Psychophysiology of Addictions

RADACT
Spring Academy, Jan. 14-15, 2026
James M. Fitterling, Ph.D.

1

Acknowledgements

- The Neuroscience of Addiction and Recovery. Kevin McCauley, MD
- Pleasure Unwoven video series. Kevin McCauley, MD
- RADACT Trainees, Oct. 25, 2023

2

2

About This Course

- Not a graduate neuroscience course
- Some basics in neuroanatomy and neurophysiology
- Balance of range and depth of information
- Avoid
  - "*A little knowledge is a dangerous thing*"
  - Too many facts instead of understanding
- Focus on bottom line, big picture – not memorizing details

3

3

Aim

Learn

- How the brain works
- How drugs work in the brain
- Fundamentals of psychophysiology and psychopharmacology – with specific application in addictions

So we can

- Better understand why people use drugs
- Treat their addictions more effectively – and compassionately

4

4

Outline

1. Neuroanatomy
2. Neurons
3. Neurotransmitters
4. Fear, Reward, Action
5. Psychopharmacology
6. Addiction – and Drugs of Addiction
7. (Medication-Assisted Tx of SUDs in next session)

5

5

Part 1: Neuroanatomy

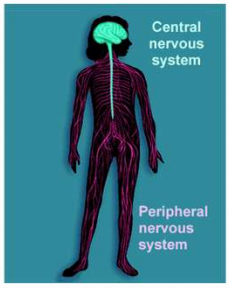
6

6

Central & Peripheral Nervous Systems

Central Nervous System (CNS)
- Brain and Spinal Cord

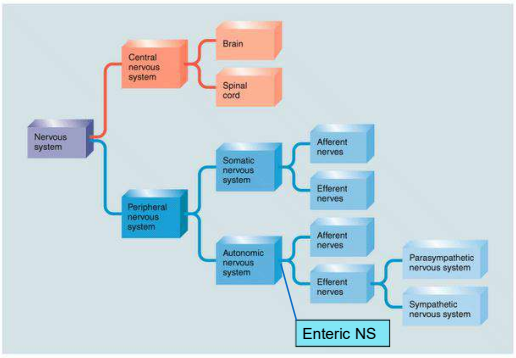
Peripheral Nervous System (PNS)
- Nerves
- Sensory Organs
- Autonomic Nervous System
  - Sympathetic
  - Parasympathetic



https://www.docsity.com/en/news/education-2/systems-human-body-interactive-gifs/

7

► Major Divisions of the Nervous System



8

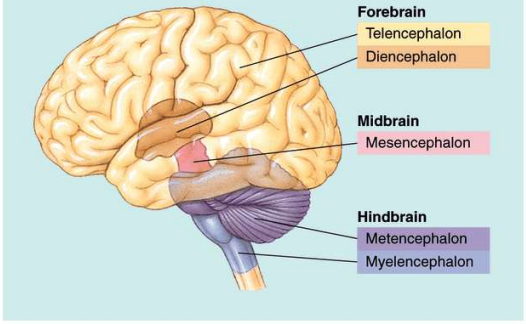
8

Enteric Nervous System

- More serotonin in gut than in brain
- Endogenous BZ receptors
- 100 Million neurons
- Located in sheaths of linings of gut
- Fear, arousal -> butterflies, shut down OR diarrhea, "choke with emotion", heartburn
- SSRIs – small doses can increase gut motility, large doses -> constipation
- Neurogastroenterology

9

Telencephalon



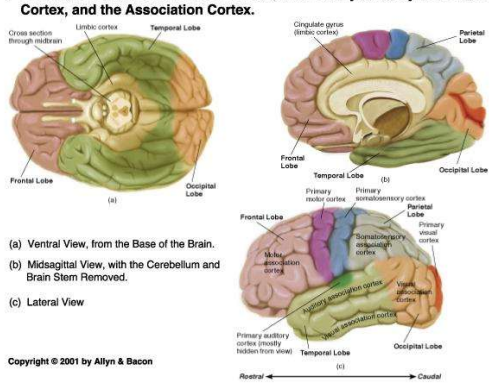
10

Telencephalon (Forebrain)

- Cerebral Cortex
  - 2-5 mm thick sheet of neural tissue (6 layers)
  - Function
    - Memory
    - Attention
    - Perceptual awareness
    - Thought
    - Language
    - Consciousness
- Basal Ganglia
- Limbic System

11

► The Four Lobes of the Cerebral Cortex, the Primary Sensory and Motor Cortex, and the Association Cortex.



(a) Ventral View, from the Base of the Brain.

(b) Midsagittal View, with the Cerebellum and Brain Stem Removed.

(c) Lateral View

12

Forebrain - Telencephalon

- Cerebral Cortex
- Basal Ganglia – ***Major Structures***
  - Striatum [Caudate (learning & memory), Putamen (movement & learning)]
  - Globus Pallidus (movement at subconscious level)
  - Substantia Nigra (movement)
  - "Limbic Sector" (Ventral Tegmental Area, Nucleus Accumbens, Ventral Pallidum)
- Limbic System

13

Forebrain - Telencephalon

- Cerebral Cortex
- Basal Ganglia - ***Functions***
  - Learning
  - Motor Control
  - Action Selection
    - Inhibitory influence on motor systems
    - Release of inhibition permits motor system activation
  - Motivation
- Limbic System

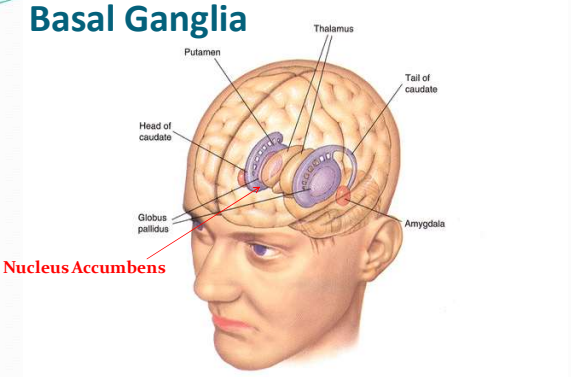
14

Forebrain - Telencephalon

- Cerebral Cortex
- Basal Ganglia - ***Pathologies***
  - Movement disorders
  - Addictions
- Limbic System

15

Basal Ganglia



16

Forebrain - Telencephalon

- Cerebral Cortex
- Basal Ganglia
- Limbic System – ***Main Structures***
  - Hypothalamus
  - Hippocampus
  - Amygdala
  - Fornix

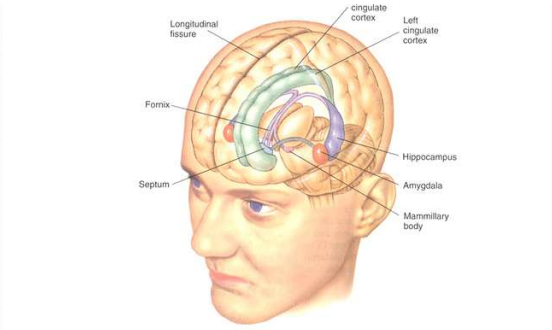
17

Forebrain - Telencephalon

- Cerebral Cortex
- Basal Ganglia
- Limbic System – ***Functions***
  - Hypothalamus – homeostasis, arousal, aggression
  - Hippocampus – memory consolidation from short-term memory
  - Amygdala – emotional response to stimuli
  - Fornix – Regulates hippocampus, transmits mnemonic information to brain for LT storage

18

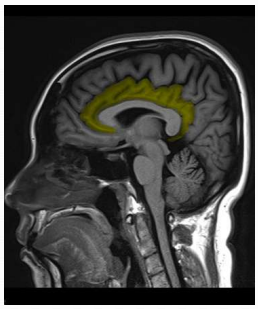
Limbic System – Major Structures



19

Cingulate Gyrus (Part of Limbic Cortex)

