Orexin neurons, reward and addiction: It all comes together in the lateral hypothalamus

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Orexin (hypocretin) neurons:

- located only in hypothalamus
- widespread projections
- mutations produce narcolepsy symptoms
- prominent hypothesis: arousal
Not all orexin neurons are created equal
Activity of orexin neurons in LH does not correspond to arousal rhythm

LH orexin neurons: Possible role in reward processing

• Orexin administration increases feeding
• Orexin neurons send projections to brain areas involved in reward (e.g., PFC, Nac, VTA)
• Lateral hypothalamus long implicated in reward functions

• Q: Are LH orexin neurons important in reward processing and addiction?
Place conditioning procedure

Conditioned place preference (CPP)

3 drug or food pairing days, balanced design
Preference tested next day, drug-free
Brains taken 2 hr after preference test for Fos measurements
Fos activation in orexin neurons with exposure to morphine environment

Preference scores correlate with percentage of LH orexin cells that are Fos+

<table>
<thead>
<tr>
<th>Groups:</th>
<th>Cell Types:</th>
<th>Percentage Fos+</th>
<th>Correlations R:</th>
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<tr>
<td>Morphine</td>
<td>Orx LH</td>
<td>48±2*</td>
<td>.72 p&lt;.01*</td>
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<td>55±6</td>
<td>.30 p=.34</td>
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<td>63±5</td>
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Conclusion: LH orexin neurons are potently activated in proportion to reward preference

Q: Could activation of LH orexin neurons be involved in drug-seeking and relapse?
Orexin antagonist attenuates expression of CPP
Drug-seeking during protracted withdrawal: 
Animal Model of Relapse

3 days of morphine CPP conditioning

Repeated testing for 1 to 3 weeks daily without drug to extinguish preference

CPP extinguished for 2 consecutive days

Stimulate LH orexin neurons to test for reinstatement (rat pancreatic polypeptide, rPP, microinjection in LH)

Brains taken for Fos staining 2 h after test for reinstate.
rPP in LH reinstates morphine preference

Correlation: rPP-induced reinstatement and % LH orexin neurons with Fos

\[ r = 0.99 \]

rPP-induced reinstatement is blocked by selective orexin antagonist

Orexin injected into VTA reinstates morphine preference

Orexin is also involved in plasticity and learning


Borgland et al, Neuron 49 (2006)
LH orexin neurons are stimulated during drug pairing.
Bilateral disconnection of LH orexin projections to VTA blocks acquisition of a morphine CPP

Unilateral excitotoxic lesion of LH + SB in contra VTA

Go see: Wimmer et al., poster 00-74
Monday PM
SUMMARY

• LH orexin neurons (but not other orexin neurons) are stimulated in proportion to reward preference.
• Blockade of orexin receptors attenuates expression of drug preference.
• Exogenous stimulation of LH orexin neurons reinstates extinguished drug preference (relapse).
• Orexin in VTA dopamine neuron area reinstates extinguished drug preference (relapse).
• Orexin projections from LH to VTA are critical for learning stimulus-drug relationships.

_Hypothesis:_ LH orexin neurons are involved in reward-based learning and memory
Reward-related inputs:
- Morphine
- Cocaine
- Food

Projections to forebrain and midbrain reward areas:
- VTA
- NAc
- Amy

Arousal-related inputs:
- Waking
- Stress

Projections to brainstem arousal areas:
- LC
- TMN
- PPT/LDT
Collaborators

Matt Wimmer
Glenda Harris
Toastmaster
Role of LH orexin neurons in reward-based learning and memory circuitry

Harris and Aston-Jones, TINS 29: 571-7 (2006)
Bilateral neurotoxic lesions of LH orexin neurons blocks acquisition of a morphine CPP