BASIC SCIENCES & ADDICTION

AUGUST 30, 2023

Addiction Medicine Board Review

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CONFLICT OF INTEREST DISCLOSURE

I, Waseem Khader, DO have nothing to disclose. I will not be discussing the “off-label” use of any treatments.

EDUCATIONAL OBJECTIVES

After attending this presentation, participants will be able to:

1. Describe neurobiological substrates of addiction.
2. Explain basic pharmacological principles related to addiction
3. Summarize 3 phases in the prevailing neurobiological model of addiction
4. Identify genetic factors that influence risk for addiction

BASIC SCIENCES: NEED TO KNOW

- Neural pathways and CNS regions implicated in or affected by addiction
  - Including prevailing model of 3 phases of addiction neurobiology
- Neurotransmitters:
  - how they mediate effects of various substances
  - How they are affected by various substances
- Hereditary & Epigenetic factors related to addiction
- Basics of pharmacokinetics as they pertain to addictive substances

QUESTION 1

The heritability of most substance use disorders falls in the range of....?

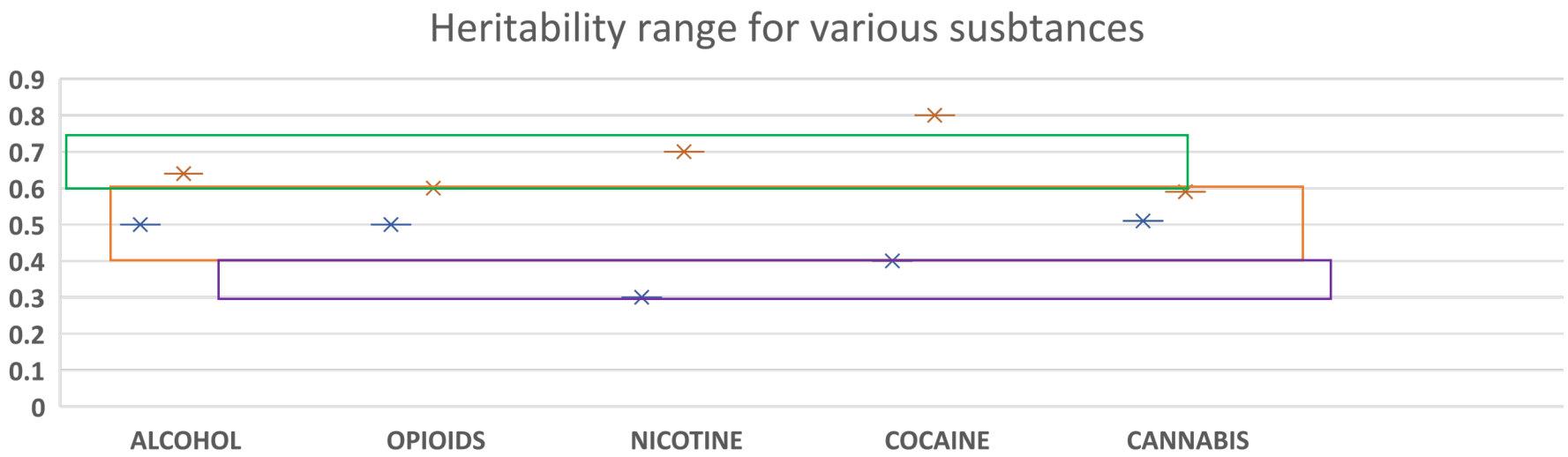
a) 10-20%
b) 30-40%
c) 40-60%
d) 60-75%

Question 1

ANSWER: c) 40-60%

- **Heritability describes the proportion of phenotypic variability (e.g. DSM5 substance use disorder -vs- not) in a population that is attributable to genetic variation (as opposed to environmental factors).** A 2021 review indicated heritability for substance use disorders as a whole is around 50%.

- **Studies of heritability are most often twin or adoption studies, which allows correction for the confound of postnatal exposure to parental psychopathology/substance use.**



Deak JD, Johnson EC. Genetics of substance use disorders: a review. Psychol Med. 2021 Oct;51(13):2189-2200.

QUESTION 2

A first-time user of cocaine reports a sudden rush of euphoria and energy. Which of the following neurological pathways is primarily responsible for this effect?

a. dorsal raphe nucleus' serotonin neurons projecting to ventral striatum

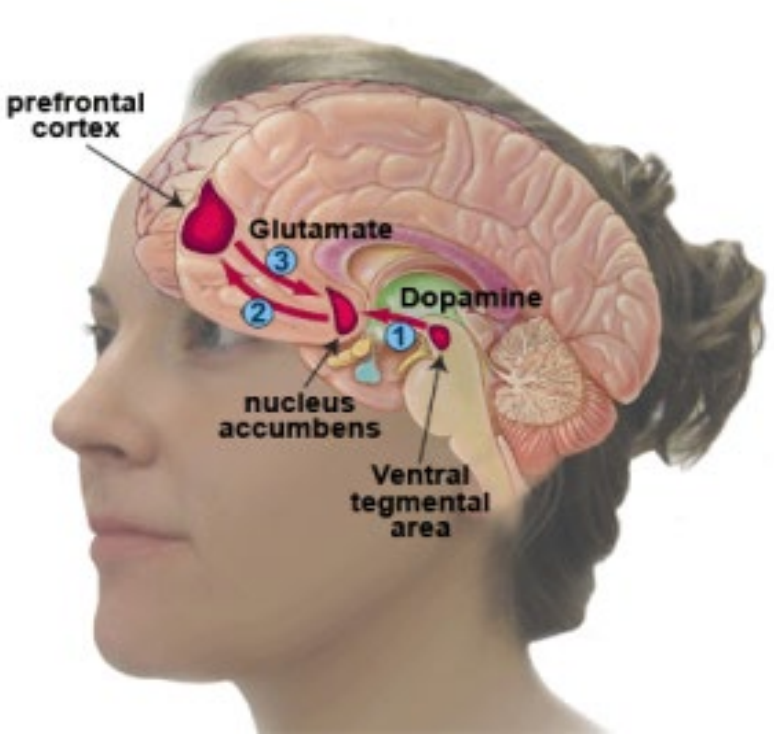
b. nucleus accumbens' dopamine neurons projecting to the extended amygdala

c. ventral tegmental area's dopamine neurons projecting to dorsal raphe nucleus

d. ventral tegmental area's dopamine neurons projecting to the nucleus accumbens

Question 2

ANSWER: d) ventral tegmental area's dopamine neurons projecting to the nucleus accumbens



