Pharmacodynamics of Alcohol and Opioids: Pathways to Addiction and Euphoria

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Which are the pathways to Euphoria and Addiction

Which brain regions and which neurotransmitters are involved in Euphoria and Addiction
Dopamine in Drug Reinforcement

• Increased Dopamine in the NAcdb has been suggested to mediate the positive reinforcing properties of many drugs of abuse.

• If a drug increases Dopamine at the level of NAcdb it is likely that the drug will be abused.

• However, the reverse is not necessarily true. Drug reinforcement can occur in the absence of Dopamine in the NAcdb. The NAcdb can be lesioned and drugs can still be abused.

• Additional systems may be involved in reinforcement.
<table>
<thead>
<tr>
<th>Neurotransmitters</th>
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<tbody>
<tr>
<td><strong>Amino Acids</strong></td>
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<tr>
<td>Glutamate</td>
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<tr>
<td><strong>Biogenic Amines</strong></td>
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<tr>
<td>Dopamine</td>
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<tr>
<td>Serotonin</td>
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<tr>
<td><strong>Neuropeptides</strong></td>
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<tr>
<td>Opioid Peptides</td>
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<tr>
<td>NPY</td>
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<td><strong>Other</strong></td>
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<td>Endocannabinoids</td>
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The endogenous opioid system and the mesolimbic Dopamine system have been shown to interact in inducing drug reinforcement and addiction.
The Endogenous Opioid Peptide Family and Receptors

β-Endorphin → Enkephalin → Dynorphin

μ-opioid receptor  δ-opioid receptor  κ-opioid receptor

* Size of arrows indicates the affinity of the opioid peptides to receptors.
Endogenous Opioid and Dopamine System Interactions

**OPIOID - DOPAMINE INTERACTIONS**

- **Nucleus Accumbens**
  - Dynorphin
  - Enkephalin

- **A10 DA**
  - Dynorphin

- **VTA**
  - GABAa receptors
  - Inhibitory GABA (-)
  - μ-,δ-opioid receptors
  - Inhibitory β-endorphin

- **Arcuate N. of Hypothalamus**
  - Enkephalin
Ethanol and Opioids

Ethanol lacks specific binding sites (receptors) yet it has numerous effects in the central nervous system (CNS).

Ethanol’s effects in the CNS may be mediated by its effects on other neurotransmitters.

The Endogenous opioid system may mediate some of ethanol’s effects, such as those of reward and reinforcement.
Evidence of Ethanol-Opioid Interactions
Effect of Naltrexone on Alcohol Self-Administration in Monkeys

Altshuler et al. (1980) LifeSci 26:679
Effect of Naltrexone on Craving and Drinking in Alcohol-Dependent Human Subjects

Effect of Naltrexone on Maintenance of Abstinence to Alcohol in Humans

Alcohol will increase the release of opioid peptides in brain regions associated with the processes of reward and reinforcement.
Microinjections of opioid antagonists into specific areas of the brain (VTA) attenuate, or abolish alcohol induced increase of Dopamine release in the NAc

(Spanagel et al., 1990, Spanagel et al., 1992).

However, it is not known which opioid peptides are involved
PROPOSED HYPOTHESIS
If we accept that endogenous opioids mediate, at least in part, some of the reinforcing effects of ethanol

THEN
Acute ethanol exposure should alter the activity of distinct components of the endogenous opioid system.

