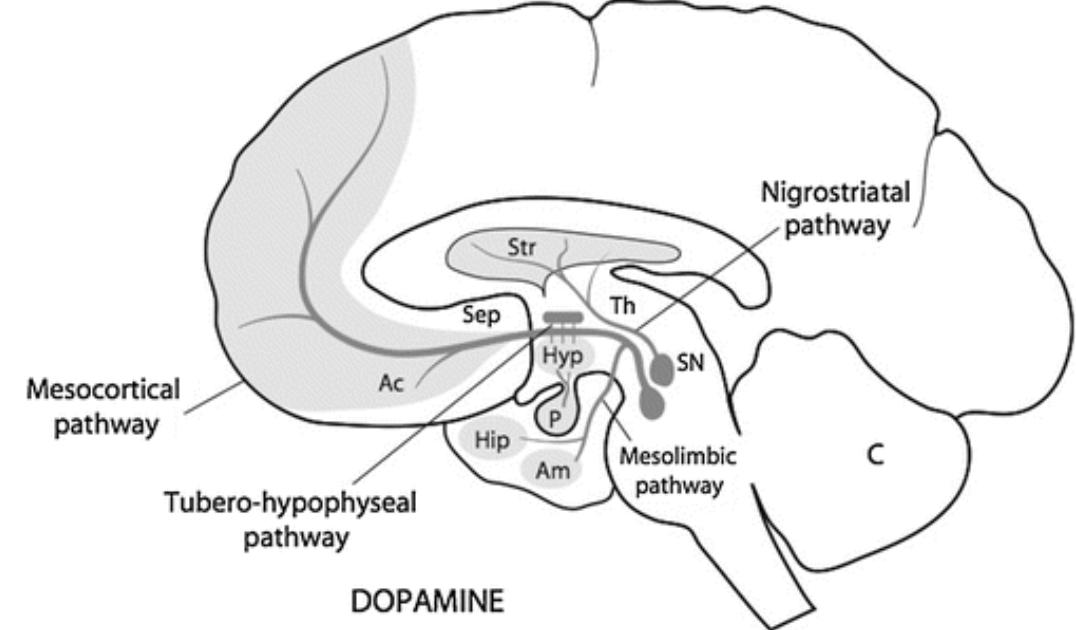


- Almost all metabotropic—play a modulatory role

Monoamine neurotransmitters

Dopamine (DA)

- Originates from two nuclei in the tegmentum
 - Substantia nigra pars compacta
 - Ventral tegmental area
- Projects to some (but not all) brain areas
- DA also made in hypothalamus
 - Here, it's a hormone
- Precursor from diet: **tyrosine** (and phenylalanine)
- Converted into DA via enzymes
- Overlaps with norepinephrine
 - They are both **catecholamines**
- Five DA receptors: D₁R-D₅R / D1-D5
 - All metabotropic
 - Some positive modulatory, some negative
- The pleasure/reward molecule? (NO)

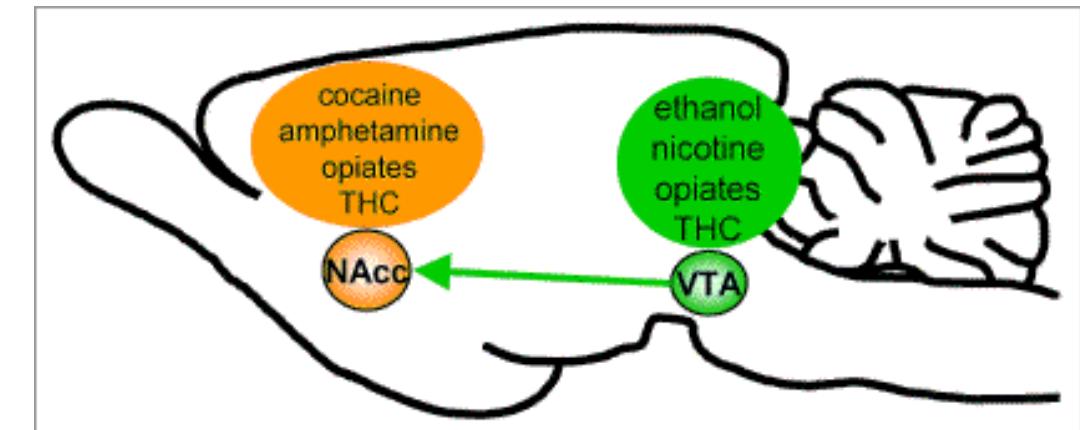
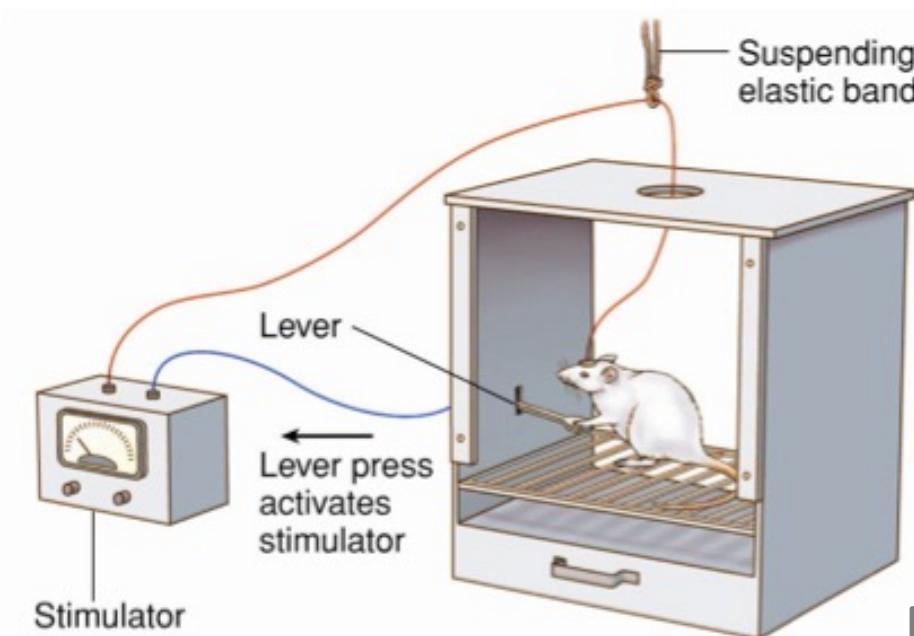


Note: I could not find a single perfectly accurate/complete schematic! This one is missing VTA → NAcc

Monoamine neurotransmitters

Motivation for... Brain Stimulation?

