Medical Model of Addiction

- **Pathophysiology**
  - To identify changes that drugs produce in a vulnerable brain to cause addiction.

- **Individual Risk**
  - To identify specific genes and non-genetic factors that determine an individual’s risk for (or resistance to) addiction.
  - About 50% of the risk for addiction is genetic.

Only through an improved understanding of the biology of addiction will it be possible to develop better treatments and eventually cures and preventive measures.
Scope of Drug Addiction

• 25% of the U.S. population has a diagnosis of drug abuse or addiction.

• 50% of U.S. high school graduates have tried an illegal drug; use of alcohol and tobacco is more common.

• >$400 billion incurred annually in the U.S. by addiction:
  - Loss of life and productivity
  - Medical consequences (e.g., AIDS, lung cancer, cirrhosis)
  - Crime and law enforcement
Diverse Chemical Substances Cause Addiction

- Opiates (morphine, heroin, oxycontin, vicodin)
- Cocaine
- Amphetamine and like drugs (methamphetamine, methylphenidate)
- MDMA (ecstasy)
- PCP (phencyclidine or angel dust; also ketamine)
- Marijuana (cannabinoids)
- Tobacco (nicotine)
- Alcohol (ethanol)
- Sedative/hypnotics (barbiturates, benzodiazepines)
Chemical Structures of Some Drugs of Abuse

- Cocaine
- Morphine
- Nicotine
- $\Delta^9$-tetrahydrocannabinol
- Ethanol
Use of Drugs of Abuse

% of US population as weekly users

- Caffeine
- Alcohol
- Nicotine
- Cannabinoids
- Opiates
- Cocaine
- PCP
- Hallucinogens
Definition of Drug Addiction

• Loss of control over drug use.

• Compulsive drug seeking and drug taking despite horrendous adverse consequences.

• Increased risk for relapse despite years of abstinence.
Definition of Drug Addiction

• **Tolerance** – reduced drug effect after repeated use.

• **Sensitization** – increased drug effect after repeated use.

• **Dependence** – altered physiological state that leads to withdrawal symptoms upon cessation of drug use.
Definition of Drug Addiction

- BUT: many non-addictive drugs can cause tolerance, sensitization, or dependence.

- Therefore, tolerance, sensitization, and dependence do not per se define addiction.

- Rather, addiction is caused by drug-induced changes in reward or reinforcement.

- These changes may include tolerance, sensitization, or dependence in reward-reinforcement mechanisms.
What is Reward and Reinforcement?

Reward
• Positive emotional effects.

Reinforcement
• A stimulus that causes a response to be maintained and increased.
  • *Positive reinforcement*: increases behavioral response to get a positive reward (food, sex, etc.).
  • *Negative reinforcement*: increases behavioral response to end punishment (pain, starvation).

In this way, rewards and reinforcements in the environment powerfully shape an individual’s behavior.
Animal Models of Drug Addiction

How can one model reward, reinforcement, and addiction in laboratory animals?
Animal Models of Drug Addiction
Animal Models of Drug Addiction

Conditioned place preference
  • Animals learn to prefer drug-paired environment.

Drug self-administration
  • If left unchecked, a portion of animals overdose.

Relapse to drug self-administration
  • Stimulated by drug itself or by drug-associated cues or stress.

Intra-cranial self-stimulation
  • Drugs promote an animal’s choice to electrically stimulate brain reward regions.
Highly integrated “limbic” circuits innervated by dopamine neurons in the VTA.
C. elegans (round worms) contain 4-8 dopamine neurons (depending on sex).

Worms normally slow down when they encounter food (bacteria).

This behavior is lost in worms upon ablation of these dopamine neurons.

Thus, the use of dopamine in a neural circuit that controls motor responses to natural rewards goes back >1 billion years in evolution.
Role of Dopamine in Mammals

• VTA dopamine neurons are “rheostats” of reward:
  – Rewards activate the neurons
  – Expectation of rewards activates the neurons
  – Absence of expected rewards inhibits the neurons
  – Unexpected rewards activate the neurons even more.

• Drugs directly and powerfully activate these neurons with no connection to purposeful behavior.

• This leads to a profound corruption of the brain’s reward mechanisms: drugs gradually, progressively, and insidiously replace natural rewards as the major shaper of behavior.
The human VTA is activated by unexpected rewards, less so by expected rewards, and is inhibited by lack of expected rewards.

Effect of monetary rewards on functional MRI (fMRI), which provides a measure of neural activity

D’Ardenne et al., 2008
Brain Imaging Demonstrates Drug Actions on Brain Reward Regions

Drugs of abuse activate the same brain areas that are activated by natural rewards, only they activate them more strongly.

fMRI scans show which brain regions are activated in response to a drug or natural reward.

Breiter et al., 1998
Drugs mimic neurotransmitters by activating receptors:
- Morphine & other opiates
- Nicotine
- Marijuana

Drugs block the dopamine pump:
- Cocaine
- Amphetamine

Drugs activate or inhibit channels:
- Alcohol
- PCP, ketamine
Convergence of Drugs of Abuse on the VTA-Nucleus Accumbens Reward Circuit

- **Opiates**
- **Nicotine**
- **Alcohol**
- **Stimulants**
- **Cannabinoids**
- **Glutamate inputs (e.g. from cortex)**
- **Alcohol**
- **PCP**

- **VTA** (Ventral Tegmental Area)
- **Nucleus accumbens**
- **DA** (Dopamine)
- **GABA**
- **VTA interneuron**
- **Nicotine input**
- **Glutamate inputs (e.g. from amygdala)**
Drugs of Abuse Act at the Synapse

