The Neurobiology of Addiction and Pharmacological Concepts

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Addicting Molecules

- Nicotine
- Alcohol
- Heroin
- Cocaine

Stahl S M. Essential Psychopharmacology (2000)
Is there a single pathway to addiction?

• Drugs of abuse have very different structures and neurotransmitter targets in the brain, but they all exhibit:
  • acute reward
  • chronic reward
  • sensitization
  • negative withdrawal symptoms
  • associative cue learning
  • incentive motivation (relapse)
• A progression from impulsive to compulsive drug use (which defines the progression from abuse into addiction).

The Body’s Own Psychotropics

• The brain makes its own morphine (beta endorphin) and its own marijuana (anandamide)
• The brain may even make its own antidepressants, anxiolytics, and hallucinogens
• Drugs often mimic the brain’s natural neurotransmitters
• Often, drugs are discovered prior to the natural neurotransmitter
Exogenous vs. Endogenous Drugs

We knew about:
- Morphine before the discovery of β-endorphin
- Marijuana before the discovery of cannabinoid receptors and anandamide
- Valium and Xanax before the discovery of benzodiazepine receptors
- Elavil & Prozac before the discovery of the serotonin transporter site

TRANSITION TO ADDICTION

Taking drugs may begin as a voluntary choice to seek a pleasant stimulus, but for addicts, that choice is no longer volitional, even in the face of terrible personal consequences.

- During the initial stages of addiction
  - The pleasure derived from various drugs' activation of the brain's natural reward system promotes continued drug use
  - Repeated exposure to drugs induces the brain mechanism of dependence
  - Dependence leads to daily drug use to avert the unpleasant symptoms of drug withdrawal
  - Further prolonged use of drugs lead to more long-lasting changes in the brain that may underlie the compulsive drug-seeking behavior and related adverse consequences that are the hallmarks of addiction.
The ‘Changed Set Point’ Model

Variants

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<tr>
<th>Variant #1</th>
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<tr>
<td>Neurons of the mesolimbic reward pathways are naturally &quot;set&quot; to release enough DA in the N-Ac to produce a normal level of pleasure.</td>
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<tr>
<td>Abused drugs cause addiction by initiating a vicious cycle of changing this set point</td>
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<td>The release of DA is reduced when normally pleasurable activities occur and the abused drugs are not present</td>
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<td>A change in the set point occurs in the LC, but in the opposite direction, so NE release is increased during withdrawal accounting for the drug withdrawal aspects of addiction</td>
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The ‘Changed Set Point’ Model

- Variant #2
  - DA neurons can become dysfunctional through an alteration of their baseline ("resting") levels of electrical activity and DA release.
  - The resting level is the result of two factors that influence the amount of resting DA release in the N-Ac
    - Cortical excitatory (glutamate) neurons that drive the VTA DA neurons to release DA.
    - Autoreceptors ("hockies") that shut down further release when DA concentrations become excessive.
  - With continued drug use, there is an increase in number and strength of autoreceptors.
  - When drug use stops, DA deprivation results, manifesting in dysphoria (pain, agitation, malaise) & other w/d symptoms.

- Variant #3
  - Emphasizes the sensitivity to environmental cues that leads to drug wanting or craving.
  - During periods when the drug is not available to addicts, their brains can remember the drug, and desire or craving for the drug can be a major factor leading to relapse.
  - This craving may represent increased activity of glutamate and NE.
  - This leads to drug craving and increased withdrawal symptoms.

- The Cognitive Deficits Model
  - Proposes that individuals who develop addictive disorders have abnormalities in the prefrontal cortex.
  - The PFC is important for regulation of judgment, planning, and other executive functions.
  - Normally, the PFC sends inhibitory signals to the VTA DA neurons of the mesolimbic reward system to help overcome some of our impulses for immediate gratification.
  - Stimulant drugs appear to damage the specific brain circuit (frontostrital loop) that carries inhibitory signals from the PFC to the mesolimbic reward system.
  - Chronic alcohol abusers have abnormally low levels of GABA, the neurochemical that the PFC uses to signal the reward system to release less DA.
  - Opiates apparently damage the PFC itself.
Addiction as a neurodevelopmental disorder

Normal developmental processes might result in a higher risk of drug use at certain times in life than others.
• Stressors can trigger drug craving in addicts.  
• One explanation is that abused drugs raise levels of cortisol which plays a primary role in stress responses.
• Cortisol raises the level of activity in the mesolimbic reward system.  
• By these mechanisms, stress may contribute to the abuser’s desire to take drugs in the first place, as well as the subsequent compulsion to keep taking them.