- Olds and Milner (1954)
- Dopamine axons project from Ventral Tegmental Area (VTA) to Nucleus Accumbens (NAcc)
- Their conclusion: dopamine related to pleasure



Monoamine neurotransmitters

Drugs of addiction and dopamine

- All addictive drugs directly or indirectly increase dopamine transmission
 - Implication?
- Amphetamine*, cocaine*, heroin, nicotine, oxycodone, ethanol, cannabinoids, and on and on

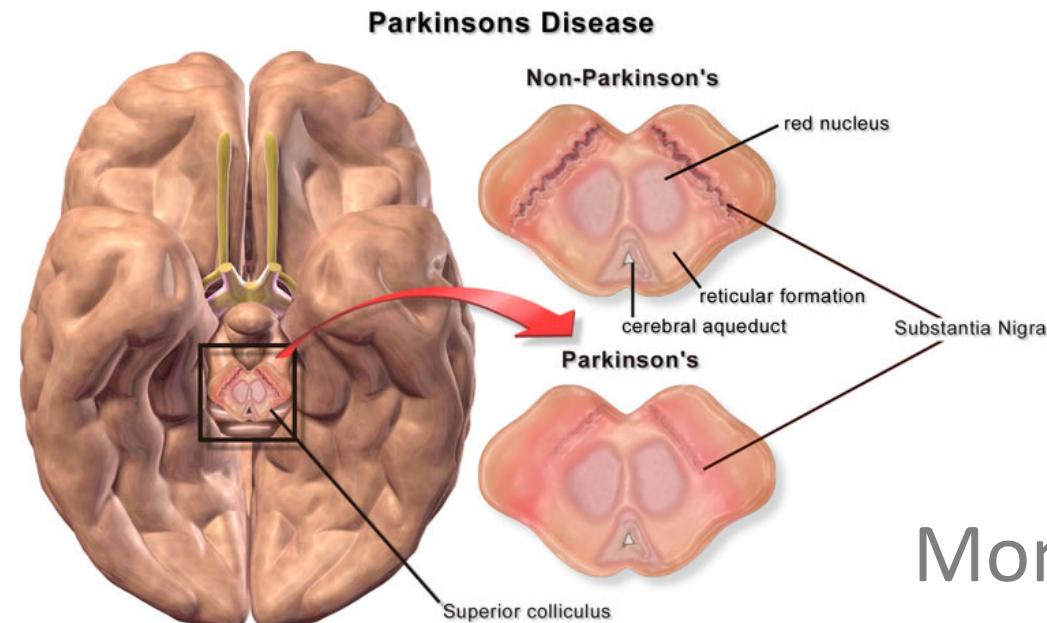


*directly increase DA transmission

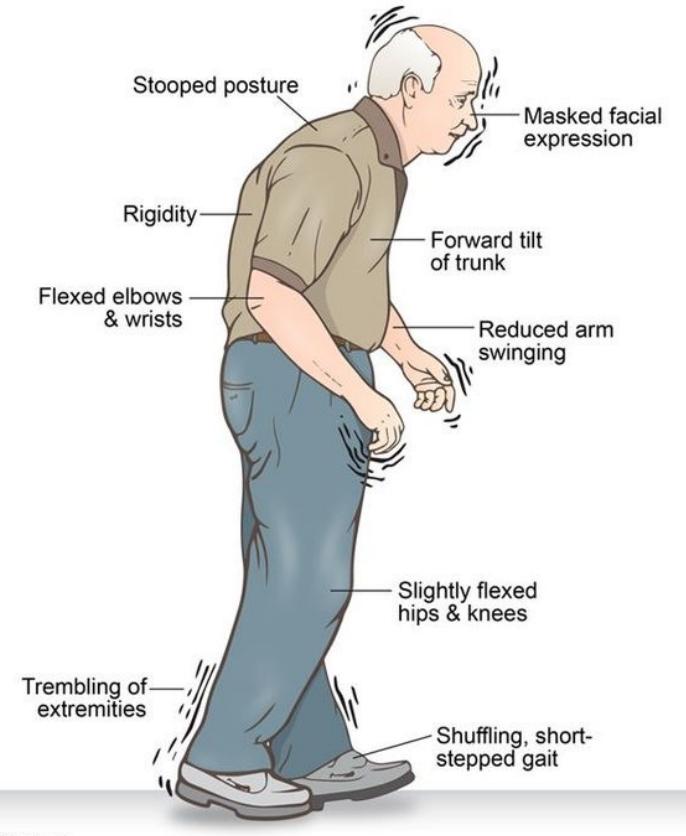
Monoamine neurotransmitters

Dopamine and Parkinson's Disease (PD)

- PD caused by the loss of the substantia nigra pars compacta (SNc)
- PD is a motor disorder
- L-DOPA as gold standard PD treatment
- PD, L-DOPA, and pleasure?
- Other PD drugs (e.g. D1 agonist)
- PD drug side effects? (Not pleasure)



Typical appearance of Parkinson's disease



Monoamine neurotransmitters

What about L-DOPA for healthy participants?

