The Neuroscience of Addiction: Implications for Health Professionals

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Definitions

- Addiction
- Craving
- Dysphoria
- Drug-induced neuroplasticity
- Euphoria
- Negative reinforcement
- Positive reinforcement
- Substance-use disorder

DSM-5 Criteria

- Hazardous use
- Social/interpersonal problems related to use
- Neglected major roles to use
- Withdrawal
- Tolerance
- Used larger amounts/longer
- Repeated attempts to quit/control use
- Much time spent using
- Physical/psychological problems related to use
- Activities given up to use
- Craving

Substance-use disorder

1. Mild (2-3)
2. Moderate (4 to 6)
3. Severe (>6)

HEALTH | BURNING QUESTION

Are You Addicted to Coffee?

A psychologist reveals how to tell if you're hooked on caffeine and ways to kick the habit

Hot coffee being poured into a cup from a stainless steel French press

By Heidi Mitchell

Oct. 30, 2017 12:01 a.m. ET

10 COMMENTS

With pumpkin spice latte season in full swing, many Americans may be finding themselves waiting in line for coffee more than usual. While a cup of joe undoubtedly can give a jolt of focus to a fuzzy morning, it also has real side effects. Caffeine use disorder was added to the most recent edition of "The Diagnostic and Statistical Manual of Mental Disorders" as a condition for further study, and caffeine is the most-used drug in the world.

What are the signs that you've addicted, and how can you kick the habit? One expert, Laura Juliano, a psychology professor at American University who specializes in addiction, spills the beans.

This Is Your Brain on Caffeine

When you ingest caffeine, it occupies the brain's adenosine receptors, whose job is to tell the body it's sleepy. By blocking that neuromodulator, the caffeine makes you feel alert. There is also evidence that caffeine stimulates the reward center of the brain.

"So the brain says, 'This feels good. How can I do this again?'" Dr. Juliano says. Because

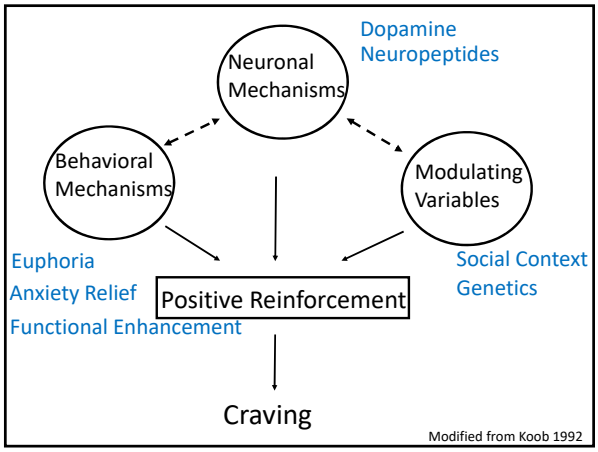
Major Characteristics

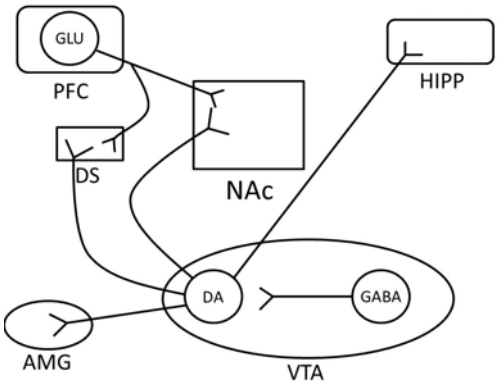
- Compulsivity
- Impulsivity
- Impairment in health
- Impairment in social function

Difficulty arises when attempting to draw the lines between legitimate drug use and loss of control, and by extension, the molecular and cellular mechanisms that lead to addiction.

