Neuropharmacology and substance use

Why does someone try a substance/drug?

Terms

- Drugs: Chemical substances that arise from outside the body (exogenous) that can impact a person's physical or mental state
- Neuropharmacology: The study of drugs that affect the nervous system
- Pharmacodynamics: Effect of drugs on the body
- Pharmacokinetics: Effect of the body on the drugs

Common routes of drug administration

- Enteral (must be absorbed through GI tract)
  - Oral
  - Rectal
  - Sublingual
  - Transbuccal
- Parenteral (avoids GI tract)
  - Intravenous
  - Intramuscular
  - Subcutaneous
  - Inhalation
  - Insufflation
  - Transdermal
  - Topical

Impact of GI tract

- Substances ingested orally are absorbed through gut wall and into the hepatic portal system
- This blood is passed through the liver (the body's filter)
- Variety of degradation enzymes destroy some of the drug OR prodrug is enzymatically activated
  - e.g., psilocybin -> psilocin
- Then the drug enters the rest of the circulation to impact the body
- This process is called first-pass metabolism
- Other enteric routes are less impacted by first-pass administration

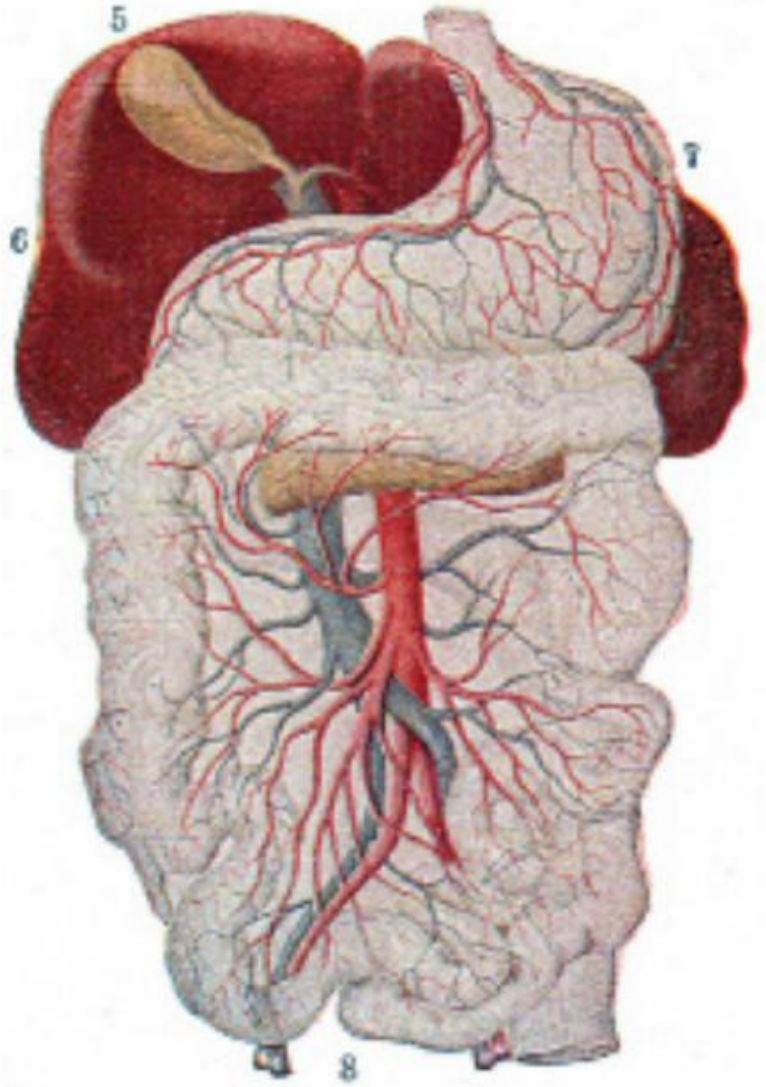


Figure 11.2 The hepatic portal system moves substances taken orally through the liver for enzymatic processing before entering total circulation.

Aside: Detoxes

- https://www.health.harvard.edu/staying-healthy/the-dubious-practice-of-detox

A few comments about parenteral administration methods

- Subcutaneous: only works for lipid-soluble drugs
- Inhalation: rewarding sensations of inhalant misuse are often due to hypoxia
- Insufflation: word for snorting drugs

Drug interactions

Aside: David Bailey was also the first Canadian to run a four-minute mile!

- What are they?
- In 1989, pharmacologist David Bailey (et al.) were investigating interactions between ethanol (alcohol) and blood pressure medication
- They wanted to mask group assignment and used grapefruit juice to hide the taste of alcohol
- Methods:
- Results: Groups that had also consumed grapefruit juice had extremely high bioavailability of the blood pressure meds, risking overdose
- No interaction with alcohol!
- The bioavailability of the blood pressure meds was 108-469% higher when taken with grapefruit juice compared to water

Impact of grapefruit: Mechanism

- Drugs can interact with foods to change their effectiveness
- The chemical bergamottin is found in grapefruits
- Bergamottin inhibits activity of a class of enzymes in the liver and small intestines that metabolize cytochrome P450s (CYP)
- Can increase or decrease a drug's potency
  - Less degradation of the prodrug codeine into morphine
  - More degradation of anti-anxiety drug buspirone, allowing more to be able to able to impact the brain
- Read the labels on your Rx!

Neural circuitry involved in reward

- Sense of reward is a highly adaptive trait
- Motivates behaviours important for survival and reproduction
- Circuits are highly conserved through evolution (similar in many species)

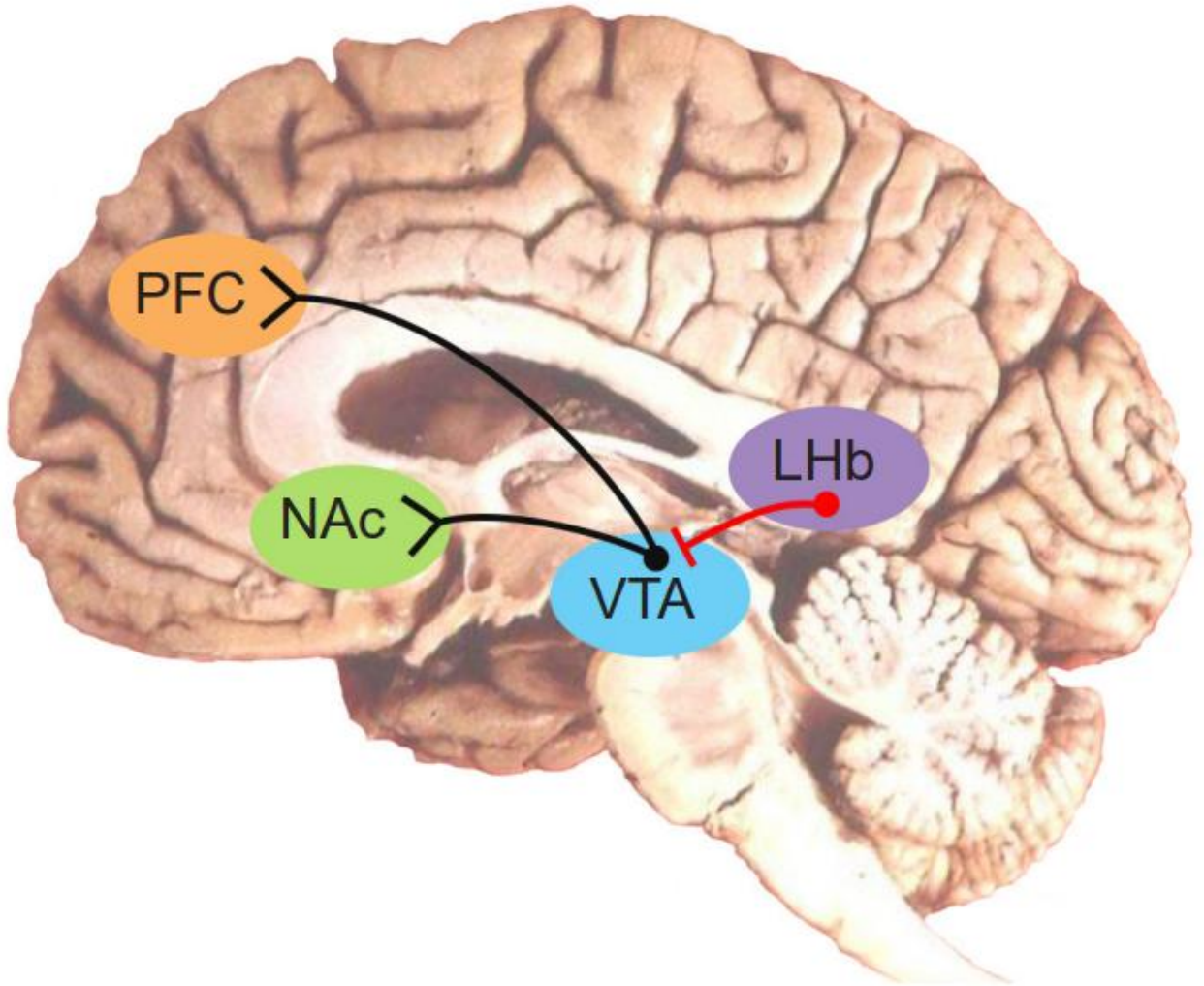
PFC: Prefrontal cortex

NAc: Nucleus accumbens (part of ventral striatum)