OPEN  ACCESS Freely available online



The Dopamine Augmenter L-DOPA Does Not Affect Positive Mood in Healthy Human Volunteers

John Liggins, Robert O. Pihl, Chawki Benkelfat, Marco Leyton*

Department of Psychiatry, McGill University, Montréal, Québec, Canada

Abstract

Dopamine neurotransmission influences approach toward rewards and reward-related cues. The best cited interpretation of this effect proposes that dopamine mediates the pleasure that commonly accompanies reward. This hypothesis has received support in some animal models and a few studies in humans. However, direct assessments of the effect of transiently increasing dopamine neurotransmission have been largely limited to the use of psychostimulant drugs, which elevate brain levels of multiple neurotransmitters in addition to dopamine. In the present study we tested the effect of more selectively elevating dopamine neurotransmission, as produced by administration of the immediate dopamine precursor, L-DOPA (0, 100/25, 200/50 mg, Sinemet), in healthy human volunteers. Neither dose altered positive mood. **The results suggest that dopamine neurotransmission does not directly influence positive mood in humans.**

Citation: Liggins J, Pihl RO, Benkelfat C, Leyton M (2012) The Dopamine Augmenter L-DOPA Does Not Affect Positive Mood in Healthy Human Volunteers. PLoS ONE 7(1): e28370. doi:10.1371/journal.pone.0028370

Editor: Bernard Le Foll, Centre for Addiction and Mental Health, Canada

Received July 1, 2011; **Accepted** November 7, 2011; **Published** January 4, 2012

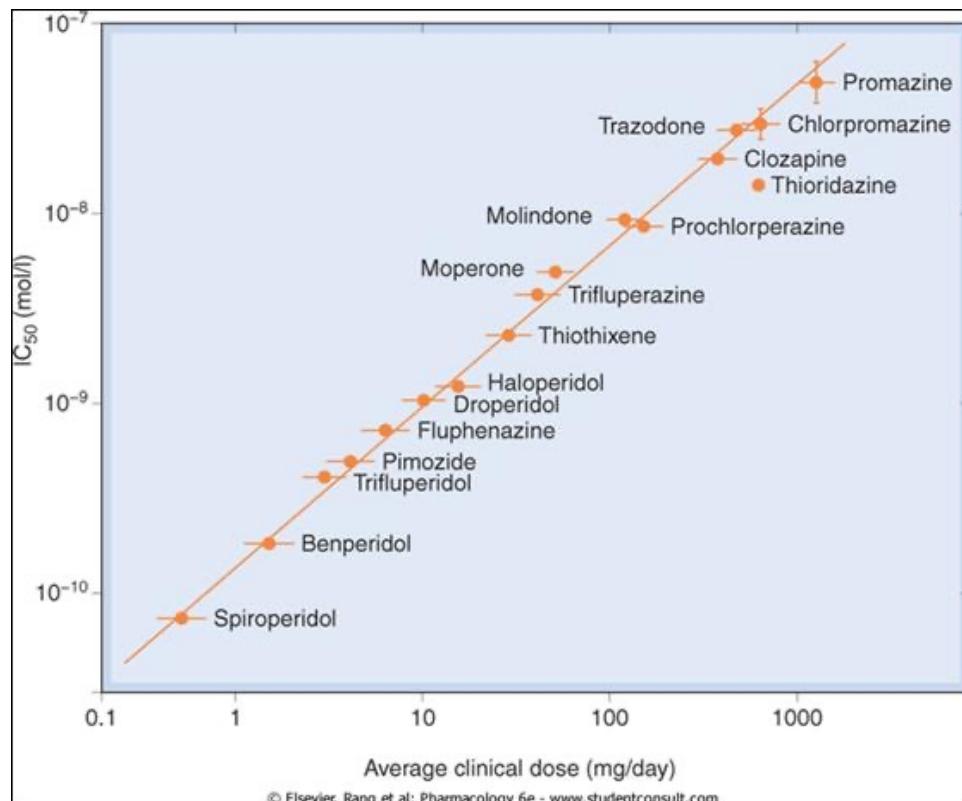
Monoamine neurotransmitters

Dopamine and schizophrenia

Schizophrenia medications are dopamine D₂R antagonists

Dopamine theory of schizophrenia

Do individuals with schizophrenia have higher baseline pleasure? (NO)



**I Was Diagnosed With
Schizophrenia At The Age Of 17, So
I Started Drawing My
Hallucinations To Cope With It**

<https://www.boredpanda.com/18-year-old-schizophrenic-artist-drawing-hallucinations/>

Monoamine neurotransmitters

Psychostimulants and dopamine

Psychostimulants act on the monoamine systems, esp. DA, NE, 5-HT

You can think of them like monoamine agonists

e.g. Cocaine, crack cocaine, methamphetamine, amphetamine, cathinones

These drugs cause a wide variety of effects (including euphoria)

But high doses, they can also cause temporary psychosis

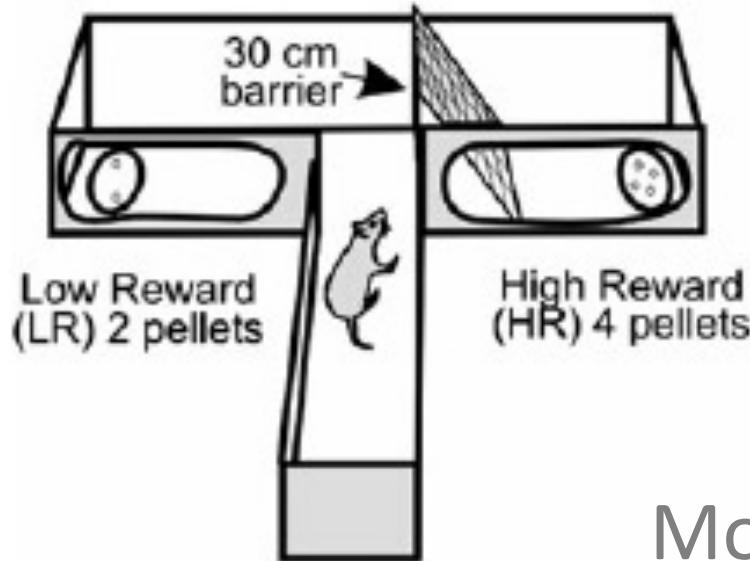
Not easily distinguished from positive symptoms of schizophrenia



