Sleep-Endocrinology

Dr R Goswami MD, DM FASc, FNASc
Professor Endocrinology & Metabolism,
AIIMS, New Delhi

Circadian Rhythm and Sleep

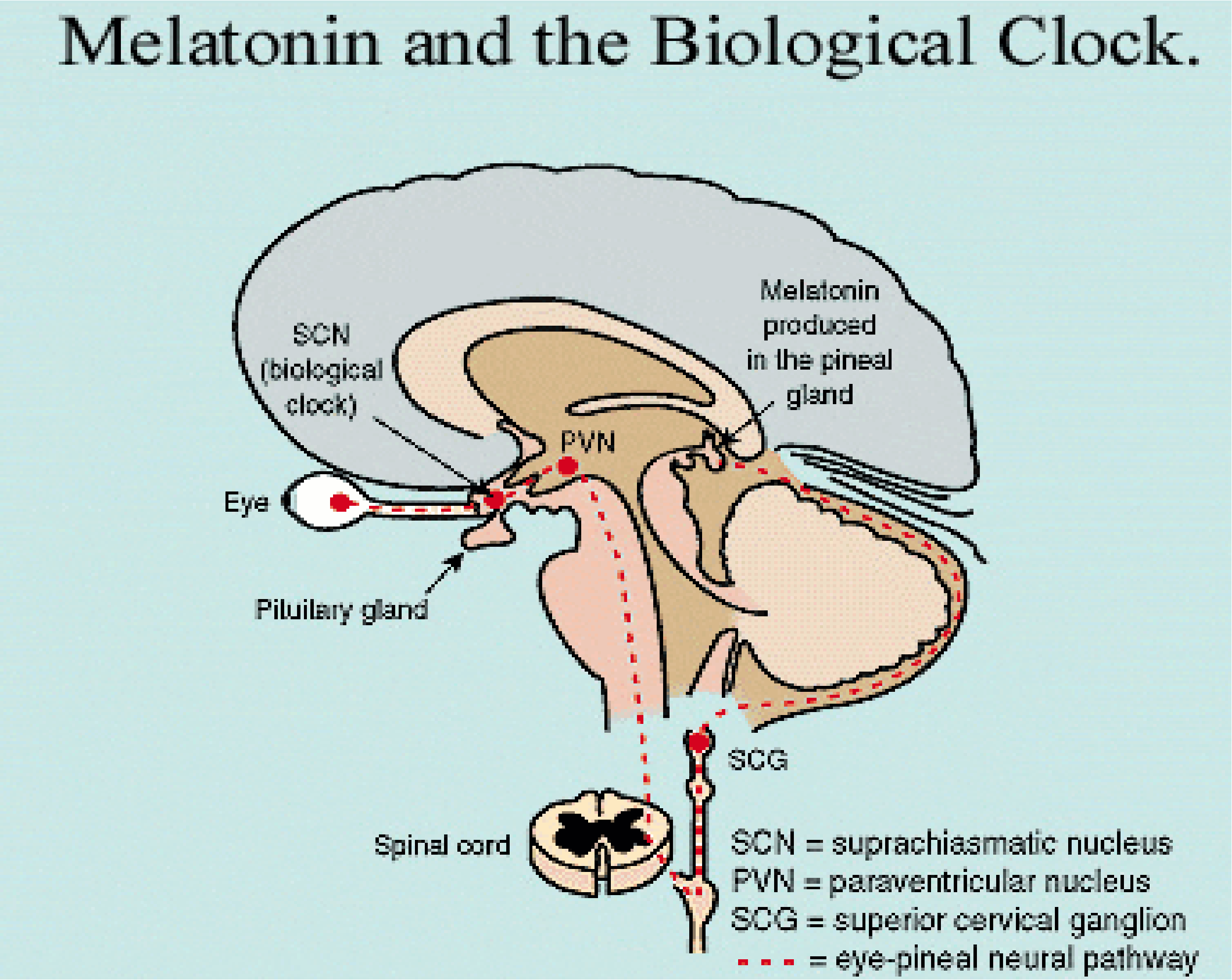
- There is endogenous rhythm which optimally synchronizes with body physiology (rest/activity or biological day/night)
- Suprachiasmatic nuclei: Master circadian clock, Bilateral, in Ant. hypothalamus near 3rd ventrical
- Its neuron has autorythmicity of ~ 25-24 hr.
- But it requires constant entrainment

