Sleep physiology and pathophysiology of sleep disorders

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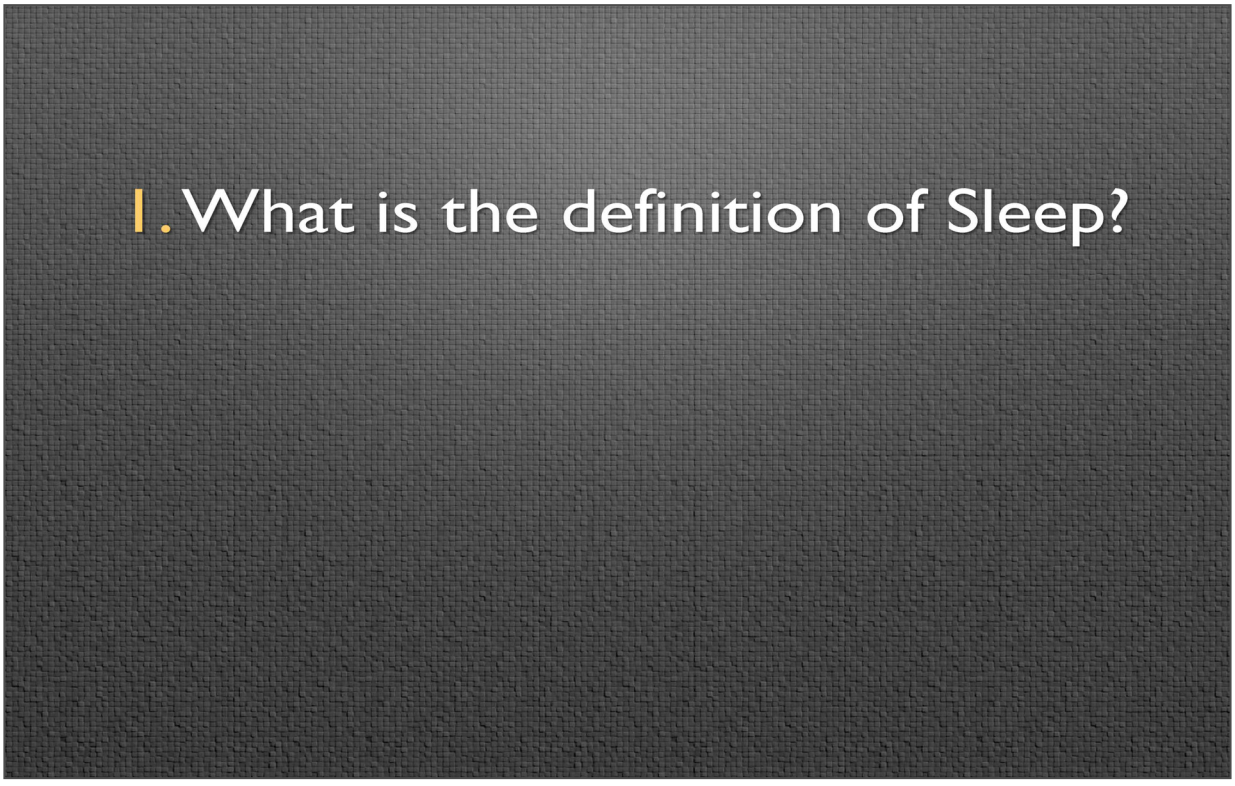


Sleep Definition

Sleep Definition

1. Behavioral Criteria of Sleep

Species-specific posture

Behavioral quiescence

Reversible upon stimulation

Elevated arousal threshold

Rebound after deprivation

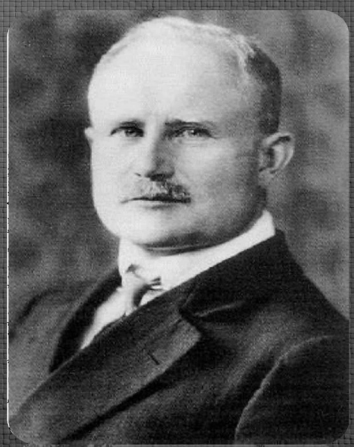
Sleep Definition

2. EEG Criteria of Sleep

Wakefulness	Vigilance state characterized by a **low amplitude, high frequency, mixed EEG pattern.**
NREM sleep	Vigilance state characterized by **high amplitude, low frequency oscillations,** dominated by the **slow/delta and spindle oscillations** and a relaxed muscle tone. In animal studies that use the term paradoxical sleep, NREM sleep is referred to as **slow wave sleep.**
REM sleep	Vigilance state characterized by an EEG resembling **wake or stage-1 sleep in humans, in association with muscle atonia.** In rodents, REM sleep is dominated by theta oscillations.
Slow wave sleep (SWS)	The **deepest stages of NREM sleep** (stages 3 and 4 in humans) during which **slow/delta waves** are especially prevalent and **arousal thresholds are highest.**

EEG

- Hans Berger (1873-1941, University of Jena, Germany)
  - ✓"Father of Electroencephalography"
  - ✓- In 1929, first report about EEG evidence of human brain oscillation
  - ✓- 8~12 Hz spontaneous oscillation, named as alpha (basic) rhythm first, and later beta rhythm (13~30 Hz).
  - ✓ "The brain waves changed dramatically if the subject simply shifts from sitting quietly with eyes closed (short or alpha waves) to sitting quietly with eyes opened (long or beta waves). Furthermore, brain waves also changed when the subject sat quietly with eyes closed, "focusing" on solving a math problem (beta waves)."



EEG

First EEG apparatus & the recordings

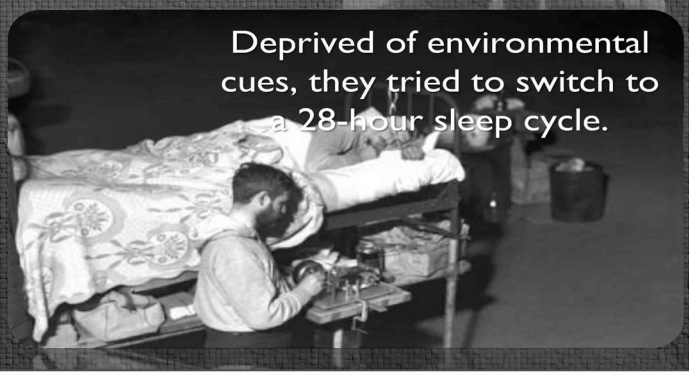
Sleep Spindles

- Alfred Lee Loomis (1887-1975)
- In 1937, Loomis first documented the characteristic EEG patterns of NREM sleep: vertex waves, sleep spindles, K complexes, and delta slowing (Loomis et al. *J Exp Psychol* 1937;21:127–44).
- He divided sleep into 5 stages of increasing depth from A through E, the basis for the current classification of NREM sleep.

Alfred Lee Loomis 1887-1975

Circadian Rhythms

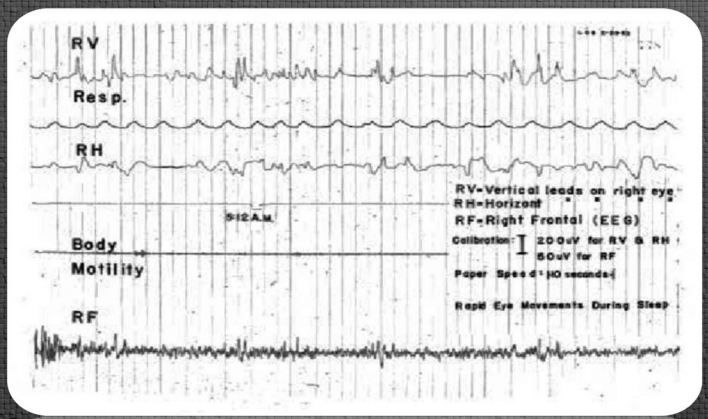
- Nathaniel Kleitman (Chicago Univ.)
- Became famous with "Mammoth Cave" study for identifying circadian rhythm is dependent on light exposure for 32 days.
- Father of US sleep medicine and AASM



Deprived of environmental cues, they tried to switch to a 28-hour sleep cycle.

REM Sleep

- Nathaniel Kleitman & Eugene Aserinsky
- In 1949, during his graduate schooling Aserinsky worked at studying attention in children. He decided to record eyelid movement using the electrooculogram (EOG).



First recording of Rapid eye movement during REM sleep. *Science*, 1953.

SOREMs/MSLT (1963/1977)

- William Dement, the founder of Stanford sleep laboratory, proposed the measure for the clinical definition of sleep apnea and the rating of its severity **"AHI"**
- In 1963, Dement and Rechtschaffen, "patients with narcolepsy often went directly into REM sleep during nighttime sleep testing" - SOREMs
- Found canine-narcolepsy in 1973
- Dement and Carskadon developed the multiple sleep latency test (MSLT) in 1977

Rechtschaffen A, Wolpert EA, Dement WC Noctural sleep of narcoleptics. Electroencephalogr Clin Neurophysiol. 1963;15:599–609.

Sleep Cycles

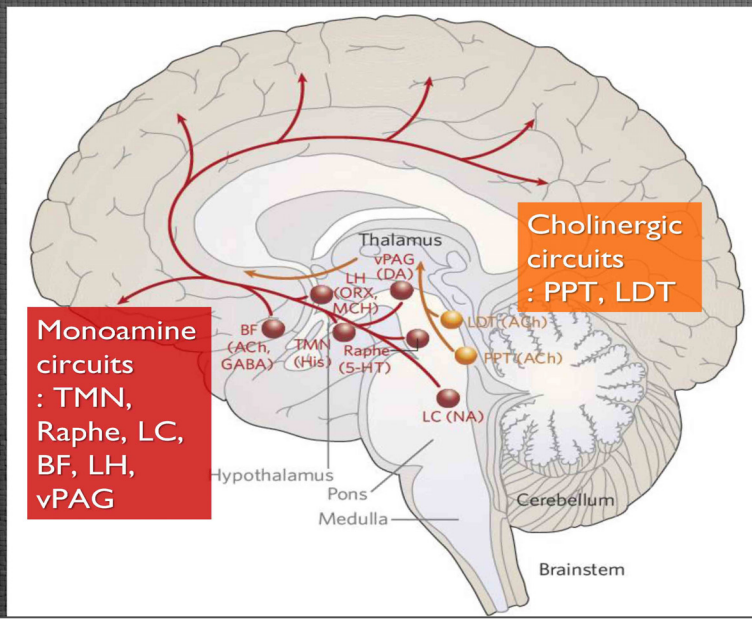
- Stage W (Wakefulness)
- Stage N1 (NREM 1): < 10%
- Stage N2 (NREM 2): ~ 50%
- Stage N3 (NREM 3 & 4, Slow-wave sleep): 5~40%
- Stage R (REM): 20~25%

  * 4 to 7 cycles per night: N1 – N2 – N3 –N2 – R

  * N3 predominates in the first 1/3, and R increases during the last few hours

Ascending Reticular formation System

Awakening Structures: ARAS



ARAS – 2 main streams:

Choline:

pedunculopontine nucleus (PPT), laterodorsal tegmentum (LDT)

Monoamines:

dorsal raphe N (5-HT)

LC (NE)

tuberomammillary N (His)