VTA: Ventral tegmental area

LHb: Lateral habenula

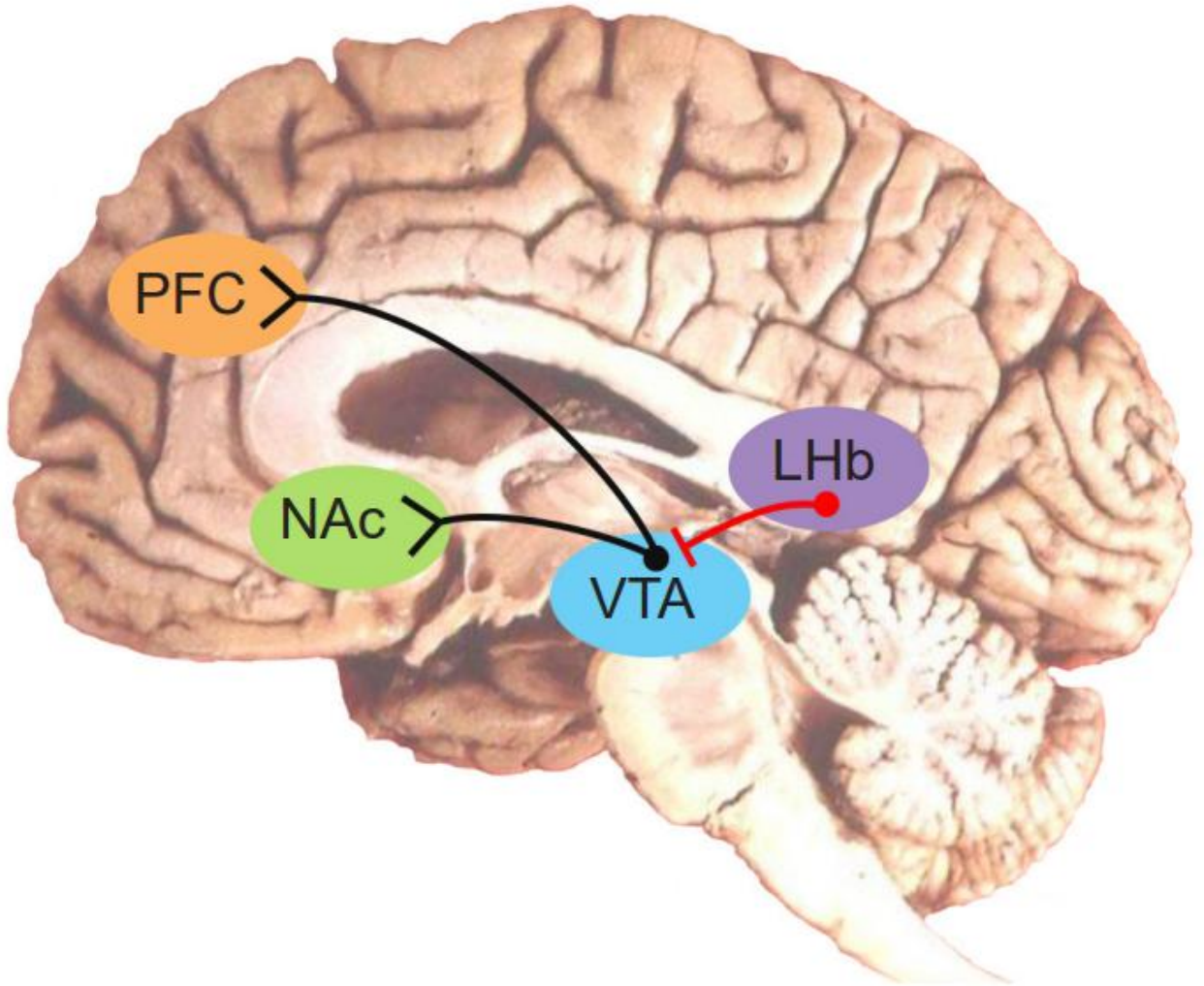
Figure 11.7 Neural structures involved in reward and aversion.



Ventral tegmental area

- Contains neurons that synthesize dopamine (A10 neurons)
- Send projections to
  - nucleus accumbens (mesolimbic or reward pathway)
  - prefrontal cortex (mesocortical pathway, important for decision making)

Figure 11.7 Neural structures involved in reward and aversion.



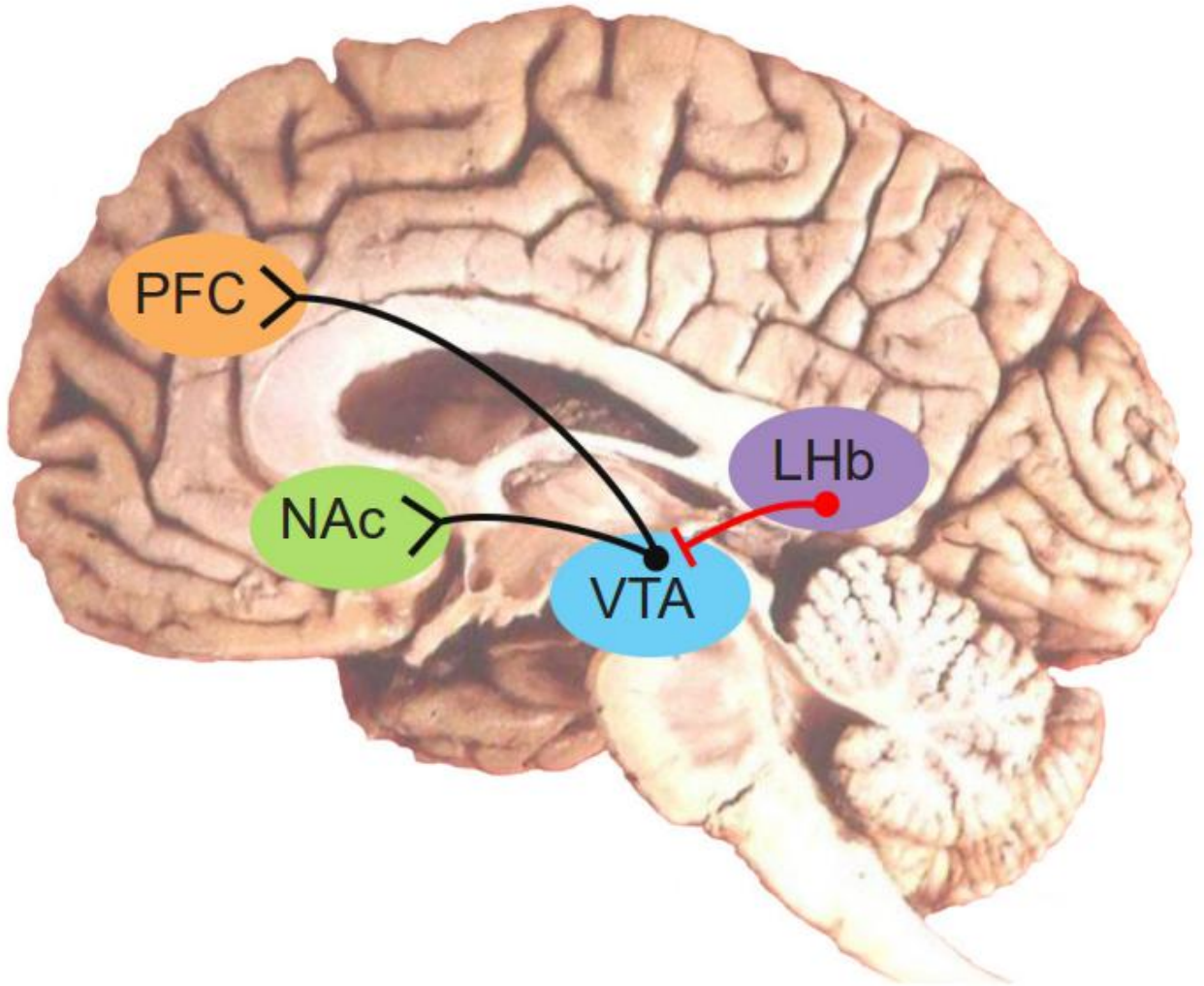
Neuroscience method: Microdialysis

- Insert cannula to measure neurotransmitter concentration in a given brain region
- Rats engaged in rewarding activities (e.g., eating, sex) have increased dopamine concentrations in the NAc
- What method could we use to study dopamine concentration in different brain regions in healthy humans?

Aversion (anti-reward) pathway

- Lateral habenula sends GABA projections onto the VTA dopaminergic neurons
- Reduces DA in the NAc

Figure 11.7 Neural structures involved in reward and aversion.



