Pharmacology For the Addiction Professional
The Neuroscience of Addiction 2014:
The Anti-Reward Brain System – Part 1

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The Neuroscience and Pharmacology of Addiction 2014

Addiction is a Complex Illness
...with biological, sociological and psychological components
What is Addiction????

- Changes in neurochemistry
- Changes in neurohormones
- Changes in neuropathways
- Changes in stress response
- Changes in limbic system
- Changes in the autonomic systems
- Changes in pain pathways
- Changes in perception

The Addicted Brain- 1994-2013

DEFINITIONS OF PSYCHOACTIVE CHEMICAL USE, ABUSE, AND DEPENDENCE

Psychoactive Chemical Use

This term can be applied to a single episode of psychoactive chemical self-administration. Psychoactive chemical use can have adverse consequences that require treatment, and it can lead to psychoactive chemical abuse or dependence, but it may also be self-limiting and have no adverse effects. Psychoactive chemical use has no diagnostic criteria in the DSM-IV.
Psychoactive Chemical Use

- Single episode
- May have consequences: allergic reactions
- May lead to abuse, addiction, and dependence

Endorphins/Dopamine Receptors

Psychoactive Chemical Abuse

- Failure to meet a role obligation
- Placing yourself or others in physically hazardous situations
- Legal problems
- Repeat of the above
- 12 Month Period
- Estimate 50% Population US meet criteria

DSM IV TR Criteria
Psychoactive Chemical Dependence

- Tolerance
- Physical Withdrawal
- Chemical taken longer/larger amounts than intended
- Preoccupation
- Time acquiring, using, recovering from drug
- Important people, places, things become less important
- Compulsivity

DSM IV TR Criteria
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Addiction and the Brain Antireward System – 2014

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Drug addiction (substance dependence) is characterized by:
- Compulsion to seek and take the drug
- Loss of control in limiting intake
- Emergence of a negative emotional state when drug access prevented

**Stages of the Addiction Cycle**
- Usually a single episode
- May have consequences depending on amount of drug taken:
  - 1. Physical - allergic reactions to the drug, similar to a penicillin-like reaction;
  - 2. Emotional - may cause depression or over-excitation depending on the drug classification;
  - 3. Social/Legal: violence, fights or DUs

**Psychoactive Drug Use**
- Usually a single episode
- May have consequences depending on amount of drug taken:
  - 1. Physical - allergic reactions to the drug, similar to a penicillin-like reaction;
  - 2. Emotional - may cause depression or over-excitation depending on the drug classification;
  - 3. Social/Legal: violence, fights or DUs
**Drug Abuse**

Drug abuse (includes alcohol) is a patterned use of a substance (drug) in which the user consumes the substance in amounts or with methods neither approved nor supervised by medical professionals. Substance abuse/drug abuse is not limited to mood-altering or psycho-active drugs. If an activity is performed using the objects against the rules and policies of the matter (as in steroids for performance enhancement in sports), it is also called drug abuse. Therefore, mood-altering and psychoactive substances are not the only types of drugs abused.

- There is a wanting to use the drug again;
- A physical withdrawal syndrome may occur;
- May have consequences similar to drug use depending on amount of drug taken.

**Desire Corresponds with Drug Use**

- **Liking**
  - Non-problematic Use

- **Wanting**
  - Abuse

- **Craving**
  - Addiction

**An authoritative definition of drug addiction is that propounded by the World Health Organization:**

"Drug addiction is a state of periodic and chronic intoxication detrimental to the individual and to society, produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include:

1. An overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means;
2. A tendency to increase the dose;
3. A psychic (psychological) and sometimes a physical dependence on the effects of the drug."
Substance Use Disorder - A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 2 (or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)

2. Recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

3. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)

4. Tolerance, as defined by either of the following:
   a. Need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b. Markedly diminished effect with continued use of the same amount of the substance (Note: Tolerance is not counted for those taking medications under medical supervision such as analgesics, antidepressants, ant-anxiety medications or beta-blockers.)