Monoamine neurotransmitters

Separating Pleasure from Motivation

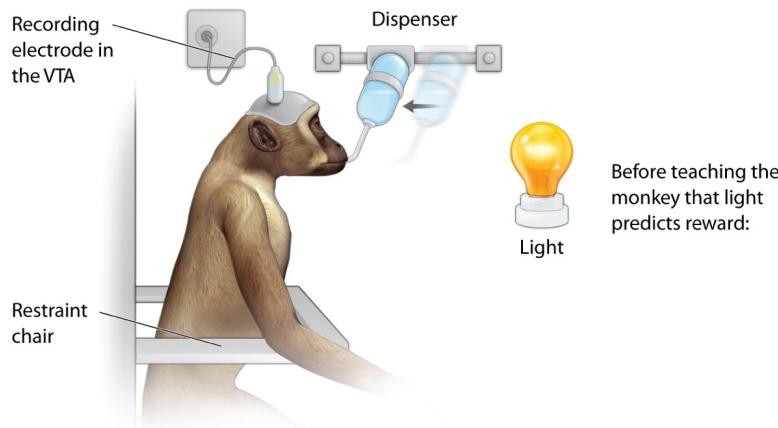
- Salamone (1990s) – T-maze task
 - Low effort, low reward vs. high effort, high reward
- Dopamine antagonists
 - Decrease motivation but not pleasure
 - Can be systemic or directly injected into VTA or NAcc



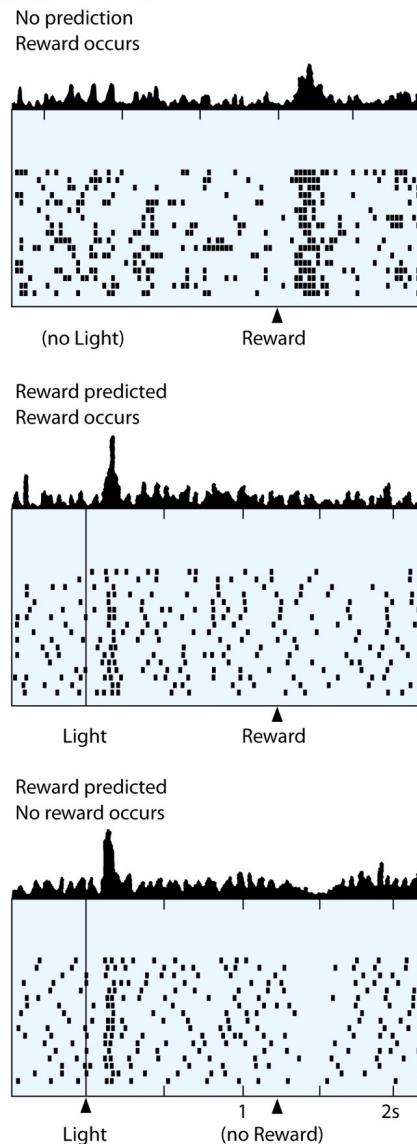
1. Training
2. Free choice baseline
3. Choice + DA antagonist
4. Choice + DA antagonist + no barrier

Monoamine neurotransmitters

Dopamine and reward prediction error



Before teaching the monkey that light predicts reward:



- Schultz *et al.* (1990s)
 - Pavlovian learning
 - VTA (DA) neurons
 - Fire at first for unexpected reward
 - Shift their firing to stimuli that predict reward
 - Go silent when predicted reward not delivered
 - Can be chained forward in time

So what does dopamine do?

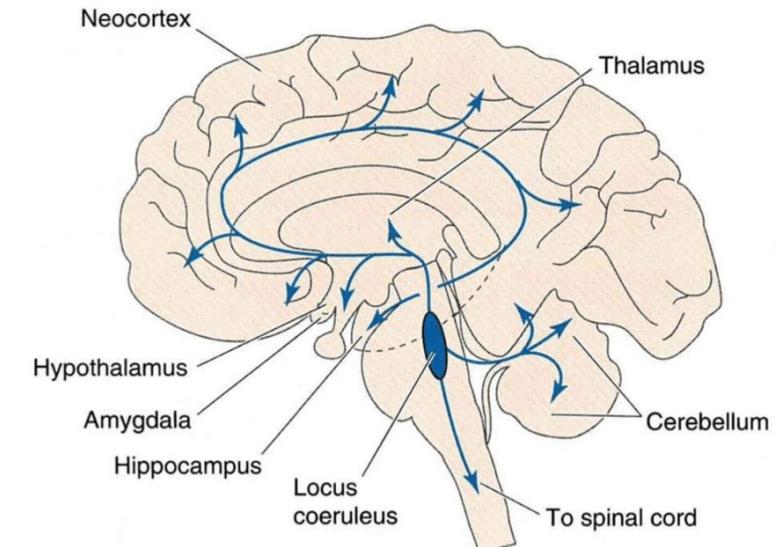
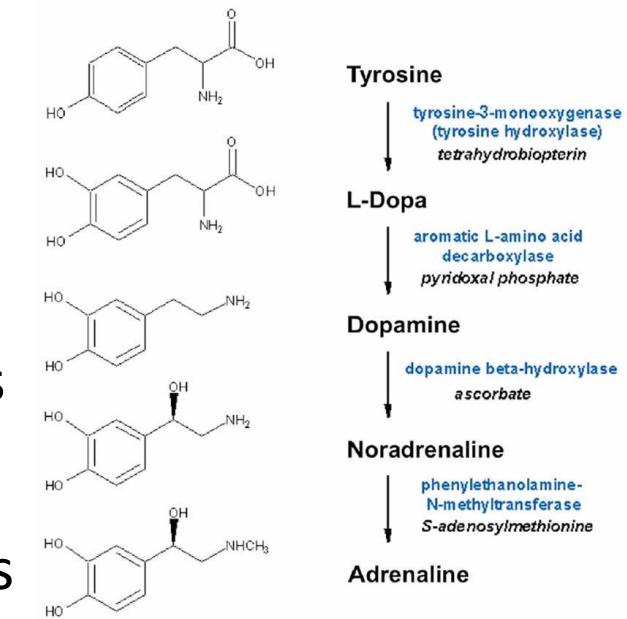
- Important for movement
- Important for motivation
- Important for learning as related to movement and motivation
- Important for levels of arousal, attention, executive function
- More on all of these later
- It is NOT the pleasure molecule!