- The **positive reinforcing effects of substances** and pleasurable sensations due to **dopaminergic projections from the ventral tegmental area (VTA) to the nucleus accumbens (Nacc) [located in the ventral striatum] represents the neural mechanism most consistently implicated in the development of addiction**, especially in early **binge-intoxication** stages.
- The dorsal raphe nucleus is a midbrain cluster of serotonergic neurons, which may be relevant for the effects of certain substances such as hallucinogens and MDMA but is not universally implicated in substance and behavioral positive reinforcement.
- While cocaine can inhibit reuptake of multiple monoamines, its principle euphorigenic and reinforcing effects are attributed to elevations in synaptic dopamine levels.

Koob GF(1), Volkow ND(2). Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016 Aug;3(8):760-73. doi: 10.1016/S2215-0366(16)00104-8.

Question 3

You are designing a medication to make persons with substance use disorders more resistant to cravings driven by dysphoria typical during early abstinence from substance use. Which of the following would be best the potential neurotransmitter target to antagonize?

a) Dopamine

b) Dynorphin

c) Gamma-aminobutryric acid (GABA)

d) Neuropeptide Y

Question 3

ANSWER: b) Dynorphin

Dynorphin is a dysphoria inducing substrate of opioid kappa receptors, which are blocked by buprenorphine.

Neurotransmitter	Activity level in withdrawal-negative affect stage
Dopamine	↓
Norepinephrine	↑
GABA	↓
Neuropeptide Y	↓
Dynorphin	↑
CRF	↑

Neural adaptations that occur in response to chronic overstimulation of the reward circuitry during chronic substance use have been described as an **“anti-reward system”.**

- It attempts to counterbalance the neuronal effects of addiction
- Is part of the process of **allostasis**.
- However, upon substance cessation, often hyperactive and contributes to the **negative affective state** typical of **withdrawal/early abstinence.**

Koob GF(1), Volkow ND(2). Neurobiology of addiction: a neurocircuitry analysis. Lancet Psychiatry. 2016 Aug;3(8):760-73. doi: 10.1016/S2215-0366(16)00104-8.

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Question 4

Given the functional effects of the polymorphisms for enzymes involved in alcohol metabolism listed in the side box, which genotype would be most likely to decrease the risk for developing alcohol use disorder?

a) ADH1B*1 homozygote & ALDH2*1 homozygote

b) ADH1B*1 homozygote & ALDH2*2 homozygote

c) ADH1B*3/ADH1B*1 & ALDH2*2/ALDH2*1

d) ADH1B*3 homozygote & ALDH2*2 homozygote

ADH1B*1:
slower alcohol dehydrogenase activity

ADH1B*2, ADH1B*3:
faster alcohol dehydrogenase activity

ALDH2*1:
faster aldehyde dehydrogenase activity

ALDH2*2:
slower aldehyde dehydrogenase activity

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Question 4

ANSWER: d) ADH1B*3 homozygote & ALDH2*2 homozygote

Alcohol is primarily metabolized in the liver in a two-step oxidation process, from alcohol to acetaldehyde (by **alcohol dehydrogenase**, ADH) and then from acetaldehyde to acetic acid (by **aldehyde dehydrogenase**, ALDH).

ADH1B∗1:

slower alcohol dehydrogenase activity

ADH1B∗2, ADH1B∗3:

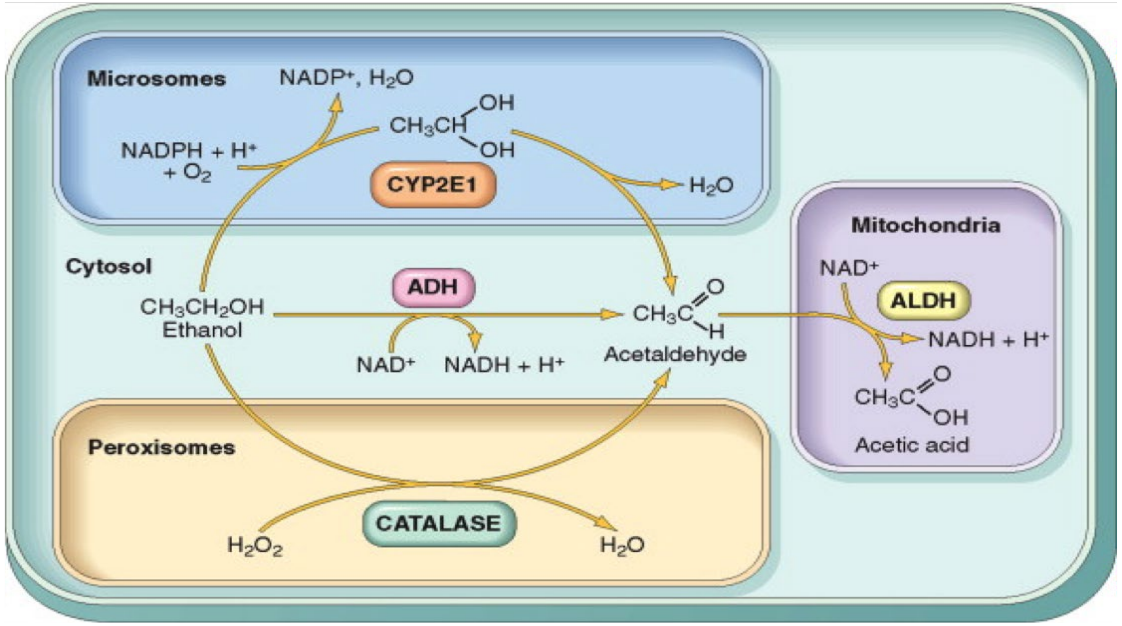
faster alcohol dehydrogenase activity

ALDH2∗1:

faster aldehyde dehydrogenase activity

ALDH2∗2:

slower aldehyde dehydrogenase activity



Question 4

ANSWER: d) ADH1B∗3 homozygote & ALDH2∗2 homozygote

ADH1B∗1:

slower alcohol dehydrogenase activity

ADH1B∗2, ADH1B∗3:

faster alcohol dehydrogenase activity

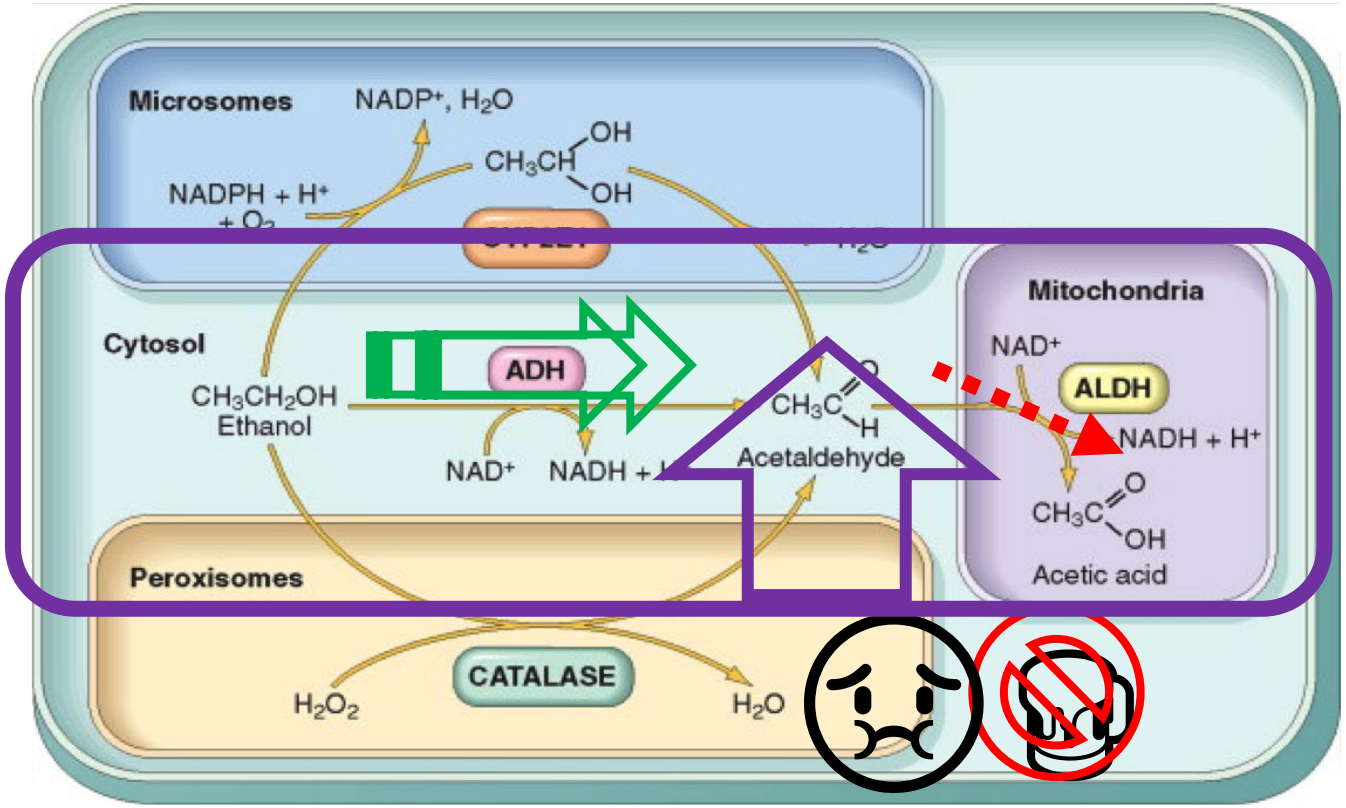
ALDH2∗1:

faster aldehyde dehydrogenase activity

ALDH2∗2:

slower aldehyde dehydrogenase activity

- **Acetaldehyde** buildup causes an aversive physical reaction (alcohol **flush reaction**, characterized by nausea, vasodilation, dizziness, & headaches).
- Any changes in metabolism that increase accumulation of acetaldehyde *increase* risk of this aversive reaction and consequently ***decrease*** risk of alcohol use disorder.
- What **increases acetaldehyde** accumulation?
  - **faster ADH activity**, e.g. ADH1B∗2 (East Asia), ADH1B∗3 (Africa),
  - **slower ALDH activity**, e.g., ALDH2∗2 (East Asia).



