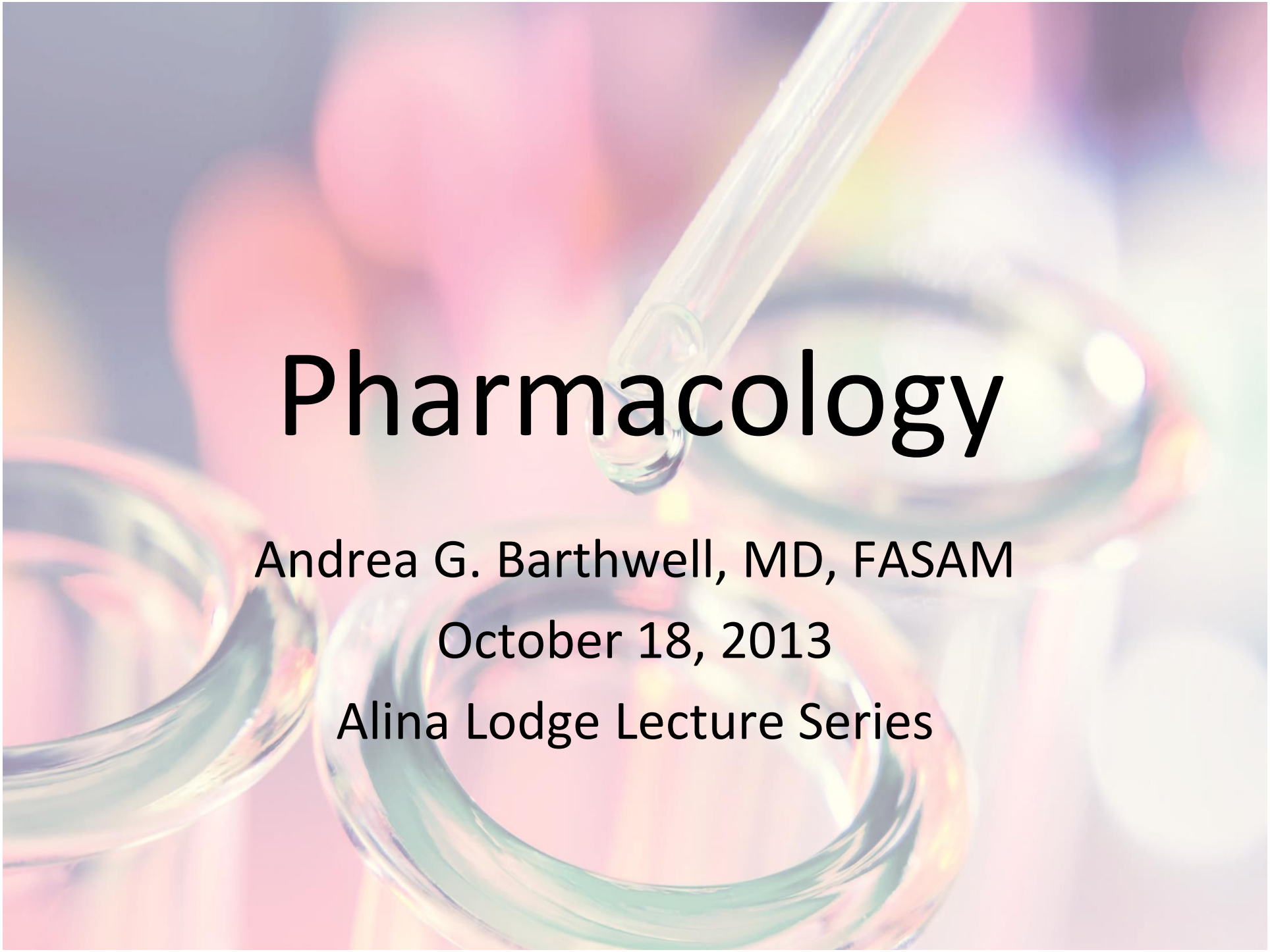

Pharmacology

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Alina Lodge Lecture Series

Disclosures

- No conflict of interest with this content
- Consultant: Braeburn Pharmaceuticals
- Director: Two Dreams
- Medical Director: Encounter Medical Group, P.C.

Objectives

- Define and discuss basic principles of pharmacology such as pharmacokinetics, pharmacodynamics, psychotropic drugs, tolerance, dependence, withdrawal, metabolism, eliminations, therapeutic dose, lethal dose, and effective dose
- To list, define, and illustrate principles of pharmacology using substances of abuse
- To explain and discuss the pharmacological properties of each of the classes
- To give clinicians a method to use for interpretation of client behavior, complaints, and physical signs

Schedule

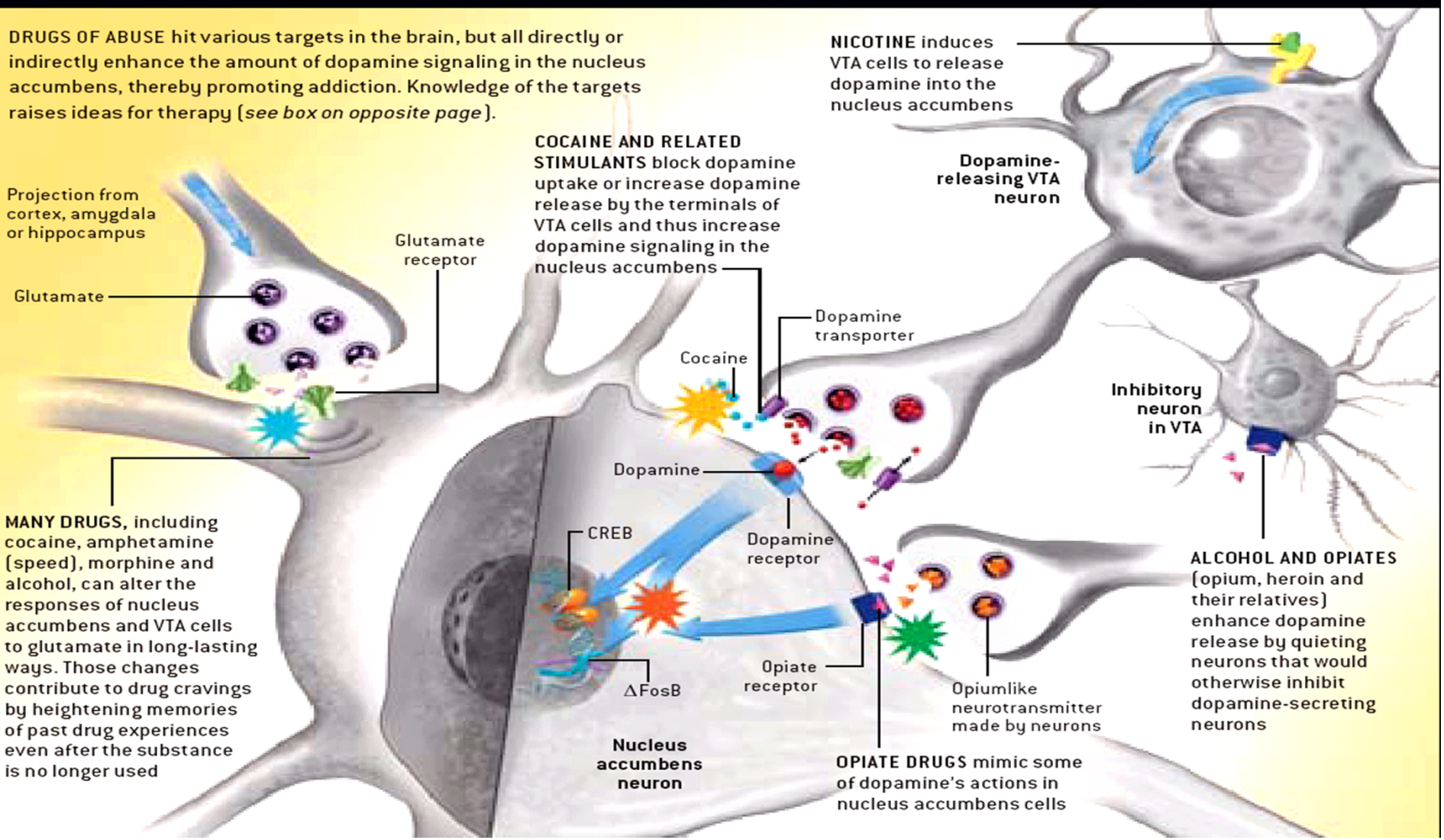
- Introduction
- Define basic principles of pharmacology
- Discuss drug outlines and introduce classes of drugs
- Alcohol
- Cannabis
- Hallucinogens, including PCP
- Inhalants
- Opioids
- Sedative, hypnotics, anxiolytics
- Stimulants, including cocaine and caffeine
- Q&A

Pharmacology

- The scientific study of the actions of drugs and their effects on a living organism and the effect of the living organism on the way the drug exerts its effects
- The classes of drugs causing substance-related disorders are not fully distinct
- All drugs that are taken in excess have in common direct activation of the brain reward system, involved in reinforcement of behaviors and production of memories
- Activation of reward system so intense that normal activities may be forgotten

DIFFERENT DRUGS, SAME ULTIMATE EFFECT

DRUGS OF ABUSE hit various targets in the brain, but all directly or indirectly enhance the amount of dopamine signaling in the nucleus accumbens, thereby promoting addiction. Knowledge of the targets raises ideas for therapy (*see box on opposite page*).



Substance-Related Disorders

- Substance use disorders
- Substance induced disorders
  - Intoxication
  - Withdrawal
  - Other substance/mediation induced mental disorders
    - Psychotic, bipolar and related, depressive, anxiety, obsessive-compulsive and related, sleep, sexual dysfunctions, delirium, and neurocognitive disorders
    - Class specific

Basic Principles

- Psychotropic substance
- Pharmacokinetics
- Pharmacodynamics
- Absorption
- Metabolism
- Action
- Excretion

Psychotropic Substance

- Chemical substance that crosses the blood–brain barrier and acts primarily upon the central nervous system where it affects brain function, resulting in alterations in perception, mood, consciousness, cognition, and behavior
- Used to purposefully alter one's consciousness, or as entheogens, for ritual, spiritual, and/or shamanic purposes, as a tool for studying or augmenting the mind
- Have therapeutic utility, e.g., as anesthetics, analgesics, or for the treatment of psychiatric disorders.

Psychotropic Substance, Continued

- Subjective changes in consciousness/mood that user finds pleasant (e.g. euphoria) or advantageous (e.g. increased alertness); thus reinforcing
- Used excessively despite health risks or negative consequences
- Psychological and physical dependence (*"addiction"*) may develop
- In some cases experiences may be so unfriendly and uncomforting that the user may never want to try the substance again
  - Deliriants (e.g. *Jimson weed*) and powerful dissociatives (e.g. *Salvia divinorum*)
  - Purely psychedelic considered non-addictive (e.g. LSD, psilocybin, mescaline)
  - "Psychedelic amphetamines" or empathogen-entactogens (such as MDA and MDMA) w/ stimulant/euphoriant effect, thus addiction potential

Pharmacology

- Pharmacokinetics: Study of biological factors that influence drug action (onset, duration, etc.)
- Pharmacodynamics: Study of drug receptor interaction
- Both interaction between chemical properties of the drug and physiological properties of the organism

Pharmacokinetics

- Dose
- Route of administration
- Absorption and distribution
  - Bioavailability
  - Passage through membranes
- Metabolism- inactivation and excretion
  - Liver
  - Concept of half life (t ½)

Efficacy, Intrinsic Activity, and Effectiveness

- Efficacy (E_{max}) refers to the maximum response achievable from a drug
- Intrinsic activity is a relative term that describes a drug's efficacy relative to a drug with the highest observed efficacy
- Effectiveness refers to the ability of a drug to produce a beneficial effect
  - 'method' effectiveness describes the effect achievable if the drug was taken as prescribed
  - 'use' effectiveness is the effect obtained under typical use with variable adherence

Therapeutic Use v. Abuse

- Dose and Frequency of Dosing
  - Lower, fixed regimes vs. higher, escalating use
- Route of Administration
  - Oral vs. injection, smoking, snorting
- Expectation of Drug Effects
  - Expectation of clinical benefits vs. euphoria “high”
- Context of Administration
  - School, clinic, home vs. bar, discotheque

Route of Administration

TWO DREAMS

- Gastrointestinal
  - Locations: mouth, esophagus, stomach, small intestine, large intestine, rectum
  - Methods: sublingual, biliary, mucosal
- Pulmonary
  - Location: Nose, lungs
  - Method: Mucosal, alveolar
- Integumentary
  - Method: topical/transdermal, intradermal, subdermal
- Muscular
- Vascular
- Neural
  - Location: CNS, PNS
  - Method: intrathecal, epidural, regional, local

Absorption

TWO DREAMS

- Variables due to Route of Administration
  - Bolus size
  - Rate of onset
  - Effective dose arriving at brain (first pass metabolism)
- Goal
  - Get drug to the brain
  - Most direct route with greatest surface area is fastest method of absorption

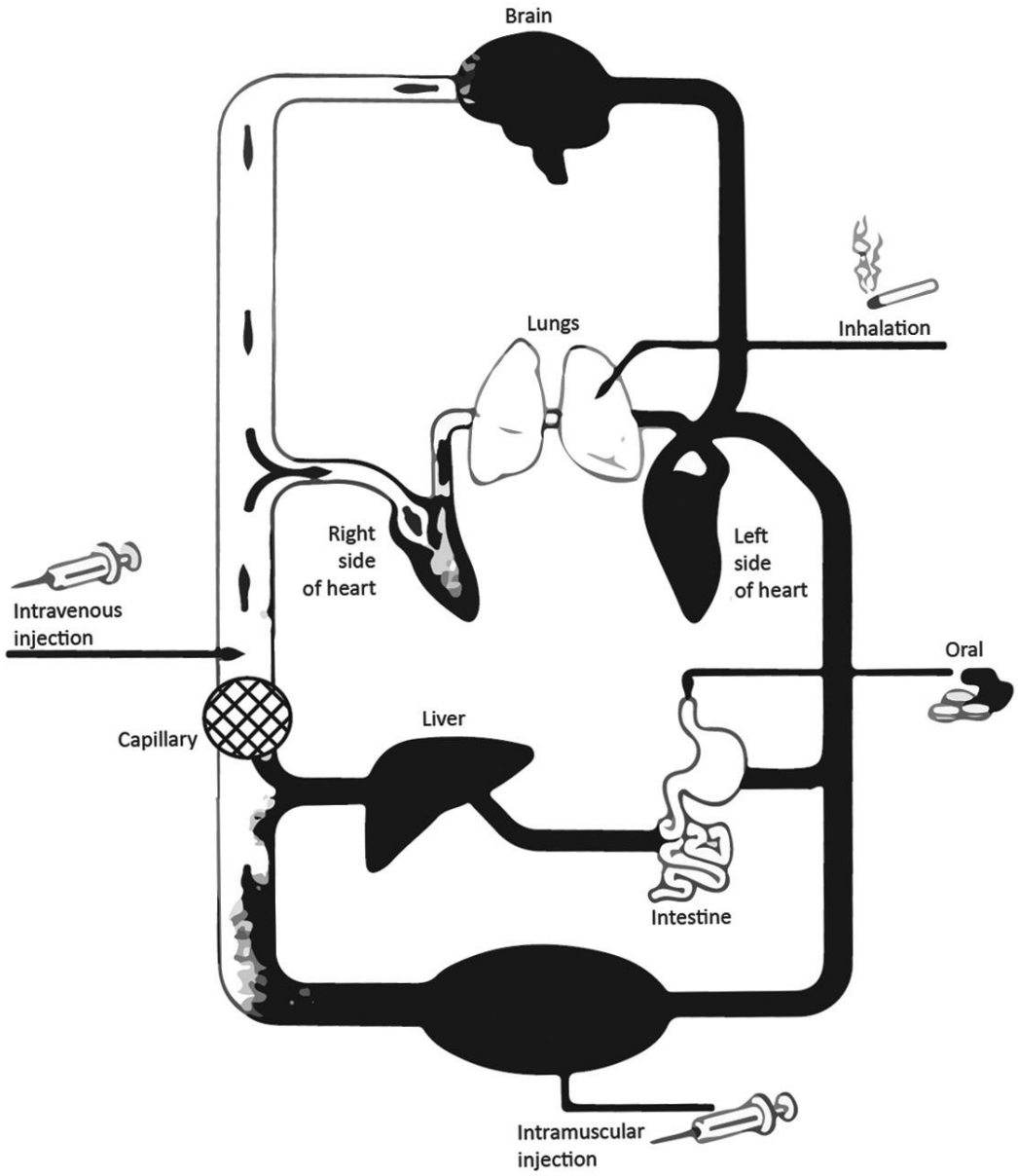
Distribution

TWO DREAMS

- Mouth to brain- 30 minutes
- Nose to brain- 3-5 minutes
- Veins to brain- 13 seconds
- Inhalation- lungs to brain- 7 seconds

Absorption, Distribution and Metabolism

- Sites of Absorption
- Sites of Loss
- Sites of Undesired Action
- Sites of Desired Action
- Sites of Metabolism
- Sites of Excretion



TWO DREAMS

Modified from *Drugs, Society, and Human Behavior,* McGraw-Hill Companies, Inc.

