The Molecular Basis of Drug Addiction Vulnerability

Edmund Azeriah Griffin, MD PhD
Assistant Professor of Clinical Psychiatry
Division of Neurobiology Brain and Behavior
Department of Psychiatry
Columbia University
Muscle anatomy/biology: development, trauma, and physical therapy
-useful metaphor for understanding neurobiology and relevance to treatment

1. **Multi-modal processing**: a simple movement requires coordinated action of multiple muscle groups
2. **Nature/nurture**: capacity for certain movements (e.g. strength) is governed by gene-environment interaction at the level of the single muscle cell
3. **Plasticity**: muscles finely tuned to environment; few invasive treatments are efficacious without (physical) therapy
4. **Development**: risk for severe trauma AND capacity for rapid healing greatest during developmental “windows”

An understanding of these principles results in better/targeted treatment (provider) and improved engagement/compliance (patient)
Multi-level processing

The brain is organized into modular systems which mediate adaptive (and sometimes maladaptive) responses to the environment based upon prior experiences. Understanding how these prior experiences are organized biologically is central to devising effective interventions.
Plasticity varies by brain region, and by age

Implications:
1. In the adult, most psychosocial interventions intervene at level of neocortex (“top down”)
2. In adult: only highly salient environmental stimuli (trauma, cocaine) facilitate changes in limbic system
3. In developing brain: limbic regions are highly responsive to environment, but neocortex less responsive (does not develop until early 20’s)
Nature/Nurture and the Synapse: new synapse formation is the building block of behavioral adaptation

Implications
1. Nature (genes in the nucleus) and nurture (environmental stimuli) converge at single cell level to form or not form a stronger synapse in response to a stimulus

2. Procedural memory is additive, never subtractive; once a synapse is strengthened, only a NEW (inhibitory) synapse can make it weak again (...meaning that previously extinguished behaviors always have the potential to re-emerge)
Development: Neuronal pruning mediates neuroplasticity in the developing brain

Implications

1. “Developmental Window” of higher plasticity (enhanced sensitivity to environmental input) during the critical period due to:

   activity dependent pruning
   +
   activity dependent gene expression
Neurobiology of addiction vulnerability

The Human Brain

Input Stimulus

Addiction (15%)

Recreational (85%)

Abstract Thought
Concrete Thought
Attachment
Sexual Behavior
Emotional Reactivity
Motor Regulation
"Arousal"
Appetite/Safety
Sleep
Blood Pressure
Heart Rate
Body Temperature
Epidemiology of addiction vulnerability

Input Stimulus
- Prior alcohol use
- Trauma
- Poverty
- Parenting
- Co-morbid PTSD, depression

Recreational (85%) cocaine use

Cocaine Addiction (15%)

The Human Brain

Abstract Thought
Concrete Thought
Affiliation
Attachment
Sexual Behavior
Emotional Reactivity
Motor Regulation
“Arousal”
Appetite/Safety
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Blood Pressure
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Body Temperature

B. Perry, MD
The Gateway Hypothesis of sequential drug abuse progression.
The Gateway Hypothesis: questions to be resolved

1) Is the order of the use between different drug classes socially or biologically determined?

2) If biologically determined, what are the cellular/molecular mechanisms?

Addressing these questions could:
* reveal new insights into pathophysiology of addiction
* identify new molecular targets for treatment
1) Address the Gateway Hypothesis in the absence of social factors known to influence the development of addiction in humans

2) Parameters of drug exposure can be varied to gain mechanistic insights
   - the order reversed from cocaine to gateway drug
   - degree of overlap/co-exposure of gateway drug and cocaine varied

3) Causality: Target specific pharmacological and genetic perturbations to test mechanistic hypothesis
Cocaine Self-Administration:
Does alcohol pre-exposure enhance compulsive cocaine use (use despite foot shock)?

Variable Shock Compulsivity Test

- Lever press 1 = Blue warning light
- Lever press 2
- Lever press 3
- Lever press 4 = foot shock
- Lever press 5 = cocaine reward

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Sequential Paradigm

Does prior, chronic alcohol use enhance compulsive cocaine self administration?

Does prior, chronic alcohol use enhance compulsive sugar pellet self administration?
Alcohol pre-treatment does NOT enhance compulsive lever pressing for natural reward in *food restricted* animals.
Chronic alcohol use enhances compulsive cocaine self-administration
What is the underlying neurobiology of alcohol-mediated increase in cocaine addiction vulnerability?
Neuroanatomy: Addiction is a disease of Learning and Memory

Cocaine acts by changing synaptic connections
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Cocaine acts by changing synaptic connections
Genes (DNA) exist in silent or active form, depending on epigenetic modulators.
Nicotine inhibits HDAC activity, “releasing the breaks” on cocaine-induced gene activation.
Does prior chronic alcohol use enhance cocaine-induced expression of proteins involved in new synapse formation?
Does prior chronic alcohol use enhance cocaine-induced expression of proteins involved in new synapse formation?
Chronic Alcohol use enhances cocaine induced gene expression
Which HDAC is inhibited?
Chronic Alcohol use creates permissive epigenetic environment accumulation of HDAC4 in the nucleus
HDAC4 as a node
A direct test of the role of HDAC4 as a “gatekeeper” of cocaine addiction vulnerability

MC1568 Chemical Structure

10 Days  21 Days

- cocaine self administration (FR5) 9am - 12pm
- Vehicle (IP) 1pm
- MC1568 (0.5mg/Kg IP) 1pm

sacrifice for western blot
progressive ratio assay
compulsivity assay
Selective degradation of HDAC4 enhances compulsive cocaine self-administration
IMPLICATIONS 1: Chronic Alcohol use promotes degradation of nuclear HDAC4 in the nucleus accumbens.
How does the PATTERN of alcohol use effect cellular compartmentalization of HDAC4?
IMPLICATIONS 2: Intermittent pattern alcohol use
- greater inhibition of HDAC4 (than daily alcohol use)
- enhanced compulsive cocaine use vulnerability
Future Directions

1. Adolescent exposure to alcohol
2. Other risk factors (such as social isolations, PTSD)?
CONCLUSIONS

1. Animals with a history of chronic alcohol use have enhanced compulsive cocaine self administration (use despite aversive consequence)

2. Alcohol, like nicotine, inhibits HDAC activity in nucleus accumbens resulting in permissive environment for cocaine-induced gene expression

3. Chronic alcohol use promotes degradation nuclear accumulation HDAC4

4. Direct inhibition of HDAC4 with selective HDAC inhibitor MC1568 recapitulates addiction-like behavior
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