Tawa EA, Hall SD, Lohoff FW. Overview of the Genetics of Alcohol Use Disorder. Alcohol Alcohol. 2016 Sep;51(5):507-14

Question 5

Because _____ is the rate-limiting step in alcohol metabolism and is an easily saturated enzyme, when blood alcohol levels are high, a constant amount (rather than percentage) of alcohol is eliminated per unit of time, which is known as _____.

a) Alcohol dehydrogenase; first-order pharmacokinetics

b) Alcohol dehydrogenase; zero-order pharmacokinetics

c) Aldehyde dehydrogenase; first-order pharmacokinetics

d) Aldehyde dehydrogenase; zero-order pharmacokinetics

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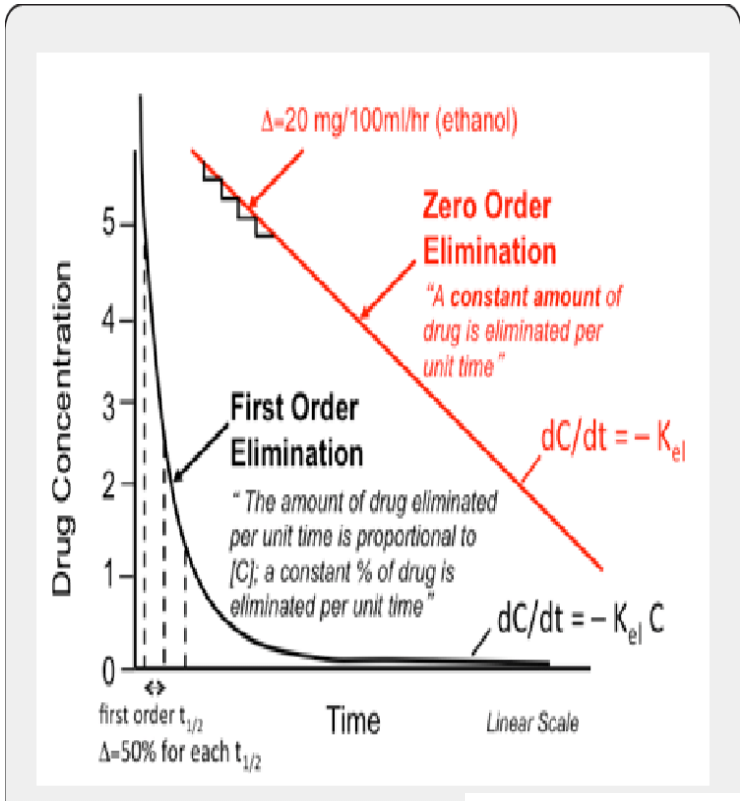
Question 5

ANSWER: b) Alcohol dehydrogenase; zero-order pharmacokinetics

Alcohol dehydrogenase = rate-limiting enzyme in alcohol metabolism

- easily saturated with its substrate of ethanol
- cannot keep up as concentrations of alcohol increase
- unlike most liver enzymes, it can only eliminate a constant ***amount*** of alcohol per unit of time when alcohol concentrations exceed its binding abilities: This is an example of **zero-order kinetics**



Most hepatic enzymes operate under **first-order kinetics**, wherein a constant ***percentage*** of a substrate is metabolized per unit of time. Such kinetics allow for the calculation of a substance's half-life ($t_{1/2}$)

Woodward JJ. The pharmacology of alcohol (2019) in The ASAM Principles of Addiction Medicine, 6th edition (p.109)

Question 6

Which of the following is an example of an epigenetic phenomenon?

a) Exposure to chronic neighborhood violence in childhood causes DNA methylation and deactivation of a gene encoding a neuronal growth factor

b) Exposure to a substance causes a DNA mutation in a gene encoding the serotonin transporter

c) Mitochondrial disorders are inherited exclusively from the mother of offspring

d) People in a certain country have exceedingly low risk for alcohol use disorder because alcohol is illegal and very difficult to access

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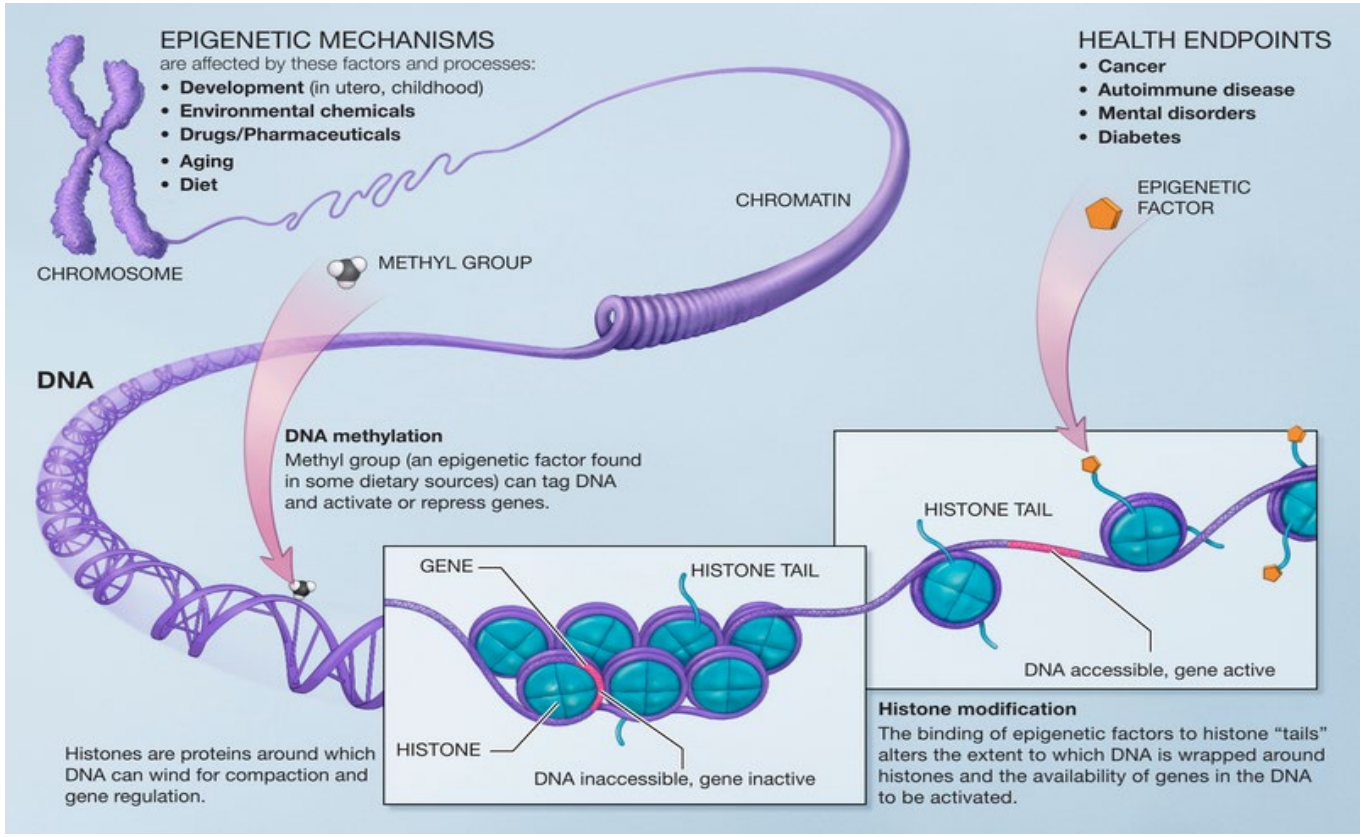
Question 6