Monoamine neurotransmitters

Norepinephrine (aka noradrenaline)

- Both a hormone and neurotransmitter!
- As NT, it originates in brain stem region called the locus coeruleus
- NE projects all over the brain
- Two main receptor types (α_{1-2} , β_{1-3}) with subtypes & sub-subtypes
 - all metabotropic (GPCRs)
- NE and epinephrine act similarly, on same receptors
- Causes heterosynaptic facilitation (via heteroreceptors)
- Baseline levels in wakefulness/arousal
- Enhancement of memory by stress/emotion
- Evolutionarily useful



Monoamine neurotransmitters

Post-traumatic stress disorder (PTSD) and propranolol

- **Propranolol** (norepinephrine receptor antagonist, aka noradrenergic receptor antagonist, aka “beta blockers”)
- Potential PTSD treatment via **reconsolidation**
- *Eternal Sunshine of the Spotless Mind?*
Not really, but not entirely unlike

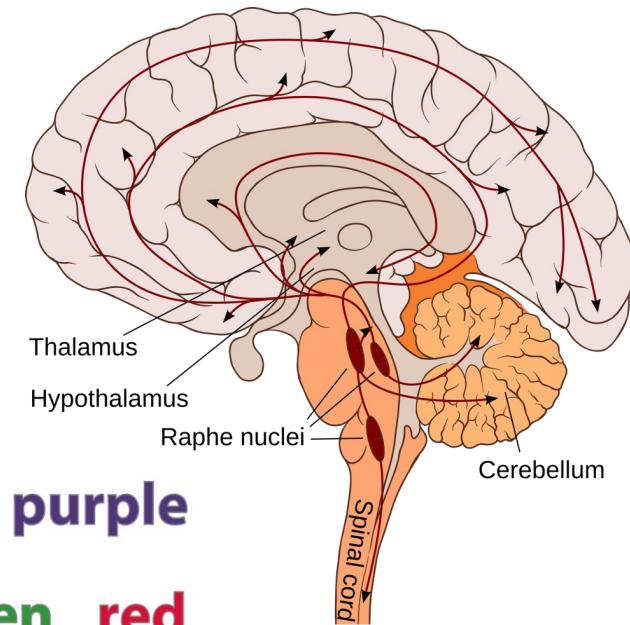
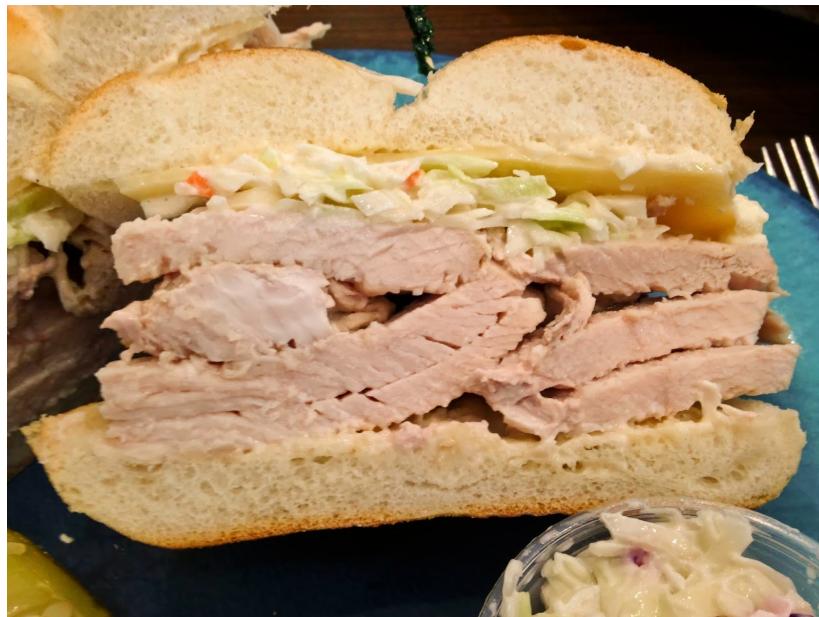


The image shows a screenshot of a CBC Radio news article. The header reads "radio" and "Top Stories". The main headline is "It may be possible to 'alter' memories of heartbreak so they hurt less, research finds". Below the headline, a subtext says "Researcher calls it 'a big step forward' for mental health — but critics warn it could have downsides". At the bottom, it says "CBC Radio · Posted: Dec 02, 2019 5:33 PM ET | Last Updated: December 2". There is also a decorative footer banner with various icons like a laptop, a briefcase, and a lightbulb.

Monoamine neurotransmitters

Serotonin

- Originates from the raphe nuclei (brain stem)
- Projects all over brain, esp. cortex, thalamus, cerebellum
- 15 receptor types, almost all metabotropic
- Precursor: tryptophan
- Serotonin depletion effects (e.g. Young, 2013)