Entrainment of Circadian clock

- **Retinohyoypthalamic tract**: Projections to the SCN
- Photopigment in rods, cones & retinal ganglion cells are sensors
- Light is the most potent time cue to the master circadian oscillator.
- Body temperature, exercise, feeding can modify this to some extent

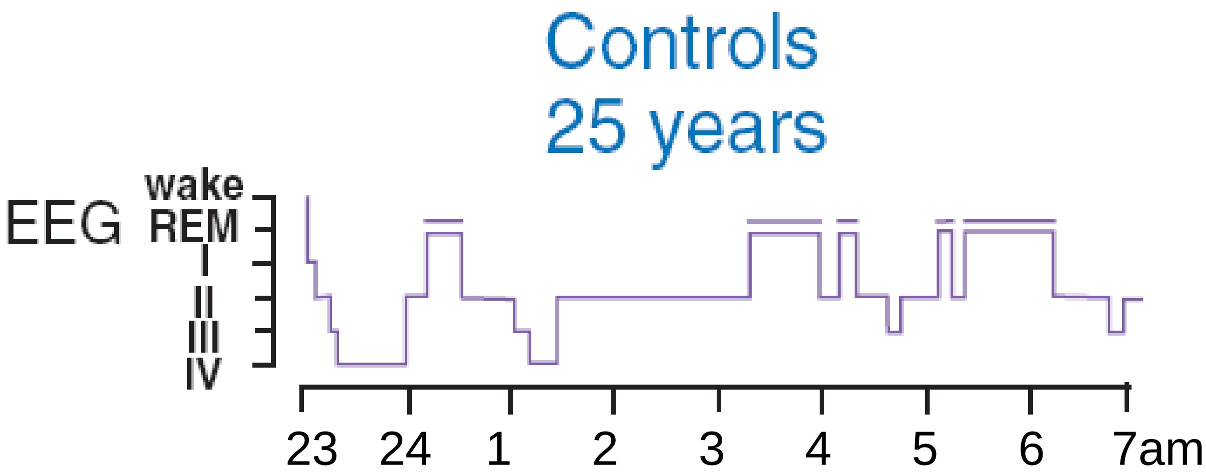
Entrainment of Circadian clock

- **SCN projections to the**
- **Hypothalamus: determines** circadian rhythm of hormones
- **Cerebral cortex: Arousal**
- **Pineal gland:** Multisynaptic pathway to PVN---IML column of upper thoracic spinal cord---- cervical ganglion -----pineal
- **Autonomic nervous system:** Maximum epinephrine secretion between 6.0 am to 9.0 am is independent of behavior.
- Explains the peak time for the MI/Stroke in the morning.
- Can be relevant for development of novel therapeutic strategy


Melatonin and the Biological Clock.
SCN
(biological
clock)
PVN
Melatonin
produced
in the pineal
gland
Eye
Pituitary gland
SCG
Spinal cord
SCN = suprachiasmatic nucleus
PVN = paraventricular nucleus
SCG = superior cervical ganglion
= eye-pineal neural pathway

General aspects of sleep

- Sleep is important & humans spends at least 1/3 of life in this activity. Reduction of motor output & consciousness.
- Sleep has cycles of NREM and REM. Phase 2 -4 of NREM correlates with slow wave EEG activity & sleep intensity



Sleep & Endocrinology

- Thus, in simplistic term both sleep & hormone changes are part of circadian system determined by SCN.
- There is some pattern in hormonal changes with sleep Difficult to say hormones modifies sleep or sleep modifies hormone.
- **Forced protocol:** Subjects sitting in dim light, relaxed, reclining, equal calories snacks distributed equally in 24 hour which allows study of circadian component
- Repeated Hormonal sampling and EEG are inherent part of this forced protocol

Sleep & Hormones

- GHRH-GH
- CRH-Cortisol
- Melatonin
- Others
- Ghrelin
- Somatostatin
- Sex hormones Testosterone and osteorgen and DHEAS
- Neuropeptides
- Increased BNP in night: poluria

