ROLE OF OREXIN IN FOOD-SEEKING: IMPLICATIONS FOR OBESITY

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Orexins are neuropeptides made exclusively in hypothalamus and orexin neurons project throughout the CNS (Peyron et al., 1998; Sakurai et al., 1998).

Orexin A and Orexin B bind to two g-protein coupled receptors, Orexin 1 receptor and Orexin 2 receptor.
DICHOTOMY OF OREXIN SYSTEM

- Orexin neurons in PFA/DMH regulate arousal whereas orexin neurons in the LH regulate reward processing (Harris et al., Nature 2005).
FOOD SELF-ADMINISTRATION MODEL
## FOOD SELF-ADMINISTRATION STUDIES

<table>
<thead>
<tr>
<th>Self-Administration</th>
<th>Veh</th>
<th>SB</th>
<th>SB</th>
<th>Extinction</th>
<th>Reinstatement</th>
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<tbody>
<tr>
<td>Sucrose + cues</td>
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<td></td>
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<td></td>
<td>(veh or SB)</td>
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<tr>
<td>No sucrose or Cues</td>
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<td>Cues</td>
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**OX₁R antagonist (SB-334867)**

![Food self-administration setup diagram](image-url)
ANTAGONISM OF OXR1 ATTENUATES SUCROSE SELF-ADMINISTRATION

Cason & Aston-Jones, Psychopharm 2012
ANTAGONISM OF OXR1 ATTENUATES CUE-INDUCED REINSTATEMENT OF SUCROSE-SEEKING

Cason & Aston-Jones, Psychopharm 2012
SUMMARY

• These results indicate that signaling at the OxR1 receptor is involved in pronounced sucrose reinforcement and reinstatement of sucrose-seeking elicited by sucrose-paired cues in food-restricted subjects.

• These findings lead us to conclude that conditioned activation of Orx neurons increases motivation for food reward during food restriction.

  This dysfunction of the orexin system may contribute to the high failure rates in dieting in obese individuals.
WHAT IS DRIVING OREXIN EFFECTS?

- Sucrose reinforcement has both a hedonic and caloric component, it remains unknown what aspect of this reward drives its reinforcing value.

- Examined the involvement of the orexin (Orx) system in operant responding for saccharin, a non-caloric, hedonic (sweet) reward, and in cue-induced reinstatement of extinguished saccharin-seeking, in ad libitum fed vs. food-restricted male subjects.
ANTAGONISM OF OXR1 ATTENUATES SACCHARIN SELF-ADMINISTRATION

Cason & Aston-Jones, in prep
ANTAGONISM OF OXR1 ATTENUATES CUE-INDUCED REINSTATEMENT OF SACCHARIN-SEEKING

Cason & Aston-Jones, in prep
These results indicate that signaling at the OXR1 receptor is involved in saccharin reinforcement and reinstatement of saccharin-seeking elicited by saccharin-paired cues regardless of food restriction.

These findings lead us to conclude that the Orx system is contributes to the motivational effects of hedonic food rewards, independently of caloric value and homeostatic needs.
FUTURE ANIMAL STUDIES

- Immunohistochemistry studies looking at immediate early gene, c-Fos, in orexin targets.
- Optogenetics to manipulate the orexin circuitry.
- Other ideas?
COLLABORATIVE IDEAS:

• Obese individuals have high plasma levels of Orexin-A that are positively correlated with body mass index (Heinonen et al. 2005).

• I would like to know:
  
  Are palatability ratings of food and ratings of hedonic hunger correlated with Orexin-A levels in obese individuals?

  Power of Food Scale (Lowe et al., 2009)

  RIA for Orexin-A

  Imaging studies?
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