- Lies closest to Limbic System, just above Corpus Callosum
- Pathway from thalamus to hippocampus
- Focuses attention on emotionally significant events
- Emotional response to pain



https://radiopaedia.org/images/11881188

20

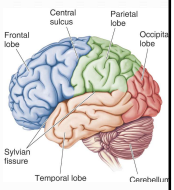
Part 2: Neurons

21

21

Neurons: Interesting Facts

- **Nervous System:**
  - **100 billion neurons**
- **Cerebral Cortex:**
  - **12-15 billion**
- **Cerebellum:**
  - **70 billion**
- **Spinal Cord:**
  - **1 billion**
- **Enteric Nervous System**
  - **500 million**



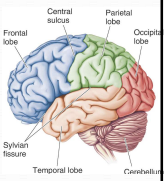
22

22

Neurons: Interesting Facts (Cont'd)

Brain

- **86 billion neurons** (~ number of stars in Milky Way)
- **Each neuron has average of 7,000 connections with other neurons**
- **100-500 <u>trillion</u> synapses**
- **Paradox:**
  - Try to understand brain with the very mental resources afforded by it
  - Hope brain simple enough to understand it; but complex enough to understand it

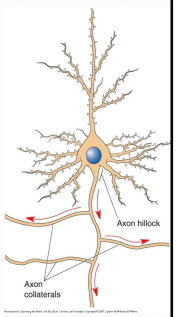


23

23

Neurons ("nerve cell")

- **Basic cell of nervous system**
- **Two Functions**
  - **Receive info**
  - **Transmit info**
- **Communicate *<u>within</u>* neuron**
- **Communication <u>between</u> neurons**
- **Information transmitted to other cells through electrochemical Impulses**
  - **"Soup vs. Spark"**



24

24

Classification by Function

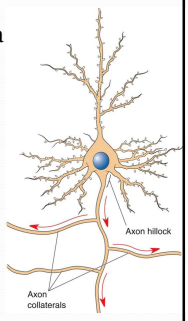
- **Sensory (Afferent) Neuron (afferent)** – detects changes in environment
  - External
  - Internal
- **Motor (Efferent) Neuron (efferent)** – controls muscles and glands
- **Interneuron: located entirely within CNS**

25

25

Neuron – Basic Structure

- **Dendrite** – "Tree" attached to soma
  - *Receives info from other neurons*
- **Soma** – Cell body
  - *"Action Potential" initiated*
- **Axon** – "Wire" leading from soma
  - *Transmits action potential (signal) from soma*
- **Terminal Button** – End of axon
  - *Releases neurotransmitter*

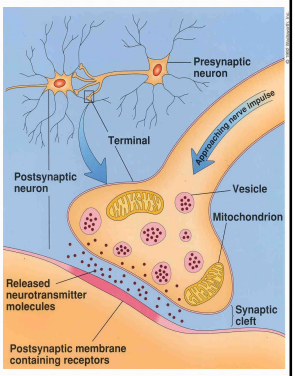


26

26

Synapse

- Presynaptic Neuron
  - Terminal button releases neurotransmitter
- Postsynaptic Neuron
  - Receptor "receives" neurotransmitter



http://www.unc.edu/~ejw/synapse.html

27

27

Membrane Potential

28

28

Diffusion

- A force
- Movement of substance from area of high concentration to area of lower concentration (concentration gradient)
- Molecules in constant motion, rate dependent on temperature

29

29

Electrostatic Pressure

- A Force
- Electrolytes – substances which, when dissolved, split into two parts (ions) with opposing electric charges
  - Cation – ion with positive charge
  - Anion – ion with negative charge
- Particles with same charge repel each other
- Particles with opposite charges attract each other
- Attraction and repulsion – electrostatic pressure

30

30

Diffusion vs. Electrostatic Pressure

- **Diffusion** moves molecules from high to low concentration
- **Electrostatic pressure** moves <u>similarly</u> charged ions from high to low concentrations

31

31

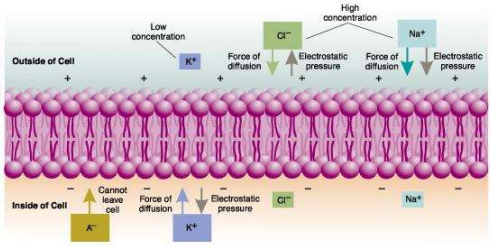
Membrane Potential

- Extracellular and intracellular fluids contain different ions
- Forces of diffusion and electrostatic pressure contributed by these ions → membrane potential
- Key ions
  - Organic ions (A^-)
  - Chloride ions (Cl^-)
  - Sodium ions (Na^+)
  - Potassium (K^+)

32

32

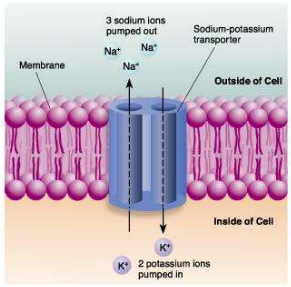
▸ **Relative Concentration of Some Important Ions Inside and Outside the Neuron and the Forces Acting on Them**



33

33

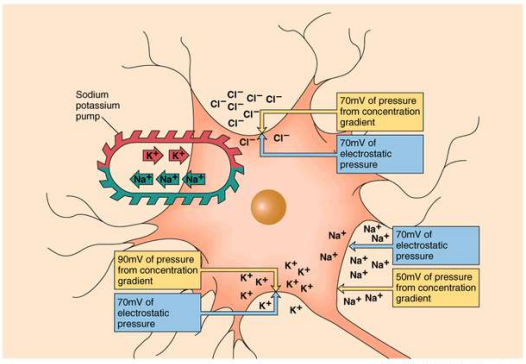
► A Sodium-Potassium Transporter, Situated in the Cell Membrane



34

34

► Ion Distribution Across the Neural Membrane



35

35

Action Potential

- Diffusion and electrostatic pressure push Na+ into cell
- But membrane not permeable to Na+, so intracellular Na+ is low
- **Q:** What would happen if membrane suddenly became permeable to Na+?
- **A:** Diffusion and electrostatic pressure would cause Na+ to rush in

36

36

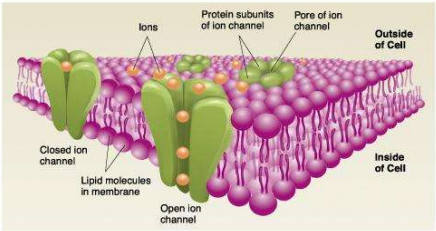
Action Potential – *Cont'd*

- **Q:** What happens when Na+ rushes into cell?
- **A:** Changes membrane potential
- Depolarization (from negative to positive)
- Brief increase in permeability to Na+ (allowing inrush) followed by transient increase in permeability to K+ (allowing K+ to rush out)
- What causes this?
  - **Ion Channel** – another protein molecule in membrane

37

37

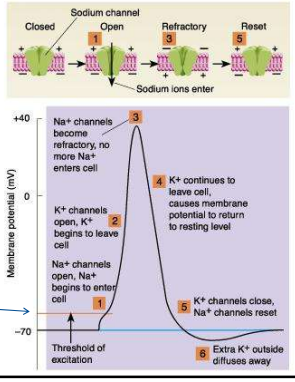
Ion Channels



38

38

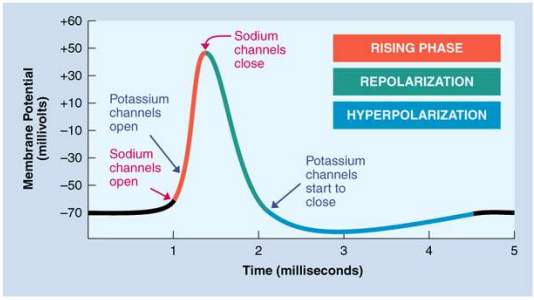
► The Movements of Ions During the Action Potential



