Neuroscience of Alcohol Addiction

David W. Oslin, MD
Associate Professor
University of Pennsylvania, School of Medicine
And
Philadelphia, VAMC

Hazelden Research Co-Chair on Late Life Addictions
Introduction

- Alcoholism costs the nation $150 Billion / annum in the US. As such it is the most expensive addictive disorder.

- Alcoholism leads to increased mortality and morbidity

- Alcoholism is common with about 7 million Americans afflicted

- Worldwide alcoholism is the 7th leading cause of disability
Alcohol Effects

- 30% of inpatients have alcohol related problems
  - Have poorer outcomes
  - Surgical complications
- 20% of inpatient health care budget
- 50% fatalities from fire and MVAs
- 67% of homicides
- 35% of suicides
- Responsible for 100,000 deaths /yr
What is the current model?
Feel Better

I am full
  Couldn’t eat just one
  Tastes good

Already ate
  It was there

Was thinking about a snack

Don’t like
  Like
  It tasted good in the past
Model of Addiction

- Craving
- Reward / Euphoria
- Control
- Emotion

- Temporal - Parietal
- Ventral Tegmentum (dopamine)
- Nucleus Accumbens
- Hippocampus
- Orbital Prefrontal Cortex
- Memory

- Orbital Prefrontal Cortex
- Nucleus Accumbens
- Hippocampus
- Temporal - Parietal
- Ventral Tegmentum (dopamine)
- Nucleus Accumbens
Addiction is not one disease

What’s the evidence and how do we study this?
Alcohol Euphoria / Craving

- Alcoholics classically lose control after their first drink
- Their desire for alcohol after the first drink is much greater than before
- Dopamine and endogenous opioids (β-endorphin, enkephalin) are released by alcohol and mediate alcohol euphoria

- **Genetic factors**
  - Vulnerability: Enhance dopamine and natural opioid responses to alcohol and increase its rewarding effect
Alcohol Euphoria / Craving

State / Trait Craving

Alcohol-Induced Craving

Cue-Induced Craving

Stress-Induced Craving
Stress and Cue-Induced Alcohol Craving in Abstinent Alcoholics

**Stress**

**Alcohol Cue**

**Neutral**

Group Difference: $F(1,55) = 81.13, p < .0001$ (AD > HC in S and Cue Response, $p < .0001$)

Group X Condition: $F(2,110) = 12.07, p < .0001$

Group X Timepoints: $F(7,385) = 3.95, p < .0004$

*Sinha et al., 2005*
Craving – Hazelden Study

• To describe the course of alcohol craving and affect (positive and negative) during the first 28 days of recovery from alcohol dependence.

• To test for associations between the course of alcohol craving and affect during the first 28 days of recovery and continued abstinence over the 6 months post discharge from the center.
Alcohol Craving by Latent Class

Day number from start

Higher Craving

Lower Craving

#1 n=17

#2 n=43

#3 n=37
6 Month Outcomes

ALCOHOL CRAVING CLASS

Survival Distribution Function

SSTAKA: al c_class=1Low  Censored al c_class=1Low  Censored al c_class=2Medium  Censored al c_class=3High  al c_class=2Medium  al c_class=3High

dur drink
Deconstructing the phenotype: An experimental medicine approach

- Premise: Alcohol reward in part due to dopamine response
- Hypothesis: Alcohol (most) rewarding related to genotype
An alcohol – endogenous opioid – DA cascade

(Tanda & Di Chiara 1998)

- EtOH releases endogenous opioid peptides in VTA
- Activation of OPRM1 receptors removes GABA "brake"
- Disinhibition of DA results
- OPRM1 blockade therapeutic by blocking EtOH induced DA release?
Naltrexone
(opioid and alcohol)

- Functions as an opioid receptor antagonist (mu >> delta or kappa)
- Alcohol consumption affects the production, release, and activity of opioid peptides (Herz, 1997)
- Opioid peptides mediate some of alcohol’s rewarding effects by enhancing midbrain dopamine release
- Opioid antagonists suppress alcohol-induced reward (Swift, 1999) and general consummatory behaviors (Boyle et al. 1998)
Meta-Analysis Oral Naltrexone vs. Placebo: Relapse to Heavy Drinking

Srisurapanont & Jarusuraisin, 2006
Long-Acting Naltrexone Results: Median Heavy Drinking Days