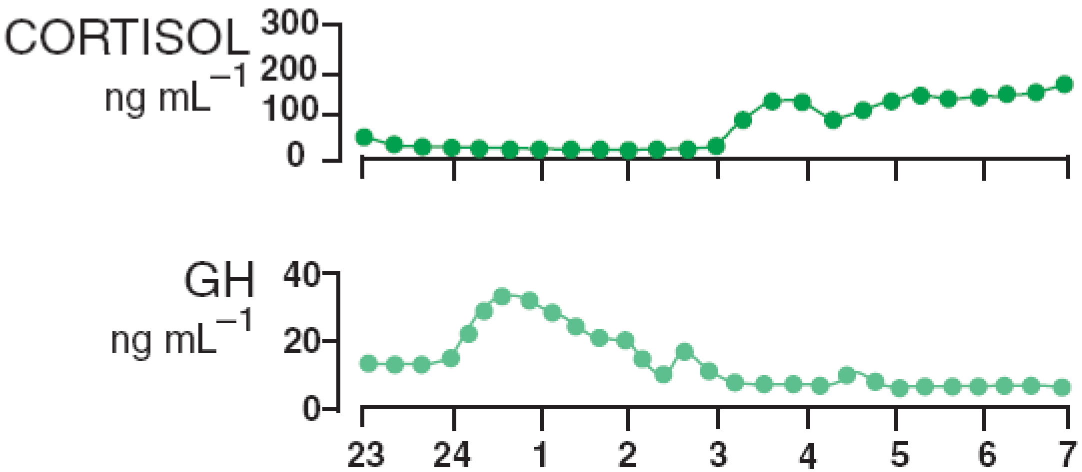
Sleep and Hormones

- 1st half of Sleep
- GHRH-GH Predominates

- 2nd half
- CRH-Cortisol predominates
- Morning normal 08.00 hr plasma cortisol higher than evening

Sleep & Hormone

1st half of Sleep GH and 2nd half Cortisol



Sexual dimorphism
Males show a single peak
Females multiple peak during sleep (Bioadaptation)

Sleep & Hypothalamic-Growth Hormone axis

- GH-Rise after sleep irrespective of sleep time
- GH releasing hormone (GHRH) is the best endogenous substance with sleep promoting activity
- After central and systemic & central administration of GHRH, SWS activity is increased in animals.
- I.V & intranasal boluses of GHRH during first few hr of sleep in normal young and elderly males lead to

Increased GH secretion and SWS

Decreased cortisol and ACTH levels

Prolonged first NREM & reduced awakenings

Sleep & Hypothalamic-Growth Hormone axis

Sexual dimorphism

However, in females there was sexual dimorphism and opposite changes were with increased ACTH and cortisol in females.

This indicate that that there is reciprocal anatgonism between GHRH and CRH in males and

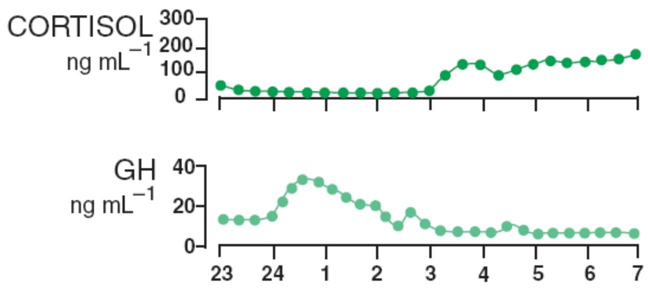
Synergism between these two hormones in females

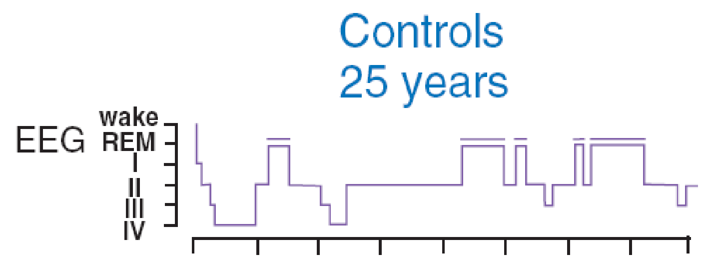
This might explain the increased prevalence of depression and Cushing's in females