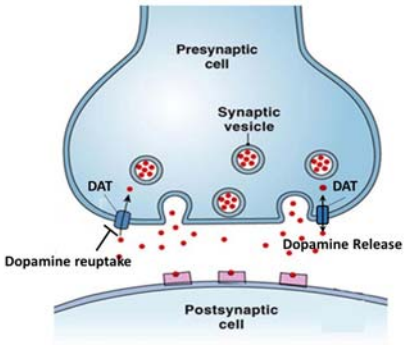
The Balance Between Happy Chemicals & Stress Hormone

- Dopamine: seek reward and joy of finding reward
- Endorphin: mask pain
- Oxytocin: safety and social bonds
- Serotonin: get respect from others
- Cortisol: stress





Dopamine

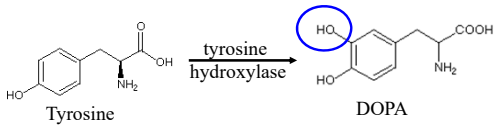


Dopamine Receptors

Subtype	Signal Transduction	Function
D1 and D5	Gs	Stimulation
D2, D3, D4	Gi	Inhibition

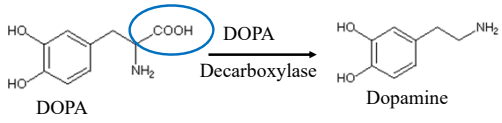
D. Biosynthesis of Dopamine

Step 1

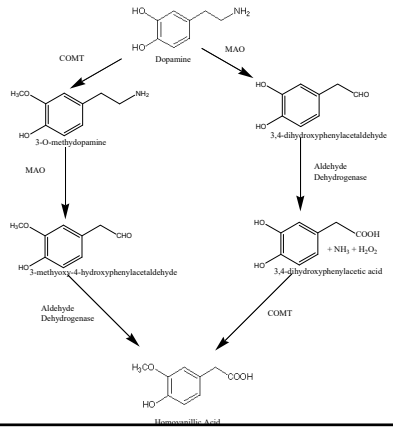


Tyrosine DOPA

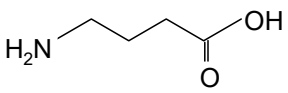
Step 2



DOPA Dopamine



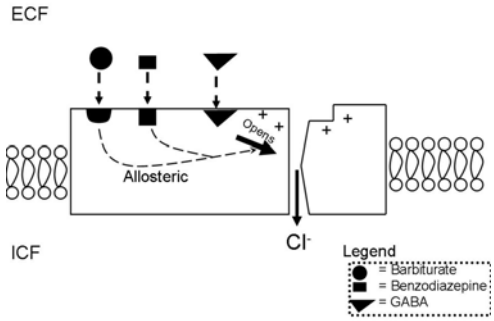
γ-aminobutryic acid (GABA)



Comments on GABA:

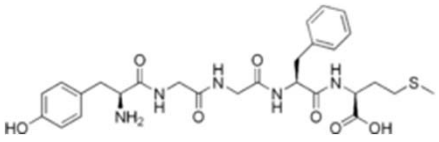
- Most abundant inhibitory amino acid
- Monocarboxylic acids are inhibitory
- regulate Cl- influx resulting in cell hyperpolarization

GABA



Endogenous Opioids

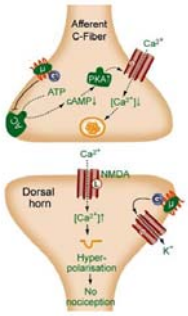
- Enkephalins
- Dynorpins
- β-endorphins



Opioid: Pharmacological Targets

- Pharmacological targets
  - Opioid receptors
    - Members of the GPCR family
      - Mu, delta, and kappa
        - $G\alpha_i$ and $G\alpha_o$
        - Inhibition AC, voltage-gated Ca^{2+} channels
        - Activation of MAPK, inwardly rectifying K^+ (GIRK) channels
    - Results in decreased neurotransmitter release and inhibition of neuronal firing

Opioids:

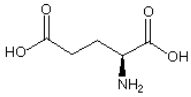


μ-receptors:

- Gi coupled

-decrease release
glutamate
substance P

Glutamate



Glutamate

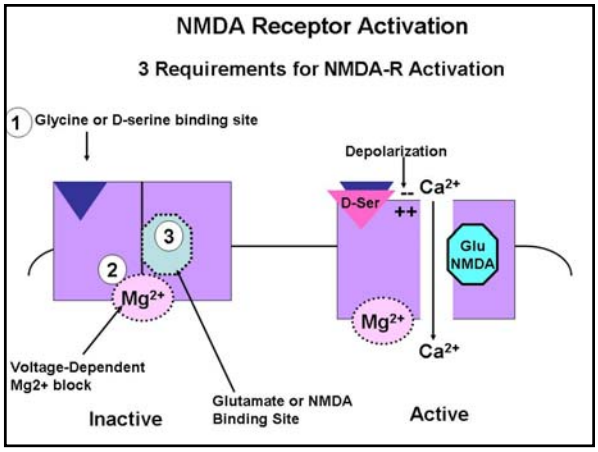
Comments on Glutamate:
-Most abundant excitatory amino acid
-dicarboxylic acids are excitatory
-Glutamate Excitotoxicity