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- Morphine
- Nicotine
- Marijuana

Drugs block the dopamine pump:
- Cocaine
- Amphetamine

Drugs activate or inhibit channels:
- Alcohol
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2nd, 3rd, etc. chemical messengers

Long-lasting changes
Addiction: Drug-Induced Neural Plasticity Mediated Via Altered Gene Expression
Examples of Signaling Pathways Inside of Neurons
Neurobiological Basis of Drug Addiction

Addiction is associated with several types of long-lasting abnormalities, induced in brain reward regions by repeated exposure to drugs of abuse:

- Reduced responses to natural rewards.
- Sensitized responses to drugs of abuse and associated cues.
- Impaired cortical control over more primitive reward pathways.
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Neurobiology of Drug Addiction

Control

- VTA
- Glutamate inputs from other limbic regions

Addicted

- Decreased size of VTA dopamine neurons
- NAc
There is increasing evidence in animal models and in humans that long-term exposure to drugs of abuse impairs dopamine neurons as well as dopamine signaling in the nucleus accumbens.

This dampens natural reward and leaves the addict “unrewarded” (amotivational, depressed) without drug. – Example of reward tolerance.

This effect is mediated in part by actual physical shrinkage of VTA dopamine neurons in response to chronic drug administration.
Some Drugs of Abuse Decrease the Size of VTA Dopamine Neurons

Chronic drug use causes dopamine cells to shrink in animals, dramatically decreasing reward signals:

Normal dopamine nerve cells

Dopamine nerve cells from a morphine-addicted rat.

The same effect is seen in humans.

Sklair-Tavron et al., 1996; Russo et al., 2007; Mazei-Robison et al., 2011
Mechanism of Shrinkage of VTA Dopamine Neurons

Drugs of abuse decrease the size of VTA dopamine neurons by depriving the neurons of a crucial nerve growth factor, BDNF (brain-derived neurotrophic factor):

- Chronic drug exposure decreases BDNF signaling in the VTA.
- Loss of BDNF signaling mediates the decrease in VTA cell size and impairs reward behavior.
- Restoration of BDNF signaling prevents the ability of drug exposure to decrease the size of VTA neurons.
Local Knockout of BDNF from VTA Mimics Effect of Chronic Morphine

Injection of AAV-Cre into VTA of floxed BDNF mice induces localized BDNF knockout and decreases VTA cell size:

Mazei-Robison et al., 2011
The Effect of Chronic Morphine is Blocked by BDNF Infusion into the VTA

Intra-VTA injection of BDNF blocks morphine action:

Sklair-Tavron et al., 1996
Chronic Morphine Decreases VTA Cell Size via Complex Actions on BDNF Signaling
Neurobiology of Drug Addiction

Control

Glutamate inputs from other limbic regions

Addicted

Increased dendritic branching of NAc neurons

VTA

NAc
Addiction: Drug-Induced Neural Plasticity Mediated Via Altered Gene Expression

Second messengers & protein phosphorylation

Regulation of many cellular processes

Transporters

Channels

Receptors

Transcription factors

Stable adaptations in neural function

Target genes
Genes Control Brain Function by Determining the Types and Amounts of Chemical Messengers in the Brain

Genes (DNA) (~25,000)

Messenger RNAs (~100,000)

Proteins (~200,000)

Chemical messengers in brain

Normal and abnormal brain function
Drugs of Abuse Regulate Master Control Proteins

Master control proteins, or transcription factors, control the expression of other genes

Genes (DNA) (~25,000)

Messenger RNAs (~100,000)

Proteins (~200,000)

Chemical messengers in brain

Normal and abnormal brain function
High levels of ΔFosB are induced in NAc uniquely by chronic drug exposure, creating a molecular switch.

ΔFosB induction then mediates sensitized drug responses.
ΔFosB Mediates Sensitized Drug Responses

Analysis of inducible bitransgenic mice in place conditioning:

These mice express ΔFosB or ΔJunD (a blocker of ΔFosB) selectively in nucleus accumbens and dorsal striatum.

Kelz et al., 1999; McClung et al., 2003
ΔFosB Sensitizes Drug Responses by Altering the Structure of Nucleus Accumbens Neurons

Viral expression of ΔFosB in NAc mimics cocaine-induced increases in spine density, while ΔJunD blocks cocaine action.

Maze et al., 2010
Numerous $\Delta$FosB targets mediate cocaine-induced dendritic growth.

Cocaine

$\Delta$FosB

Actin regulatory proteins
- RhoA, Rock
- Wasps, Waves
- Rac1 GEFs, GAPs
- Rap1
- Arc
- CDK5

Transcriptional regulators
- NF$\kappa$B
- SIRT1
- G9a
- MEF2
- Dnmt3a

Regulation of the actin cytoskeleton and induction and stabilization of dendritic spines
Translating Neurobiological Knowledge Into Better Treatments

Will it be possible to use our neurobiological understanding of drug addiction at the molecular and cellular levels?

• All current treatments for drug addiction, which remain very limited, focus on neurotransmitters and receptors.

• Studies of BDNF, ΔFosB, and many other signaling cascades suggest hundreds of potential targets for new medication treatments.

• Validation of new targets is crucial since all medications available today target perhaps a few hundred of the 100,000s of proteins expressed in the brain.
Questions for Discussion

Does the current legal status of drugs of abuse make sense given our understanding of the neurobiology of addiction?

Are all drugs of abuse equally addicting?

How much alcohol is it safe to drink?

Given that methylphenidate (Ritalin) shares cocaine’s mechanism of action, is it a safe medication for attention deficit disorder?