The University of Manchester
Institute of
Health Sciences

MANCHESTER 1824

Ageing and Sleep:
the biological clock and sleep disturbance

Biological clocks, sleep and ageing: from genes to drugs
- Dr Qing-Jun Meng, Medical Research Council Fellow in Neurosystems

The effects of sleep duration and sleep disturbance on ageing
- Tarani Chandola, Professor of Medical Sociology

Discussant – Dr Mike Horan, Professor of Geriatric Medicine

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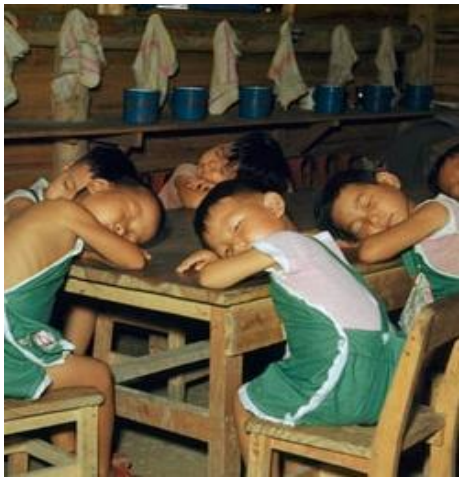
MICRA SLEEP SYMPOSIUM 06/12/2010

Professor M A Horan

Discussant

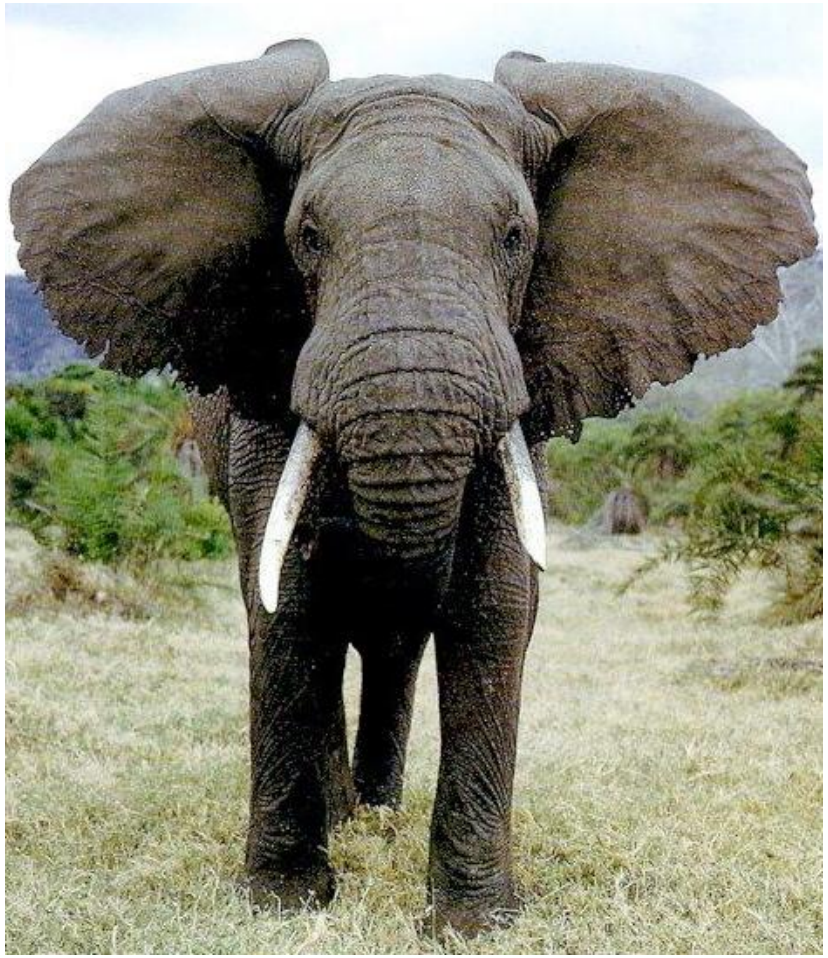
SLEEP

- Primitive biological drive
  - Even insects sleep similarly to man
    - Mutation in K channel leads to decreased sleep needs and resistance to sleep deprivation.
  - Marine mammals can sleep one hemisphere at a time



WHY DO WE SLEEP?

- Not known
  - Processing of memory
  - Preparation for next day memory processing



CONTROL OF SLEEP

- Partially understood
  - Balance between sleep promoting (GABA, galanine) neurones in ventral preoptic hypothalamus and wake-promoting (hypocretin) neurones in lateral hypothalamus.
  - Fine adjustments of sleep-wake cycle by suprachiasmatic nucleus (serotonin)
  - Adenosine reduces arousal and alertness
    - Caffeine and theophylline interfere with this
    - Adenosine deaminase breaks down adenosine
    - Mutation (slumber gene) produces less efficient enzyme and causes longer periods of deep sleep
  - Orexin producing neurones implicated in maintaining wakefulness (mutation associated with narcolepsy)
- Sleep patterns acquired in infancy persist into adult life

CONTROL OF SLEEP (2)

