Alcohol: How does it Do the Things it Does? A Neurobiological Perspective

George F. Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health


Cost and Scope of Addiction

**Prevalence**
- Alcohol: 16.7 millions
- Drug & Tobacco: 30.5 millions
- Cancer: 13 millions
- HIV/AIDS: 1.1 millions

**Cost to society**
- Alcohol: $223 billion
- Drug & Tobacco: $316 billion
- Cancer: $202 billion
- HIV/AIDS: $36 billion
Addiction — Defined as a chronically relapsing disorder that is characterized by a compulsion to seek and take drug or stimulus, loss of control in limiting intake, and emergence of a negative emotional state (e.g. dysphoria, anxiety, irritability) when access to the drug or stimulus is prevented (here, defined as the “dark side” of addiction)
Bottom Line

1. Addiction is an incentive salience disorder

2. Addiction is a reward deficit disorder

3. Addiction is a stress surfeit disorder

4. Addiction is an executive function disorder
Stages of the Addiction Cycle

Preoccupation with obtaining Persistent physical/psychological problems

Preoccupation Anticipation

Persistent desire Larger amounts taken than expected

ADDICTION

Tolerance Withdrawal Compromised social, occupational or recreational activities

Withdrawal Negative Affect

Binge Intoxication

NIH National Institute on Alcohol Abuse and Alcoholism
Theoretical Framework Relating Addiction Cycle to Motivation for Drug Seeking

Positive Reinforcement — defined as the process by which presentation of a stimulus (drug) increases the probability of a response (nondependent drug taking paradigms).

Negative Reinforcement — defined as a process by which removal of an aversive stimulus (negative emotional state of drug withdrawal) increases the probability of a response (dependence-induced drug taking)
Conceptual Framework for Neurobiological Bases of the Transition to Excessive Drinking

- **Neurocircuits** ↔ **Synaptic Systems** ↔ **Molecules**
- **Neuroadaptation**

- **Response to Alcohol**
- **Stress and Reward**
- **Preoccupation Anticipation**
- **Binge Intoxication**
- **Withdrawal Negative Affect**
Behavioral Effects of Alcohol Related to Blood Alcohol Level in mg%
• Reward and stress resemble the Roman God Janus.

• Janus was the god of doors, passages and transitions and his two faces look to the future and the past.

• Reward and stress represent different components of transitions in our brain emotional systems that lead to and perpetuate addiction.

"Stress is anything which causes an alteration of psychological homeostatic processes"
from: Burchfield SR, Psychosom Med, 1979, 41:661-672.

Reward is defined as a stimulus (drug) that increases the probability of a response, but usually includes a positive hedonic connotation
Neural Circuits of the Binge/Intoxication Stage

Incentive Salience
- euphoria
- intoxication
- cue learning
- habits

Converging Acute Actions of Drugs of Abuse on the Ventral Tegmental Area and Nucleus Accumbens

Reward Neurotransmitter Release by Alcohol-
Alcohol Consumption Induces Endogenous
Opioid Release in the Human Nucleus Accumbens

Decreased Methylphenidate-induced Dopamine Release in Striatum of Alcoholics

The Ventral-to-Dorsal Striatal Shift: Ascending Spirals from Shell to Core to Dorsal Striatum via Striato-VTA/Nigrostriatal Pathways


Everitt BJ, Robbins TW. "Nat Neurosci", 2005, 8:1481-1489

"Absinthe Drinker"
Pablo Picasso (1910)
Neural Circuits of the Withdrawal/Negative Affect Stage

Negative Affect
- dysphoria
- anxiety
- irritability
- malaise
Withdrawal-induced Negative Affect- Hamilton Depression Scores in Male Primary Alcoholics During 4 Weeks of Abstinence

Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

Positive Hedonic Effects

↑ Dopamine
↑ Opioid peptides
↑ Serotonin
↑ GABA

Negative Hedonic Effects of Withdrawal

↓ Dopamine … “dysphoria”
↓ Opioid peptides … pain
↓ Serotonin … “dysphoria”
↓ GABA … anxiety, panic attacks
Anti-Reward Transmitters Implicated in the Motivational Effects of Drugs of Abuse

- CRF ... stress
- Dynorphin ... "dysphoria"
- Vasopressin ... Stress
- Norepinephrine ... stress
Brain Actions of Corticotropin-Releasing Factor (CRF)

