Substance Use Disorder Series

MODULE 2

Pathogenesis of Substance Use Disorders

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Disclosures

- Authors of this presentation have nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation

Learning Objectives

1. Discuss the neuroscience and pathophysiology of substance use disorder (SUD)
2. Review the pharmacology of addictive substances and discuss how they contribute to SUDs
3. Explain the disease model of SUD
4. Understand an overview of SUD treatment modalities

Discuss the neuroscience and pathophysiology of substance use disorder (SUD)

MARSHALL
SCHOOL OF PHARMACY

Historical Perspective

- In Ancient Greek times, the Temple of Delphi was a place used to worship through excessive drinking and other activities
  - Inscribed on the walls are comments that translate to:
    - “Water is best”
    - “Know thyself”
    - “Nothing in excess”
- Historians believe these writings show that concerns regarding the harms of alcohol have existed for thousands of years

https://www.ancient-origins.net/history-ancient-traditions/addiction-treatment-0011113 Accessed 8-11-2019

Substance Use Disorder (SUD)

Substance use disorder is defined by the Diagnostic and Statistic Manual of Mental Disorders, 5th edition (DSM-5) as:

- **"A cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant substance-related problems."**

- In other words, SUD has both physical and mental symptoms, and substance use continues even when problems result

https://blogs.scientificamerican.com/observations/what-does-it-mean-when-we-call-addiction-a-brain-disorder/ DSM-5: Substance Use Disorders; accessed on 5-29-20

Substance Use Disorder cont.

- A "**chronic, but treatable medical condition**"
- SUD is not a moral failing
  - Imaging studies have shown changes in brain regions associated with reward, stress, and self-control
  - Brain changes caused by substance use leads to both compulsive use and a high risk of relapse
- Understanding that SUD is a disease does not disregard social and environmental influences
  - Both a person's environment and social influences can greatly affect the pathways of addiction/SUD

https://blogs.scientificamerican.com/observations/what-does-it-mean-when-we-call-addiction-a-brain-disorder/ DSM-5: Substance Use Disorders; accessed on 5-29-20

Understanding SUD

- Everyone who uses addictive substances does not develop SUD
- Genetics and environment determine susceptibility to SUD
- Pharmacological treatments for SUD do not replace a patient's desire to stop drug use
  - Cravings can be reduced by medications but are seldom eliminated
  - Medications are tools, in addition to psychological therapy, to aid patients to help themselves

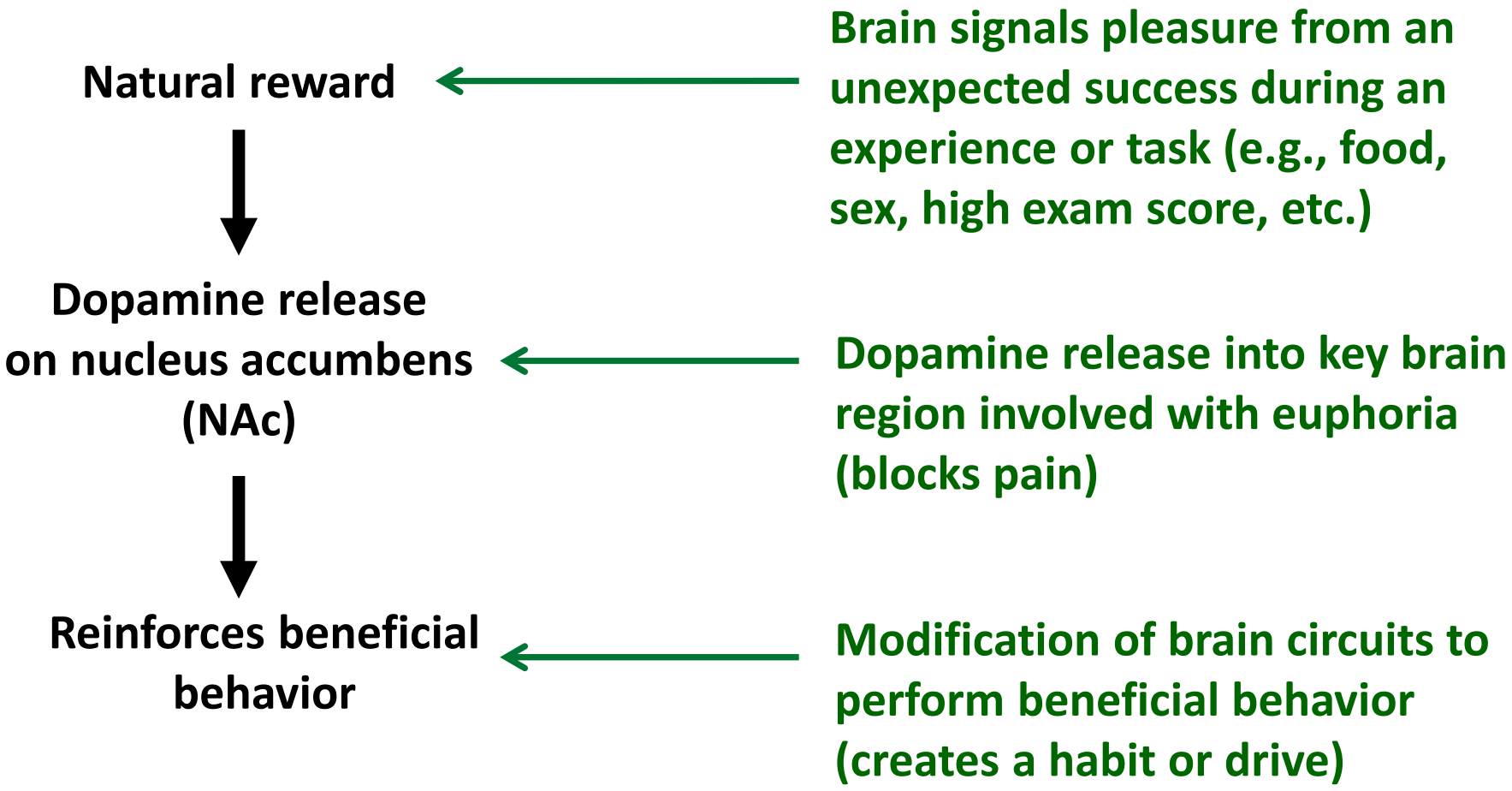
https://blogs.scientificamerican.com/observations/what-does-it-mean-when-we-call-addiction-a-brain-disorder/ DSM-5: Substance Use Disorders; accessed on 5-29-20

SUD and Brain Reward

- Reward that is not substance-induced is a natural process which reinforces the behavior so that it will be repeated (e.g., eating and drinking)
  - Note: Natural reward can be addictive (e.g., sex, food, and gambling)
- Substances associated with SUD artificially produce feelings of pleasure (i.e. reward or a “high”) and block pain temporarily
  - These substances “hijack” the natural reward pathway (driving both behavior and a need for the substance)

https://www.psychiatry.org/psychiatrists/practice/dsm Accessed 5-29-20

Brain Mechanisms of Natural Reward



https://www.drugabuse.gov/publications/teaching-packets/neurobiology-drug-addiction/section-ii-reward-pathway-addiction/1-reward-pathway-addiction Accessed on 5-29-20

Tripp G, Wickens JR. Neurobiology of ADHD. Neuropharmacology. 2009 Dec;57(7-8):579-89

Natural vs. Artificial Reward

Natural process (pleasure) induces reward

↓

Dopamine release on nucleus accumbens (NAc)

↓

Reinforces beneficial behavior

Substance(s) hijacks the natural process

Administer drug or substance of abuse

↓

Dopamine release on nucleus accumbens (NAc)

↓

Euphoria, pain blocking, and learning of substance use disorder behavior

The basic neuroscience of natural/drug-induced reward is depicted in more detail on the following slides.

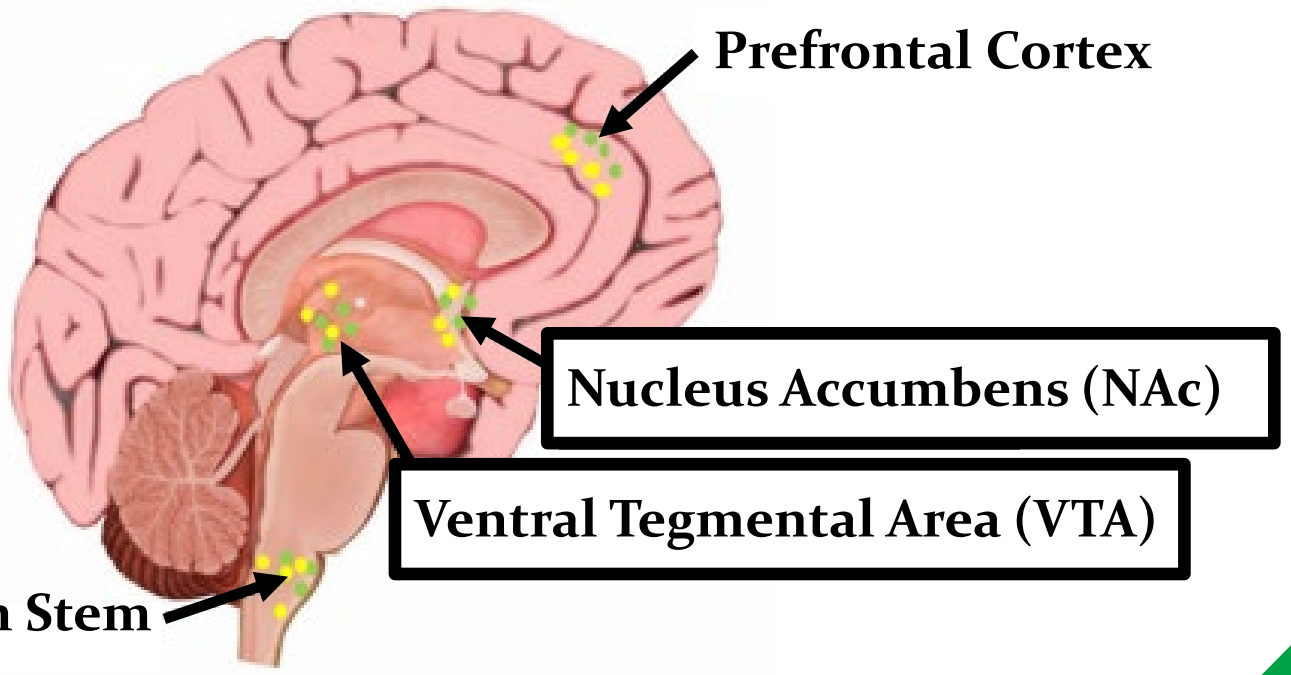
Tripp G, Wickens JR. Neurobiology of ADHD. Neuropharmacology. 2009 Dec;57(7-8):579-89.

