The Neurobiology & Pharmacology of Sleep: An Overview
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Emerging Science in Sleep: Discovery of Orexins

- Orexin (hypocretin) discovered by 2 groups (Yanagisawa et al 1999, de Lecea et al 1998) and linked with canine narcolepsy (Mignot et al 1999)
- Orexin peptides bind with different affinities to OX1R and OX2R, which are differentially expressed in the CNS

Emerging Science in Sleep: Discovery of Orexins

- Orexin signaling plays a key role in increasing arousal across species
- Orexin neurons (<100 thousand) are highly localized to the hypothalamus

Orexins as a Key Stabilizer of Wakefulness

Sleep Abnormalities in Orexin-KO Mice

- DKO, double knock-out; KO, knock-out; OX1R, orexin-1 receptor; OX2R, orexin-2 receptor

3: Sakurai T. Nat Rev Neurosci. 2007;8:171-181

4: Sakurai T. Nat Rev Neurosci. 2007;8:171-181
Orexin Signaling Throughout the Day

Orexin signaling is active during wakefulness and silent during normal sleep

Wake Promotion: Arousal Promoting Regions of the Brain

<table>
<thead>
<tr>
<th>Locus</th>
<th>Neurotransmitter(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-BBS interstitial nucleus of the posterior thalamus</td>
<td>Acetylcholine (ACh)</td>
</tr>
<tr>
<td>Lateral interpeduncular nucleus</td>
<td>ACh</td>
</tr>
<tr>
<td>Locus coeruleus (LC)</td>
<td>Noradrenaline (NA)</td>
</tr>
<tr>
<td>Raphe nuclei</td>
<td>Serotonin (5-HT)</td>
</tr>
<tr>
<td>Ventralalateral prefrontal cortex gray matter (VLPFC)</td>
<td>Dopamine (DA)</td>
</tr>
<tr>
<td>Substantia nigra</td>
<td>L-DOPA</td>
</tr>
<tr>
<td>Lateral hypothalamus (LH)</td>
<td>Orexin (ORX) or melanin-concentrating hormone (MCH)</td>
</tr>
<tr>
<td>Isolated forebrain (IF)</td>
<td>γ-aminobutyric acid (GABA) or acetylcholine (ACh)</td>
</tr>
</tbody>
</table>

Sleep Promotion: Ventral lateral preoptic nuclei (VLPO)

Saper's Flip-Flop Switch: Describing the Transitions Between Wake and Sleep