red blue orange purple

orange blue green red

blue purple green red

orange blue red green

purple orange red blue

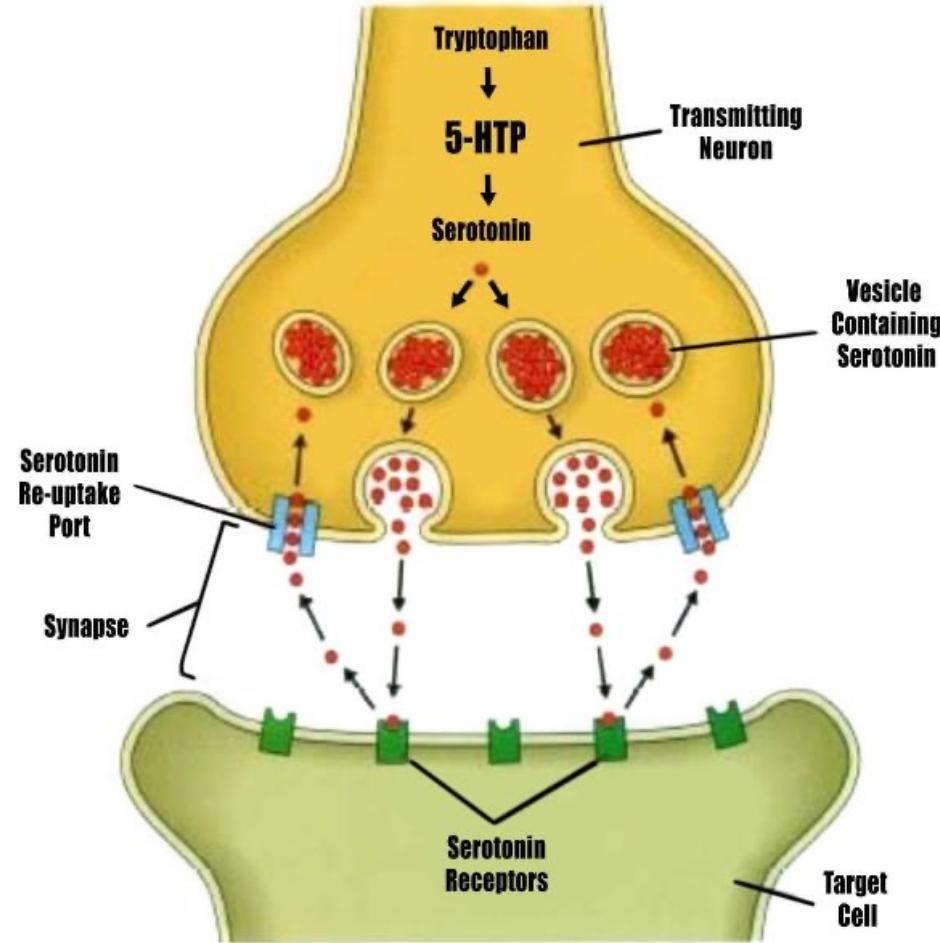
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Stroop task

Monoamine neurotransmitters

Selective Serotonin Reuptake Inhibitors

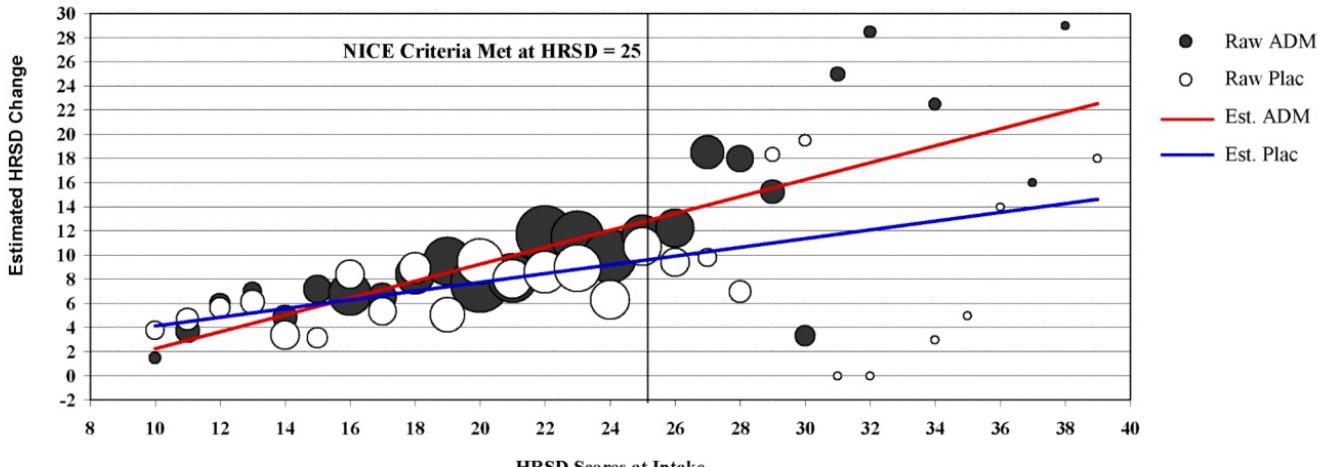
- aka SSRIs, e.g. Prozac (fluoxetine)
- For depression
- “Chemical imbalance”
 - History of monoamines implicated in mood disorders
- Block serotonin from being removed from the synapse
- Effects of SSRIs quick, improvements slow



Monoamine neurotransmitters

SSRI efficacy

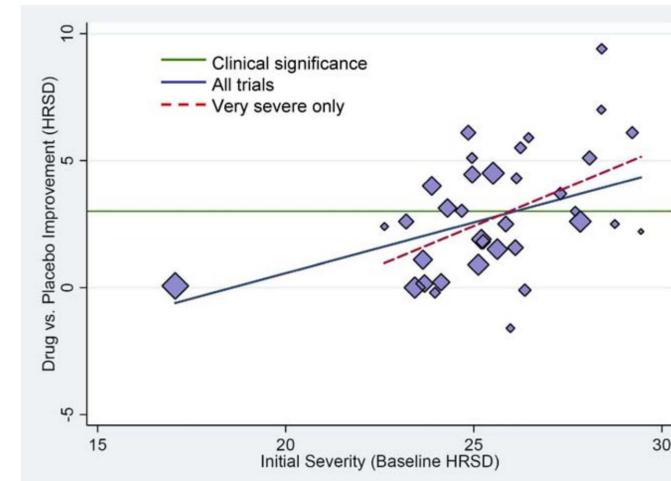
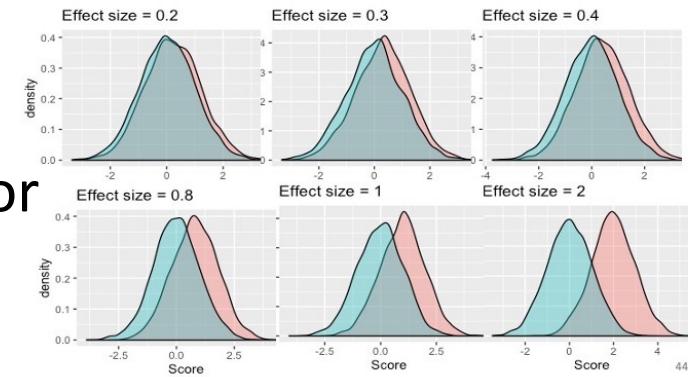
- Original meta-analyses: SSRIs no better than placebo for mild to moderate depression
- May help with major depression
- Effect size is relatively small



Conclusions

Fournier *et al.* 2013

Drug-placebo differences in antidepressant efficacy increase as a function of baseline severity, but are relatively small even for severely depressed patients. The relationship between initial severity and antidepressant efficacy is attributable to decreased responsiveness to placebo among very severely depressed patients, rather than to increased responsiveness to medication.