Molecular pharmacodynamics

- Remember: molecules move randomly
- Stochastic

Dose-response curve

- S-shaped (sigmoidal)

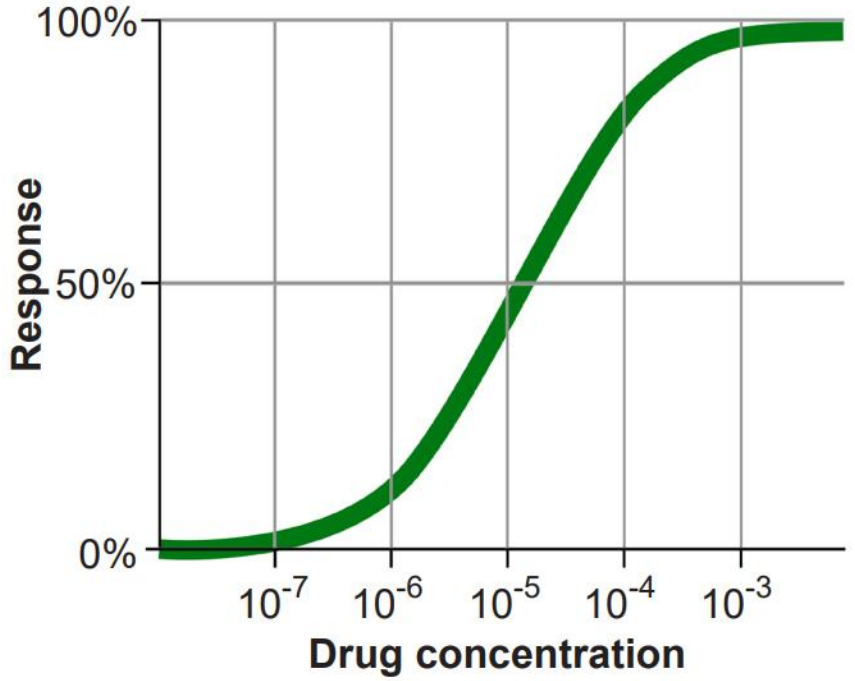


Figure 11.9 Generic dose response curve showing that drug effect (y-axis) increases as the dosage of drug (x-axis) increases.

Categories of ligands

- Agonists
- Antagonists
- Allosteric modulators

Agonists

- Activate receptors by binding to orthosteric (or active) site
- Lock and key analogy
- **Full agonist:** activates receptor to maximal degree at high concentrations
- **Partial agonist:** does not fully activate receptor at any concentration
- **Inverse agonist:** causes opposite reaction as agonist

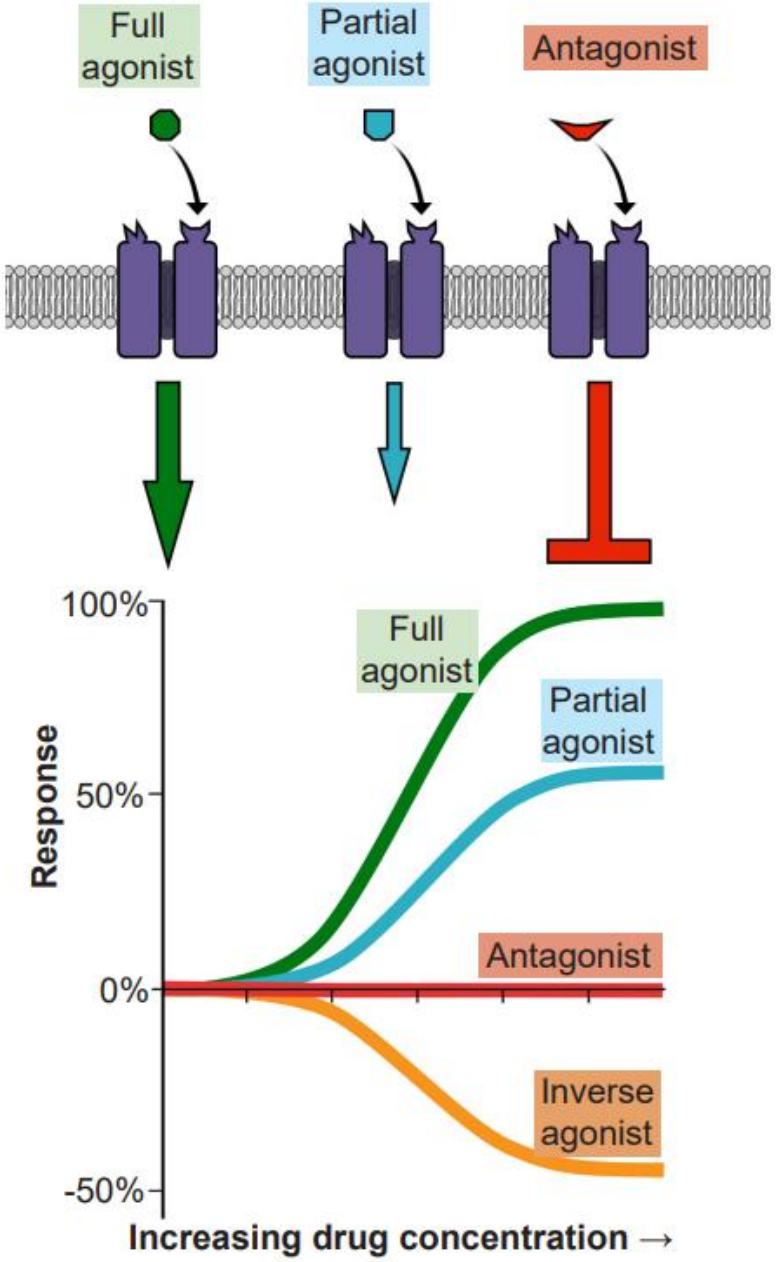


Figure 11.10 Different classes of ligands and their action on the receptors.

Antagonists

- Prevent agonists from acting
- Competitive antagonists: bind to active site and physically block it
- E.g., Narcan (naloxone)

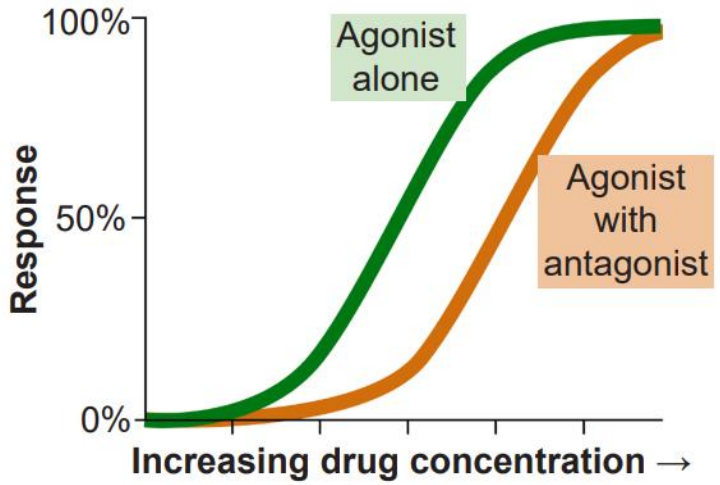


Figure 11.11 Dose response curves for agonist and for agonist plus competitive antagonist.

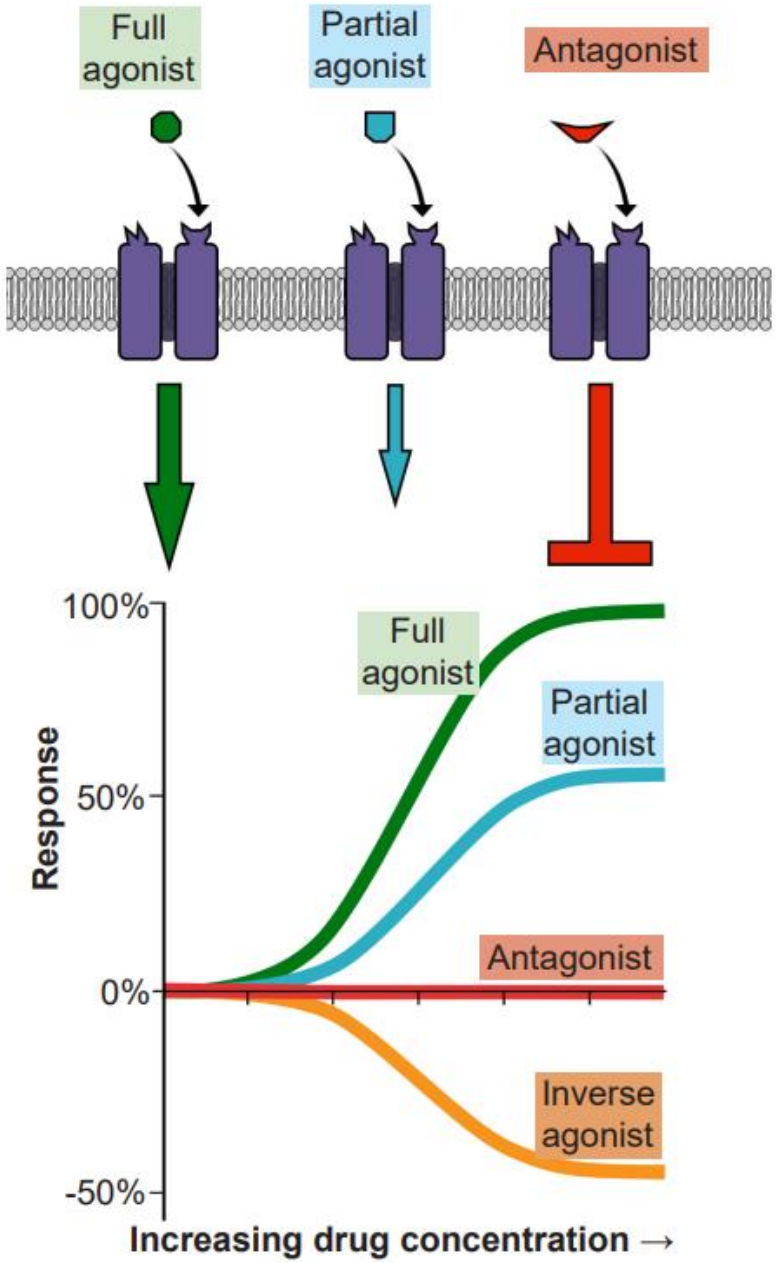


Figure 11.10 Different classes of ligands and their action on the receptors.