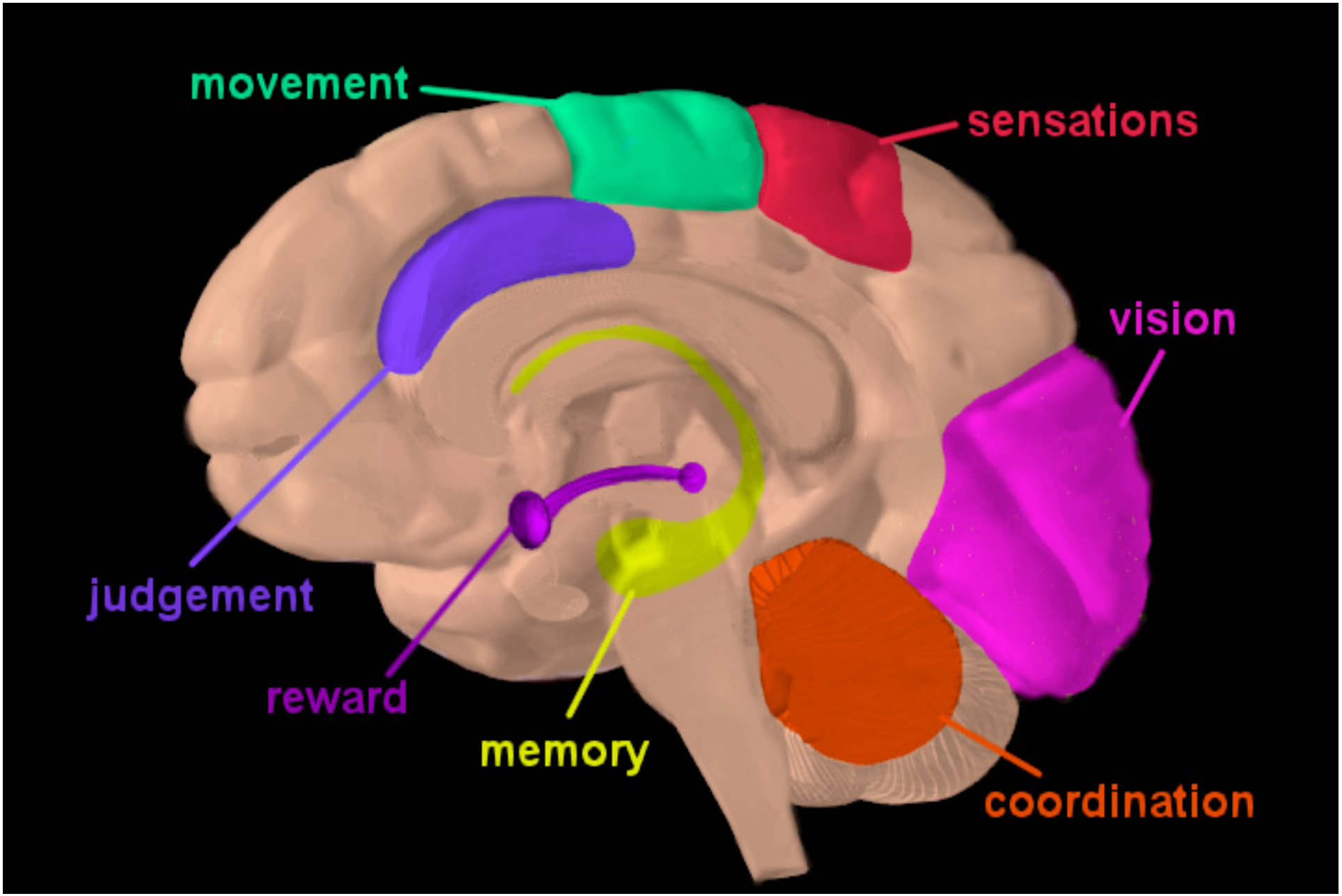
Action

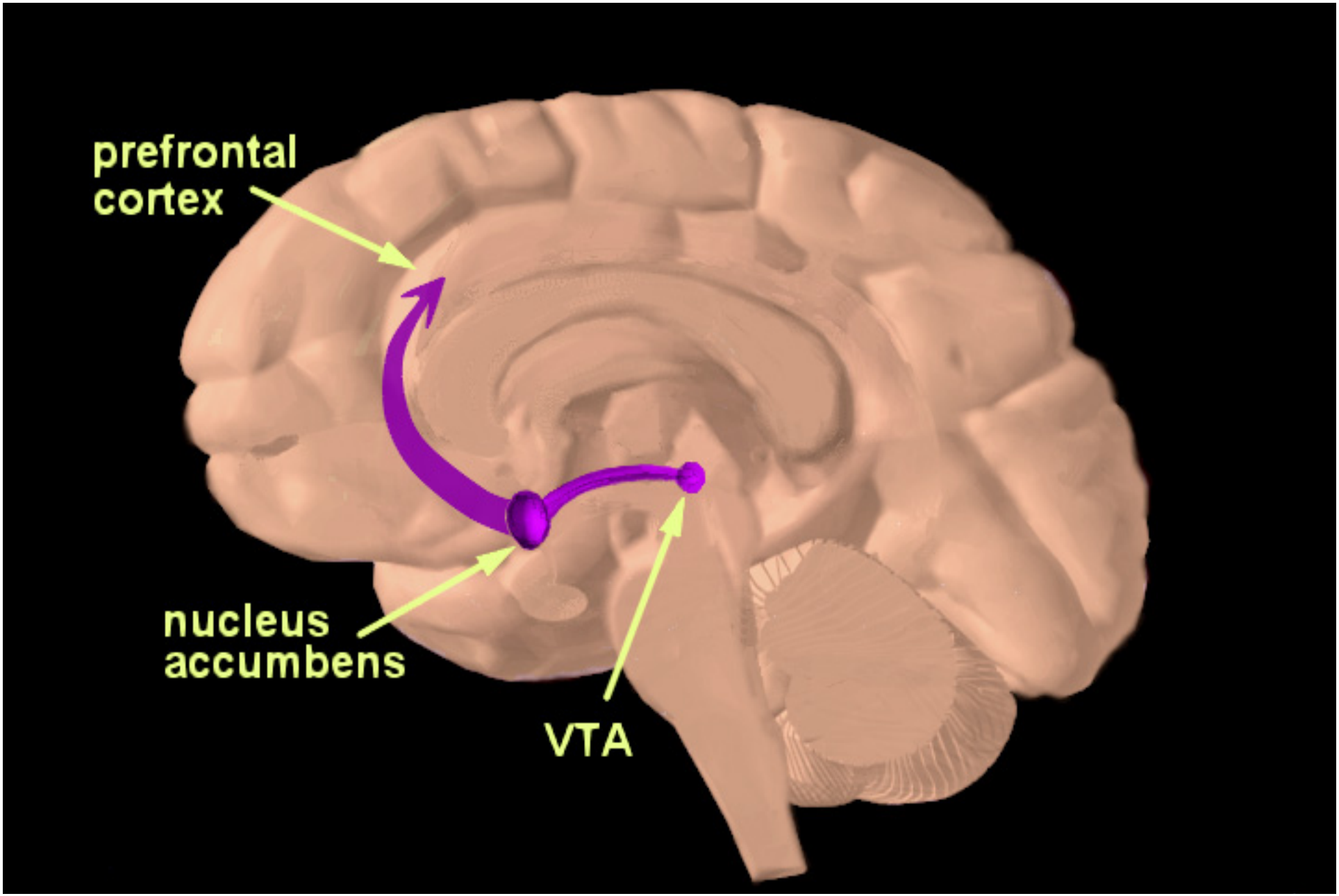
TWO DREAMS

- Site of desired action
- Site of undesired action

Receptors and Response

- Affinity and Potency
- Efficacy and Power


movement
sensations
vision
judgement
reward
memory
coordination


prefrontal
cortex
nucleus
accumbens
VTA

Drug Safety

TWO DREAMS

- Kinetic principles determine safety of drug
- Safety of drug related to dose response curve
- Effective Dose- response in 50% of individuals
- Lethal dose- dose at which substance causes death in 50%
- Therapeutic Index- LD50/ED50
  - Higher TI, safer
  - TI < 10, high OD risk

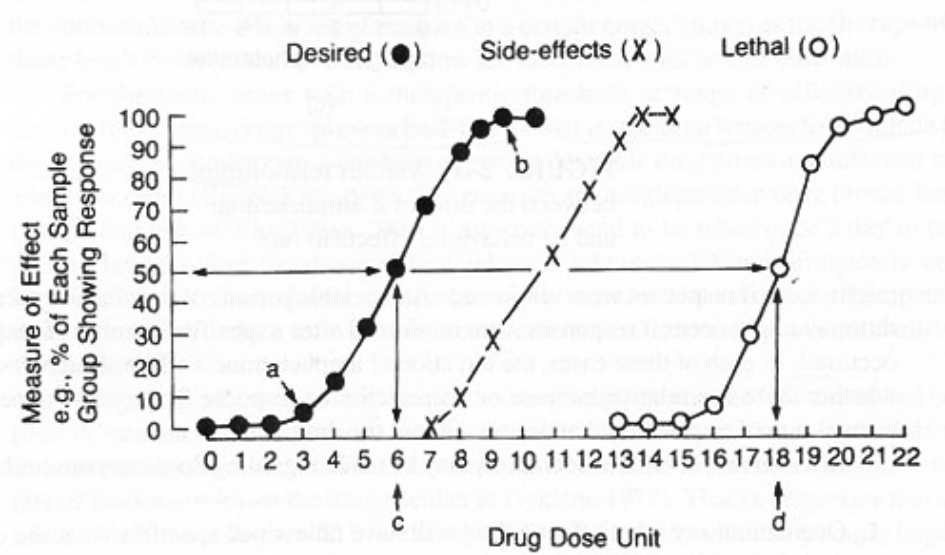


FIGURE 2–2 Stylized dose–response functions depicting (*a*) the threshold dose, (*b*) maximal (desired) response, (*c*) the ED50 of the drug, and (*d*) the LD50 of the drug.

Metabolism

- Purpose and effect: biochemical modification of pharmaceutical substances through specialized enzymatic systems
  - converts lipophilic chemical compounds into more readily excreted hydrophilic products
  - rate determines the duration and intensity of a drug's action
- Three phases- modify, conjugate, excrete
  - Small molecules to kidney
  - Large molecules to feces or back into distribution for another round of action

Types of Metabolism

- First order: t ½ specific to each substance, range from seconds to days
  - Four half lives to steady state
  - Six half lives to eliminate drug
- Zero order: metabolize at a constant rate regardless of initial dose
  - Risk of OD high with first dose
  - Alcohol is zero order
- First Pass metabolism

Elimination

- Kidneys as urine
- Intestines as feces
- Lungs as particles
- Skin as sweat
- A special note about vomiting

Pharmacokinetics – Factors Affecting Metabolism

- Presence of enzymes
- Age
- Nutrition
- Sex
- Disease

Pharmacodynamics

- Receptors: protein structures serving as substrates for endogenous ligands (neurotransmitters) and exogenous ligands (drugs)
- Agonist: drugs that bind to the receptor and mimic the effect of an endogenous ligand
- Antagonist: drugs that bind and block or produce no effect, but prevent agonists from binding

Dose response relationship

- Describes the amount of biological (and behavioral) response for a given concentration of drug
- Drugs can have wide range of effects depending upon the dose administered (ex- alcohol)

Binding and effects

- Bonds between the ligand and receptor produces a cascade of cellular events involving subcellular components of the cell producing clinically relevant effects and side effects

Key Concepts

- Selectivity- the capacity of a drug to produce an effect in preference to another
- Affinity- how the molecule fits the receptor, related to potency
- Efficacy- how well the molecule initiates an effect, ability to cause maximal effect, related to power
- Potency- relative term, amount needed to get desired effect
- Purity- molecules/ defined volume, concentration issue

Tolerance Defined

- Decreased sensitivity to a drug that develops as a result of exposure
  - Greater amounts needed to get desired effect
- Metabolic changes- reduced availability
- Functional changes- reduced efficacy at the target

Using Pharmacology to Explain Addiction

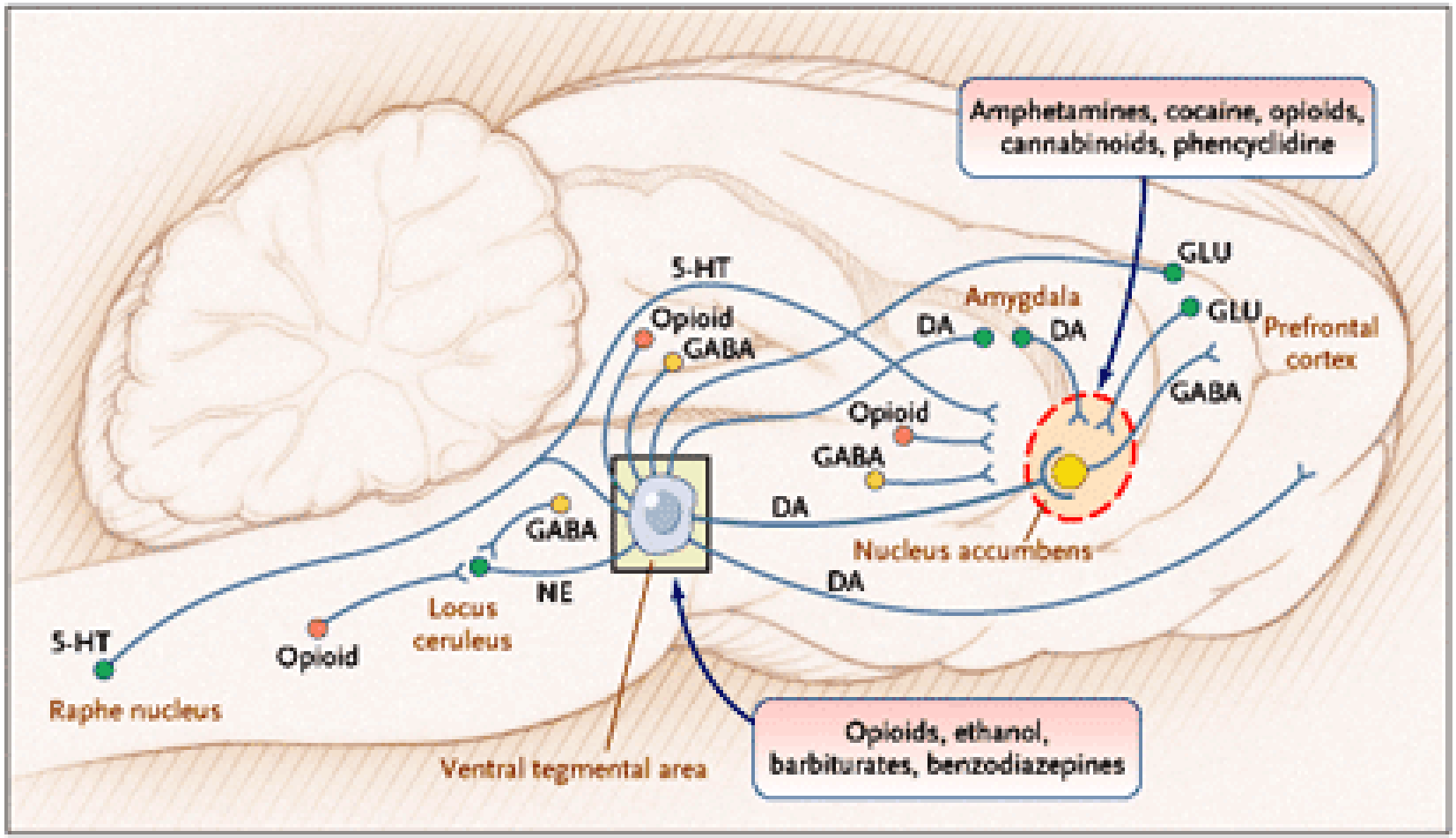
- Biological- alter chemistry of brain and body functioning, can damage organs
- Psychological- altered brain chemistry affects the brain's ability to think, alters feeling states, impacts personality of the user
- Sociological- behavioral interactions with family and other contacts are altered or misinterpreted by user or observer

Biochemical Considerations

- Interference with transmitters that allow neurons to communicate with each other, tell us/body what to do, how to react, what is experience, etc.
- Occur in “primitive brain”
- Is disease of motivation and choice

Neurotransmitter	Site	Effect	Substances
Dopamine	VTA, nucleus acumbens	Reward, stimulation	Stimulants
Serotonin		Mood, sleep, appetite, perception	THC, hallucinogens
GABA	Amygdala, bed nucleus of stria terminalis	Sedation, alertness, anxiety	S/H/A, alcohol
Glutamate	NA		
Opioid peptides	NA, amygdala, VTA	Pain	Opioids, alcohol

Reward Circuitry



Graphic from: Cami J, Farre M: NEJM 349:975-986, 2003

Reinforcement and Reward, Early

- The neural basis of addiction- a pathology of motivation and choice
  - An integrated review of neuroimaging and cellular studies in animals
- Dopamine
  - Release triggered by addicting drugs(and/or stress)
  - Critical for acute reward
  - Critical for initiation of addiction

Reinforcement and Reward, Late Charges

- Cellular adaptation
- Pathophysiological plasticity in excitatory transmission reduces capacity of the prefronal cortex to
  - Initiates behaviors responding to rewards
  - Provide executive control
- Prefrontal cortex is hyper responsive to availability predicting stimuli
  - Supraphysiological glutamatergic drive
  - Excitatory synapses with reduced capacity to regulate neurotransmission

Recap…

- Cellular adaptations in prefrontal glutamatergic innervation of the accumbens promote the compulsive character of drug seeking addicts by:
  - Decreasing the value of natural rewards
  - Diminishing cognitive control (choice)
  - Enhancing glutamatergic drive in response to drug associated stimuli

Psychoactive Drugs

- Substances that can pass the BBB and become active in the brain and CNS with effects on mood, cognition, psychomotor movement, and personality
- Psychotoxicity- ability to alter brain function and cause intoxication
- Toxicity- damage
- Tolerance- with repeated use, return diminishes
- Cross tolerance- in class drug phenomena
- Physical dependence- adverse physiologic consequences to drug use cessation, existence of a stereotypical syndrome (abstinence syndrome) also with drug use reduction

Four Principles

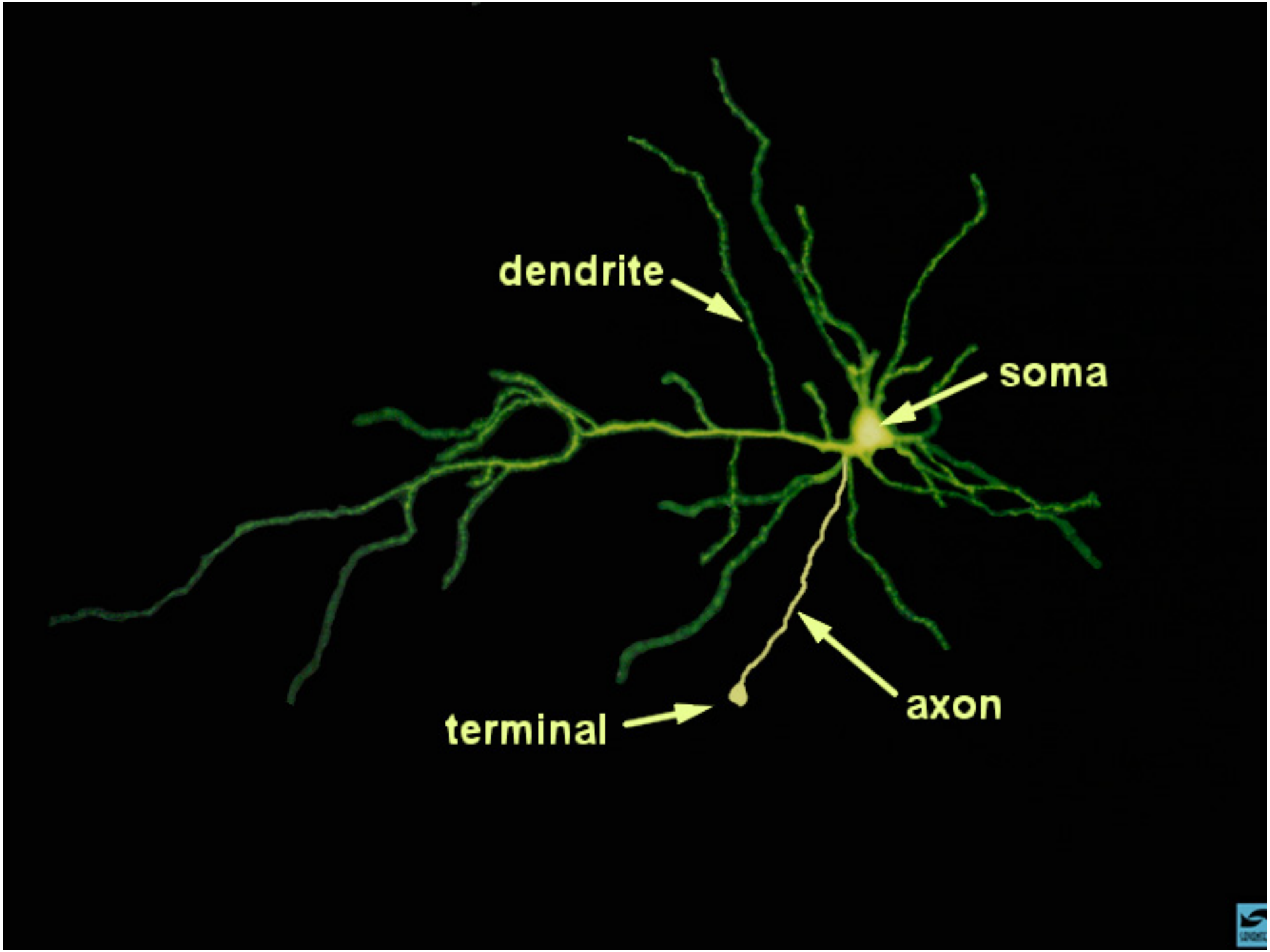
- Drugs are not good or bad, behavior causes judgment by observer about the user
- Desired and undesired effects, variable tolerance
- Extent and quality of effects depends upon dose and potency
- Use history and expectations are important

Classes of Drugs

- Alcohol
- Cannabis
- Hallucinogens
  - PCP
- Inhalants
- Opioids
- Sedatives, hypnotics, anxiolytics
- Stimulants
  - Caffeine
  - Cocaine