39

39

► Opening and Closing of Voltage-Activated Sodium and Potassium Channels



 40

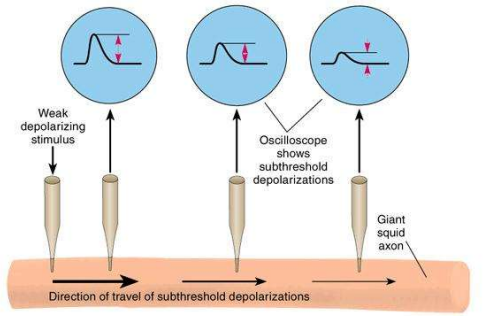
40

Conduction of Action Potential *Within* Neuron

41

41

Decremental Conduction

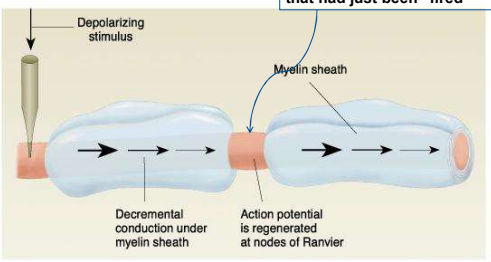


 42

42

Saltatory Conduction

Action potential directional because opened K+ channels allow repolarizing of the that area that had just been "fired"



43

43

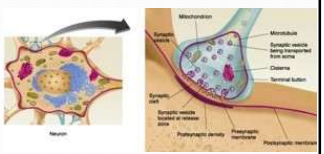
Communication *Between* Neurons

44

44

Anatomy of a Synapse

- **Presynaptic Membrane** membrane of terminal button
- **Postsynaptic Membrane** Cell that receives neurotransmitter
- **Synaptic Cleft** Space between the two membranes

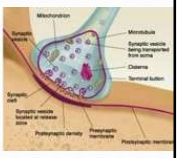


45

45

Steps in Neurotransmitter Release

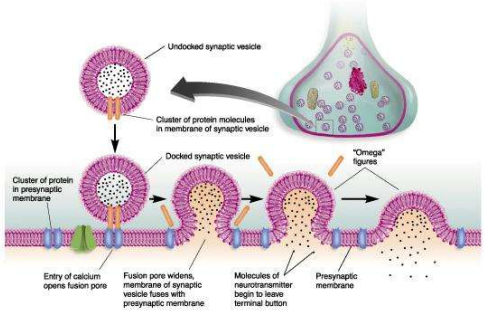
- Synaptic vesical "docked"
- Action potential reaches terminal button
- Ca^{2+} channels open
- Neurotransmitter released



46

46

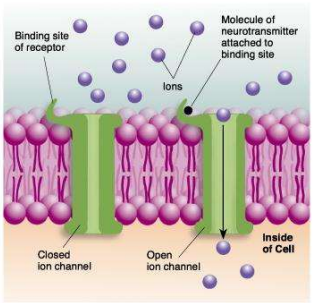
Release of Neurotransmitter



47

47

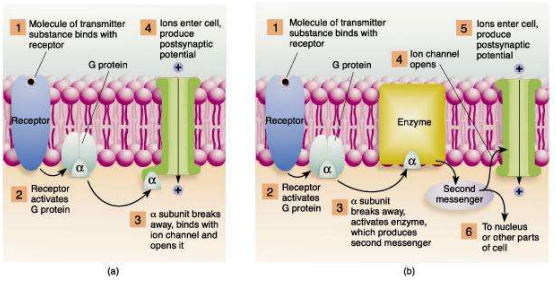
Ionotropic Receptors



48

48

Metabotropic Receptors



49

49

Activation of Receptors

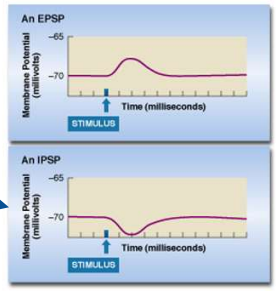
- **Postsynaptic Receptor**
  - *Binding site for neurotransmitter*
- **Neurotransmitter-Dependent Ion Channel**
  - *Channel that opens when neurotransmitter binds with and activates receptor ("key" and "lock")*
- **Excitatory Postsynaptic Potential**
  - *Depolarization of postsynaptic membrane*
- **Inhibitory Postsynaptic Potential**
  - *Hyperpolarization of postsynaptic membrane*

50

50

Excitatory and Inhibitory Postsynaptic Potential

GABA renders membrane selectively permeable to K+ and Cl- on inside but not to NA+ on outside



51

Termination of Postsynaptic Potential

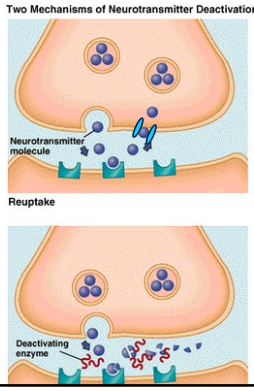
- **Reuptake**
  - *Re-entry of neurotransmitter back into presynaptic cell by transporter molecules*
- **Enzymatic Deactivation**
  - *Destruction of neurotransmitter by enzyme*

52

52

Reuptake and Enzymatic Degradation

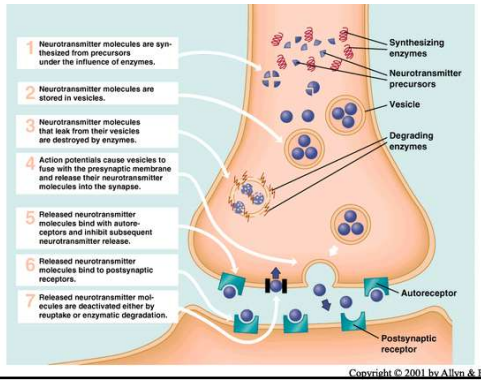
► Reuptake and Enzymatic Degradation



53

53

Seven Steps in Neurotransmitter Action



54

54

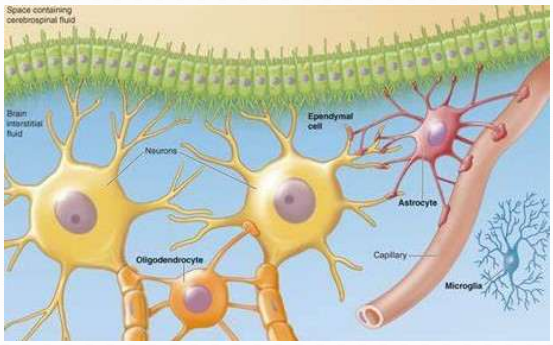
Glial Cells

- Glial – "Glue"
- More glial cells than neurons
- Three types
  - Astrocytes - "Helper" cells – Provide nutrition, maintenance, support, spatial distribution
  - Oligodendrocyte – myelination of axons, insulation, support
  - Migroglia – immune cells of CNS

55

55

Glial Cells



56

56

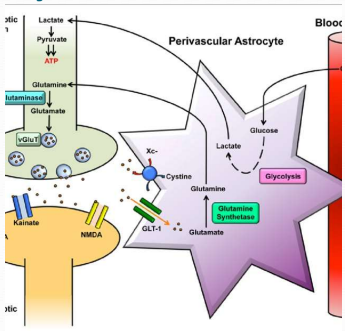
Glial Cells and Addiction

- Neuronal dysfunction in PFC, limbic structures, NA, and VTA underlie mechanisms for SUDs
- Glial cells, particularly astrocytes, regulate glutamate neurotransmission, NT metabolism, and energy supply for synaptic transmission
- Astrocytes markedly affected by alcohol and drugs
- Alterations of glial cells in reward circuits may contribute to drug addiction
- Regulation of glutamate transport and neurotrophins may become new avenues for drug abuse treatment

57

57

Glutamate-Glutamine Conversion by Astrocytes



58

58

Glucagon-Like-Peptide 1 (GLP1)

- Released in small intestine
- Promotes blood glucose homeostasis, slows gastric emptying, reduces appetite
- GLP1 agonists (e.g., Ozempic®) used to treat Type II Diabetes and Obesity
- GLP1 agonists – shown to decrease alcohol and drug intake

59

59

Part 3: Neurotransmitters

60

60

Ligand and Neurotransmitter

Ligand

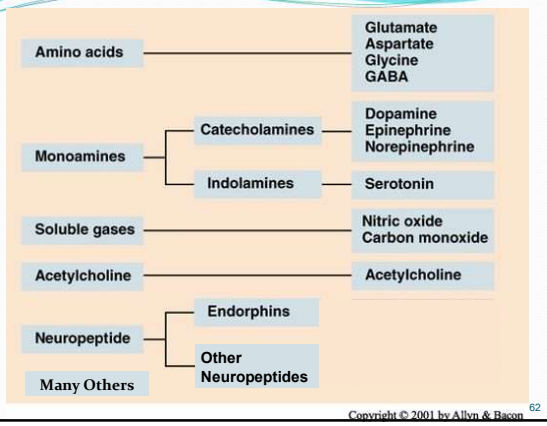
- Molecule that binds to another, forming a complex that serves a biological purpose