Kirsch *et al.* 2008

Monoamine neurotransmitters

Hallucinogens

Psychedelic drugs like LSD, DMT, psilocybin etc. are serotonin receptor agonists!

Radical changes to our conscious perception and thoughts, minimal effects on mood (implication?)

Recent reexamination of psychedelics' therapeutic value: end of life care, PTSD, addiction, and more

Serotonin: not simply a "mood molecule"!

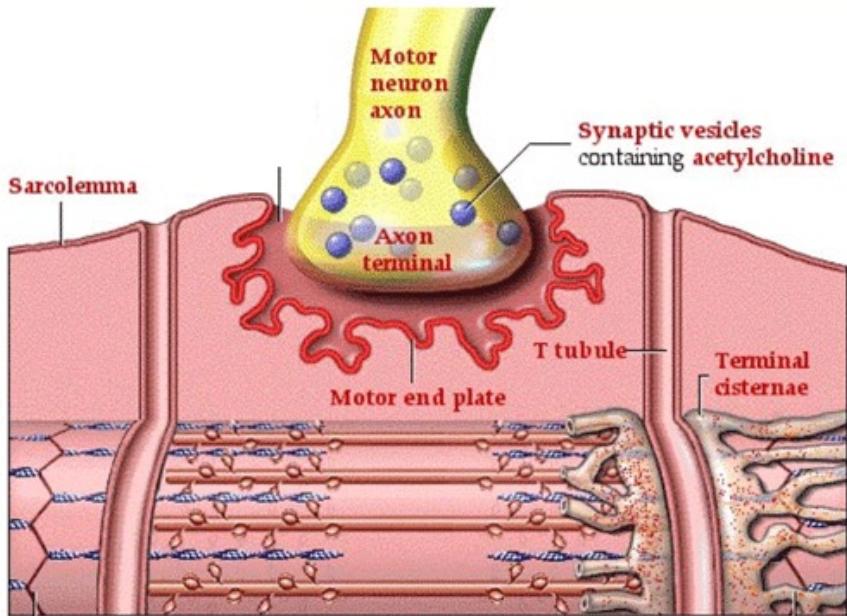


Monoamine neurotransmitters

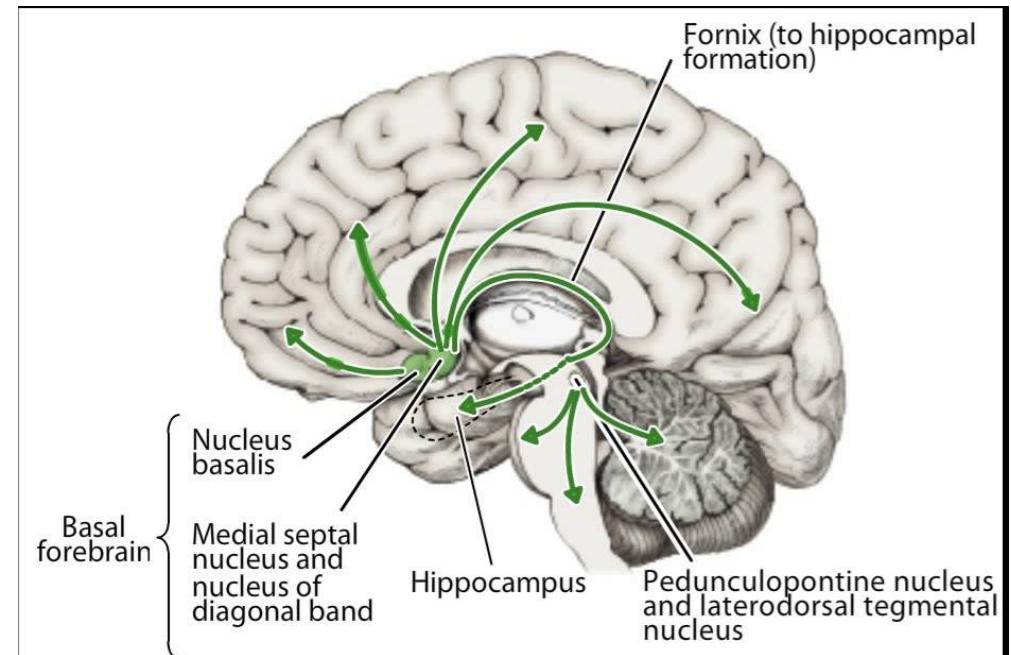
Acetylcholine

- The first discovered neurotransmitter
- The neuromuscular junction
- Also basal forebrain
 - Wakefulness, attention, etc.
- Nicotine: acetylcholine receptor agonist

Neuromuscular Junction



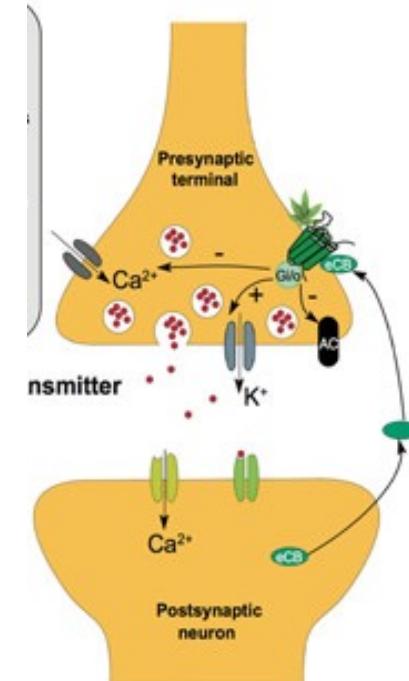
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Other small neurotransmitters