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median Heavy Drinking Days per Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>19.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.0</td>
</tr>
<tr>
<td>L-A Ntx 190 mg</td>
<td>4.5</td>
</tr>
<tr>
<td>L-A Ntx 380 mg</td>
<td>3.1</td>
</tr>
</tbody>
</table>

n = 624

48% decrease, p < 0.005
Clues on a Genetic Contribution

Monterosso et al 2001
Study Design

- Participated in 1 of 3 randomized controlled trials of naltrexone
- Minimum exposure of at least 6 weeks and adherent to medication on at least 50% of study days
- Consented to genetic study
Genetic Polymorphisms and Alcohol Treatment

Naltrexone / Asp40 Allele (A/G, G/G)

Naltrexone Asn40 Allele (A/A)

Placebo / Asp40 Allele (A/G, G/G)

Placebo / Asn40 Allele (A/A)

Oslin DW, et. al. 2003
COMBINE Study

Good Clinical Outcome (%)

Sample size:
- 31 Asp40 in the naltrexone group
- 35 Asp 40 in the placebo group
A+118G (Asn40Asp)

**Asparagine** asn – amide (neutral)

H2N-CO-CH2-CH(NH2)-COOH

**Aspartic acid** asp – (negatively charged)

HOOC-CH2-CH(NH2)-COOH

- Asp40 allele frequency of 13-20% (24.3 – 36% of European Americans have at least one copy)
“Alcohol-clamp”: a controlled way of exposing the brain to alcohol

(Ramchandani et al., Mol Psychiat 2010)
Dopamine release in ventral striatum is restricted to OPRM1 - 118G carriers

(Ramchandani et al., Mol Psychiat 2010)
Subjective as well
(Ramchandani et al., Mol Psychiat 2010)
h/mOPRM1 – 118G is sufficient to mimic increased alcohol-induced DA-release found in humans

(Ramchandani et al., Mol Psychiat 2010)
Increased alcohol-induced DA-release in 118GG mice predicts increased voluntary alcohol intake.

(Thorsell et al, in preparation)
Conclusions:
What it might mean for alcohol – related traits

- Alcohol leads to release of endogenous opioids
- This leads to activation of dopamine in ventral striatum
- Alcohol-reward cascade can be blocked with naltrexone
- Important in people with the right (or, rather, wrong) genetics

- A biological category: ”Opioid-sensitive” alcohol addiction?
- For others, other mechanisms may be important
But molecular mystery remains: 118G is e.g. a loss-of-function variant for morphine response.
Demand and consumed morphine dose in patients who received patient-controlled analgesia post arthroplasty

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Genotype frequency (%)</th>
<th>Demand in first 48 h</th>
<th>Dose in first 48 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>62</td>
<td>39.0 (24.7)</td>
<td>25.3 (15.5)</td>
</tr>
<tr>
<td>AG</td>
<td>27</td>
<td>35.3 (23.3)</td>
<td>25.6 (11.7)</td>
</tr>
<tr>
<td>GG</td>
<td>11</td>
<td>57.8 (24.7)</td>
<td>40.4 (22.1)</td>
</tr>
<tr>
<td>AA vs. GG</td>
<td></td>
<td>*P = 0.026</td>
<td>*P = 0.003</td>
</tr>
<tr>
<td>GG vs. AG</td>
<td></td>
<td>*P = 0.012</td>
<td>*P = 0.008</td>
</tr>
</tbody>
</table>

The morphine consumed doses are expressed as mean (standard deviation) milligrams.

Demand is the dose that represents the number of times the patient pushed the release button of the patient-controlled analgesia device.
Why should there be an alcohol promoting gene?
A trait that may be susceptible to selection: Maternal attachment, stronger in rhesus 77G allele carriers

*(Barr et al. PNAS 2008)*
Human translation:
Increased sensitivity to social rejection in
**OPRM1 118G carriers**

*(Way et al. PNAS 2009)*
Conclusions: What it might mean beyond alcohol

- Contributes to "hawk-like" traits:
  - bold / exploratory (mouse +; rhesus +; human ?)
  - more aggressive (mouse ?; rhesus +; human ?)
  - higher pain-threshold (mouse ?; rhesus +; human +)

- Alcohol – related traits coincidental byproducts late in evolution