Neurobiology of Sleep

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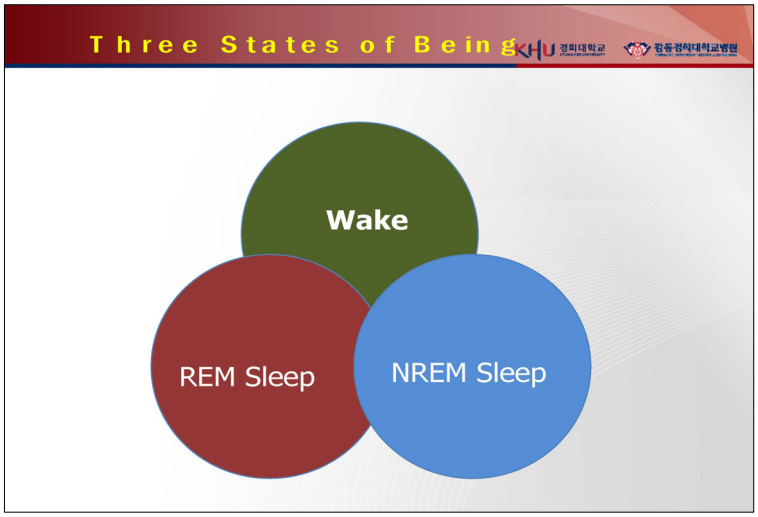
Content

- Normal Sleep
  - Sleep architecture
  - Wake and sleep mechanism
  - Circadian rhythm
- Sleep developmental changes
- Common child's sleep disorders and problems

잠의 기능

잠은 복잡한 과정으로 이루어진다.
정밀하게 체계화되어 있다.
생명 유지에 꼭 필요하다.
수면 단계에 따라서 서로 다른 뇌신경들이 관여한다.

- **정신적, 육체적 회복; 재충전**
- **에너지 보존**
- **뇌의 발육, 신경세포의 성숙과 기능 유지**
- **기억 정리**
- **면역기능의 회복과 조절 기능**
- **중요 호르몬 조절 기능**
- **체온조절 기능**
- **생존에 매우 중요한 일부 단백질들의 합성과 분해**

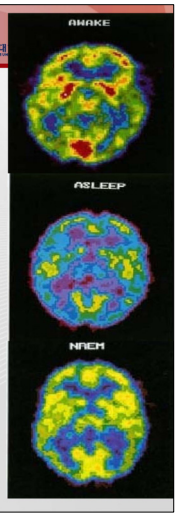


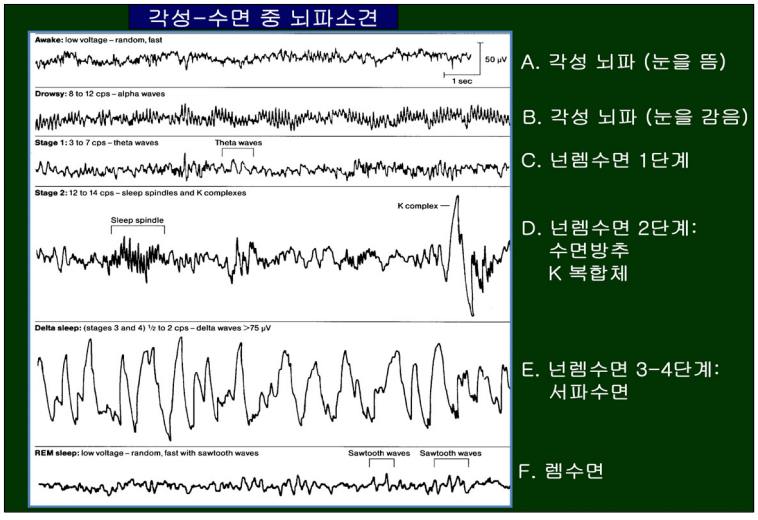
수면의 단계

- **넌렘 수면 (NREM sleep):** 75-80%
  - 1 **단계** (N 1): **선잠**, **옅은 잠**, **자다 깨다**
  - 2 **단계** (N 2): **진짜 잠**, **규칙적인 호흡**, **심박** & **체온** ↓
  - 3 **단계** (N 3)

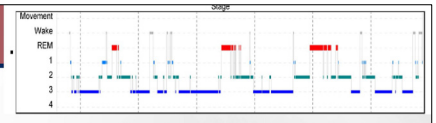
  깊은 잠, 서파수면, 회복, 혈압, 호흡 ↓
  에너지 축적, 성장호르몬 분비

- **렘수면 (REM sleep, R sleep):** 20-25%
  - Rapid Eye Movement (**빠른 눈동자 움직임**)
  - **꿈을 꾸는 잠** (dream sleep)
  - **골격근의 마비 (muscle atonia)**



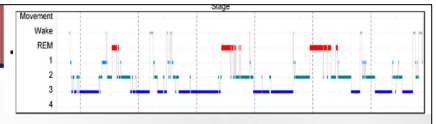


넌렘수면(NREM)



- 1 → 4 단계로 갈 수록 깨기가 어렵다.
- 부교감신경이 우세하다: 심장박동수 감소
- 혈압이 감소한다.
- 호흡이 느리고 규칙적이다.
- 정신 활동은 감소한다.
- 넌렘(NREM) 수면의 기능
  - 고갈된 에너지를 축적하게 한다.
  - 체온 조절 및 보존에 관여
  - 근골격계의 피로 회복 (musculoskeletal recovery)
  - 깊은 잠은 기억력을 강화시킴