5. Withdrawal

6. Preoccupation

7. Can't stay stopped or control use

8. Spend lots of time obtaining the substance, using the substance, or recovering from its effects;

9. Important social, occupational, or recreational activities are given up or reduced because of substance use;

10. The substance use is continued despite knowing you have a serious physical or psychological problem that is likely to have been caused or made worse by the substance;

11. Craving or a strong desire or urge to use a specific substance.
Cravings

- Craving: memory of the rewarding aspects of drug use superimposed on a negative emotional state
  - Compels drug-seeking in dependent individuals

3 Types of Cravings
- Withdrawal induced
- Drug-induced
- Cue-induced

Drug-induced Craving

[Graph showing high craving and its decrease over time]
DSM 5 Addiction Severity Levels

- Mild: 2-3 criteria
- Moderate: 4-5 criteria
- Severe: 6 or more

Factors Contributing to Vulnerability to Develop a Specific Addiction

- Genetic (25-50%)
  - DNA
  - SNPs
  - other polymorphisms
- Environmental (very high)
  - prenatal
  - postnatal
  - contemporary
  - cues
  - comorbidity
- Drug-Induced Effects (very high)
  - mRNA levels
  - peptides
  - proteomics
- Environmental
  - neurochemistry
  - behaviors

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Kreek et al., 2000
Initially, a person takes a drug hoping to change his or her mood, perception, or emotional state.

Translation –
...hoping to change their brains.

Antireward

- A concept based on the hypothesis that there are brain systems in place to limit rewards that are triggered by excessive activity in the reward system.
Neurobiology of Addiction 2014

- Addiction is increasingly understood as a neurobiological illness where repetitive substance abuse corrupts the normal circuitry of rewarding and adaptive behaviors causing drug-induced neuroplastic changes.
- Addiction is typically accompanied by alterations in the neurobiology of substance initiation to the progression of substance abuse to dependence to the enduring risk of relapse.
- Critical neurotransmitters and neuromodulators underlie the pathophysiological changes at each of these stages.
- Enhanced dopamine transmission in the nucleus accumbens is part of the common pathway for the positively rewarding aspects of drugs of abuse and for initiation of the addictive process. In Amphetamine, THC, opioids, serotonin, acetylcholine, the endocannabinoids, and glutamate systems also play a role in the initiation of addiction.
- Dopamine also plays a key role in conditioned responses to drugs of abuse, and addiction is now recognized as a disease of pathological learning and memory.
- In the path from substance abuse to addiction, the neurochemistry shifts from a dopaminergic system to a predominantly glutamatergic one marked by dysregulated glutamatergic transmission from the prefrontal cortex to the nucleus accumbens in relation to drug versus biologically oriented stimuli. This has been called the anti-reward brain.
- Understanding the neurobiology of the addictive process allows for a theoretical psychopharmacological approach to treating addictive disorders, one that takes into account biological interventions aimed at particular stages of the illness.

The Neurobiology of Addictive Disorders, Ross, Stephen MD; Peselow, Eric MD

Cycle of Addiction

- Moving from impulsive disorder to compulsive disorder, there is a shift from positive reinforcement to negative reinforcement.
- 3 stages of cycle of addiction:
  - Preoccupation/anticipation
  - Binge/intoxication
  - Withdrawal/negative affect

We know that despite their many differences, most abused substances enhance the dopamine and serotonin pathways.
“The Necessary Nine”

- stimulant, anger, fear, anxiety, flight, flight
- depressant, sleep, calm, pleasure
- relaxant, stress reduction, seizure threshold
- pain relief, pleasure
- involuntary actions, memory, motivation
- memory, new learning, calmness
- organization of brain signaling, memory, pain
- perception, movement, pleasure
- loving of one’s self, others, GOD

“Human Doing” – Neurotransmitters of Substance Use Disorders

- Addiction/Trauma
- Recovery

- Depletion may take less than 12 months
- Replenishment may take 5 to 7 years

“Human Being”
The Anti-Reward Brain

- 1. A key element of addiction is the development of a negative emotional state during drug abstinence.
- 2. The neurobiological basis of the negative emotional state derives from two sources: decreased reward circuitry function and increased anti-reward circuitry function.
- 3. The anti-reward circuitry function recruited during the addiction process can be localized to connections of the extended amygdala in the basal forebrain.
- 4. Neurochemical elements in the antireward system of the extended amygdala have as a focal point the extrahypothalamic corticotropin-releasing factor system.
- 5. Other neurotransmitter systems implicated in the anti-reward response include noradrenaline, dynorphin, neuropeptide Y, and endocannabinoids.
- 6. Vulnerability to addiction involves multiple targets in both the reward and anti-reward systems, but a common element is sensitization of brain stress systems.
- 7. Dysregulation of the brain reward system and recruitment of the brain anti-reward system are hypothesized to produce an allostatic emotional change that can lead to pathology.
- 8. Nondrug addictions may be hypothesized to activate similar allostatic mechanisms.