Sleep, GH analogues & Somatostatin

- **Ghrelin:** An endogenous ligand of GH scretagogues receptor.
- Released from stomach to increase the appetite
- In young males effects of IV Ghrelin & synthetic scertagogues and GHRH are similar with increased GH and enhanced SWS
- Unlike GHRH, ACTH and cortisol secretion is increased
- **Somatostatin:**
- In young/elderly males SWS is reduced after IV somatostatin & SC octreotide.
- Sleep is more impaired in elderly at a lesser dose
- After arginine (a somatostatin antagonist) SWS is increased

Sleep & CRH-ACTH-Cortisol Axis





CRH

Pulsatile IV CRH in young males (4 x50 ug) led to **<u>increased cortisol</u>** during first half of night,

GH surge bunted & **decreased SWS**

Changes were more with ageing including wakefulness

Sleep & CRH-ACTH-Cortisol Axis

- In stressed rats after CRH antagonist (Astressin)
- RMES sleep decreased
- This preclinical work indicates CRH promotes wakefulness

- RX of patients with CRH receptor antagonist
  NBI 30775 induced normalization of sleep changes in EEG

  A 4 wk trial of the compound in depressed patients led to increased SWS with decrease in REM density & awakenings

  Thus CRH-I receptor I antagonist is a possible way to counteract sleep changes

Sleep & CRH-ACTH-Cortisol Axis

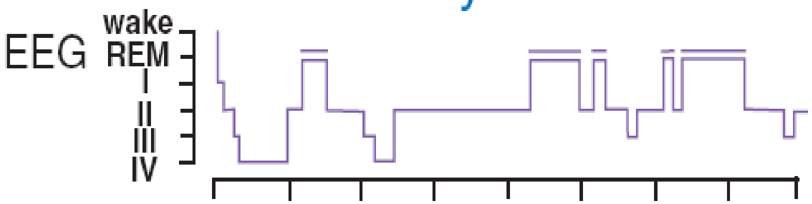
- **ACTH**
- Administration of synthetic ACTH analogue to volunteers led to general CNS activation but REMS, GH & cortisol remain unchanged
- It seems unlikely that it has an effect on Sleep disturbances

Sleep & CRH-ACTH-Cortisol Axis

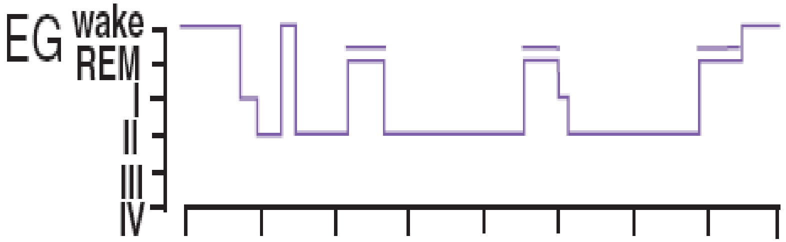
- **Steroids**
- Continuous/hrly **cortisol infusion in physiological** dose from 11.00 pm-7.0 am led to **increased SWS** and decreased REM in young/elder
- Thus CRH mediated decrease in sleep density is unlikely to be because of acute effect physiologial cortisol
- **Long term methylprednisolone** in females with multiple sclerosis:
- REM latency was shortened
- and SWS density shifted to late phases of sleep.
- **These changes are similar to that of depression**