ANSWER: a) Exposure to chronic neighborhood violence in childhood causes DNA methylation and deactivation of a gene encoding a neuronal growth factor

EPIGENETICS

- Alterations in expression of the genome that do **not** alter the DNA base pair sequence
- Common examples involve **DNA methylation** (which can turn on/off gene expression) and **histone modification** that affects how DNA is coiled
- Such epigenetic changes are often heritable to daughter cells and sometimes to offspring
- Epigenetics may play a role in mediating the effects of certain environmental risk factors for addiction (especially adverse childhood events). Such risk factors (e.g. poverty, unsafe neighborhoods) are often disproportionately present in minoritized communities.



Zhang L, Lu Q, Chang C. Epigenetics in Health and Disease. Adv Exp Med Biol. 2020;1253:3-55.
https://commons.wikimedia.org/wiki/File:Epigenetic_mechanisms.png Frank DA, et al. Problematic substance use in urban adolescents: role of intrauterine exposures to cocaine and marijuana and post-natal environment. Drug Alcohol Depend. 2014 Sep 1;142:181-90
Kim S, et al. Early adverse experience and substance addiction: dopamine, oxytocin, and glucocorticoid pathways. Ann N Y Acad Sci. 2017 Apr;1394(1):74-91.

Adverse Childhood Experiences

10 ACEs

- Parental Divorce or Separation
- Caregiver in Jail or Prison
- Caregiver Depression, Mental Illness or Suicide Attempt
- Domestic Violence or Threats
- Emotional Abuse or Neglect
- Sexual Abuse or Exposure
- Food, Clothing or Housing Insecurity
- Physical Abuse, Hitting or Slapping
- Caregiver Problem with Drugs or Alcohol
- Felt Unsupported, Unloved and Unwanted

Intergenerational Transmission

ACEs Being Studied

- Placement in Foster Care
- Bullying or Harassment at School
- Parent or Guardian Died
- Separated from Caregiver through Deportation or Immigration
- Medical Procedure(s) or Life Threatening Illness
- Frequent School or Neighborhood Violence
- Treated Badly Because of Race, Sexual Orientation, Place of Birth, Disability or Religion

Source: Center for Youth Wellness, ACE Questionnaire

Adverse Community Environments

- Poor Housing Quality and Affordability
- Discrimination
- Deterioration of Physical Environment
- Lack of Access to Educational Opportunities
- Low Sense of Collective Political and Social Efficacy

- Intergenerational Poverty
- Lack of Opportunity and Economic Mobility
- Poor Transportation Services or System
- Community Disruption
- Damaged Social Networks and Trust
- Unhealthy Products
- Long-Term Unemployment

Adapted From: Ellis W. Dietz BCR Framework *Academic Peds* (2017)

Question 7

Which of the following INCORRECTLY pairs a neuroanatomical region with one of its putative roles in the risk and/or protection from substance use disorders?