렘(REM) 수면



- 근육이 마비된다 (눈, 호흡근은 제외)
- 빠른 눈동자의 움직임이 있다.
- 심장박동과 호흡 횟수가 증가하고, 불규칙해짐.
- 발기 (penile erection)
- 활발한 정신 활동: 생생한 꿈을 꾼다.
- 체온 조절이 안 된다.
- 호흡 장애가 잘 온다.
- 렘수면의 기능
  - 정신 활동의 피로를 회복시킨다, 감정 순화
  - 낮에 경험 것을 오래 기억하게 해준다

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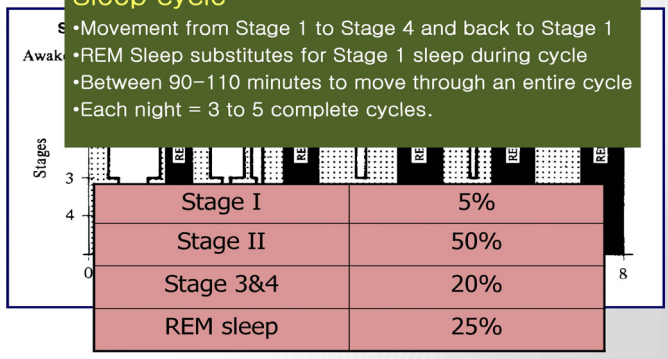
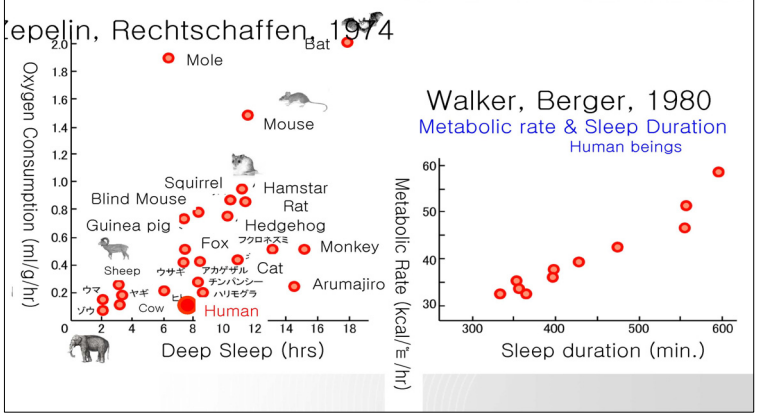
Sleep cycle

- Movement from Stage 1 to Stage 4 and back to Stage 1
- REM Sleep substitutes for Stage 1 sleep during cycle
- Between 90–110 minutes to move through an entire cycle
- Each night = 3 to 5 complete cycles.

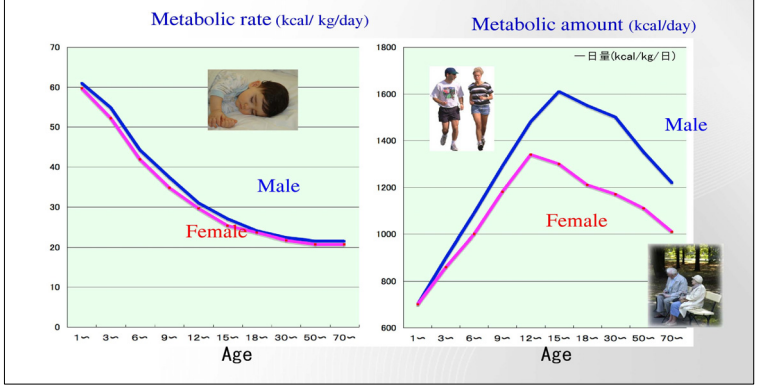


Stage I	5%
Stage II	50%
Stage 3&4	20%
REM sleep	25%

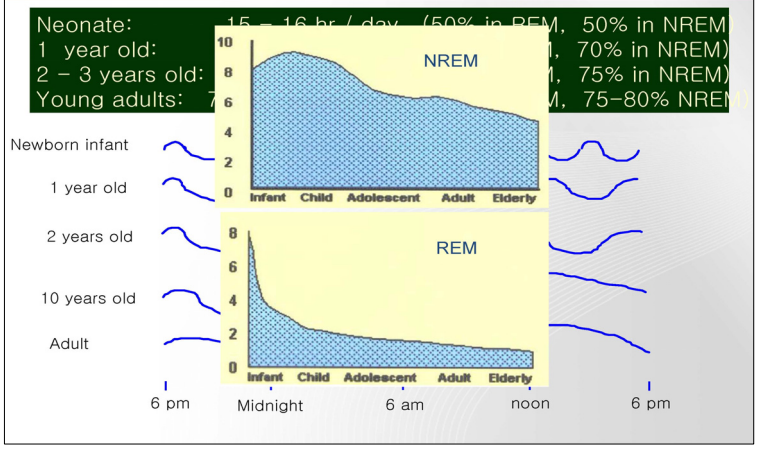
Larger Metabolic Rate, Longer Sleep Time



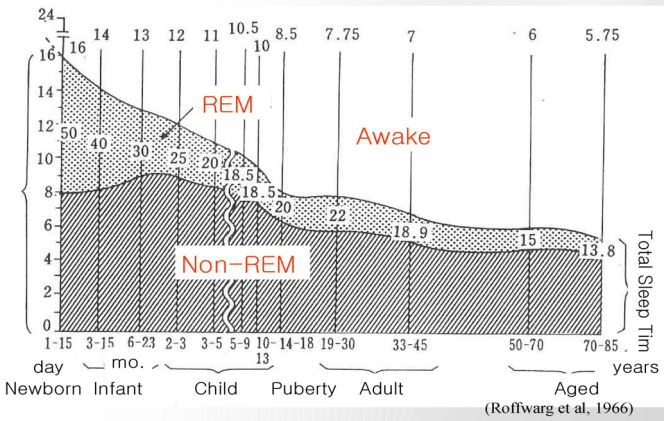
Aging and Metabolic Rate



Total Daily Sleep Time in different ages



Total sleep time, REM, Non-REM sleep and Age



(Roffwarg et al, 1966)