**TOLERANCE, WHAT IS IT?**

**TOLERANCE**

- Dopamine release  
  Stimulation of receptor
- Stimulation of receptor  
  Activation of cAMP
- cAMP enters nucleus  
  Activation of CREB
- cAMP Response Element Binding protein
- CREB activates Dynorphin
- Dynorphin desensitizes Dopamine Receptor
- Resensitization  
  (Reverse Tolerance)
- Activation of Δ fos B
GENERAL PRINCIPLES OF MANAGEMENT

Initial Medical Assessment
- Purpose:
  - to determine the need for medication and medical management
- Includes:
  - Evaluation of predicted withdrawal severity
  - Presence of medical comorbidity
  - Presence of psychiatric comorbidity

Helpful Information to Predict Severity of Withdrawal
- Amount and duration of alcohol or other drug use
- The severity of the patient's prior withdrawal experiences (if any)
- The patient's medical and psychiatric history
Strategies for Pharmacologic Management

- Two general strategies (either or both may be used):
  - Suppress withdrawal through use of a cross-tolerant medication
    - A longer acting medication typically is used to provide a milder, controlled withdrawal
    - Examples: Methadone, buprenorphine, chlordiazepoxide
  - Reduce signs and symptoms of withdrawal through alteration of another neuropharmacological process
    - Examples: clonidine, propranolol, ibuprofen

MANAGEMENT OF ALCOHOL WITHDRAWAL

Pathophysiology

- Dependency develops as a cell or organism makes homeostatic adjustments to compensate for the primary effect of a drug
  - Goldstein & Goldstein, 1966
- The primary effect of alcohol on the brain is depressant
  - With chronic exposure, there are compensatory adjustments with down-regulation of inhibitory systems and up-regulation of excitatory systems
  - The withdrawal symptoms last until the body readjusts to the absence of the alcohol and establishes a new equilibrium
Pathophysiology
- Neurotransmitter systems affected:
  - GABA
    - Mediates effects such as sedation, muscle relaxation and a raised seizure threshold
    - Chronic alcohol intake leads to an adaptive suppression of GABA activity
  - Norepinephrine
    - Chronic alcohol intake leads to upregulation of receptors
    - Discontinuation of alcohol leads to rebound overactivity of noradrenergic systems
      - Tachycardia, hypertension, tremor, diaphoresis & anxiety
  - Other systems affected: Calcium channels, glutamate receptors, cAMP systems

PHARMACOLOGIC MANAGEMENT
- The cornerstone of pharmacologic management of withdrawal is the use of benzodiazepines (Mayo-Smith et al, 1997)

Benzodiazepines
- Are pharmacologically cross-tolerant with alcohol and have the similar effect of enhancing the effect of GABA-induced sedation.
  - A specific benzodiazepine receptor site has been identified on the GABA receptor complex.
  - The provision of benzodiazepines alleviates the acute deficiency of GABA neurotransmitter activity that occurs with sudden cessation of alcohol intake.
Benzodiazepines

- Trials of different benzos indicate that all are similarly efficacious in reducing signs and symptoms of withdrawal.
- Longer acting agents may be more effective in preventing seizures
  - E.g., chloralhydrate, diazepam, clonazepam
- May also contribute to an overall smoother withdrawal course, with a reduction in breakthrough or rebound symptoms
- May also pose a risk of excess sedation in elderly and significant liver disease
  - Shorter acting agents are preferable (lorazepam or oxazepam)
- Phenobarbital is still used by some programs
  - Long-acting barbiturate with well-documented anticonvulsant activity, inexpensive, & low abuse liability

Other Agents

- Beta adrenergic blocking agents
  - E.g., atenolol & propranolol
- Centrally acting alpha adrenergic agonists
  - E.g., clonidine
- Both these agents reduce the autonomic nervous system manifestations of withdrawal
- These agents do not have known anticonvulsant activity
- Beta blockers may (rarely) cause delirium