General Approach to Study

- Class
- Street Names
- Properties
- Therapeutic Uses
- Intoxication
- Withdrawal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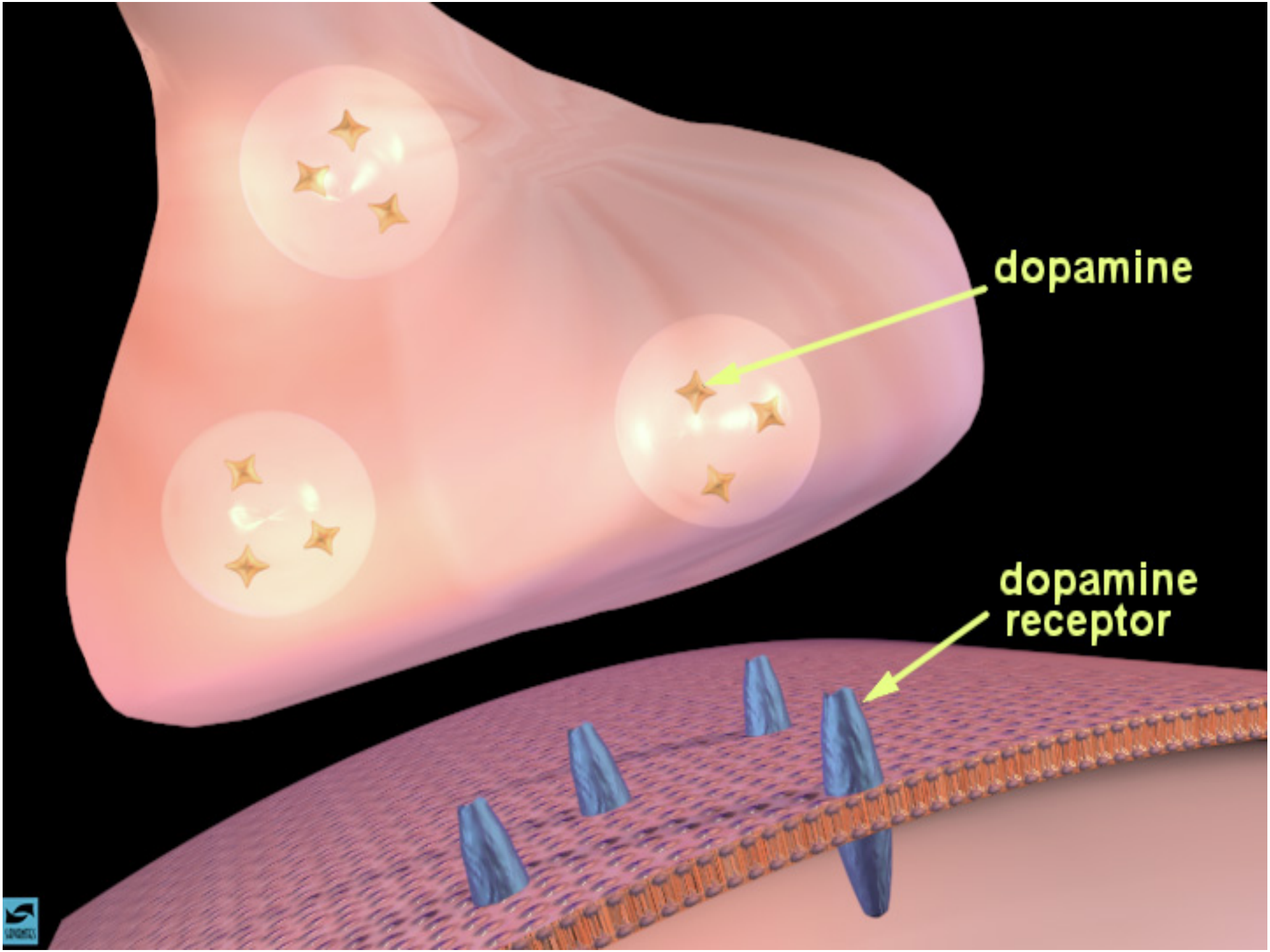
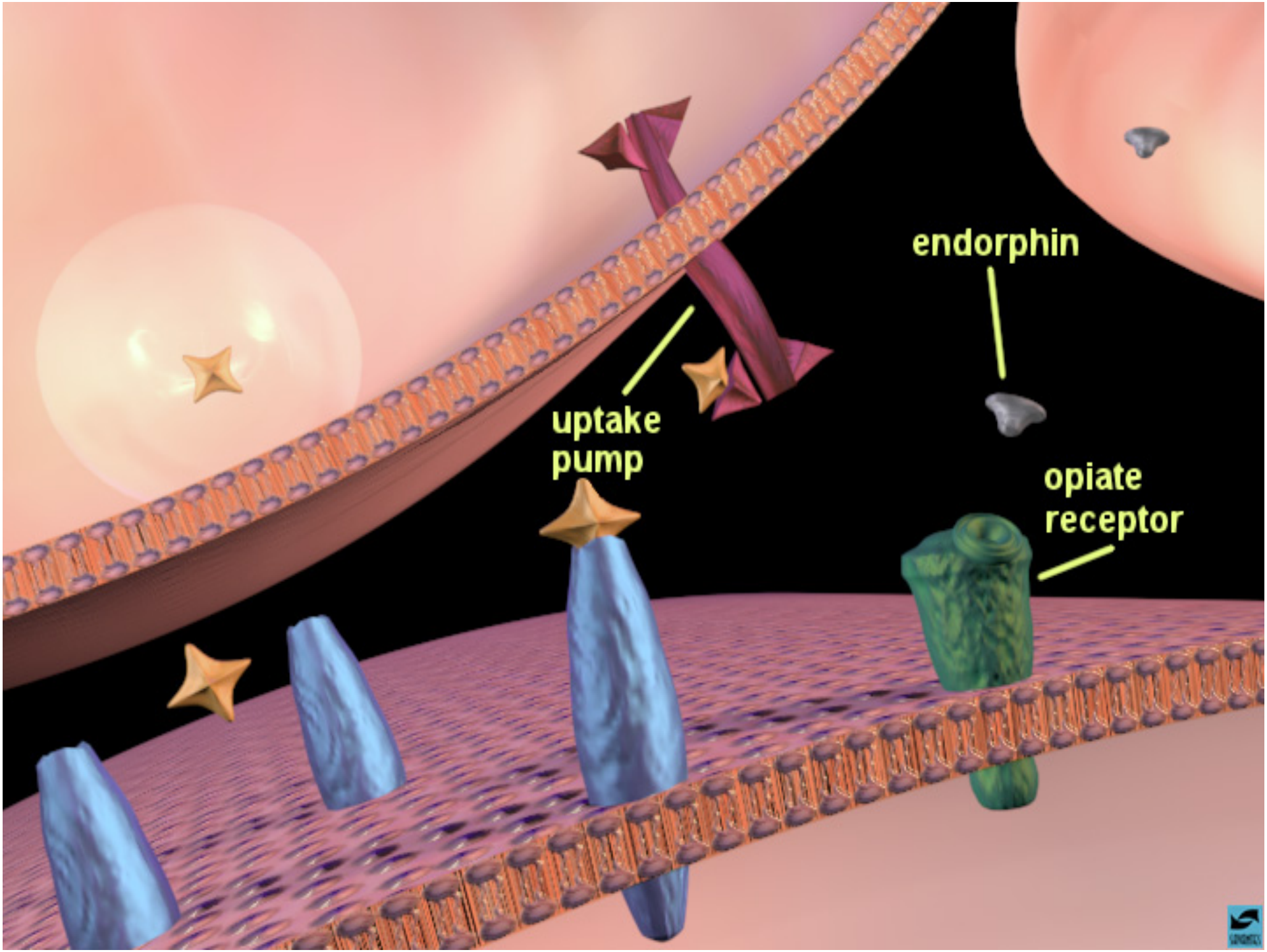

dopamine
dopamine receptor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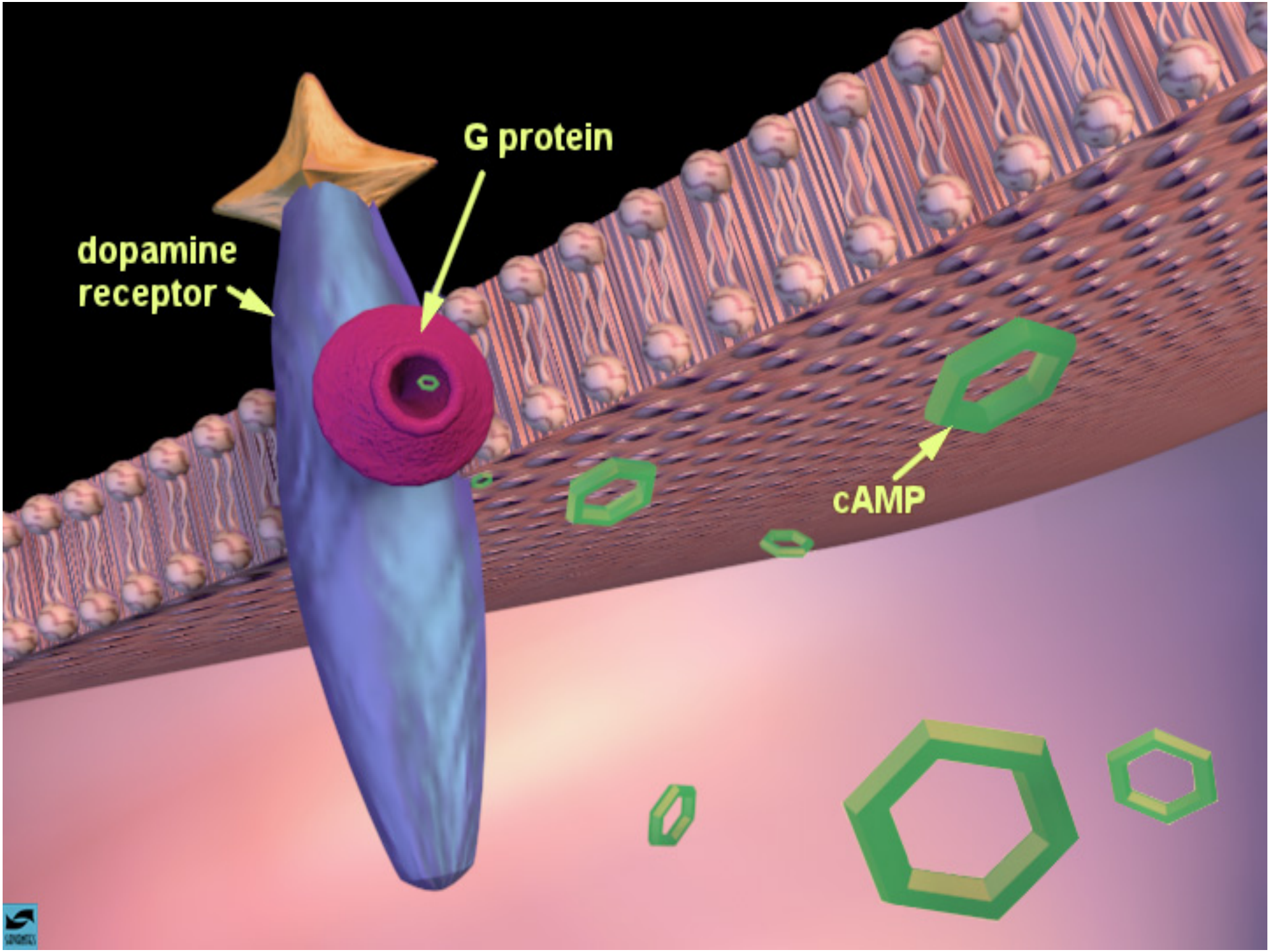
opiate
receptor


G protein
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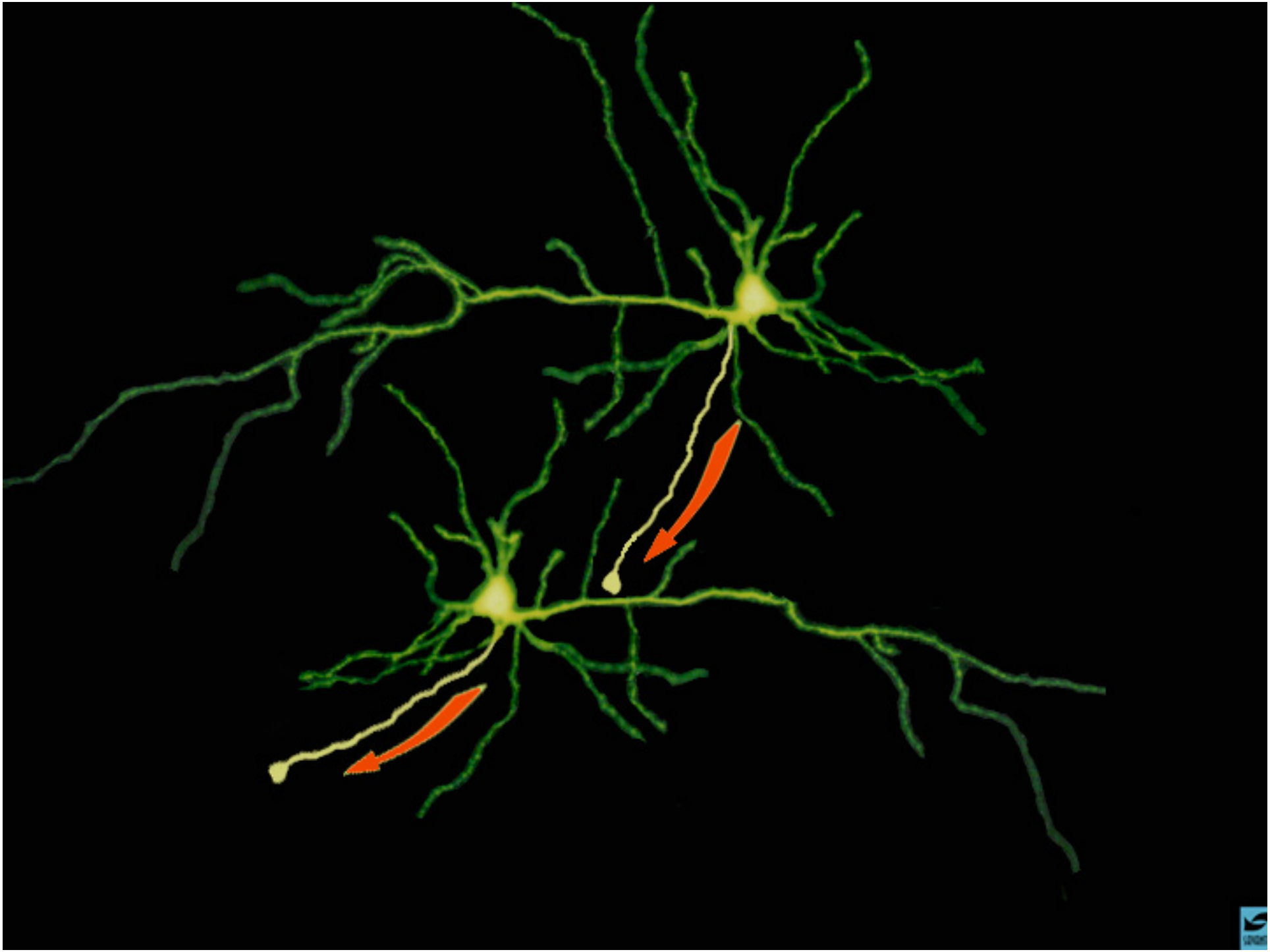

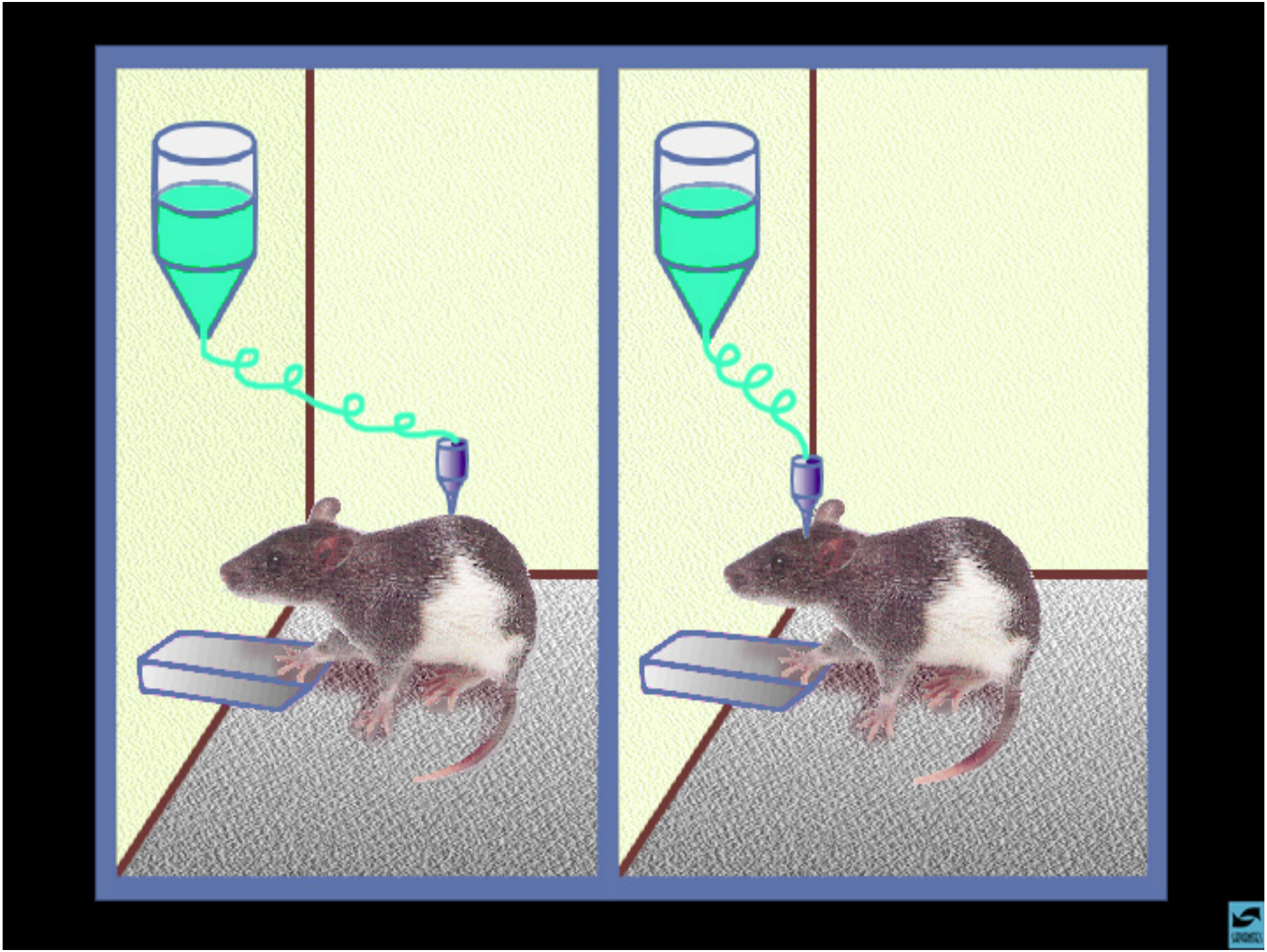

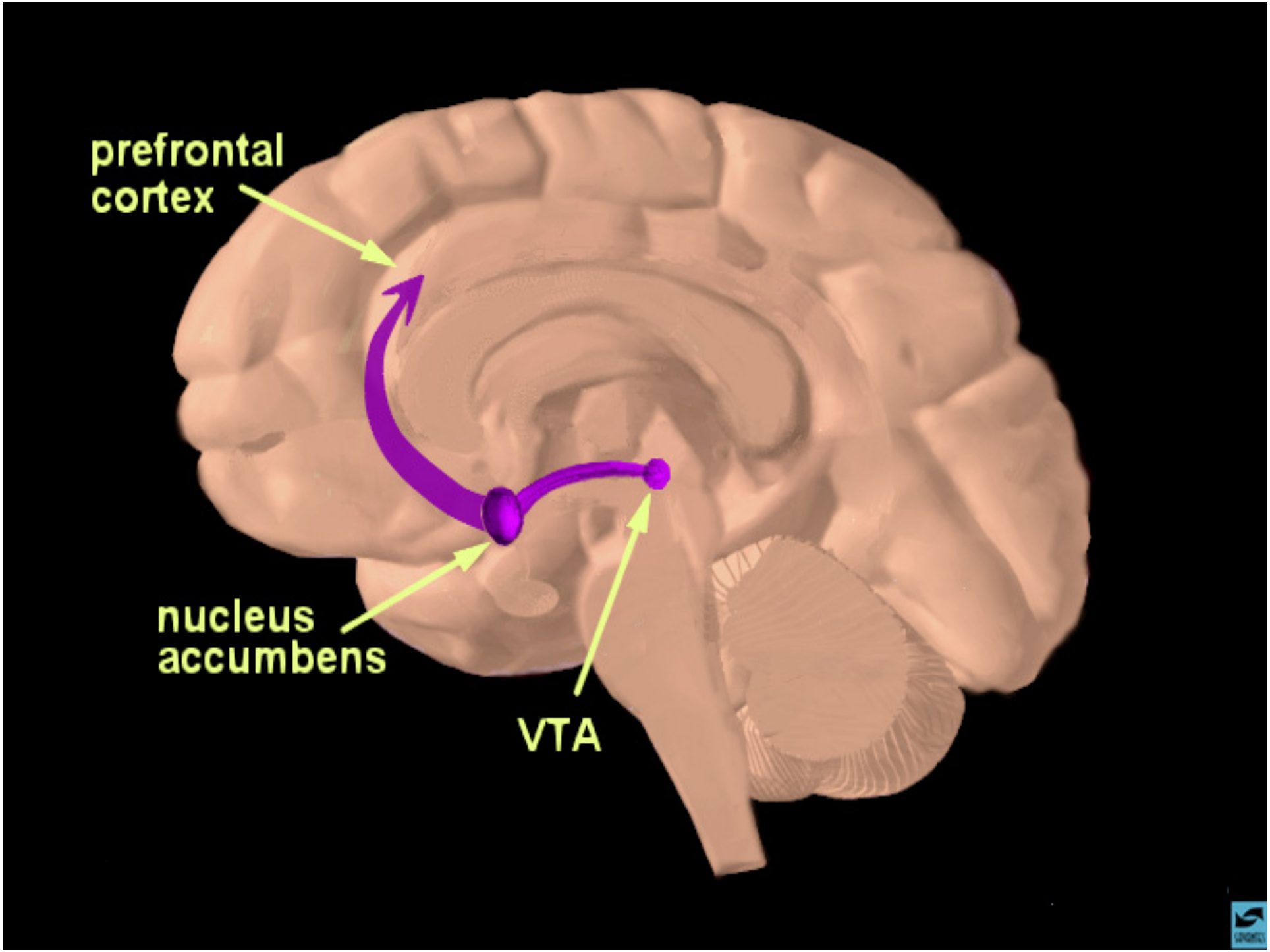
prefrontal
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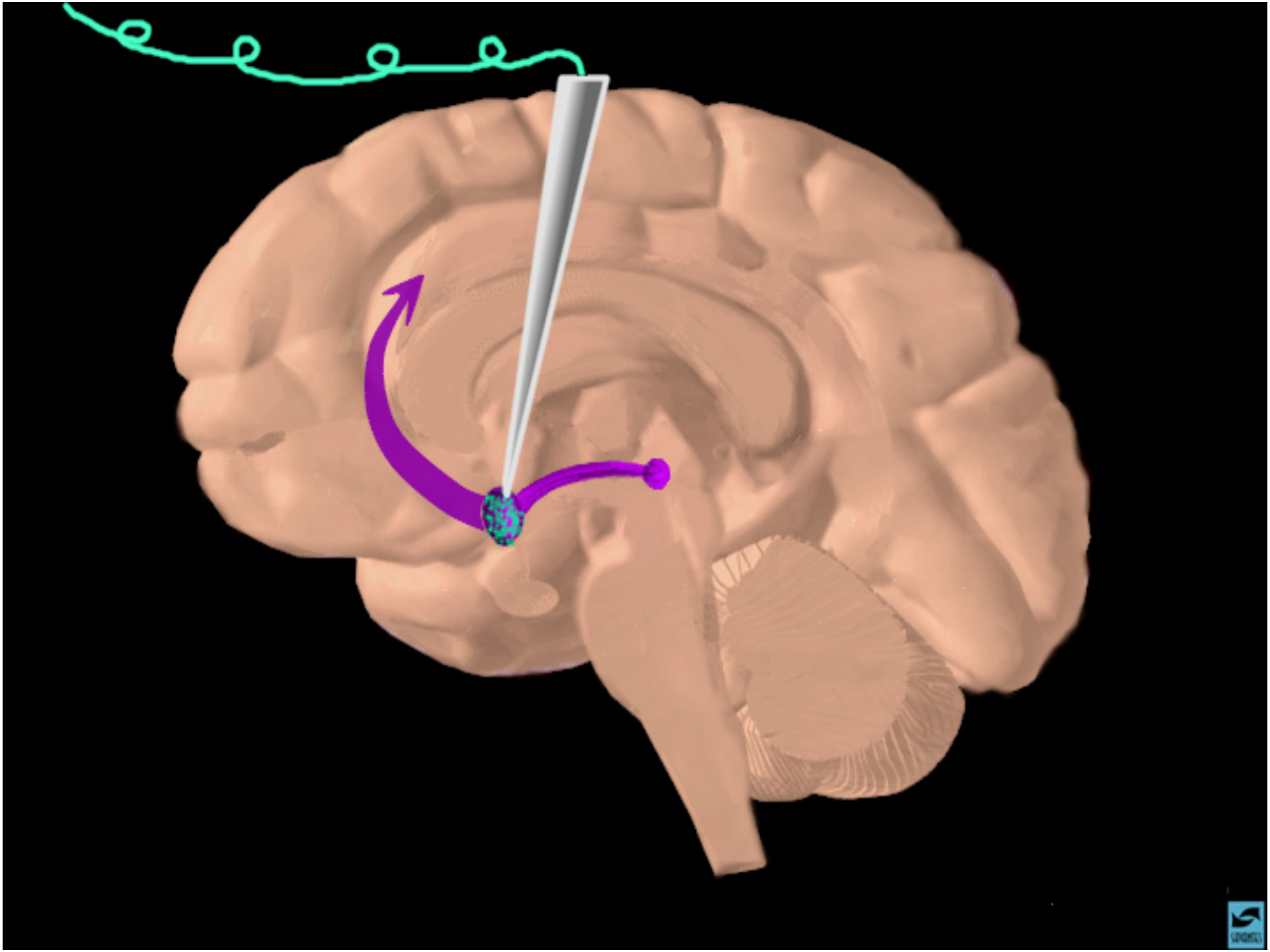
VTA