수면의 목적

- **신체의 피로를 회복시킨다**. 잠을 잘 못자면
  - 심장-폐 질환, 위장관 질환이 증가한다.
  - 근골격계 질환이 증가한다.
  - 성장이 잘 안 된다.
  - 낮에 졸리고 피곤하다.
  - 교통사고, 안전사고가 증가한다.
- **정신의 피로를 회복시킨다**. 잠을 잘 못자면
  - 집중력, 사고력, 기억력이 떨어진다.
  - 학습장애가 온다. 짜증을 잘 내고, 잘 다툰다.
  - 발기부전 등 성생활에 문제가 생긴다.

Sleep is active process ?

Sleep-wake cycle even after sensory deprivation

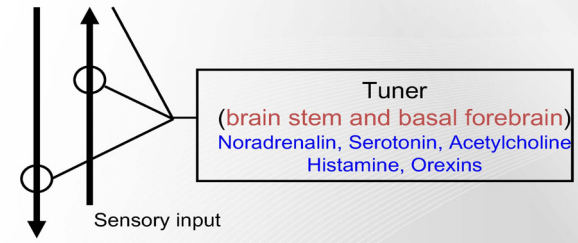
Brain stem regulates the sleep-wake cycle

Evidence

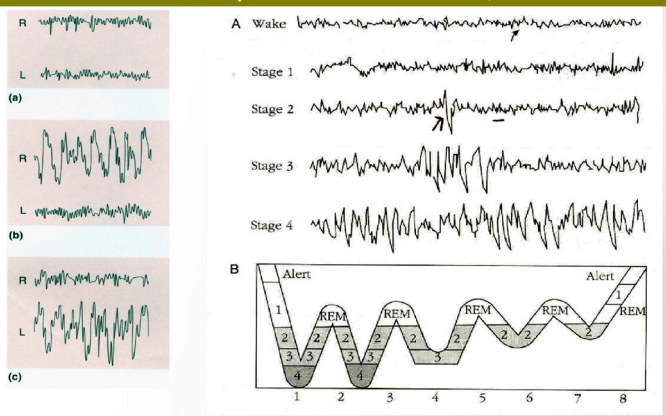
1. C1 cut at rats: normal consciousness
2. Transecting midbrain: permanent synchronized EEG (delta-wave)
3. High-frequency stimulation of midbrain → arousal & desynchronized EEG
4. Caudal brainstem (medulla and pons) actively generates sleep

Cerebral cortex activity

(Alertness & sleep)



Almost all vertebrates do sleep (without REM except homeotherms)



wakefulness

- **ARAS**
  - Aminergic neuron, cholinergic activity, excitability glutamate
  - Aminergic and cholinergic neurons promote the wake cycle by direct activation effect on the cortex
  - NE, 5-HT : Arousal, inhibit REM sleep
  - Ach : Arousal, REM sleep
  - Dopamine & Histamine : wakefulness

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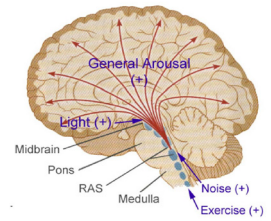
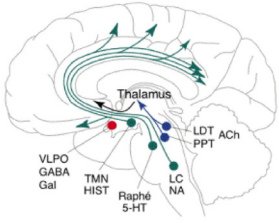
Reticular Activating System (RAS) determines the level of alertness





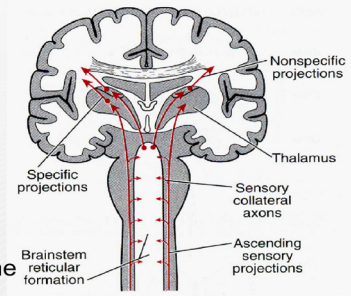
Ascending RAS

(reticular activating system)

Midline tegmentum, not lateral tegmentum

Locus ceruleus: noradrenalin (NA)
Raphe nuclei: serotonin
Pontine and basal forebrain: acetylcholine
Hypothalamus & midbrain: histamine

= Reticular inhibiting system



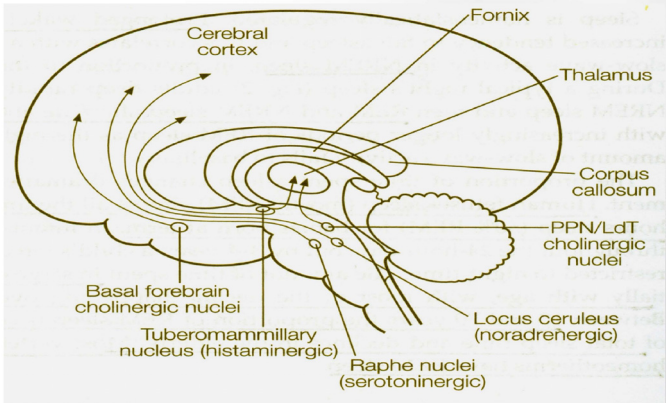
Ascending arousal system (monoaminergic neurons)

Two pathways

Noradrenalin (NA) neuron in locus ceruleus
Serotonergic neuron in raphe nucleus
Histaminergic neuron of tuberomammillary nucleus (TMN) in hypothalamus
→ Lateral hypothalamus (medial forebrain bundle) → cerebral cortex
Cholinergic neuron in basal forebrain (supporter)