THUS
↑ expression of opioid peptides and/or receptors
↑ binding of opioid ligands to receptors
↑ activity of opioid receptors
↑ release of opioid peptides from synapse

In brain regions associated with the processes of Reward and reinforcement.
OBJECTIVE OF THE PRESENTATION

Is to demonstrate that acute alcohol administration stimulates the release of opioid peptides

  - Endorphins,
  - Enkephalins and
  - Dynorphins

In brain regions associated with the processes of reward and reinforcement such as:

  - Ventral tegmental area (VTA)
  - Nucleus accumbens (NAcb)
  - Central amygdala (CeA)
In vivo Microdialysis
Experimental Design: *In vivo* Microdialysis

i.p. injection of saline or various doses of alcohol

- 120 -90 -60 -30 0 30 60 90 120 150 180 210 240

Flow rate Turned to 2.0 μl/min

2h Stabilization Period

Basal Release = Mean of the 4 baseline collections

Response = % change from basal release

Data is analyzed with a 2-way Mixed ANOVA + Tukey HSD
EFFECT OF ALCOHOL ON THE RELEASE OF OPIOID PEPTIDES AT THE LEVEL OF VTA
Basal Peptide Levels in Ventral Tegmental Area

pg / 50 μl

β-Endorphin  Enkephalin  DynorphinA1-8
Ethanol dose
- 0.0g
- 0.8g
- 1.2 g
- 1.6g
- 2.0g
- 2.4g

VTA β-Endorphin

Time in Minutes

β-Endorphin % of Basal Release

E/S

Jarjour et al Alc Clin Exp Res (under revision)
Jarjour et al Alc Clin Exp Res (under revision)
VTA Dynorphin

Dynorphin A 1-8 % Basal Release

Ethanol Dose
- 0.0g
- 0.8g
- 1.2g
- 1.6g
- 2.0g
- 2.4g

Time in Minutes

E/S

Jarjour et al Alc Clin Exp Res (under revision)
**VTA: Dose Dependent effect**

- Early long lasting increase of $\beta$-endorphin release (1.2; 1.6 and 2.0 g dose) supports its role in the inhibition of GABAergic neurons leading to the disinhibition of DAminergic neurons and increased DA release at the level of nucleus accumbens.

- Small delayed increase in the release of dynorphin peptides in response to 1.2 g ethanol dose Significance??

- No significant responses of enkephalin in the ethanol doses used.
Nucleus Accumbens

Dynorphin

A10 DA

GABAaa receptors

Inhibitory GABA (-)

β-endorphin

Arcuate N. of Hypothalamus

Inhibitory β-endorphin

VTA

µ-, δ-opioid receptors
Basal Peptide Levels in Nucleus Accumbens

pg / 50 μl

β-Endorphin
Enkephalin
Dynorphin A1-8
Ethanol Dose
- 0.0g
- 0.8g
- 1.6g
- 2.4g

N. Accumbens β-Endorphin

β-Endorphin % Basal

Time Post-Injection in Minutes

N.Accumbens Dynorphin

Dynorphin A1-8 % Basal Release

Ethanol

- 0.0g
- 1.6
- 3.2

Dose

- 0.8
- 2.4

Time in Minutes

-90 -60 -30 0 30 60 90 120 150 180 210 240

CONCLUSIONS

Nucleus Accumbens: Dose Dependent effect

- Delayed increase of $\beta$-endorphin release (2.4 g ETOH dose at 90 minutes) in agreement with previous findings by Olive et al. (2001)

- Early and long lasting increase of Enkephalin release (1.6g/kg dose)

- Early short lasting increase of Dynorphin release (3.2g/kg dose)
Nucleus Accumbens

A10 DA

Dynorphin

Dynorphin ??

GABAa receptors

Inhibitory GABA (-)

µ-, δ-opioid receptors

Inhibitory β-endorphin

Arcuate N. of Hypothalamus

VTA

Enkephalin
Central Amygdala
Opioids and Alcohol Consumption

The central division of the amygdala is part of a larger neural complex called the Extended Amygdala Complex consisting of:

- Central Amygdala
- Shell Region of the Nucleus Accumbens
- Sublenticular Substantia Inominata and
- Bed Nucleus of the Stria Terminalis

A role of the endogenous opioid system in central amygdala on alcohol consumption has been suggested by the observation that blocking the activity of the endogenous opioid system in central amygdala attenuates alcohol consumption (Heyser et al 1999; McBride 2002).
Opioid antagonist in central amygdala attenuates EtOH consumption

Basal Peptide Levels in Central Amygdala

- β-Endorphin
- Enkephalin
- Dynorphin A1-8

(pg / 50 μl)

Time post-injection in minutes
Lam et al. (2008). Psychopharmacology. Epub ahead of print

Time post-injection in minutes
CONCLUSIONS

Central Amygdala: Dose Dependent effect.