Brain Mechanisms of Reward

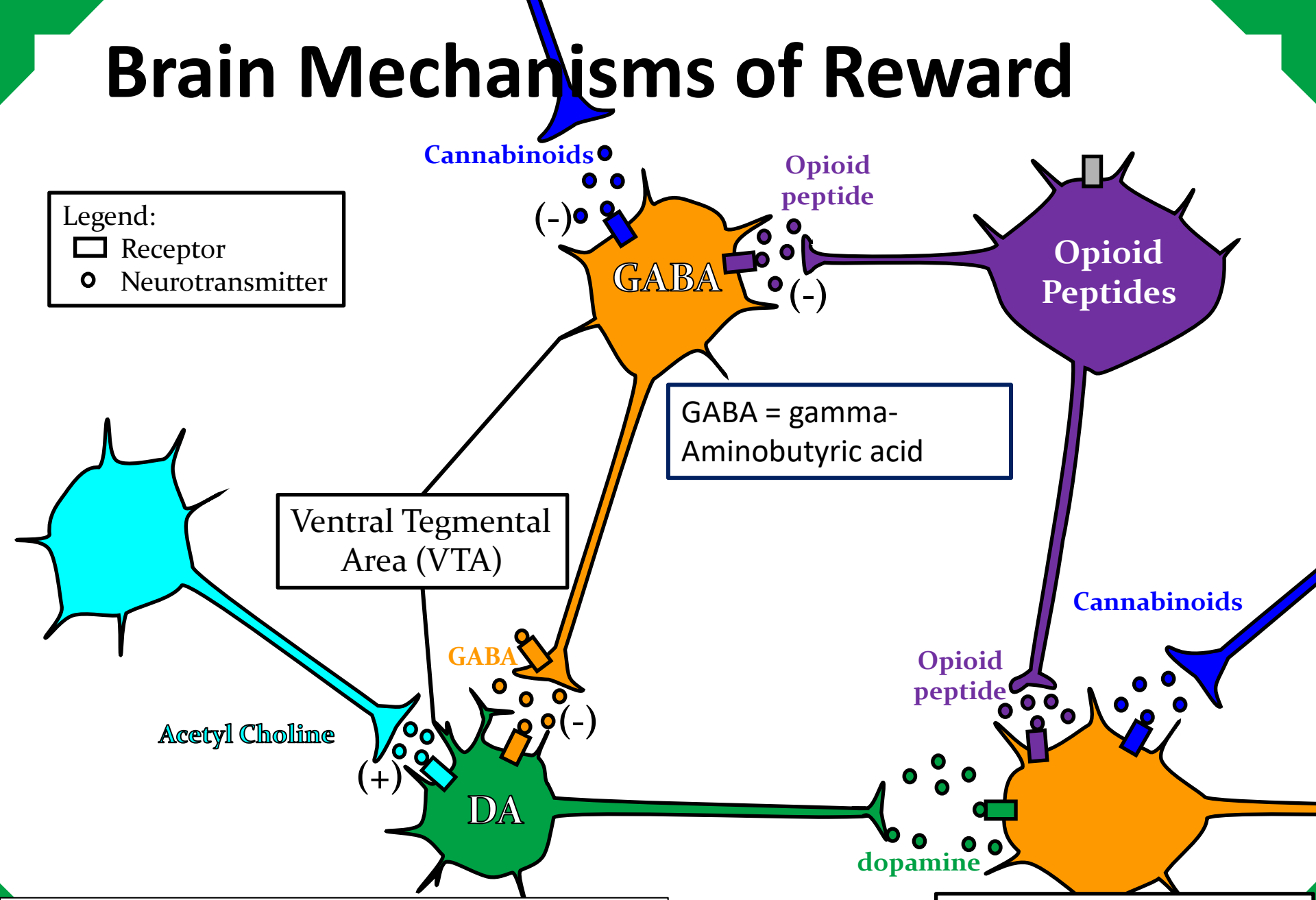
- Release of dopamine (DA) from the ventral tegmental area (VTA) onto dopamine receptors in the nucleus accumbens (NAc) is the common step of the reward pathway (regardless if the trigger is natural or drug induced)

Yellow dots represent DA

DA in the NAc causes euphoria and blocks pain



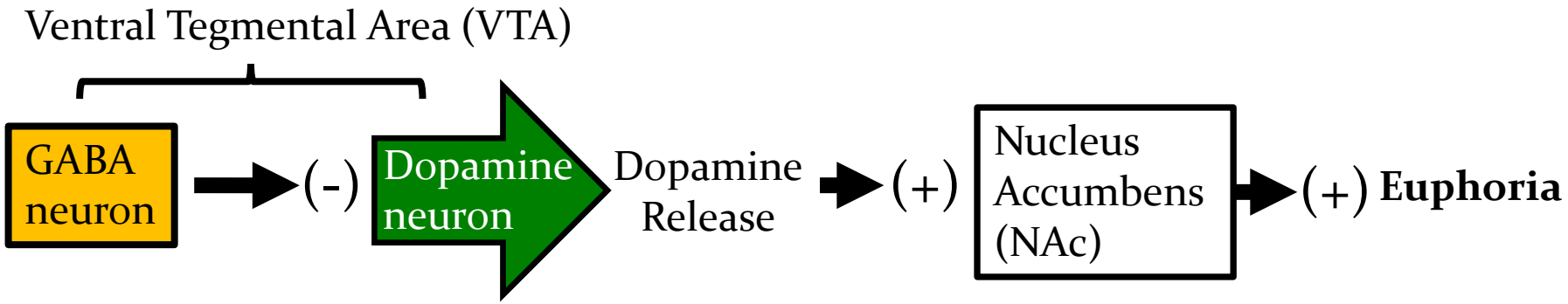
Brain Mechanisms of Reward



Figures adapted from: https://www.ncbi.nlm.nih.gov/books/NBK424849/
Horsfall JT, Sprague JE. The Pharmacology and Toxicology of the 'Holy Trinity'. Basic Clin Pharmacol Toxicol. 2017 Feb;120(2):115-119.

Brain Mechanisms of Reward

- The brain circuit for the subjective sensation of reward is considerably more complex than the schematic on the previous page
  - (i.e., there are additional connections within the circuit depicted in the figure and many effects beyond the dopamine release in the nucleus accumbens)
- Drug effects on this pathway can be adequately described by the following schematic:



Drugs of Abuse and "Artificial" Reward

- SUD results from substances that activate the reward pathway through a variety of different mechanisms
  - **Understanding how a drug produces reward (the "high") is needed to understand how drug exposure can result in SUD (i.e. addiction)**
- Examples of drug categories that produce a "high" through common mechanisms despite having a wide variety of effects in the body:
  - CNS depressants or "downers"
    - Opioids
    - GABA related sedatives
  - CNS stimulants or "uppers"
  - Other:
    - Dissociative anesthetics

Review the pharmacology of addictive substances and discuss how they contribute to SUDs

MARSHALL
SCHOOL OF PHARMACY

Overview of Categories of Substances of Abuse

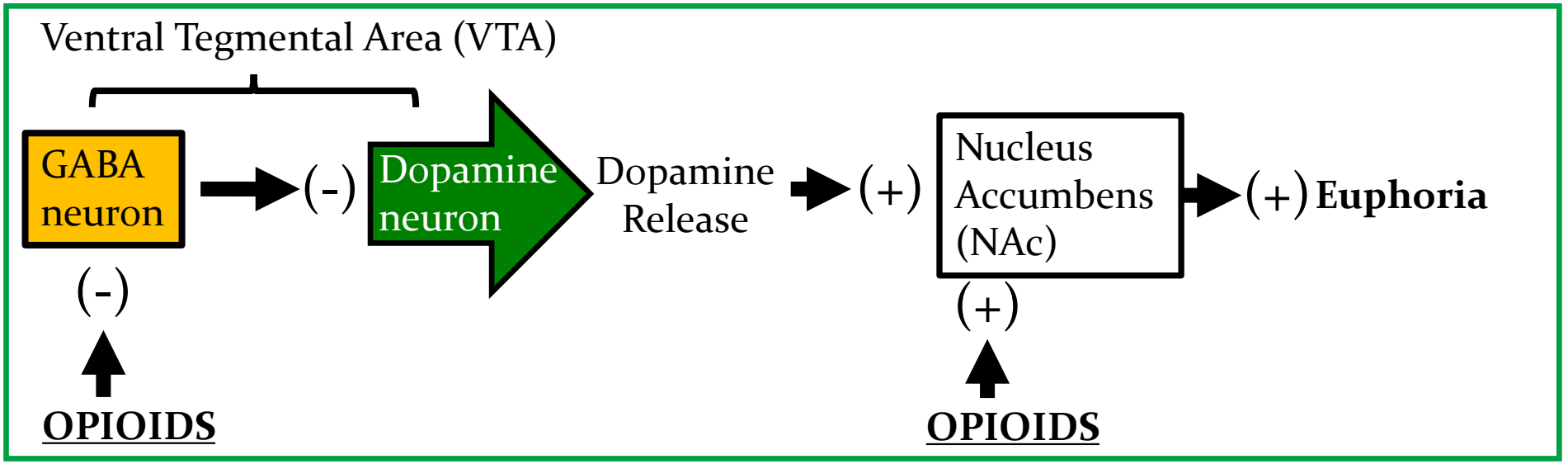
Sedatives (or "downers")	Stimulants (or "uppers")	Other
• Opioids • GABA-related sedatives • THC	• Nicotine • Cocaine • Amphetamines	• Inhalants • Dissociative anesthetics • Classic hallucinogens

Opioids

- Mechanism of action: bind opioid receptors
- Effects:
  - Pain relief
    - Disrupts pain transmission in both CNS and periphery
  - Sedation and respiratory depression
  - Cough suppression
  - Euphoria
  - Addiction with chronic use
- Examples: morphine, hydromorphone, oxymorphone, oxycodone, hydrocodone, heroin, codeine (prodrug), meperidine, fentanyl, sufentanyl, carfentanil (“elephant tranquilizer”), methadone

Opioids

- Opioids affect pathway receptors at two different sites
  - Inhibits GABA neurons from preventing the release of dopamine into the nucleus accumbens (net effect, ↑ DA release)
  - Direct actions on the nucleus accumbens (↑ reward, ↓ pain)