Long-Term Potentiation (LTP)

- Prolonged increase in the size of a post synaptic response to a pre-synaptic stimulus.
- NMDA receptors
- Major role in memory acquisition

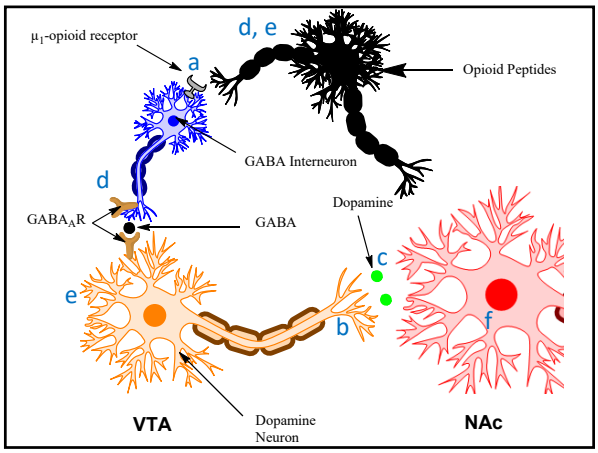
Ionotropic Glutamate Receptors

Subtype	Signal Transduction	Function
NMDA (N-methyl-D-aspartate)	Na+/K+/Ca++ influx	Excitation
AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole proprionic acid)	Na+/K+/Ca++ influx	Excitation
Kainate	Na+/K+/Ca++ influx	Excitation



Metabotropic Glutamate Receptors

Subtype	Signal Transduction	Function
mGluR1 & mGluR5	Gs and Gq	Stimulation
mGluR2-4 & mGluR6-8	Gi	Inhibition

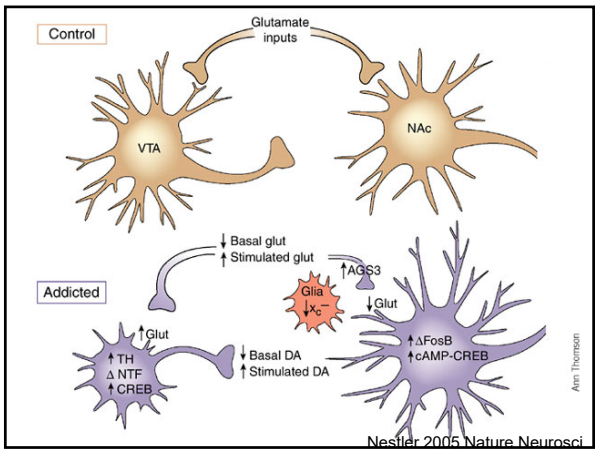


Pharmacological Targets of Drugs of Abuse

Drugs	Target
a. Opiates	Agonists at mainly the μ_1 receptor
b. Cocaine	Increase DA levels by blocking DAT
c. Amphetamine	Stimulate DA release
d. Ethanol	Facilitates $GABA_A$ receptor function
e. Nicotine	Agonist at NAChR
f. Cannabinoids	Agonists at CB_1 receptors
g. Hallucinogens	Agonists at 5-HT_{2A} receptors