Histaminergic neuron of TMN in hypothalamus
→ excitatory synapse with thalamocortical neuron (TCN, relay N)
Cholinergic neuron in pons (pedunculopontine (PPN) & lateral dorsal tegmental (LdT) nu.)
→ Inhibit GABAergic thalamic reticular neuron (TRN) → excite TRN cells

Summary (monoaminergic neurons)



Sleep

Non-REM (NREM) sleep

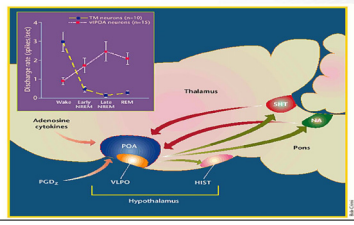
Decreased activity of RAS (except some forebrain Ach)
Low frequency and high voltage EEG (synchronized)
Sleep spindle

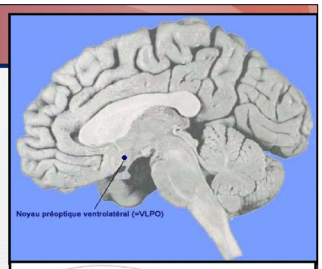
Decreased cerebral blood flow, glucose utilization by 40%
No muscle tonus change, postural adjustment
Decreased RR, HR, BP
Increased GI motility and GH secretion
→ Parasympathetic dominant period

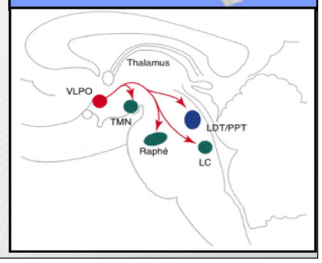
NREM sleep

Ventrolateral preoptic area (VLPO) of ant. hypothalamus
- sleep active neurons
- GABAergic of VLPO

→ ARAS → de-inactivation thalamic reticular neuron
→ post. Hypothalamus, histamine







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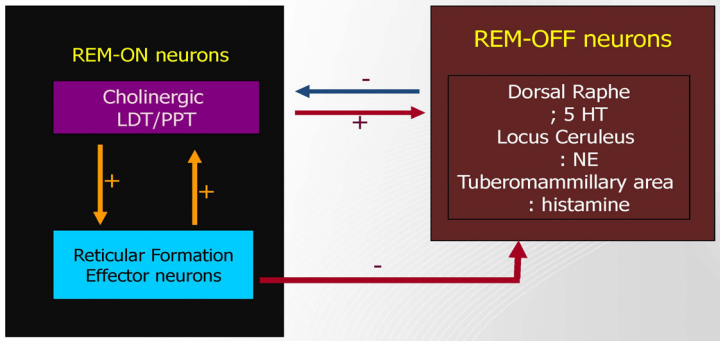
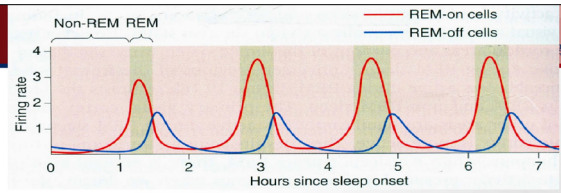
REM sleep

Pontine cholinergic neuron activation (wake-on/REM-on cell)
Desynchronized EEG (high frequency and low voltage)
Occur 90 min after sleep
Absence of muscle tone apart from EOM, middle ear muscle
Dreaming (short-term memory)

Irregular RR, HR, BP, core temperature, penile erection
Metabolically active
→ Sympathetic dominant period

REM Sleep





Pontine cholinergic
Active during both wakefulness and REM sleep
Quiescent during NREM sleep
→ wake-on/REM-on cells

Others (particularly NA and serotonergic)
Highly active in alert & lower active in NREM
Silent during REM
→ wake-on/REM-off cells

Orexin-using neurons
tuberal regions of hypothalamus
Modulation neuron
→ Maintenance as the state is (awake or REM)

Physiology of NREM sleep

Trigger: hypothalamic nuclei (ventrolateral preoptic area; VLPO)

GABA inhibition
1. to histaminergic neuron in TMN (*antihistamine*)
→ TCN hyperpolarized (→ burst firing → sleep spindles in EEG)

2. to NA and serotonergic in LC/RN & orexigenic neurons

Ach in PPN/LdT

Decrease activity of all RAS

What makes VLPO excited ?
Suprachiamatic nucleus, elevated core temperature,
endogenous hypnogenic (melatonin, IL-1)

Physiology of REM sleep

Trigger: Periaqueductal gray matter (REM-on cell) in midbrain

GABA inhibition
to LC/RN cells but not orexin and PPN/LdT cells

Further activation of PPN/LdT cells
& basal forebrain cholinergic cells

Inhibition of sensory input (GABA)
& motor output (Glycine)
via pontine reticular Nu.

Depolarization of TCN → tonic firing mode (β-wave in EEG)

During REM, uncoupling of brain from external world (off-line)
Pons lesion: *REM sleep disorder*

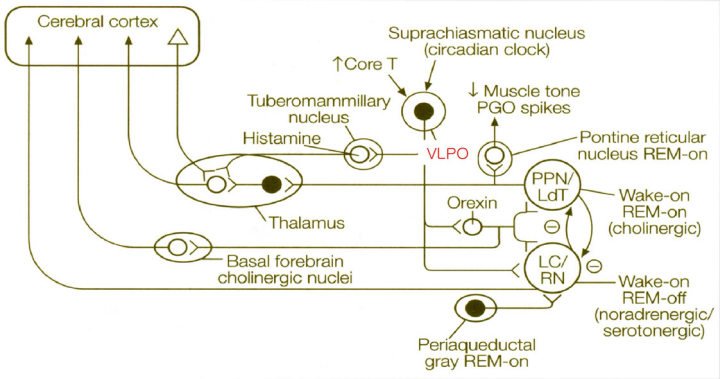
Periodic PGO (pontine-geniculate-occipital) spikes in EEG

Mainly during REM from cholinergic pontine reticular nu.