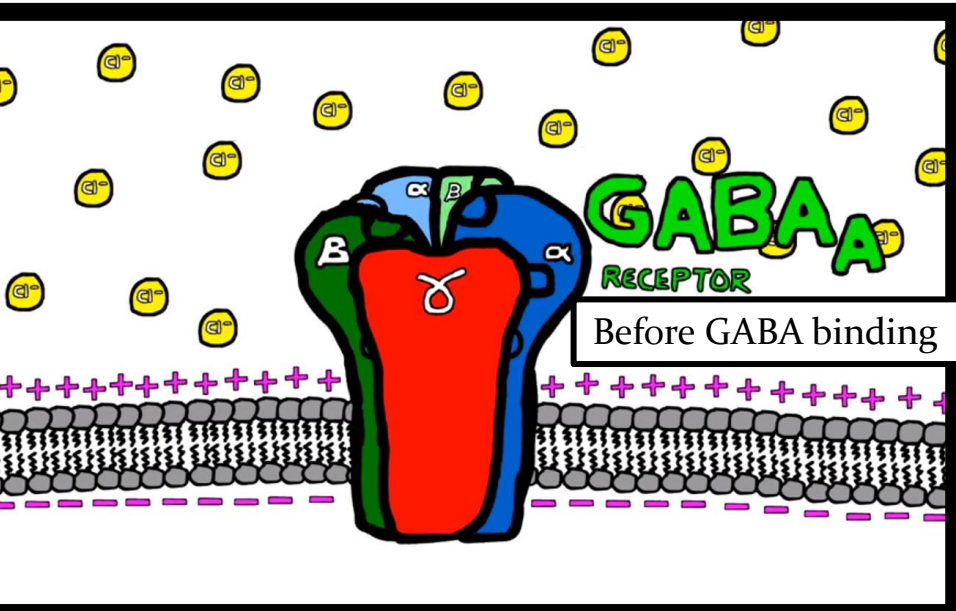


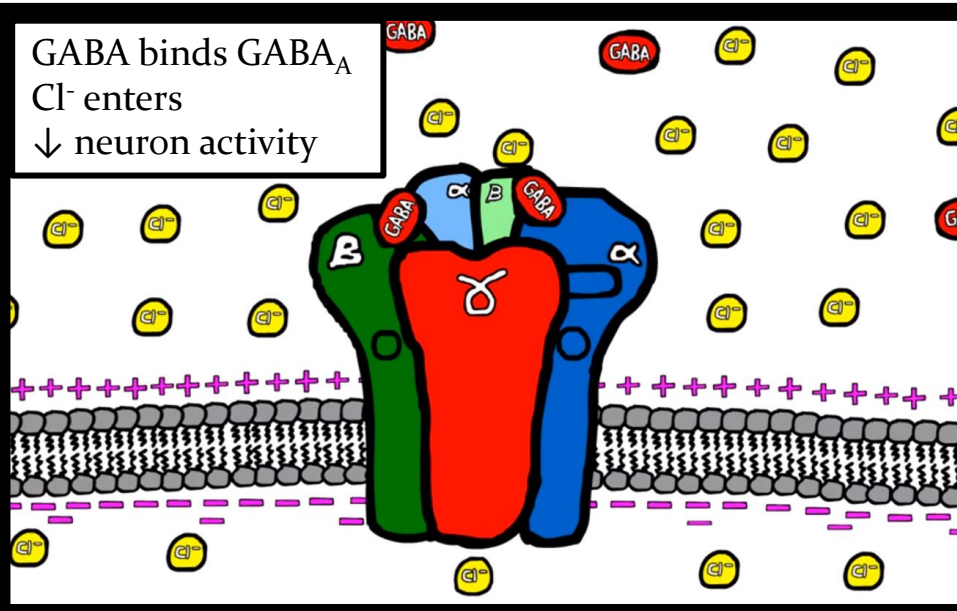
GABA-related Sedatives

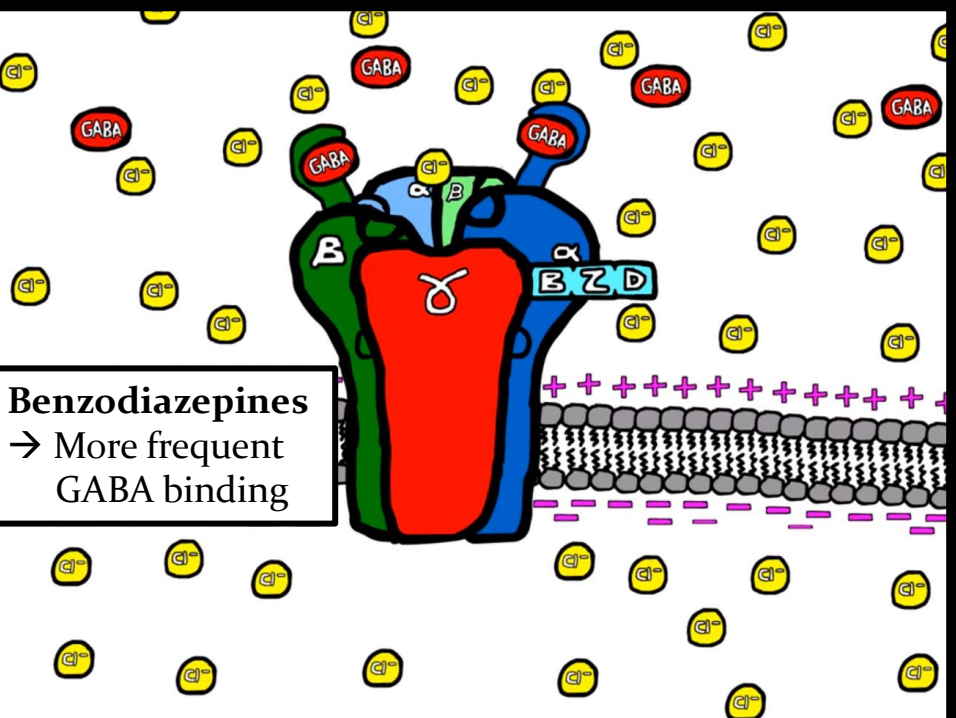
- Mechanism of action: GABA receptor facilitation
  - GABA = gamma-Aminobutyric acid
- Effects:
  - Sedation/anxiolysis/muscle relaxation
  - Respiratory depression (more so with barbiturates than benzodiazepines)
  - Euphoria and block pain
  - Addiction/SUD with repeated use
- Examples:
  - Ethanol
  - Benzodiazepines: e.g., alprazolam, diazepam, clonazepam, and lorazepam
  - Gamma-hydroxybutyric acid (GHB)
  - Barbiturates: e.g., phenobarbital, pentobarbital, and secobarbital