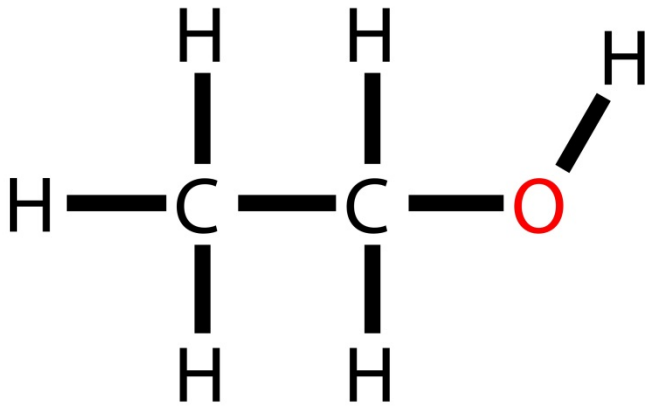


Alcohol

General Considerations

Alcohol: General Considerations

- 25-50 mg of ethanol for every 100 mL of blood to get BAC of 0.025-0.05% (1 ounce= 29 mL)
  - 0.08% is legal limit in most states
- Alcohol equivalents
  - 1.5 oz. 80 proof (40% ethanol)
  - 6 oz. wine
  - 12 ox of beer



Alcohol: Distribution

- Absorbed rapidly after drinking
  - Modifiers: food in the stomach, enzymes in the stomach
- 90% within an hour
- Metabolized at rate of 1.5 oz. of 80 proof/hour
- BAC 0.4 = LD 50 = 5x legal limit

Alcohol: Pharmacological Properties

- Duration: one unit per hour, zero order kinetics
- Tolerance: Rapid development
- Physical Dependence: yes
- Psychological Dependence: yes
- Onset: oral route of administration, 15 minutes
  - Gender differences in metabolism in lining of stomach (gastric alcohol dehydrogenase)
- Pattern of Use: daily, binging, maintenance use
- `Withdrawal: 4 stages

Alcohol: Effects

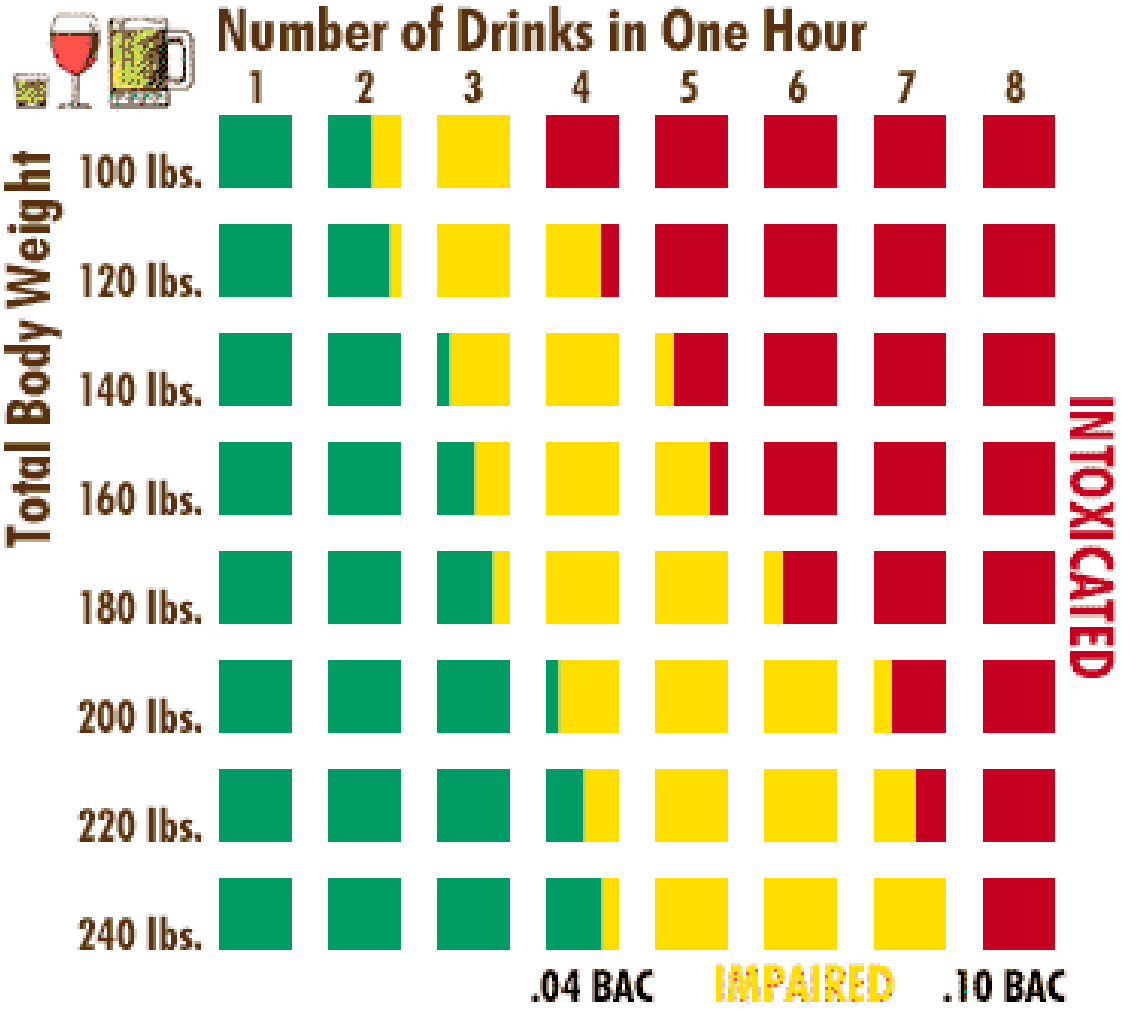
- Neurotransmitter: GABA agonist
  - Additive effect when used with S/H/A
- Makes cell membrane more fluid- inhibits the movement of Na+ and K+
  - Prevents action potentials
- Decreases glutamate; potentiates depression
- Increases release of DA in NA
- Risk of Addiction- 15%

Alcohol: Therapeutic Uses

- Topical cleanser
- Pain relief
- Stimulant
- Appetite stimulant
- Lactation aide
- “Hamburger Hat Therapy”

Alcohol: Intoxication

- Low dose- stimulant then depressant
- Overdose- cardiorespiratory collapse



- 0.2 - 0.3
  - Respiratory depression, blackouts
- > 0.3
  - Unconsciousness, significant respiratory and CV depression, can cause death
- > 1.2
  - Highest known concentration with survival

BAC and Behavior	
0.05	Lowered alertness, usually good feeling, loss of inhibitions, impaired judgment
0.10	Slowed reaction time, impaired motor function, less caution
0.15	Large, consistent increase in reaction time
0.10	Marked depression in sensory, motor capability changed; intoxication
0.25	Sever motor disturbance, staggering, sensory perceptions, great impairment
0.30	Stuporous but conscious, no comprehension of what is going on
0.36	Surgical anesthesia, about LD, minimal level causing death
0.40	Approximates LD50

Alcohol Poisoning

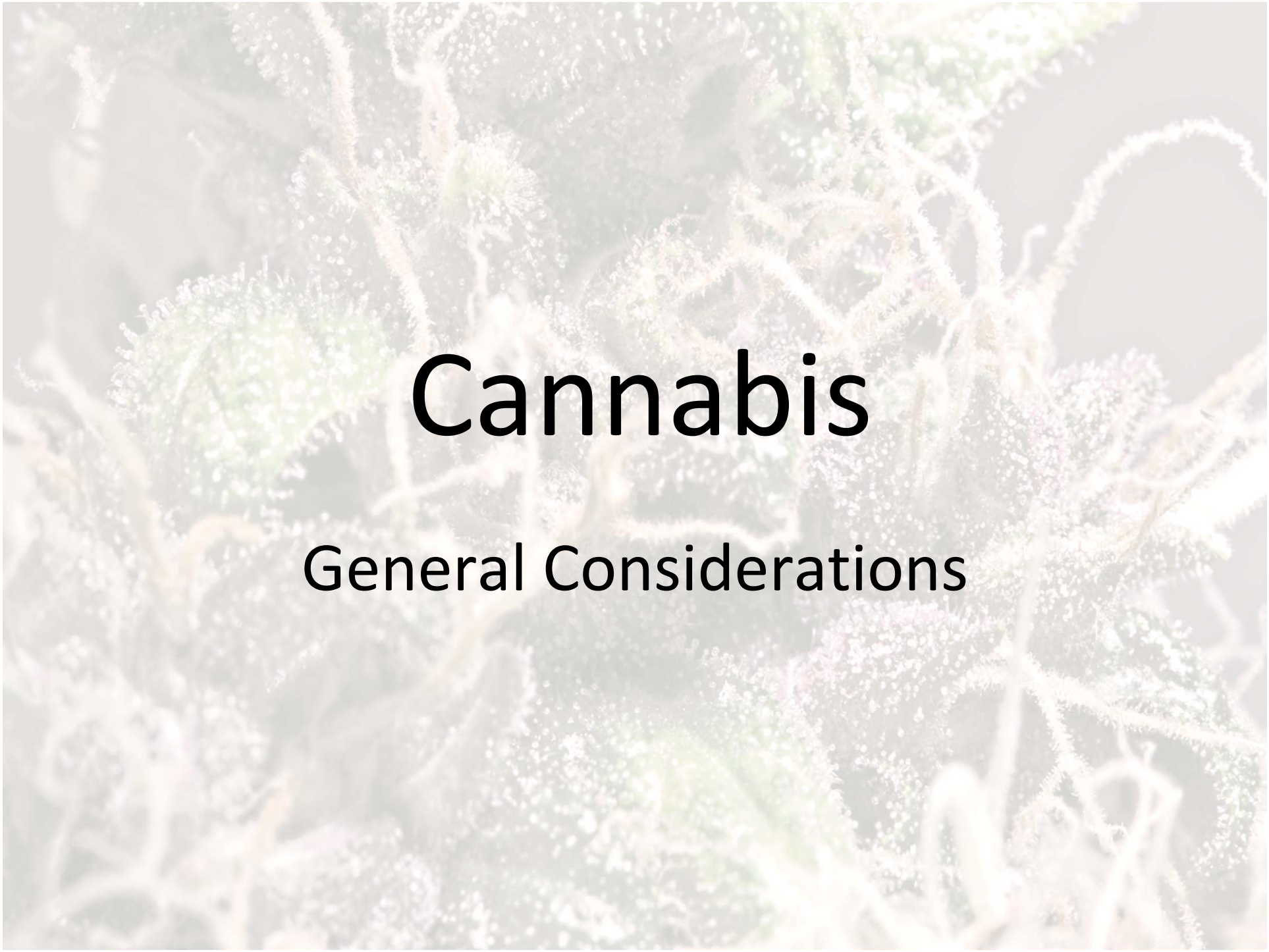
- TI= 10
- With tolerance, increases amount taken to get desired effect so approaches LD
- Risk of alcohol poisoning increases with tolerance as one approaches upper limits of LD to get desired effect
- Signs
  - Mental confusion, stupor, coma
  - Vomiting while asleep
  - Seizures
  - Irregular, reduced breathing, blush tint to skein
  - Cold, clammy

Withdrawal

- Stage 1- onset 6-8 hours
  - Agitation, anxiety, tachycardia, HTN, N7V, anorexia, headache, insomnia, craving, diaphoresis, tremor
- Stage 2- onset 24 hours (delayed up to 6 days)
  - Hallucinations, illusions, disordered perception, autonomic hyperactivity of stage 1 continues
- Stage 3- onset 7-48 hours
  - Grand mal seizures, 3-5%progress if untreated, > 50% have multiple seizures, > 30% progress to DTs
- Stage 4- onset over 3-5 days
  - DT- global confusion, autonomic hyperactivity, hallucinations. 5% progress to stage 4, 15% resolve in 24 hours, 80% in 3 days

Treatment

- Benzodiazepines
- Dilantin
- Adjunctive Therapy- thiamine, fluids, electrolytes, psych evaluation, management of co-existing disease, nutrition, referral to rehab



Cannabis

General Considerations

Cannabis:
General Considerations

- Delts-9-terahydrocannabinol (THC)
- Spectrum of behavioral effects is unique, preventing classification of the drug as a stimulant, sedative, tranquilizer, or hallucinogen
- Increased popular interest in therapeutic properties of marijuana
- Some states have legalized and allow marijuana dispensaries
- Little evidence that will guide this process in a rational, ethical manner that guarantees patient safety

Cannabis: Historical Issues

- Cannabis rose to prominence in early 19th century
- Preparations lacked standardization, and active ingredients were unknown
- Patient response was unreliable
- Marijuana Tax Act of 1937 restricted prescription of cannabis preparations
- Variable potency
- Erratic and unpredictable individual responses
- Introduction of synthetic and more stable pharmaceutical substitutes

Cannabis: Historical, continued

- In 1964, THC discovered to be main psychoactive ingredient in marijuana
- Interest in smoking of marijuana for its psychoactive effects began to rise
- Interest in finding therapeutic uses began to rise
- Technological “lag” produced “medical marijuana”

Cannabis:
Historical, continued

- Dawn of cannabinoid neuroscience: discovery of endocannabinoid receptors and endogenous cannabinoid ligands in late 1980s and early 1990s
- Endocannabinoid system (ECS) acts in “just about every physiological system”[1].

Cannabis: Understanding the Plant

- Mix of leaves, flowers, stems, and seeds from the hemp plant *Cannabis sativa*
- Rich source of variety of compounds
- Cannabinoids
- Terpenoids
- Flavonoids
- Exact content of chemical composition varies

Cannabis: Understanding, continued

- Sixty (60) different cannabinoids 30 metabolites
- US cannabis bred to exhibit (only) high levels of THC
- When inhaled, THC has effect on central nervous system and produces “high”

Cannabis: How Taken

- Average THC concentration in marijuana is 1-5%, hashish 5-15%, and hashish oil 20%
- *Sinsemilla* derived from the unpollinated female cannabis plant, up to 17% THC
- Single intake called a hit, approximately 1/20th of a gram
  - 1-3 hits of high potency Sinsemilla average
    - Calculate hits for “ditch weed”
  - drop or two of hash oil equal to a “joint”
  - Initial starting dose of Marinol® is 2.5 mg, twice daily

Cannabis: Street Names

- Pot
- Reefer
- Buds
- Grass
- weed
- Dope
- Ganja
- Kilobricks
- Thai sticks
- Marinol®
- Herb
- Boom
- Gangster
- Mary Jane
- Sinsemilla
- Joint
- Hash, hash oil
- Blow
- Blunt
- Green

Cannabis: Pharmacological Properties

- Duration: smoked 1-3 hours, oral 4-10 hours, 30 metabolites
- Tolerance: rapidly develops
- Physical Dependence: yes
- Psychological Dependence: yes
- Onset: smoked 15 sec to 1 minute, oral- ½ to 1 hour
- Pattern of Use: smoking, daily. Joint delivers 10 mg THC; average dose 20-30 mg/day
- LD 50 1270 mg/kg in male rat, 730 mg/kg in female rat.
- TI 40,000

Cannabis: Distribution

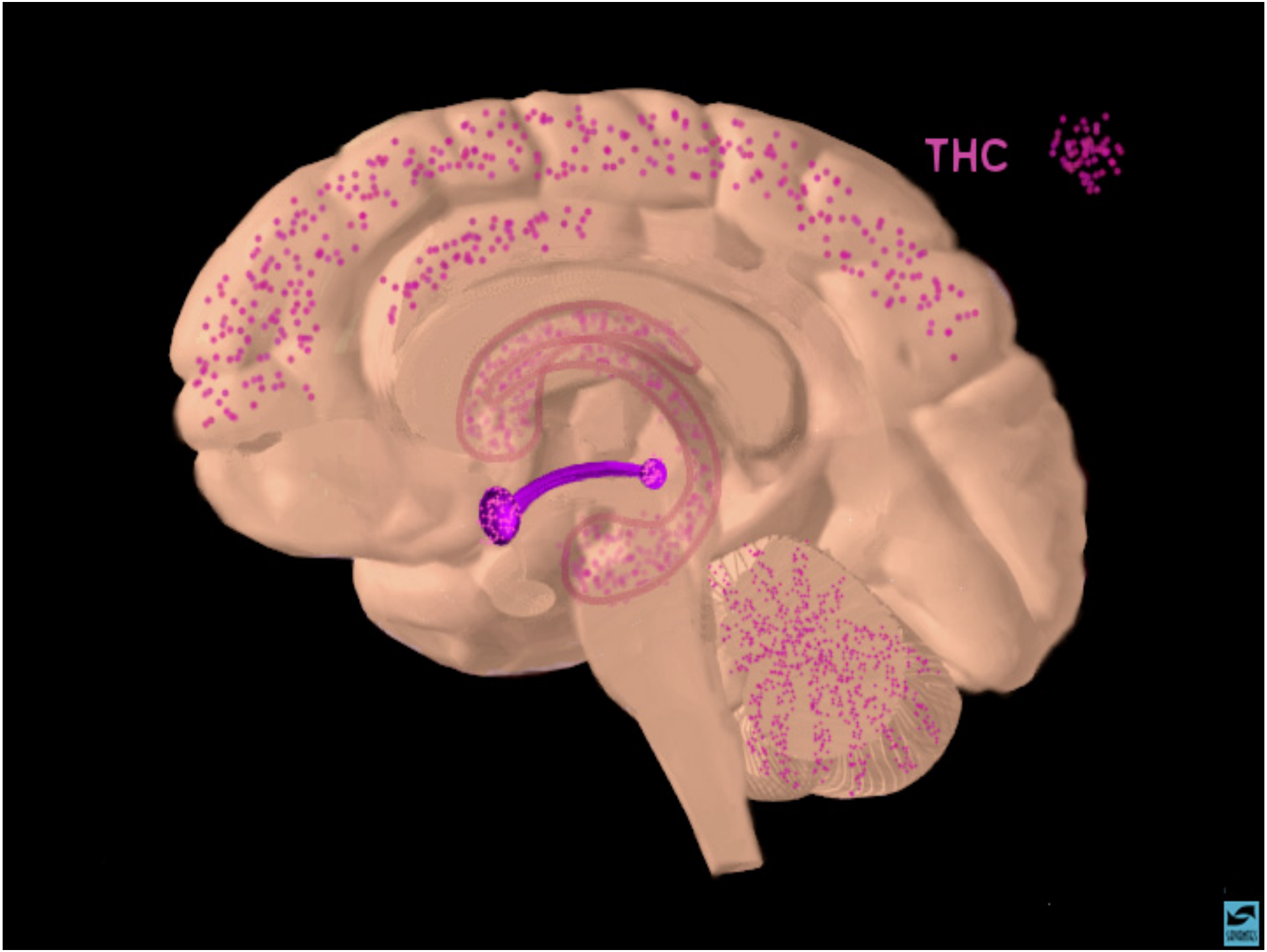
- THC acts on cannabinoid receptors in the brain, higher than any other receptor, naturally occurring- anandamide
- Cannabinoid receptors are part of the ECS
  - CB1 receptors concentrated in the hippocampus, amygdala, basal ganglia, cerebellum, nucleus accumbens and cortex
  - CB2 receptors are peripheral
- Functions: relax, eat, sleep, forget, and protect (DiMarzo et al 1998)