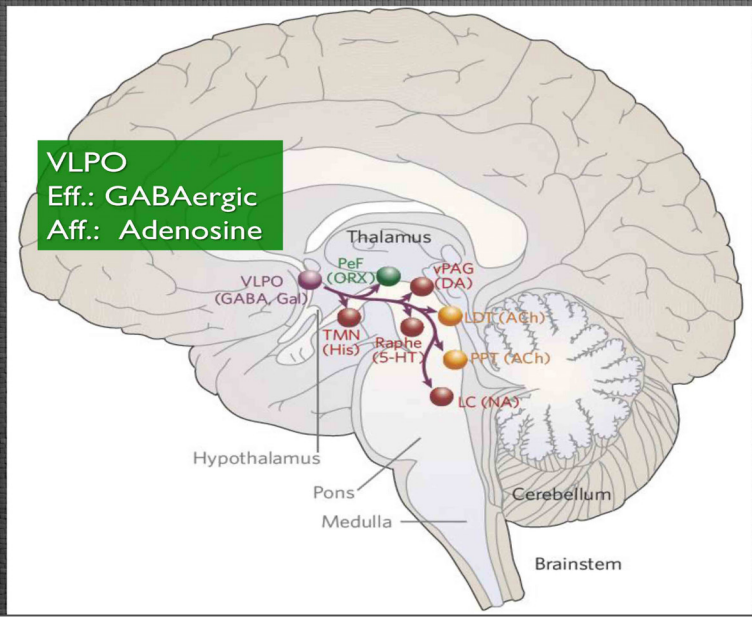
ventral periaqueductal gray (DA)

lateral hypothalamus (orexin)

Saper et al. *Nature* 2005

Sleep Promotion

VLPO – the key of sleep promotion



VLPO (ventrolateral preoptic nucleus:

inhibition of arousal-associated structures

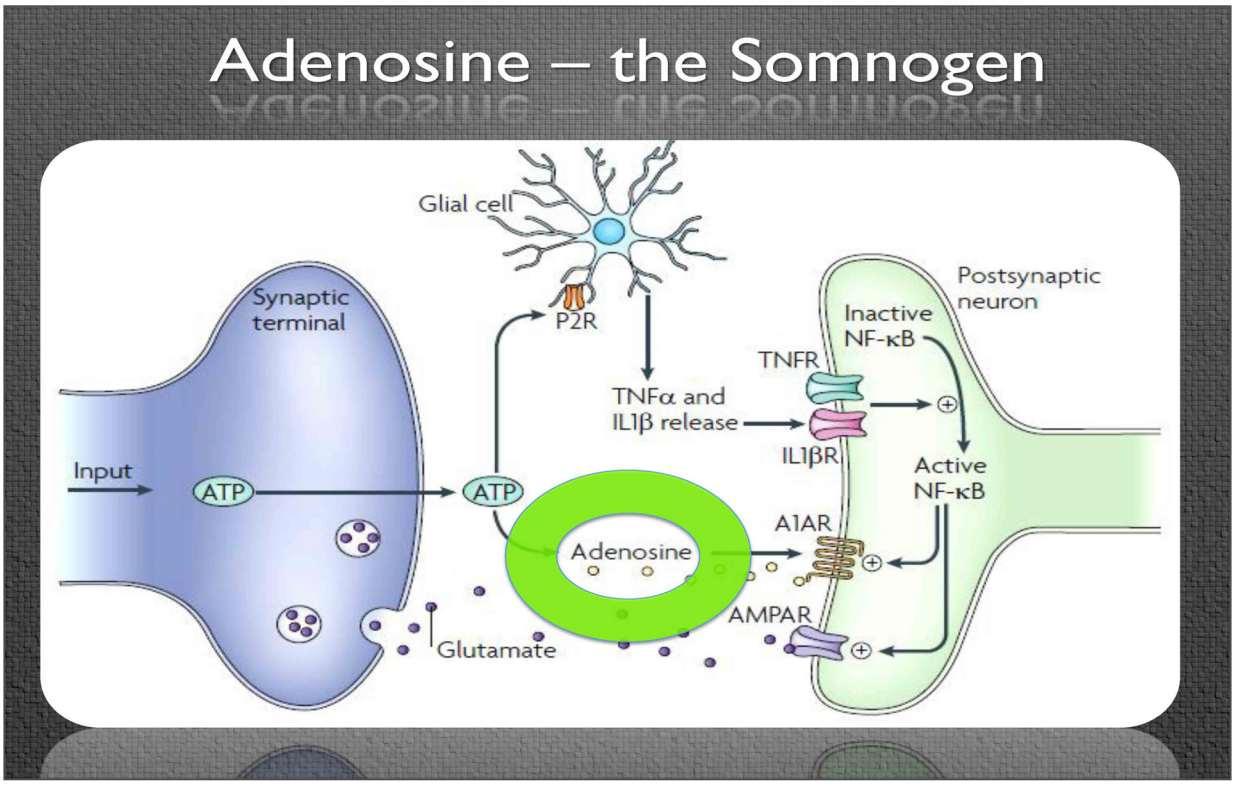
Efferents:

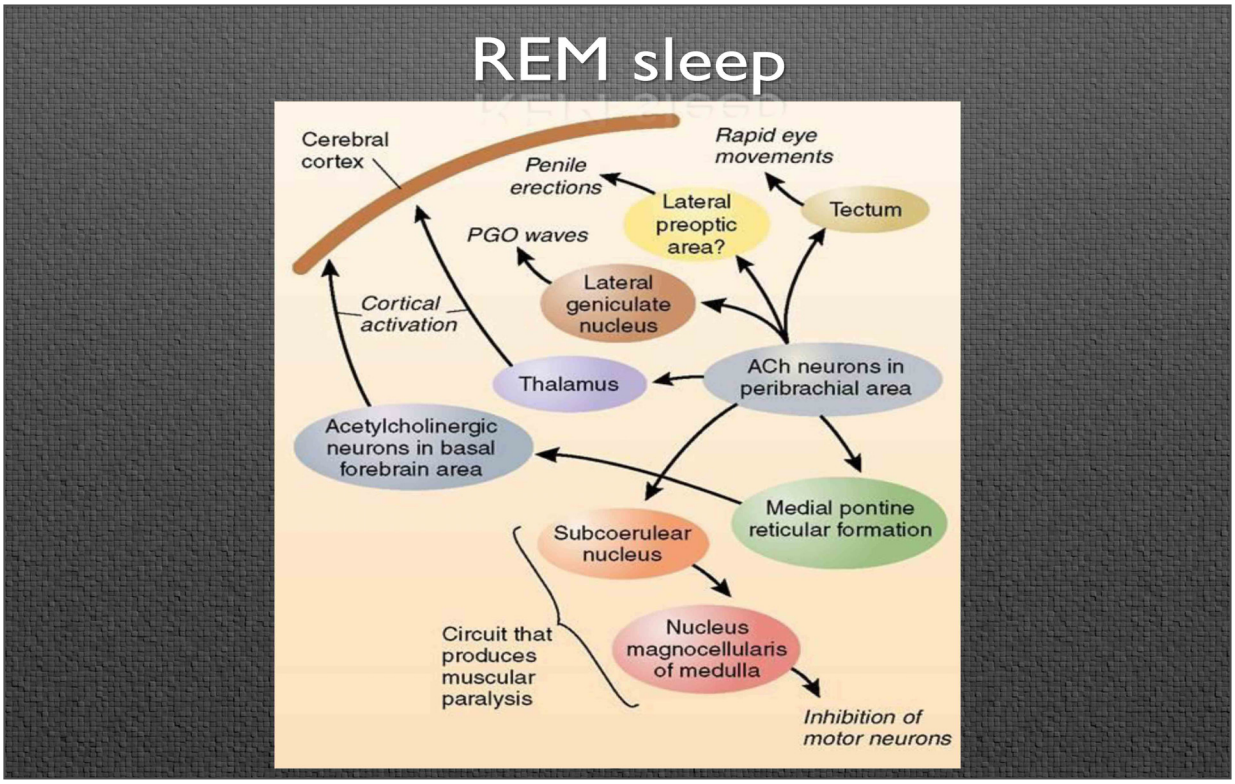
GABA, Galanin

Affected by:

Adenosine

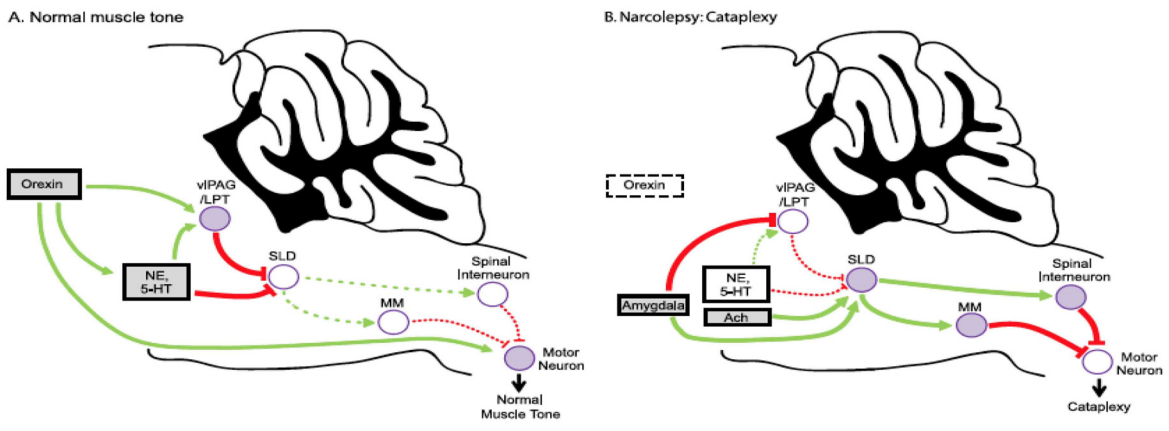
Saper et al. *Nature* 2005


Adenosine – the Somnogen
Glial cell
Synaptic terminal
P2R
Postsynaptic neuron
Inactive NF-κB
TNFR
TNFα and IL1β release
IL1βR
Active NF-κB
Input
ATP
ATP
Adenosine
A1AR
AMPAR
Glutamate


REM sleep
Cerebral cortex
Rapid eye movements
Penile erections
Lateral preoptic area?
Tectum
PGO waves
Lateral geniculate nucleus
Cortical activation
Thalamus
ACh neurons in peribrachial area
Acetylcholinergic neurons in basal forebrain area
Medial pontine reticular formation
Subcoerulear nucleus
Circuit that produces muscular paralysis
Nucleus magnocellularis of medulla
Inhibition of motor neurons