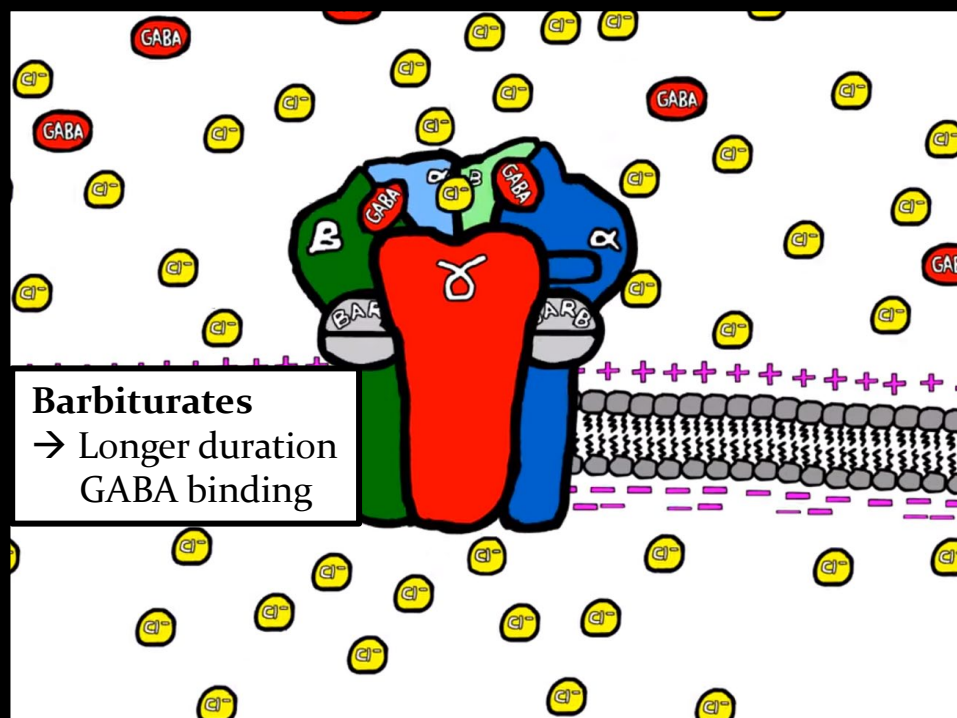
GABA Sedatives

See MOA in motion: https://youtu.be/Iggk69QMIiQ



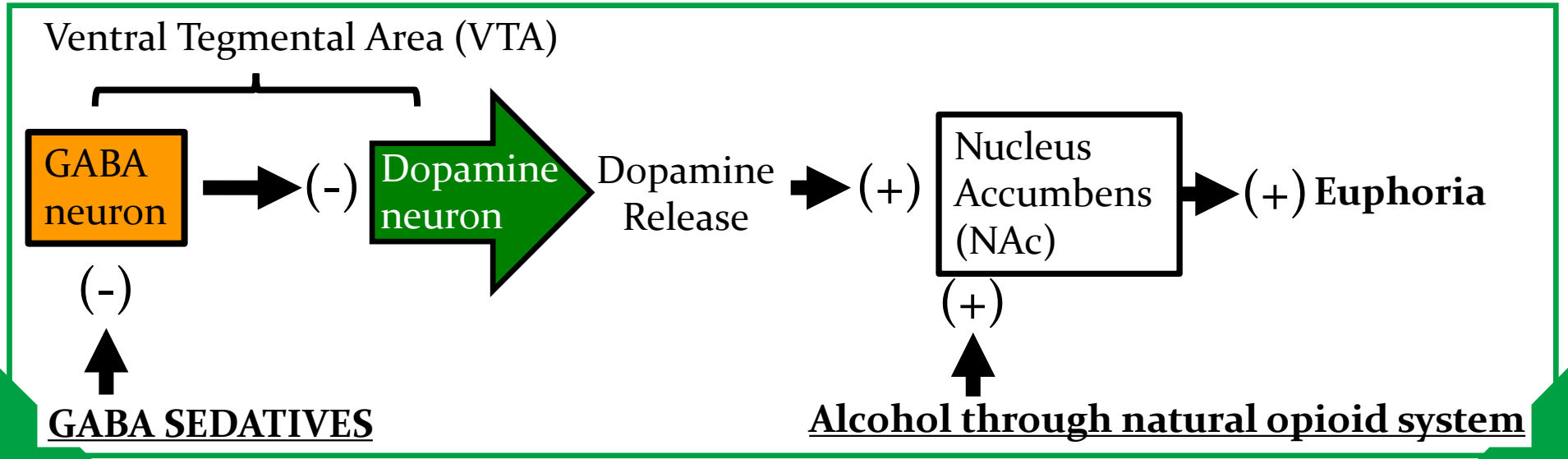






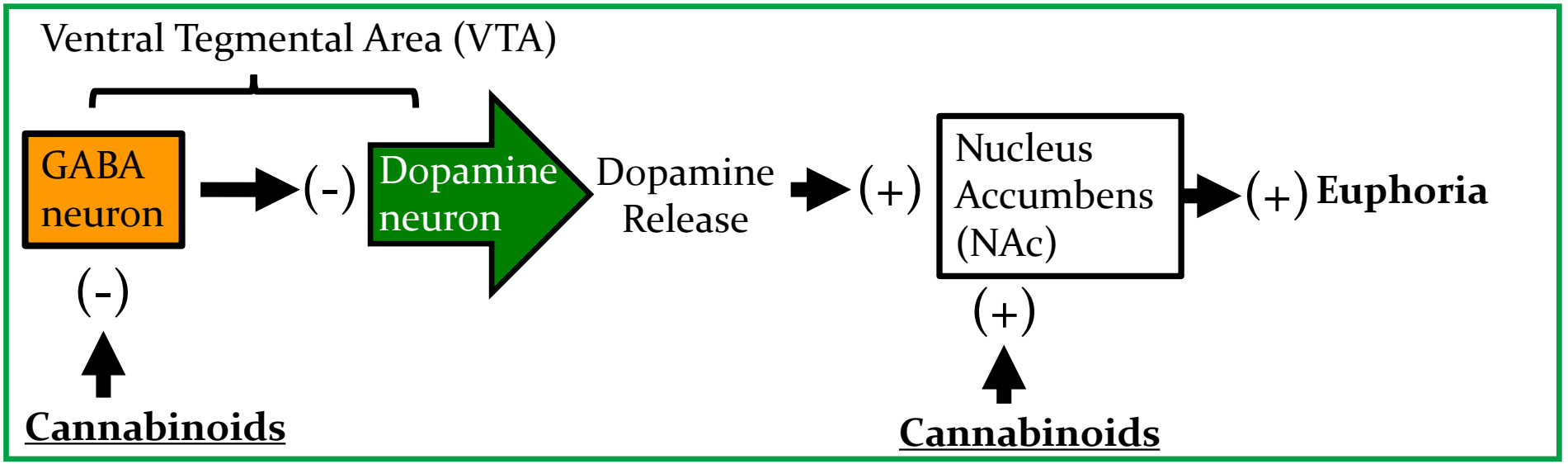
GABA Sedatives cont.

- Differences in GABA actions between drug classes:
  - Benzodiazepines: facilitate GABA binding to $GABA_A$ receptor (higher frequency)
  - Barbiturates: prolong binding to $GABA_A$ receptor (longer duration)
    - High dose effect leads to respiratory depression (by itself)
  - Alcohol: has other non-GABA effects
  - Gamma-hydroxybutyric acid (GHB)
    - MOA: similar to sedatives, but with $GABA_B$ receptor
- Drug interaction: ↑ sedation/respiratory depression if multiple sedatives (or sedatives and opioids) combined



Δ^9-tetrahydrocannabinol (THC)

- Mechanism of action: binds cannabinoid receptors
  - Effects:
    - Altered senses/mood/quality of thinking/memory/euphoria/pain
    - Affects the receptor pathway in two places

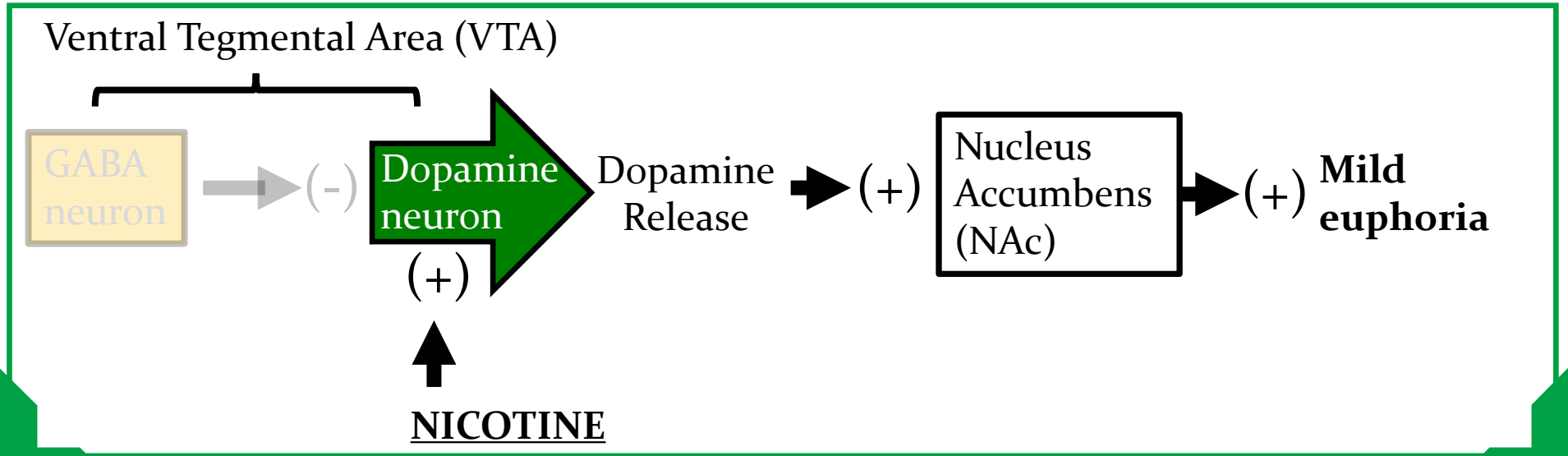


- Synthetic analogues (e.g., K2) have different effects
  - Greater effect on cannabinoid receptors (full rather than partial agonist)
  - Can bind other receptor types also

https://www.drugabuse.gov/publications/drugfacts/marijuana Accessed on 8-13-19

Nicotine

- Mechanism of action: binds nicotinic receptor
  - Mild euphoria
    - Dopamine release onto nucleus accumbens (NAc)
  - Cardiovascular effects (not dopamine-mediated)
- Highly addictive despite only mild euphoria
  - Key non-reward mechanisms for substance use disorder (SUD) discussed later (i.e., intense euphoria is not required for SUD)



Nicotine Taking New Form

- "Juuling" (vaping with Juul® brand vaporizer)
  - Administer higher nicotine doses per inhalation than standard cigarettes
    - 1 pod = 1 pack of cigarettes (20 cigarettes)
  - Pods are more user-friendly than previous generations of vaporizers that required liquid refills
- Improvement of vaporizer e-liquid flavor can increase nicotine exposure
  - In a study of strawberry vs. nicotine flavor, users performed longer inhalations with the flavored e-liquid

Talih et al. Characteristics and toxicant emissions of JUUL electronic cigarettes. 2019 Feb 11. pii: tobaccocontrol-2018-054616.
St Helen et al. Impact of e-liquid flavors on nicotine intake and pharmacology of e-cigarettes. 2017 Sep 1;178:391-398.

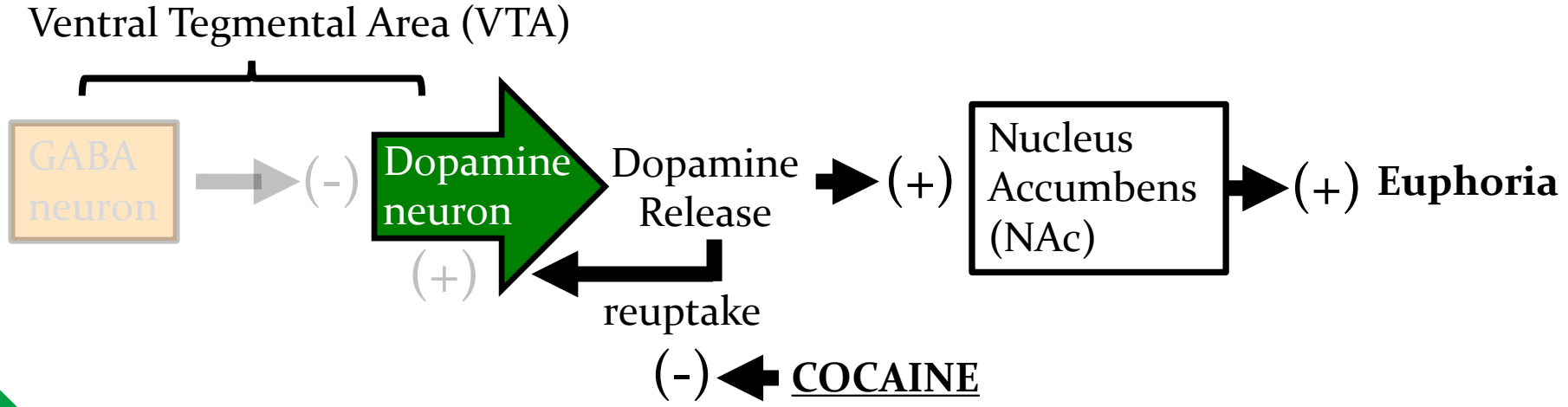
Is vaping better than smoking?

- Vaping is not a proven treatment for nicotine dependence
- Can vaping reduce the amount of carcinogens a patient inhales?
  - It potentially can (brand dependent)
  - It will take years before long-term studies are conclusive
- For now, health care providers should know that vaping nicotine could be less harmful than smoking, but the safety is being questioned
  - Do not recommend vaping any other products
  - Concern about vaping-related lung injuries and deaths

https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html Accessed 6-1-20

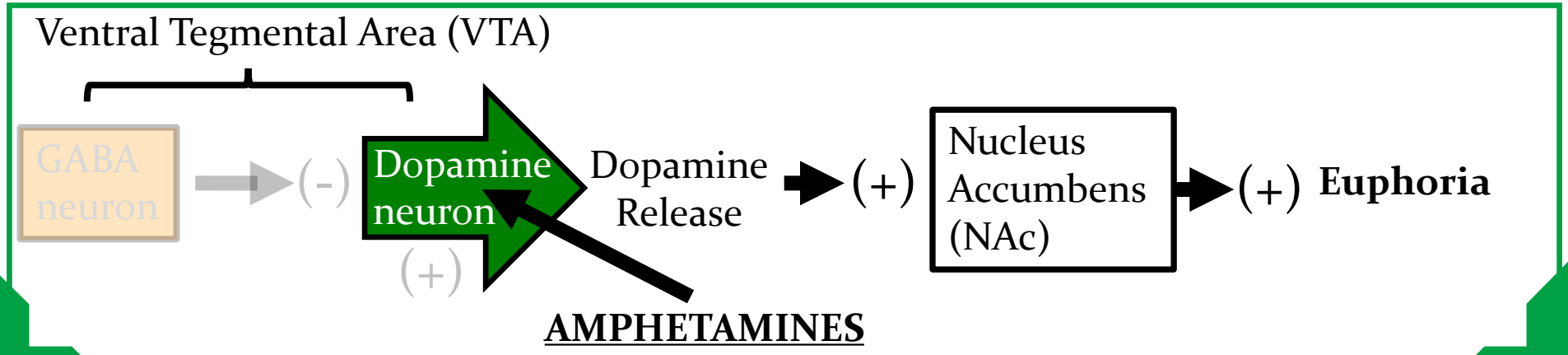
Cocaine

- Mechanism of action: inhibits reuptake of dopamine, norepinephrine, & serotonin → up to 3 times more than physiological accumulation
- Effects:
  - Cardiovascular effects (e.g., ↑ HR and BP, arrhythmia, clotting)
  - Psychiatric effects (e.g. psychosis, mood disturbance, anxiety, panic attacks)
  - Behavioral disinhibition, ↑ energy, ↓ appetite
  - Euphoria
    - Dopamine release onto nucleus accumbens (NAc)



