Causes of Alcohol Abuse and Alcoholism: Biological/Biochemical Perspectives

Neurobehavioral Aspects of Alcohol Consumption

Source: *Eighth Special Report to the U.S. Congress on Alcohol and Health*

Secretary of Health and Human Services

N.W. Gilpin, and G. F. Koob, "Neurobiology of Alchohol Dependence: Focus on Motivational Mechanisms" Alcohol Research and Health, 31, 185 (2008)

Braun: pp 88-106

Alcohol-Seeking Behavior and the Development of Chronic Drinking

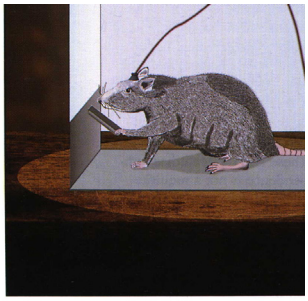
- Physical Dependence
  - tolerance
  - withdrawal
  - cause or consequence?
- Psychological Dependence
  - compulsive alcohol seeking behavior
  - comorbidity with psychiatric disorders: anxiety (44%) and depression/bipolar disorders (50%)
- A fundamental question is: Are the reported pleasure sensations that lead to alcohol-seeking due to its euphoric effect, or to the reduction of some underlying anxiety?

Reinforcement

- Reinforcement is the process whereby the probability of a behavioral response is increased if it results in a particular effect
- positive reinforcement
  - learned behavior to achieve a reward
- negative reinforcement
  - learned behavior to escape discomfort

Brain Stimulation Reward (BSR)

- BSR is intracranial self-stimulation (recently ICSS)
  - Measure threshold current needed to sustain self-stimulation
  - Measure how hard rats will work (maximum number of required presses) to receive self stimulation



Drawing courtesy of Robert Czechowski and Clare Little

Alcohol's Effects on Brain Stimulation Reward (BSR)

- Threshold current lowered and maximum bar press raised during initial BAC rise; no effect during BAC drop phase
- Thought to be analogous to human sensations of pleasure and euphoria during BAC rise.

Biphasic Action of Alcohol: Stimulation(low BAC) then Sedation (high BAC)

- Low doses stimulate "Spontaneous Motor Activity" (SMA) in rats during rising BAC
- High doses give sedation and sleep
- SMA stimulation occurs through elevating dopamine levels in ventral tegmental area of the brain (nucleus acumbens reward center)
- These changes are correlated with the enhancement of the brain stimulation reward threshold

Neurochemical Mechanisms of Positive Alcohol Reinforcement

- Dopamine
  - alcohol and cocaine stimulate concentrations in nucleus acumbens and other reward centers
  - Dopamine antagonists increase alcohol intake in rats, e.g.., more alcohol is required to achieve pleasurable response
  - Dopamine agonists decrease alcohol intake in rats , e.g.., less alcohol is required to achieve pleasurable response

Neurochemical Mechanisms of Positive Alcohol Reinforcement

- Serotonin
  - alcohol increases serotonin concentrations in certain regions of the brain
  - brain of alcohol preferring rats contain lower concentrations of serotonin than wild type rats.
  - Serotonin agonists reduce alcohol intake

Neurochemical Mechanisms of Positive Alcohol Reinforcement

- Endogenous Opiates
  - alcohol stimulates release of enkephalins and endorphins…producing euphoria and pain attenuation
  - Opiate receptor antagonists reduce the reinforcing effects of alcohol

Negative Reinforcement

- Withdrawal during transition to physical dependence
  - Rats show increases in alcohol seeking during withdrawal
- Neural adaptation (tolerance) produce deficits in arousal, reward, and stress reducing positive reinforcement and increasing negative reinforcement (due to withdrawal)
- Other examples of negative reinforcement?
- Is negative reinforcement a likely early factor in the development of dependence?
  - Comorbidity with psychiatric disorders

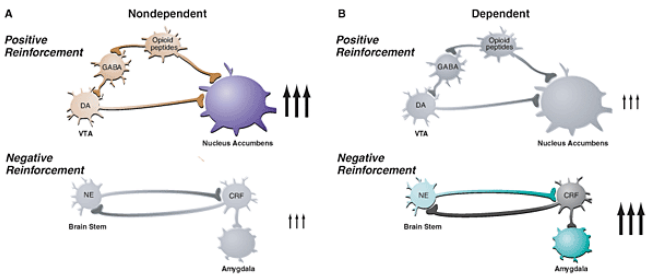
How does Tolerance Affect Reinforcement?

- Tolerance would seem to reduce the reward and, therefore, the desire to seek alcohol
- Neural adaptations alter reward circuits

Circuit

Reward

Stress



Changes in the activity of the reward circuit mediating the acute positive reinforcing effects of alcohol and the stress circuit mediating negative reinforcement of dependence during the transition from nondependent alcohol drinking to dependent drinking. Key elements of the reward circuit are dopamine (DA) and opioid peptide neurons that act at both the ventral tegmental area (VTA) and the nucleus accumbens and which are activated during initial alcohol use and early stages of the progression to dependence (i.e., the binge/intoxication stage). Key elements of the stress circuit are corticotropinreleasing factor (CRF) and norepinephrine (NE)-releasing neurons that converge on γ-aminobutyric acid (GABA) interneurons in the central nucleus of the amygdala and which are activated during the development of dependence.

Late Stages of Alcohol Dependence

- Neurodegeneration
  - Changes in morphology, proliferation, and survival of neurons
- Protracted Abstinence and Relapse
  - Naltrexone (opioid antagonist) block relapse caused by environmental cues previously associated with alcohol use
  - CRF antagonists block stress-induced relapse

END