Hypocretin/orexin

- Cataplexy



Burgess and Scammell J. Neurosci., September 5, 2012

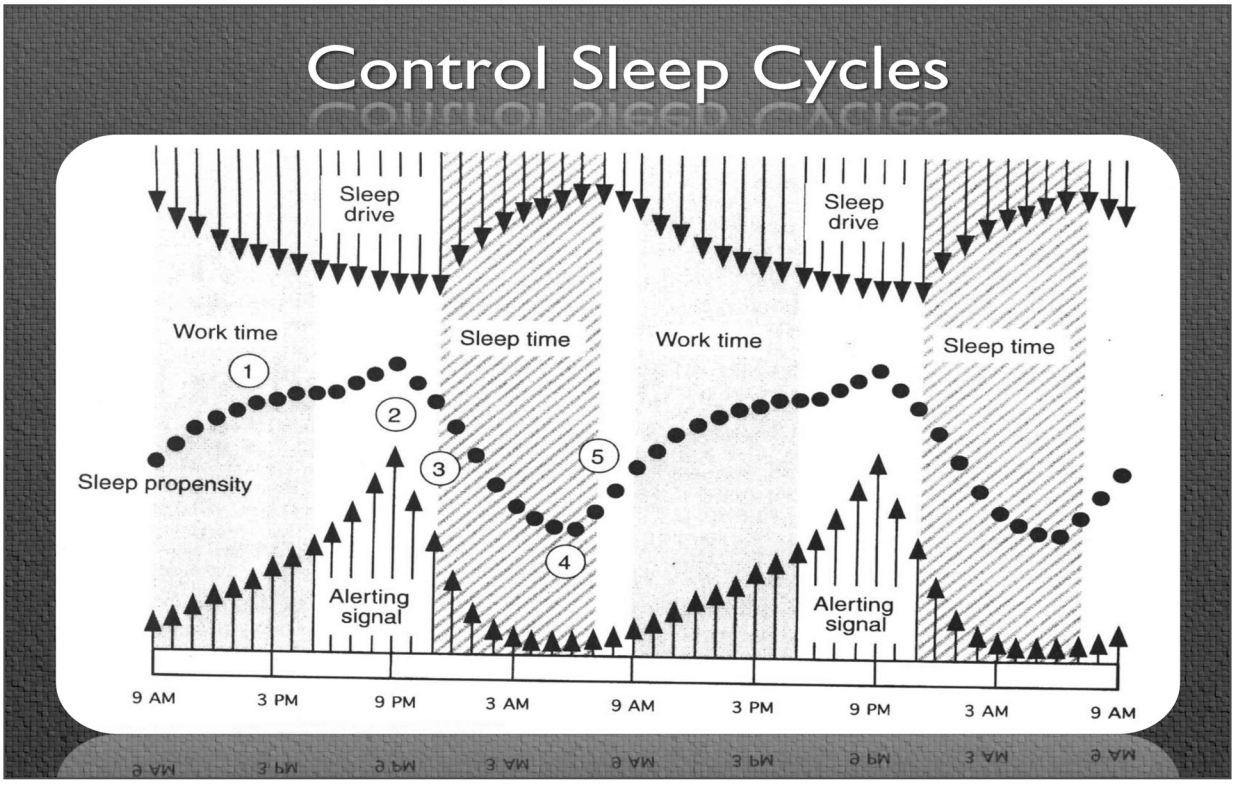
Control Sleep Cycles

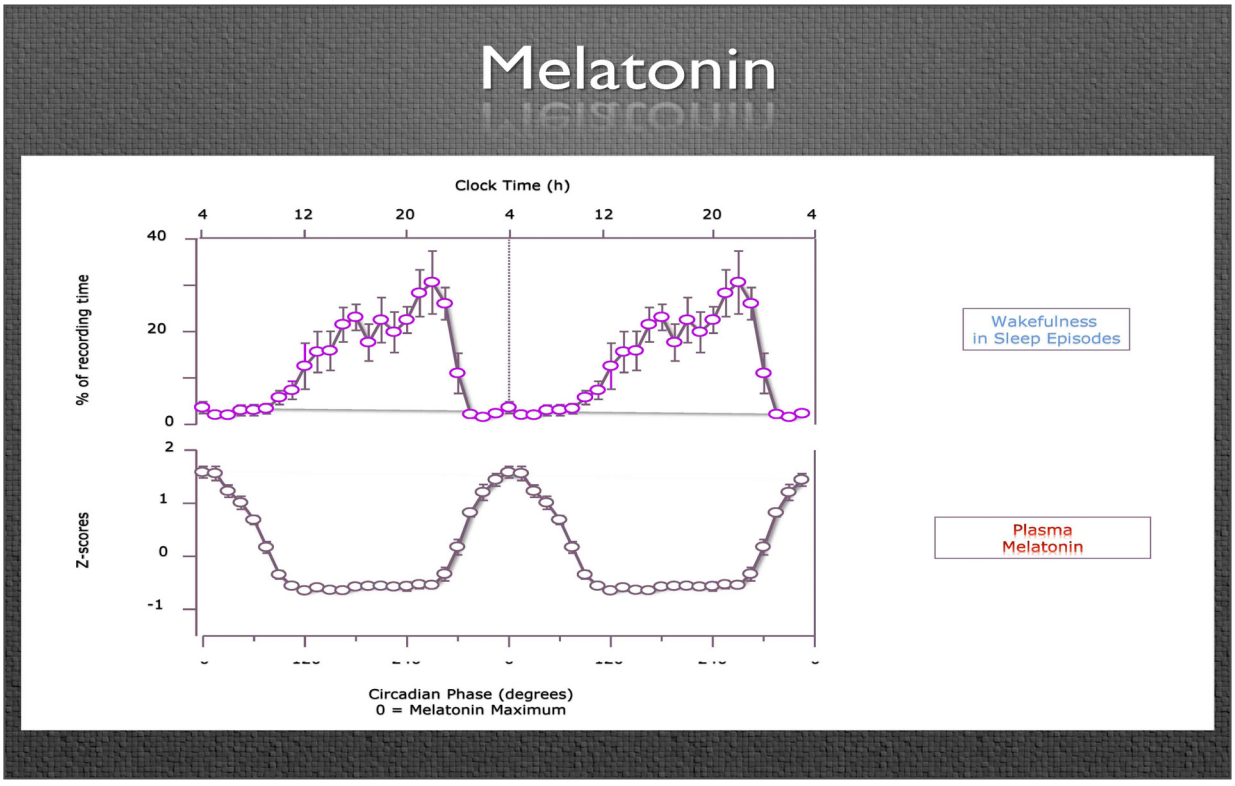
- Process S (homeostatic):

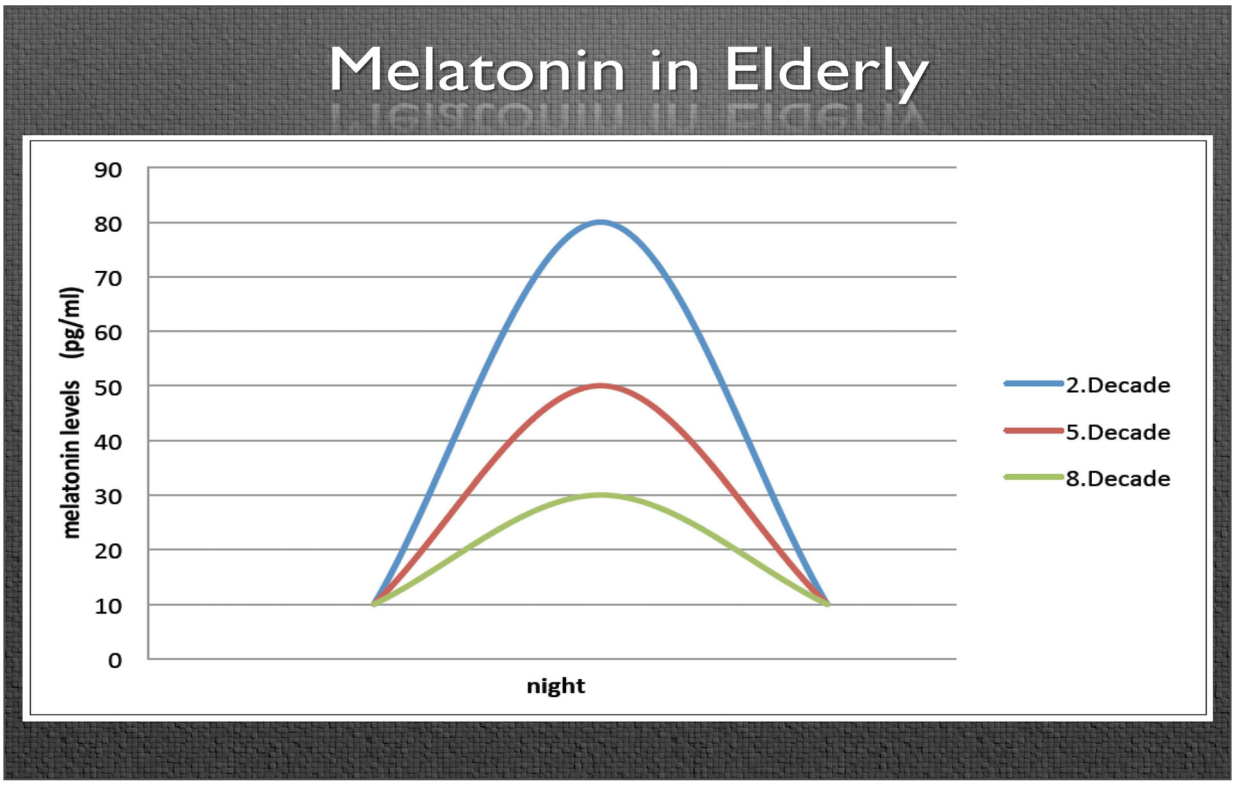
  VLPO (ventrolateral preoptic area): adenosine an endogenous somnogen, its concentration gradually rising with increased duration of wakefulness.

- Process C (circadian):

  SCN (Suprachiasmatic nucleus) – promoting arousal
  hypothalamic neurons containing arousal-promoting neuropeptides, orexin 1 & 2
  Pineal gland (Melatonin) – promoting sleep, inhibited by light


Control Sleep Cycles
Sleep drive
Sleep drive
Work time
Sleep time
Work time
Sleep time
1
2
3
4
5
Sleep propensity
Alerting signal
Alerting signal
9 AM
3 PM
9 PM
3 AM
9 AM
3 PM
9 PM
3 AM
9 AM

