Stress, Addiction, and Relapse Behaviors: The case of alcoholism

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"Why we like to drink": Similar to other drugs, alcohol can activate brain reward circuitry

(Gilman et al. J Neurosci 2008)
But, the brain changes as addiction runs its course: anti-reward mechanisms are recruited

Heilig & Koob, TiNS 2007
Key features of the post-dependent state:
Excessive drinking and up-regulated stress sensitivity
Excessive dependence-induced drinking that persists...

(Rimondini et al, FASEB J 2002)

Ethanol intake (g/kg/day)

3 week "detox"
...as does increased behavioral sensitivity to stress following a history of dependence  
(Valdez et al. 2003; Overstreet et al. 2002; Breese et al. 2005a,b; Sommer et al. 2008)
Human translation: Exaggerated brain responses to negative affective stimuli in recently detoxified alcoholics

(Gilman and Hommer, 2008)
Does stress make animals (and people) drink alcohol? The rat answer: Only if they have a history of dependence! (Sommer et al, Biol Psychiat 2008)
A range of anti-stress mechanisms may have potential to treat excessive post-dependent alcohol use.

<table>
<thead>
<tr>
<th>System</th>
<th>Principle</th>
<th>Compound / Partner</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticotropin-Releasing Hormone (CRH)</td>
<td>CRH1 - antagonism</td>
<td>Antalarmin (intramural); MTIP (Eli Lilly)</td>
<td>Under tox</td>
</tr>
<tr>
<td>Neurokinin (Substance P)</td>
<td>NK1 - antagonism</td>
<td>Eli Lilly</td>
<td>Phase Ila completed</td>
</tr>
<tr>
<td>Nociceptin</td>
<td>NOP - agonism</td>
<td>Confidential</td>
<td>Under tox</td>
</tr>
<tr>
<td>Neuropeptide Y (NPY)</td>
<td>Y2 - antagonism</td>
<td>Confidential</td>
<td>Preclinical evaluation ongoing</td>
</tr>
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</table>
A prime suspect stalking the dark side: CRH, the master signal of HPA-axis activation

(Holsboer, J Psychiat Res 1999)
Extensive extra-hypothalamic CRH systems mediate behavioral effects of CRH

- CRH mimics effects of stress on
  - feeding, exploration, anxiety
- Effects independent of HPA-axis
  - unaffected by dexamethasone or adrenalectomy
- Behavioral effects CNS-mediated
  - blocked by central injection of antagonist
A history of dependence recruits amygdala expression of CRH receptor 1…
(Sommer et al, Biol Psychiat 2008)
...and CRH1 antagonism selectively suppresses alcohol self-administration in post-dependent animals

(Hansson et al, PNAS 2006; Gehlert et al, J Neurosci 2007)
Stress Induced Relapse: Prevented by CRH1 blockade in post-dependent animals
(Gehlert et al, J Neurosci 2007)

Operant self-administration

Extinction (~15 days)

Foot-shock stress (10 min)

30 min reinstatment session

![Graph showing responses over 30 minutes for non-dependent and post-dependent Wistar rats with different MTIP doses.]
Substance P and its NK1 receptor

Substance P: an 11-a.a. peptide

Classically: A C-fiber transmitter involved in pain and inflammation
...but also widespread central distribution of SP and its NK1 receptor, visualized as displaceable binding.

(Frank and Hargreaves, Nat Rev Drug Disc 2003)

Placebo  Increasing doses of NK1-antagonist (aprepitant) →
Why NK1-antagonism?
Because it looks like "CRH-light"

- Pathological amygdala activation in alcoholism
  (e.g. Heilig and Koob, TiNS 2007; Sommer et al. 2008)

- SP release in rat amygdala mediates emotional stress
  (e.g. Ebner et al., PNAS 2004)

- Social stress activates human amygdala
  (e.g. Tillfors et al. Am J Psychiat 2001)

- Amygdala activation to social stress SP-dependent
Decreased voluntary alcohol consumption and conditioned place preference for alcohol in NK1R – null mutants

(George et al, Science 2008, Thorsell et al in preparation)
Let’s get (almost) real - simulating a relapse risk situation: Stress- and alcohol-cue induced craving
Attenuated challenge induced craving by the NK1 receptor antagonist LY686017... (George et al, Science 2008)
...and robustly attenuated cortisol response to the challenge  
*(George et al, Science 2008)*
Responses to negative affective stimuli (IAPS)
- recently shown to be exaggerated in alcoholics
- right anterior insula a responsive region
- structure encodes (primarily aversive) interoceptive cues
- of recent interest for cravings (Bechara et al, Science 2007)

Responses to positive affective stimuli
- recently shown to be dampened in alcoholics
- ventral striatum a responsive region
- structure encodes reward
Positive and negative affective stimuli (IAPS)

Positive

Negative
Attenuated fMRI responses to negative affective stimuli following treatment with the NK1 antagonist LY686017

(George et al, Science 2008)
Up-regulated fMRI responses to positive affective stimuli following treatment with the NK1 antagonist LY686017

(George et al, Science 2008)
Some conclusions

- **Reward from alcohol**
  - relevant in early stages of addiction
  - and / or in genetically susceptible individuals
  - limited value as treatment target

- **Stress systems**
  - are recruited over time as addictions develops
  - can be "pre-kindled" through genetic susceptibility
  - offer attractive treatment targets

- **Several anti-stress compounds currently in development**
### Lab. of Clinical and Translational Studies

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- **Brain imaging section**
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  - Jodi Gilman
- **Molecular pathophysiology section**
  - Annika Thorsell
  - Anita Hansson
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- **Primate section**
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### Eli Lilly:

- Don Gehlert
- Johannes Tauscher
- John Brandt
- et. al