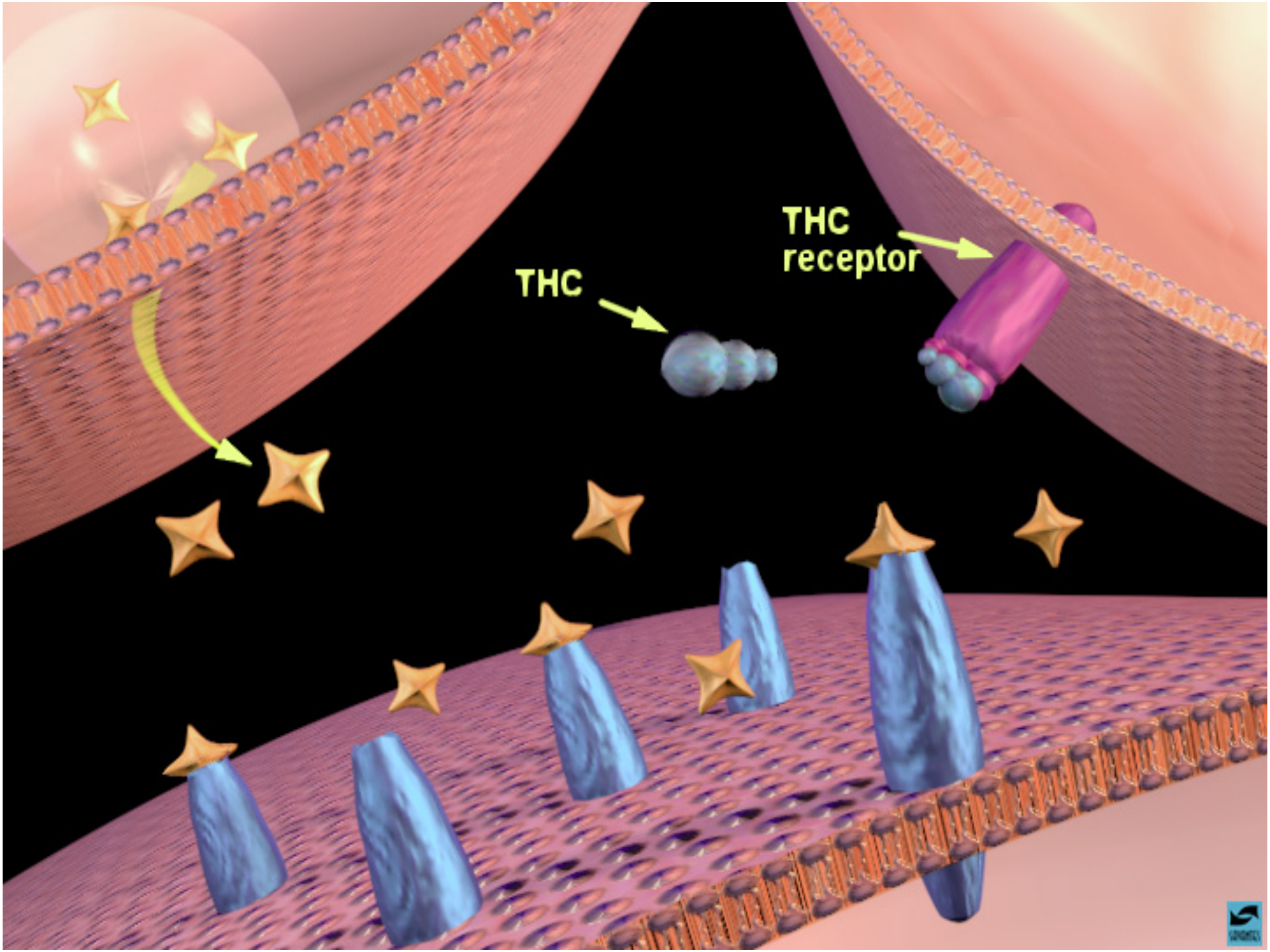
Cannabis: Effects, continued

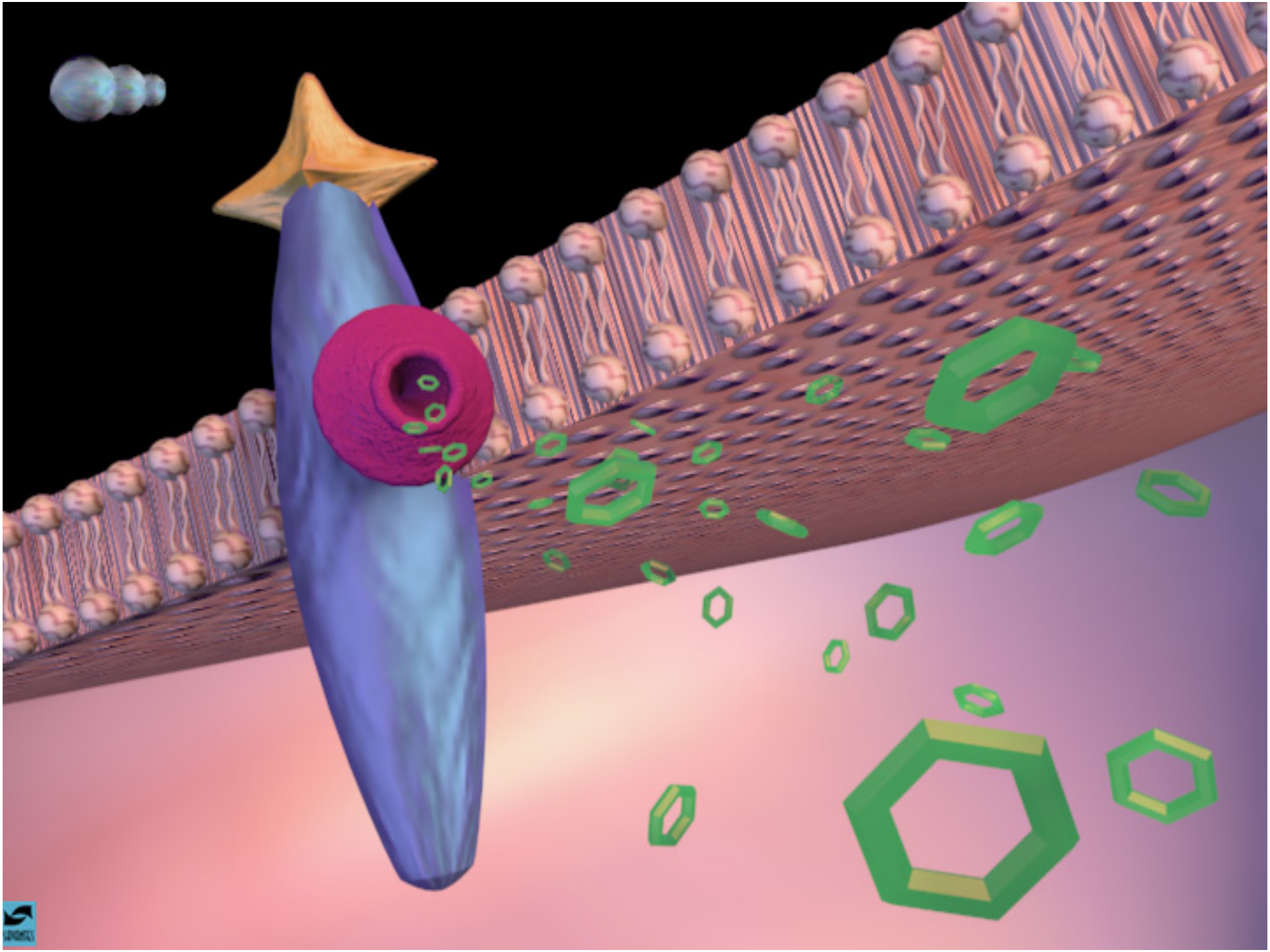
- Activity in ECS is constantly modulating huge variety of brain and physiological functions
- Short term memory
- Motivation changed
- Learning
- Appetite
- Anxiety and fear
- Pain
- Spontaneous motor activity

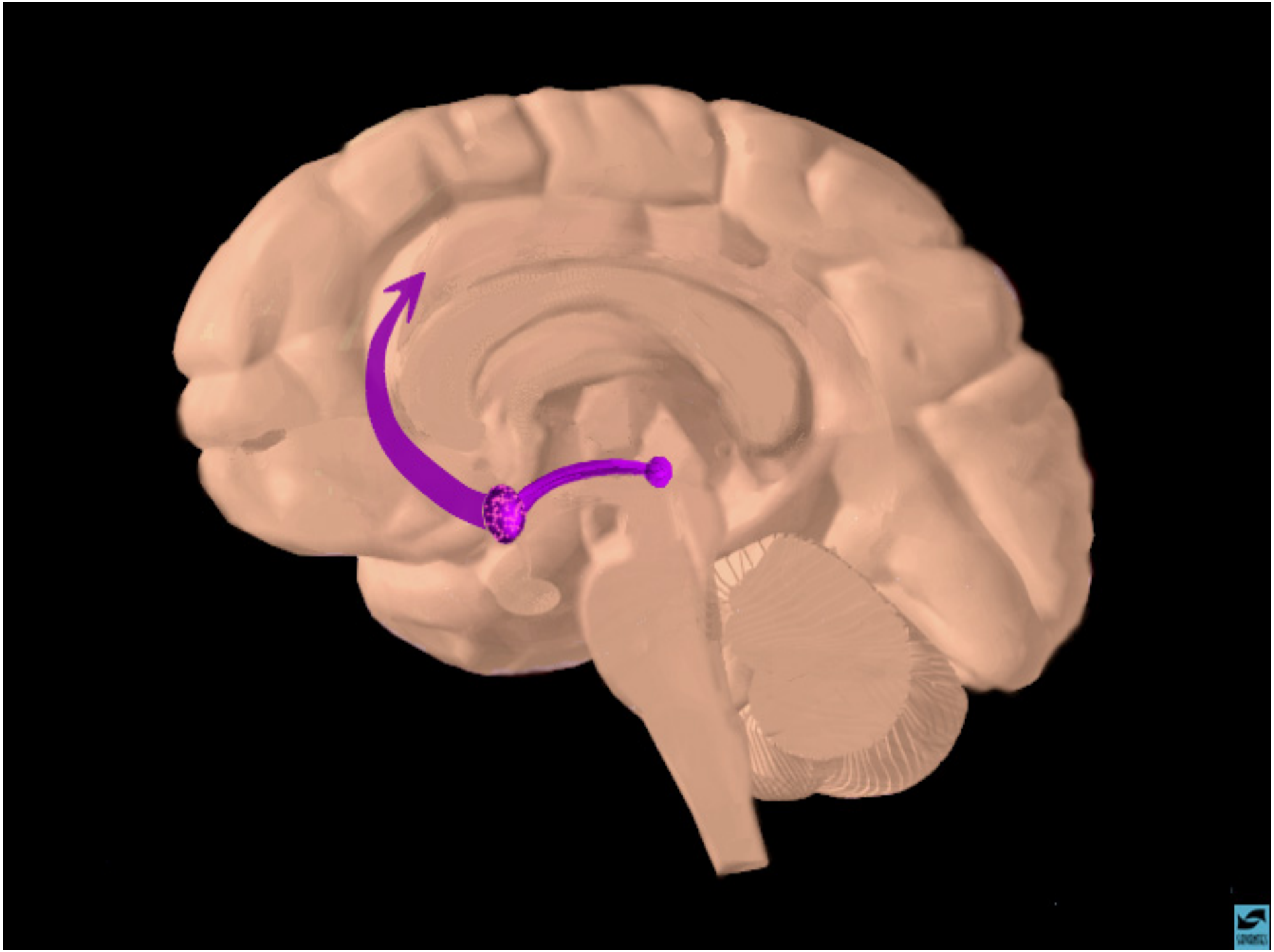
Cannabis: Effects, continued

- Aspects of ECS are important from addiction medicine perspective
- Downregulation of cannabinoid receptors by up to 60% in response to exogenous cannabinoids
- THC and similar molecules are able to affect the brain because they mimic naturally occurring neurotransmitters and flood receptor sites with stimulation
- Risk of addiction – 11%


THC


THC
THC receptor





Cannabis: Acute Effects

- Time sense alterations
- Short term memory loss
- Attention skills
- General difficulty expressing simple thoughts in words
- Motor skills
- Increase in hunger
- Nausea
- Dizziness

Cannabis: Acute continued

- Altered mood
- Euphoria
- State of relaxation
- Panic
- Trait and state anxiety
- Tension and anger
- Confusion
- Depersonalization and other behavioral effects

Cannabis: Post Acute Effects

- Human aggressive responding
- Conditions
  - Provoke subjects coming off drug
  - Provide opportunity to retaliate
  - Measure amount of retaliation
- Acute Marijuana, subjects with ASPD
  - Increased aggressive responding

Cannabinoid: Therapeutic Uses

- Nausea and Vomiting
- HIV Wasting

Cannabis: Intoxication and Overdose

- Continued use causes reverse tolerance
  - User becomes more sensitive to small amounts of substance
- Below 10 mg/person/day unlikely to experience tolerance
- Psychological dependence more likely to develop than physical dependence
  - Stereotypical abstinence syndrome described
- Acute intoxication increases HR and conjunctival reddening
- Fingertip titration of dose mediates risk of OD, more likely with oral consumption

Cannabis: Treatment

- Standard CD treatment
- Challenge- belief that it is not dependence producing
- Challenge- difficulty in creating acceptance for patient in milieu

PCP

General Considerations

PCP: General Considerations

- PCP= 1-phenylcyclohexylpiperidine
- Angel dust, Kristal Joint (KJ), wet, fry stick, sherm, leak, amp, lovely, toe tag, dipper, happy stick, angel dust, animal tranquilizer, dips, dust, elephant, embalming fluid, formaldehyde, fry, hog, ozone, peace pill, rocket fuel, Sernyl, Sernylan, super kools, TicTac, tranq, water
- $10-15 per cigarette
- Dissociative drug, formerly used as an anesthetic agent (Sernyl ®)
- Has hallucinogenic effects

PCP, General continued

- First synthesized in 1926
- MDMA receptor antagonist, more dangerous than other categories of hallucinogens- antiglutamatergic
  - Others include ketamine, tiletamine, dextromethorphan, nitrous oxide
- Analogues of PCP used and outlawed in 70s, 80s

PCP: Distribution

- Ingested, smoked, inhaled
  - Free base form is dissolved in oil
  - In salt form is crystal or powder
  - Dissolved and smoked on leaves- tobacco, mint, etc.
- Metabolized to PCHP, PPC, and PCAA
- Acts in brain, may mimic schizophrenia
- Long half life in human

PCP: Properties

- Duration: 8-12 hours
- Tolerance: high, frequent use leads to rapid development of tolerance
- Physical Dependence: unknown
- Psychological Dependence: low
- Onset: route of administration determines onset
- Pattern of Use: weekenders, unpredictable, related to underlying pathology, most people use for brief period of time then return to former lifestyle
- Withdrawal: syndrome not described

PCP: Effects

- MDMA receptor antagonist
  - MDMA is excitatory
  - PCP unexpectedly produces cortical activation
- Inhibits nicotinic acetylcholine receptors
- Acts as D2 partial agonist- may mediate psychotic features
  - D2 receptor antagonist (Haloperidol) used to treat PCP psychosis
- Also interacts with endorphin and encephalin receptors to produce analgesia
- May inhibit reuptake of Dopamine

PCP: Effects, continued

- Vary by dosage
- Low dose- (1-5 mg) numbness in extremities and intoxication
  - Staggering, unsteady gait, slurred speech, bloodshot eyes, loss of balance
- Moderate dose- (5-10 mg intranasal, 0.01-0.02 mg IM or IV)- analgesia and anesthesia
- High dose- (10 mg) convulsions and death
- Unreliable manufacturing produces user confusion
- Risk of death- high due to low TI (LD50/ED50= 10/1= 10)
- Risk of Addiction: Low

PCP: Psychological Effects

- Changes in body image, loss of ego boundaries
- Paranoia and depersonalization
- Hallucinations, euphoria
- Suicidal impulses
- Aggressive behavior
- Detached or animated
- Delusions and hallucinations may drive behavior
- Suggestions of increased strength- may be due to anesthesia effect

PCP: Therapeutic Uses

- 1920s as surgical anesthesia
  - Side effect profile (hallucinations, mania, delirium, disorientation) caused it to be shelved
- Reintroduced in 1950s- again stopped because of SE

PCP: Withdrawal

- Normally do not develop dependence
- Forced acid diuresis (ascorbic acid) may boost elimination but only 10% renal clearance

PCP: Treatment

- RED DANES- rage, erythema, dilated pupils, delusions, amnesia, nystagmus, excitation, skin dryness
- Supportive care- controlled breathing, circulation, body temperature, and psychiatric symptoms
- Benzodiazepines- control agitation and seizures
- Antipsychotics- control psychotic symptoms
- Phenothiazine may reduce seizure threshold, worsen hyperthermia

Hallucinogens

General Considerations

Hallucinogens: Street Names

- LSD- acid, window pane
- Psilocybin- shrooms
- Mescaline- mesc, buttons
- PCP- angel dust, blast
- STP, MDA- love drugs
- Marijuana- grass, pot, weed, chronic, herb

Hallucinogens, street continued

- Club drugs (most with amphetamine base)
  - Methyaminedioxymethamphetamine (MDMA)- ecstasy, XTC, Molly (liquid, pure form)
  - Rohypnol (Flunitrazepan, Xyrem®)- GHB- liquid XTC, lollipops, liquid X, liquid E
  - Ketamine
  - LSD- acid, window pane

Hallucinogens: Historical Considerations

- Among oldest used by humans
- Naturally occur in mushrooms, cacti, other plants
- Taxonomy: subjective effects, mechanisms of action, chemical structure
  - Lewin's classes- only historically of interest
  - Pharmacological- psychedelics (5-HT, serotonic, cannabinoid), dissociatives (NMDA antagonists), Deliriants (anticholinergic)

Hallucinogens: General Considerations

- Subjective changes in perception, thought, emotion, consciousness
- Induce experiences that are qualitatively different from ordinary consciousness
  - Compared to trance, meditation, dreams or insanity

Hallucinogens: General Considerations

- Hollister's criteria
  - Changes in thought, perception, mood predominate
  - Intellectual or memory impairments minimal
  - Stupor, narcosis, or excessive stimulation not integral
  - Autonomic nervous system effects minimal
  - Addictive craving absent

Hallucinogens: General, continued

- Psychedelics
- Dissociatives
- Deliriants

Psychedelics (psychoto-mimetic, hallucinogen)

- Mind, soul + manifest, reveal: make manifest a hidden aspect of the mind, eliminate filtering
- Allows classical hallucinogens (LSD, psilocybin, mescaline), cannabinoids, and some dissociative (*salvia divinorum* and ketamine)
- Receptor- 5-HT2 serotonin receptors
- Perception altering drugs
  - Prototype- LSD
  - Herbal and fungal- psilocynin, peyote, mescaline
  - Animal- bufo alvarius
  - DMT, 2C-B, DOB, other tryptamines, phenethylamine, etc.

Psychedelics: Pharmacological Properties

- Trips vary by drug, dose, set and setting
  - Short trip with DMT, protracted with ibogaine (days)
  - Dose extremely low for LSD, rather high for mescaline
  - Single sense affected by DiPT (auditory hallucinogen) to diffuse effects (LSD)
  - Some conducive to social bonding, others solitary
- Designer drugs in amphetamine class extremely dangerous, most not studied for effects

Dissociatives

- Produce analgesia, amnesia, catalepsy at anesthetic doses
- Produces detachment from surrounding environment
- Symptoms include disruption or compartmentalization of integrated functions of consciousness, memory, identity or perception
- Dissociation of sensory input causes derealizaiton- world is dream-like
  - Depersonalization- feeling detached from one's body, unreal, unable to control one's actions, unable to recognize self in mirror

Dissociatives: Effects

- Block signals received by NMDA receptor set
  - Include ketamine, PCP, DXM, and nitrous oxide
- *Salvinorin A (k* agonist) is most potent dissociative
- CNS depressant (similar to opioids)
  - Slow breathing, slow heart rate
- Pain is processed as far away, disembodied experience, less emotion
  - Nitrous oxide risk due to lack of oxygen

Dissociatives: Pharmacological Properties

- Tolerance- cellular tolerance develops with exposure, thus continuous exposure to NMDA antagonists does not necessarily lead to neurotoxicity

Deliriants

- Induce state of delirium characterized by extreme confusion, inability to control one's actions, subjective effect similar to people with delirious fevers
- Includes deadly nightshade, angel's trumpet, jimson weed, henbane, mandrake, nutmeg, uncured tobacco and pharmacologicals like Benadryl, Dramamine
- Antcholinergics- toxic, dehydration, dilated pupils, risk of death
- Cause rage- historically used before going into battle

Hallucinogens: Class-wide Properties

- Duration: 8-12hours, except amphetamine variants to days, DMT 0-1 hour
- Tolerance: high, frequent use leads to rapid development of tolerance
- Physical Dependence: amphetamine analogues- unknown; other none
- Psychological Dependence: low
- Onset: varies by type and route of administration
- Pattern of Use: unpredictable, related to underlying pathology, brief period of time then return to former lifestyle. Introduced via experimenting, episodic use because time must be set aside for many trips
- Risk of Addiction: Low
- Withdrawal: Not reported
- Flashback: re-experiencing perceptual symptom without active drug in body

Hallucinogens: Therapeutic Uses

- Long history of use within medicinal and religious traditions
- Shamic forms of ritual healing and divination
- Initiation rites
- Religious rituals
  - Entheogens
- Most not known to have long-term physical toxicity
  - MDMA release free radicals which are associated with Parkinson's, senility, schizophrenia, Alzheimer's
- Explored in depression, PTSD, OCD, alcoholism, drug addiction, cluster headaches, etc.