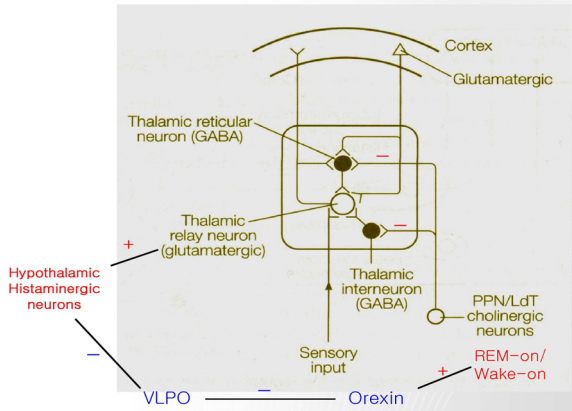
Oculomotor (REM) and vestibular neurons
Phasic alteration of RR, HR, BP
Occasional limb muscle twitches

Lateral geniculate nu. in thalamus and visual cortex
During awake, inhibition by serotonin (startle response)

sleep-wakefulness circuitry



Reciprocal thalamo-cortical transmission



Two mode of firing in thalamus

1. **Tonic firing of single action potential**

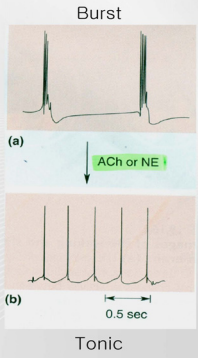
Awake state and REM (β-wave)
When TCN depolarized by arousal system
→ Transmission of sensory input from thalamus to cortex

2. **Burst firing**

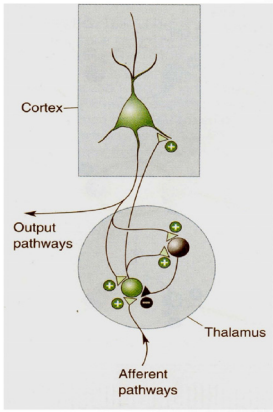
NREM
When TCN hyperpolarized by loss of stimuli
Synchronized burst of cortical neuron (sleep spindle)
→ Limitation of transmission to cortex

3. δ-rhythm

Deepest NREM sleep
TCN so hyperpolarized → silent
Decoupling to cortex



Switching between two modes



Sleep induction

GABA from thalamic reticular neuron
→IPSP of thalamocortical neuron
→hyperpolarization of thalamocortical neuron
→IT_{Ca} activation → Burst → Sleep spindle

Alertness

hypopolarization of thalamocortical neuron
→ IT_{Ca} inactivation → Tonic → β wave

Disorders of sleep-wakefulness circuitry

1. Narcolepsy
Impairment of orexigenic nucleus that stabilizes awaking or REM as it is
Shift to REM from awake (atonia, dream)

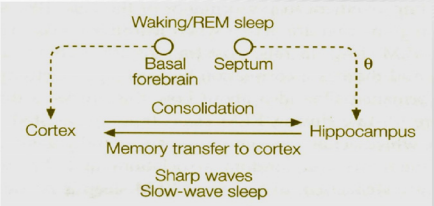
2. Cortical arousal impairment
Cortical origin: mainly metabolic origin
Ascending reticular formation: mainly local damage origin

Hypocretin-containing neurons

Function of sleep

Not known
1. Metabolic hypothesis
Replenishment of energy for brain and non-neuronal tissues
Smaller animals → increased sleep time and metabolic rate
Preoptic area of hypothalamus: body temperature and NREM

2. Memory hypothesis
Consolidation & reorganization during sleep

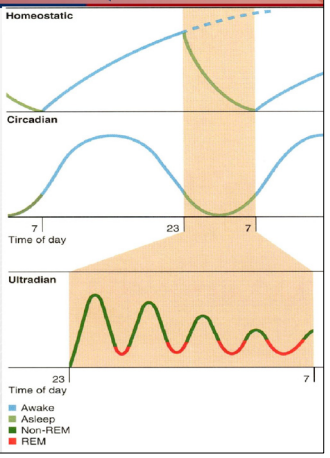


Regulation of wakefulness and Sleep

Homeostatic process
-accumulation of sleep need
; delta sleep-inducing peptide (DSIP) or Factor S

Circadian systems:
1. Sun light
2. Biologic clock: suprachiasmatic nucleus
3. Circadian rhythms in temperature, hormone, fatigue

Ultradian mechanism
- balance between REM and NREM sleep



Homeostatic process

- Duration and intensity of sleep
- Slow-wave sleep is highly influenced by the amount of prior wakefulness : good marker
- ? REM sleep is much less so.