Neurotransmitter

- Endogenous chemical messenger involved in neural synaptic transmission
- Endogenous ligand

61

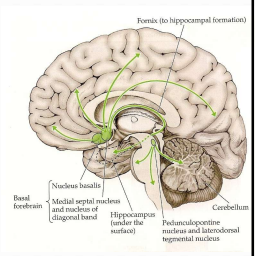
61



62

Acetylcholine

- Functions
  - *Muscle Contractions (PNS)*
  - *Learning & Memory* (CNS)
- Two Receptor Types
  - Nicotinic: excitatory, ionotropic
  - Muscarinic: slow or inhibit, metabotropic
- Regulated by acetylcholinesterase



63

63

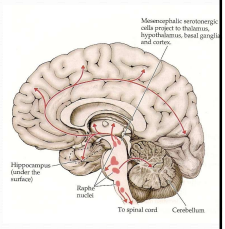
When Nicotinic Receptors are not Blocked Enough

64

64

Monoamines: Serotonin (5-HT)

- 200,000 neurons in CNS (More in enteric NS)
- Exert *wide-spread* influence in brain
- Functions:
  - Sleep, Mood, Anxiety, many others
  - "Implicated in everything, responsible for nothing"



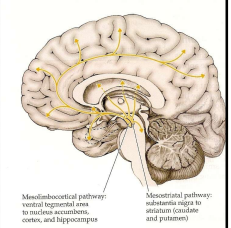
65

65

Monoamines: Dopamine

- **1 Million neurons**
- **Two Pathways**
  - Mesostriatal

    Mesencephalon -> striatum (caudate & putamen)
    - "Motor Pathway"
    - Parkinson's Disease
  - Mesolimbocortical mesencephalon → limbic → cortex
    - "Reward Pathway"
    - Pleasure
    - Addiction



66

66

Role of Dopamine in Reward

reward

67

67

The Few Rule the Many

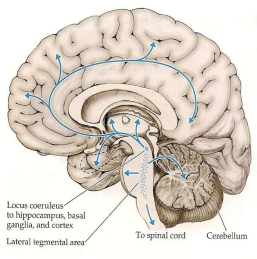
- Dopamine and serotonin released by small number of neurons in brain
- But each connects to thousands of other neurons
- For this reason, dopamine and serotonin have great influence over complex brain processes

68

68

Monoamines: Norepinephrine (NE)

- Regulates mood, arousal, and sex
- Both a neurotransmitter *AND* hormone
- Key role in "fight, flight, flee" response



69

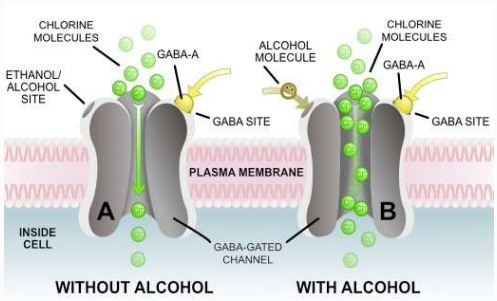
69

GABA (Gamma Amino Butyric Acid)

- Most common inhibitory neurotransmitter
- Induces inhibitory postsynaptic potentials
- Three types of receptors (a, b, & c)
  - Metabotropic (b) & Ionotropic (a & c)
- Opens Cl- channels
- Alcohol ➡ $GABA_a$ ➡ Inhibition
- Benzodiazepines ➡ $GABA_a$ ➡ Inhibition

70

GABA Receptor Sites (Neurotransmitter and Neuromodulator)



71

Amino Acids: Glutamate

- Most common excitatory neurotransmitter
- Functions
  - "Long-Term Potentiation": cellular basis for memory
  - Excitotoxicity: neural injury, such as a stroke or trauma, provokes excessive release of glutamate
    - Excessive glutamate → cell death
    - Causes secondary injury to brain

72

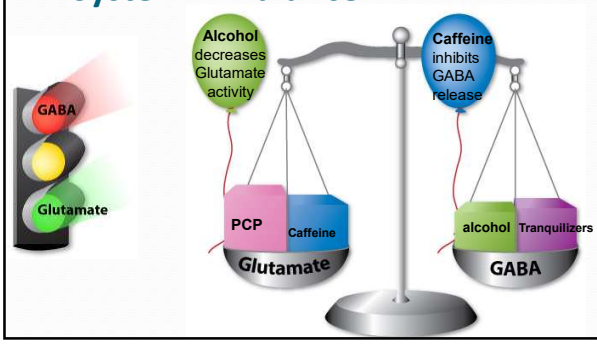
72

Role of Dopamine and Glutamate in Addiction

73

73

Glutamate and GABA: A System in Balance



74

74

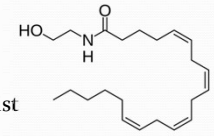
Peptides: Two Classes

- **Neuropeptides**
  - Opioid Peptides (mimic opiates and opioid drugs)
  - Three primary receptor subtypes (δ, κ, μ)
- **Peptide Hormones**
  - Substance P – mediates pain signaling
  - Cholecystokinin – released from duodenum
    - Initiates satiety
    - Major role in inducing tolerance to opioids, and partly implicated in pain *hypersensitivity* during opioid withdrawal
    - Neuropeptide Y – released in hypothalamus –> increases hunger

75

75

Anandamide



- A fatty acid NT
- Endocannabinoid – partial agonist
- CB1 Receptor
  - In CNS – eat, sleep, pain relief, mood, anxiety, motivation, pleasure
- CB2 Receptor
  - In PNS – primarily immune system
  - More recently discovered in CNS – mood, other functions
- THC structurally similar, but full agonist

76

76

Part 4: Fear, Reward, and Action

(Relationship between Emotion and Behavior)

77

77

Why Do We Behave

- **APPETITIVE BEHAVIOR:**
  - Procure/produce things we need (food, clothing, shelter, sex)
  - Procure/produce things we want (fill in blank _____)
- **AVOIDANT BEHAVIOR:**
  - Avoid danger - (real or perceived)
  - Avoid discomfort
- **Anything else?**

78

78

Biological Basis of *Avoidant* Behavior

Nervous systems designed to:

- Recognize danger
- Initiate and enact behavioral responses to it (flee, fight)
- Experience those responses and their consequences (relief, safety)

79

79

Biological Basis of *Appetitive* Behavior

Nervous systems designed to:

- Develop "drives" or "appetites"
  - Hunger, thirst, sex
  - Conditioned appetites
- Initiate, enact, (& refine) behavioral responses to stimuli
  - Eat, drink, copulate
  - Listen to Debussy's Claire de Lune; play Scrabble
- Experience those responses and their consequences
  - Satisfaction, pleasure, satiety

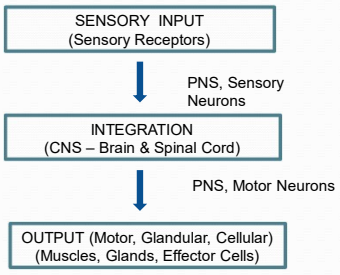
80

80

How Nervous Systems Serve Avoidant and Appetitive Behavior?