- Corticotropin-Releasing Factor (CRF) stimulates the pituitary gland to release ACTH.
- ACTH stimulates the adrenal medulla to release neurosteroids (NE).
- CRF stimulates the amygdala, leading to behavioral response to stressors and behavioral activation.
- CRF also stimulates the medulla oblongata, leading to sympathetic activation.
- Sympathetic activation increases cardiac output, stroke volume, peripheral vascular resistance, blood glucose, heart rate, and blood pressure.
- CRF stimulates the adrenal medulla to release epinephrine, which increases blood glucose and heart rate.
- CRF stimulates the medulla oblongata to release gastric acid secretion and gastric emptying.

NIH: National Institute on Alcohol Abuse and Alcoholism
Effect of CRF Antagonist D-Phe-CRF$_{12-41}$ in Central Nucleus of the Amygdala on Ethanol Self-Administration During Withdrawal in Wistar Rats (30 min session 2 h into withdrawal)

Summary of Drugs of Abuse Interactions with Corticotropin-Releasing Factor Systems

Koob GF, Neuron, 59:11-34
Dynorphin Control of Mesocorticolimbic Dopamine- Within System?

Nor-Binaltorphimine Blocks Dependence induced Increases in Ethanol Self-administration in Rats

Summary of Drugs of Abuse Interactions with \(\kappa\)-Opioid/Dynorphin Systems

Koob GF. Neuron, 2008, 59:11-34.
Reward/Stress Neurocircuitry in the Transition to Dependence (Within and Between System Neuroadaptations)

**Within System**
- DA
- GABA
- Opioid peptides
- Positive Reinforcement
- VTA
- Nucleus Accumbens

**Between System**
- NE
- CRF
- Negative Reinforcement
- Brain Stem
- Amygdala

Positive Reinforcement

Negative Reinforcement
Brain Arousal-Stress System Modulation in the Extended Amygdala

↑ Corticotropin-releasing factor
↑ Norepinephrine
↑ Vasopressin
↑ Orexin (hypocretin)
↑ Substance P

↓ Neuropeptide Y
↓ Nociceptin (orphanin FQ)
↓ Endocannabinoids

From: Koob, G.F. 2008 Neuron 59:11-34
Executive Dysfunction
- impulsivity
- compulsivity
- impaired decision making

Stimulus value
Action value/cost
Anticipation/Availability
Context
Action inhibition
Emotion control
Outcome valuation
Drug subjective value

Executive Dysfunction
- impulsivity
- compulsivity
- impaired decision making

Stress
Affective state
Incentive to action

Gray Matter Volume Deficits Predict Time to Relapse in Alcohol-Dependent Patients

From: Rando K, Hong K-I, Bhagwagar Z, Li C-S R, Bergquist K, Guarnaccia J, Sinha R.
Am J Psychiatry 168:2, February 2011
Loss of Control Over Intake: Role of PFC and Executive Control

- Escalation of drug intake
- Neuron/oligodendrocyte death
- Impairment of Executive Control
  - Initial intake
  - PFC DA/NE?
  - VTA CRF Neurons?
- Prefrontal Cortex Abnormalities/Hypofunction
  - PFC CRF/GABA interneurons
  - Withdrawal

Initial intake

Caused by:

Dr. Olivier George
Bottom Line

1. Addiction is an incentive salience disorder

2. Addiction is a reward deficit disorder

is a stress surfeit disorder

4. Addiction is an executive function disorder
Conclusions

1. **Conceptual Framework for Addiction:** Alcoholism is a syndrome of compulsive alcohol seeking composed of multiple stages and a “hijacking” of multiple sources of reinforcement.

2. **Binge/Intoxication Stage:** Brain Reward Circuits. Early neuroadaptations in nucleus accumbens and basal ganglia involve activation of incentive salience and habit formation via activation of dopamine and opioid peptide systems.

3. **Withdrawal/Negative Affect stage:** Brain anti-reward systems. Reward system deficits (decreases in dopamine and opioid peptide function) and brain stress system recruitment (increases in CRF and dynorphin brain stress function) in the extended amygdala.

5. **Preoccupation/Anticipation Stage:** Executive function deficits. Neurocircuitry changes in frontal cortex may contribute to impulsivity and compulsivity via dysregulation of glutamatergic systems.
Thank You!

George F. Koob, Ph.D.
Director
National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health