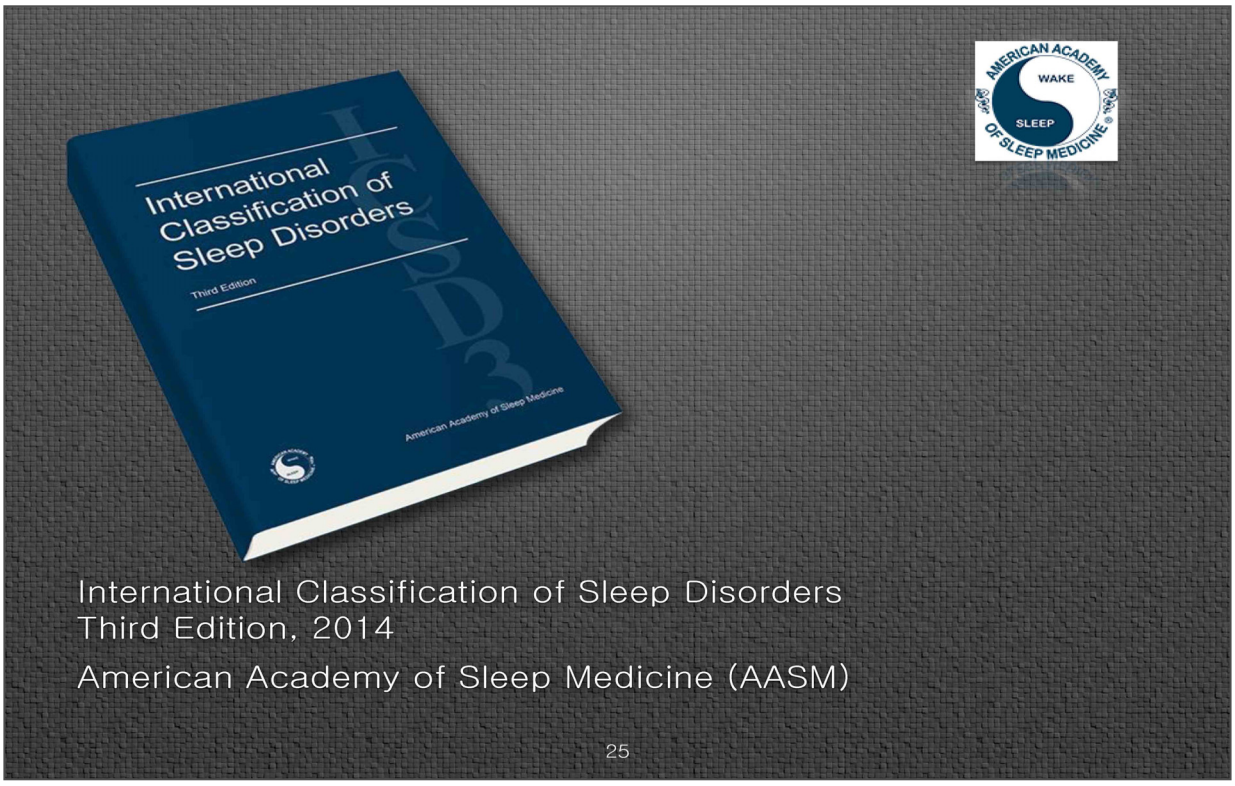

Melatonin
Clock Time (h)
4
12
20
4
12
20
4
40
20
0
% of recording time
2
1
0
-1
Z-scores
Wakefulness in Sleep Episodes
Plasma Melatonin
Circadian Phase (degrees)
0 = Melatonin Maximum


Melatonin in Elderly
melatonin levels (pg/ml)
90
80
70
60
50
40
30
20
10
0
night
2.Decade
5.Decade
8.Decade


Q. 왜 커피를 마시면 잠이 안올까요?


Q. 감기약을 먹으면 졸리는 이유는?
타이레놀
콜대
하벤허브
samil


Q. 과연 술을 마시면 잠을 잘 잘까요?
한라산
순한소주
좋은데이
참이슬


International Classification of Sleep Disorders
Third Edition
American Academy of Sleep Medicine
AMERICAN ACADEMY OF SLEEP MEDICINE
WAKE
SLEEP
International Classification of Sleep Disorders
Third Edition, 2014
American Academy of Sleep Medicine (AASM)
25


ICSD-3
Insomnia
Sleep-Related Breathing Disorders
Central Disorders of Hypersomnolence
Circadian Rhythm Sleep-Wake Disorders
Parasomnias
Sleep-Related Movement Disorders
Other Sleep Disorder
6

Insomnia

Disorders

Chronic Insomnia Disorder

Short-Term Insomnia Disorder (< 3 Ms)

Other Insomnia Disorder

33%

No more
primary insomnia
secondary insomnia
comorbid insomnia

Chronic Insomnia Disorder
Subtypes

Insomnia due to (another) mental disorder
Insomnia due to (a) medical condition
Insomnia due to drug or substance
Inadequate sleep hygiene
Behavioral insomnia of childhood

Psychophysiological insomnia
Idiopathic insomnia
Paradoxical insomnia "sleep state misperception"

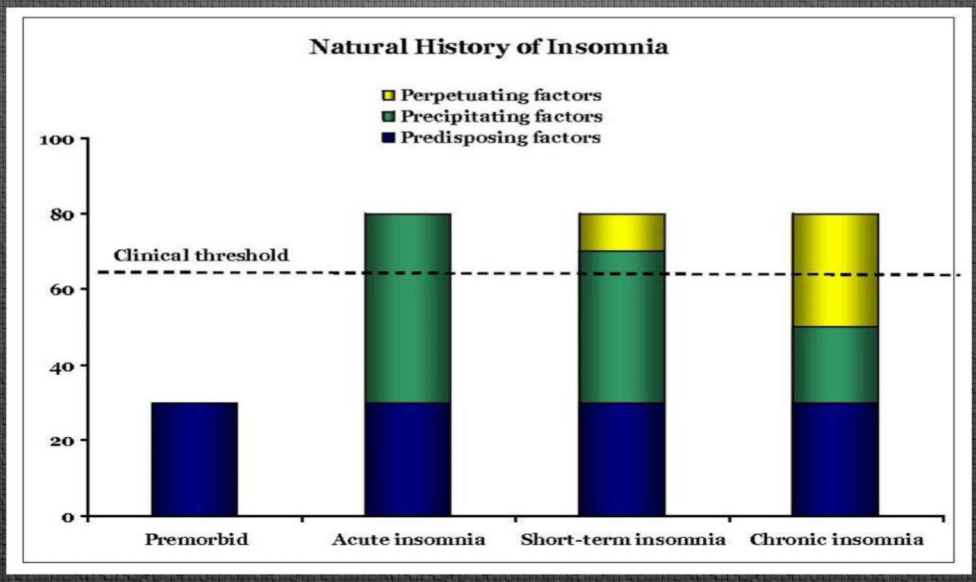
Psychophysiologic Insomnia?
What is this?

characterized primarily by heightened arousal and learned sleep-preventing associations that result in a complaint of insomnia. Patients presumed to have this type of insomnia often have sleep difficulty when trying to sleep in their usual sleep setting at home but may fall asleep easily in a novel sleep setting or when not trying to sleep. They also demonstrate excessive focus on and worry about sleep and suffer from elevated levels of cognitive and somatic arousal, particularly at bedtime.

Increased level of anxiety or excessive concerns

Increased level of sympathetic tones

Mechanism of Insomnia
Spielman's 3P model of Insomnia



Treating Insomnia
Identify treatable cause first!

1. Elimination of Provoking factors
   : Pain? – analgesics
   : Psychic disorders? – treat anxiety
   : RLS? – treat RLS
   : Daytime exercise, improve sleep hygiene

2. Elimination of Perpetuating factors
   : CBTI (Cognitive & Behavioral Therapy of Insomnia)

3. Get help from Hypnotics

Parasomnias

Parasomnias
Subtypes

NREM-related Parasomnias
- Confusional Arousals
- Sleepwalking
- Sleep Terrors
- Sleep Related Eating Disorder

REM-related Parasomnias
- REM Sleep Behavior Disorder
- Recurrent Isolated Sleep Paralysis
- Nightmare Disorder

Other Parasomnias
- Exploding Head Syndrome
- Sleep Related Hallucinations
- Sleep Enuresis

Isolated Symptoms and Normal Variants
- Sleep talking

10%

NREM-related Parasomnias (Disorder of Arousal) with Variants

A. Confusional Arousal

: There is an absence of terror or ambulation outside of the bed.

B. Sleep Walking

: associated with ambulation and other complex behaviors out of bed.

C. Sleep Terrors

: beginning with an alarming vocalization such as a frightening scream, and signs of autonomic arousal, including mydriasis, tachycardia, tachypnea, and diaphoresis.

D. Sleep related Eating Disorder

NREM Parasomnia in Adults

수면제 부작용인 경우가 많이 보고됨.

NREM Parasomnia

Table 3 Provoking NREM parasomnias

	Increase sleep fragmentation	Increased sleep inertia	Both
Conditions	Noise	Sleep Deprivation	OSA
	Pain	Circadian Misalignment	Orexin dysfunction (narcolepsy)
	RLS/PLM	Sedative hypnotic medication	

REM Sleep Behavior Disorder

Criteria A–D must be met

A. Repeated episodes of sleep related vocalization and/or complex motor behaviors.1,2

B. These behaviors are documented by polysomnography to occur during REM sleep or, based on clinical history of dream enactment, are presumed to occur during REM sleep.

C. Polysomnographic recording demonstrates REM sleep without atonia (RWA)3

D. The disturbance is not better explained by another sleep disorder, mental disorder, medication, or substance use.

Notes

1. This criterion can be fulfilled by observation of repetitive episodes during a single night of video polysomnography.
2. The observed vocalizations or behaviors often correlate with simultaneously occurring dream mentation, leading to the frequent report of "acting out one's dreams."
3. As defined by the guidelines for scoring PSG features of RBD in the most recent version of the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events.
4. Upon awakening, the individual is typically awake, alert, coherent, and oriented.
5. On occasion, there may be patients with a typical clinical history of RBD with dream-enacting behaviors, who also exhibit typical RBD behaviors during vPSG, but do not demonstrate sufficient RWA, based on the current evidence-based data, to satisfy the PSG criteria for diagnosing RBD. In such patients, RBD may be provisionally diagnosed, based on clinical judgment. The same rule applies when vPSG is not readily available.
6. Medications may unmask latent RBD with preexisting RWA, according to current expert opinion. Therefore, medication-induced RBD can be diagnosed as RBD, using clinical judgment, pending future longitudinal studies.

REM Sleep Behavior Disorder

Dream Enacting Behavior

0.5%

Clinical Presentations

: 0.5~1.0 % Prevalence

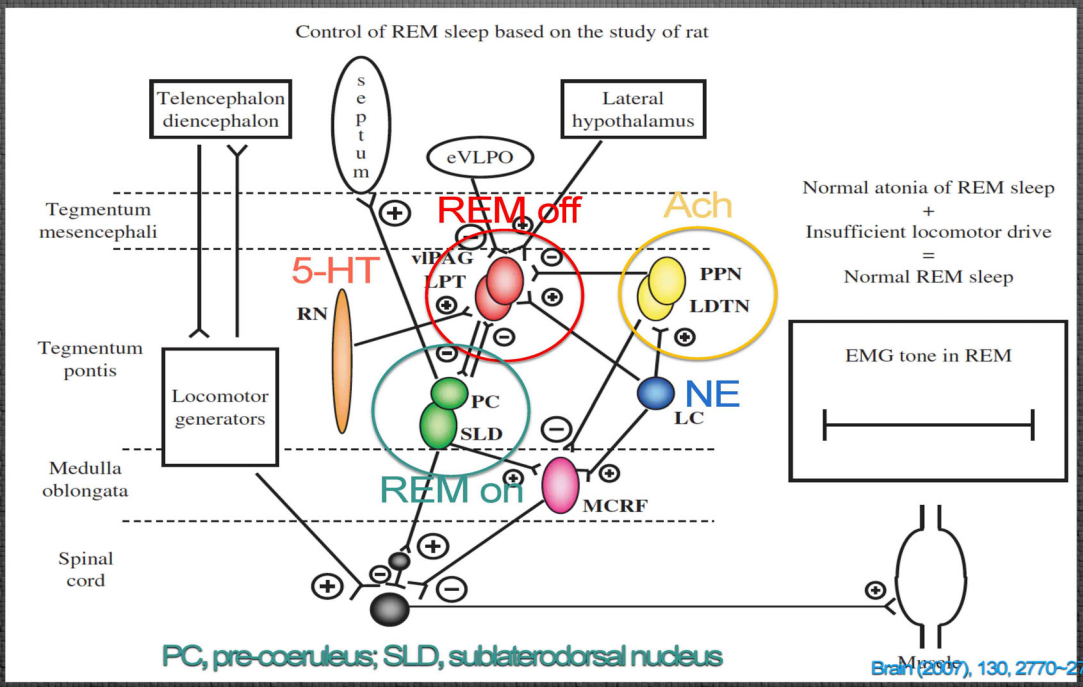
: Dream enacting behavior, usually can be recalled. Mechanism responsible for normal skeletal muscle atonia is not functioning.