NOTE:

- Although appears unidirectional, continual afferent innervation (feedback on motor and other output)
- CNS continually reassesses, integrates, interprets/processes , and provides consequent output

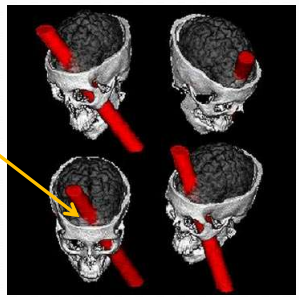


81

81

Biopsychological Investigations of Emotions – Phineas Gage

Medial Prefrontal Lobes



Complete loss of social inhibition, often leading to inappropriate behavior

82

82

Biopsychological Investigations of Emotions – Sham Rage

(No images of decorticated cats)

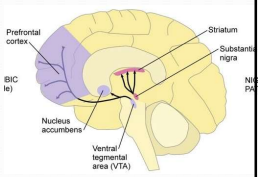
- Hypothalamus critical for expression of aggression
- Function of cortex is to inhibit and direct responses (similar to Phineas Gage)

83

83

Mesocortical Pathway

- Begins in VTA, connects to PFC
- Involved in cognitive control, motivation, emotion
- Pathology
  - Schizophrenia (Negative symptoms)
  - Hypofrontality – loss of executive decision-making

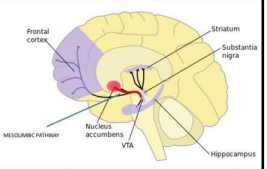


84

84

Mesolimbic Pathway

- Begins in VTA of midbrain
- Connects to Limbic System via
  - Nucleus Accumbens
  - Amygdala
  - Hippocampus
- Modulates behavioral responses to stimuli that activate feelings of reward through Dopamine
- "Reward Pathway"



85

85

Mesolimbocortical OR Mesocorticolimbic Pathway

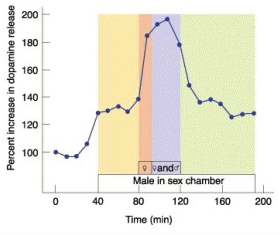
- **BOTH** mesocortical **AND** mesolimbic pathways
- Function together

86

86

Mesolimbic Pathway & Reinforcement

- Dopamine Release Correlated with Reinforcement
  - Sex
  - Food
  - Drugs
  - Pictures of attractive people (humans)



Pfaus et al. (1990)

87

87

Intracranial Electrical Self-Stimulation of the Brain

88

88

Part 5: Psychopharmacology

89

89

Psychopharmacology

- **Study of drug effects on nervous system and behavior**
- **Drug:**
  - Medication to treat disease
  - Chemical likely to be abused
  - "Exogenous" chemical that significantly alters function of certain bodily cells taken in relatively low doses (<u>not</u> required for normal cellular functioning)

90

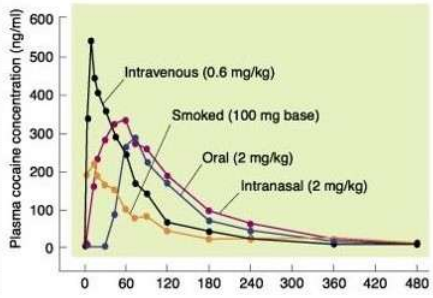
Pharmacokinetics – "ADME"

What the body does to the drug

- **Process by which drugs:**
  - **Absorbed**
    - Oral, Intravenous, Intraperitoneal, Subcutaneous, Sublingual, Intrarectal, Inhalation, Topical, Insufflation, Intracerebral, Intracerebroventricular
  - **Distributed**
  - **Metabolized**
  - **Excreted**

91

Cocaine Concentration in Blood Plasma



Source: Adapted from Feldman, Meyer, and Quenzer, 1997; after Jones, 1990.

92

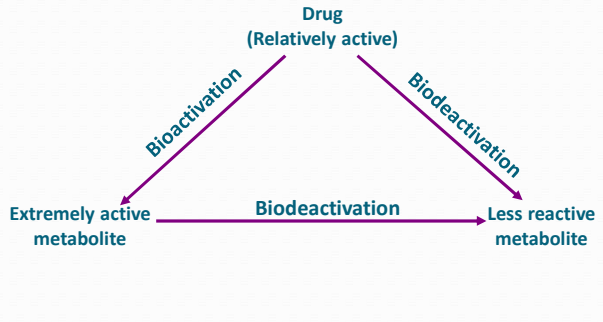
Distribution of Drugs in Body

- Lipid solubility
  - Heroin vs. Morphine
- Depot binding
  - Albumin
  - Fat tissue, bones, muscle, liver
- Inactivation and Excretion

93

93

Biotransformation



94

94

Pharmacodynamics

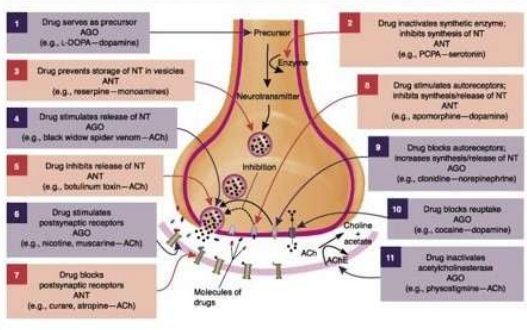
What the drug does to the body

- Process by which drugs affect synaptic transmission
- **Agonist (AGO)** – stimulates transmission
- **Antagonist (ANT)** – blocks or decreases transmission

95

95

Ways Drugs Affect Synaptic Transmission



96

96

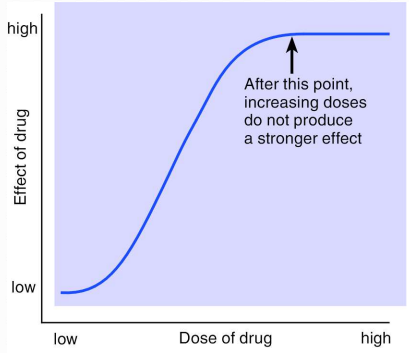
Pharmacokinetics and Pharmacodynamics

- Together, they explain the relationship between dose and response (effects)

97

97

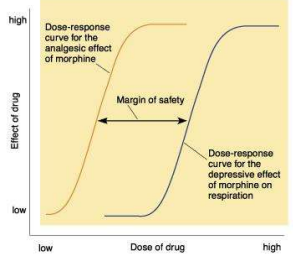
Drug Effectiveness: Dose-Response Curve



98

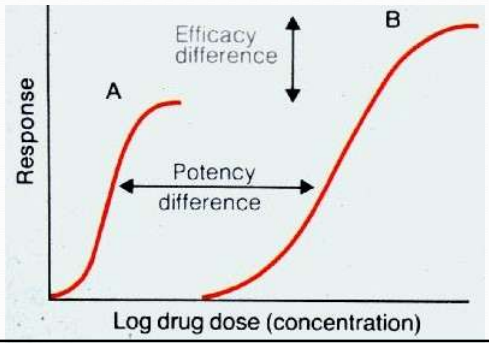
Dose-Response Curves for Analgesic and Depressant Effect on Morphine

TI = LD50/ED50



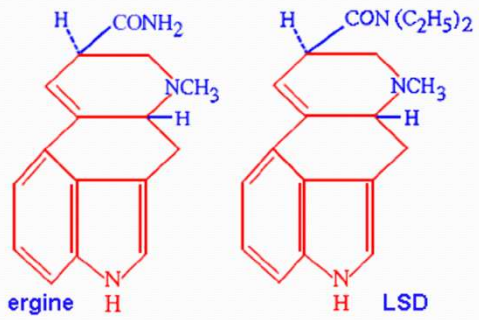
99

Potency (Affinity) vs. Efficacy



100

Drug Potency: Dose-Response



101

Drug variability and toxicity assessment

- **ED50:** Effective dose for 50% of subjects
  - (Ideal: LOW)
- **LD50:** Lethal dose for 50% of subjects
  - (Ideal: HIGH)
- **Therapeutic index:** LD50 / ED50
  - (Ideal: HIGH)
    - Barbiturates: 2.0 to 3.0
    - Valium: 100.0

102

Tolerance and Sensitization

- **Tolerance:** Diminished effect (or requires increased dosage to maintain effect)
  - Can reflect decreased drug-receptor binding or reduced postsynaptic action of drug
- **Withdrawal:** effects often opposite of drug effect; often accompany tolerance
- **Sensitization:** Heightened drug effectiveness

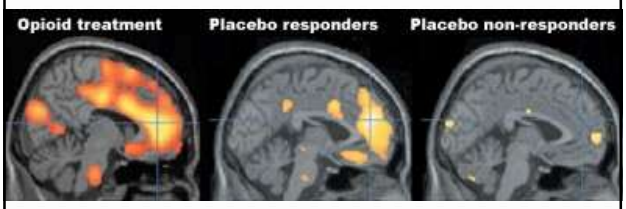
103

Reverse Tolerance

- Decrease in liver capacity to process alcohol as person ages
- As liver is taxed by excessive alcohol, its capacity is diminished
- Older person can become intoxicated with one or two drinks

