การประชุมสัมมนาวิชาการด้านวิทยาศาสตร์การแพทย์เรื่อง “การพัฒนายุทธศาสตร์งานวิจัยเกี่ยวกับสมอง จิตใจ และพฤติกรรม” (Development of Research Strategies for Brain Mind and Behaviour)

จัดโดย สาขาวิทยาศาสตร์การแพทย์ สานักงานคณะกรรมการวิจัยแห่งชาติ (วช.) ร่วมกับสถาบันวิจัยระบบสาธารณสุข (สวรส.)

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Introduction to sleep and importance of sleep on health and brain functions

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Sleep

From Wikipedia, the free encyclopedia

Sleep is a naturally recurring state characterized by reduced or absent consciousness, relatively suspended sensory activity, and inactivity of nearly all voluntary muscles. It is distinguished from quiet wakefulness by a decreased ability to react to stimuli, and is more easily reversible than being in hibernation or a coma. Sleep is also a heightened anabolic state, accentuating the growth and rejuvenation of the immune, nervous, skeletal and muscular systems. It is observed in all mammals, all birds, and many reptiles, amphibians, and fish.

The purposes and mechanisms of sleep are only partially clear and are the subject of intense research. Sleep is often thought to help conserve energy, but actually decreases metabolism only about 5–10%. Hibernating animals need to sleep despite the hypometabolism seen in hibernation, and in fact they must return from hypothermia to euthermia in order to sleep, making sleeping “energetically expensive.”

โรคใหลตาย ( Sudden Unexplained Nocturnal Death Syndrome: SUNDS ) คือการตายอย่างเฉียบพลันซึ่งเกิดขึ้นในผู้ชายที่มีอายุระหว่าง 18-45 ปี ที่เคยมีสุขภาพเป็นปกติ ในระหว่างการนอนหลับหรือขณะที่กำลังพักผ่อน และภายหลังการตาย การชันสูตรผ่าศพ และตรวจทางพยาธิวิทยาตามปกติไม่สามารถอธิบายถึงสาเหตุการตายได้อย่างแน่นอน
แผนที่แสดงการกระจายของผู้ตายดื้อโรคใหลตายในภาคอีสาน

แผนที่แสดงสมมุติฐานของความเกี่ยวข้องระหว่างเชื้อชาติในชนชาติของเอเชียที่ทำให้มีการถ่ายทอดความผิดปกติทางพันธุกรรมที่เป็นความเสี่ยงของการโรคใหลตายในกลุ่มชนบางประเทศในทวีปเอเชีย

สรุปผลการตรวจชันสูตรผ่าศพและสาเหตุที่น่าจะเกี่ยวข้องกับความผิดปกติต่างๆที่ร่างกายอาจมีการตั้งสมมุติฐานว่าการตายในโรคใหลตายอาจเกี่ยวข้องกับสาเหตุที่เป็นไปได้หลายประการอาทิเช่น:

1. ความผิดปกติทางพันธุกรรม
2. ความผิดปกติในระบบเนื้อเยื่อนำไฟฟ้าภายในหัวใจ
3. การขาดสารอาหารเช่นการขาดสารไธอามีน (B1)
4. การมีปริมาณโปแตสเซียมในเลือดต่ำ
5. ความผิดปกติในระบบสารเคมีสื่อนำการสื่อสารในระบบประสาท (Neurotransmitters)
6. ความผิดปกติในระบบประสาทอัตโนมัติ (Autonomic Nervous System)
7. ภาวะความเครียดทางร่างกายและจิตใจ
8. ภาวะความเครียดทางจิตใจ
9. ความผิดปกติในการควบคุมการหายใจระหว่างการนอนหลับ (Sleep related breathing disorders e.g. Sleep apnea Syndromes)
10. การได้รับเชื้อโรค เช่น เชื้อไวรัส (Influenza virus Type A)
11. โรคเมลลอยด์โดซีส (Melloidosis) จากการติดเชื้อ Pseudomonas mellei
12. การใช้ยาเสพติด เช่น แอลกอฮอลและสารพิษ
What are the possible biomarkers on the X chromosome?

- pyruvate dehydrogenase
- ornithine carbamyl transferase
- glyceraldehyde-3 phosphate dehydrogenase
- α-phosphorylase kinase
- monoamine oxidase A and B
- glycine receptor
- GABA receptor

_is SUNDS an X-linked recessive inheritance_?
Table showing abnormalities in several areas of the DNA sequence of the MAO-A gene.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control</th>
<th>SUNDS</th>
<th>Control</th>
<th>SUNDS</th>
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<td>0.00</td>
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<tr>
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<td>SNP1.25</td>
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<td>Control</td>
<td>0.00</td>
<td>5.00</td>
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</tbody>
</table>