a) Dorsal striatum → Executing habitual substance use behaviors

b) Dorsolateral prefrontal cortex → Cognitive flexibility and planning

c) Extended amygdala → Positive reinforcement & euphoria

d) Orbitofrontal cortex → Processing motivational salience of stimuli

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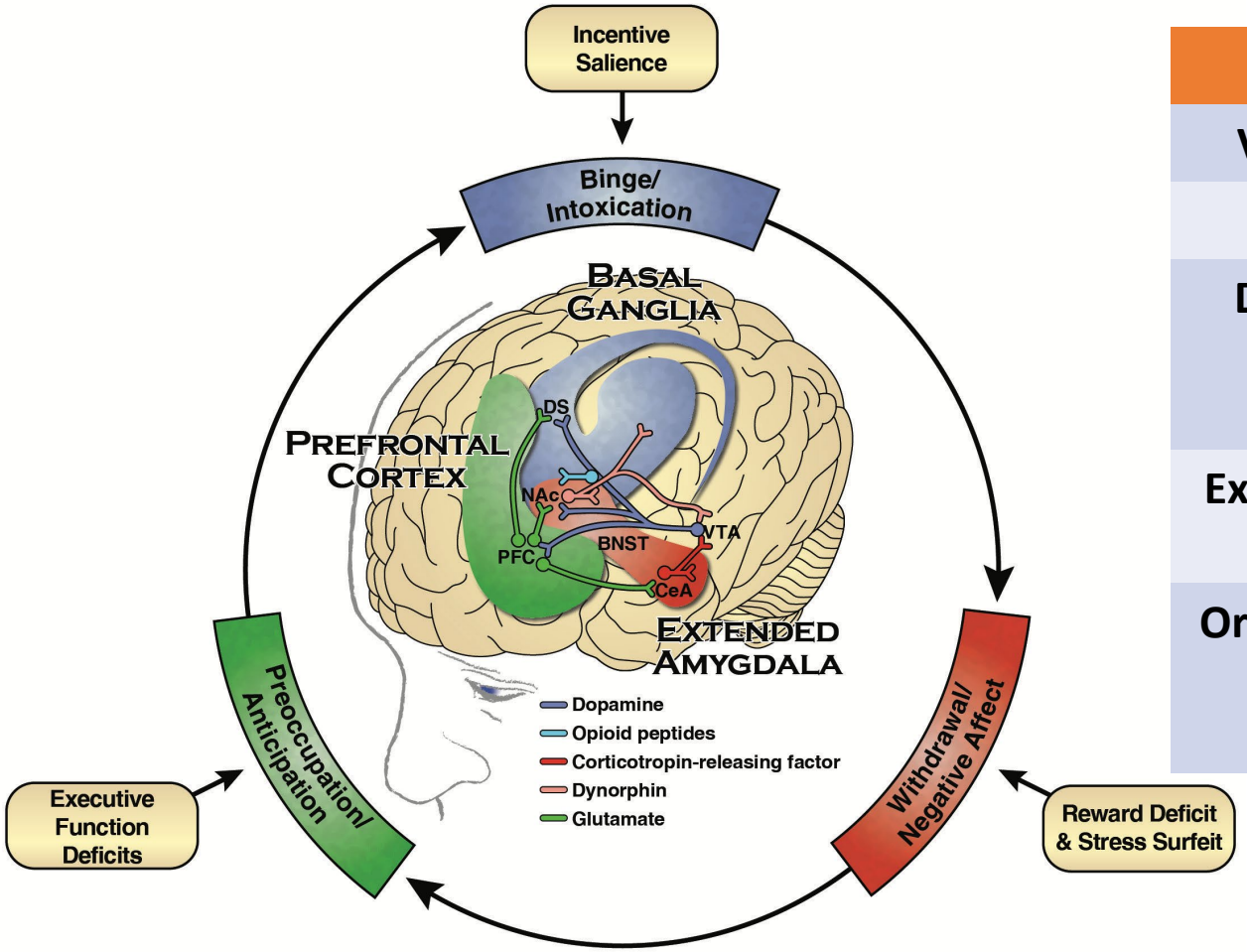
Question 7

ANSWER: c) Extended amygdala → Positive reinforcement & euphoria



BRAIN REGION	ROLE IN ADDICTION
Ventral striatum	Reward processing & prediction, euphoria
Dorsal striatum	Habitualization of drug seeking & taking
Dorsolateral PFC	(malfunctioning) Preoccupation, craving, lack of planning, delay discounting, poor executive functions, poor impulse control
Extended amygdala & Habenula	Withdrawal related stress/dysphoria; encoding negative feedback
Orbitofrontal cortex	Salience attribution (learning, predicting & decision making for emotional & reward related behaviors)

https://addiction.surgeongeneral.gov/executive-summary/report/neurobiology-substance-use-misuse-and-addiction

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Question 8

Which of the following is a TRUE statement about genetic and environmental influences on the development of addiction?

a) Both genetic & environmental factors are equally influential on risk for substance initiation and substance addiction

b) Environmental factors exert a greater influence on risk for substance initiation than for substance addiction

c) Genetic factors exert a greater influence on risk for substance initiation than for substance addiction

d) Genetic factors have no influence on substance initiation.

Question 8

ANSWER: b) Environmental factors exert a greater influence on risk for substance initiation than for substance addiction

- Given the average heritability of addiction is 50%, one can infer about a 50-50 split for genetic vs environmental influence on the development of substance use disorders.
- Genetics also influence substance initiation (thus also indirectly influencing addiction risk) since genetics influences personality traits such as impulsivity & reward dependence as well as psychiatric disorders that influence drug initiation risk, but environmental factors are stronger in determining initiation of substance use (e.g., never use, early-onset use, late-onset use).
- Genetics, however, plays a bigger role in determining risk among those who initiate a substance to go on to development unhealthy use/addiction, especially as adolescents transition into adulthood.

Rhee SH, et al. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. Arch Gen Psychiatry. 2003 Dec;60(12):1256-64.
Fowler T, et al. Exploring the relationship between genetic and environmental influences on initiation and progression of substance use. Addiction. 2007 Mar;102(3):413-22.
Meyers JL, Dick DM. Genetic and environmental risk factors for adolescent-onset substance use disorders. Child Adolesc Psychiatr Clin N Am. 2010 Jul;19(3):465-77.

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Question 9

Which of the following correctly matches the primary inhibitory neurotransmitter system in the CNS to the pharmacologic characteristics of its receptor?

a) $GABA_A$ receptor → Metabotropic heterodimer composed of R1 and R2 heptahelical membrane protein subunits

b) $GABA_A$ receptor → Ionotropic transmembrane pentamer consisting of 2α, 2β, 1γ subunits

c) Glutamate NMDA receptor → Ionotropic assembly of seven subunits (GluN1, GluN2A-D, GluN3A-B) into tetrameric receptor complexes

d) Serotonin 5HT-1A receptor → Metabotropic polypeptide chain of 422 amino acids with an α-helical structure, forming 7 transmembrane domains