How are inverse agonists different from competitive antagonists?

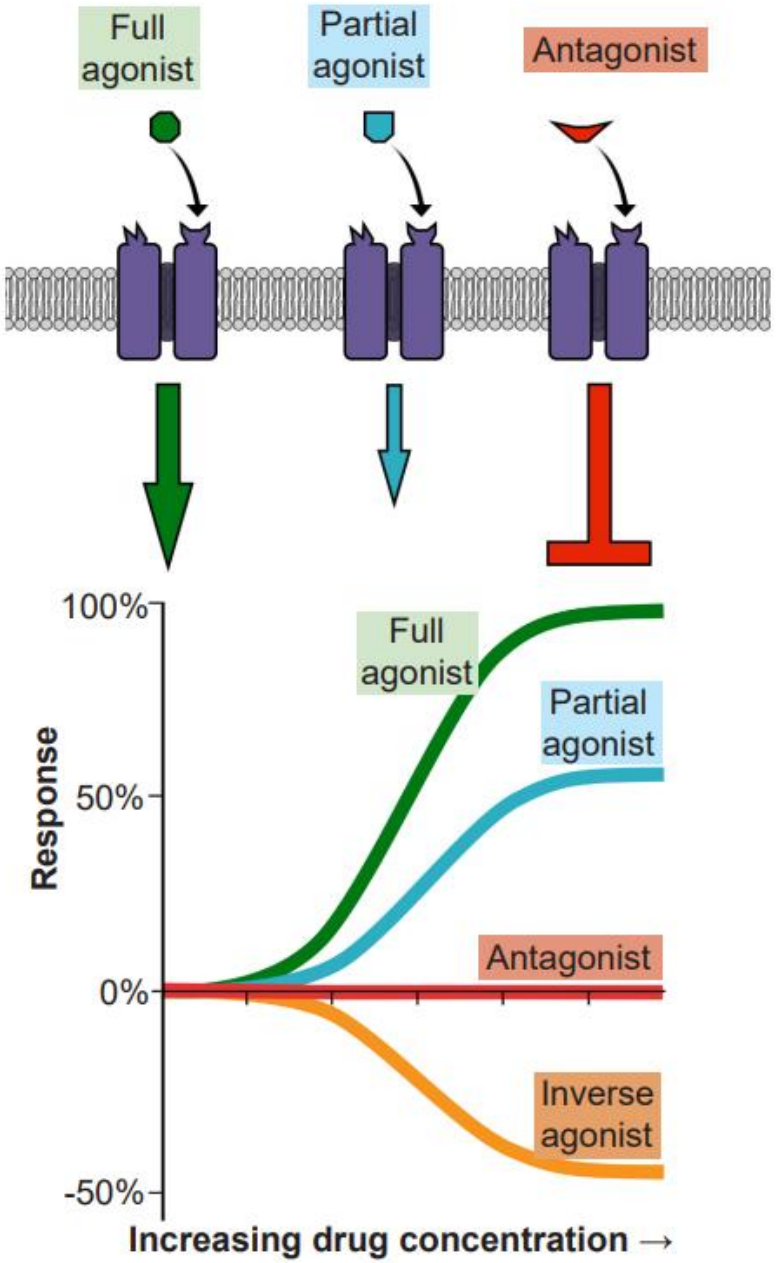
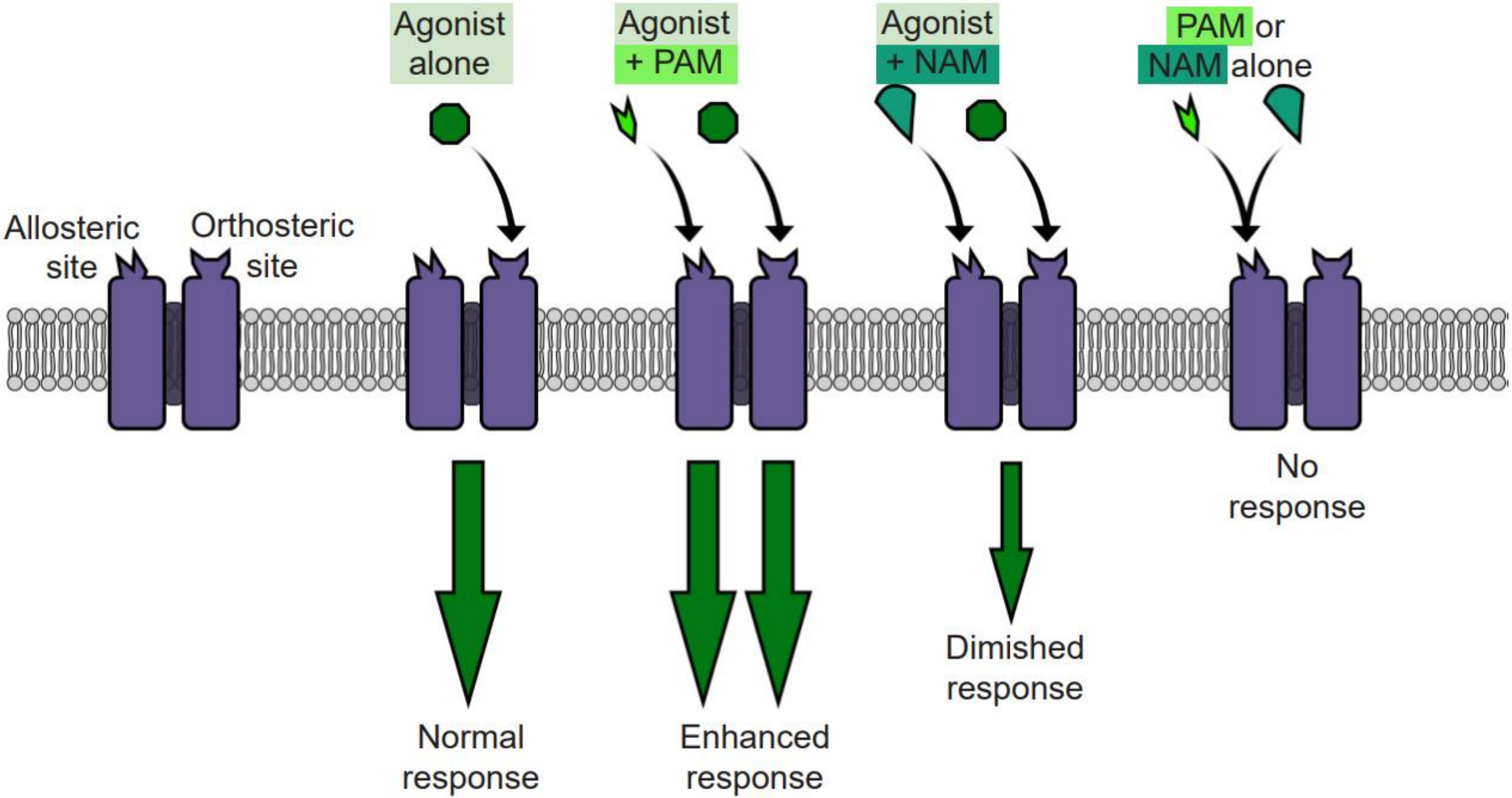


Figure 11.10 Different classes of ligands and their action on the receptors.

Allosteric modulators

- Bind to allosteric site on receptor to impact effect of agonist
- E.g., Benzodiazepine increase’s GABA’s impact

Figure 11.12 A receptor interacting with an allosteric modulator changes it's response following agonist binding to the orthosteric site.



Dirty drugs

- Single drug can have different actions at different classes of receptors
- E.g., antipsychotic clozapine is an antagonist at some dopamine and serotonin receptors, as well as a partial agonist of a different population of serotonin receptors

Commonly misused substances

What does it mean to misuse a substance?

