Addiction Bench Research and its Clinical Translation

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Overview of Addiction

1. Addiction is a common disorder with a lifetime prevalence of nearly 15%.
2. Addiction is often a chronic and relapsing condition.
3. Addiction is a complex disorder with multiple psychological, biological, and genetic etiologies.
4. Addiction is treatable with effective psychotherapeutic (including extinction learning) and medication treatments.
Magnitude of Problem (USA)

- Nicotine - over 50 million dependent
- Alcohol - 12 - 18 million alcoholics and problem drinkers
- M.J. - over 3 million dependent
- Cocaine - 2-3.5 million dependent
- Heroin - 800,000 - 1 million dependent
- Prescription opioids – 2-4 million misuse
Narcotic Pain Reliever Misuse - Results from 2004-2008 SAMSHA Drug Warning Network

FIGURE 1. Rates of emergency department (ED) visits* for nonmedical use of selected opioid analgesics, by type — United States, 2004–2008

* Rates are per 100,000 population, and are adjusted for age, gender, and race.

Type of opioid analgesic: Fentanyl, Hydrocodone, Hydrocodone, Methadone, Morphine, Oxycodone


Legend:
- Fentanyl
- Hydrocodone
- Hydrocodone
- Methadone
- Morphine
- Oxycodone

Rate Scale: 0 to 50

Note: *Significant difference from 2004

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[Further analysis and data not shown]
Narcotic Pain Reliever Misuse-Results from 2008 SAMSHA Survey

Figure 2.3 Past Month Nonmedical Use of Types of Psychotherapeutic Drugs among Persons Aged 12 or Older: 2002-2008

- Pain Relievers
- Tranquilizers
- Stimulants
- Sedatives

Percent Using in Past Month

- 2002: 0.8
- 2003: 0.6
- 2004: 0.7
- 2005: 0.7
- 2006: 0.7
- 2007: 0.7
- 2008: 0.7
Cue and Contextual Reactivity is Important to Relapse in Addiction

Epstein et al. Psychopharmacology, 2006
Mechanisms - Neuroanatomy of Addiction

Kaplan et al., Pharmacol, Biochem & Behavior, 2011
Neurotransmitter Mechanisms of Drugs of Abuse

Neural Adaptations in Addiction

Figure 5

Dopamine-glutamate interactions in the striatum. The major neuronal cell type in both the nucleus accumbens (NAc) and dorsal striatum is the medium spiny neuron, which is, as implied by its name, characterized by dendritic spines. As shown, glutamatergic afferents from the cerebral cortex and dopaminergic afferents from the ventral tegmental area (VTA) or substantia nigra (SN) interact at spines in the NAc (colored box) and dorsal striatum permitting integration of information-rich sensorimotor data from the cortex with information about the motivational state of the organism from the midbrain. As shown in the inset (left panel), the glutamatergic afferents synapse on the heads of spines and dopaminergic afferents provide synapses “en passant” on the necks of spines, providing an arena for interaction.

Hyman et al., 2004
Use of conditioned place preference to measure addiction related behaviors

Phases of CPP:
Development
Expression
Extinction
Reinstatement

Cami and Farre, NEJM, 2003
Opiate Place Conditioning and Extinction: Experimental Timeline

The sequence of experimental procedures necessary to condition and extinguish a morphine place preference are shown from left to right in the schematic timeline above. ↑ = injection: Vehicle, Morphine (10 mg/kg).
Proteins at the Postsynaptic Density - Dillon and Goda (2005)
Pharmacotherapies which Regulate Plasticity and in the NAc Signaling may Enhance Cue Extinction Efficacy

- NMDA receptor agonists e.g. D-cycloserine
- AMPA receptor agonists e.g. N-Acetylcysteine Cystine prodrug, glutathione prodrug
- Plasticity agents e.g. Histone deacetylase inhibitors, actin cycling agents
Summary/Conclusions

• Morphine place preference is an animal model for conditioned drug reward and its extinction that occurs in human addiction.

• Morphine place preference produces activation of neurons in the NAc that are associated with reward conditioning and are reversed in extinction.

• Morphine CPP extinction produces reductions in NAc dendritic spine number and complexity.

• This model of drug reward and its extinction suggests neuroplastic mechanisms that can be utilized for the design of potential addiction-related pharmacotherapies.

• Now, the clinical translation into addiction pharmacotherapy…. 
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