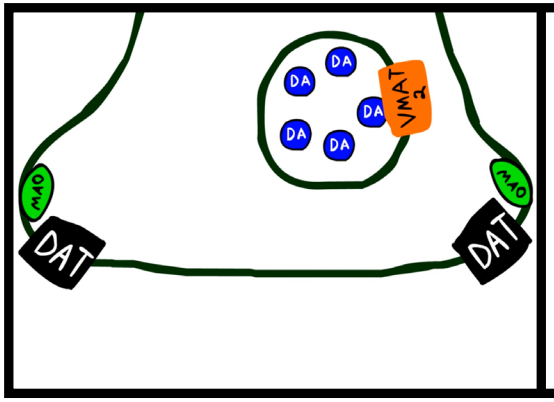
Amphetamines

- Examples: amphetamine, methamphetamine, MDMA, synthetic cathinones ("bath salts," also block reuptake, like cocaine)
- Mechanism of action: causes dopamine, norepinephrine, & serotonin to be directly released from intracellular storage. Neurotransmitters leave cell to produce effects.
- Effects
  - Cardiovascular effects (e.g., ↑ HR and BP)
  - Psychiatric effects (e.g. psychosis, mood disturbance, anxiety, panic attacks)
  - Behavioral disinhibition, ↑ energy, ↓ appetite
  - Euphoria
    - Massive dopamine released onto nucleus accumbens (up to 1,000 – 3,000 times more than normal physiological accumulation)

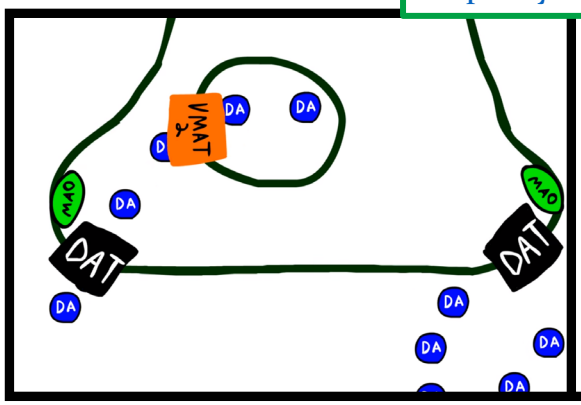


Dopamine Release/Reuptake

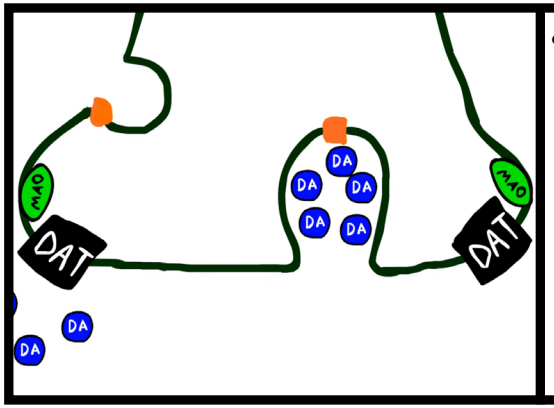
In motion:
https://youtu.be/2uBuHcFspeA



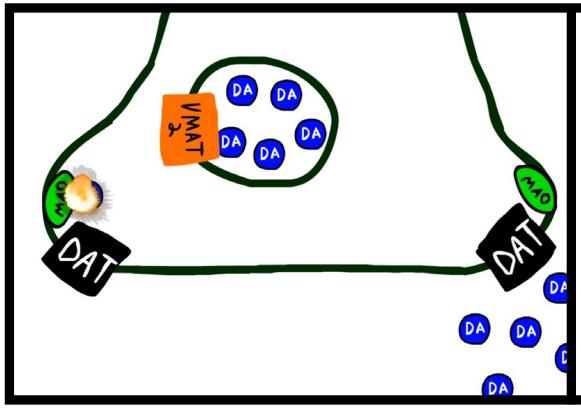
- Dopamine (DA) is stored in vesicles prior to release.



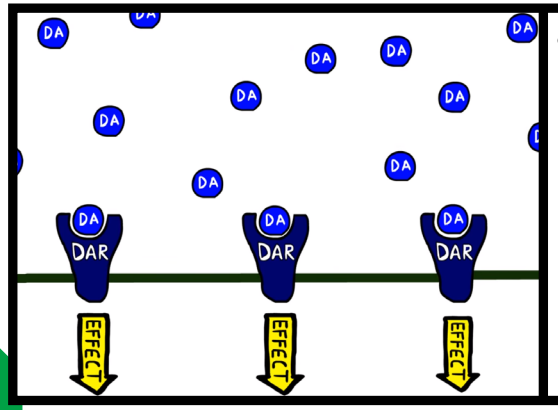
- DA returned to vesicle by the DA transporter (DAT) and vesicular monoamine transporter 2 (VMAT-2).



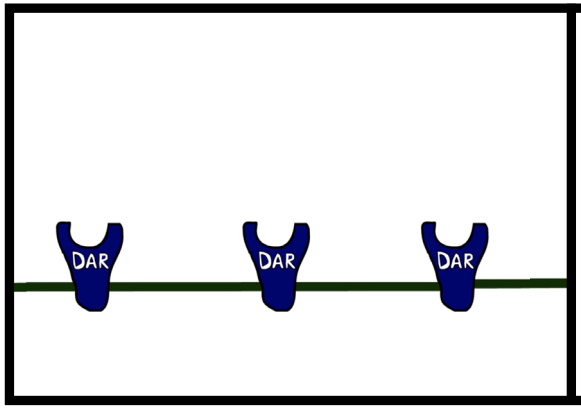
- Signal from neighboring neuron results in vesicle fusion with cell membrane and release of DA.



- DA can be metabolized by monoamine oxidase (MAO).



- DA binds receptors in neighboring neurons to produce an effect.

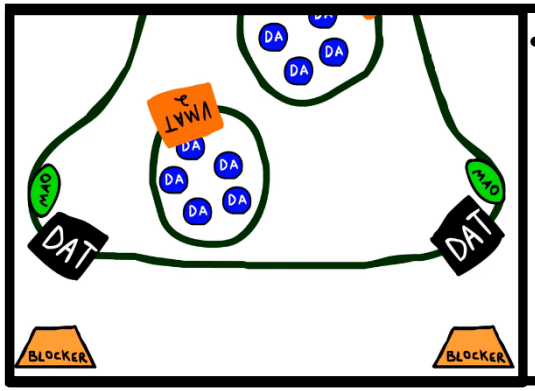


- DAT, VMAT-2, and MAO remove DA from its receptor to stop its action.

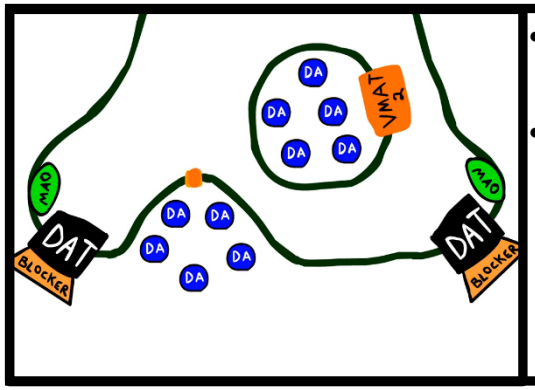
Note: other neurotransmitters such as norepinephrine and serotonin work similarly

Cocaine vs Amphetamine - Effects on DA

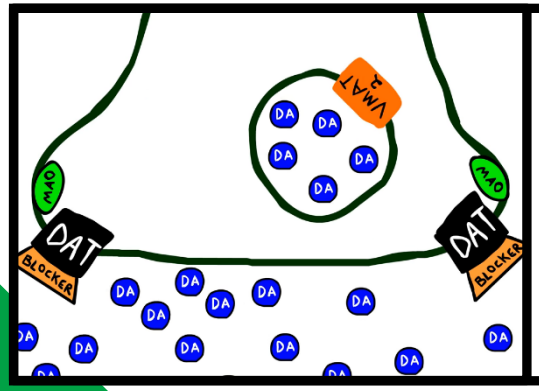
In motion (cocaine) https://youtu.be/P_VsP4fDFuQ



- Cocaine and other transporter blockers do NOT enter the neuron and do NOT cause DA release.

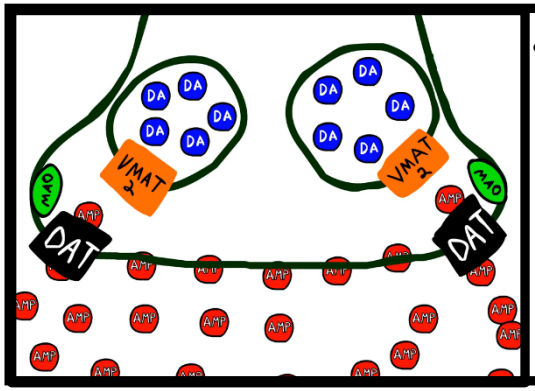


- They do, however, block DAT.
- DA release continues normally, but it is not being removed.

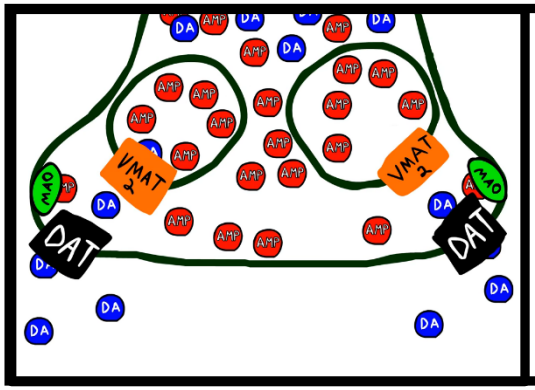


- DA accumulates beyond normal physiological levels.
- Greater than physiological effects result.

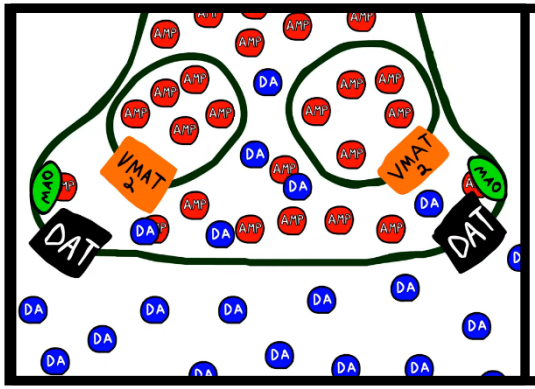
(amphetamines) https://youtu.be/Ms9sEGOaZlM



- Amphetamines enter the neuron through both DAT and by crossing the cell membrane.



- Amphetamines increases DA levels inside the cell membrane, then increase DA release.



- The drug interacts with VMAT-2 to dump DA into the cytoplasm.
- Excessive DA exits neuron through DAT to produce effects.