Professor Soichi Katayama and Dr. Ronald Munger in front of NBBC, 30th November 1992.
1992  Foundation of Asian Sleep Research Society (ASRS)
1994  1st ASRS Congress in Tokyo, Japan
1997  2nd ASRS Congress in Jerusalem, Israel
2000  3rd ASRS Congress in Bangkok, Thailand
2004  4th ASRS Congress in Zuhai, China
2005  5th ASRS Congress in Seoul, Korea
2008  6th ASRS Congress in Kyoto, Japan
2011  WorldSleep 2011 and 7th ASRS, Kyoto
2012  8th ASRS Congress in Taipei, Taiwan

3rd ASRS Congress Pre-Congress Training Workshop
December 1-2, 2000, Salaya, Thailand

3rd ASRS Congress
December 3-7, 2000 Bangkok, Thailand

World Association of Sleep Medicine (WASM)
www.wasmonline.org
Sleep is NOT just the absence of wakefulness

- Active
- Complex
- Highly Regulated
- Involves different areas in the brain
- The whole purpose is not fully understood
- Essential to life
  - We all do it

---

One-third of the life span is spent in sleep, a state that is crucial for physical, mental and emotional well-being.

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**Wake / Sleep Pattern Development**

As a child develops, its sleep gradually becomes restricted to the night.

**Infants**
- Birth–2 months need 12–18 hours
- 3–11 months need 14–15 hours

**Toddlers/Children**
- 1–3 years need 12–14 hours
- 3–5 years old need 11–13 hours
- 5–10 years old need 10–11 hours

**Adolescents**
- 10–17 years need 8.5–9.5 hours

**Adults**
- need 7–9 hours

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Sleep is regulated by the brain, its genetic clocks, neurochemical transmitters, hormones, and mediators.

Sleep is determined by genetic factors and developmental learned experience.

Sleep is sensitive to environmental factors e.g. temperature, noises, pollution, psychological anxiety and stress, foods and drugs etc.

How do aquatic mammals sleep? With one half-brain at a time!!!
The optimal amount of sleep is not a meaningful concept unless the timing of that sleep is seen in relation to an individual's circadian rhythms.

A person's major sleep episode is relatively inefficient and inadequate when it occurs at the "wrong" time of day; one should be asleep at least six hours before the lowest body temperature.

The timing is correct when the following two circadian markers occur after the middle of the sleep episode and before awakening:
1. Maximum concentration of the hormone melatonin, and
2. Minimum core body temperature.

Human sleep needs can vary by age and among individuals, and sleep is considered to be adequate when there is no daytime sleepiness or dysfunction. Moreover, self-reported sleep duration is only moderately correlated with actual sleep time as measured by actigraphy, and those affected with sleep state misperception may typically report having slept only four hours despite having slept a full eight hours.
Two distinctive phases of sleep:

1. Non-REM Sleep
2. Rapid Eye Movement (REM) Sleep

Sleep was discovered by Eugene Aserinsky and Nathaniel Kleitman in 1954, and was later found to be associated with dreaming.
REM Sleep

• "Rapid Eye Movement"
• REM called paradoxical sleep
  – Brain waves similar to waking state, but person is deeply asleep and unable to move
• Most dreaming takes place during REM

What Happens When We Sleep?

• Stage 1
  – A twilight zone between full wakefulness and sleep.
  – The brain produces small, irregular, rapid electrical waves.
• Stage 2
  – Brain waves with characteristics of Sleep Spindles and K-Complex before slipping into unawareness of the surrounding.
  – Eyes unresponsive and bodily functions slow.
• Stage 3 and 4
  – The most profound state of unconsciousness and quiet resting sleep
  – The brain produces slower, larger waves, "Delta" or slow-wave sleep.
• REM sleep
  – Vivid dreaming during rapid eye movements, and body with no muscle tone to prevent body movements.
  – Brain waves resemble those of waking more than quiet sleep.

These stages are repeated four or five times a night.
Human Brain areas related to Waking, Sleep and dream
Serotoninergic pathways from Raphe nuclear complex

SLEEP

NON-REM SLEEP

SEROTONIN
Simultaneous sleep and functional magnetic resonance imaging (fMRI) studies

The process of falling asleep could thus be shown to consist of a successive downregulation of specific brain networks as reflected in alterations in regional BOLD (blood oxygen level dependent) signals. During rapid eye movement (REM) sleep, a functional network fostering this sleep stage previously shown in animal models, could for the first time be demonstrated in humans. High activity in cortico-limbic areas is specifically enhanced during times of high phasic activity, characterized by a high number of rapid eye movements.

Max Planck Institute of Psychiatry

During phasic REM sleep periods with high number of rapid eye movements, high cortico-thalamic activity (red) is generated in the brain.

During wakefulness, acoustic stimulation elicits activation of the auditory cortex (red). Similar stimulation during light NREM sleep stage 2 evokes transient down-regulation of widespread cortical areas (blue), supposedly a sleep protective mechanism.