ANTIREWARD

The concept of an anti-reward system was developed to explain a component of time-dependent neuroadaptation in response to excessive utilization of the brain reward system. The brain reward system is defined as activation of circuits involved in positive reinforcement with an overlay of positive hedonic valence. The neuroadaptation simply could involve state-shifts on a single axis of the reward system (within-system change; dopamine function decreases). However, there is compelling evidence that brain stress/emotional systems are recruited as a result of excessive activation of the reward system and provide an additional source of negative hedonic valence that are defined here as the anti-reward system (between-system change; corticotropin-releasing factor function increases). The combination of both a deficit in the reward system (negative hedonic valence) and recruitment of the brain stress systems (negative hedonic valence) provides a powerful motivational state mediated in part by the anti-reward system. (Koob & Le Moal 2005).
What is an unconscious emotion?

“Our feeling is the emotion.”
William James
What is an emotion? (1894)

“So for emotions, feelings and affects to be unconscious would be quite out of the question.”
Sigmund Freud
The Unconscious (1915)

Unconscious emotion?
Damasio, LeDoux, Winkelman
Analogous to nonconscious blindsight or implicit memory...

What causes hedonic ‘liking’?
Brain hedonic hotspots

Generating pleasure ‘liking’ via a network of opioid islands


Implications of ‘liking’ vs ‘wanting’?
Incentive-Sensitization theory of Addiction
Terry Robinson

Neural Sensitization of mesolimbic dopamine systems: Hyper-excitability
Caused by amphetamine, cocaine, heroin, alcohol, nicotine...
Lasts years...

Initial Use
Incentive Value
Subjective Pleasure

Addiction
Time

Positive affect (reward)

‘want’
‘like’

Incentive

Relative Effect

Incentive Value

Subjective Pleasure

Time
Reynolds & Berridge, 2003

Aversive fear
(bite, distress, ‘dislike’)

Posterior

Appetitive positive
(eat, prefer, ‘like’)

Anterior

Nucleus Accumbens shell
Bivalent emotion from corticolimbic tweaks
(Glutamate AMPA blockade by shell DNQX)

+ Positive front □ Negative back △
+ No neutral center
+ Ambivalent middle: +/- together ○

Desire Corresponds with Drug Use

• Non-problematic Use

• Abuse

• Addiction

Natural ‘dread reaction’
Fearful defensive treading
(from Donald Owings & Richard Coss)
Natural 'dread reaction'
Fearful defensive treading
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Why Do People Abuse Prescription Drugs?
These prescription drugs, like other drugs of abuse (cocaine, heroin, marijuana), raise brain dopamine levels

BUT dopamine is also elevated by natural re-enforcers

CNS Actions of Corticotropin Releasing Factor (CRF)
Stages of the Addiction Cycle

Neurobiology of Addiction

Binge/Intoxication Stage
Withdrawal/Negative Affect Stage

Preoccupation/Anticipation “Craving” Stage

The Nervous System

- Neural Networks
  - interconnected neural cells
  - with experience, networks can learn, as feedback strengthens or inhibits connections that produce certain results
  - computer simulations of neural networks show analogous learning

Neurons in the brain connect with one another to form networks

The brain learns by modifying certain connections in response to feedback

CANNABINOIDS

- Receptors have also been found in the
  - Cerebellum - body movement and coordination
  - Cortex - higher cognitive functions
  - Nucleus accumbens - reward
  - Basal ganglia - movement control
  - Hypothalamus - body temperature, salt and water balance, reproductive functions
  - Amygdala - emotional responses, fear

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Positive Reinforcement

Negative Reinforcement

Dependent

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Brain Arousal-Stress System Modulation in the Extended Amygdala

From: Koob, G.F. 2008 Neuron 59:11-34
Animal Models of Addiction

- Animals and humans will readily self-administer drugs in the non-dependent state
- Good correspondence between the ability of drugs to decrease brain reward thresholds and their abuse potential
- Increased self administration during withdrawal has been observed with cocaine, methamphetamine, nicotine, heroin, and alcohol

Animal Studies

- Rats did not show suppress drug seeking behavior despite aversive condition stimulus or punishment (DSM-IV)
- Animals have also displayed reinstatement of drug seeking behavior after the behavior has been extinguished
  - Drug-induced reinstatement
  - Stress-induced reinstatement

