Normal Sleep:
Neurobiological Mechanisms
Objectives

- Why sleep?
- What makes us sleep?
- How is normal sleep achieved?
- When do we sleep?
...why do we need sleep?

Biologic and Homeostatic Drives

• …eat to satisfy hunger, and provide nutrients

• …sleep to feel rested, and provide….?
Totals sleep time is inversely proportional to body size

Sleep time in mammals

Normal sleep Architecture

- Sleep entered through NREM sleep
- Sleep cycles: NREM and REM sleep alternate thru the night in the cyclic fashion
- First Cycle
  - average length 70 - 100 minutes
- Second and later cycle
  - average length 90 - 120 minutes

- Stage 1: 2-5%
- Stage 2: 45-55%
- SWS: 15-20%
- REM: 20-25%
Sleep (NREM and REM) is present in ancestral organisms even fruit flies and has some biologic advantage.

Unresolved issues: Sleep in birds and mammals may have evolved independently.

Developmentally sleep and REM sleep in particular are often expressed at a high level before the emergence of NREM and adult patterns of wake/sleep transition.

Sleep is embedded in a circadian rhythm.
Current theories

Primary
• Remodel synaptic plasticity induced by wakefulness.
• Restore brain energy stores.

Secondary
• Consolidation of certain kinds of learning
• Endocrine functions
• Restore body systems
Why we need NREM?

Reverse toxic effects of Wakefulness

– ROS are found in hypothalamus but not on neo-cortex
  • Sleep enables decline in ROS production and facilitates replacement of cellular components of neurons and ganglia

– Protein synthesis and neurogeneration
  • SWS is associated with higher rates of protein synthesis throughout the brain

Memory consolidation: conceptual

Ramp P, Smith CT *Physiol Behav* 1990
Why we need REM?

- What is REM?
  - State of high brain metabolic and neuronal activity rates
  - Reduced muscle tone
  - Diminished thermoregulation

Reinoso-Suarez F, *Sleep Medicine Reviews*, 2001
Why we need REM?

- REM amount/TST correlates with immaturity at birth
  - Giraffe & guinea pigs (precious) versus the platypus (atricial)
- Monoamine “replenishment”
  - Transport mechanisms & receptors
- Prime for awake state
- Memory
  - Complex Motor performance

Siegel J, PLoS Biol, 2005
Madhu K, Metabolism Clinical and Experimental, 2006
REM and Developmental Plasticity

Development (MD is monoocular light deprivation)

<table>
<thead>
<tr>
<th></th>
<th>Cell size non-patched eye</th>
<th>Cell size from patched segment</th>
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<tr>
<td>MD w/ REM deprivation</td>
<td>233.92</td>
<td>206.21*</td>
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<tr>
<td>MD Non-REM deprived</td>
<td>274.61</td>
<td>250.36</td>
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- Endogenous activity that tend to prevent abnormal brain connections
- Prevents programmed cell death
- Eliminating superfluous brain matter

How or what makes us sleep?

Starting with neurotransmitters and wakefulness
Wake Neurotransmitters

**Histamine (TMN)**
- Determinant of wakefulness & consciousness
- Involved in forebrain arousals
- Inactive in REM

**Adrenergic (Various)**
- Regulate awake muscle tone/activity
- Inactive in REM

**Dopamine (Ventral tegmentum of Midbrain)**

**Serotonin (LC and midbrain raphe)**
- Highest in Wake/ Lowest in REM
- Regulate muscle tone in REM (inhibits eye movements of REM and muscle twitch generation)

**Hypocretin (perifornical region of lateral Hypothalamus)**
- Drive the other arousal NT’s

Saper *Trend Neurosci* 2001
Reticular Activating System (RAS)

dorsal and ventral pathways

Acetylcholine
- Basal forebrain
- LDT/PPT
  - Thalamic relay (+)
  - Reticular nucleus of the Thalamus (-)

Histamine
- Broad activation
- Specific inhibition of VLPO sleep

Aminergic system

Saper *Trend Neurosci* 2001
Orexin: Awake & Sleep

Activates histaminergic, serotonergic, and cholinergic systems

Periformical region of the hypothalamus

PPT/LDT

Activates histaminergic, serotonergic, and cholinergic systems Orexinergic
Awake & Sleep NT’s