Histamine

Figure 1A–C. Schematic illustration of the distribution of histamine-containing neurons in brain. M.R.E., mesencephalic reticular formation; M.B., mammillary bodies; M.F.B., medial forebrain bundle. (Modified from Schwartz et al., 1988)

<table>
<thead>
<tr>
<th>Agonists</th>
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<tbody>
<tr>
<td>Prostaglandin D2</td>
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<td>Prostaglandin E2</td>
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<tr>
<td>Histamine</td>
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</tbody>
</table>

H1 agonists and antagonists.
1. Prostaglandin D2 (PGD2) is a major prostanoid produced in rat brain. (Narumiya et al., 1982)

2. PGD2 induces sleep in rats and monkeys after intracerebroventricular administration. (Ueno et al., 1983; Onoe et al., 1988)

3. Deep sleep in patients with mastocytosis or African sleeping sickness is likely due to overproduction of PGD2. (Roberts & Oates, 1985; Pentreath et al., 1990)

**Mechanisms of Sleep-wake Regulation by PGD2 and PGE2**

<table>
<thead>
<tr>
<th>Sleep Center</th>
<th>Wake Center</th>
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<tbody>
<tr>
<td>Basal forebrain</td>
<td>Posterior hypothalamus</td>
</tr>
<tr>
<td>Preoptic area</td>
<td></td>
</tr>
<tr>
<td>PGD2</td>
<td>GABA</td>
</tr>
<tr>
<td>Histamine</td>
<td>Adenosine</td>
</tr>
<tr>
<td>Caffeine</td>
<td>VLPO</td>
</tr>
</tbody>
</table>

Hayaishi & Urade, Neuroscientist 2002

**Sleep Disorders - Socioeconomic Consequences**

- 40 million Americans suffer from chronic disorders of sleep and wakefulness.
- 95% of these remain unidentified and undiagnosed.
- The annual direct cost of sleep-related problems is $16 billion, with an additional $50-$100 billion in indirect costs (accidents, litigation, property destruction, hospitalization, and death).

**What else about sleep?**

- Sleep disorders are **common**
- Sleep disorders are **serious**
- Sleep disorders are **treatable**
- Sleep disorders are **underdiagnosed**
Major sleep disorders:

1. Insomnia (Depression, Situational etc.)
2. Hypersomnia
   - Excessive daytime sleepiness
   - Narcolepsy
3. Parasomnia
   - Night terrors, Nightmares
   - Snoring
   - Sleep apnea syndrome
     - Central or Obstructive, or mixed
   - Sleep walking, Sleep talking, Bruxism
   - Sudden Nocturnal Death Syndrome etc.
How can patients sleep when their legs are on the move?

Restless Legs Syndrome (RLS) is a neurological sensorimotor disorder which has a significant impact on sleep.

Typical polysomnographic recording of periodic leg movements (PLMs)

Pain & the Sensory Symptoms of RLS

Brain: iron tissue concentrations low on MRI

R2* images in a 70 year old RLS patient and a 71 year old control subject. Much lower R2* relaxation rates are apparent in the RLS case in both red nucleus and substantia nigra. (From Wayne Hening, 2004)

PLMD/RLS

Figure 2. Representative example of [14C]methylphenidate binding potential in the striatum of a RLS and Control subject

Hypocretin/Orexin

Abnormalities of Sleep

- **Night Terrors**
  - Abrupt, anxious awakening from a nREM sleep
  - More common in children than in adults

- **Sleep Talking**
  - Can occur in REM or nREM sleep
  - Harmless

- **Sleep Walking**
  - Usually in Stages 3 or 4 sleep
  - Early in the night
  - More common in children
**Obstructive Apnea**

A complete blockage of the airway despite efforts to breathe. Notice the effort gradually increasing ending in airway opening.

**Daytime Sleepiness (ESS) in a Population-Based Sample**

- **N** = 3,283
- **Mean** = 8.0 ± 4.6
- **Moderate OSA** = 11.5
- **Severe OSA** = 16.0
- **Narcolepsy** = 17.3

- **OSA** = obstructive sleep apnea; Myers et al. (2003), Sleep 26(suppl):A194

**Daytime Sleepiness (MSLT) in a General Population, N=259**

- **Mean** = 11.4
- **8 hours TIB x 5 nights**

- **TIB** = time in bed; Drake CL et al. (2002), Sleep 25(suppl):A91
Car Crashes in Sleep Apnea Patients


The Consequences of Sleep Apnea

The Consequences of Sleep Apnea

Endothelial Function in Obstructive Sleep Apnea

Amy Atkinson, Susan Yin Yeh, Arul Mathur and Sanja Jelic

Progress in Cardiovascular Diseases, Vol. 51, No. 5 (March/April), 2009: pp 351-362
A study using high-resolution magnetic resonance imaging (MRI) scans reports that mammillary bodies — brain structures involved in memory — were 20% smaller in patients with sleep apnea than in controls. These findings, by Rajesh Kumar, PhD, from the University of California, Los Angeles (UCLA), and colleagues, are published in the June 27 issue of Neuroscience Letters, 2008;438:330-334.