Positive Reinforcing Effects

- Focus of research on the activation of the circuitry related to the origins and terminals of the mesocorticolimbic dopamine system.
  - Evidence that all major drugs of abuse activate this system
- Research suggests that multiple parallel pathways mediate drug reward
Within-System Neuroadaptational Processes

- Increases in brain reward threshold (decreased reward) occur that highly correlate with the increase in drug intake with extended access
- It is hypothesized that decreases in reward neurotransmitter function contribute significantly to the negative motivational state during acute withdrawal and may trigger long-term biochemical changes that may explain vulnerability to relapse

Between-System Neuroadaptational Processes

- The hypothalamic–pituitary–adrenal (HPA) axis and the brain stress system are dysregulated by chronic administration of drugs of abuse
  - Both mediated by corticotropin–releasing factor (CRF)
- In the case of alcohol withdrawal in rats, administering CRF receptor antagonists decreased anxiety–like behavior and ethanol self administration
  - Similar results have been seen with heroin, cocaine, and nicotine
Allostasis - Definition

“The ability to achieve stability through change”

“To obtain stability, an organism must vary all of the parameters of its internal milieu and match them appropriately to environmental demands.”


Neural Bases of Protracted Abstinence and Relapse

- Dark side may contribute to chronic relapse
- Hypofunctioning and reorganized prefrontal system drive drug-, cue-, and stress-induced reinstatement neurocircuits, which can cause vulnerability to craving
- Animal models of craving:
  - Drug seeking induced by stimuli paired with drug taking
  - Drug seeking induced by an acute stressor or state of stress
Preadolescent and adolescent exposure to alcohol, tobacco, or drugs of abuse significantly increases the propensity for dependence in adulthood.

Adolescents first intoxicated with alcohol at age 16 or younger are 2–3 times more likely to develop dependence (similar to tobacco).

Early onset of drug use is a predictor of subsequent drug problems.

Sensitivity to Antireward Neuroadaptations

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The Hiker and the Rattlesnake

LeDoux, Scientific American, 1994

AMYGDALA

Medial Prefrontal Cortex
Anterior Cingulate Cortex

Sights
Sounds

Hippocampus

Thalamus

Dys-coordination of Threat Response & Dissociation

Battlemind: Dys-coordination of Threat Response & Dissociation

Psychodynamic self-medication hypothesis
- Focuses on underlying developmental difficulties, emotional disturbances, structural factors, building of self, and personality organization
- Individuals hypothesized to take drugs as a means to cope with painful and threatening emotions

Comorbid Psychiatric disorders
- Some of the strongest associations are found with mood disorders, antisocial personality disorders, and conduct disorders

Sensitivity to Antireward Neuroadaptations
There is no single gene for addiction. Stress, trauma, prenatal stress, and early-life rearing experiences may alter addiction pathology later in life, via gene expression changes. Chronic use of drugs can even lead to DNA modification at particular target genes.

Genetic and Epigenetic Mechanisms:

- Allostasis
  - Defined as stability through change
  - Involves a feed-forward mechanism rather than negative feedback mechanisms of homeostasis
  - Continuous re-evaluation of need and continuous readjustment of all parameters toward new set points
  - Thus, a fine matching of resources to needs
**Homeostasis to Allostasis of the Reward System**

- **Allostatic state**
  - State of chronic deviation of the regulatory system from its normal (homeostatic) operating level.
- **Allostatic Load**
  - Long-term cost of allostasis that accumulates over time and reflects accumulation of damage that can lead to pathological states

**Temporal Dynamics of Allostasis**

- The same physiological mechanism that allows rapid response to environmental challenges becomes the engine of pathology if adequate time or resources are not available to shut off the response.
- Two components are hypothesized to adjust to challenges to the brain produced by drugs of abuse:
  - Overactivation of brain reward transmitters and circuits
  - Recruitment of the brain antireward or brain stress systems
- Which leads to the compulsivity of drug seeking and drug taking

**Nondrug Addictions**

- Impulse control disorders with characteristics similar to drug addiction:
  - Kleptomania
  - Trichotillomania
  - Pyromania
  - Compulsive gambling
- Other disorders outside of accepted diagnostic disorders:
  - Compulsive shopping, compulsive sexual behavior, compulsive eating, compulsive exercise, etc.