Inhalants

- Examples include nitrites, ketones, and aliphatic and aromatic hydrocarbons from various products
- MOA: dependent on agent (NMDA antagonism, GABA facilitation, reduction of oxygen levels in the brain, etc.)
- These substances do not create physical dependence, and the euphoria (or “high”) typically does not last very long
  - Not commonly associated with SUD

Dissociative Anesthetics

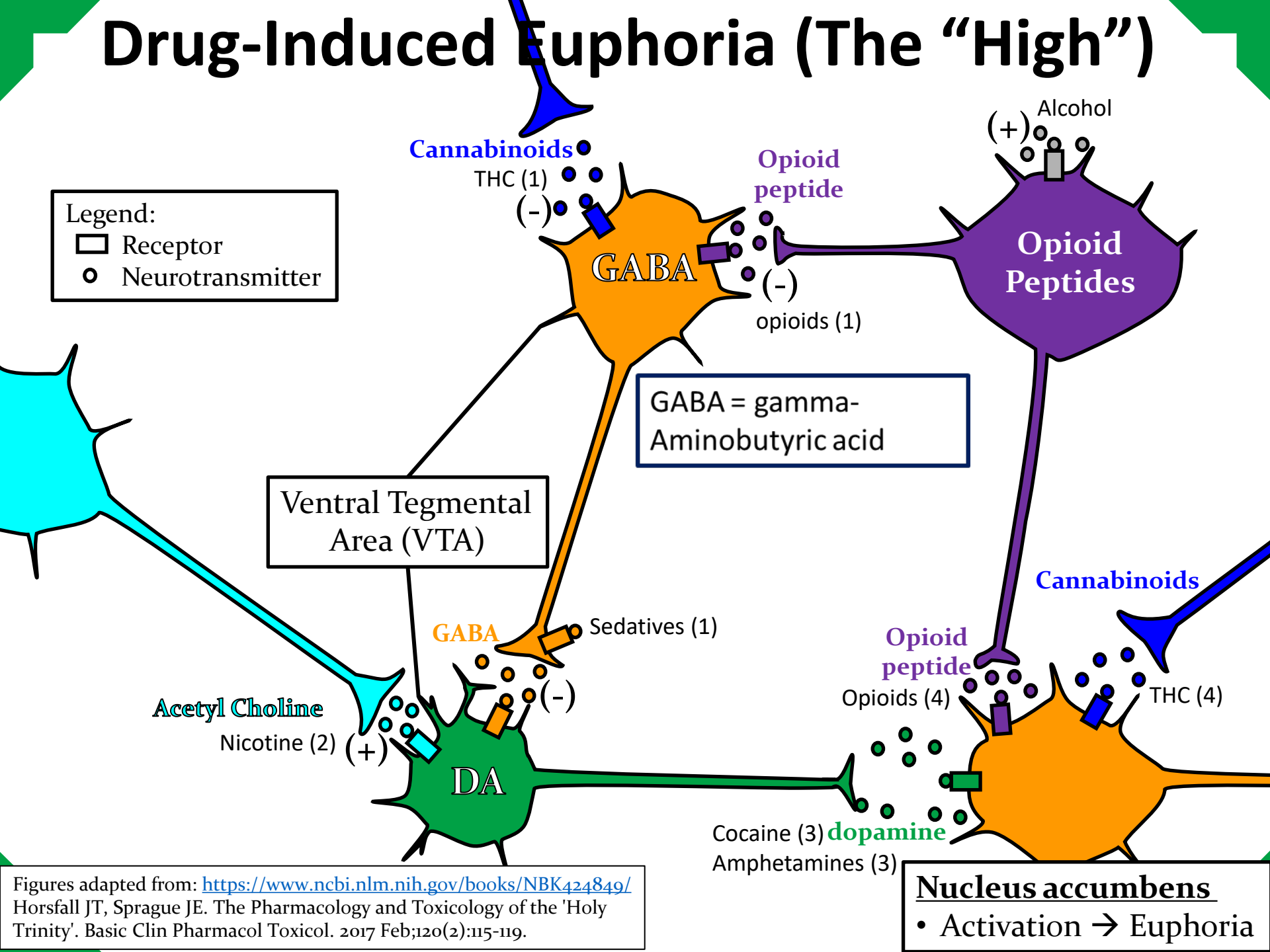
- Examples: ketamine, phencyclidine (PCP), high dose dextromethorphan
- MOA: N-methyl-D-aspartate (NMDA) antagonists (block excitatory glutamate signaling)
  - Note: also results in dopamine release but the mechanism is poorly understood
- Effects: dissociative anesthesia (vivid dreams, hallucinations, unpleasant out of body experiences with high doses)
  - PCP is more potent than ketamine with considerably longer duration of action (more dangerous)
  - Some over-the-counter medications are a concern due to ease of availability (dextromethorphan)

Kokkinou et al. The effects of ketamine on dopaminergic function: meta-analysis and review of the implications for neuropsychiatric disorders. Mol Psychiatry. 2018 Jan;23(1):59-69.
Lodge et al. Ketamine and phencyclidine: the good, the bad and the unexpected. Br J Pharmacol. 2015 Sep; 172(17): 4254–4276.
Romanelli, F., & Smith, K. M. (2009). Dextromethorphan abuse: Clinical effects and management. Journal of the American Pharmacists Association, 49(2), e20–e27.

Classic Hallucinogens

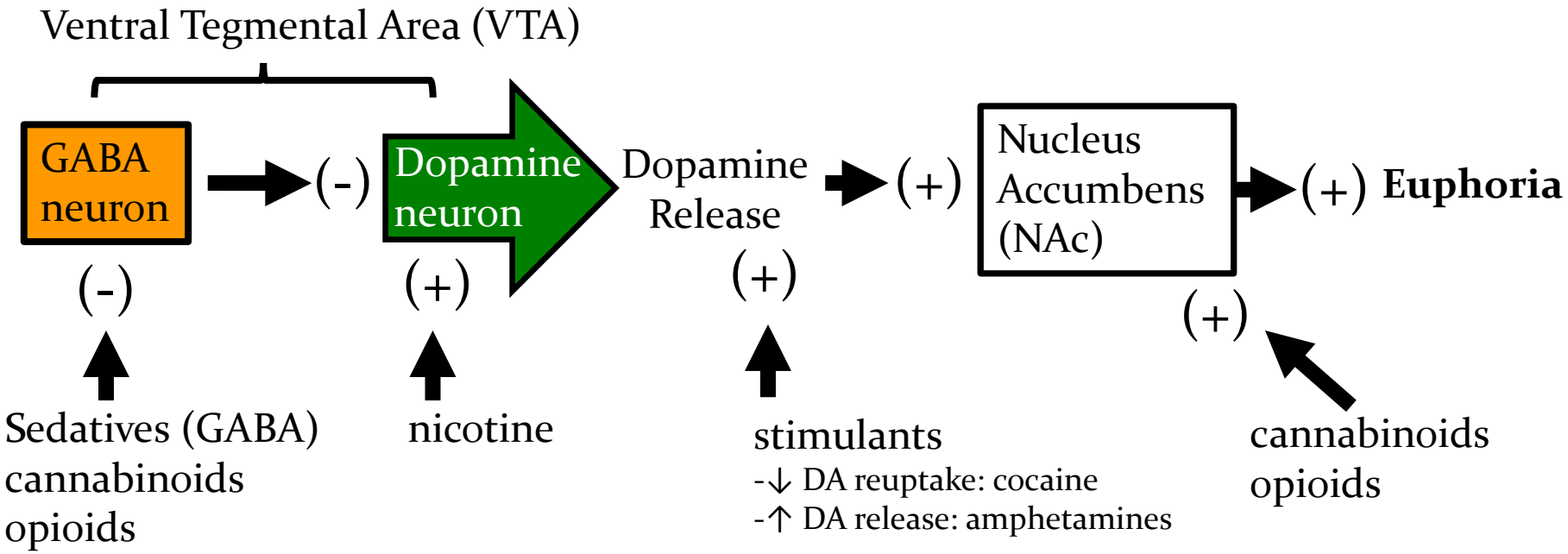
- Examples: LSD, mescaline, psilocybin
- MOA: serotonergic properties that alter input to cortex
  - Weak dopamine effects, not full agonists
- Effects: change perception (color/shape distortion), psychosis (hallucinations)
- Hallucinogens do not cause physical dependence
  - Not commonly associated with SUD but are abused substances

Drug-Induced Euphoria (The "High")



Figures adapted from: https://www.ncbi.nlm.nih.gov/books/NBK424849/
Horsfall JT, Sprague JE. The Pharmacology and Toxicology of the 'Holy Trinity'. Basic Clin Pharmacol Toxicol. 2017 Feb;120(2):115-119.

Drug-Induced Euphoria and Pain Blockade



1) Inhibit the inhibition of dopamine neurons

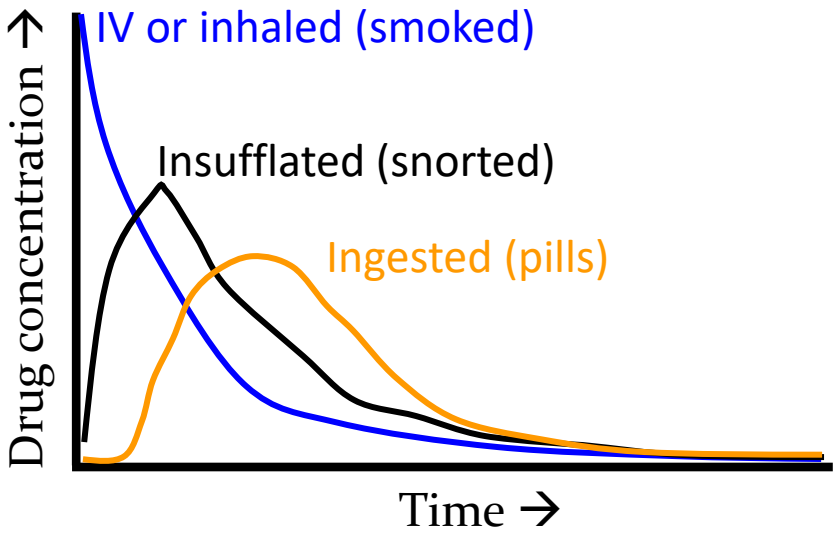
2) Activate dopamine neurons

3) Direct effect on dopamine release/reuptake

4) Direct effect on NAc

Administration and Absorption

- How a drug is administered can enhance the extent of the euphoria or "high" produced as well as other drug effects
- The faster a drug reaches the brain, the more the effect is enhanced
  - Intravenous and inhaled (smoked): very rapid brain entry → INCREASED EFFECT → **higher likelihood for SUD**
  - Insufflation ("snorting"): rapid brain entry
  - Oral administration: slower brain entry → lesser effect → **less likelihood for SUD**



Explain the disease model of Substance Use Disorder (SUD)

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Reward and Association with SUD

- Drug-induced reward is **not** the sole cause of substance use disorder (SUD)
  - If reward was the only factor, SUD could be cured by enforced abstinence
- Examples that cannot be explained by level of dopamine euphoria or "high" produced by a substance:
  - Smoking nicotine produces a minor euphoria or high compared to smoking methamphetamine, but nicotine remains highly dependent/addictive
  - In experimental conditions, squirrel monkeys trained to press a lever to self-administer doses of cocaine will eventually substitute pressing a lever (i.e. the same drug use activity) to self-administer electric shock rather than cocaine

Spealman et al. Behavioral effects of self-administered cocaine: responding maintained alternately by cocaine and electric shock in squirrel monkeys. J Pharmacol Exp Ther. 1979 Aug;210(2):206-14.