In Thailand, sleepy and drunk driving have been found to be the major causes of higher mortality and morbidity, and the loss of life and property during the last few years which require annual public health policies and campaigns against sleepy and drunk driving.
Adequate sleep is not only important for good health and well-being but also for road safety of driving automobiles. Sleepiness, fatigue and/or drowsiness related traffic accidents are very common, particularly among long-distance private, public or truck drivers.

At present traffic accidents kill 1.2 million people each year. By 2020 traffic accidents will kill 2.3 million people annually and will be the third leading cause of death.

In Asia Pacific region traffic accidents account for about 50% of global road deaths despite having only 16% of the world vehicles.

Road deaths jumped by nearly 40% in Asia between 1987 and 1995 while in developed nations they fell by about 10% because of better awareness and various safety measures.

Sleepiness can be considered as a possible cause of an accident if there are some combinations of the following:
- sleep deprivation from short and inadequate sleep preceding the accident,
- long wakefulness exceeding 8 to 12 hours of driving,
- driving at early morning hours, and
- history of alcohol drinking or taking some sedatives or medicines which induce sleepiness.

In this lecture, we explore the current evidence on impacts of sleepiness, fatigue and drowsiness with or without alcohol drinking on automobile accidents in different countries, and the campaign to stop sleepy driving.

### Numbers of accident caused by sleepy driving / year

<table>
<thead>
<tr>
<th>YEAR</th>
<th>2000</th>
<th>2001</th>
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<td>448</td>
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</tbody>
</table>

Source: National Police Bureau of Thailand

### Crashes killed 4 Thais an hour

**New Year accidents**

The road accident rate is declining in Thailand. In 2005, there were approximately 48,000 road accidents, reducing from 50,000 in 2004, according to the Ministry of Public Health.

On December 27 to January 3, the ministry said preliminary statistics had so far recorded 10,000 road accidents, 12,000 people injured and 3,000 people killed.

The number of traffic fatalities in 2005 was down from 4,000 in 2004.

**Chatchai Chaiya, who heads a road safety unit, told the newspaper**

"There is a need for more efforts in promoting seat belt use and alcohol-free driving."

As the New Year holidays draw to a close, thousands of holidaymakers continue to flock to Bangkok for a week in the capital.

The number of motor accidents increased by 10% on the road to Bangkok. On the motorway, traffic congestions have been severe with long lines of cars waiting to enter the capital.

Chatchai Chaiya, a Thai traffic police officer, has urged drivers to take extra care during the holidays.

10 died as lorry driver falls asleep

A lorry driver fell asleep and his vehicle crashed into a wall, killing 10 people.

Source: National Police Bureau of Thailand
The accident took place on the Bangkok-bound side of the Mittraphap Highway in tambon Thap Kwang of Kaeng Khoi district about 4.30am. An 18-wheel lorry ran across the traffic island and slammed into the Bangkok-Roi Et double-decker bus of state-owned Transport Co. The bus did not overturn but burst into flames. The resulting blaze caused many of the fatalities. Both vehicles ran on natural gas. Ten men, including the bus driver, and nine women were killed. Sa-ard Boonyoung, the 29-year-old driver of the lorry, said he fell asleep at the wheel.

Recent train crash which was blamed on the sleepy train drivers (15 January 2007)

Sleep deprivation was a contributing factor in biggest disasters in history, e.g.,
1979 nuclear accident at Three Mile Island,
the massive Exxon Valdez oil spill,
1986 nuclear meltdown at Chernobyl,
1986 space shuttle Challenger accident, and many others.
Japan, 新幹線 Shinkansen Driver fell asleep when driving

In March 2003, a shinkansen train stopped at about 100 meters before its regular stopping point after the driver of the train fell asleep for eight minutes while the train was traveling at speeds up of up to 270 kilometers per hour. A disaster was averted because the train was equipped with an automatic control system that stopped the train when it pulled into the station. It was later revealed that the driver had a sleep disorder.

Experimental set up on the driving simulator

Study in the public bus driving

Her Royal Highness Princess Galyani Vadhana Krom Luang Narathiwas Rajanagarinda

And Members of the Committee for the Anti-Drowsy Driving Fund Ramathibodi Hospital Foundation, Under the Royal Patronage of Her Royal Highness Princess Galyani Vadhana Krom Luang Narathiwas Rajanagarinda

"Drowsy or Sleepy, don't drive campaign"

Have a good night sleep sweet dream

Thank you