Alcohol

- https://www.ccsa.ca/canadas-guidance-alcohol-and-health
- Used very widely
- Leading risk factor for premature death among males 15-59 globally (WHO)
- Low concentrations: improve mood, decrease anxiety, increase risk taking, slow reflexes, impair judgement
- High concentrations: memory deficits, loss of consciousness, analgesia, areflexia, respiratory depression & death
- Acts on GABA receptors, glutamate receptors, potassium channels, serotonin receptors, and more
- Depressant effect on neurons (but activates dopaminergic neurons in the VTA)

Nicotine

- Main psychoactive chemical in tobacco products
- Tobacco use kills 46000 Canadians each year
- Stimulant; agonist of nicotinic ACh receptors (excitatory, ionotropic receptors)
- Activates the sympathetic nervous system to induce release of norepinephrine
- Nicotine can promote cancer progression but is not a carcinogen
- Smoking rates decreasing among young people, but vaping is on the rise

Cannabis

- Contains several psychoactive substances, with the main one being delta-9-tetrahydrocannabinol (THC)
- Activates cannabinoid receptors
- CB1: Psychoactive

Warning labels

- Dr Kara Thompson
- Right here at StFX

Opioids

- **Opiate**: natural compounds derived from the poppy plant, such as heroin or morphine
- **Opioid**: natural **or** derived in a lab
- **Endorphin:** Most well-known endogenous substances that activates opioid receptors
- Analgesic (pain reliever)
- Feelings of euphoria
- “Opioid drugs the current gold standard for pain relief.”
- https://pubmed.ncbi.nlm.nih.gov/35717988/

Opioid epidemic

- https://health-infobase.canada.ca/substance-related-harms/opioids-stimulants/
- https://journalofethics.ama-assn.org/article/how-fda-failures-contributed-opioid-crisis/2020-08 (USA focused)
- https://www.cbc.ca/news/canada/british-columbia/class-action-lawsuit-opioids-certified-1.7438995

Cocaine

- Sympathomimetic – activates the sympathetic nervous system
- Reuptake inhibitor
  - Physically prevents presynaptic transporters from clearing dopamine, norepinephrine, and serotonin out of the synapse
  - Elevates their levels in the synapse
  - Greater chance they will activate postsynaptic receptors

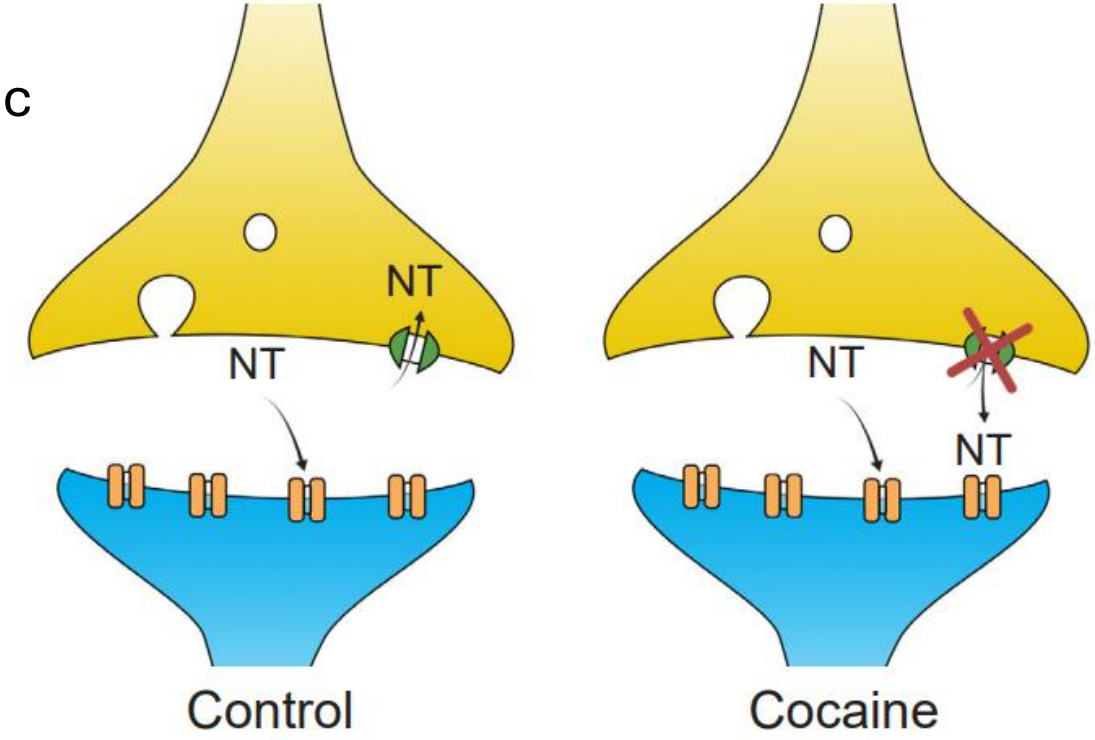


Figure 11.20 Cocaine blocks reuptake of neurotransmitters, increasing signaling.

Cocaine

- Acts directly on dopamine (among other neurotransmitters)
- Medicinal applications
  - Local anesthetic
  - Vasoconstrictor
  - Used in surgeries

Psychedelics

- Formally called hallucinogens
- Examples
  - Psilocybin: made from mushrooms
  - Lysergic acid diethylamide (LSD): synthetic
- Cause visual distortions, synesthesia, altered sense of self
- Cultural significance
- Potential therapeutic applications under investigation
  - PTSD, depression associated with a terminal illness, and substance use disorder

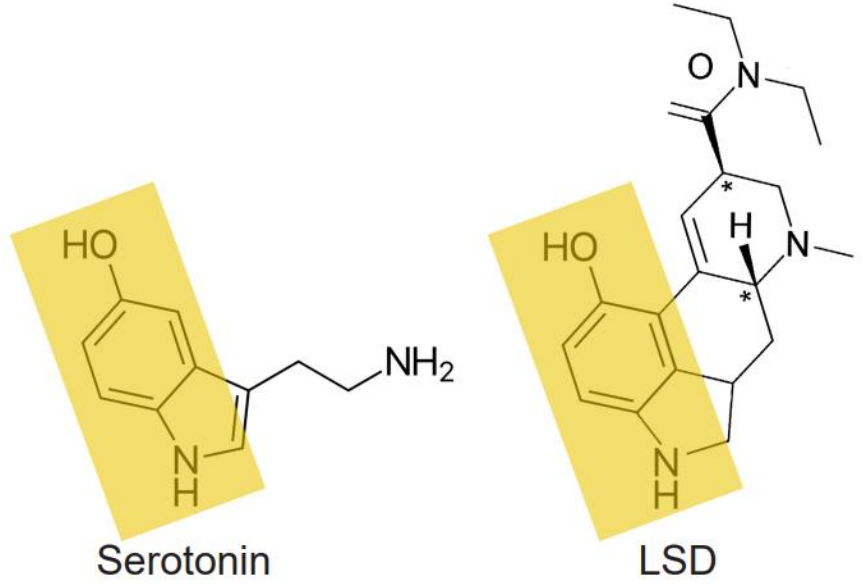
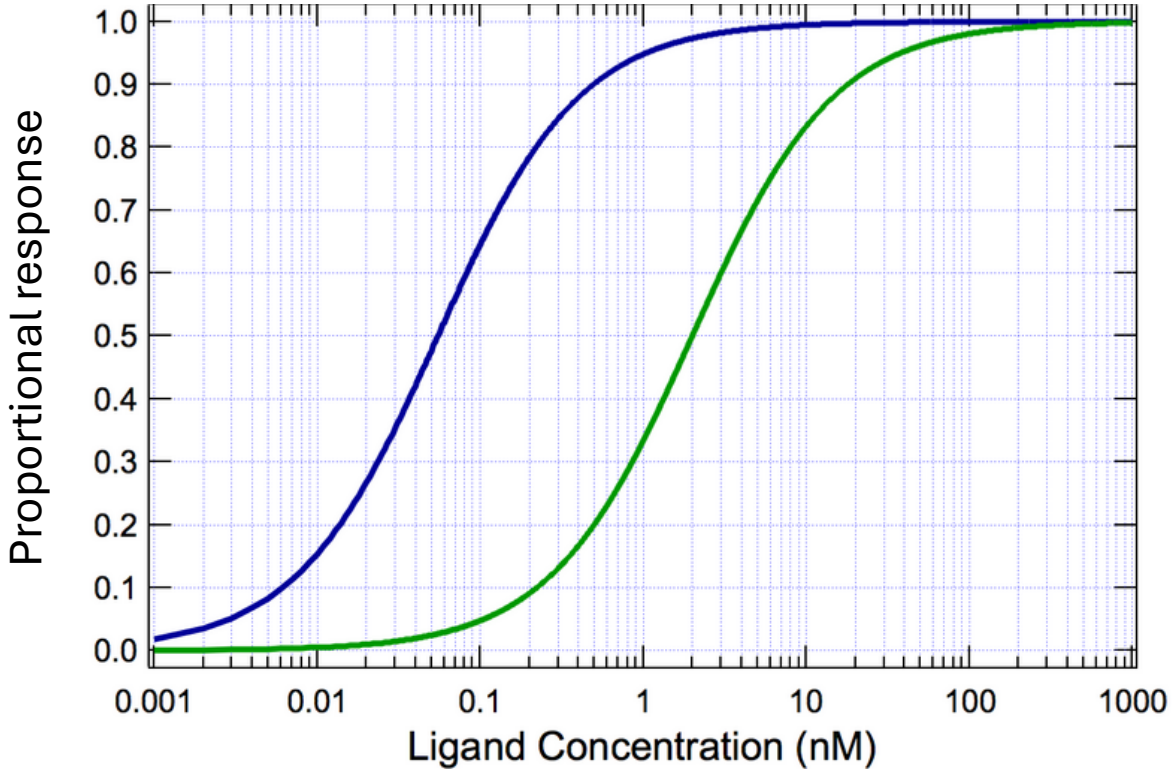


Figure 11.21 LSD is chemically very similar to the endogenous neurotransmitter serotonin.