: Onset 50 ~ 60 years old, men are affected more frequently than women (men ~ 80%).

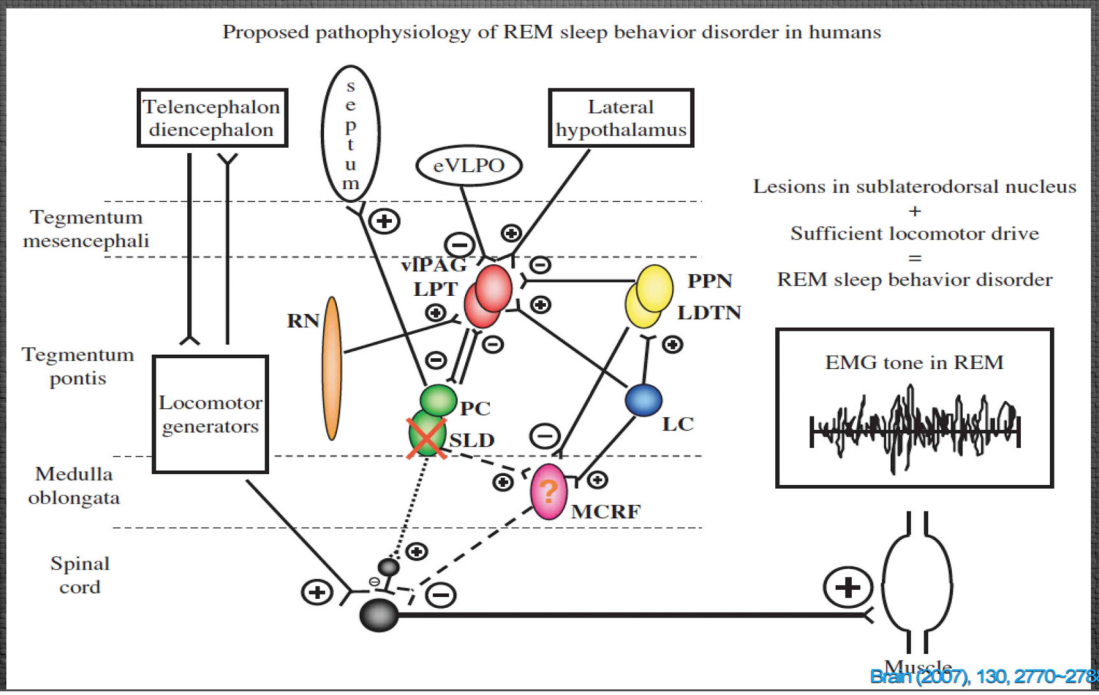
: Can cause severe injury themselves or bed-partner.

: Strong association with PD, MSA, DLB, alcohol, narcolepsy, use of withdrawal of psychotic medications (TCA, SSRI)

REM Control



REM Control

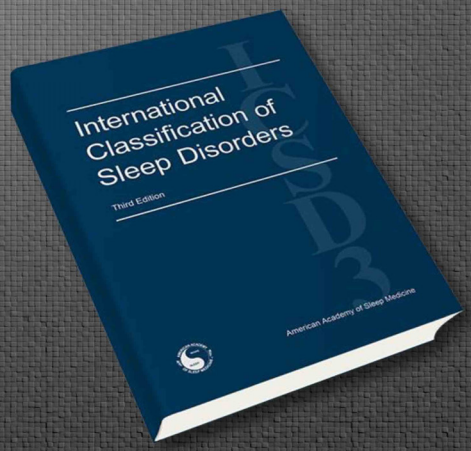


REM Sleep Behavior Disorder

Dream Enacting Behavior

1. RBD is a sole sleep disorder related with neurodegeneration, not homogenous disease.
2. Although clinical history alone is sometimes sufficient for diagnosis, the sensitivity of PSG is much higher due to RWA and patient unawareness.
3. Studies from sleep centers (mainly natural history data) indicated 50~90% RBD developed neurodegeneration over 10 years; however there are lack of large, collective studies and population studies.
4. In synucleinopathy, most patients have RBD; however, the association with AD is unclear.

Narcolepsy



Central Disorders of Hypersomnolence (ICSD-3)
(Formerly, the hypersomnias not due to a breathing disorder, ICSD-2)

Narcolepsy

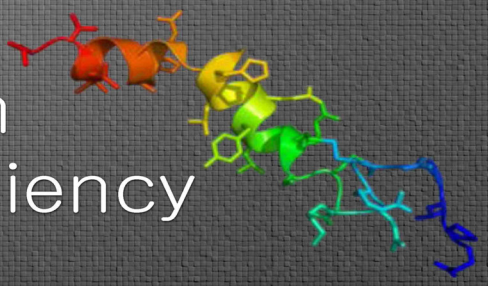
Occurs in 0.02% to 0.18% of the US and EU.

Closely associated with HLA DQB1*0602 and DR2/DRB1*1501.

Onset usually occurs between ages 10 and 25 years.

Pathophysiology of Narcolepsy?

Disorder of Orexin (hypocretin) Deficiency



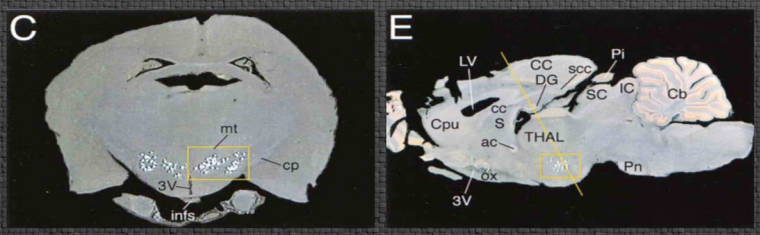
HLA (1984)

- Juji and Honda found 100% association of HLA-DR2 and DQ1 in Japanese narcoleptics (25% in control)
- The HLA genes, also called major histocompatibility (MHC) genes, are essential contributors to genetic diversity in the immune response, allowing more diverse epitope presentation.
- In 1992, stronger association with HLA-DQB1*06:02 and DQA1*01:02 loci rather than DR2 was found as the best marker for narcolepsy.
- However, the evidence of autoimmune reaction was not found, and no association of Mendelian inheritance was found (1% penetrance, 30% in monozygotic twin).

Juji T, Satake M, Honda Y, Doi Y.
HLA antigens in Japanese patients with narcolepsy. All the patients were DR2 positive.
Tissue Antigens. 1984;24(5):316–9.

Hypocretin/Orexin (1998)

- Almost simultaneously identified by De Lecea & Sakurai, independently.
- De Lecca et al. coined the name "hypocretin" because the peptide producing neurons are located in the dorsal and lateral hypothalamus, and the peptides shared similar structure of gut hormone "secretin".
- Sakurai et al. termed " Orexin" because the Greek word 'orexis' means 'appetite' after their finding that these peptides stimulate food consumption.



De Lecea et al. The hypocretins: hypothalamus–specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA. 1998:95:322–7.
Sakurai T et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein–coupled receptors that regulate feeding behavior. Cell. 1998:92:573–85.

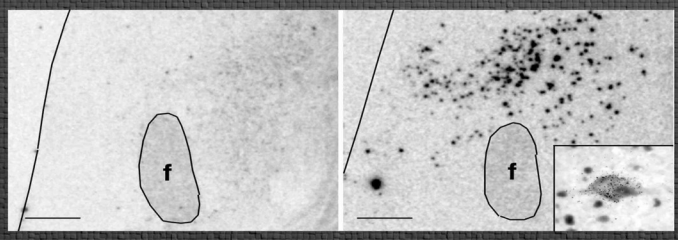
Connection with narcolepsy (1999)

- Dense projections to monoaminergic cell groups such as the locus coeruleus, the raphe, and tuberomammilary nuclei, suggested a possible involvement in sleep regulation.
- Canine narcolepsy related with hypocretin 2 gene mutation, and orexin KO mice showed narcoleptic behavior.

Lin L, et al. The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene. Cell. 1999:98(3):365–76.
Chemelli RM, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. Cell. 1999:98(4):437–51.

Human narcolepsy (2000)

- In 2000, Peyre found almost loss of hypocretin-secreting neuron in human narcoleptics, but failed to find loss of hypocretin gene.
- Cell loss was very specific, melanin-concentrating hormone (MCH) neurons, which are intermixed with hypocretin cells in the normal brain, were not affected. Increased histaminergic neuron was found (remodeling of wake-promoting system?).



Peyron C, et al. A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains. Nat Med. 2000;6(9):991–7.

Human narcolepsy (2000)

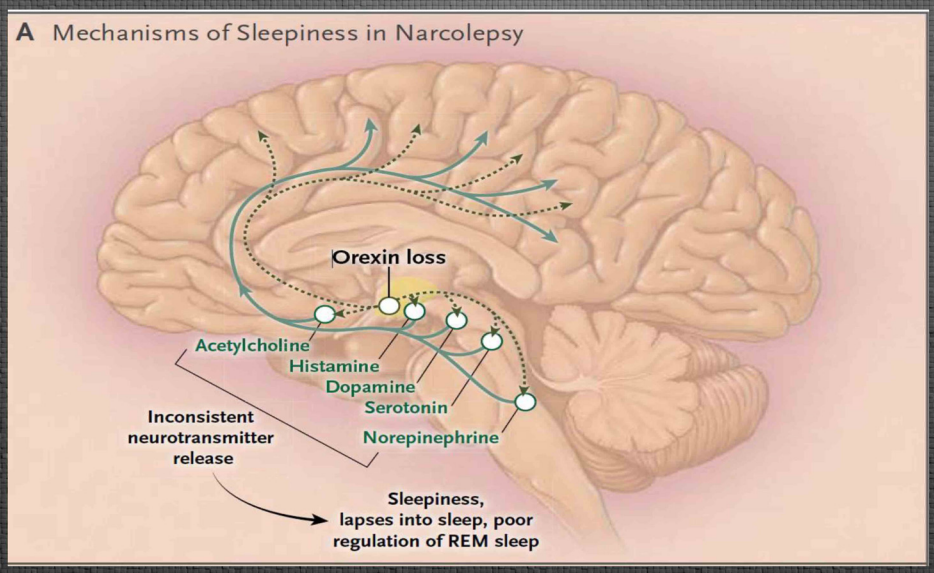
- In 2000, Nishino et al. found 7 out of 9 narcolepsy patients had undetectable hypocretin 1 levels in their CSF

Subjects	Age (yrs)	Sex	MSLT		Cataplexy	Duration of illness (yrs)	Current pharmacological treatment (daily dose)	Hypocretin-1 (pg/ mL)
			SL (min)	SOREMP				
Patients								
1	27	M	1·0*	3*	+	9	GHB 5·6 g/methylphenidate 5–10 mg	<40
2	34	M	0·9	5	+	4	untreated for 2·5 months	<40
3	39	F	2·0*	2*	+	1	Clomipramine 10 mg	<40
4	45	F	3·0	2	+	14	Methylphenidate 30 mg	255
5	50	M	6·3*	3*	+	19	Clomipramine 30 mg/GHB 3·0 g	638
6	50	M	1·2	3	+	32	GHB 5·4 mg/modafinil 400 mg	<40
7	53	F	1·2	1	+	19	GHB 4·0 g	<40
8	69	F	2·8	2	+	38	Clomipramine 10 mg/modafinil 200 mg	<40
9	70	M	2·1	2	+	53	untreated for 20 years	<40
Controls								
1	22	M	na	na	–	na	–	285
2	23	F	na	na	–	na	–	285
3	33	M	na	na	–	na	–	250
4	45	M	na	na	–	na	–	280
5	45	F	na	na	–	na	–	280
6	46	F	na	na	–	na	–	285
7	48	F	na	na	–	na	–	280
8	61	F	na	na	–	na	–	285

Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Hypocretin (orexin) deficiency in human narcolepsy. Lancet. 2000;355(9197):39–40.