Common Cellular & Molecular Adaptation

Translational Changes



Nestler 2005 Nature Neurosci

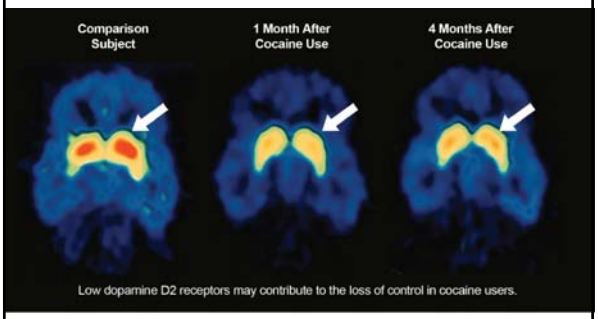
Epigenetic Changes

1. Increases in histone deactylase in the NAc & VTA

2. Decreases in histone methyltransferase in the NAc

Genetic Changes

1. D2 receptors (D2R)
2. D4 receptors (D4R)
3. Catechol-O-methyltransferase (COMT)



U.S. Department of Health & Human Services Report, 2016

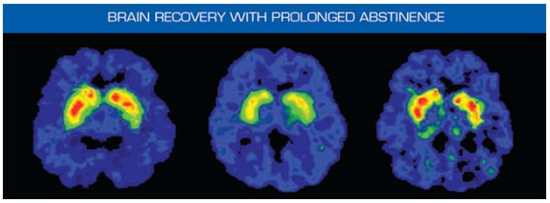
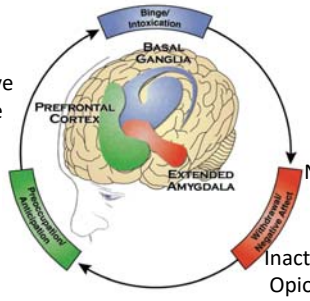


Photo courtesy of NIDA Drugs, Brain, and Behavior: The Science of Addiction

Positive Reinforcement
Activation of DA and Opioid Systems



Incentive salience

Memory

Negative Reinforcement

Inactivation of DA & Opioid Systems & Increase CRF

Binge Intoxication

	Response
• Dopamine	increase
• Opioid peptides	increase
• Serotonin	increase
• GABA	increase
• Acetylcholine	increase

Koob & Volkow Lancet Psychiatry 2016

Withdrawal/negative effects

	Response
• Dopamine	decrease
• Opioid peptides	decrease
• Serotonin	decrease
• Corticotropin-release factor	increase
• Dynorphin	increase
• Norepinephrine	increase

Koob & Volkow Lancet Psychiatry 2016

Preoccupation/anticipation

	Response
• Dopamine	increase
• Opioid peptides	increase
• Serotonin	increase
• Glutamate	increase
• CRF	increase

Koob & Volkow Lancet Psychiatry 2016

Pharmacogenomic Application of the Neurobiology to the Opioid Crisis

Definitions

Molecular Level

- Pharmacogenomics: The study of variations of DNA and RNA characteristics as related to drug response.[1]
- Pharmacogenetics: The study of variations in DNA sequence as related to drug respose.[1]

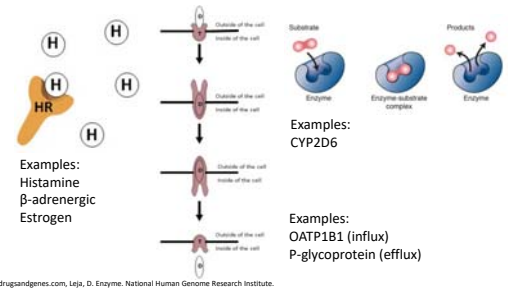
Clinical Level

- Pharmacogenomics: The study of many genes, in some cases the entire genome, involved in response to a drug.[2]
- Pharmacogenetics: The study of a gene involved in response to a drug.[2]

[1]E15 Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. Available at www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073162.pdf. Accessed November 4, 2016.
[2] Kisor DF, Kane MD, Talbot JN, Bright DR, Sprague JE. Pharmacogenes: Scientific Background and Clinical Applications. 2017. Reproduced with permission.

DNA to Protein Drug Targets: Pharmacogenes

Receptors or Transporters or Enzymes



Examples:
Histamine
β-adrenergic
Estrogen

Examples:
CYP2D6

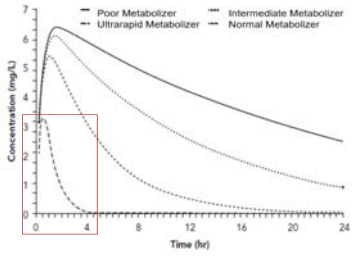
Examples:
OATP1B1 (influx)
P-glycoprotein (efflux)

Sources: drugsandgenes.com, Leja, D. Enzyme. National Human Genome Research Institute.