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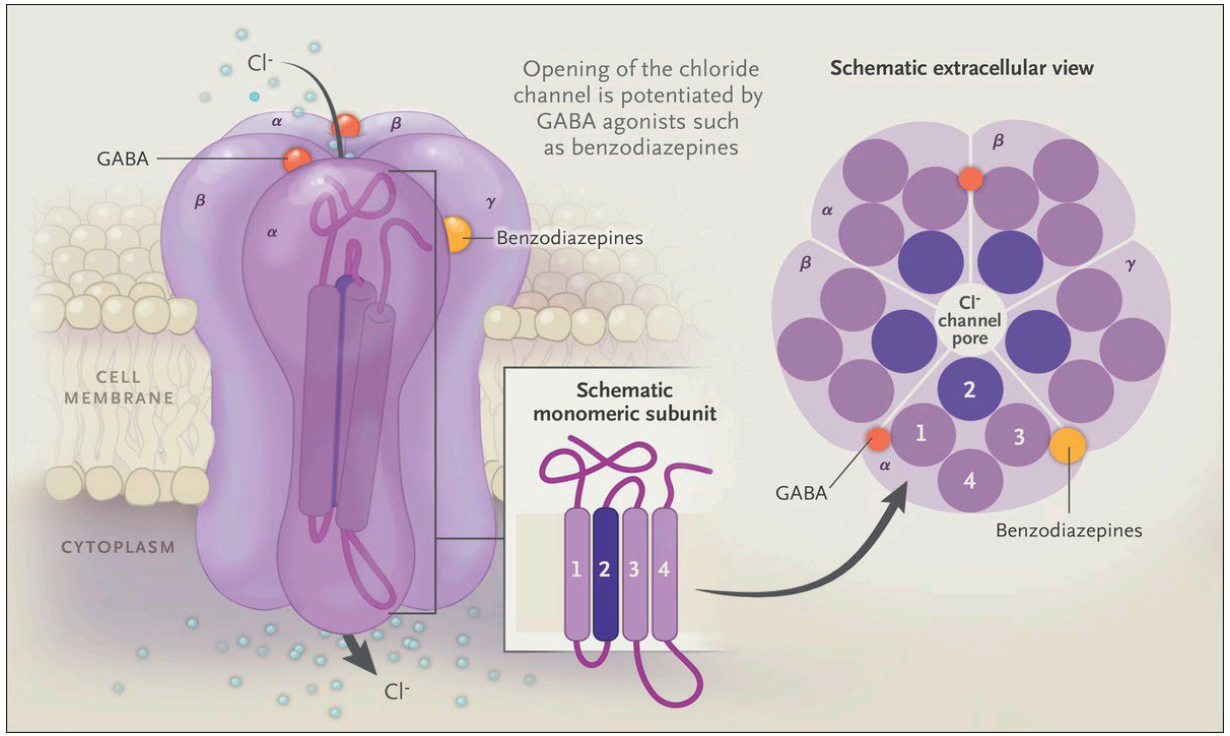
Question 9

ANSWER: b) $GABA_A$ receptor → Ionotropic transmembrane pentamer consisting of 2α, 2β, 1γ subunits

RECEPTOR	TYPE
D1-D5	Metabotropic
Nicotinic Ach	Ionotropic
Muscarinic Ach	Metabotropic
5HT 1, 2, 4-7	Metabotropic
5HT3	Ionotropic
α & β adrenergic	Metabotropic
Glu NMDA, AMPA	Ionotropic
GABA-A	Ionotropic
GABA-B	Metabotropic



The ASAM Principles of Addiction Medicine, 6th edition

Soyka M. N Engl J Med 2017;376:1147-1157.

Question 10

Which of the following neurotransmitters is primarily responsible for the increase in blood pressure and heart rate during substance withdrawal?

a) Glutamate

b) GABA

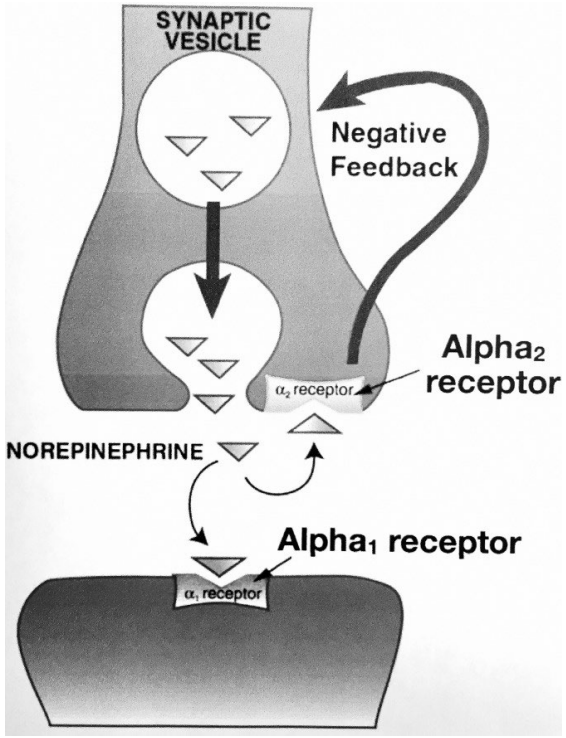
c) Dopamine

d) Norepinephrine

Question 10

ANSWER: d) Norepinephrine

Receptor	*Physiologic Action (Agonism)*
α1	Constriction of vascular smooth muscle
	Contraction of radial muscle of the eye
	Contraction of the vas deferens smooth muscle
α2	Inhibition of norepinephrine release from presynaptic neuron
	Centrally induced sedation via locus ceruleus
	Centrally mediated pain modification via dorsal horn
	Inhibition of insulin release from pancreatic β cells
β1	Increased cardiac output (increased chronotropy, dromotropy, inotropy)
	Increased renin release from kidney
β2	Bronchial smooth muscle relaxation
	Vascular smooth muscle relaxation (vasodilation)
	Reduction of mast cell degranulation and histamine release
β3	Increased adipose tissue lipolysis

