Stress, Arousal and Addiction:
The hypocretin connection

Luis de Lecea, Ph.D.
Department of Psychiatry and Behavioral Sciences
Stanford University
Human narcolepsy-cataplexy

- Excessive daytime sleepiness
- Cataplexy
- Sleep paralysis
- Hypnagogic hallucinations
- Disturbed nocturnal sleep

Prevalence: 1/2000, onset during adolescence
Treatment: Psychostimulants (EDS) and Antidepressants (Cataplexy)
Narcolepsy is a disease of the hypocretinergic system.

**mRNA in situ Hybridization**

Hypocretin

MCH

Narcoleptic  Control  Peyron et al., 2000

Hcrt ko are narcoleptic

Chemelli et al., 1999

Abrupt arrest

Gradual arrest

"nodding"
Two new members of the incretin neuropeptide family

<table>
<thead>
<tr>
<th>Signal</th>
<th>Hcrt1</th>
<th>Hcrt2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34-mer</td>
<td>28-mer</td>
</tr>
</tbody>
</table>

**A**

**B**

<table>
<thead>
<tr>
<th>Protein</th>
<th>Sequence</th>
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<tbody>
<tr>
<td>Hcrt1</td>
<td>QPLPDCCRQKTCSCKLYELLHGAGNHAAGILT</td>
</tr>
<tr>
<td>Secretin</td>
<td>HSDGFTTSKLSRLDRSARLQRLLQGLVHS</td>
</tr>
<tr>
<td>VIP</td>
<td>HSDAVFTDNYTRLRQMAVKKYLNIN</td>
</tr>
<tr>
<td>Glucagon</td>
<td>HSQGTFTSDYSKYLDSRRAQDFVQWLMT</td>
</tr>
<tr>
<td>Hcrt1</td>
<td>HAAGILT</td>
</tr>
</tbody>
</table>

GILT motif

α-HELIX
Anatomy of the hypocretinergic system

(de Lecea et al., 1998; Peyron et al., 1998)
The hypocretins in hyperarousal
Hcrt and hyperarousal: acute stress

![Graph showing Hcrt 1 levels in different brain regions under control and restraint stress conditions.](image)

**Hcrt 1 (pg/mg protein)**

<table>
<thead>
<tr>
<th>Region</th>
<th>Control</th>
<th>Restraint Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothalamus</td>
<td>3000</td>
<td>7000</td>
</tr>
<tr>
<td>Dorsal Raphe</td>
<td>4000</td>
<td>6000</td>
</tr>
<tr>
<td>Locus Coeruleus</td>
<td>2000</td>
<td>3000</td>
</tr>
</tbody>
</table>

Fabre et al., 2003

Reyes et al., 2003
Hypocretins and stress response
CRF terminals contact HCRT cell bodies

CRF receptors are expressed in hcrt neurons

CRF depolarizes HCRT neurons through CRFR1

Winsky- Sommerer et al., 2004
Effects of Drugs of Abuse on Subregions of the Extended Amygdala

- Nucleus Accumbens Core
- Nucleus Accumbens Shell
  - Cocaine
  - Amphetamines
  - Opiates
  - Ethanol
  - Nicotine
  - THC

- Caudate-Putamen
- Dorsal/Ventral Pallidum
- Medial Amygdala
- Optic Tract
- Lateral Olfactory Tract
- Anterior Commissure
- Bed Nucleus of the Stria Terminalis
  - Cocaine
  - Ethanol
- Central Nucleus of the Amygdala
  - Cocaine
  - Ethanol
  - Opiates
  - Nicotine
  - THC
Does Hcrt affect brain reward?
Hypocretin negatively regulates brain reward

Hcrt-1 (5μg; n=9)
Hcrt-1 + anti-Hcrt-1 (n=5)
Saline (n=5)
Cocaine self-administration
Hypocretin-1 does not affect cocaine intake
Hcrt-1 does not change motivation for cocaine intake

- Number of infusion earned
- Total number of responses
- Final ratio attained
- Percent of the baseline

Sessions
- Saline infusion
- Hcrt-1 5ug infusion

- Saline
- Hcrt-1 5ug
- Day after
The addiction spiral

- Acquisition
- Dependent state
- Relapse
- Negative effects of withdrawal

Positive effects on brain reward
Neuronal circuits involved in reinstatement

Shalev and Shaham, 2003
Hcrt1 (icv) reinstates cocaine-seeking behavior

<table>
<thead>
<tr>
<th>Cocaine SA Baseline (5 sessions)</th>
<th>Extinction (13 sessions)</th>
<th>Hcrt-1 challenge (1 session)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active lever responses</td>
<td>Inactive lever responses</td>
<td></td>
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</tbody>
</table>

- **Average cocaine sessions**
- **Average last 3 extinction sessions**
- **Hcrt-1 (1.5 nmol) challenge**
Blockade of both CRF and NE prevents Hcrt-induced reinstatement
The BNST is involved in hypocretin-induced reinstatement

- **Hcrt-1 (0.25 µg per side)**
- **D-Phe (0.5 µg per side)**
- **+ Hcrt-1 (0.25 µg per side)**

Reinstatement in % of extinction

(n=5)
• Stress induces CRF
• CRF stimulates hcrt neurons

• CRF produces reinstatement
• Hcrt produces reinstatement

• CRF-R antagonists block stress-induced reinstatement

• Do Hcrt antagonists block stress-induced reinstatement?
Hcrt receptor antagonist blocks stress-induced reinstatement
Acknowledgements

TSRI

- Ben Boutrel
- Raphaëlle Winsky
- Chisa Suzuki
- Covadonga Pañeda

Yale

- George Koob
- Paul J. Kenny
- Athina Markou

Tamas Horvath