PGx: Drug Efficacy • Adverse Drug Events

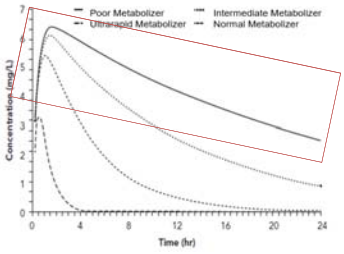
NIH, National Human Genome Research Institute. Available at www.genome.gov/27530645/faq-about-pharmacogenomics/. Accessed November 4, 2016.

Ineffective Medication



Kisor DF, Kane MD, Talbot JN, Bright DR, Sprague JE. Pharmacogenes: Scientific Background and Clinical Applications. 2017. Reproduced with permission.

Adverse Drug Events



Kisor DF, Kane MD, Talbot JN, Bright DR, Sprague JE. Pharmacogenes: Scientific Background and Clinical Applications. 2017. Reproduced with permission.

Adverse Drug Events: Example

Rani Jamieson
- Son Tariq was born April 18, 2005;
  - Episiotomy:
    - Received acetaminophen with codeine;
- 12 days later Tariq died.

Owen Dyer. National Review of Medicine June 15, 2007.

Adverse Drug Events: Example

– Cause: morphine overdose
– Tariq not receiving morphine
  – Brain/nervous system depression
  – Slow breathing
  – Inactivity/inaction
  – Skin color
  – Poor feeding/failure to thrive

Gene Form	Drug (Std. Dose)	Response	Outcome
*CYP2D6**1/*2xN	Codeine	Morphine overdose	Adverse Drug Reaction - Death

http://babygooroo.com/2007/06/is-codeine-safe-for-breastfeeding-mothers-and-infants/

CPIC: *CYP2D6*-Codeine

Table 1 Assignment of likely codeine metabolism phenotypes based on cytochrome P450 2D6 (*CYP2D6*) diplotypes

Likely phenotype[a]	Activity score	Genotypes	Examples of diplotypes
Ultrarapid metabolizer (~1–2% of patients)	>2.0	An individual carrying more than two copies of functional alleles	*1/*1xN, *1/*2xN
Extensive metabolizer (~77–92% of patients)	1.0–2.0[b]	An individual carrying two alleles encoding full or reduced function; or one full-function allele together with either one nonfunctional or one reduced-function allele	*1/*1, *1/*2, *2/*2, *1/*41, *1/*4, *2/*5, *1/*10
Intermediate metabolizer (~2–11% of patients)	0.5[b]	An individual carrying one reduced-function and one nonfunctional allele	*4/*10, *5/*41
Poor metabolizer (~5–10% of patients)	0	An individual carrying no functional alleles	*4/*4, *4/*5, *5/*5, *4/*6

Table 2 Codeine therapy recommendations based on cytochrome P450 2D6 (*CYP2D6*) phenotype

Phenotype	Implications for codeine metabolism	Recommendations for codeine therapy	Classification of recommendation for codeine therapy[a]	Considerations for alternative opioids
Ultrarapid metabolizer	Increased formation of morphine following codeine administration, leading to higher risk of toxicity	Avoid codeine use due to potential for toxicity.	Strong	Alternatives that are not affected by this CYP2D6 phenotype include morphine and nonopioid analgesics. Tramadol and, to a lesser extent, hydrocodone and oxycodone are not good alternatives because their metabolism is affected by CYP2D6 activity.[b]

KR Crews KR, A Gaedigk A, Dunnenberger HM, et al. Clinical Pharmacogenetics Implementation Consortium Guidelines for Cytochrome P450 2D6 Genotype and Codeine Therapy: 2014 Update. Clin Pharmacol Ther. 95(4):376-382.

The Ohio Opioid PGx Study

- Supported by the Ohio Attorney General's Office
- Collaboration with the Emergency Departments at the University of Cincinnati and The Ohio State University
- Sample size: 1200 patients
- PGx screening of 180 genes associated with opioid metabolism and pharmacodynamic response of the reward pathway

The Ohio Opioid PGx Study: Specific Aims

- *Aim 1:* Determine which genes are associated with development of opioid use disorder.
- *Aim 2*: Develop a Genomic Opioid Addiction Risk Score (G-OARs).

Sample Gene Targets

Pharmacokinetic
- ABCB1
- CYP2D6
- CYP2B6
- UGT2B7

Pharmacodynamic
- TH
- COMT
- OPRM1
- DRD2

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