Hypocretin/orexin

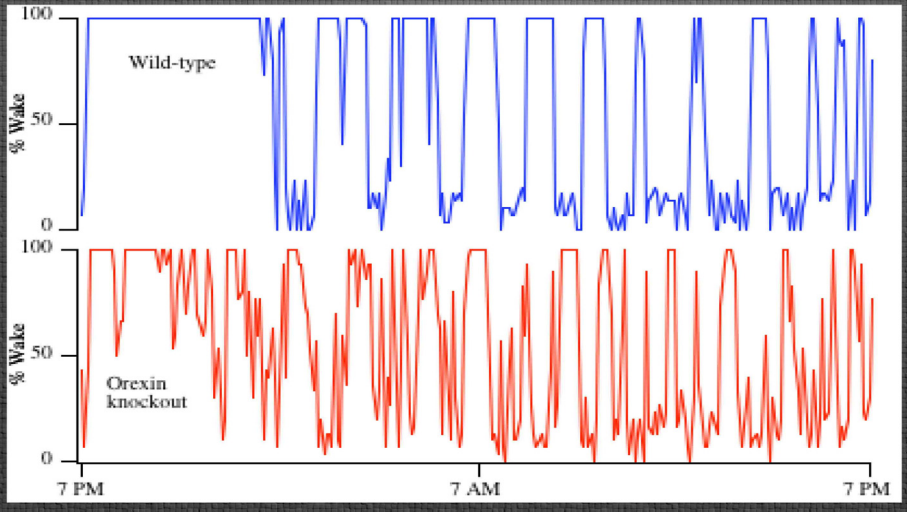
- Excessive sleepiness



Thomas E. Scammell,.
N Engl J Med 2015;373:2654-62.

Hypocretin/orexin

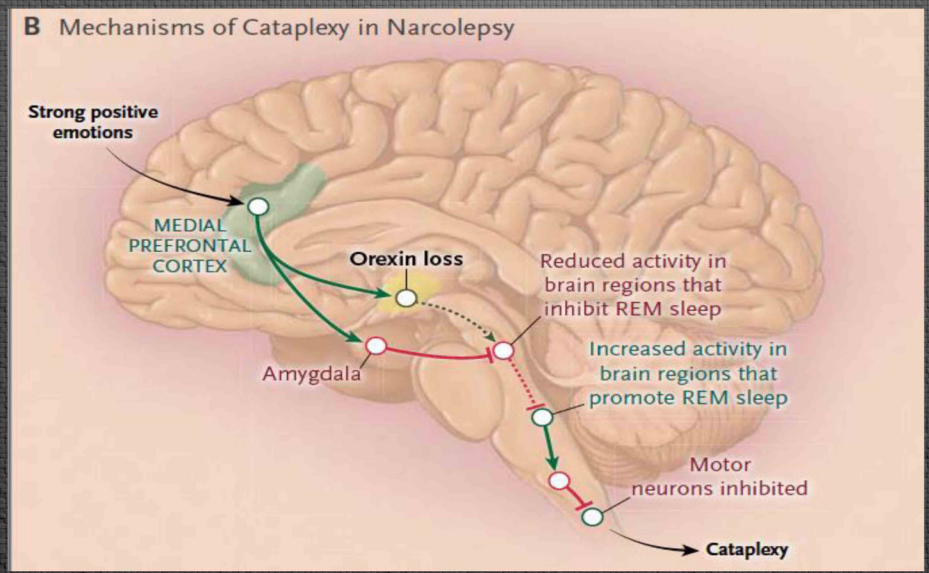
- Orexin may stabilize wake/sleep



Mochizuki T, Crocker A, McCormack S, Yanagisawa M, Sakurai T, Scammell TE (2004) Behavioral state instability in orexin knock-out mice. J Neurosci 24:6291- 6300.

Hypocretin/orexin

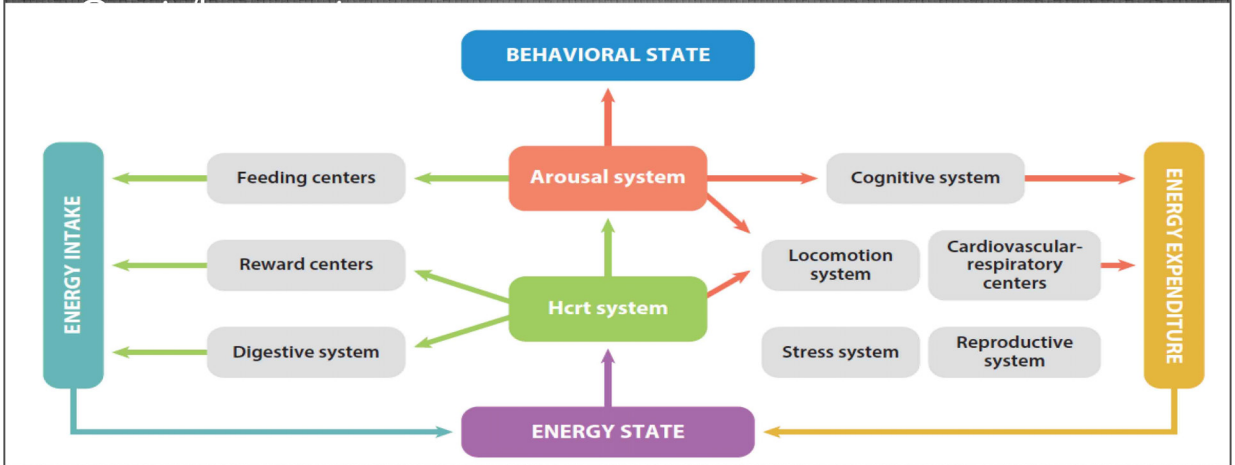
- Cataplexy



Thomas E. Scammell,.
N Engl J Med 2015;373:2654-62.

Hypocretin/orexin

- Obesity is common in Narcoleptics



Xiao-Bing Gao and Tamas Horvath,
Annu. Rev. Neurosci. 2014. 37:101-16

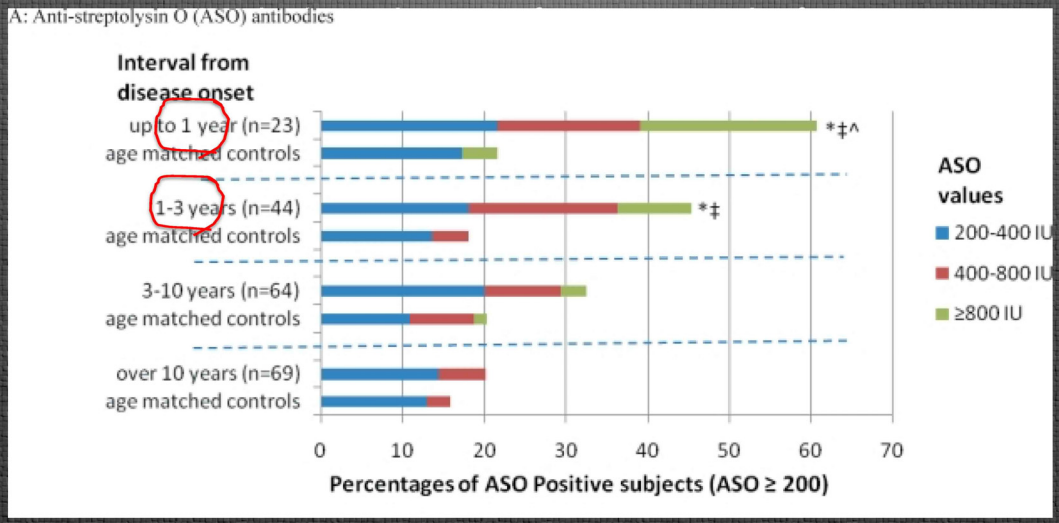
Why orexin neurons are damaged?

- HLA-DQB1*06:02 is found in ~90% of the patients with narcolepsy, and relative risk is 200 fold
- GWA studies showed association with T-cell receptor loci (TCR)
  – Many researchers speculate the association between HLA antigen and autoimmunity

- However, autoantibodies targeting hypocretin peptides were not found.
  : No anti-hypocretin/orexin Ab
- Immunostaining of hypothalamic tissue with human narcolepsy sera did not reveal autoantibodies
- Passive transfer of experiments of human sera to animal failed to show selective orexin neuronal death.

Role of upper airway infections

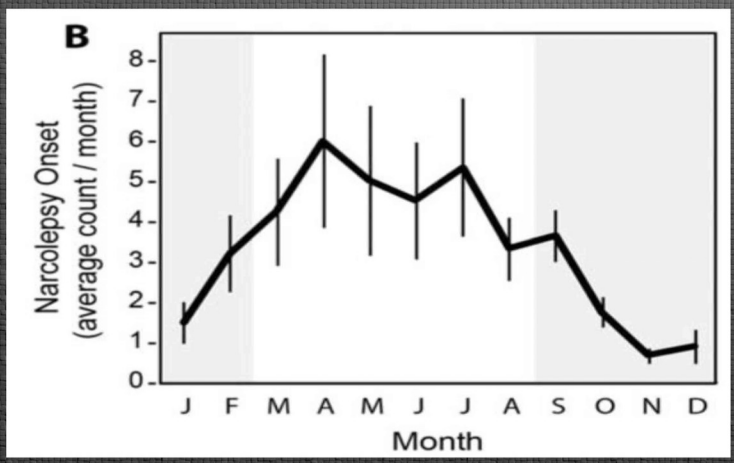
- Since 1989, the association with streptococcal infection was suggested.



Aran A, et al. Elevated anti-streptococcal antibodies in patients with recent narcolepsy onset. Sleep. 2009;32(8):979–83.

China cohort studies

- Narcolepsy onset was about 6 times more frequent in late spring versus early winter: narcolepsy were triggered by winter URI?



Han F, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. Ann Neurol. 2011;70(3):410–7.