. Early long lasting increase of $\beta$-endorphin release (2.0; 2.4 and 2.8 g doses) supports the observation by Heyser et al. (1999) that a lower dose of opioid antagonist is required in the Central Amygdala than in the N. Accumbens to decrease alcohol consumption

. No significant responses of Enkephalin

. Delayed increase in the release of Dynorphin peptides in response to 2.8 g ethanol dose.
VTA 

Nucleus Accumbens

Arcuate N. of Hypothalamus

A10 DA

GABAa receptors

Inhibitory GABA (-)

µ-δ-opioid receptors

Dynorphin ??

Central Amygdala

β-endorphin

Inhibitory β-endorphin

Arcuate N. of Hypothalamus
GENERAL CONCLUSIONS (1)

Alcohol **INCREASES** the release of opioid peptides **BY DISTINCT BRAIN REGIONS.**
General Conclusions(2)
The dose inducing a response or maximum response seems to be different for the different opioid peptide systems and specific brain region.

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Maximum Response</th>
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<tbody>
<tr>
<td>VTA Endorphin</td>
<td>1.6 g Ethanol / Kg B.Wt.</td>
</tr>
<tr>
<td>VTA Enkephalin</td>
<td>No significant response</td>
</tr>
<tr>
<td>VTA Dynorphin</td>
<td>1.2 g Ethanol / Kg B.Wt.</td>
</tr>
<tr>
<td>NAC Endorphin</td>
<td>2.4 g Ethanol / Kg B.Wt.</td>
</tr>
<tr>
<td>NAC Enkephalin</td>
<td>1.6 g Ethanol / Kg B.Wt.</td>
</tr>
<tr>
<td>NAC Dynorphin</td>
<td>3.2 g Ethanol / Kg B.Wt.</td>
</tr>
<tr>
<td>C.Amy Endorphin</td>
<td>2.8 g Ethanol / Kg B.Wt.</td>
</tr>
<tr>
<td>C.Amy Enkephalin</td>
<td>No significant response</td>
</tr>
<tr>
<td>C.Amy Dynorphin</td>
<td>2.8 g Ethanol / Kg B.Wt.</td>
</tr>
</tbody>
</table>
CONCLUSIONS (3)

We must always keep in mind that,

The low sensitivity of the method in detecting low levels of release of the opioid peptides could lead to the false conclusion that a specific dose of ethanol has no effect on the release of specific opioid peptides by specific brain regions.

Large number of doses should be tested.
Impact of Genetic Factors on the Plasma $\beta$-Endorphin level under basal conditions in human

Low Risk = No Alcoholics in their Family
High Risk = Alcoholics (Father, Grandfather +++)

Low Risk
Low Genetic

High Risk
High Genetic

Plasma $\beta$-endorphin pg/ml
Effect of 0.75 g ethanol /Kg B.Wt. on the release of Pituitary β-Endorphin in Low Risk and High Risk Subjects
IMPORTANT COMMENTS
Genetically determined differences in ENDORPHINS may Play a role in the increased predisposition to develop Alcoholism by some individuals.

Differences in endorphins are not the only component of the endogenous opioid system associated with high alcohol consumption. SNP OF μ OPIOID RECEPTOR have been found to be associated with alcohol consumption.

Genetically determined differences associated with alcoholism have been found in OTHER NEUROTRANSMITTER SYSTEMS

Differences in components of either the opioid or other neurotransmitter system may not be inherited by all individuals genetically predisposed to develop alcoholism.
Most Important Contributors

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Thank you