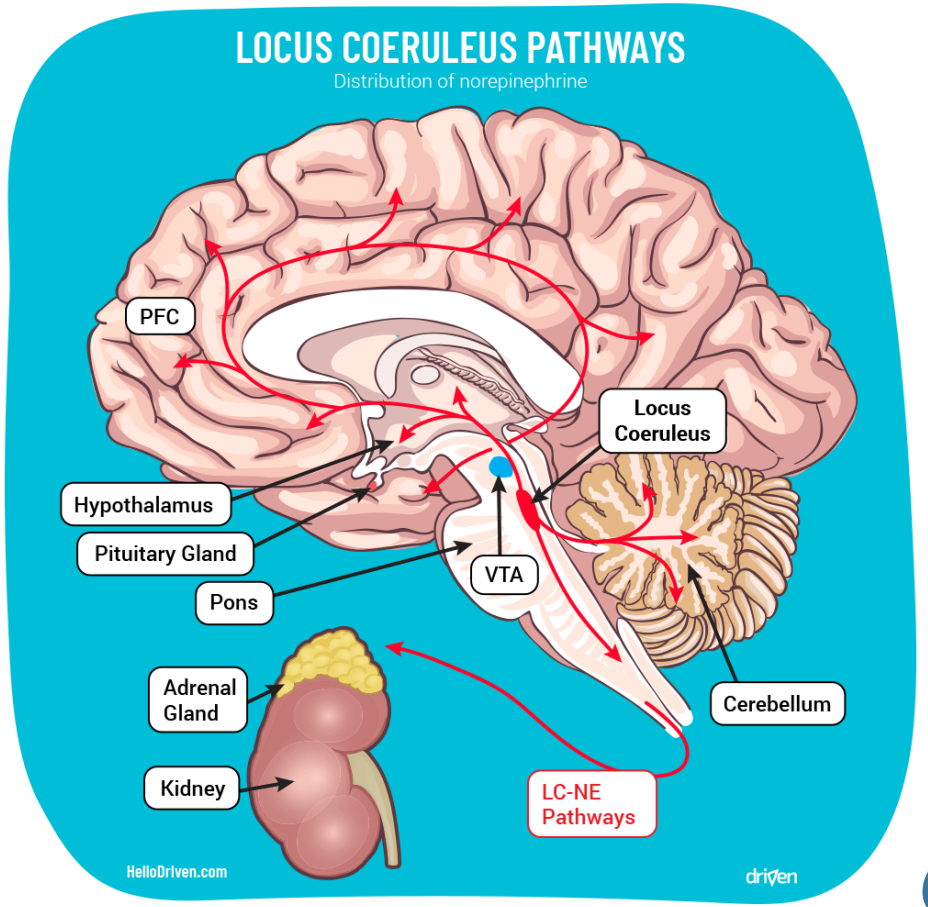


Giovannitti, J. A., Jr, Thoms, S. M., & Crawford, J. J. (2015). Alpha-2 adrenergic receptor agonists: a review of current clinical applications. *Anesthesia progress*, *62*(1), 31–39. https://doi.org/10.2344/0003-3006-62.1.31

Question 10

ANSWER: d) Norepinephrine

- NE plays a significant role in stress-induced reinstatement of drug-seeking behaviors as well as withdrawal processes
- In an acute setting, peripheral NE signaling via the sympathetic nervous system, in concert with central NE signaling upon the HPA axis, instigate the “flight or fight” response.
- LC contains the largest number of central noradrenergic neurons and they project to almost all areas of the forebrain
- Noradrenergic drugs such as the α2 agonists clonidine and lofexidine are effective at reducing opioid withdrawal symptoms



Downs, A. M., & McElligott, Z. A. (2022). Noradrenergic circuits and signaling in substance use disorders. *Neuropharmacology*, *208*, 108997. https://doi.org/10.1016/j.neuropharm.2022.108997

Question 11

Which of the following exerts its effects in the central nervous system by mimicking retrograde signaling?

a) Alcohol

b) Cathinone

c) Mirtagynine

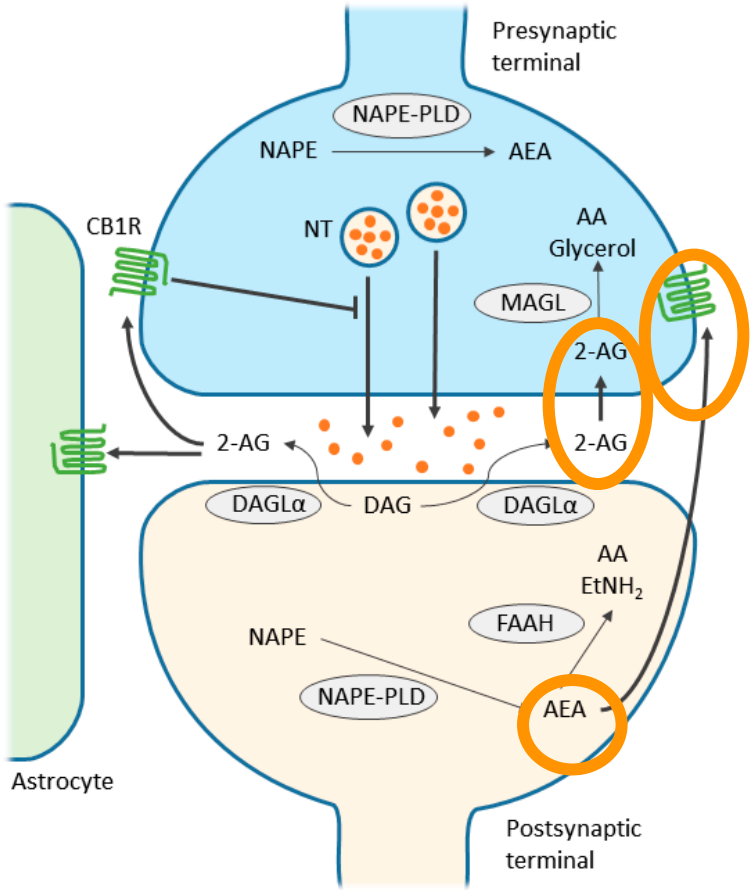
d) Tetrahydrocannabinol

Question 11

ANSWER: d) Tetrahydrocannabinol

Retrograde signaling

- Post-synaptic neurons communicate to pre-synaptic neurons
- Classic examples are **endocannabinoids** and nitrous oxide



AEA = anandamide

AA = arachidonic acid

DAG = diacylglycerol

2-AG – 2-arachodonal glycerol

FAAH = fatty acid amide hydrolase

MAG = monoacylglycerol lipase

Zou S, Kumar U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. Int J Mol Sci. 2018 Mar 13;19(3):833.


KEEP
CALM
AND
CARRY
ON