Hallucinogens: MDMA- XTC

- 1900, appetite suppressant, stimulant and hallucinogen
- 1.5-3 hour onset, t 1/2 8 hours
- Serotonin, NE, Dopamine
- Mechanisms of action
  - Oxytocin release- human bonding
  - Decrease amygdala to improve emotional regulation and reduce avoidance
  - Increase NE and cortisol to increase emotional engagement and extinguish fear; increases HR, altertness, energy
- SE- confusion, depression, sleep problems, anxiety, paranoia lasting up to one month

Hallucinogens: Gamma hydroxy-butyric acid (GHB)/Rohypnol

- t1/2 30-60 minutes, liver metabolism, 5% renal excretion
- Onset 10-20 minutes, peak 20-45 minutes, last 2-5hours
- Therapeutic use: loss of muscle control (cataplexy) and narcolepsy, also muscle building for release of HGH
- Low dose- aphrodisiac and stimulant, retrograde amnesia and impairment for 8-12 hours with EtOH
- Tolerance: yes; Cross-tolerance: alcohol
- Neurotransmitters: GHB- excitation, GABAa- inhibitory
- Dependence: yes to both
- Withdrawal: combative, anxiety, agitation, confusion, tremor, cramps, insomnia, paranoia, delirium, tachycardia, hypotension 1-2 hours after last dose may last to days (3 normal)

Hallucinogens: Ketamine

- Therapeutic Uses: Pediatric anesthetic, asthma, nerve pain, field surgery, antidepressant
- Smoked, snorted, injected: onset peak 5-15 injected, 30 oral; duration ½-2 hours injected, 4-6 hours oral; first pass metabolism
- T ½ 2.5-3 hours, renal excretion 90%
- Neurotransmitters: MDMA antagonist, mu opioid, muscarinic

Hallucinogens: LSD

- Induces abnormal sensory perceptions, unpredictable effects- amount, purity, users personality, mood and expectations
- Onset: 30-90 minutes
- Effects: dilated pupils, higher body temperature, increased heart rate, increased BP, sweating, loss of appetite, sleeplessness, dry mouth, nausea FLASHBACKS

Inhalants

General Considerations

Inhalants: General Considerations

- Volatile vapors taken in by nose and trachea at room temperature or from pressurized container
  - Aerosols- paint sprays, hair sprays
- Classified by intended function or effect on the body
  - Solvents- polish and paint removers, lighter fluid, gas
  - Adhesives- airplane glue, rubber cement
  - Cleaning agents- spot removers, dry cleaning fluid
  - Room deodorizers- glade, etc.
  - Nitrous oxide- shipped cream, laughing gas
- Many exert effect through oxygen deprivation

Category	Examples
Aliphatic hydrocarbon	Petroleum products, propane, butane
Aromatic hydrocarbon	Toluene (paint thinner, model glue) and xylene
Ketone	Acetone
Haloalkanes	Hydro- and chloro- fluorocarbons, trichloroethylene (aerosols and propellants)
Nitrites	Alkyl nitrites (poppers), nitrous oxides (whipped cream)

Inhalants: Specific Risks

Substance	Toxicity
Methylene chloride	Carbon monoxide poisoning
Gasoline	Lead poisoning
Alkyl nitrites	Methemoglobinemia, ingestion only
Carbon tetrachloride	Liver injury
Butane, propane	Burns
Benzene	Bone marrow depression, cancer
Toluene	Damages myelin

Inhalants: Pharmacological Properties

- Duration: very short, 15-45 minutes
- Tolerance: yes, but typically increased use over time with more periods of intoxication and increased preference for higher levels of intoxication
- Physical Dependence: unknown
- Psychological Dependence: unknown, thought high
- Onset: extensive capillary surface of lung delivers rapid peak levels similar to IDU
- Pattern of Use: high several hours to throughout days

Inhalants: Effects

- Short term headache, nausea and vomiting, slurred speech, loss of motor coordination, wheezing
- Some injury due to other chemicals in product used, dangerous behavior while intoxicated, frostbite, explosion
- Regular use leads to brain, heart, kidney, and liver disease
  - Pneumonia, cardiac failure, aspiration of vomit, hearing loss, limb spasms

Inhalants: Mechanism of Action/ Neurotransmitters

- Variety of mechanisms due to large class of substances
- Anesthetic gasses (NO, enflurane) NMDA receptor antagonists bind inside of Ca+2 channel with high blockade for short time (differ from ketamine which bind regulatory site on receptor for long, predictable time)
- Risk of addiction: unknown

Inhalants: Therapeutic Uses

- Nitrous Oxide- dental anesthetic

Inhalants: Intoxication

- Low dose- belligerence, assaultiveness, apathy, impaired judgment, dizziness, nystagmus, slurred speech, unsteady gait, impaired functioning, lethargy, decreased reflexes, tremor, blurred vision, diplopia, stupor
  - Intense euphoria, hallucinations, distortions in time and space
- Overdose- high acute or chronic heavy- neurologic signs of incoordination, muscle weakness, psychomotor retardation
- Death- cardiac arrhythmia or CNS depression, suffocation

Inhalants: Withdrawal

- Syndrome not described (note- short duration of action)
- Glue sniffer's rash and odor of paint or solvents on clothes, skin, breath and residues in sweat
  - Excessive anal secretions, watering of eyes, eye and lung irritation
- Search to identify family dysfunction, schoolwork slippage, adjustment problems

Opiods

General Considerations

Opioids:
General Considerations

- Produce action by interacting with opioid receptors to activate endogenous opioids

Opioids: Therapeutic Uses

- CNS effects
  - Analgesia
    - Drowsiness is a SE
    - Changes in mood- euphoria also numbing
    - In pain free individuals, not always pleasant, induces vomiting
  - Decreases diarrhea
  - Quiets cough
  - Opioid dependence as maintenance therapy

Opioid Pharmacology

- Classes
  - Agonist- natural, semi-synthetic, synthetic
  - antagonist
  - mixed antagonist-agonist
- Receptors
  - Mu
  - Delta
  - Kappa

Opioids: Agonists- naturally occurring

- Opium/ paregoric
- Morphine-
- Codeine (methlymorphine)

Opioids: Agonists-semisynthetic

- Heroin (diacetylmorphine)
- Hypromorphone (percocet)
- Oxycodone (percocet)
- Hydrocodone (vicodin, hycodan, lorcet)
- Oxymorphone (numorphin)

Opioids: Agonists- synthetic

- Methadone (dolophine)
- LAAM (orlaam)
- Propoxyphene (darvon)
- Fentanly (sublimaze, duragesic)
- Diphenoxylate (lomotil)
- Meperidine (demerol)

Opioids: Antagonists

- Naloxone (narcan)
- Naltrexone (revia)
- Nalmefene (revex)

Opioids: Mixed agonist-antagonist

- Pentazocine (talwin)
- Buprenorphine (buprenex)
- Nalorphine (nalline)
- Nalbuphine (nubain)
- Butorphanol (stadol)

Opioids: Mu Receptors

- Mu-1
  - supraspinal analgesia
- Mu-2
  - respiratory depression
  - gastrointestinal stasis
  - urinary retention
  - bradycardia
  - pruritus
  - euphoria

Opioids: Delta Receptors

- spinal analgesia
- modulates mu

Opioids: Kappa Receptors

- supraspinal analgesia
- spinal analgesia
- sedation
- miosis
- Hyperalgesia

Opioids: Actions and Selectivity

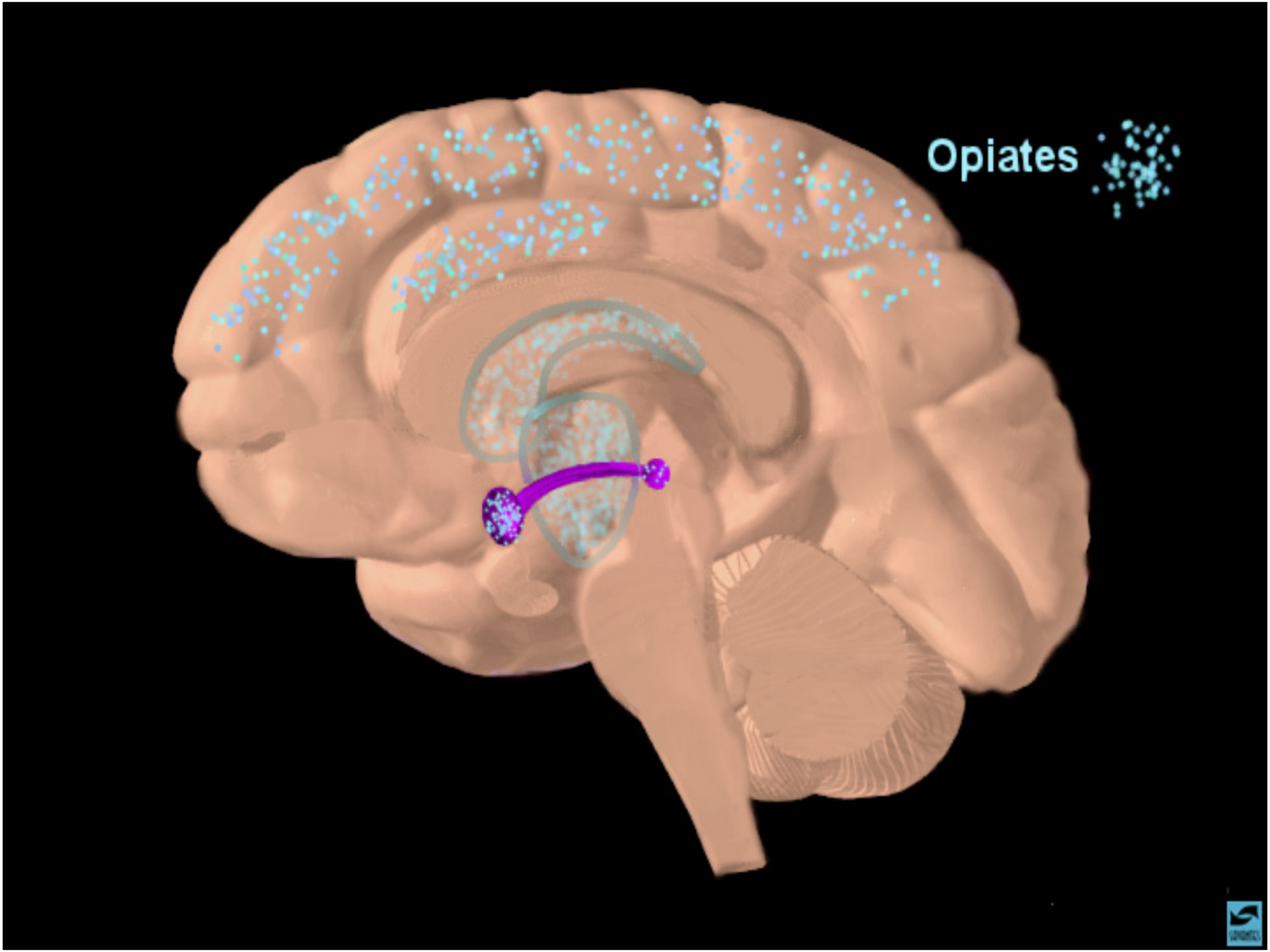
Substance	Receptor
Morphine	Mu, kappa
Methadone	Mu
Buprenorphine	Mu- partial, kappa antagonist
Naloxone	Mu- antagonist, kappa antagonist
Pentaxzocine	Mu- partial agonist, kappa agonist

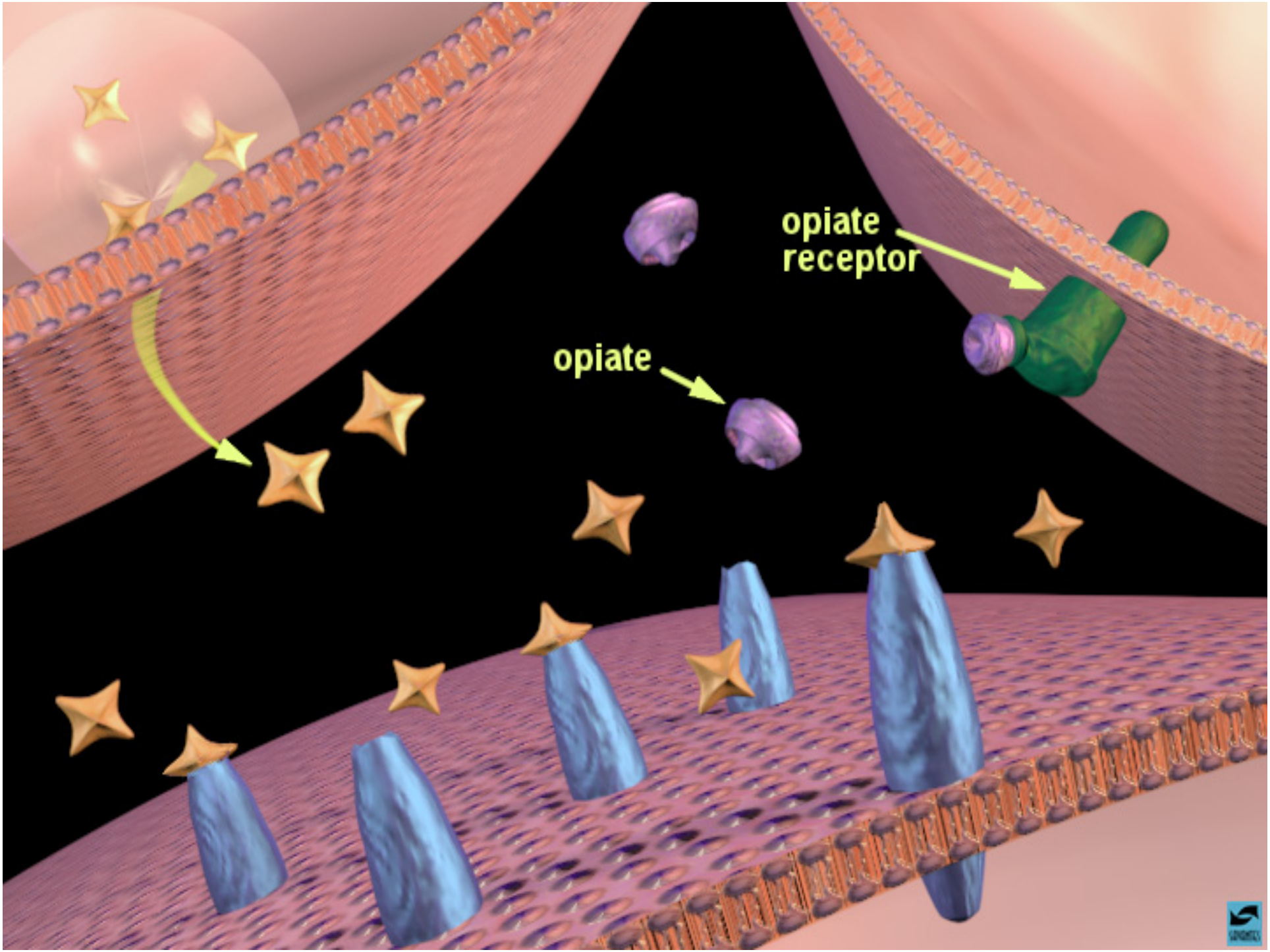
Opioid Analgesic Comparisons

Substance	Route of administration	Dose	Duration (hours)	Half-life (hours)
Morphine	IM, SC, PO	10 (60 mg)	4-5 (4-7)	3-4
Heroin	IM, SC, PO	5 (60 mg)	4-5	3-4
Codeine	IM, PO	125 (200 mg)	4-6	2-4
Fentanyl	IV, IM, intrathecal	0.1 mg	1-2	½
Methadone	IM, PO	10 (20- 150 mg)	4-5 (4-6)	1.5-40

Opioids: Pharmacological Properties

- Duration: ultra short, short, moderate, long acting substances
- Tolerance: yes
- Physical Dependence: yes
- Psychological Dependence: yes
- Onset: route of administration and pharmacology determine onset
- Pattern of Use: 0.05% increasing. Six weeks to catch a habit
    - High percentage of regular users become addicted


Opiates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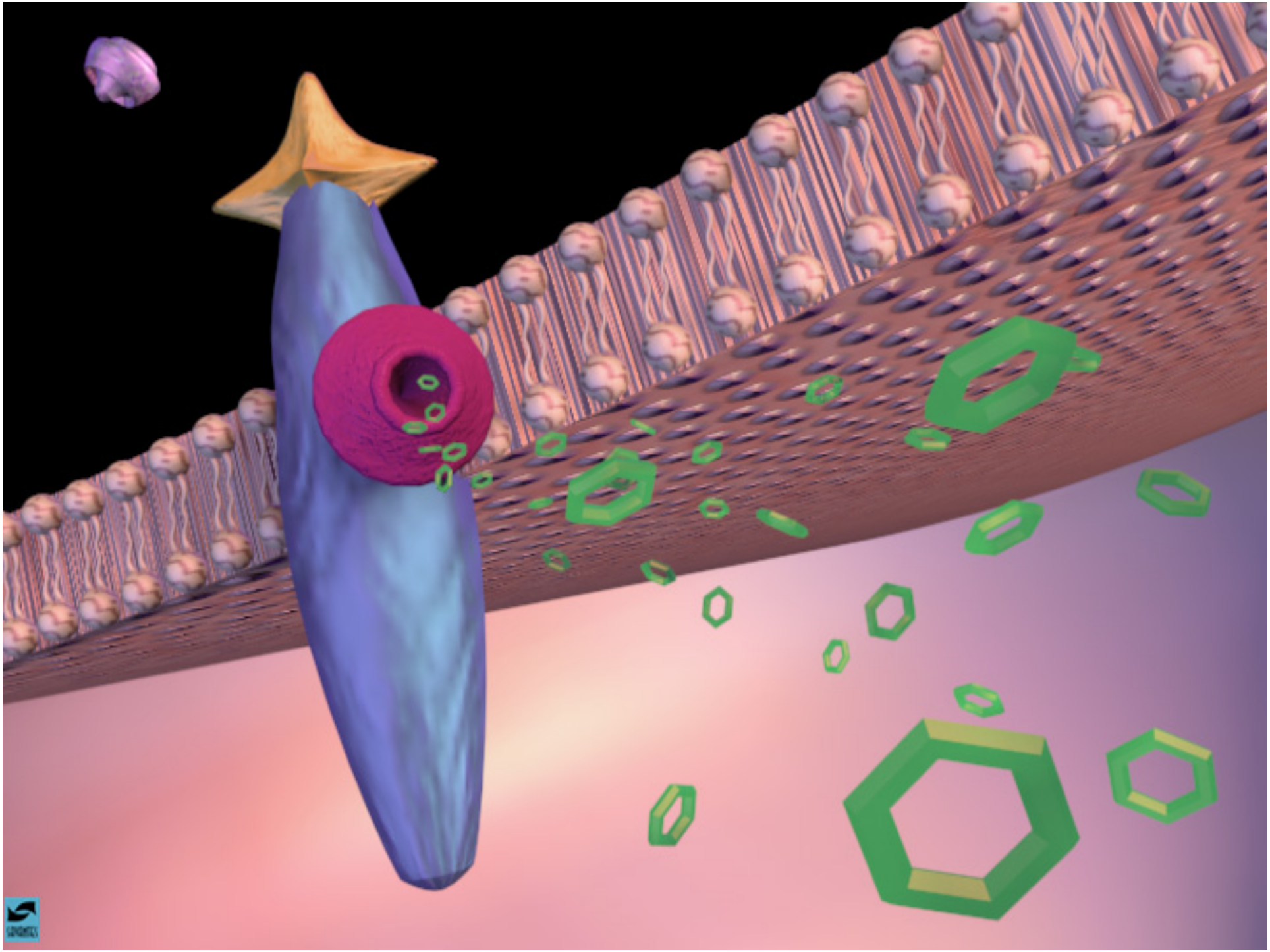
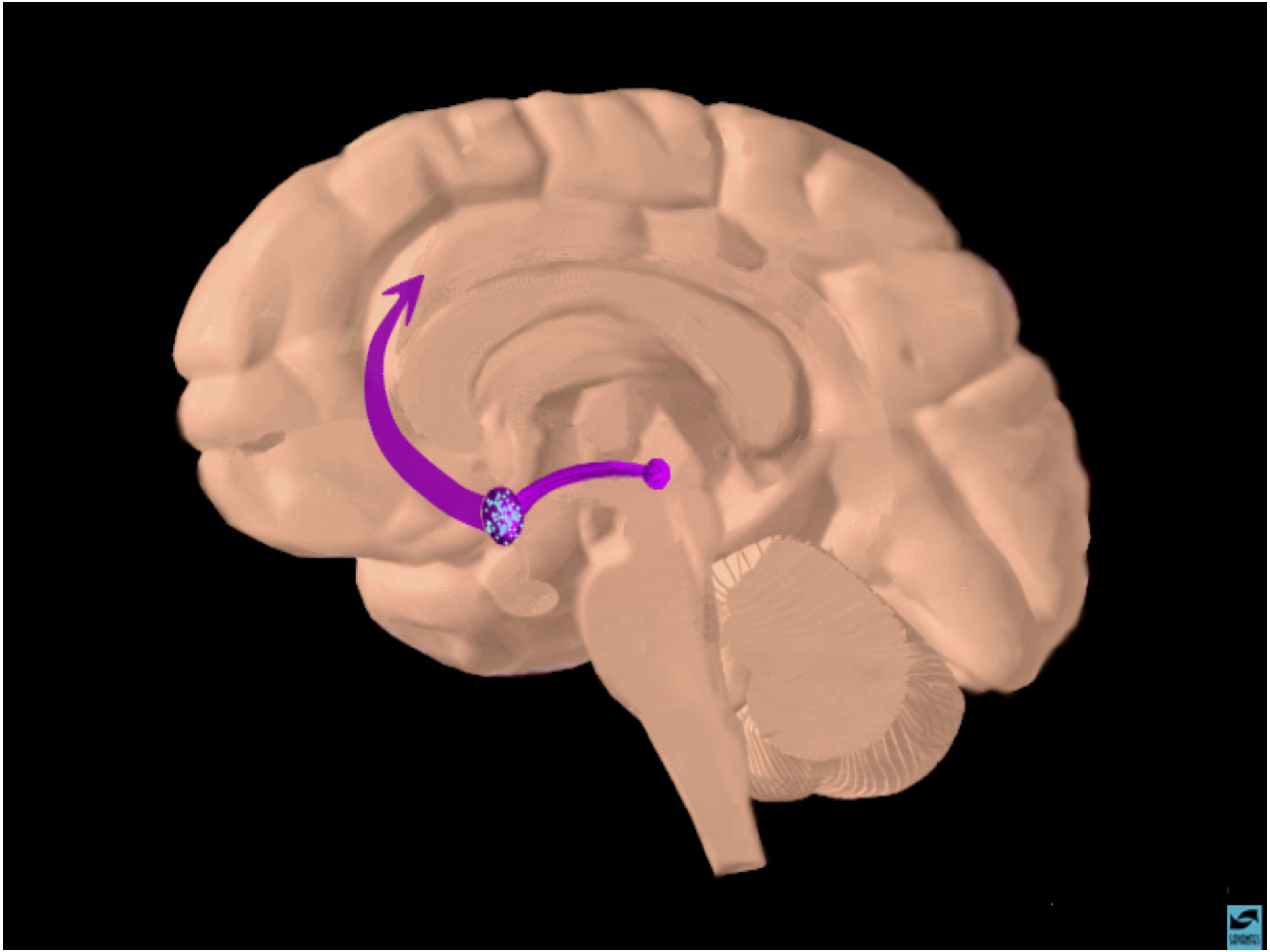