- Nocturnal activity in humans but not all species
  - Follows a circadian cycle
  - Associated with physiological changes (melatonin, temperature, alertness and performance)
- Key role of SCN
- Genetic disorders of sleep-wake cycle
- Molecular Clock

CK1 inhibition as a therapeutic target

PER dimer with CRY inhibits transcription

CK1 degrades PER

CK1 epsilon mutant (hamster) has a more rapid clock and more rapid degradation of PER

CK1 antagonism changes the phase of the cycle

PHASES OF SLEEP (1)

- Non-REM sleep progresses through 4 stages
  - Stage 1 (light sleep) – drift and awake easily and have hypnic myoclonus
  - Stage 2 – eye movements stop and electrical activity slows + occasional bursts of rapid waves (sleep spindles)
  - Stage 3* – extremely slow (delta) waves interspersed with smaller, faster waves
  - Stage 4* – dominated by delta waves.

  - * = Deep sleep – No eye movement or muscle activity. Hard to awaken. Feel groggy and disoriented for several minutes.

PHASES OF SLEEP (2)

- REM SLEEP
  - Respiratory rate increases with irregular and shallow breaths
  - Eyes jerk rapidly in various directions
  - Limb muscles temporarily paralysed
  - HR increases
  - BP rises
  - Penile erections
  - If awakened, recall bizarre stories (dreams)

SLEEP CYCLE

- First REM sleep period 70-90 min after falling asleep
- A complete sleep cycle takes 90-110 min
  - First sleep cycle – little REM & lots of deep sleep
  - Subsequent cycles, less deep sleep and more REM
  - By morning, mainly stages 1,2 and REM
- If awakened more than a few minutes after sleep starts fail to recall the few minutes before sleep onset (forget phone calls, alarm clock, etc.)

REM SLEEP DISORDER

- Failure to immobilise skeletal muscles during REM sleep
- Arises from brainstem damage
- >50 % develop neurodegenerative disorder
  - Parkinson's disease
  - DLB
  - Alzheimer's disease
  - MSA

YAWNING

Chasma, Oscitation, Pandiculation, Ganiaen

- Activated by same hypothalamic neurones (PVN) that activate penile erection
- Main neurotransmitter is DA
- All vertebrates yawn
  - Deep inspiration through open mouth
  - Shorter expiration through open mouth
  - Often accompanied by stretching (pandiculation)
  - Stroke patients stretch the paralysed limb (locked-in syndrome and anencephaly)
- Antagonises sleep and maintains alertness
- Yawning is contagious (man, chimpanzees and benobos)
  - Not occur in children or autism
- Pathological yawning (chasma) usually repetetive

HOW MUCH SLEEP?

- Infants ~ 16 h/day
- Adults ~ 7-8 h/day (5 – 10)
- Need more after sleep deprivation
  - Sleep debt must always be repaid
  - Sleep deprivation impairs hand-eye coordination (as bad or worse than Et-OH intoxication)
  - Sleep deprivation magnifies the effects of Et-OH
  - Sleep deprivation triggers inflammatory response
  - Daytime somnolence, falling asleep within 5 min. of lying down and microsleeps imply lack of sleep

HOW MUCH SLEEP (2)?

SPECIES	AVERAGE PER DAY (hours)
Python	18
Tiger	15.8
Cat	12.1
Chimpanzee	9.7
Sheep	3.8
African elephant	3.3
Giraffe	1.9

MICROSLEEPS

- Brief, unintended episodes of loss of attention
  - Blank stare
  - Head snapping
  - Prolonged eye closure (but eyes may be open)
  - Often accompany fatigue + monotonous task (driving, reading, listening to a lecture)
  - Not respond to external information
  - Last a few seconds to minutes

ELSA 2010

- Oldest more likely to report longest sleep duration (>8 hours) but not shortest
  - How accurate is self-reporting of sleep?
  - Seems independent of wealth/deprivation
- Older people least likely to be in “worst quartiles”, though women over-represented at all ages
- Long sleep duration ↑RR of death
  - Possible mechanisms unclear
  - Diabetes association suggests a role for cortisol
- More modest effect for short sleep duration
  - Possible mechanisms unclear
  - Change in sleep pattern also associated with increased RR of death
- Interaction between short sleep duration and restless/disturbed sleep in association with RR of CAD
  - Possible mechanism unclear

ELSA 2010

- Cortisol Results
  - Longer duration sleep the lower the nadir
  - Effect of injury is not on concentration but duration

SLEEP DISORDERS

- Insomnias
  - Change in pattern of falling asleep
  - Frequent waking
  - Early waking
  - Unrefreshing sleep
- Pseudo-insomnia
  - Believe not get enough sleep, even when sleep studies show the contrary
- Parasomnias
  - Myoclonic jerks
  - Nightmares
  - Night terrors
  - Somniloquy
  - Bruxism
  - Somnambulism (deep sleep)
- Hypersomnias
  - Primary (e.g. OSA, CSA, narcolepsy)
  - Secondary (medications, brain disorders)

INSOMNIA

- Primary
- Secondary
  - Medications (many)
  - Pain
  - Depression
  - Restless legs
  - Hypnic headache (severe pulsating headache)
- Chronicity may develop if lasts >3-4 weeks