Neurobiology of Addiction:
CAPTASA 2010 Update

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Pre-Talk Questions

- Addicts/Alcoholics are:
  - Good people gone bad?
  - Healthy people become ill?
  - Are there new classes of addictions?

Definition of Alcoholism/Addiction

"Alcoholism is a primary, chronic disease with genetic, psychosocial, and environmental factors influencing its development and manifestations. The disease is often progressive and fatal. It is characterized by continuous or periodic: Impaired control over drinking, preoccupation with the drug alcohol, use of alcohol despite adverse consequences, and distortions in thinking, most notably denial."

American Society of Addiction Medicine/NCADD (1992)
**Territory to be covered:**
- Chemical effect
- Mechanism of addiction at cellular & systemic level
- Cross-tolerance and cross-dependence
- Progression
- Craving

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**The Architecture: The Synapse**

*From Mithic & Harris, 1997*

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**Mechanism of Effect**
- Cocaine & Amphetamines
  - dopamine
- Opiates
  - μ-receptor (6 variants)
  - dopamine
- Benzodiazepines & Barbiturates
  - GABA, dopamine
Mechanism of Effect

- Ethanol
  - GABA
    - α1 - sedative, amnestic, ataxic, anticonvulsant
    - γ1 - anticonvulsant
  - Glycine
  - Acetylcholine (nicotinic)
  - ATP
  - Glutamate
    - NMDA
    - non-NMDA
  - Voltage-gated
    - K+
    - Ca++
  - Dopamine

GABA: the receptor level

- from Mihic & Harris, 1997

The Architecture: The GABA Receptor

- GABA-A subtypes:
  - α, β, δ, ρ, σ, γ
    - α2 - antianxiety
    - α1 - sedative, amnestic, ataxic, anticonvulsant
    - γ6 - associated with sleep
    - β3 - hyperresponsiveness, seizure threshold, severity of alcoholism
    - γ2L - intoxication
  - Final effects dependent on subunit composition and post-translational modifications
Mechanism of Effect

- Marijuana
  - CB1 receptors
- Antidepressants
  - SSRIs
    - Serotonin
    - Older meds like paroxetine (Paxil)
  - Mixed receptors
    - Serotonin, norepinephrine
    - Newer meds like citalopram (Celexa)

How does Effect translate to Addiction?

Neural Reward Circuits Important in the Reinforcing Effects of Drugs of Abuse

Known cellular, genetic markers with behavioral correlates:
- Serotonin Transporter Gene (SLC6A4)
  - Chromosome 17p11.2
- D2R receptor:
  - Chromosome 11p15.5
- Alcohol-induced hypothermia, consumption, amphetamine, morphine responses:
  - Chromosome 17 (5-HT1B)
- Susceptibility to effects of cocaine:
  - Chromosome 1p (DRD4)
- Opioid effects:
  - Chromosome 2 (opioid receptor)
  - Flushing, initial serum load of alcohol, male vs. female differences, brain wave oscillations
  - Chromosome 4q (alcohol dehydrogenase)
- Effects of alcohol, BZ, barbiturates:
  - Chromosome 4q (GABA-A, GABA-B)
  - Chromosome 15 (GABA-B)
- Serotonin level:
  - Chromosome 11 (tryptamine hydroxylase)
- Severity of Alcoholism:
  - Chromosome 16

Breaking news from the Human Genome
- DNA regions with susceptibility genes:
  - Chromosomes 1, 2, 7
- DNA regions with protective genes:
  - Chromosome 4
- DNA regions affecting co-morbid depression:
  - Chromosome 7
  - Depression alone
  - Chromosome 2
- DNA regions affecting P300 electrophysiology:
  - Chromosomes 2, 5, 6, 13

For further information from the Human Genome, see The Collaborative Study on the Genetics of Alcoholism (COGA):

From the Garden of Eden
The Y-problem: 5HT transporter

The X-factor

- Chromosome 4 - Alcohol dehydrogenase polymorphisms (ADH2)
- Assures:
  - higher serum alcohol levels in females for equal oral ingestion as males
- Results in:
  - 50% females vs. 33% male skeletal muscle clinical weakness, histologically proven
  - 33% male and female cardiomyopathy (LEF)
  - Female CM at 60% male lifetime dose of alcohol

- Blume, 1986
- Enoch and Goldman, 1999
- Urbano-Munoz et al., 1995

How does progression occur, even in the absence of usage?
Mother Nature never forgets, once the lesson is learned!

How do cross-tolerance & cross-dependence occur?
The conventional wisdom is "one drug, one receptor"

The Architecture: The Synapse

- from Mihic & Harris, 1997

Cross-tolerance: the receptor level

- from Mihic & Harris, 1997
How does craving occur? How does one substance trigger a craving for another? (i.e., relapse)
The Endocannabinoid System and Obesity

- EC system activation is associated with both central mechanisms (increased appetite) and peripheral effects (stimulation of adipogenesis and fat accumulation).
- Overactive EC system in tissues controlling energy balance may contribute to development of obesity and associated cardiovascular and metabolic risk factors.
- May be caused by high-fat diets.
- May be reversed by insulin resistance associated with obesity.
- Peripherally active EC system reactivity may explain why CB1 blockers may affect peripheral tissues, such as adipose tissue.
Interactions among Hormonal and Neural Pathways That Regulate Food Intake and Body Fat Mass

Neural Reward Circuits Important in the Reinforcing Effects of Drugs of Abuse

Hypothalamic Endocannabinoid Levels in Relation to Fasting and Eating
Physiologic Effects of the Endocannabinoid System

- Affect a number of physiologic processes:
  - Increased feeding behavior
  - Memory and learning
  - Immune and inflammatory responses
  - Neuroprotection
- Summary of effects: Relax, eat, sleep, forget and protect

Cessation of endocannabinoid natural (or exogenous) stimulation results in withdrawal and resultant reversal of "Relax, sleep, eat, forget and protect"

Effect of the endocannabinoid system on other drug systems
- Alcohol
  - CB1 receptor "knock out" mice do not withdraw but have normal responses to alcohol administration
- Polysubstance iv drugs
  - CB1 receptor gene allele expression correlates to iv drug usage in human studies
- Cocaine
  - CB1 blockade stops cocaine self-administration in mice
- Nicotine
  - CB1 blockade reduces nicotine self-administration in humans
The Endocannabinoid System

- may be the "missing link" in understanding cross-tolerance and craving.
- bridges between food, alcohol, opiates, cocaine, nicotine, marijuana
- explains H.A.L.T.! (the Big Book was right all along!)

Questions:
- Addicts/Alcoholics are:
  - Good people gone bad?
  - Healthy people become ill?
- Are there new classes of addictions?
Answers:

- Healthy people become ill!!!!!
  - ... but some are "loaded for bear" (or bear) from Day #1 of exposure
- Obesity
  - Meets addiction criteria for
    - exposure
    - tolerance
    - cross-dependence
    - withdrawal
    - craving

... and is mediated by the same neurophysiological system that mediates alcohol and other drug addiction and tolerance.

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We all get heavier as we get older because there's a lot more information in our heads. So I'm not fat. I'm just really intelligent and my head couldn't hold any more so it started filling up the rest of me!

That's my story and I'm sticking to it!

Thank you!!!
CAPTASA 2010 References

**Journal publications:**


**GENERAL REFERENCES and RESOURCES**