Opioids: Signs and Symptoms of Intoxication

- Euphoria
- Sedation/light sleep (nod)
- Relief of pain/ anxiety
- Miosis
- Constipation

Opioids: Overdose

- Classic triad
  - Unconsciousness
  - Miosis
  - Respiratory depression
- Hypotension
- Pulmonary edema

Opioids: Signs of Use/ Dependence

- Urinalysis
- Fresh and old needle marks
- Hyperpigmented veins
- Abscesses
- Scars
- Edema
- Signs and symptoms of use and withdrawal

Opioids:
Medical complications

- Overdose, accidental or intentional
- Abscesses
- Cellulitis
- Septicemia
- Infectious endocarditis

Opioids: Complications continued

- Hepatitis
- Tuberculosis
- HIV infections
- Heroin associated nephrology
- Nasal septal perforations

Opioids: Long Term Use

- Sexual impotence
- Constipation
- Insomnia
- Sweating

Opioids: Abstinence Syndrome Defined

- Opioids used
- Route of administration
- Half-life
- Other drugs
- Physical/psychological state

Opioids: Abstinence Syndrome Defined

- Opioids used
- Route of administration
- Half-life
- Other drugs
- Physical or psychological state

Opioids: Grade 0

TWO DREAMS

- Anxiety
- Craving

Opioids: Grade 1

- Yawning
- Perspiration
- Lacrimation
- Rhinorrhea

Opioids: Grade 2

- Mydriasis
- Gooseflesh
- Tremors
- Hot and cold flashes

Opioids: Grade 3

TWO DREAMS

- Elevated vital signs
- Nausea
- Restlessness
- Aches
- Cramps
- Insomnia

Opioids: Grade 4

TWO DREAMS

- Vomiting
- Diarrhea
- Ejaculation

Opioids: Protracted Abstinence Syndrome

- Insomnia
- Irritability
- Inability to concentrate

Opioids: Withdrawal Techniques

- Gradual taper of agent
- Methadone (agonist) withdrawal
- Clonidine (symptomatic)
- Clonidine and naltrexone (symptomatic, block)
- Rapid (ultra-short) opioid withdrawal

Opioids:
Maintenance Agents

- Methadone
- LAAM
- Buprenorphine

Opioids:
Goals of Pharmacology

- Prevention or reduction of withdrawal symptoms
- Prevention or reduction of drug craving
- Prevention of relapse to use of addictive drug
- Restoration to or toward normalcy of any physiological function disrupted by drug use

Opioids:
Profile of Potential Agent

- Effective oral administration
- Long half life
- Minimal side effects during chronic administration
- Safe, no true toxic or serious adverse effects
- Efficacious for a substantial percentage of people with the disorder

Opioids: Buprenorphine

- ‘76 martin described as a partial agonist
- ‘78 Jasinski suggested utility in opioid dependence
- ‘80 Mello found decreases heroin self-administration
- ‘90 Clinical trails comparing to methadone
- Today- widely used

Buprenorphine: Pharmacology

- partial (weak) agonist at μ receptor
- opioid antagonist at the kappa receptor
- effect sublingually and subcutaneously

Buprenorphine: Pharmacology continued

- long duration of action (30 hours)
- strong affinity for receptor
- slow dissociation from receptor
- highly lipophilic
- once a day dosing
- smooth onset of action

Buprenorphine: Unique Characteristics

- ceiling effect
- effective doses equal to or less than 16 mg
- safety implications- addicted push dose
- low toxicity at high doses
- limited, clinically significant opioid effects
- low physical dependence
- mild withdrawal syndrome
- good name on the street

Buprenorphine: Complementary Uses

- cocaine abuse- contradictory studies
- acts synergistically with cocaine to augment reinforcing effects
- suppresses cocaine self-administration in rhesus monkey
- depression (Kosten et al)
- alternative to methadone for depressed addicts
- similar response to tricyclics
- opiate withdrawal

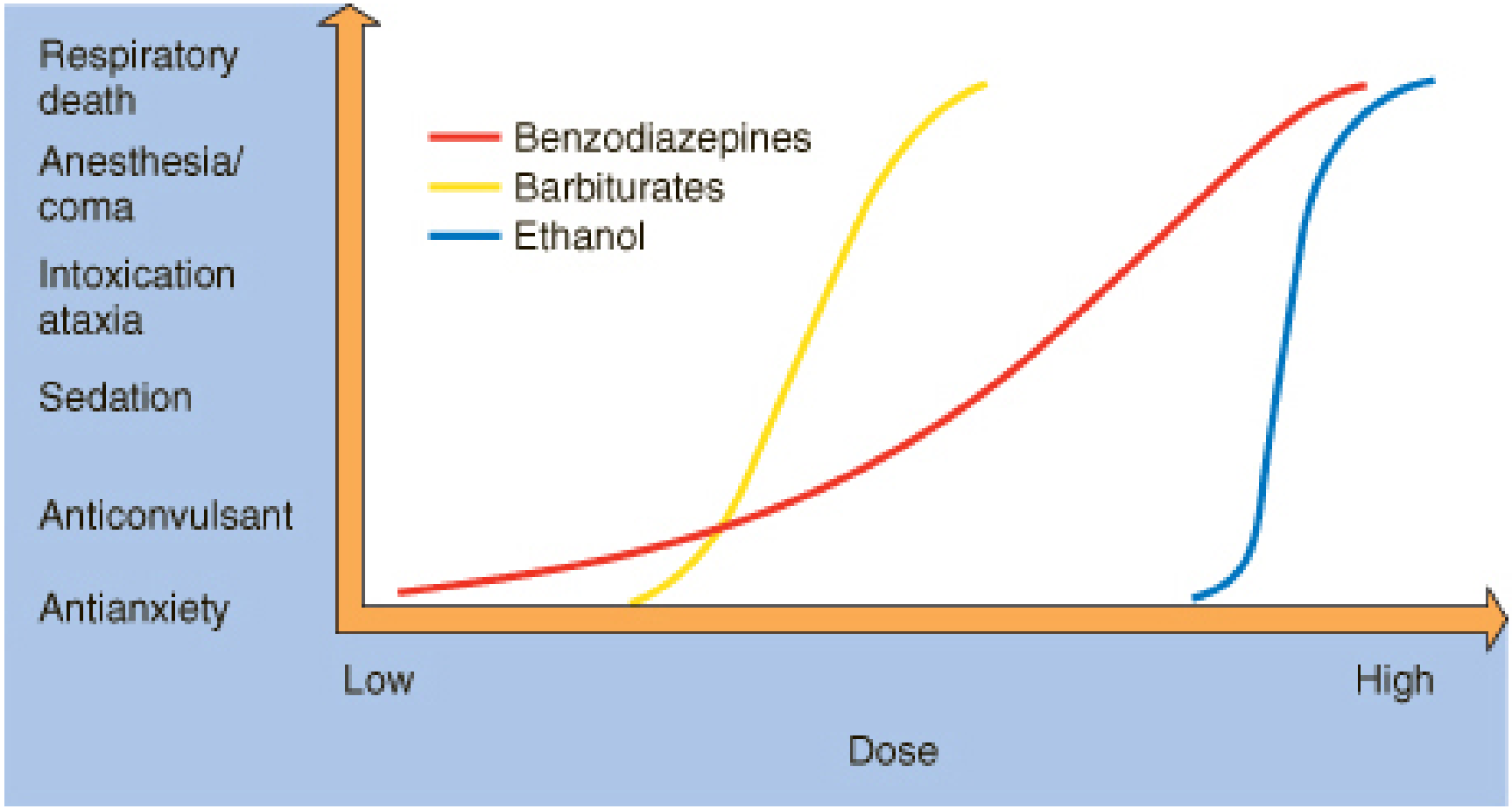
Buprenorphine: Concerns

- poor bioavailability
- sublingual administration requires longer observation
- abuse in Europe, Australia, and New Zealand and now the U.S.

Sedatives, Hypnotics, Anxiolytics

General Considerations

Sedatives: Dose-Response Curves



Sedative-Hypnotic- Anxiolytics: Street Names

Barbiturates	Benzodiazepines
Barbs	BZDs
Downers	Benzodiazepines
Sleepers	Downers
Stumblers	Goofballs
Yellow Jackets, red dolls, blue devils	Heavenly Blues, Yellows
Ludes	Quaaludes
Tootsies	Robital
Rainbows	Stupefy
Goof balls, doors, 4s	Tranx
Sopors	Valley Girl (for Valium ®)

Sedatives-Hypnotics- Anxiolytics: General Considerations

- GABA agonists
- Decrease excitability of neurons
- Reduces heart-rate & respiration
- Parasympathomimetic
- **Cross tolerance w/ alcohol**
- Used in high doses for anesthesia
- Moderate doses for sleep
- Low doses for anti-anxiety (anxiolytic) anti-depressive

S/H/As: Examples

- Benzodiazepines- diazepam (valium), clonazepam (klonopin), estazolam (prosom), flunitrazepam (Rohypnol®), lorazepam (Ativan), midazolam (versed), nitrazepam (mogadon), oxazepam (serzx), triazolam (halcion), temazepam (restoril), chlordiazepoxide (Librium), alprazolam (Xanax)
- Barbiturates-amobaribtal, pentobarbital, secobarbital, phenobarbital

S/H/As: Examples, continued

- "Z-drugs"- eszopiclone (lunesta), zaleplon (sonata), zolpidem (Ambien), zopiclone (imovane)
- Anti-histamines- diphenhydramine, dipenhydrinate, doxylamine, mirtazapine, promethazine
- Other- chloral hydrate, Mickey Finn, alcohol, trazodone, opiates and opioids, GHB
- Herbal sedatives

S/H/As:
General Rules of Thumb

- Class of substance that induces sedation by reducing irritability or excitement
- Dose highest with hypnotic (induce sleep), relieve anxiety (moderate), or provide peaceful, calming sedative effect (lowest)
- Sedatives also cause hypnotic effects
- Targeting of receptors and selectivity of agents allow more precision in prescribing

S/H/As: Sedatives

- Even at therapeutic doses, can cause dependence when taken regularly over time
- Feel need drug to function in absence of physical dependence when psychologically dependent
  - Role of the “signal”

S/H/As: Sedative Misuse

- More common in people with difficulty dealing with stress, anxiety, sleeplessness
- Heroin users supplement or substitute for heroin
- Stimulant users use to calm jitters
- Some take to relax or forget worries
- Barbiturate OD factor in 1/3 of all OD deaths
- Alcohol compounds respiratory depression sedative user

S/H/As: Sedative Amnesia

- Long and short term amnesia occur
- Lorazepam known for anterograde amnesia

S/H/As: Sedative Crime

- Alcohol, GHB, and temazepam (restoril) and midazolam (versed) used as date rape drugs in descending order
- Administered to unsuspecting person to reduce defenses
- Self-administration of rhohypnol reduces inhibition and makes it difficult to interrogate

S/H/As: Hypnotics

- Soporific or sleeping pill are synonymous for hypnotics- WORSEN SLEEP ARCHITECTURE OVER TIME
- Function is to induce sleep and used to treat insomnia and in surgical anesthesia
- In anesthesia produces and maintains unconsciousness- no sleep cycles
- Range of responses due to dose from anxiolysis to unconsciousness

S/H/As: Hypnotics, continued

- Are dependence producing, should be used for shortest period of time
  - Rather use sleep hygiene, exercise, etc.
- Benzo and non-benzo also produce side effects- daytime fatigue, elderly and young particularly vulnerable
- Gradual taper leads to improved health without worsening of sleep

S/H/As:
Hypnotics, continued

- Benzodiazepines better known and often prescribed
- Melatonin and non-benzo types increasing in popularity
- Tolerance to hypnotic effects occurs after 1-2 weeks

S/H/As: Anxiolytics

- Anxiotrophic compounds consist of
  - Anxiolytic, antipanic, antianxiety agents that inhibit anxiety
  - Anxiogenic agents that increase anxiety
- Alcohol produces anxiolysis
- Beta blockers assist with reducing somatic symptoms of anxiety, but are not anxiolytics
- Sometimes referred to as minor tranquilizers
  - Contrast with major tranquilizers such a neuroleptics and antipsychotics

S/H/As: Types of Anxiolytics

- Benzodiazepines, serotonergic antidepressants, azapirones (buspar), barbiturates, hydroxyzine (antihistamine), pregabalin, herbal treatments
- OTCs- antihistamines, melatonin
- Common drugs- alcohol, inhalants
- Alternatives to medication- exposure, CBT, psychotherapy

S/H/As: Types, continued

- Benzodiazepines first choice when short-term sedation CNS sedation is needed or longer term treatment for sever disorder
  - Tolerance and dependence may occur
  - Moderate doses are used for anxiolysis
- SSRIs- used in doses higher than for antidepressants
  - Can be Anxiogenic at onset so may need benzodiazepine to tolerate
  - Older TCAs are anxiolytic but with bad SE profiles

Sedatives: Pharmacological Properties

- Duration: 30 minutes to 12 hours, active metabolites
- Tolerance: benzo- moderate, barbiturates- high
- Physical Dependence: high
- Psychological Dependence: high
- Onset: depends upon route of administration
- Pattern of Use:
- Withdrawal: stereotypical

Sedatives: Effects

- Neurotransmitters:
  - GABA-A: barbiturates, benzodiazepines, nonbenzodiazepines, and chloral hydrate, clomethiazole, diethyl ether, ethanol, ethylchlorvynol, glutethimide, methaqualone, propofol, valerian, antihistamines, melatonin agonists
  - mixed Mechanism of Action-antihistamines, 5-HT 2a antagonists, anticholinergic, alpha blockers, dopamine agonists: antidepressants, antipsychotics, and niaprazine

Sedatives: Effects, continued

- Others- cannabis, opioids, sodium oxybate
- Risk of Addiction:
  - Benzodiazepines- moderate
  - Barbiturates- high

Sedatives: Therapeutic Uses

- Dull anxiety related to painful or anxiety provoking procedures
- Muscle relaxation and anti-spasmodic
- Anti-convulsants
- Sedatives and hypnotics- induce relaxation, drowsiness, sleep
  - Prior to surgery as a part of balanced anesthesia
  - Adjunct to analgesics in preparing patients for surgery

Sedatives: Therapeutic Uses continued

- Amnestic or time shortening effect
- Withdrawal agent for other in class or alcohol
- Induce anesthesia
- Seizure disorder
- Increase tractability and compliance of children or troublesome, demanding patients

Sedatives: Intoxication

- Low dose- maladaptive behavioral changes and physical signs secondary to ingestion, disinhibition of sexual and aggressive impulses, mood liability, impaired judgment, impaired social or occupational functioning
- Over dose- slurred speech, incoordination, unsteady gait, impairment in attention or memory, drowsiness, confusion, paradoxical excitement, dizziness, hypotension, decreased respiratory function
  - Similar to alcohol, less aggression

Sedatives:
General Withdrawal

- N&V, malaise or weakness, autonomic increased activity (tachy, sweaty), anxiety, irritability, orthostatic hypotension, coarse tremor or hand/tongue/eyelids, marked insomnia, grand mal seizures (can occur with reduction in dose)
- Onset 2-3 days after cessation

Sedatives: Benzodiazepine Withdrawal Syndrome

- Benzodiazepine- insomnia, anxiety, confusion, disorientation, hot flashes, cold sweats, diaphoresis, chills, fever, perspiration, nightmares, perceptual disturbances
- Severe: seizures, hallucinations, suicidal ideation, panic attacks, depersonalization, tremors, delirium, DTs
- First 12-15 hours, patient appears to improve
- 16+ hours
  - Restless, anxious, tremulous, weak, abdominal cramping
  - Vomiting, orthostatic hypotension, tremors, increased deep tendon flexion, convulsions

Sedatives: Benzodiazepine Withdrawal continued

- Days 2-3
  - Delirium, hallucinations (persecutory) disorientation to time & place
  - Once delirium starts can't be reduced by administration of other sedative hypnotics-has to run its course
  - Includes hyperthermia (increased body temp), exhaustion, cardiovascular collapse & sometimes death
  - Depending upon type of drug, withdrawal symptoms reach peak severity at days 2-3 & last upwards of a week (& in some cases, some of the symptoms may last several weeks)

Sedatives: Barbiturate Abstinence Syndrome

Clinical complaint	Incidence (%)	Time onset (day)	Duration (day)	Notes
Apprehension, uneasiness	100	1	3-14	Vague
Muscle weakness	100	1	3-14	Evident with mildest exertion
Tremors	100	1	3-14	With movement
Postural faintness	100	1	3-14	With movement
Anorexia	100	1	3-14	With vomiting
Twitches	100	1	3-?	
Seizures	80	2-3	8	
psychoses	60	3-8	3-14	Resemble DTS

Sedatives: BAS

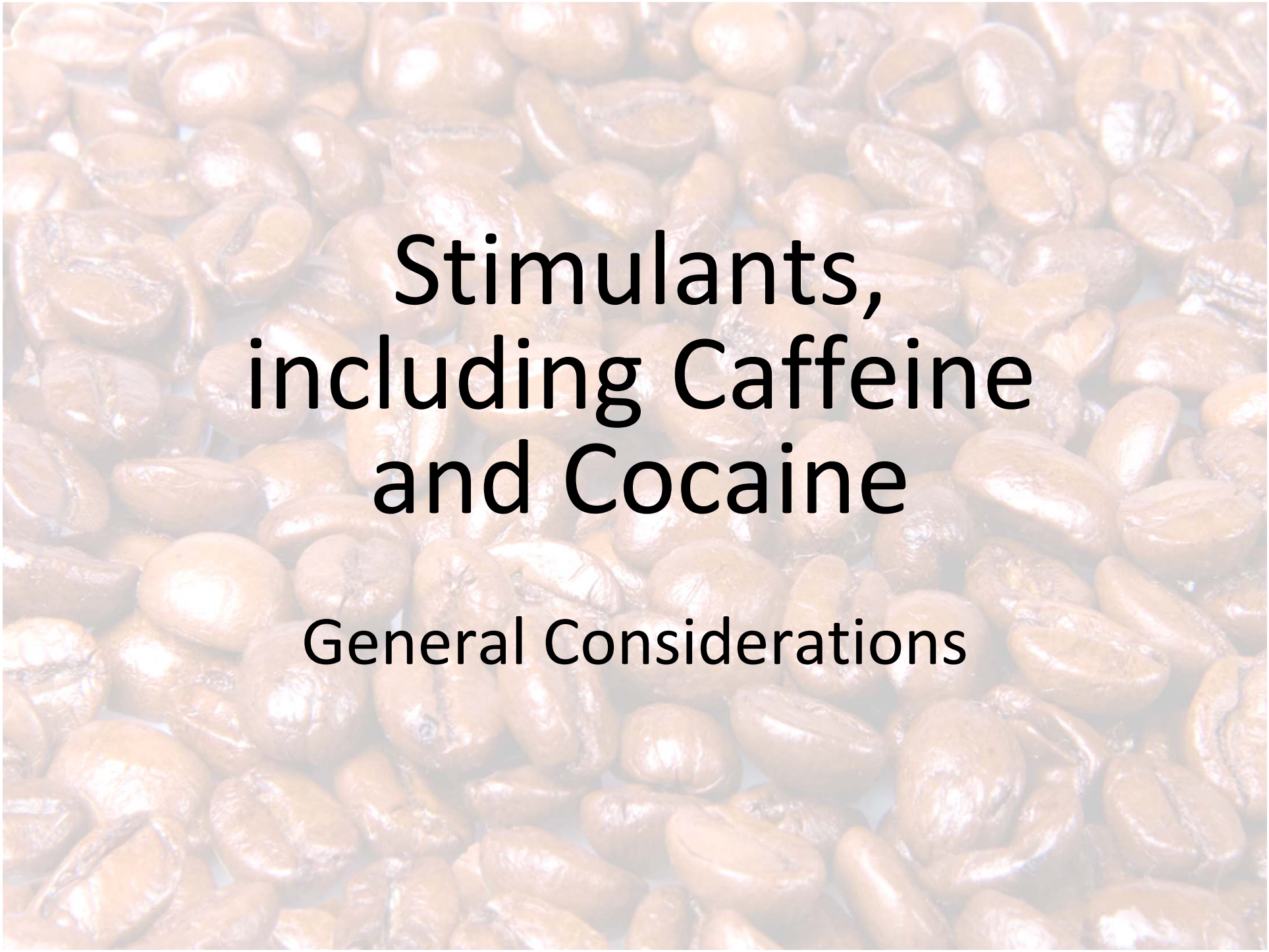
- Stage I depends on amount and half life of drug; may begin as early as 12 hours but be delayed up to several days
- Signs- tremulousness, vomiting, tendon hyperreflexia, diaphoresis, postural hypotension
- Symptoms- anxiety, insomnia, anorexia, nausea, abdominal cramps
- All Abstinence Syndrome can progress to Stage II, III (seizures), IV (hyperpyrexia, psychosis, delirium) BUT should be prevented with replacement therapy and taper
- Benzodiazepine withdrawal is same

Sedatives: Special Notes

- Symptom reemergence is an issue
- Accidental overdose with alcohol is too common
- Amnesia for substance taking contributes to accidental overdose

Sedation: Alcohol

- Large dose to get effect as compared to other sedatives
- Addictive, rapid tolerance, low TI, GABA agonist, decreased glutamate, increased release of DA ta nucleus accumbens for reinforcement
- Works great for sleep- the first time!



