Neurobiology of Sleep and Waking:  
Waking III  
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The orexin system

Orexin A and B

Sakurai et al., Cell 92: 573-585, 1998
Release of orexin

Activation of orexergic neurons by photostimulation

Genetic targeting of channelrhodopsin-2 to orexin neurons

Orexin and performance

Nasal orexin, more than i.v. orexin, rescues performance in difficult trials
**Orexin antagonists and sleep**

**Rats**

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<th>ACT-078573</th>
<th>(Actelion Pharmaceuticals)</th>
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**Dogs**

**Humans**

**Orexin and Parkinson’s disease**


**The Hypocretin/orexin system – Summary**

- H/O is probably important for maintaining waking

- H/O probably affects waking/EEG activation through both receptors 1 and 2

- H/O probably acts through many regions, one of which is the locus coeruleus

- H/O may increase performance, but it remains to be proven that H/O antagonists can induce physiological sleep
The Dopamine system

- DA is clearly involved in the regulation of locomotor activity and motivation, but its role in sleep regulation is complex and still unclear.
- Early findings suggested no direct role based on the absence of changes in firing rates in VTA cells across the S/W cycle; however...
- VTA cells show prominent burst firing during waking appetitive behavior and REM sleep (Dahan et al., 2007).
- Amphetamines and modafinil act at least partially via DA.
- KO mice lacking the DA transporter (DAT) show more waking and less sleep in the light phase.
- D1 receptor agonists increase waking and decrease NREM and REM sleep, D1 antagonists do the opposite.
- D2 receptor agonists increase sleep at low doses (via autoreceptors?), but increase waking at high doses (via post-synaptic D2 receptors?).


Waking systems: brain mechanisms of arousal

modified from Jones B, SRS Basic of Sleep Guide

Glutamate

Jasper et al., Science 147: 1448, 1965
There is no "necessary" waking system.

Denoyer et al., Brain Res 529: 297-303, 1991

Slow EEG for 24h
Hypothermia for 2 days + hypotension
Coma for 2-3 days

The discovery of ARAS,
the Ascending Reticular Activating System -3


A
B
C or D

There is no "necessary" waking system

Sleep Centers or Systems?

...low frequency (8-14Hz) peripheral or central stimulation... induce synchronized waves over the cortex even when applied to structures known to have activating properties. The variety of structures implicated in "sleep" simply because their stimulation led to EEG synchrony extends from the neo and allo cortices down to the medulla...Thus, if we accept this criterion, we would be forced to conclude, as remarked by Jouvet (1967) that "the whole encephalon has hypnogenic properties".

(Steriade and McCarley, Brainstem Control of Wakefulness and Sleep, 1990, p.18)

The solitary tract nucleus in the medulla

(Batini et al., Persistent patterns of wakefulness in the pretrigeminal midpontine preparation. Science 128: 30-32, 1958)
The solitary tract nucleus in the medulla


Sleep and Waking Systems

The basal forebrain/hypothalamic sleep promoting system

The basal forebrain and sleep

Griti et al., Neuroscience 146: 1591-1604, 2006
The basal forebrain and sleep


The basal forebrain and sleep


The preoptic area and sleep

The preoptic area and sleep

Szymusiak et al., Brain Res 803: 178-188, 1998

The preoptic area and sleep

Suntsova et al., J Physiol 543: 665-677, 2002

The preoptic area and sleep

Suntsova et al., J Physiol 543: 665-677, 2002
The preoptic area and sleep

Suntsova et al., J Physiol 543: 665-677, 2002

Most sleep-active neurons in the preoptic area are GABAergic

Gong et al., J Physiol 556: 935-946, 2004

The preoptic area and sleep

Gong et al., J Physiol 556: 935-946, 2004
**The “sleep-wake switch”**

McGinty and Szymusiak, Principles and Practice of Sleep Medicine, 2005, p. 175
Saper, Nature Insight 2005

**Sleep-promoting systems**

James B. Principles and Practice of Sleep Medicine, 2005, p. 139

**Sleep homeostasis**

after sleep deprivation, sleep becomes:
- longer
- more intense (more slow waves in NREM sleep, fewer brief awakenings)
- what are the underlying mechanisms?
Basal forebrain: cholinergic vs non-cholinergic cells

Loss in caudal BF after bilateral IBO lesions:
- 43% PARV+ cells (non-cholinergic)
- 21% cholinergic cells
- 41% cortical AChE staining
- No effects on sleep/waking states after 1-27 days post-lesion
- Persistent increase in SWA in all states (negatively correlated with loss of PARV+ cells)

Loss in caudal BF after bilateral SAP lesions:
- 69% cholinergic cells
- 11% PARV+ cells
- 84% cortical AChE staining
- Transient increase (13%) in NREM sleep (back to normal by day 17)
- No effects on EEG power spectrum in any state


Bilateral IBO and SAP lesions:
- Similar changes after 6h SD performed at day 27
- Reduced increase in NREM duration
- Same peak SWA, but more rapid decline after 4h of recovery sleep


The cholinergic basal forebrain and sleep

Blanco-Centurion et al., J Neurosci 26: 8092-8100, 2006
CONCLUSIONS

Cholinergic BF neurons support waking, but are not essential.

The “slowing” of the EEG after BF lesions is due to loss of non-cholinergic (presumptive glutamatergic) cells.

All BF lesions affect to some extent the sleep rebound after sleep deprivation, whether or not they include mainly cholinergic neurons.