104

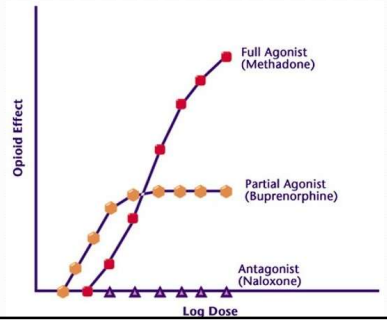
Placebo – Physiological Basis



Petrovic, Kalso, Petersson & Ingvar, 2002)

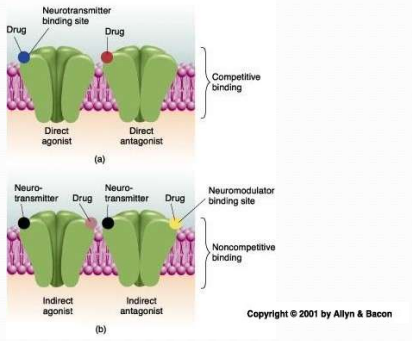
105

Dose Response Curves for Full Agonist, Partial Agonist, Antagonist



106

Actions of Drugs at Receptor Binding Sites



107

Part 6: Addiction and Drugs of Addiction

108

Drugs of Abuse

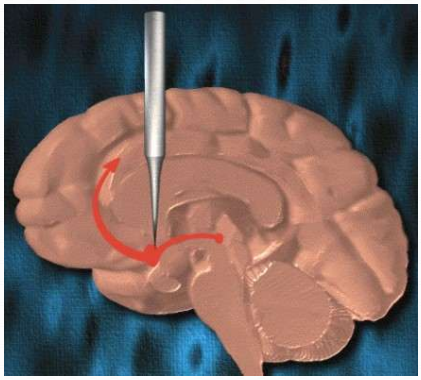
Drug	Site of Action
Cocaine and Amphetamine	Increases Dopamine in Nucleus Accumbens (by inhibiting Dopamine transporters); GABA in Amygdala
Nicotine	Dopamine in Nucleus Accumbens $GABA_A$ receptor (indirect agonist) in Ventral Tegmental Area Opioid peptides in Amygdala Nicotinic Acetylcholine receptor (agonist)
Benzodiazepine	$GABA_A$ receptor (indirect agonist); Dopamine
Cannabis (THC)	CB1 cannabinoid receptor in Ventral Tegmental Area Opioid peptides in VTA Dopamine in VTA
Ethyl Alcohol	Dopamine in Nucleus Accumbens; Opioid peptides in Ventral Tegmental Area; $GABA_A$ receptor (indirect agonist in Amygdala; Glutamate, Endocannabinoids
Opioids	μ and δ opiate receptor agonist (opioid peptides) in Nucleus Accumbens; Dopamine in Ventral Tegmental Area; endocannabinoids

109

Pleasure Unwoven – Periodic Table of Intoxicants

110

110

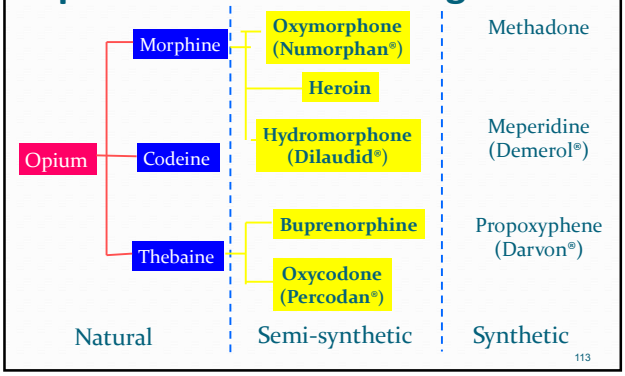


111

111

112

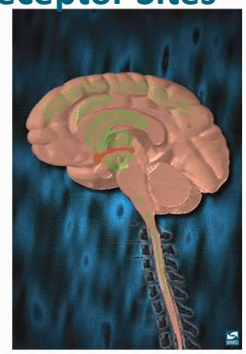
Opium and Related Drugs



113

113

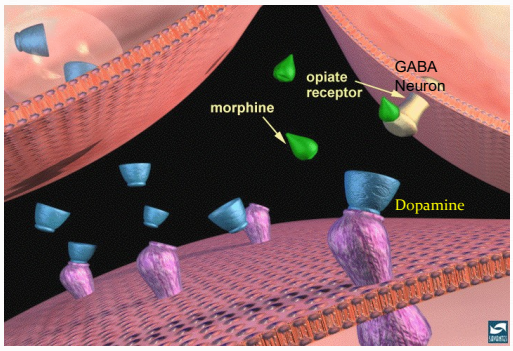
Opioid Receptor Sites



http://archives.drugabuse.gov/NIDA

114

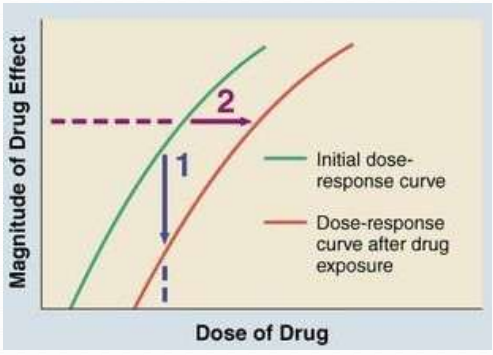
How Morphine Indirectly Agonizes Dopamine



115

115

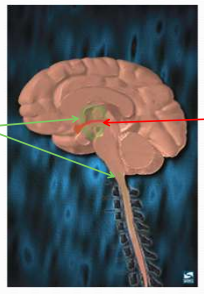
Drug Tolerance



116

Brain Regions Mediating Development of Morphine Tolerance

Thalamus and spinal cord – important in mediating nociception and analgesic effects of morphine



Reward pathway – shown for comparison

http://archives.drugabuse.gov/NIDA

117

Dependence

A state in which an organism functions normally only in the presence of a drug

- manifested as a physical disturbance when the drug is removed (withdrawal)

http://archives.drugabuse.gov/NIDA

118

Opioid Effects vs. Withdrawal Symptoms

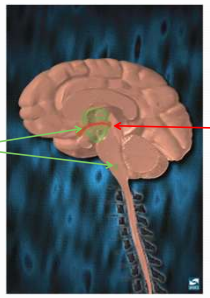
Effects	Withdrawal Symptoms
Numbness	Pain
Euphoria	Anxiety
Dryness	Sweating, runny nose
Constipation	Diarrhea
Slow pulse	Rapid pulse
Warm feelings	Chills (goose flesh)
Shallow breathing	Coughing
Restricted pupils	Dilated pupils
Sluggishness	Hyper-reflexes , muscle cramps

119

119

Brain regions mediating development of morphine dependence

Thalamus and brainstem – important in mediating nociception and analgesic effects of morphine

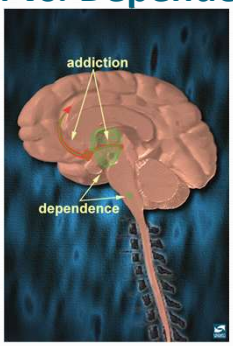


Reward pathway – shown for comparison

http://archives.drugabuse.gov/NIDA

120

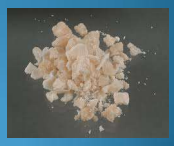
Addiction vs. Dependence



http://archives.drugabuse.gov/NIDA

121

Cocaine



122

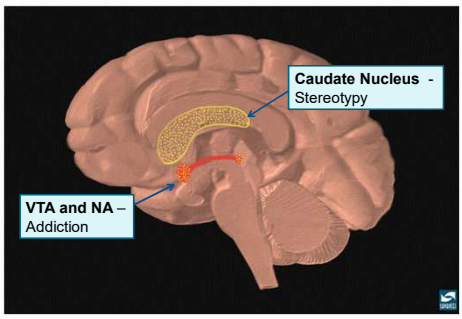
Pharmacokinetics of Insufflated Cocaine

- Self-limiting
- Vasoconstriction of nasal capillaries
- Dose-dependent: Higher dose, slower absorption
- Withdrawal/rebound: Nasal tissues swell causing runny sniffling nose, characteristic of cocaine snorters