Stimulants, including Caffeine and Cocaine

General Considerations

Stimulants: General Considerations

- Psychoactive drugs induce temporary improvements in either mental or physical functions
- Enhanced alertness, wakefulness, and locomotion
- Stimulants are widely used throughout the world as prescription medicines and as illicit substances of recreational use or abuse

Stimulants: Classes

- Amphetamine, dextroamphetamine, methamphetamine, methylpenidate (Ritalin), tenuate (diet pills), phenmetrazine (preluding), Benzedrine, Benzpethamine, phenteramine, caffeine, methadrine, Dexedrine
- Street names- uppers, pep pills, meth, crystal, bennies, moth crank, speed, dexies, hearts, whites, black beauties, croak

Stimulants: Pharmacological Properties

- Physical Dependence: Low
- Psychological Dependence: High
- Tolerance: Moderate
- Duration: 1-8 hours
- Risk of Addiction: High
- ONSET: Depends upon route of administration

Stimulant Effects

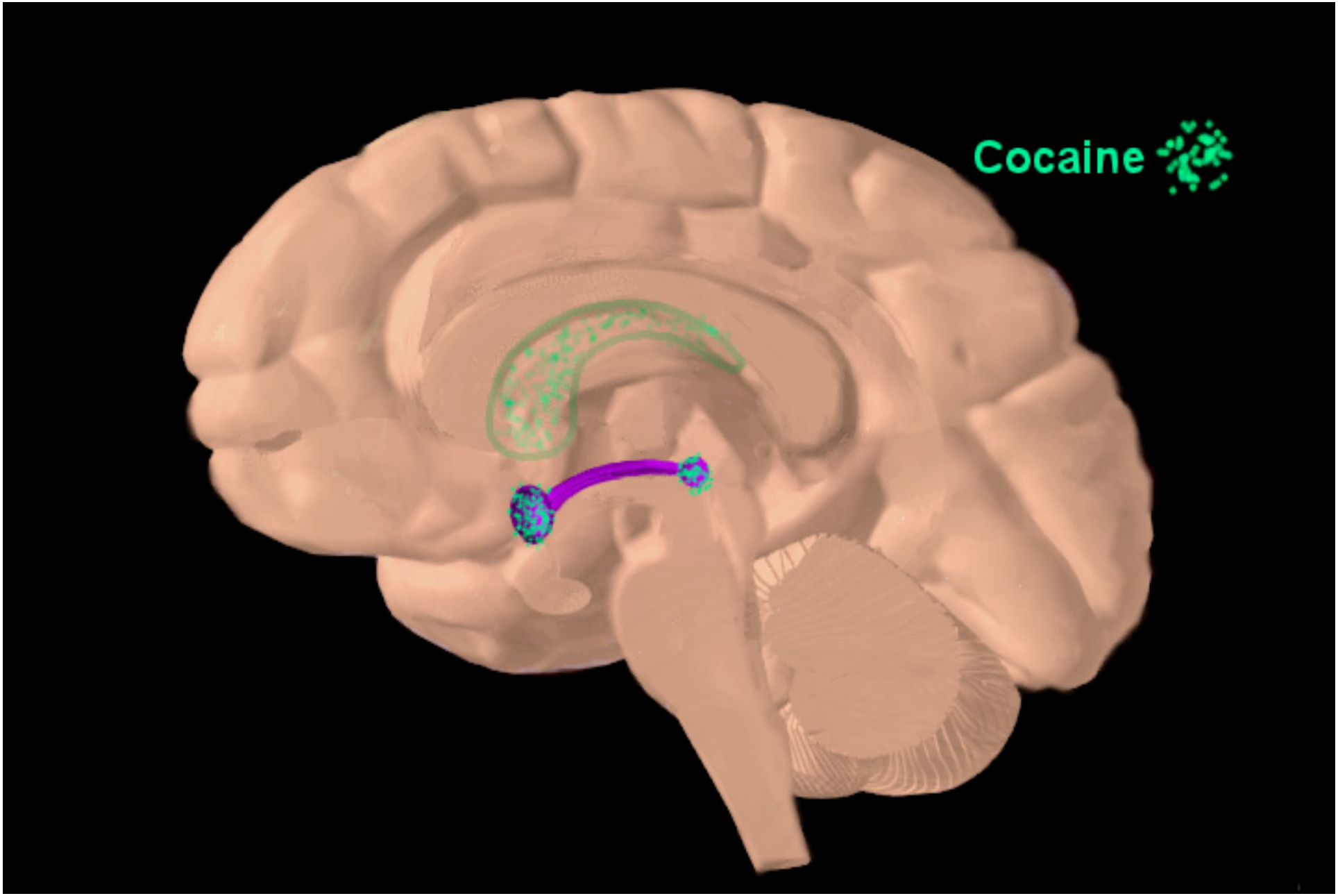
- Convulsants and respiratory stimulants (thebaine, xanthines)
- Psychomotor stimulants (amphetamines and cocaine)
  - Become busier, not brighter
  - Release biogenic amines
- Psychomimetics (hallucinogens)

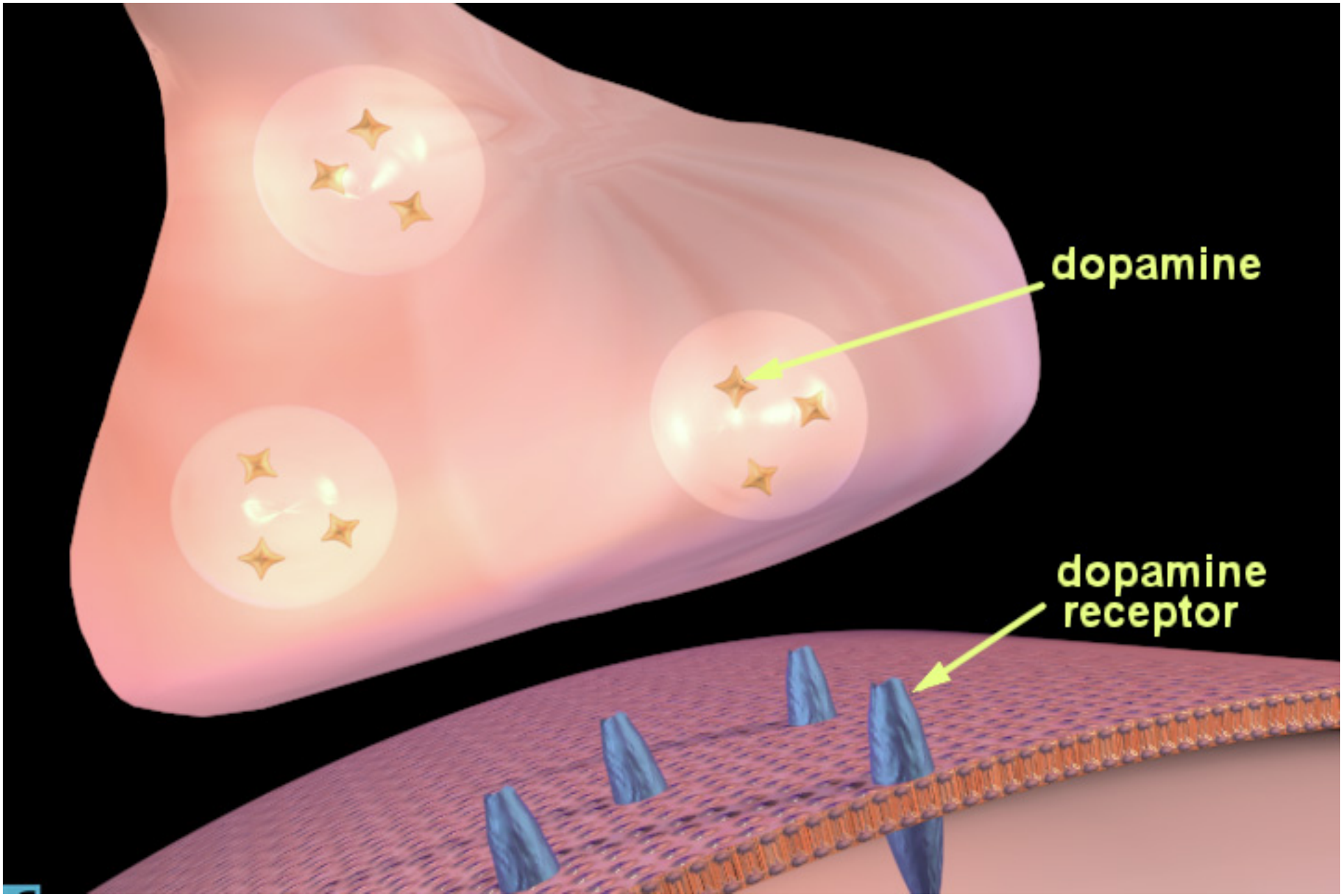
Stimulants: Effects

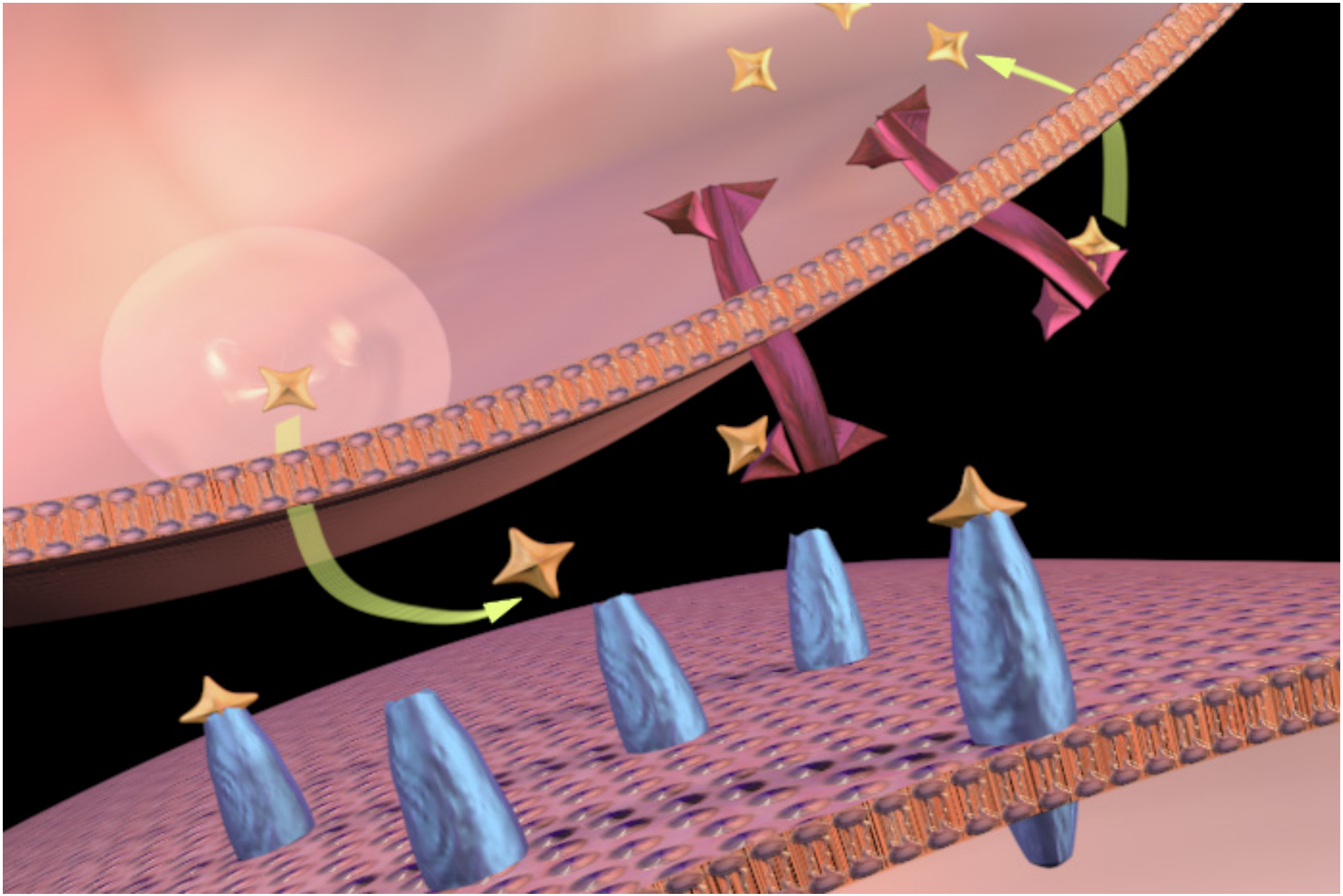
- Enhance activity of the central and peripheral nervous systems
- Enhanced alertness, awareness, wakefulness, endurance, productivity, and motivation, increased arousal, locomotion, heart rate, and blood pressure, and the perception of a diminished requirement for food and sleep
- Improve mood and relieve anxiety, induce feelings of euphoria
- Cause anxiety and heart failure
- Facilitation of norepinephrine (noradrenaline) and/or dopamine activity adenosine receptor antagonism, and nicotinic acetylcholine receptor agonism

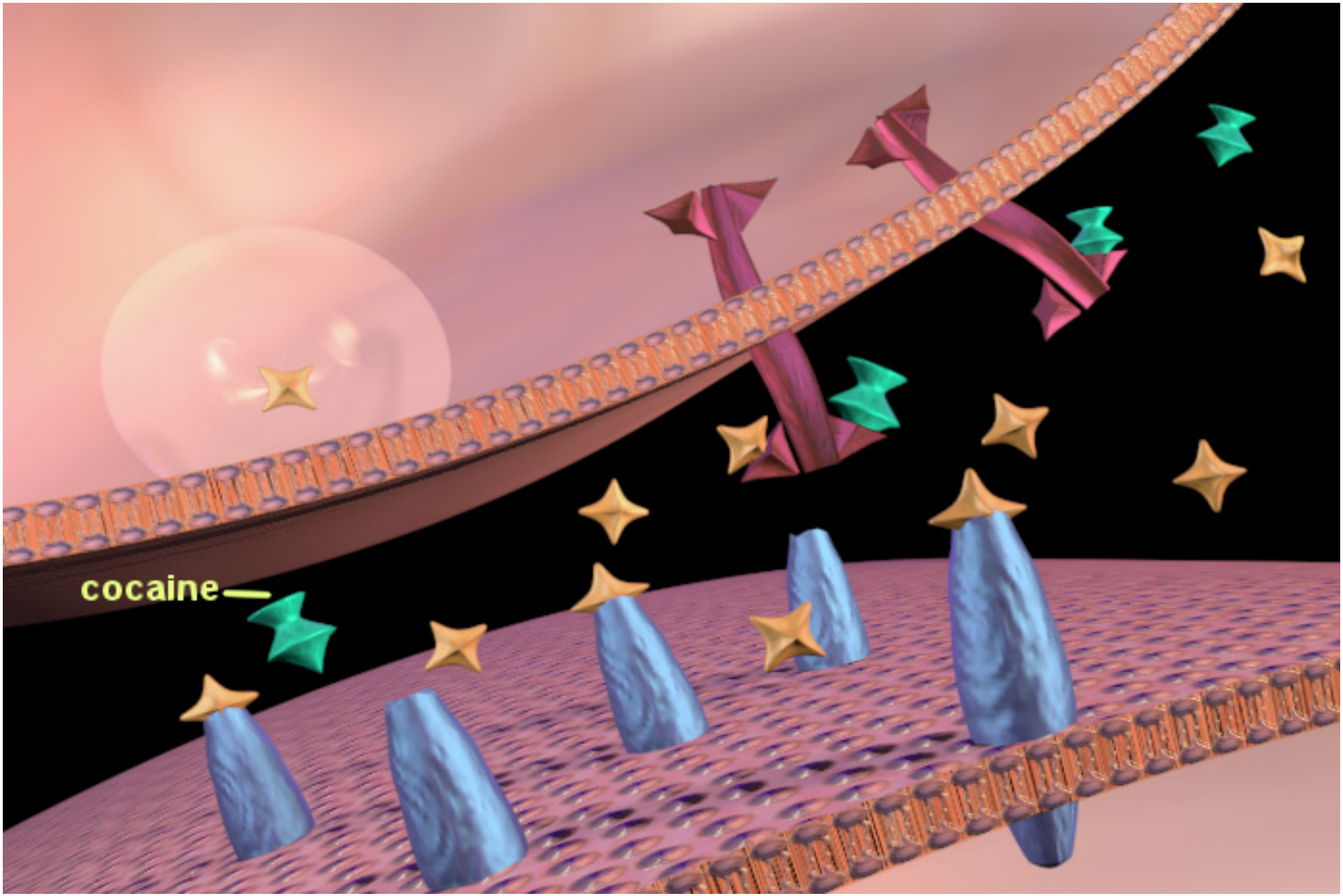
Stimulants: Receptors

- Monoamine neurotransmitters in the brain using catecholamine neurotransmitters
- Effects on dopamine, serotonin, norepinephrine, acetylcholine, glutamate, and histamine
- Dopamine D2 receptors in the hippocampus, a region of the brain associated with forming new memories, appear to be unaffected by the presence of amphetamine


Cocaine


dopamine
dopamine receptor




cocaine

Stimulants: Therapeutic Uses

- Counteract lethargy and fatigue throughout the day while at work or while doing other activities.
- Reduce sleepiness and to keep the person awake when necessary, as well as to treat narcolepsy.
- Decrease appetite and promote weight loss, as well as to treat obesity.
- Improve concentration and focus while at work or school, especially for those with attentional disorders such as ADHD.
- Vasoconstriction, topical anesthesia (cocaine)
- Occasionally, off label to treat clinical depression, more particularly, non-typical depression and treatment-resistant depression

Stimulants: Intoxication

- Effects vary by age and person
- Abdominal pain, acne, arrhythmias, blood shot eyes, blurred vision, bruxism, constipation, diaphoresis, diarrhea, dilated pupils, dizziness, dry and/or itchy skin, dry mouth, erectile dysfunction, fever, flushing, headache, hypertension or vagal hypotension, indigestion, insomnia, loss of appetite, mood swings, nausea, nervousness, numbness, pallor, palpitations, Raynaud's phenomenon (secondary), reduced seizure threshold, restlessness, tachycardia, tachypnea, tics, vasoconstriction or vasodilation, vomiting, and weight loss

Stimulants: Overdose

- Moderate: “profound thoughts”,” agitation, arrhythmia, confusion, dysuria, hypertension or hypotension, hyperreflexia, myalgia, tachypnea, tremor, urinary hesitancy, and urinary retention
- Large: adrenergic storm, anuria, cardiogenic shock, circulatory collapse, hyperthermia, psychosis, pulmonary hypertension, renal failure, rhabdomyolysis
- Fatal dose with convulsions and coma
- DDx: manic episodes, cocaine intoxication, PCP

Stimulants: Withdrawal

- Crash- unpleasant, apathy, dysphoria, craving, anxiety, tremulousness, irritability, feelings of fatigue and depression
- Course: peaks 2-4 days, depression may last months
- Complications: Suicide

Stimulants: Amphetamine

- “Speed”
- Wakefulness and stimulation
- Used to treat ADHD, obesity, and narcolepsy
- Also used as performance and cognitive enhancer
- Unlike methamphetamine, is not neurotoxin
- Increases NT DA and NE, also serotonin

Stimulants: Cocaine

- Crystalline tropane alkaloid obtained from the leaves of the coca plant
- Stimulant, an appetite suppressant, and a nonspecific sodium channel blocker, which in turn causes it to produce anesthesia at low doses
- Serotonin–norepinephrine–dopamine reuptake inhibitor, also known as a triple reuptake inhibitor (TRI)
- Markedly more dangerous than other CNS stimulants, including the amphetamine class, at high doses due to its effect on sodium channels, as blockade of Nav1.5 can cause sudden cardiac death

Stimulants: Cocaine Metabolism

- Complex relationships of blockade of the dopamine transporter protein
- Prolonged exposure to cocaine, as occurs with habitual use, leads to homeostatic dysregulation of normal
- Decreased dopaminergic signaling after chronic cocaine use may contribute to depressive mood disorders and sensitize this important brain reward circuit to the reinforcing effects of cocaine
- Taken in small amounts usually makes the user euphoric, energetic, talkative, mentally alert- sight, sound, touch, decreases need for food and sleep

Forms of Crack/Cocaine

TWO DREAMS

- Common street names:
  - Coke
  - Snow
  - Flake
  - Blow

Wafer or Paste form

Rock form (Crack)

Powder form

Cocaine: Routes of Administration

Form	Administration	Onset	Risk of Addiction
Cocoa leaf	Chewed	30 minutes	1+
Cocaine	Snorted	20 minutes	2+
Cocaine, dissolved	IV	10-15 seconds	3+
Cocoa paste, freebase	Inhalation	5-8 seconds	4+

Caffeine

- Behavioral Effects
  - t ½ 5 hours
  - Psychological & mild physiological dependence & withdrawal effects
  - Increased alertness, attentiveness, decrease fatigue

Caffeine

TWO DREAMS

- Mechanism of Action
  - Blocks adenosine receptors (chronic use causes up-regulation of receptors
  - Vasoconstrictor
  - Increases DA in nucleus accumbens-to some degree
- Average American 200-300mg p/day
- Negative effects/withdrawal at >500mg p/day
  - Too much-restlessness, jitters, anxiety
  - Increase gross motor functioning, decreases fine motor skills


Thank You!
Questions?