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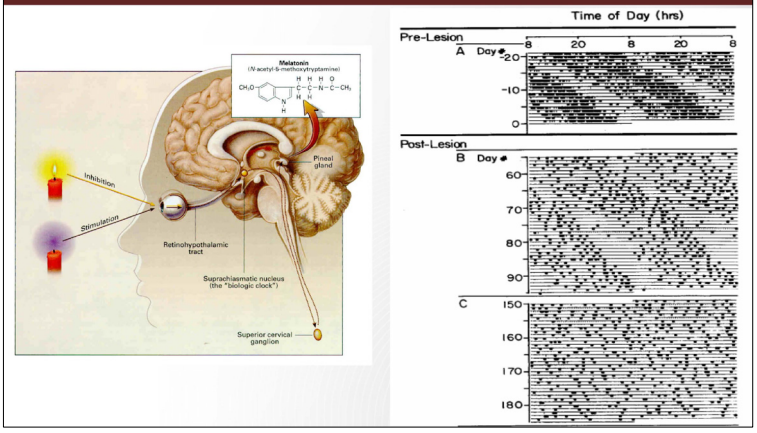
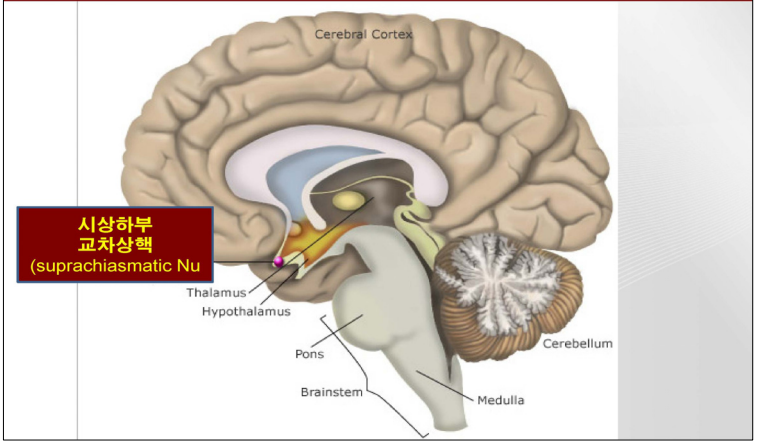
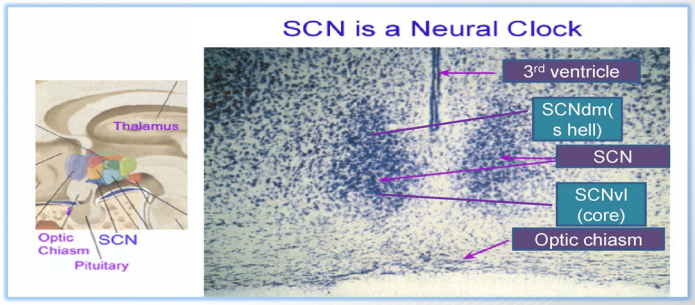
수면-각성주기 ; Circadian rhythm



