The Neurobiology of Addiction and Pharmacological Concepts

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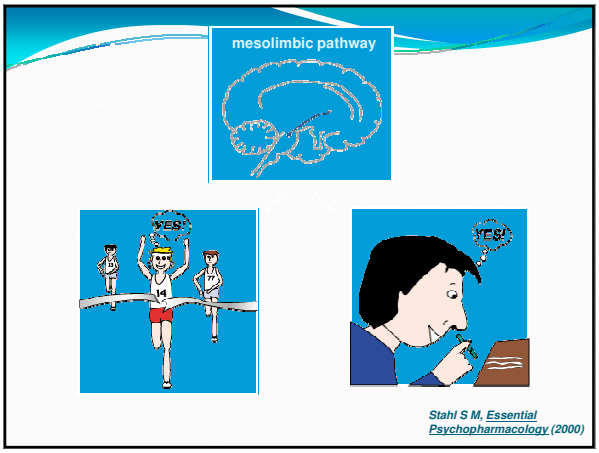
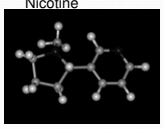


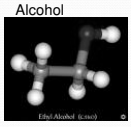
Stahl S M, Essential Psychopharmacology (2000)

Addicting Molecules

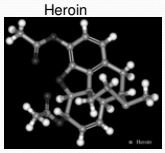
Nicotine



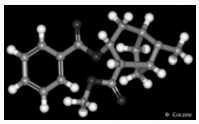
Alcohol



Heroin

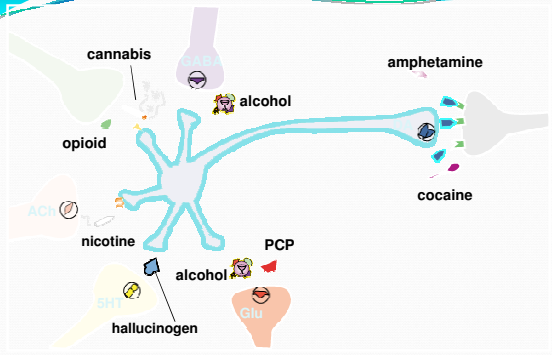


Cocaine



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).



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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.

BIOLOGIC MODELS OF ADDICTION

The 'Changed Set Point' Model

- There are several variants of this model based on the altered neurobiology of:
  - Dopamine neurons in the VTA
  - Norepinephrine neurons in the LC
- These alterations occur during the early phases of withdrawal and abstinence .
- The basic tenet is that drug abuse alters a biological or physiological setting or baseline.

The 'Changed Set Point' Model

- Variant #1
  - Neurons of the mesolimbic reward pathways are naturally "set" to release enough DA in the N-Ac to produce a normal level of pleasure.
  - Abused drugs cause addiction by initiating a vicious cycle of changing this set point
    - The release of DA is reduced when normally pleasurable activities occur and the abused drugs are not present
    - 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
      - Koob GF & LeMoal M. (2001). Drug addiction, dysregulation of reward, and allostasis. *Neuropsychopharmacology*, 24, 97-129.

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 ("brakes") 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
    - Grace AA. (2000). The tonic/phasic model of dopamine system regulation and its implications for understanding alcohol and stimulant craving. *Addiction*, 95(Suppl 2), S119-S128.

The 'Changed Set Point' Model

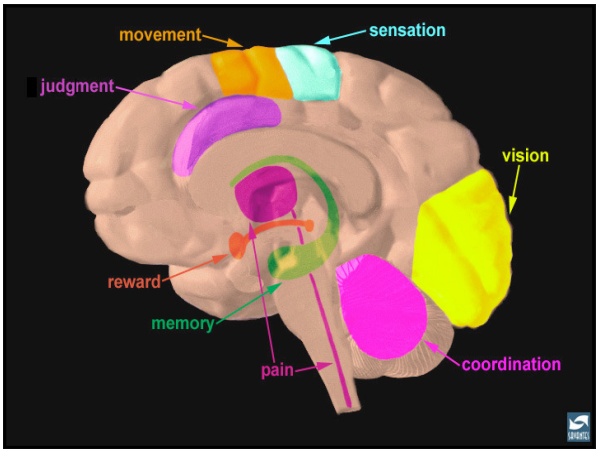
- Variant #3
  - Emphasizes the sensitivity to environmental cues that leads to drug wanting or craving .
    - During periods when the drug is not available to addicts, their brains can remember the drug, and desire or craving for the drug can be a major factor leading to relapse.
      - This craving may represent increased activity of glutamate and NE
        - This leads to drug craving and increased withdrawal symptoms.
      - Robinson TE & Berridge KC. (2000). The psychology and neurobiology of addiction: An incentive-sensitization view. *Addiction*, 95(Suppl 2), S91-S117.

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 (frontostriatal 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



THE IMPORTANT ROLE OF STRESS

- Stressors can trigger drug craving in addicts.
  - Sinha R, Catapano D & O'Malley S. (1999). Stress-induced craving and stress response in cocaine dependent individuals. *Psychopharmacology*, 142, 343-351.
  - 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.
    - Kreek MJ & Koob GF. (1998). Drug dependence: Stress and dysregulation of brain reward pathways. *Drug & Alcohol Dependence*, 51(1-2), 23-47.
  - 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, 1961
- 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
  - Norephinephrine
    - 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., chlordizepoxide, 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 preferrable (lorazepam or oxazepam)
- Phenobarbital is still used by some programs
  - Long-acting barbiturate with well-documented anti-convulsant 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)
  - Oxycodone (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
    - Piloerection
  - 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 CO_2
  - 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, 1990)
- 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, 1999)
- 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, 1990)
- 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