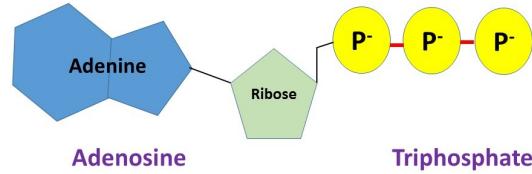
Endocannabinoids

- Two NTs, two receptors (both GPCRs)
- Travel from dendrite to axon, i.e. **retrograde transmission**
- Weaken connection between two cells at a synapse
- THC (in cannabis) is a cannabinoid receptor agonist
 - CBD (also in cannabis) is a less clear story

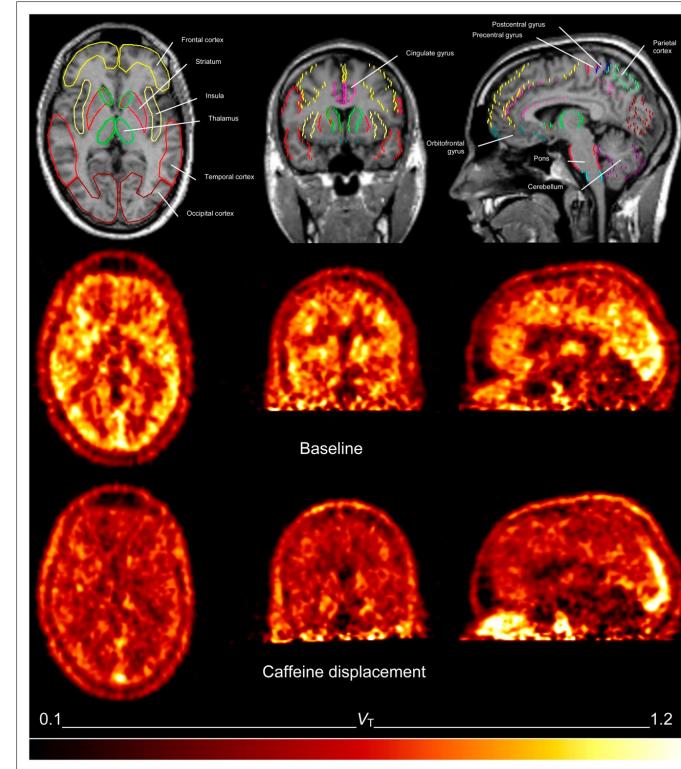
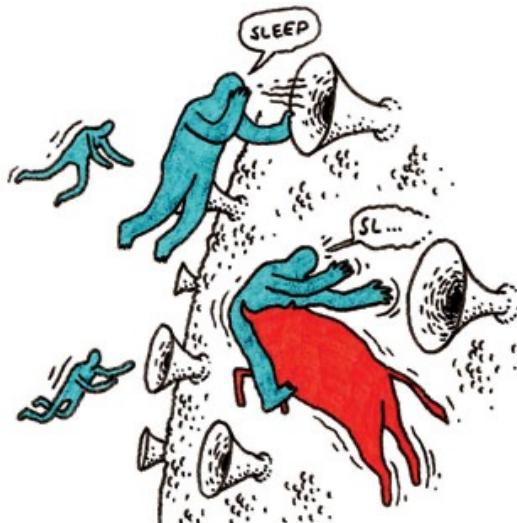


Other small neurotransmitters

Adenosine



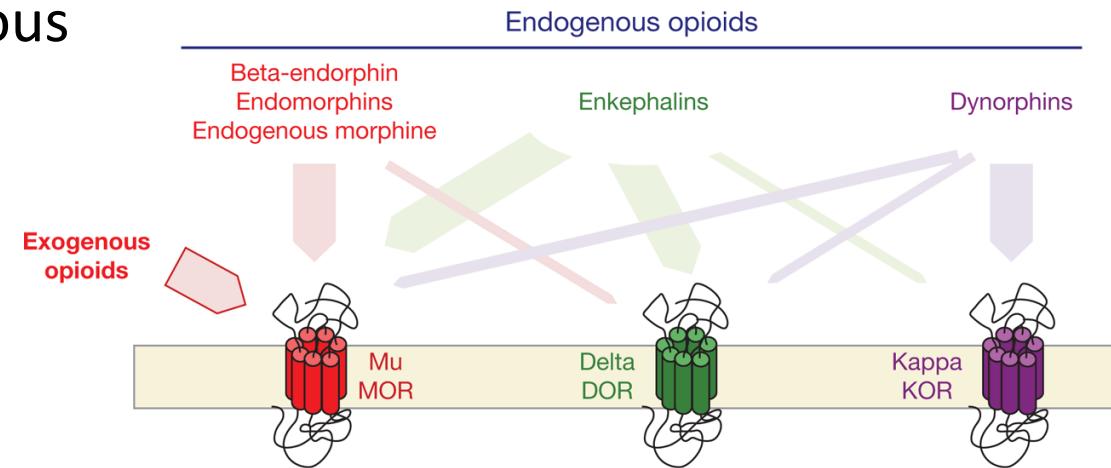
- Remember: ATP is cellular energy
- Adenosine is ATP byproduct
- Adenosine receptors
- Caffeine/theophylline



Other small neurotransmitters

Endogenous opioids

- aka Endorphins
- Giant peptide neurotransmitters
- Receptors are all GPCRs
- Many NT and receptor types/subtypes
- The neurotransmitter system that exogenous opioids (e.g. heroin) mimic
- Fentanyl and naloxone
- Receptors found in spinal cord, periacqueductal grey (PAG), nucleus accumbens, more



Large molecule neurotransmitters