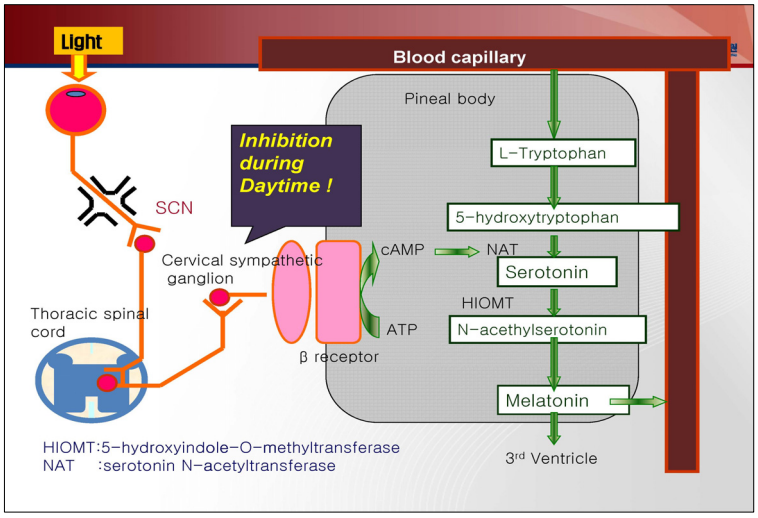
생체시계



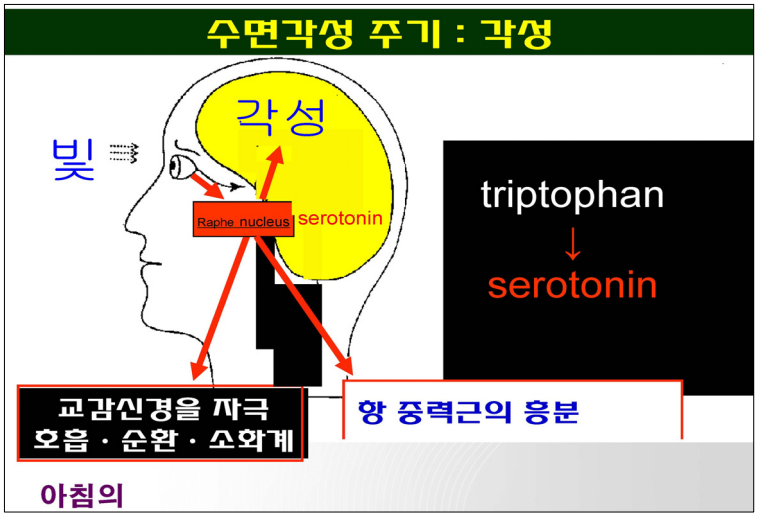
시신경교차상핵

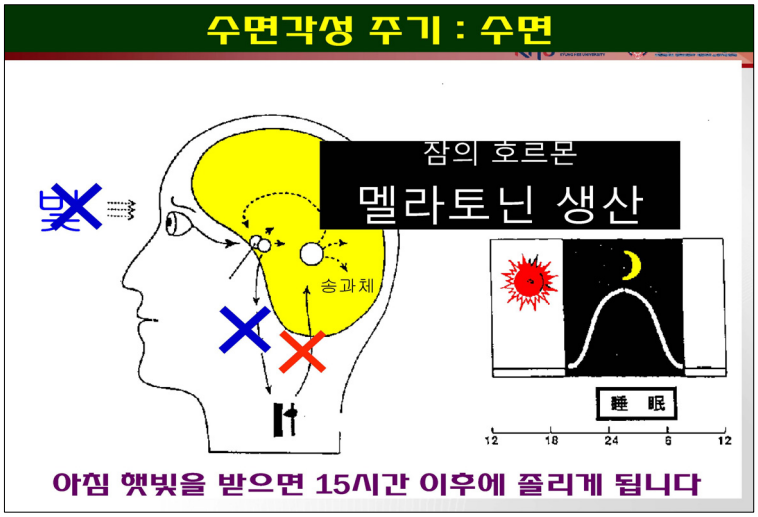


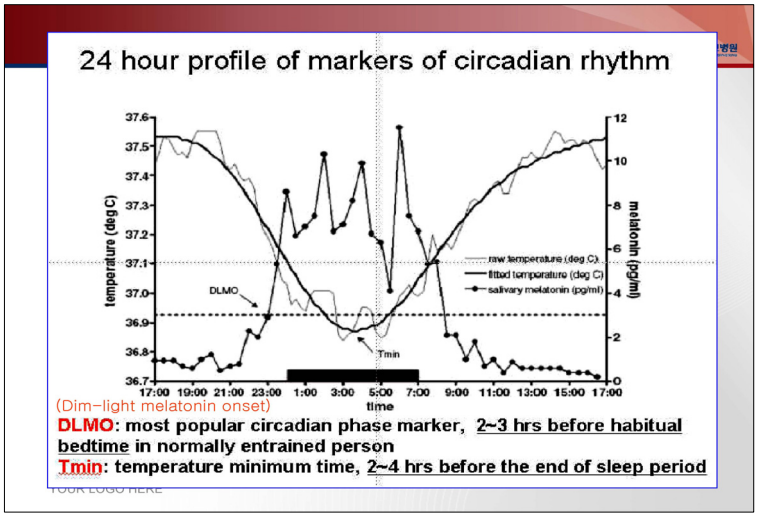
- Location – dorsal to optic chiasm, lateral to 3rd ventricle
- Composition - dorsomedial : SCNdm, ventrolateral : SCNvl

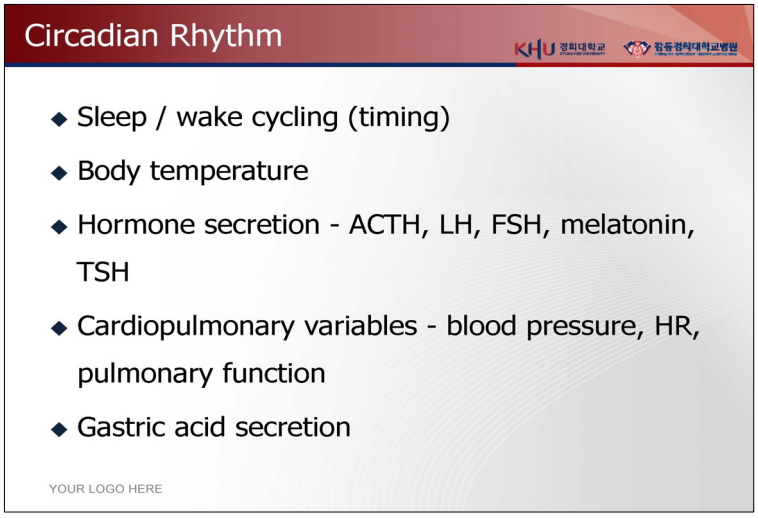


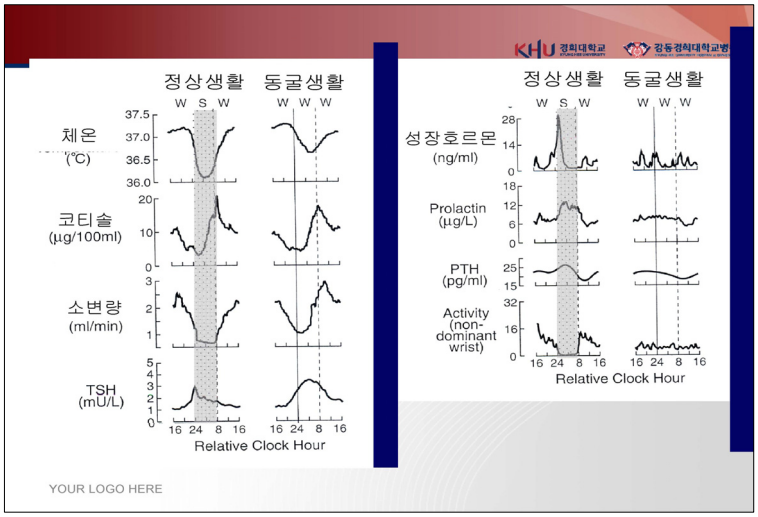
수면각성 주기 : 각성




수면각성 주기 : 수면
잠의 호르몬
멜라토닌 생산
송과체
睡 眠
12 18 24 6 12
아침 햇빛을 받으면 15시간 이후에 졸리게 됩니다

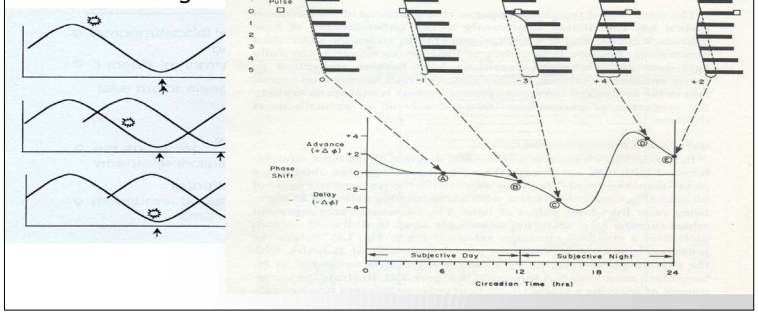

24 hour profile of markers of circadian rhythm
temperature (deg C)
melatonin (pg/ml)
raw temperature (deg C)
fitted temperature (deg C)
salivary melatonin (pg/ml)
DLMO
Tmin
time
(Dim-light melatonin onset)
DLMO: most popular circadian phase marker, 2~3 hrs before habitual bedtime in normally entrained person
Tmin: temperature minimum time, 2~4 hrs before the end of sleep period