123

123

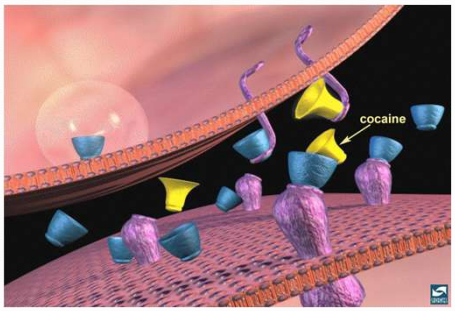
Localization of Cocaine "Binding Sites"



http://archives.drugabuse.gov/NIDA

124

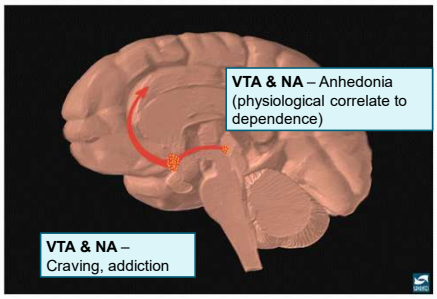
Dopamine Binding to Receptors and Uptake Pumps in Nucleus Accumbens: Action of Cocaine



http://archives.drugabuse.gov/NIDA

125

Cocaine dependence and activation of reward pathway

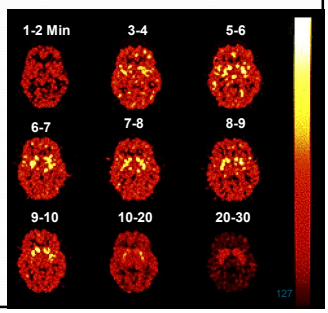


http://archives.drugabuse.gov/NIDA

126

SPECT Scan of Brain *on* Cocaine

Single-photon emission computed tomography of cocaine binding site



127

Crack Cocaine

- Freebase form processed from powdered cocaine HCl to smokable form
- Processed with ammonia or sodium bicarbonate (baking soda) and water, and heated to remove HCl
- Brief (5-10 min), but rapid pharmacokinetics
  - More readily absorbed since more fat-soluble than cocaine HCl
  - Larger surface area of lungs than nasal passages

128

128

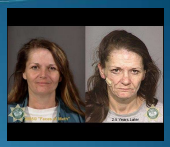
Cocaine and Alcohol - Cocaethylene

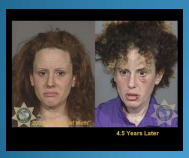
- When combined, they produce cocaethylene
- Cocaethylene is longer acting – and more toxic than either drug alone
- Intensifies cocaine's euphoric effects and increases risk of sudden death
- Since half-life of cocaethylene is 3 Xs more than cocaine alone (2 hr vs. 38 min), its effects, including increased blood pressure last longer
- Many cocaine abusers "front load" with alcohol to prolong effects of more expensive cocaine

129

129

Methamphetamine





130

Amphetamine

- Synthetic (also semi-synthesized from ephedra), quite lipid soluble drugs
- CNS effects within 30 min of oral dose
- Ingested, injected, snorted, inhaled
- Amphetamines last 4-6 hr
- Cocaine lasts 40 min to 1.5 hr
- Medical uses: obesity, narcolepsy, ADHD

131

131

Amphetamine Pharmacodynamics

- Blocks reuptake of DA (like cocaine)
- ALSO, *reverses* DA reuptake transporter
  - (Even MORE dopamine in synaptic cleft)
- Blocks VMAT-2 (vesicular monoamine transporter 2)
  - Prevents intracellular storage of DA into vesicles, leading to cell damage

132

132

Tweaking

- Most dangerous stage when abuser has not slept in 3 or more days
- Major symptoms
  - Teeth grinding
  - Dilated pupils and staring/trance state
  - Severe paranoia and hallucinations
  - Formication – picking at 'Meth bugs'
  - Stereotypy – performing repetitive acts

133

133

Formication

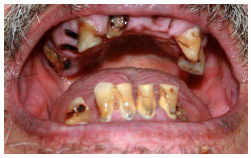
- Side effect of long term or high dose of meth (or cocaine)
- Imbalance of sensory neurons causes tactile sensations that feel like hundreds of tiny bugs ("meth bugs") crawling under skin
- Scratch self bloody to get at imaginary bugs

134

134

Meth Mouth

- Bruxism -> wear and cracks of tooth enamel
- Oral hygiene neglect
- Hyposalivation -> loss of saliva's natural protective effects directly -> increased tooth decay, particularly at gum line



135

135

Alcohol

136

Alcohol's Effect on Brain

- **Glutamate - Antagonist**
  - Relaxation, discoordination, slurred speech, blackouts
  - (Ether and chloroform)
- **GABA – Agonist at GABAa Receptor)**
  - Anxiolytic, soporific
  - (Benzodiazepines)
- **Dopamine - Agonist**
  - Excitement, stimulation
  - (Cocaine and amphetamine)
- **Endorphins – mu opioid receptor agonist**
  - Analgesia, pleasant feeling
  - (Heroin, oxycodone)

137

137

Alcohol Metabolism

(1) Alcohol → (Alcohol dehydrogenase) → Acetaldehyde

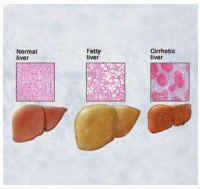
(2) Acetaldehyde → (Acetaldehyde dehydrogenase) → Acetic Acid

(3) Acetic Acid → (O_2) → $Co_2 + H_2o$ + Energy

About one ounce of alcohol eliminated every 3 hours

138

138



- Accumulation of fatty acids. When drinking stops, fat deposits usually disappear
- Cirrhosis – toxic effects of alcohol cause scar tissue to replace healthy tissue – permanent, even when drinking stops

139

139

Biological Measures of Alcohol Misuse

- Carbohydrate-Deficient Transferrin - 2-4 weeks of abstinence to return to normal limits
- Ethylglucuronide – sensitive but not specific; up to 96 hrs
- GGT (Gamma-Glutamyl Transferase) - 2-6 weeks of abstinence to return to normal limits
- Macrocytic volume – slow return to NL, even with abstinence
- AST/ALT Ratio - > 2.0 alcoholic-related, especially with elevated GGT

140

140

Cannabis

141

141

Cannabis Pharmacokinetics

- Smoking approx. 3 times as effective in delivering THC to bloodstream as ingestion
- Peak blood concentrations of THC 1-30 min
- THC highly fat soluble; remains in brain and fat tissue long time because of slow metabolism
- Must pass back through liver to be metabolized
- Clinical Implication?