Susceptibility to SUD/Addiction

- Not uniform in a population
  - As previously stated, everyone who uses addictive substances does not develop SUD
- Genetics and environment determine susceptibility
  - Family history is present in ~39-72% of cases
  - Genetics are less predictive as people age
  - Environment and genetics overlap in many cases
  - Familial and social factors are important in initiating substance use

Bevilacqua and Goldman. Genes and Addictions. Clin Pharmacol Ther. 2009 Apr; 85(4): 359–361.

Environmental Factors

- The adverse childhood experiences study by Vincent Felitti in 1998 confirmed what had been described by many before the study
- Since then, it has been estimated that up to 67% of substance use problems may be from adverse childhood experiences
- Many adults never recover emotionally from traumatic experiences

Felitti, et al. **Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults**. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med. 1998;**14**(4):245-258

Tilson EC. **Adverse Childhood Experiences (ACEs): An Important Element of a Comprehensive Approach to the Opioid Crisis**. N C Med J. 2018 May-Jun;79(3):166-169.

Environmental Factors cont.

- The human brain functions via circuits consisting of neurons that signal through neurotransmitters
  - Subjective emotions can alter this function
  - If emotions are never addressed or treated (i.e., comorbidities such as depression or anxiety), they may become the driving force for behaviors (such as abusing substances)
- Epigenetics is the study of how gene expression changes (phenotype) without DNA changes (genotype) due to environmental factors
  - Epigenetic modifications have been implicated in facilitating behavioral and neuronal changes associated with substance use disorder

Mahgoub and Monteggia. Epigenetics and Psychiatry. Neurotherapeutics. 2013 Oct; 10(4): 734–741.

Basic Principles of SUD

- Chronic disease: like diabetes rather than pneumonia (i.e., prevent or treat rather than cure)
- Relapsing: likelihood of restarting use if abstinent
  - Stress
  - Exposure to people, places, things, and situations associated with prior use (triggers)
  - Re-exposure to drug
- Compulsive use despite negative consequences (by definition)

https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-misuse-addiction
DSM-5: Substance Use Disorders. Accessed 8-13-19.

Addiction

- The compulsive need for and use of a habit-forming substance characterized by tolerance and by well-defined physiological symptoms upon withdrawal
  - Derivation - in part borrowed from Latin *addictiōn-, addictiō* “adjudging (of disputed property), assignment of a debtor to the custody of his creditor," from *addīcere* "to assign (property), hand over, give up to"
    - Negative connotation based on derivation

https://www.merriam-webster.com/dictionary/addiction#learn-more Assessed 8-6-2019

Addiction cont.

- The connotation of addiction in our society is negative
  - DSM-5 does not recommend using the term addiction
    - Replaced with “Substance Use Disorder” (SUD)
- Much of society still uses the term addiction

- What other terms might be used to reduce stigma and the negative connotation that society has for the word addiction?

https://blogs.scientificamerican.com/observations/what-does-it-mean-when-we-call-addiction-a-brain-disorder/
DSM-5: Substance Use Disorders. Accessed 8-13-19.

The Brain on Drugs

- Basic pathophysiology: drug-induced modification of central nervous system processes involving reward, anxiety, and executive control
- Components of pathophysiology
  - Tolerance, dependence, and withdrawal
  - “Re-wiring” of the brain includes:
    - Reward dysfunction
    - Disruption of higher brain function
    - Compulsive drug use
    - Relapse
- Susceptibility to SUD or addiction is determined by both physiology and environment

https://www.drugabuse.gov/publications/drugs-brains-behavior-science-addiction/drug-misuse-addiction

DSM-5: Substance Use Disorders. Accessed on 8-13-19.

Reward Function Without SUD

Normal learning:

1. Unexpected reward → DA release
2. DA release due to expected reward cues behavior → decreased DA release due to reward
3. DA release due to expected reward cues behavior without DA release due to reward

Translation = repeat the behavior without the DA reward

Tripp G, Wickens JR. Neurobiology of ADHD. Neuropharmacology. 2009 Dec;57(7-8):579-89.
Koob and Volkow. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016 Aug; 3(8): 760–773.

Reward Dysfunction in SUD

Drug-induced learning (Drug craving):

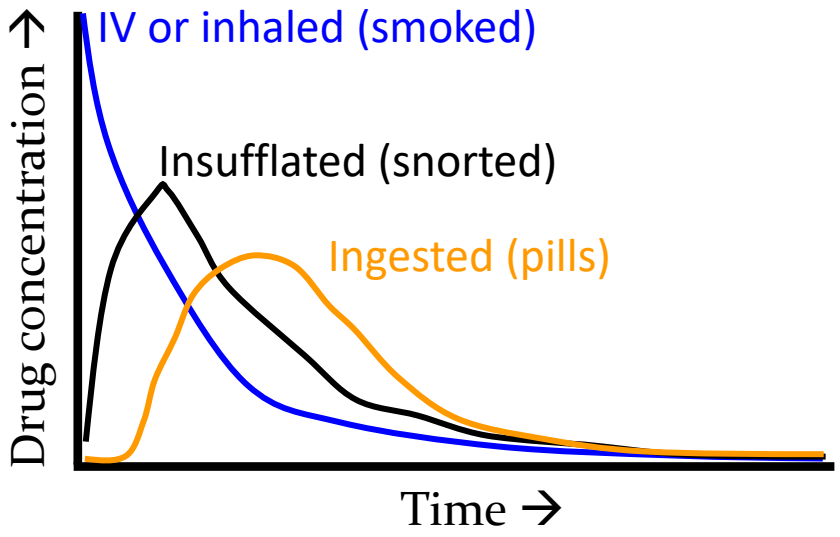
1. Drug administration → unusually large DA release
2. DA release due to expected drug use cues drug use behavior → unusually large DA release due to drug use
   - Stimuli (e.g., people, places, experiences, etc.) become paired with drug use
   - They become "triggers" for craving the drug and expecting the large DA increase

Tripp G, Wickens JR. Neurobiology of ADHD. Neuropharmacology. 2009 Dec;57(7-8):579-89.
Koob and Volkow. Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016 Aug; 3(8): 760–773.

Reward dysfunction in SUD cont.

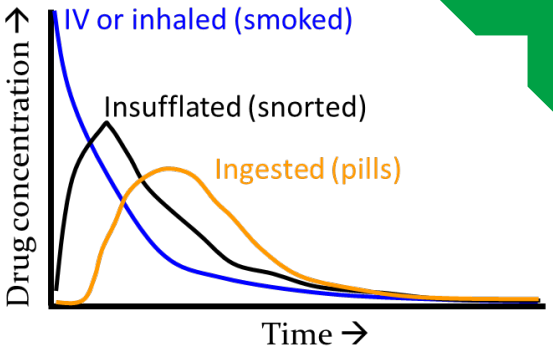
Tolerance:

- More drug needed to produce euphoria/"high"
  - Increased drug doses
  - Higher or more rapid absorption route of administration = greater euphoria/"high"



Tripp G, Wickens JR. Neurobiology of ADHD. Neuropharmacology. 2009 Dec;57(7-8):579-89.

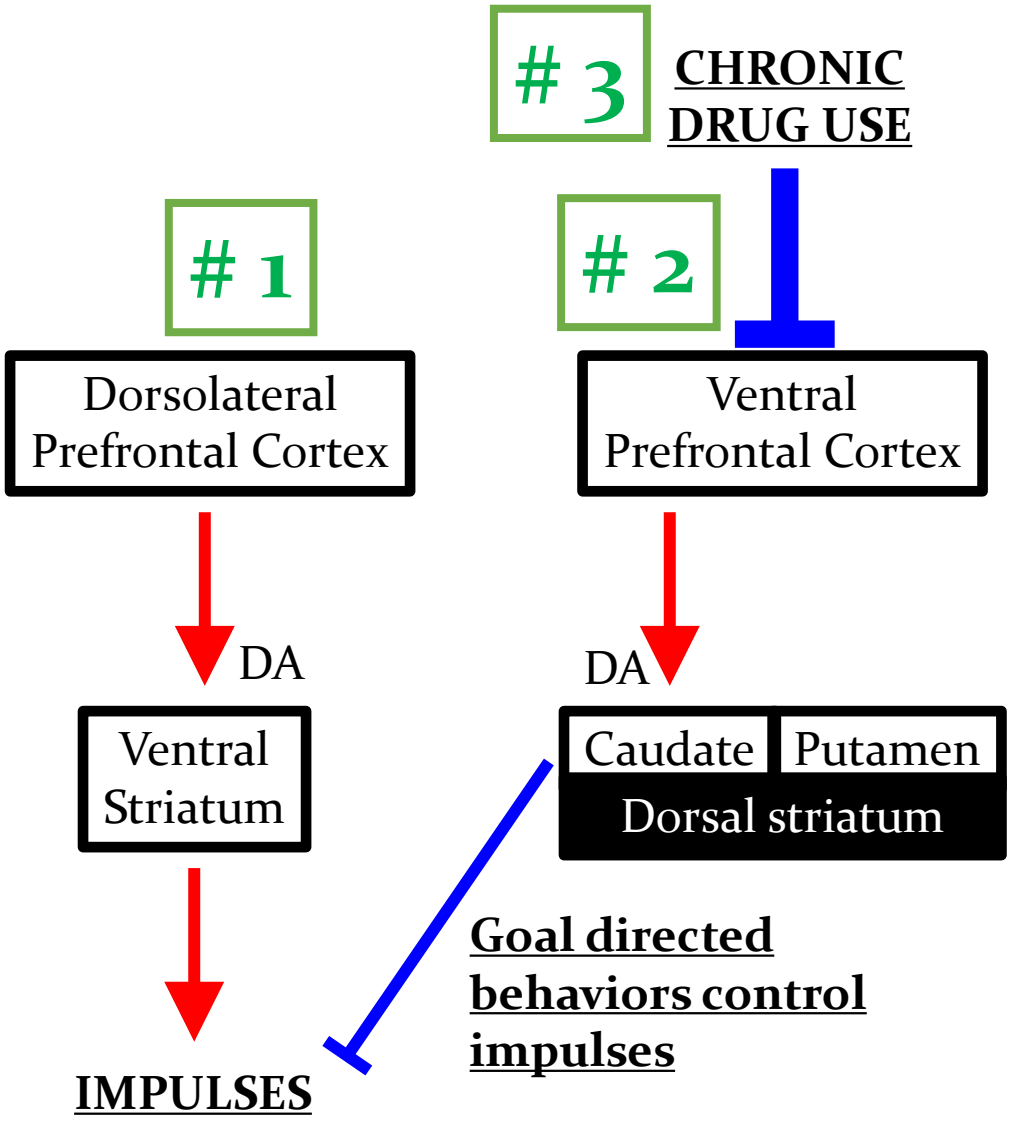
Hijacking Slowly



- The rate of absorption plays a part in SUD
- Many patients will begin using drugs orally (typically prescription opioids or others)
  - Once tolerant to oral doses (cannot attain euphoria), they search for new ways to attain the feeling
- Snorting or smoking creates a higher drug concentration in the blood and brain than swallowing a pill
  - Again, tolerance develops
- IV usage creates an even higher concentration
  - Yet again, tolerance develops