- Serotonin
- Adrenergic
- Histamine
- Orexinergic

ACH Dopamine

GABA
Sleep transitions from Wake NT’s

- Serotonin
- Adrenergic
- Histamine
- Orexinergic

Adenosine

GABA
Hypothalamic VLPO control: Flip-Flop

GABA “Sleep-on”  Reticular Activating System (RAS)  “Sleep-off”

Kryger, *Principles of Sleep Medicine*, 2006
Reticular Activating System

Lu et al., 2002, 2006
GABA “Sleep-on”

Lu et al., 2002, 2006
Sleep Arousal

FLIP-FLOP
Prevents intermediate states

ORX

VLPO

TMN LC/DR

Stabilizer

NE 5HT
Histamine

Awake

Lu et al., 2002, 2006
Saper et al., 2006
Lin et al., 1999

nREM
REM (VLPO-ex)
PPT LPT
Flip-flop Switch

nREM ← VLPO ← REM ← TMN → NE, 5HT Histamine

OREXIN

Sleep

Wake
Ventrolateral peri-aqueductal grey matter

Lu et al., 2006
Peri-aqueductal grey matter - Pons

5-HT

hypoqueretin

Timing of REM

Nor-adrenergic

Acetylcholine

REM-off

vIPAG

Lateral Pontine Tegmentum

REM-on

Sub-Laterodorsal Nucleus


Peri-aqueductal grey matter - Pons

LD/PPT

Lateral Pontine Tegmentum

Hypocretin

Sudden, strong emotions → Limbic System → Hypocretin

RAS 5-HT, NA, Hist

Norepinephrine, 5-HT

Glutamate*, Glycine** → Motor neurons

Postural muscles

Excitation

Inhibition

“REM-on”

* Adapted from Siegel J, 2006

** Lateral reticulospinal tract

*magnocellular nucleus of medulla

* Adapted from Siegel J, 2006
When do we sleep?
Cues for sleep: Circadian “zeitgebers”

- Light
- Food
- Social
  - Exercise
- Indirect
- Melatonin
- Adenosine
Hormonal rhythm control

**Light:**
1. Strong phase shifter
2. MLT peak is proportional to light portion 24h/cycle
3. Pulse of light at peak MLT levels produces rapid suppression

Adenosinergic modulation of basal forebrain and preoptic/anterior hypothalamic neuronal activity in the control of behavioral state


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VLPO
Sleep
LP Orexin
PVH Steroids
Limbic System
Visceral Cortex
Dorsomedial Nucleus
Sympathetic system via superior cervical ganglion
 SCN
Temp
Gremlin appetite
Leptin satiety
Pineal
Cho T, et al., 2003
Saper C, 2005
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Pineal
Cho T, et al., 2003
Saper C, 2005
• Uncomfortable social interactions dampen circadian rhythms
  – Quality of sleep is principally affected

• Stress neuroendocrine signals ("stress") do not have a major effect on circadian rhythm
  – AVP may delay clock
Sex Differences

Normal Menstrual Cycle

- Progesterone = soporific
- Subjective sleepiness in luteal phase

No significant differences in sleep between follicular and luteal phases:
  - EEG
  - Total sleep time
  - Sleep onset
  - REM and non-REM time
LH and sleep

- LH surge during sleep is the harbinger of puberty in women.
- In adult life LH is not closely associated with sleep states.
Growth Hormone and Sleep

- NREM sleep and GH surges
ACTH/Cortisol and Sleep

• In contrast to GH, more driven by circadian than sleep
• CRF/ACTH and then Cortisol increase are associated with a rising temperature profile and alerting process at the end of the major sleep cycle.
• Inverse relationship between delta waves and cortisol
Prolactin and Sleep

• Increases in prolactin with sleep onset SWS even when there is a change in circadian rhythm
  – The mechanism may be a reduction in dopamine, which usually inhibits prolactin

• Increased SWS with prolactinomas

• Prolactin elevations increase REM sleep and reductions reduce REM sleep.
Summary

• Sleep is necessary for brain cell structure health & wellness
• N-REM is homeostatic for brain metabolism
• REM arranges neurophysiologic state
• Specific opposing neurotransmitters action
• Awake/sleep is regulated by stable “flip-flop” mechanism
• Circadian control mediated by light > melatonin
  – Somatic, limbic cues are strong regulators
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