Sigma Receptors: New target for alcohol addiction?

Valentina Sabino, Ph.D.
Assistant Professor
Laboratory of Addictive Disorders
Dept. of Pharmacology and Exp. Ther.
Alcohol Addiction

- Over 15 million Americans are dependent on alcohol
- >100,000 deaths every year
- Alcohol & alcohol-related problems cost the U.S. economy $185 billion in health care & lost productivity each year
Different Stages of the Addiction Cycle

Chronic relapsing disorder

Compulsive Use—The Core Concept of Addiction:

- Hyperresponsiveness to stimuli predicting drug availability
  -- > Decrease of cognitive control (choice)
  -- > Exaggerated drive towards the drug.

- Addiction is associated not with an augmented pleasurable response to the drug but with an enhanced motivation to procure the drug.
- Addiction is associated with hypohedonia, i.e. pleasure deficit.
- Addiction is associated with a negative emotional state when access to drug is prevented.
Animal Models for the Different Stages of the Addiction Cycle

- Animal Models for the Binge/Intoxication Stage
  1. Oral or intravenous drug self-administration
  2. Brain stimulation reward
  3. Place preference

- Animal Models for the Transition to Addiction
  1. Drug taking in selected lines of drug preferring animals
  2. Dependence-induced drinking
  3. Escalation in drug self-administration with prolonged access
  4. Drug taking despite aversive consequences
Oral Ethanol Self-Administration in Rats

Oral Ethanol Self-Administration in Alcohol-Preferring Lines

Selective breeding has produced stable lines of rats that exhibit high vs. low voluntary alcohol consumption

- Voluntarily consume 5-8 g ethanol/kg/day
- Attain BALs of 0.05 – 0.25 g%
- Work to obtain ethanol
- Consume ethanol for its pharmacological effects (not taste or calories)
Ethanol vapor exposure: Model of transition to ethanol dependence

Self-administration training

Sweetened solution fading used to train animals to lever press for 10% EtOH vs. water.

Dependence induction

Chronic intermittent alcohol vapors (4+ wks)

Target blood alcohol levels (BALs): 175-250 mg/dl

Acute Withdrawal from alcohol vapors

Negative emotional state and hypohedonia:
- Anxiety-like behavior
- Reward threshold deficits and behavioral despair

Excessive drinking:
- 2-3 fold higher alcohol intake
- Increased motivation for alcohol

Ethanol vapor exposure: Model of transition to ethanol dependence
Neurochemical Circuitry of Alcohol Reward
Sigma Receptors

✓ 223 aa intracellular protein with very little homology with any other mammalian protein.

✓ Localized in the brain (particularly limbic areas and brainstem) and in the periphery (liver, spleen, heart, retina, gonades, etc.).

✓ Has two transmembrane domains at the ER with C- and N-termini in the lumen of the ER.

✓ Endogenous ligands: Neurosteroids
✓ Exogenous ligands: Several

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<tr>
<th></th>
<th>$\sigma_1$</th>
<th>$\sigma_2$</th>
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<td>40%</td>
</tr>
<tr>
<td>Heart</td>
<td>90%</td>
<td>10%</td>
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Sig-1Rs function as ligand-activated molecular chaperones at the mitochondrion-associated endoplasmic reticulum membrane.

Low conc. of Sig-1R ligands cause the dissociation of Sig-1Rs from another ER chaperone, BiP, allowing Sig-1Rs to chaperone IP3Rs at the MAM.

High concentrations of ligands cause the translocation of Sig-1Rs to the plasma membrane.

Inhibition of dendritic morphogenesis in Sig-1R-knockdown hippocampal neurons

Tsai S et al. PNAS 2009;106:22468-22473
Sig-1Rs and Psychostimulants

Sig-1R antagonists attenuate the rewarding effects of Cocaine:
- Attenuate cocaine-ind. Conditioned Place Preference (CPP);
- Attenuate cue-ind. reinstatement of cocaine seeking.

Sig-1R antagonists block the toxic effects of Cocaine and Meth:
- Reduce convulsions;
- Reduce lethality.

Sig-1R agonists:
- Potentiate drug-induced CPP but do not induce it per se;
- Are self-administered by cocaine-experienced rats.
- Increase the potency of cocaine in self-administration;
Questions...

-- Does the activation of Sig-1Rs mediate the reinforcing effects of alcohol?

-- Do Sig-1Rs contribute to binge-like and excessive drinking?

-- Is the high susceptibility to self-administer high ethanol levels associated with alteration of the Sig-1R system?
The Sig-1R Antagonist BD-1063 reduces excessive ethanol intake in sP rats

The efficacy of BD-1063 positively correlates with the individual ethanol intake under vehicle

**Fixed Ratio 1 sP rats**

**Progressive Ratio sP rats**

The Sig-1R Antagonist BD-1063 does not affect saccharin intake

Fixed Ratio 1
sP and Wistar rats

Sabino et al., *Neuropsychopharmacology* (2009); 34(6): 1482-93.
The Sig-1R Antagonist NE-100 reduces home-cage ethanol drinking.

NE-100 does not modify pharmacokinetics of ethanol.

NE-100 also reduces “Alcohol Deprivation Effect”

Day 0: Baseline (veh) abstinence ADE test (Veh / NE-100) Day 1 Day 7 Day 8

The Sig-1R Antagonist BD-1063 reduces ethanol intake in Ethanol-Dependent rats

Dependent rats were tested following 6 weeks of ethanol vapor exposure, 6-8 hr into withdrawal.

![Graph showing ethanol intake vs. dose of BD-1063](image)

Sabino et al., *Neuropsychopharmacology* (2009); 34(6): 1482-93.
Questions...

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The SigR Agonist DTG Induces Binge Drinking

The DTG effect is mediated by Sig-1Rs

Increases motivation to drink
Questions...

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Sig-1R mRNA is reduced in the Nucleus Accumbens of Alcohol-Preferring rats and Ethanol Dependent rats

Genetically Selected Rats
- Ethanol Naive

Ethanol Dependent rats
- 24-hr Withdrawal
Neurochemical Changes Associated with the Transition from Drug Use to Dependence

Within-system changes:

**INTOXICATION**
- Reward transmitters: Dopamine
- DA$_1$ receptor
- DA$_2$ receptor
- Opioid Peptides
- $\uparrow$ neurotransmitter
- $\uparrow$ neurotrophic factor

**DEPENDENCE**
- Reward transmitters: Dopamine
- DA$_1$ receptor
- DA$_2$ receptor
- Opioid Peptides
- $\downarrow$ neurotransmitter
- $\downarrow$ neurotrophic factor

$\uparrow\uparrow\uparrow$ Sig-1Rs
$\downarrow\downarrow\downarrow$ Sig-1Rs
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