Disruption of Higher Brain Function

1. Rapid DA release into the **ventral striatum** drives attention to stimulus **(impulses)**
   - Note that a smoked amphetamine produces a similar effect
2. Slow, sustained DA release into **caudate** maintains attention & controls impulses **(cognition and goal directed behavior)**
   - Note that extended-release amphetamine (i.e., for ADHD) produces a similar effect
3. Chronic illicit drug use impairs the executive control processes **(reduced impulse control)**

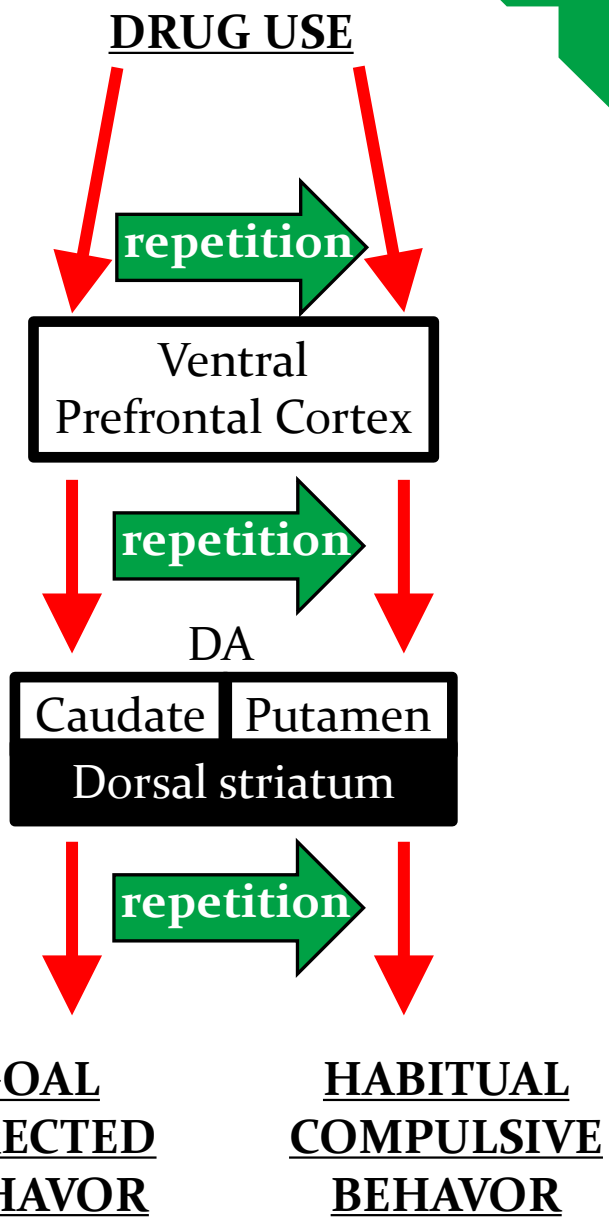


Volkow and Baler. NOW vs LATER brain circuits: implications for obesity and addiction. Trends Neurosci. 2015 Jun;38(6):345-52.

Compulsive Drug Use

1. Repetition of deliberate cognitive goal
   - Natural: brushing teeth before bed
   - Self-administration of drug
2. With repetition, the task is transferred from deliberate control by the caudate to a habitual task by the putamen
3. **Repeated drug use (plus drug itself activating pathway)**
   - **Accelerate development of habitual drug use behavior**
   - **"Wanting without liking"**

- Example:
  - Smoking nicotine is highly addictive despite weak "high" compared to other addictive drugs
  - See major repetition with smoking 1 or more packs (1 pack = 20 cigarettes) per day



Natarajan and Yamamoto. The Basal Ganglia as a Substrate for the Multiple Actions of Amphetamines. Basal Ganglia. 2011 Jul 1; 1(2): 49–57.

Considering Compulsive Behaviors

- Nearly everyone has experience in trying to change a habit
  - Common examples: drinking soda pop, eating fatty or high carbohydrate foods, or exercising
- How successful were you at changing initially?
- Did your brain circuits push you to “use” again?
- What if your whole life revolved around a habit?
  - Would that make it more or less difficult to stop?

Relapse

- Occurs after re-exposure to drug following a period of abstinence due to a combination of previously mentioned mechanisms in disease state which may include:
  - Anticipation of drug use (due to people, places, etc.)
  - Withdrawal
  - Lack of pleasure derived from natural activities
    - Can take a long time (years) for receptors to return to baseline function
  - Previous development of compulsive behavior
    - Habits are hard to break
  - Dysfunction of higher order cognitive processes
    - This can take years to return to normal

Understand an overview of substance use disorder treatment modalities

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Differing Pharmacotherapy Strategies

Strep throat (Acute)

- Appropriate antibiotic destroys infection
- No additional intervention is required

Type 2 Diabetes (Chronic)

- Life-style modifications
- Chronic treatment with insulin and/or other pharmacotherapy
- Disease stays under control if patient continuously complies with medications

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- Substance use disorder is a chronic disease and thus requires continuous therapy and monitoring

Treating SUD

- FDA-approved pharmacotherapy does not exist for all substances (such as cocaine, methamphetamine, phencyclidine, etc.)
- Non-pharmacologic therapies have extremely important mechanisms. For example:
  - Contingency management: non-drug reinforcers for continued abstinence
  - Learning to avoid cues (such as people, places, etc.) associated with prior drug use
  - Training/coping skills help to manage impulses
  - 12 step programs, religion, and non-religious recovery
- Treatment should combine treatment modalities (pharmacologic and non-pharmacologic)

McHugh et al. Cognitive-Behavioral Therapy for Substance Use Disorders. Psychiatr Clin North Am. 2010 Sep; 33(3): 511–525.

Pharmacotherapy

Animation for agonist, partial agonist, antagonist mechanism: https://youtu.be/w3d37cAL7VU

- Agonist replacement (full agonist with different pharmacokinetics)
  - Replaces the drug of abuse in more controllable manner (prevents withdrawal)
  - Examples:
    - Methadone for opioids (such as heroin)
    - Oral or transdermal nicotine for smoked or buccal nicotine
- Partial agonist (activation of drug receptor target at lower level of intensity)
  - Same as full-agonists except it activates the receptor at lower level than the drug of abuse
  - Examples:
    - Buprenorphine for opioids
    - Varenicline for nicotine

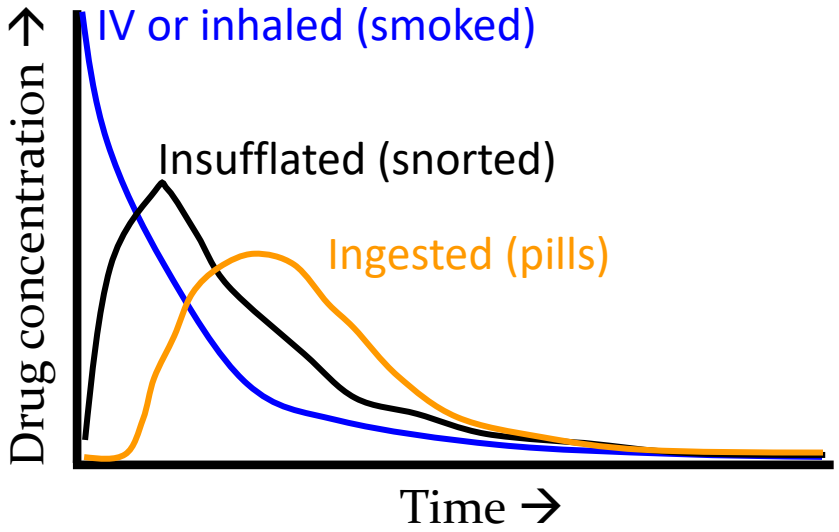
Pharmacotherapy cont.

Animation for agonist, partial agonist, antagonist mechanism: https://youtu.be/w3d37cAL7VU

- Antagonist (blocks drug effect)
  - Help patient resist relapse
  - Example:
    - Naltrexone for opioids and alcohol
- Negative reinforcement
  - Patient feels awful if they self-administer the drug of abuse and potentially will associate this sensation with future use
  - Example:
    - Disulfiram for alcohol
      - Alcohol metabolite accumulation leads to discomfort (and may cause vomiting)

Pharmacokinetics

- More slowly absorbed/eliminated medication (sustained concentrations rather than rapidly achieved peaks) has less effect than more rapidly absorbed drug of abuse but can ward off withdrawal and craving
  - See slow oral (gum) or transdermal (patch) absorption of nicotine vs rapidly absorbed cigarette
  - See more slowly absorbed, longer half-life oral methadone or buprenorphine compared to intravenous heroin



Pain and SUD

- According to Eckhart Tolle, all addictions are attempts to soothe pain
  - “Every addiction arises from an unconscious refusal to face and move through your own pain. Every addiction starts with pain and ends with pain.”
- Dr. Gabor Maté claims that all substances of abuse are pain killers and that any attempt to escape pain only creates more pain
  - Physical and emotional pain are felt the same in the brain (same areas affected)
  - “Whatever you do, don’t try to escape from your pain, but be with it.”
    - Tibetan Book of Living and Dying paraphrased by Gabor Maté

Paraphrased from https://www.youtube.com/watch?v=T5sOh4gKPIg Accessed 8-12-2019
Maté, G. (2008). In the realm of hungry ghosts: Close encounters with addiction. Toronto: Knopf Canada.

Living with Pain and SUD

- How can people be with their pain?
  - “Only through compassion can people confront their pain without running away”
- Showing empathy and compassion when treating patients with SUD helps to engage them in treatment and recovery
  - Support patients to be with themselves
- People with SUD need to be with their pain, but they must have support to do it
  - Paraphrased from Gabor Maté

Paraphrased from https://www.youtube.com/watch?v=T5sOh4gKPIg Accessed 8-12-2019

Conclusion

- The neuroscience of SUD is complex
  - The pathophysiology is different for all classes of medications
- Review the pharmacology
  - All substances of abuse and actions of abuse (gambling, etc.) increase levels of dopamine
- SUD/Addiction is a disease
  - Recognition of SUD involves continued substance use despite negative consequences
  - Treatment often involves social support programs, behavioral therapy, and pharmacologic treatments

QUESTIONS?

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