Carbamazepine

- Has been shown to be equal in efficacy to benzodiazepines
  - No significant toxicity
  - Associated with less psychiatric distress and a faster return to work
  - Does not potentiate the CNS and respiratory depression
  - Does not inhibit learning
  - Has no abuse potential
Neuroleptic Agents
- Less effective than benzos in preventing delirium
- Actually increases the rate of seizures
- Haloperidol has least effect on seizure threshold
- Widely used to calm agitated patients

Agents No Longer Recommended
- Magnesium
- Phenytoin
  - No evidence of effectiveness in preventing recurrent withdrawal seizures

Thiamine
- Alcoholics are at risk for thiamine deficiency.
  - Leads to Wernicke's Disease and the Wernicke-Korsakoff Syndrome
- Wernicke's: illness of acute onset characterized by the triad of
  - mental disturbance
  - paralysis of eye movements (weakness or paralysis of abduction [CN-VI])
    - Invariably is bilateral, but rarely symmetric
    - Accompanied by diplopia, strabismus and nystagmus
  - ataxia
    - Affects gait and stance
Thiamine

- Delay in provision of thiamine increases the risk of permanent memory damage.
- The provision of intravenous glucose solutions may exhaust a patient's reserve of B vitamins, acutely precipitating Wernicke's disease.

 MANAGEMENT OF OPIOID WITHDRAWAL

The Opioids

- Drugs Derived Directly from the Opium Poppy
  - Morphine
  - Codeine
- The Semisynthetic Opioids
  - Heroin (diacetylmorphine)
  - Hydromorphone (Dilaudid)
  - Oxycodeone (Percocet, OxyContin)
  - Hydrocodone (Loricet, Vicodin)
- The Synthetic Opioids
  - Methadone
  - Fentanyl
  - Propoxyphene (Darvocet)
  - Meperidine (Demerol)
Opioid Withdrawal

- The opioid abstinence syndrome is characterized by two phases:
  - Acute Withdrawal
  - Protracted Abstinence Syndrome
- Current pharmacotherapeutic strategies are based on this duality.

Acute Withdrawal

- The patient typically experiences a range of symptoms for various lengths of time.
- Symptoms include:
  - Vital Sign Changes
    - Tachycardia, Hypertension, Hyperpyrexia
  - CNS Changes
    - Restlessness, Irritability, Insomnia, Craving, Yawning
  - Eye & Nose Changes
    - Pupillary dilation, Lacrimation, Rhinorrhea
  - Skin Changes
    - Pilosecretion
  - GI Changes
    - N/V/D

Chronic Dependence & Protracted Abstinence

- The time required for return to baseline ranges from one week to about six months
- Symptoms include:
  - Changes in Vital Signs
  - Decreased sensitivity of the respiratory center to CO2
  - Irritability, insomnia, craving
Clinical Picture
- Clinical phenomena associated with opioid withdrawal include neurophysiologic rebound in the organ systems on which opioids have their primary action (Jaffe, 1991).
- The severity varies with the dose and duration of drug use.
- Route of administration is important.
- Injection drug use is associated with significantly higher withdrawal symptom scores than with inhaled opioid use (Smolka & Schmidt, 1991).
- The time to onset depends on the half-life of the drug being used.
- E.g., Withdrawal may begin 4 to 6 hours after the last use of heroin, but up to 36 hours after the last use of methadone.

Clinical Picture
- Neuropharmacologic studies of opioid withdrawal have supported the clinical picture of increased CNS noradrenergic hyperactivity (Jaffe, 1991).
- Therapies to alter the course of opioid withdrawal (e.g., clonidine) are designed to decrease this hyperactivity, which occurs primarily at the locus ceruleus.

SUMMARY
- Substantial progress has been made in the development of pharmacotherapies for the treatment of SUDs.
- These treatments must be utilized in conjunction with a program addressing the psychosocial needs of the patient.
- Research is ongoing to continue to broaden the number of pharmacotherapies available for SUDs.
- The search for effective medication treatments for other SUDs, such as stimulant and cannabis use disorders continues.
Questions and comments