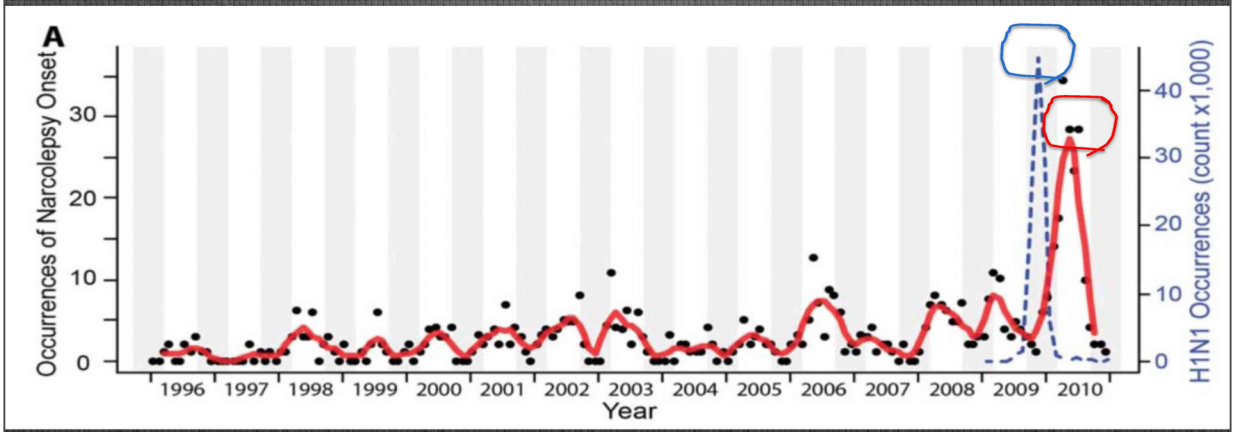
Pandemrix and 2009 H1N1 influenza

- In 2009, swine influenza H1N1 spread rapidly in humans with fatality rate of 0.4 %.
- In Spring of 2010, 3–5 times increase in the number of children with narcolepsy when compared to prior years, a peak that appeared 4–6 months after the peak of H1N1 infections
- In both Finland and Sweden, cases of childhood onset narcolepsy were reported a few months following vaccination with a particular pH1N1 vaccine called Pandemrix, documenting a tenfold increased risk

Nohynek H, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy in Finland. PLoS ONE. 2012;7(3):e33536.
Szakacs A, Darin N, Hallbook T. Increased childhood incidence of narcolepsy in western Sweden after H1N1 influenza vaccination. Neurology. 2013;80(14):1315–21.

China cohort studies

- Narcolepsy onset occurrences over the past 15 years in 629 patients with narcolepsy/hypocretin deficiency diagnosed at the People's Hospital, Beijing University, China.



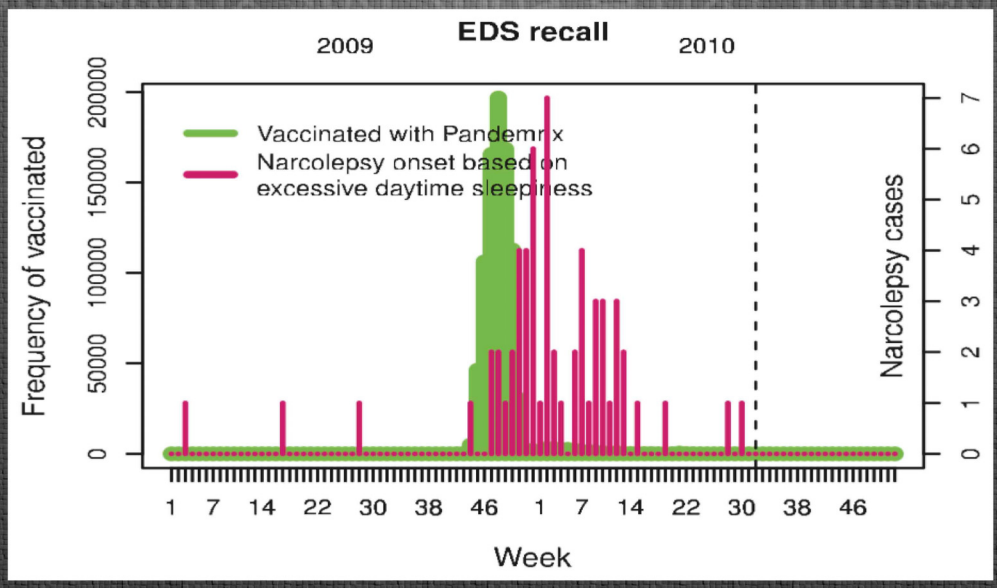
Han F, et al. Narcolepsy onset is seasonal and increased following the 2009 H1N1 pandemic in China. Ann Neurol. 2011;70(3):410–7.

Pandemrix and 2009 H1N1 influenza

- In Finland, a Retrospective cohort study showed
  - : Of the 67 confirmed cases of narcolepsy, 46 vaccinated
  - : 9.0 in the vaccinated as compared to 0.7/100,000 person years in the unvaccinated
  - : 1:16,000 vaccinated 4 to 19-year-olds

Nohynek H, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy,in Finland. PLoS ONE. 2012;7(3):e33536.

Pandemrix and 2009 H1N1 influenza



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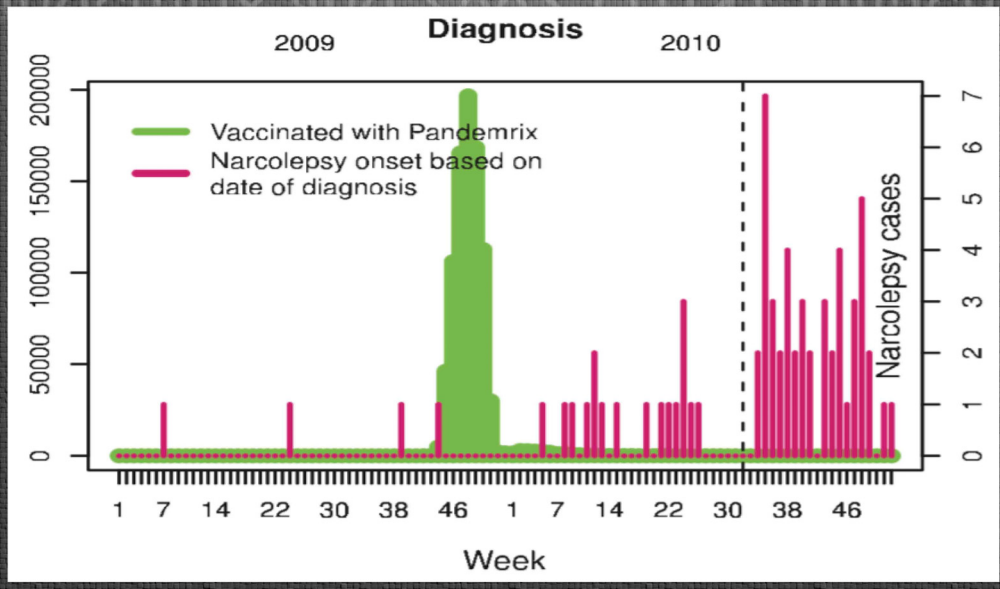
Pandemrix and 2009 H1N1 influenza



Nohynek H, et al. AS03 adjuvanted AH1N1 vaccine associated with an abrupt increase in the incidence of childhood narcolepsy,in Finland. PLoS ONE. 2012;7(3):e33536.

Why Pandemrix?

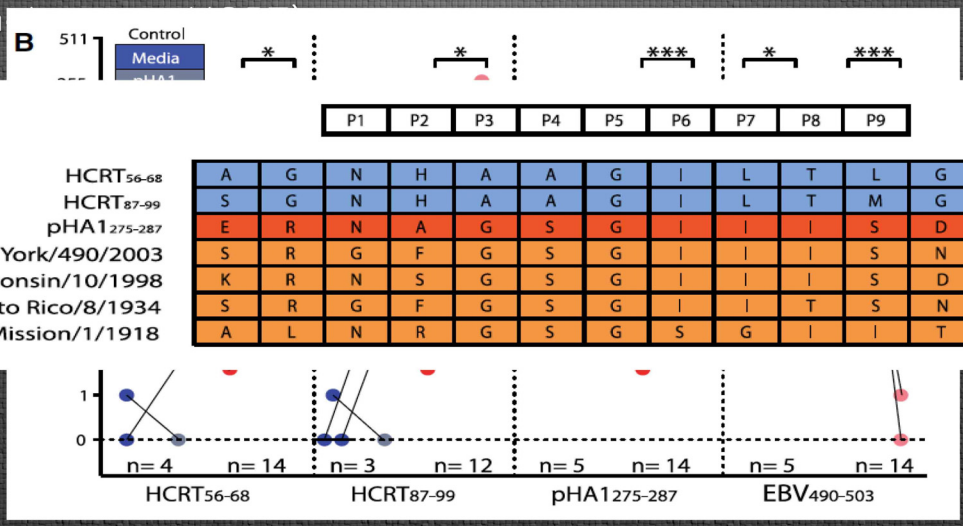
- Manufactured in Dresden by Glaxosmithkline (GSK)
  - Use purified HA(hemagglutinin) antigen (of H1N1) with specific adjuvant (AS03A), potent at stimulating CD4 T-cell responses and it is clear that vaccine efficacy was high
  - HA itself is lower in Pandemrix
- Focetria, a Novartis vaccine, uses a MF59 adjuvanted and more pure H1 preparation – no report yet.
- Arepandrix by same GSK, used different HA isolation technique reported to have 1.5- to 3-fold risk of narcolepsy in Canada
  : Same AS03A adjuvant, why different? purification problem?

Why Pandemrix?

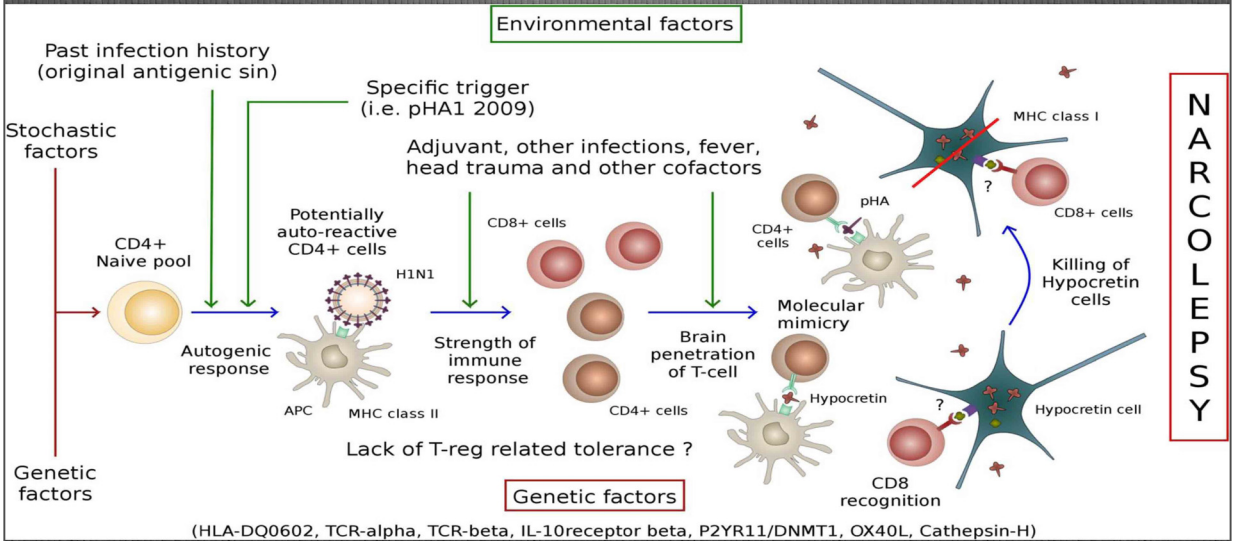
The full ECDC-VAESCO report confirmed the association between pandemic influenza vaccination and narcolepsy and EMA recommend H1N1-AS03-P immunization should not be administered to children and adolescents younger than 20 year

H1 2009 flu peptide as a mimic of hypocretin

- Cultures of narcolepsy T cells with pHA1275–287 (A hemagglutinin (HA) pHA1 epitope specific to the 2009 H1N1 strain, partly hom



Pathophysiological model for narcolepsy



Emmanuel J. M. Mignot.
Immunol Res (2014) 58:315–339.