Circadian Rhythm
Sleep / wake cycling (timing)
Body temperature
Hormone secretion - ACTH, LH, FSH, melatonin, TSH
Cardiopulmonary variables - blood pressure, HR, pulmonary function
Gastric acid secretion
YOUR LOGO HERE

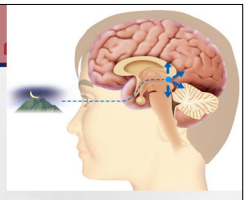


Effect of Zeitgeber
; Phase relationship

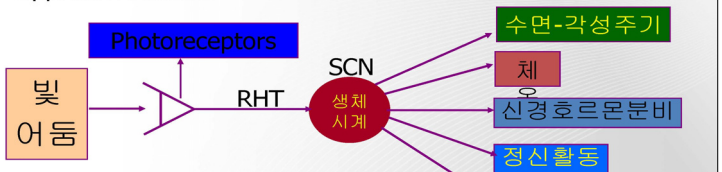
- Entrainment strength
  - strength of zeitgeber
  - sensitivity of p
  - weakening wi



What regulates sleep-wake cycle ?



- Circadian systems: Major functions in the human body cycles over a period of approx. 24 hours.

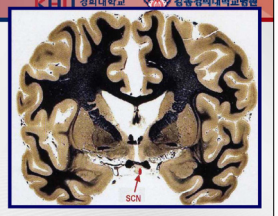


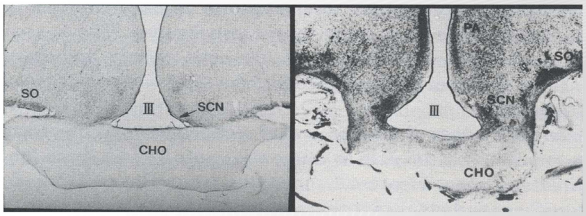
RHT: retinohypothalamic tract
SCN: suprachiasmatic nucleus

YOUR LOGO HERE

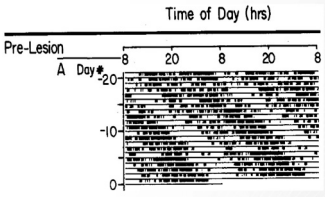
Circadian Clock

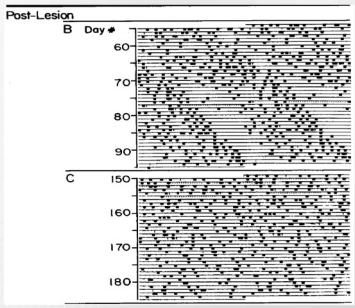
- de Marian (250 yrs ago)
  "Circadian rhythms persist even when an organism is isolated from time cues….."



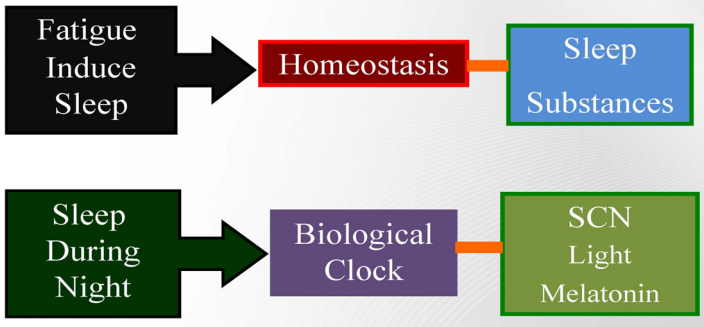


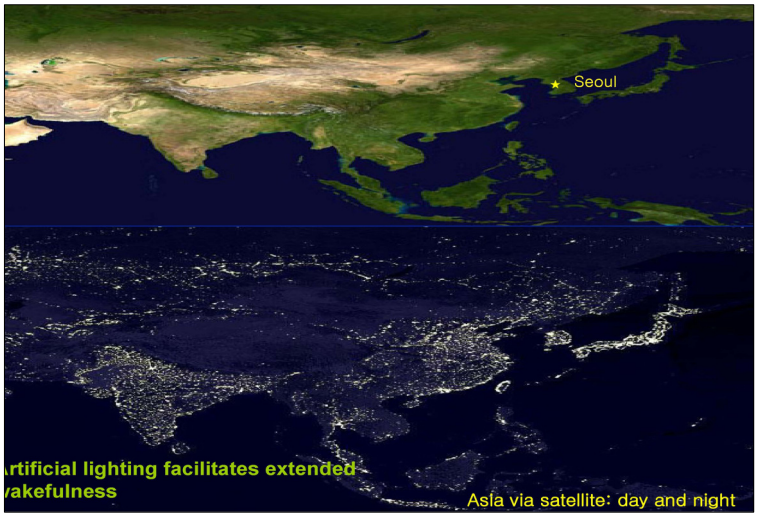
Circadian pacemaker : Biological clock





Sleep Regulation




Seoul
rtificial lighting facilitates extended
vakefulness
Asia via satellite: day and night


KHU 경희대학교
6th World Congress on Sleep Medicine
March 21-25, 2015 Seoul, Korea
KOREA TOURISM ORGANIZATION
WASM