Tolerance

- Decrease in action of a drug due to repeated exposure
- Mechanism: Homeostatic adaptations
- Result: Same effect can only be achieved with higher doses (i.e., rightwards shift of the dose response curve)



Forms of tolerance: Metabolic

Differences in enzyme activity also explain genetic variations in alcohol sensitivity

- Body becomes more efficient at eliminating the substance
- Less substance able to get to site of action
- Usually due to an increase in the activity or number of enzymes degrading the substance

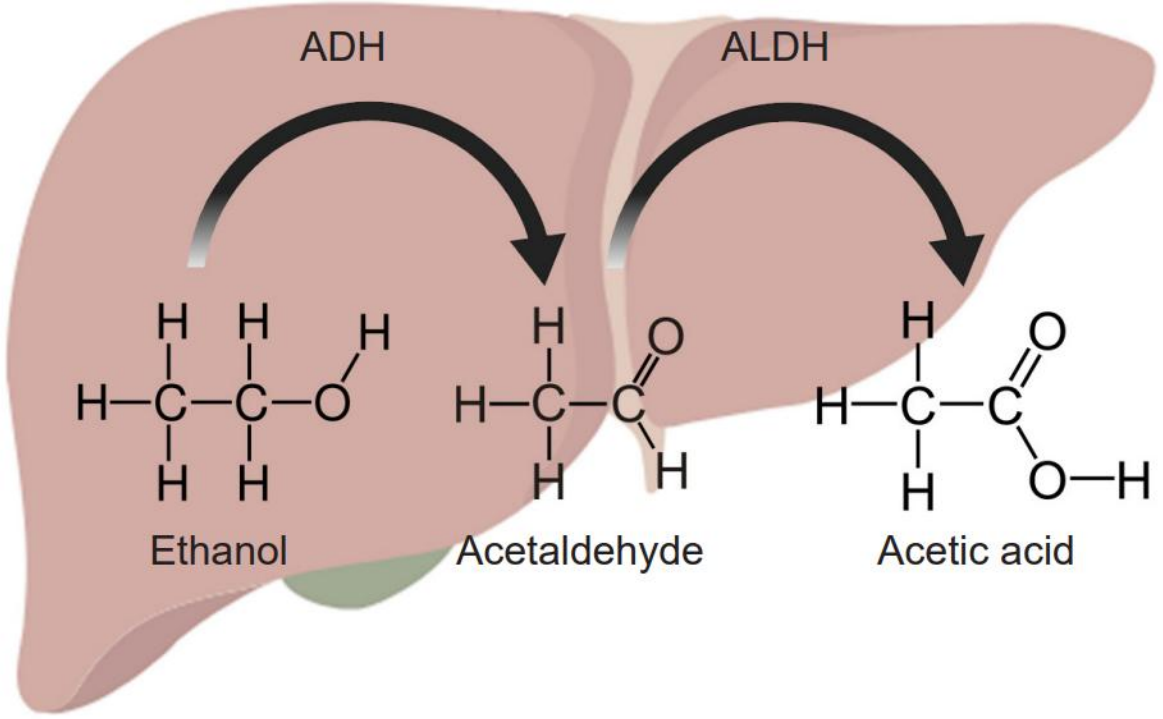
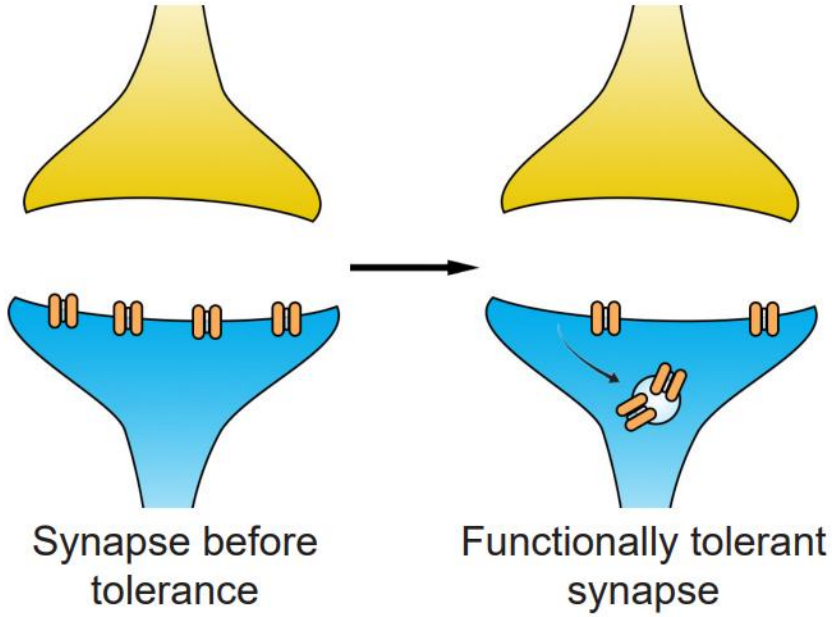


Figure 11.22 The liver breaks down alcohol in a two-step enzymatic process. Frequent alcohol use upregulates the speed by which degradation happens, causing tolerance.

Forms of tolerance: Functional

- Decrease in receptor expression after chronic exposure to an agonist



Forms of tolerance: Conditional

- Body initiates an opposite somatic effect from what the substance is expected to do
- Anticipatory bodily changes in the reverse direction
- Protective mechanism
- Unconscious form of learning also know as … ?
- Can be lethal

Reverse tolerance

Interpreting the graph: What are the black and red circles?

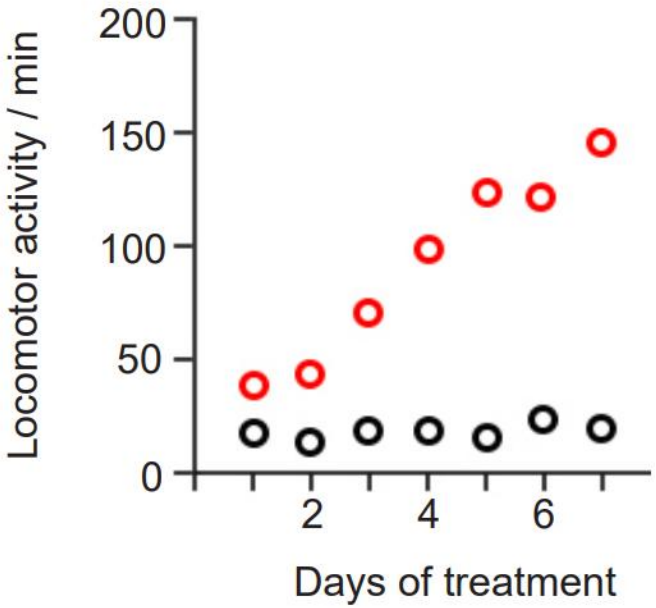


Figure 11.24 A rat exposed to amphetamine over multiple days shows locomotor sensitization, an increase in activity in response to drug.

- Can also occur conditionally
- Mechanisms vary
  - Example: reverse tolerance to alcohol can occur after excessive drinking damages liver, reducing its ability to metabolize alcohol

More: https://en.wikipedia.org/wiki/Reverse_tolerance

Different types of tolerance can occur to different effects of the same drug

- Think about dirty drugs

Cross tolerance

- Tolerance to one substance can result in tolerance to another, even if the 2nd substance has never been administered before
- Example: Alcohol tolerance will result in tolerance to benzodiazepines (CNS depressant used to treat anxiety and seizures)

Other terms (mix and match)

- Pharmacodynamic tolerance
- Pharmacokinetic tolerance
- Sensitization
- Drug-induced neuroplasticity

Withdrawal

- Set of symptoms experienced when abstaining from a substance
- Frequently the opposite of the effects of the substance
- Caused by long-lasting homeostatic changes associated with tolerance
- Highly aversive state that can be relieved by administering substance
- Urge to take the drug during withdrawal symptoms is a sign of **dependency**

Tolerance and withdrawal from antagonists

- Example: Caffeine

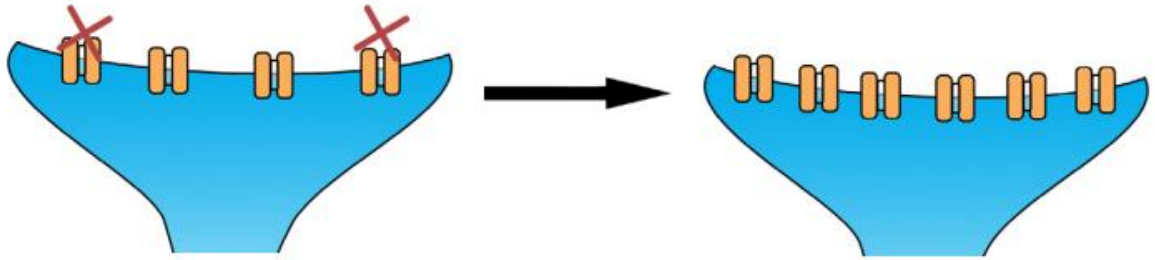


Figure 11.25 The regular presence of an antagonist like caffeine may cause increases of adenosine receptor levels postsynaptically.

Dependency

- Physical dependency: somatic symptoms associated with tolerance and withdrawal
- Psychological dependency: “where the person has intense cravings for the drug such as a fixation on drug acquisition, or mood or behavioural changes in the absence of drug”
- **Discussion**: Is it meaningful to distinguish between physical and psychological dependency? Why or why not?