Sleep Related Movement Disorders

Sleep Related Movement Disorders
Subtypes

Restless Legs Syndrome
Periodic Limb Movement Disorder
Sleep Related Leg Cramps

Sleep Related Bruxism
Sleep Related Rhythmic Movement Disorder
Benign Sleep Myoclonus of Infancy
Propriospinal Myoclonus at Sleep Onset
Sleep Related Movement Disorder Due to a Medical Disorder
Sleep Related Movement Disorder Due to a Medication or Substance
Sleep Related Movement Disorder, Unspecified

Restless Legs Syndrome
Clinical Features

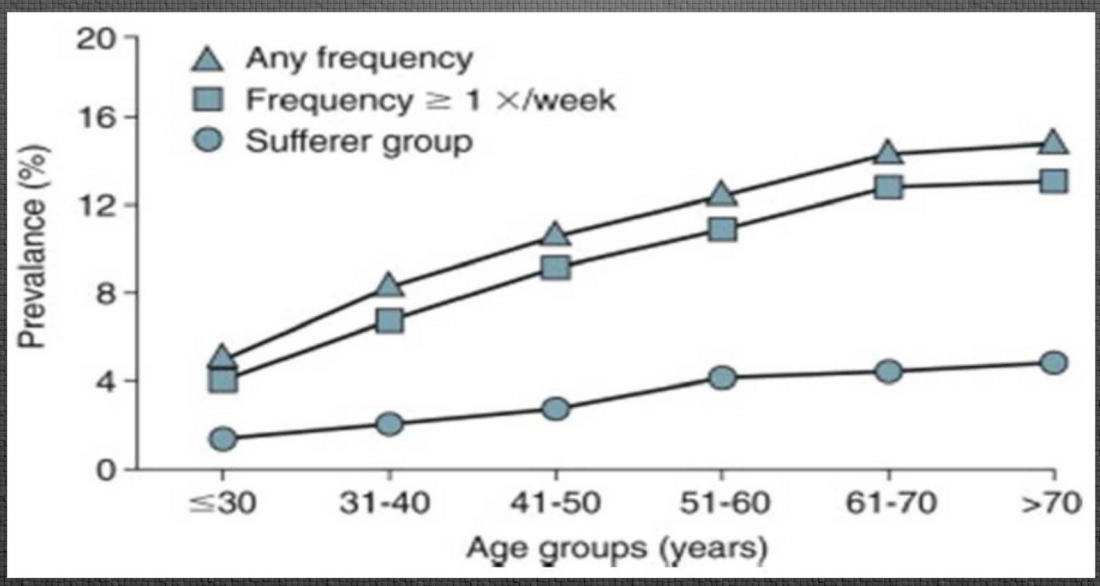
The overall prevalence of has been estimated at 5~10% in EU & US population-based studies. (clinically significant RLS to be 2% to 3% ?)
: In Korea, 0.9 to 12.1% in various studies

Women > Men

10%

Can begin at any age
RLS can be intermittent
Variable course
- Early onset (< 50 yrs): onset is insidious
- Late onset: abrupt and more severe

Restless Legs Syndrome – Prevalence by Age
Age and symptoms



Restless Legs Syndrome
Causes

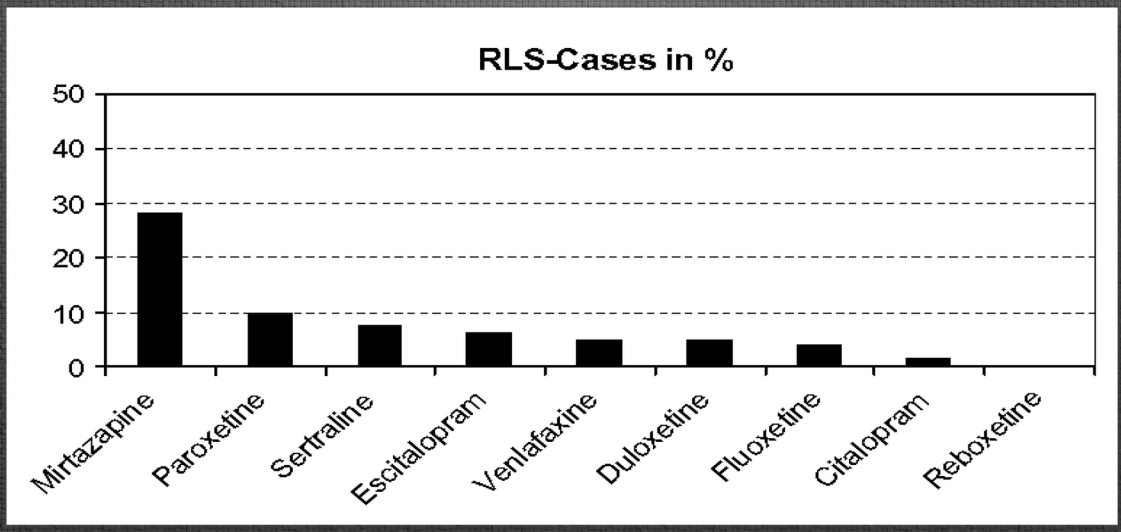
Primary RLS
- Familial
- Idiopathic

Characteristics
- Earlier age of onset and slower progression
- Familial occurrence more likely

70%

Secondary RLS
- Iron deficiency
- Pregnancy
- Neuropathy: diabetic and others
- Multiple sclerosis
- Renal failure (transplant but NOT dialysis cures RLS)
- Parkinson's disease
- Medications
  - First-generation (sedating) antihistamines (diphenhydramine)
  - Dopamine receptor blockers: metoclopramide?
  - Antidepressants (SSRIs, SNRIs): exception is bupropion

Restless Legs Syndrome
Check medication history …

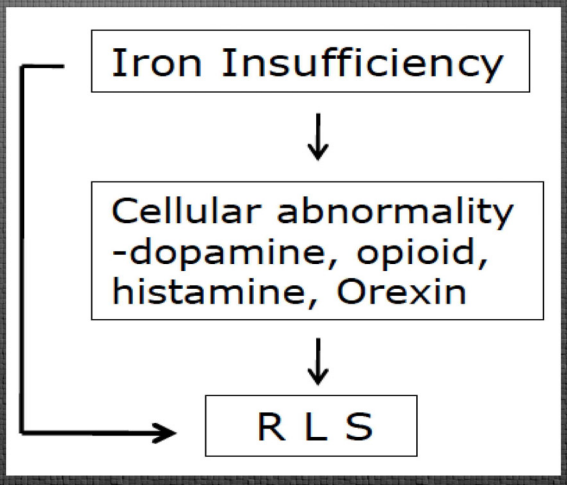


Restless Legs Syndrome
Mechanism?

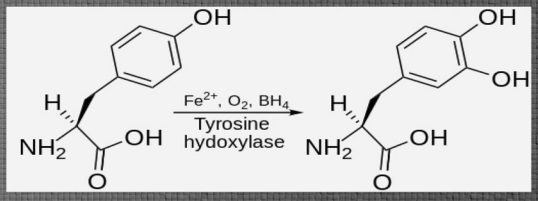
Iron

Dopamine

Opioids



Restless Legs Syndrome
Mechanism?



Iron – dopamine connection
- relative brain iron deficiency
- CSF, autopsy, brain imaging study: all brain iron deficiency
- substantia nigra, striatum: dopamine-producing cell
- BDBT9 allele related to iron deficiency and RLS/WED

Dopamine pathology
- cellular iron deficiency →
- Increased tyrosine hydroxylase activity →
- Increased extracellular dopamine →
- Decreased D2 receptor activity, DAT activity
- In Night, decreased DA and decreased D2R may evoke symptoms

hyperdopaminergic condition with apparent postsynaptic desensitization

Restless Legs Syndrome
Ferritin, ferritin, and ferritin...

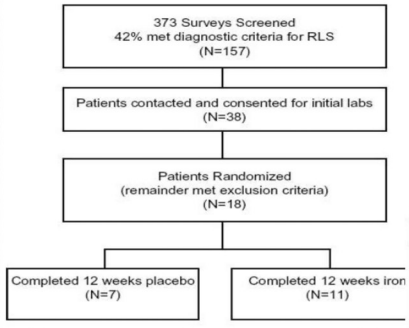
Table 2 Relations of serum ferritin level and change in restless legs syndrome severity scale score in patients treated with iron supplements

	Initial Serum Ferritin (μg/L)		
	≤18	>18–≤45	>45–<100
Patients (n)	6	4	5
Median change in severity score (range)	4 (0–8)	3 (0–5)	1 (0–2)
Change in severity score ≥2 points (%)	5 (83)	3 (75)	2 (40)

Restless Legs Syndrome
Ferritin, ferritin, and ferritin...

Efficacy of oral iron in patients with RLS and a low-normal ferritin: A randomized double-blind, placebo-controlled study

Sleep medicine 2009



g. 1. Study design and randomization of patients to iron and placebo gr

325 mg ferrous sulfate along with 100 mg vit C on an empty stomach 2 times daily

Results values at baseline to 12 weeks for patients randomized to iron and placebo groups.

	Iron group	Placebo group	*p*-Value*
IRLS baseline score (mean ± SD)	24.8 ± 5.72	23.0 ± 5.03	0.49
IRLS score change at 12 weeks (mean ± SD)	−10.3 ± 7.40	−1.14 ± 5.64	*0.01*
Ferritin baseline (mean ± SD)	40.6 ± 15.3 (ng/ml)	36.7 ± 20.8 (ng/ml)	0.68
Ferritin change at 12 weeks (mean ± SD)	+25.1 ± 20.3 (ng/ml)	+7.5 ± 13.7 (ng/ml)	*0.04*
Overall quality of life[a]			
Improved	7	1	0.07
Stayed the same or worsened	4	6	

[a] Dichotomous variable of improvement.
* Two-tailed *p*-value, 95% confidence interval.

Restless Legs Syndrome
Ferritin, ferritin, and ferritin…

IV iron dextran for severe refractory RLS

Ondo WG, Sleep medicine 2010

- ✓ 25 subjects (age 53.2 ± 11.9, 7 male)
  IV iron for RLS refractory to conventional treatments.
  1 g of high molecular weight iron dextran over five hours
  Baseline ferritins ; 5 ~ 248 ng/ml (mean 43.5 ± 58.0)
  20/25 ; <50 ferritins.
- ✓ Overall, 2 subjects reported complete amelioration of all RLS symptoms, 11 reported marked improvement, 2 moderate improvement, 3 mild improvement, and 6 reported no improvement.
- ✓ The duration of effect was highly variable
  : mean 15.8 ± 17.7 weeks, (range 1–60 weeks).
- ✓ Iron dextran can dramatically improve refractory RLS but results are inconsistent and not predicted by patient demographics.
  Although burdened by a higher rate of anaphylactic reactions, iron dextran may be superior to other IV iron preparations.

Thank You for Your Attention!