142

142

Cannabis and Schizophrenia/Psychosis – Association

- Cannabis associated with increased risks of psychosis or psychotic symptoms
- Longitudinal studies showed odds ratios range from 1.77 to 10.9, with median of 2.3

143

143

Cannabis and Schizophrenia/Psychosis – Dose Response

- Odds ratios or relative risk for groups with highest use groups increasing to 6.0 - 6.81

144

144

Cannabis and Schizophrenia/Psychosis – Reverse Causality

- Possible development of psychotic symptoms encourages cannabis use (e.g., self treatment)

145

145

Cannabis and Schizophrenia/Psychosis – Effect Modification

- Cannabis use linked with development of psychotic Sxs in *susceptible* subjects (past dx of psychotic d/o, BL report of psychotic symptom, family Hx of psychotic disorder)
- Link stronger in those with gene variant that has role in regulating dopamine implicated in development of schizophrenia

146

146

Cannabis and Schizophrenia/Psychosis – Bottom Line / Current State of Research

- Longitudinal research suggests robust causal link between cannabis use and development of psychotic symptoms – especially in adolescents, young adults; less so after adulthood
- However, questions remain regarding measurement of psychotic sxs, control for confounding factors, and possibility of reverse causality

147

147

"Spice" – Synthetic "Marijuana"

- Synthetic cannabinoids (5 of which DEA classified as Schedule I controlled substances)
  - Primarily Cannabicyclohexanol (synthetic cannabinoid receptor agonist – Pfizer 1978)
- Experiences similar to marijuana but
  - More Potent – higher binding affinity to CB receptors)
  - Psychotic effects (extreme anxiety , paranoia, hallucinations)
    - Missing many psychoactive compounds found in marijuana, especially cannabidiol, which has antipsychotic properties

148

148

Tetrahydrocannabinol (THC) with and without Cannabidiol (CBD)

149

Tobacco

150

Nicotine Pharmacokinetics

- ~ 90% nicotine in smoke that reaches alveoli in each breath is absorbed
- ~ 25% immediately carried to brain
- Excretion is immediate, small amounts nicotine exhaled. Small portion excretion unchanged by kidneys
- Approximately 50% nicotine leaves body in <30 min

151

151

Nicotine Pharmacodynamics

- **CNS:** Binds to nicotinic acetylcholine receptors, and subsequently increases levels of other NTs ("volume control") such as DA in mesolimbic reward pathway
- **SNS:** Stimulates release of epinephrine and norepinephrine
- Other compounds in tobacco – beta-carboline alkaloids (harman & norhaman) – serve as MAO inhibitors, potentiating DA'ic neural transmission)
- Ammonia added

152

152

Iqmik

- Mixture of smokeless tobacco, ash made from burning punk fungus, and saliva
- Greatly increases pH content (less acidic and more alkaline)
- Greatly enhances absorption of nicotine
- Greater nicotine rush

153

153

Tobacco and Alcohol

- > 85% of adults with hx of alcohol abuse smoke
- May be more addicted to nicotine than smokers without a drinking hx [1]
- More alcoholics die from tobacco-related diseases than from alcoholism [2]

1 Monti et al., 1995

2 Hurt et al., 1996

154

154

Health Risk of Smokeless Tobacco

- Vasoconstriction
- Slow-healing mechanisms
- Coronary Heart Disease
- Stroke
- Oral cancer

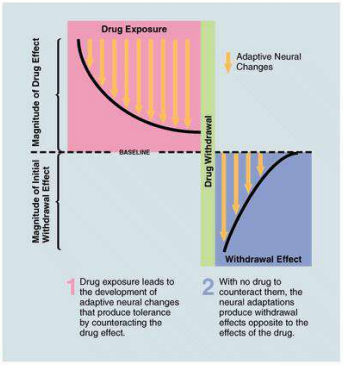
155

155

But Aren't Drugs Supposed to Be Fun?

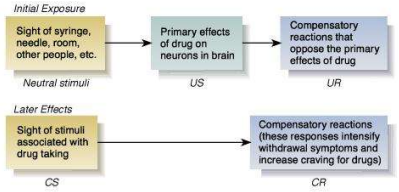
156

Relation Between Drug Tolerance and Withdrawal Effects



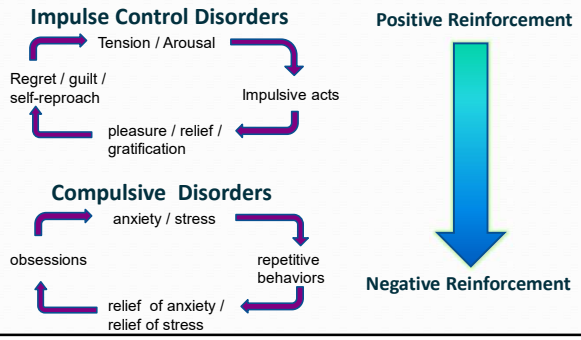
157

Classical Conditioning Model of Drug Tolerance (Siegel, 1978)



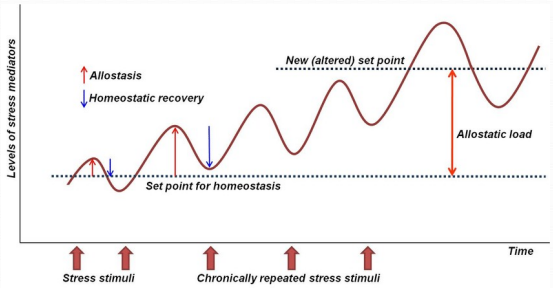
158

Stages of Impulse Control Disorder and Compulsive Disorder Cycles Related to Sources of Reinforcement



159

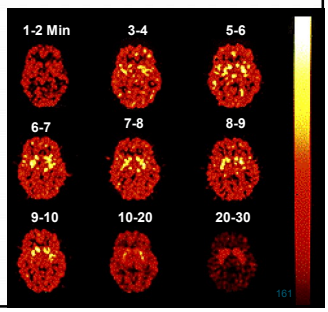
Stress, Homeostasis, Allostasis, Allostatic Load



160

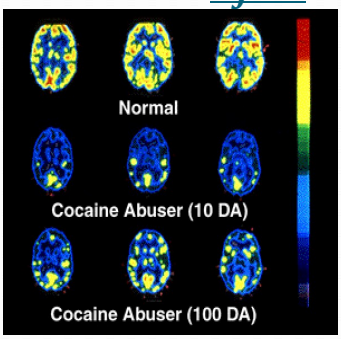
SPECT Scan of Brain *on* Cocaine

Single-photon emission computed tomography of cocaine binding site



161

PET Scan of Brain *After* Cocaine

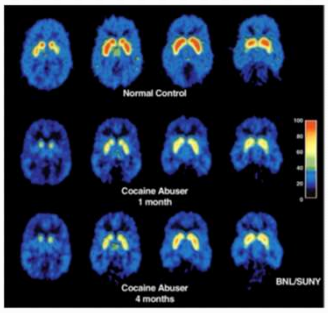


Volkow et al., (1993)

162

162

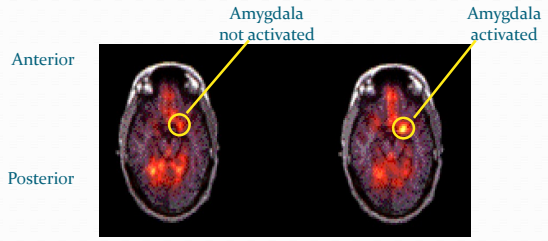
Decreased Dopamine D_2 Receptor Activity in Cocaine Abuser



Volkow ND, Fowler JS, Wang GJ, Hitzemann R, Logan J, Schlyer DJ, Dewey S and Wolf AP, Synapse, 1993, 14:169-177.

163

The Memory of Cocaine



Nature Video Cocaine Video

164

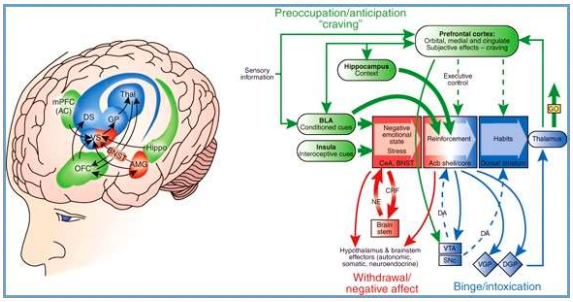
164

Hypofrontality in Addiction

165

165

Molecular and Cellular Targets within Brain Circuits Associated with Addiction



166

166

SUMMARY

- Our brains are very complex, designed to help us avoid pain and seek pleasure
  - both good and natural
- Mesolimbocortical pathway (reward pathway) plays central role in goal-directed behavior (desire)

167

SUMMARY

- Same pathway can be a neurological foundation for basic survival as well as our most noble aspirations
- OR for addiction and human suffering for the addict, his/her family, and society

168

SUMMARY

- At cellular level, synapse is where it all happens
  - Drugs of Abuse
  - Pharmacotherapy for Drug Addiction

169

SUMMARY

- Understanding the dopaminergic mesolimbocortical pathway helps us better understand:
  - What is different about an addict
  - AND YET
  - How the addict is no different than those of us who are not thus afflicted

170

Medication-Assisted Treatment – Pharmacotherapy for Addictions

(Covered in Next Session)

171