Theories of addiction

Terminology

- Substance use disorder
- Compulsive gambling or gambling disorder

- Notes:
  - Food addiction
    - Not in the DSM-5
  - Compulsive sexual behaviour disorder
    - In the International Classification of Diseases (ICD-11) of the WHO
    - Not considered an addiction
    - Not in the DSM-5

Individual differences

- Susceptibility to substance use disorder varies between individuals
- Area of active investigation in order to generate new treatments for substance use disorder

Models of substance use disorder

- Self-administration paradigm
- Conditioned place preference

Self-administration

- Operant conditioning
- Monkeys given unrestricted access to cocaine will self-administer themselves to death
- Rodents will endure negative consequences such as foot shock to self-administer cocaine or morphine

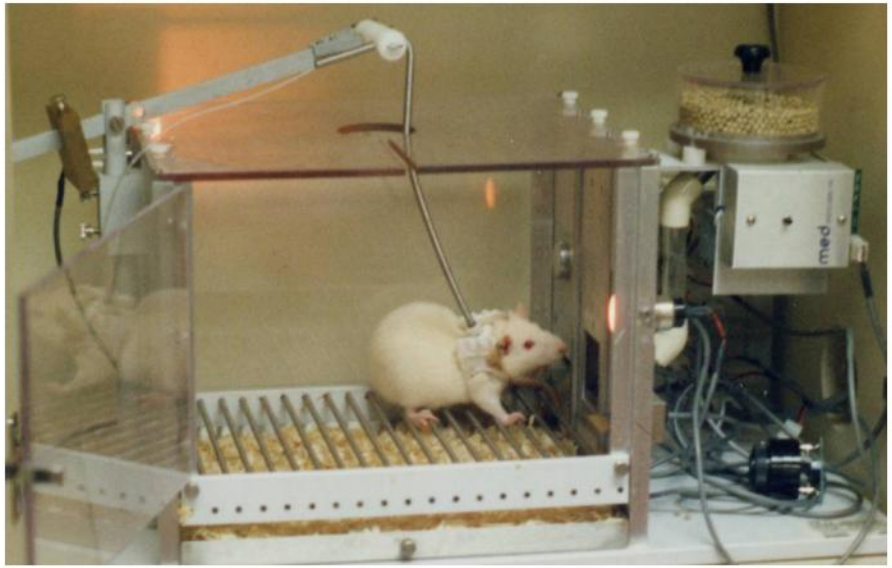
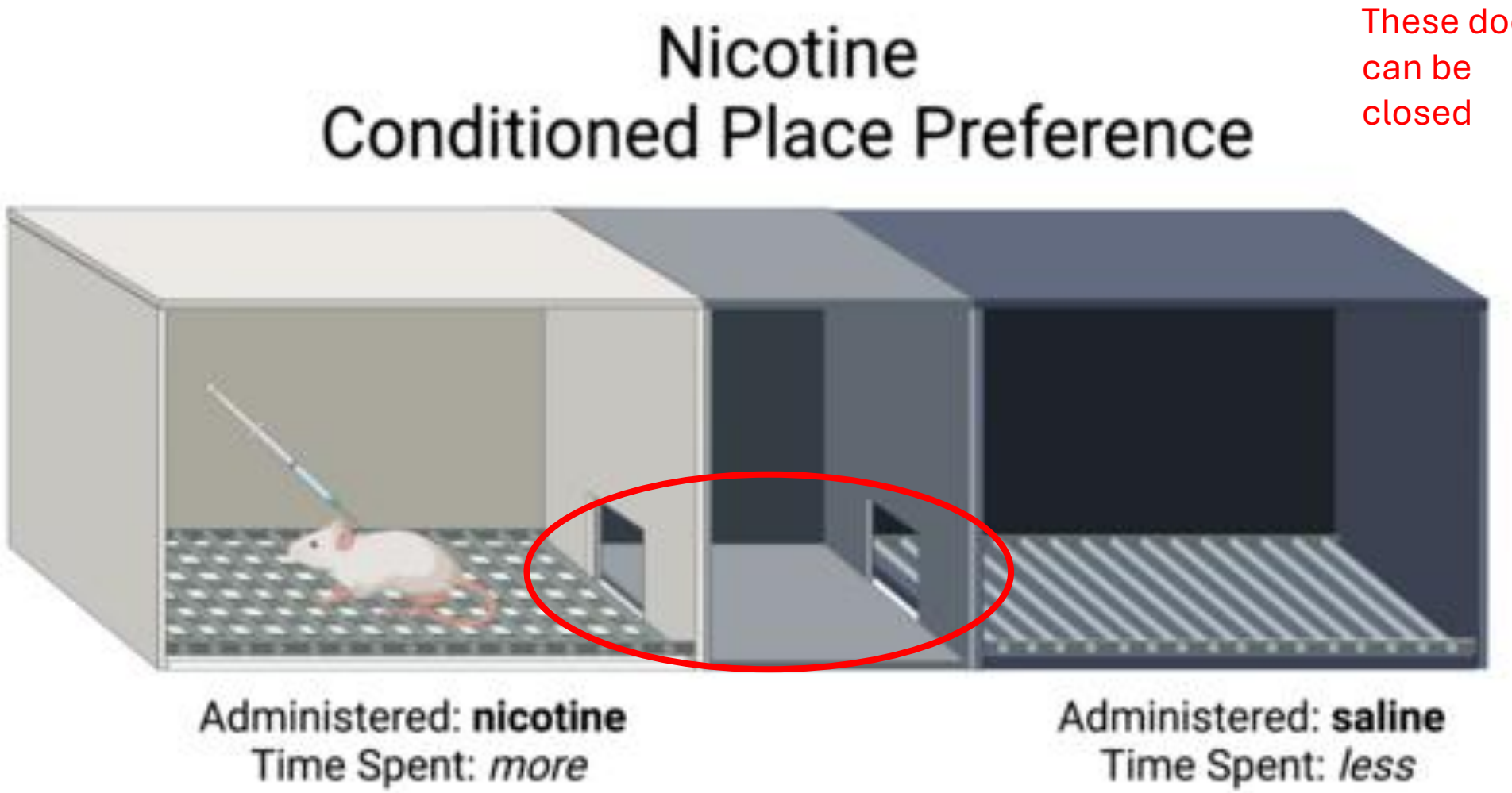


Figure 11.26 In a Skinner box, animals can be trained to give themselves a variety of drugs.

Conditioned place preference



These doors can be closed

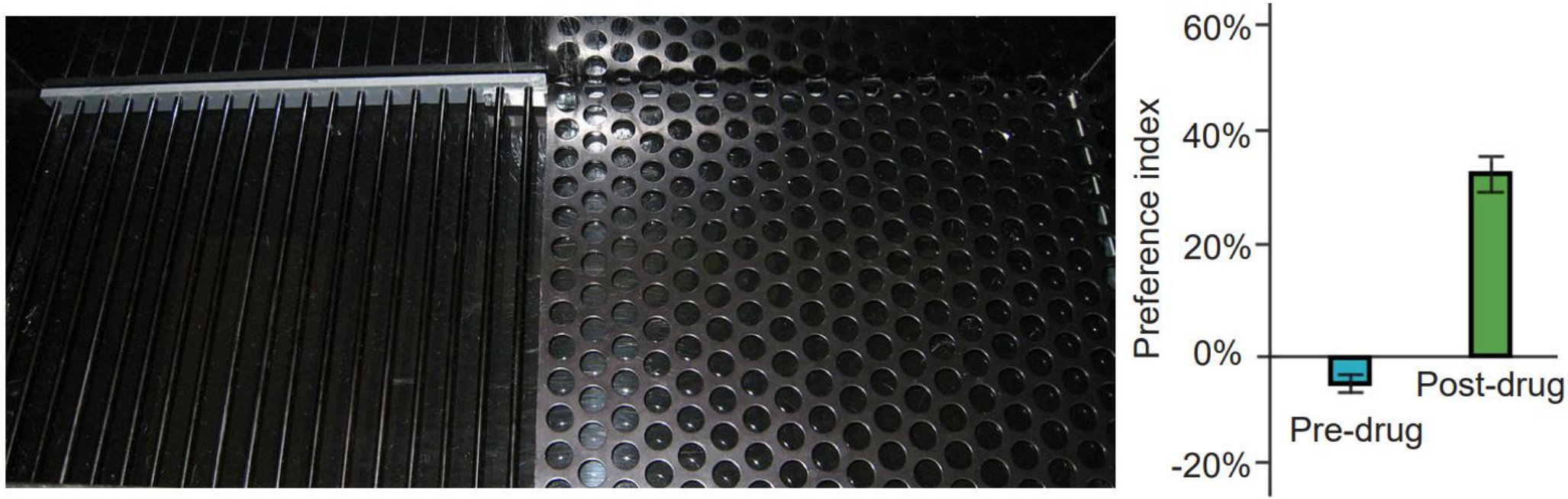


Figure 11.27 In a conditioned place preference test, increased time spent (preference index) in a chamber previously paired with drug is interpreted as an increase in drug liking.

Comparing models

- Which model measures drug seeking? Which measures drug liking? How do you know?
- What is the difference between liking and wanting?

Hedonia hypothesis

- **Context:** Dopamine is the “pleasure neurotransmitter”
- **Hedonia hypothesis:** all substances that can result in substance use disorder increase dopamine
- **Evidence for:**
  - Microdialysis studies found increased dopamine release in the the mesolimbic pathway with many substances associated with substance use disorder
- **Evidence against:**
  - Some stimulants increase dopamine without a concurrent rewarding sensation (so then, is dopamine really the “pleasure” chemical?
  - Blocking dopamine receptors isn’t an effective approach to preventing cocaine use disorder

Incentive sensitization model

- Initial liking of drug followed by period of wanting drug
- Increased sensitivity to drug-related cues
- Exposure to cues can trigger substance use relapse
- According to this model, what behaviour would you predict
  - in the self administration paradigm?
  - in the conditioned place preference paradigm?

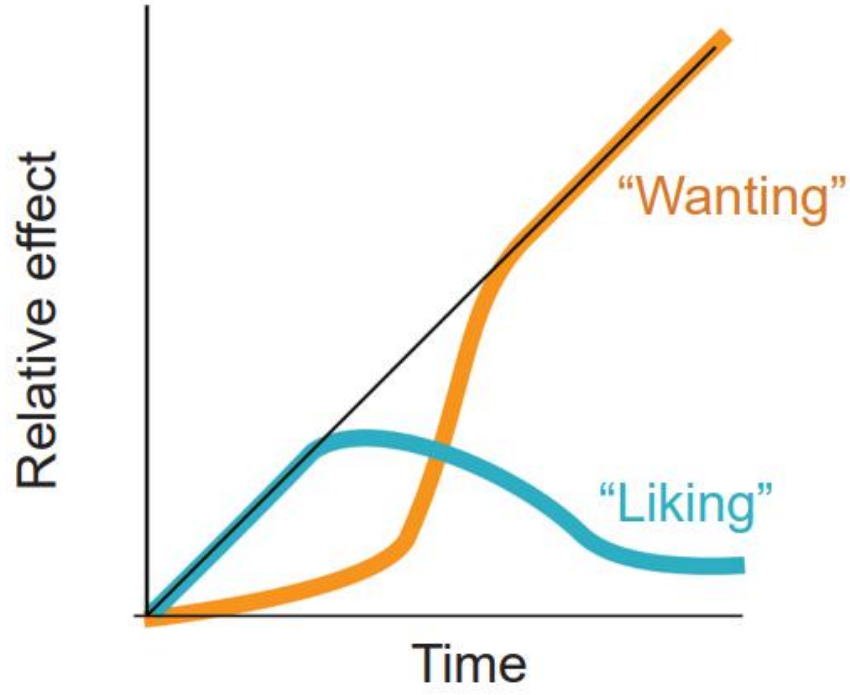


Figure 11.28 The incentive sensitization model suggests a difference between "wanting" and "liking" the effects of a drug.

Incubation of craving

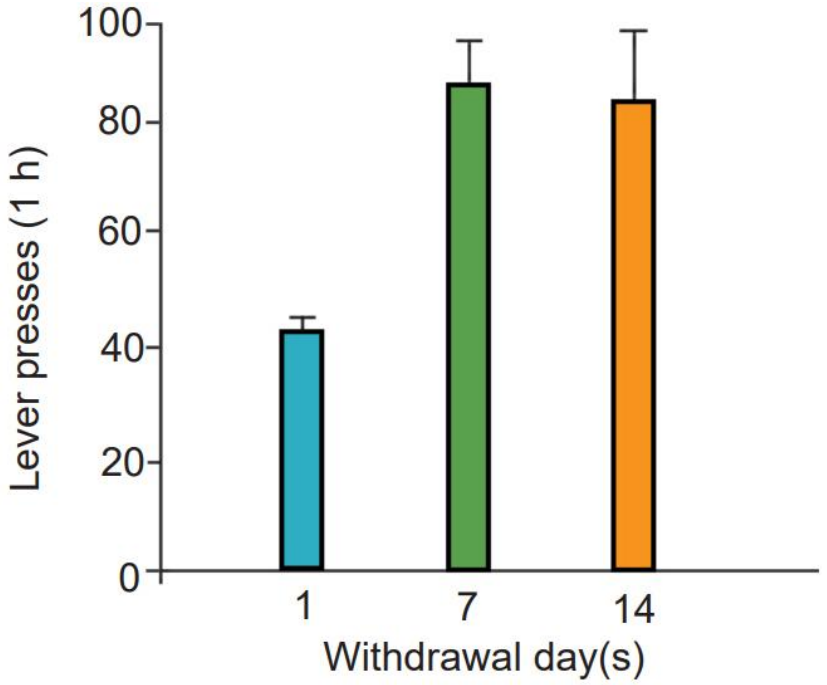


Figure 11.29 In a self-administration paradigm, lever pressing increases the longer an animal is abstinent from drug.

Brain disease model of addiction

- Acknowledges role of genetics
- De-emphasizes concept of “willpower” (Definition of willpower? Mechanism of willpower?)
- Emphasizes impact of neural circuitry
- Public health policy implications
- Evidence against:
  - “Most people stop their addictive patterns by themselves spontaneously without any treatment”
  - The Brain disease model of substance use disorder “has not produced a successful therapeutic strategy to help with addiction”

- FACT CHECK

Fact check: **Most** people stop their addictive patterns by themselves spontaneously without any treatment

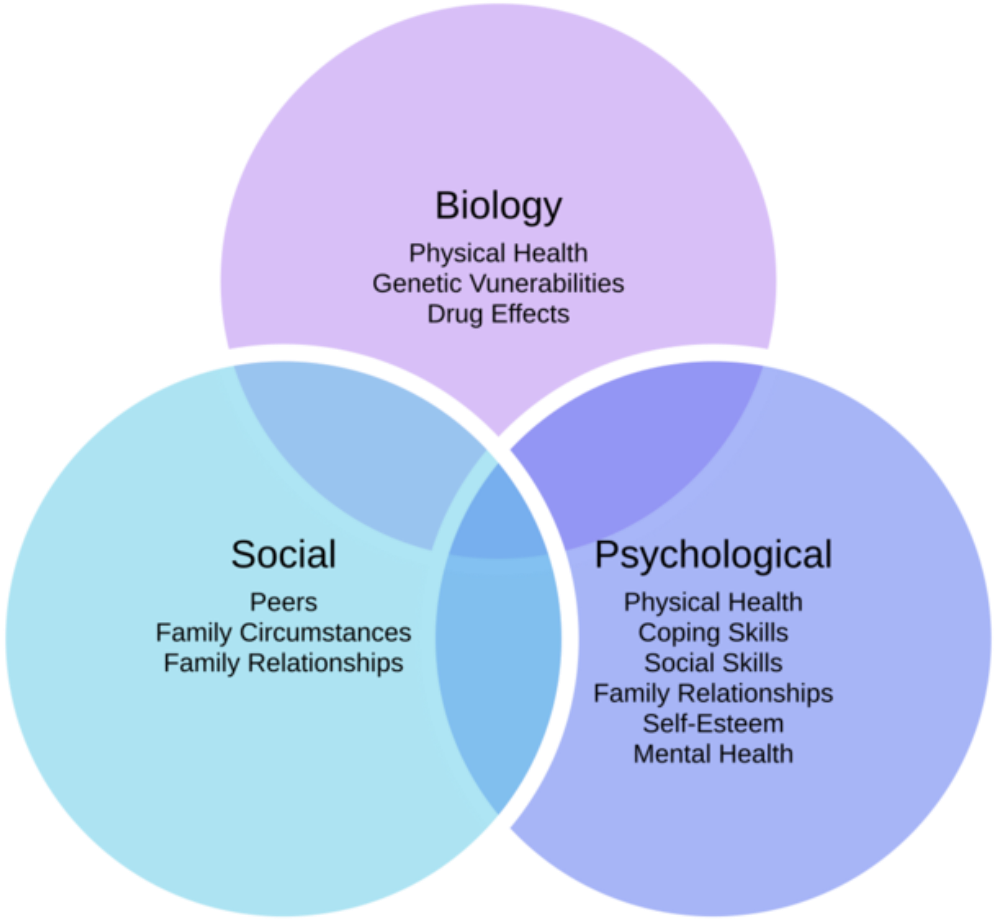
- I cannot find any evidence for this statement
- Informal survey with N = 1 did find that this view might be held by general public
- Some relevant studies:
- De Meyer et al., 2024:
  - "Recent representative studies have estimated that the prevalence of natural recovery (NR) is approximately 50% of all persons who have resolved their alcohol and drug use problems [9] or were in remission from a DSM-5 alcohol use disorder [11]."
  - "Higher education level, lower severity of dependence, and cannabis use as the main problem substance (vs. alcohol) were statistically significant ($p < 0.05$) correlates of NR."
- Mellor et al., 2019:
  - "This review identified 124 estimates of untreated remission from alcohol problems, which were taken from the 27 studies. These estimates ranged enormously; from 2.7% to 98.3%. "

Fact check: Brain disease model of addiction “has not produced a successful therapeutic strategy to help with addiction”

- There are numerous effective pharmacological treatments for substance use disorders
- https://www.farcanada.org/treatment/medications/
- Further reading:
  - https://pubmed.ncbi.nlm.nih.gov/30167705/
  - https://pubmed.ncbi.nlm.nih.gov/35597734/
  - https://pmc.ncbi.nlm.nih.gov/articles/PMC3767185/

Biopsychosocial model of addiction

- Accessible read on the topic here
- Acknowledges numerous biological, psychological, and social factors impact the risk of addiction
- Bio – from brain disease model of addiction
- Psycho – personality, mental health, life experiences, etc.
  - E.g., ACEs
- Social – norms, availability, accessibility, legality, expectancies, societal approval, visibility, cultural beliefs, access to treatment, etc.



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