Sleep & Aging & Depression

Controls
25 years

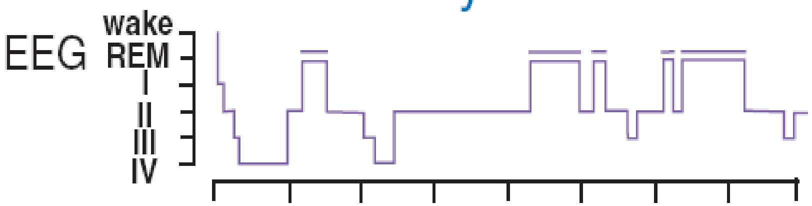


65 years

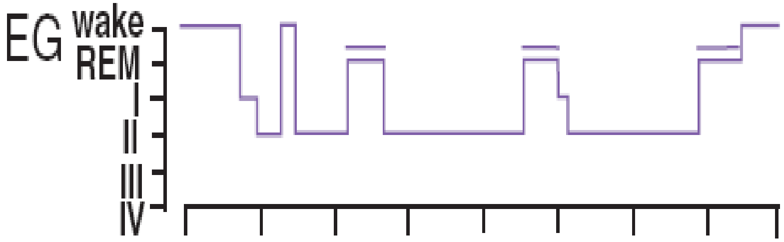


Sleep & Aging & Depression

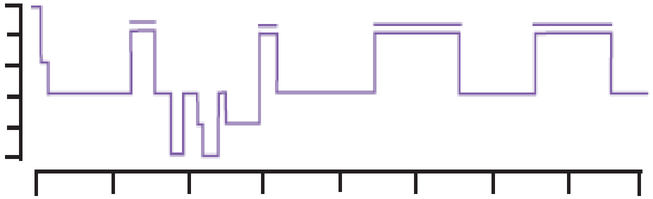
Controls
25 years



65 years

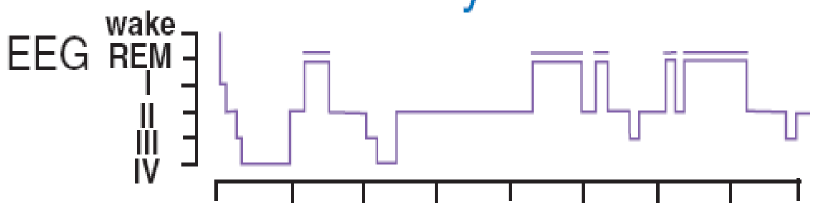


Patients with depression
25 years

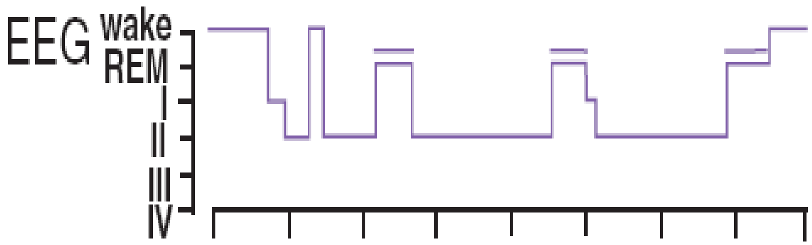


Sleep, Aging & Depression

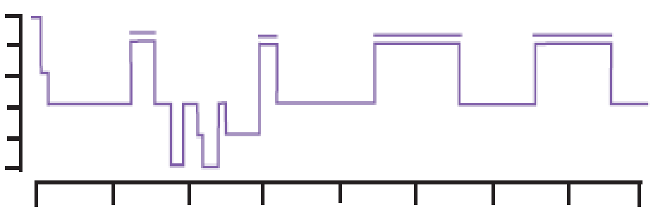
Controls
25 years



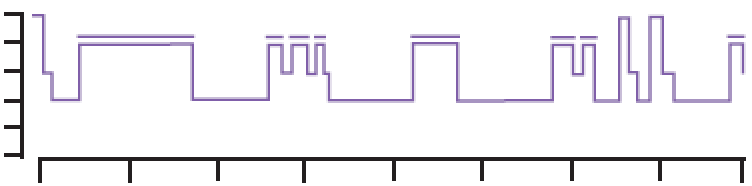
65 years



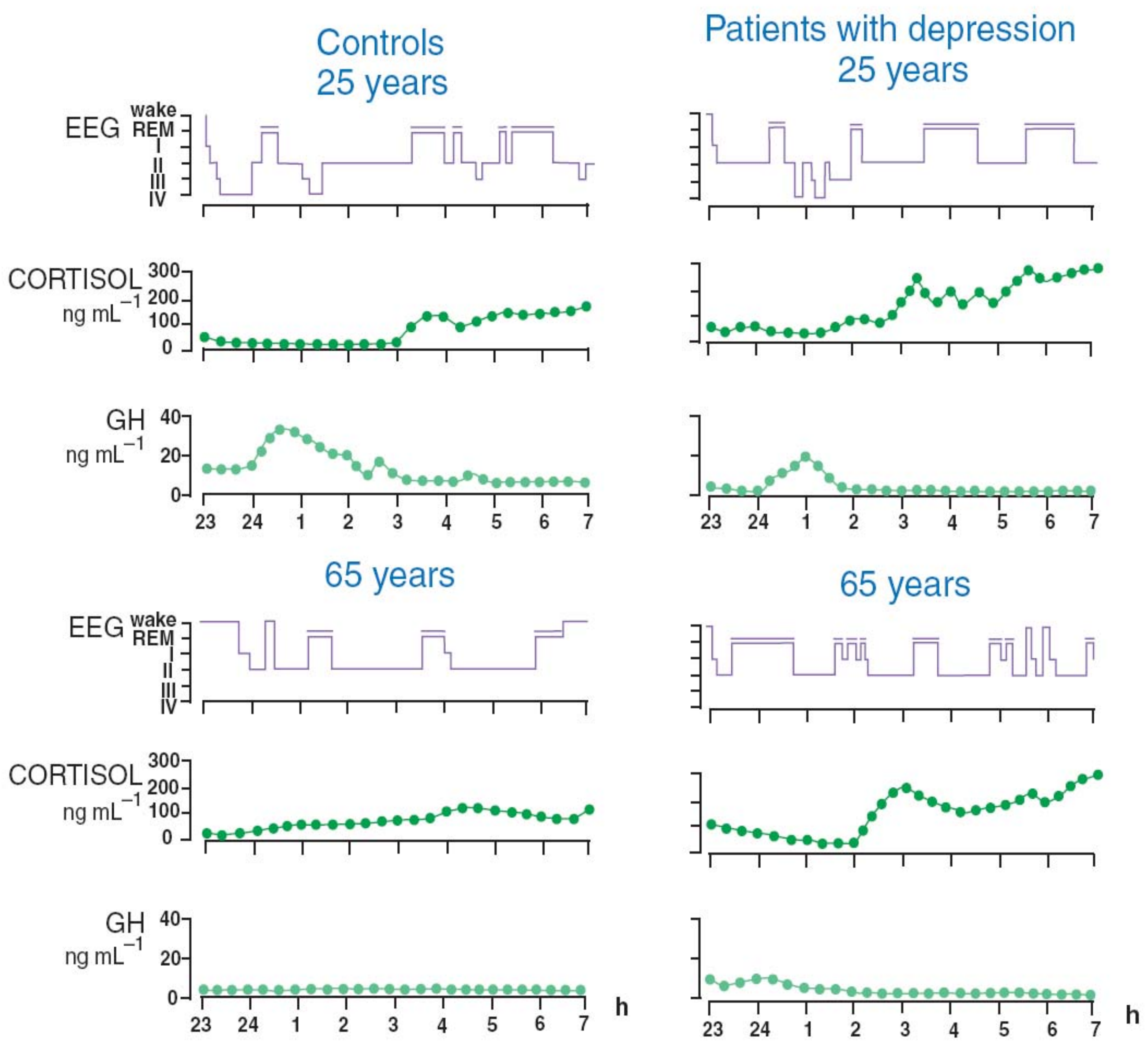
Patients with depression
25 years



65 years



Sleep, Depression, Aging & Hormone



Clinical Relevance: Sleep associated changes

Disorders of sleep due the misalignment in sleep cycle with circadian rhythm as in night shift workers

Jet lag due to time differences in two countries

Patients with depression and senior citizens with sleep disturbances

Cushing’s disease and patients requiring subchronic steroids as in Multiple sclerosis

Common drugs like betablockers are known to increase wake time

Adverse consequences of Misalignment in Day and night sleep

OPEN ACCESS Freely available online PLoS MEDICINE

Rotating Night Shift Work and Risk of Type 2 Diabetes: Two Prospective Cohort Studies in Women

An Pan[1], Eva S. Schernhammer[2,3], Qi Sun[1,3], Frank B. Hu[1,2,3]*

1 Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts, United States of America, **2** Department of Epidemiology, Harvard School of Public Health, Boston, Massachusetts, United States of America, **3** Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, United States of America

Abstract

Background: Rotating night shift work disrupts circadian rhythms and has been associated with obesity, metabolic syndrome, and glucose dysregulation. However, its association with type 2 diabetes remains unclear. Therefore, we aimed to evaluate this association in two cohorts of US women.

Methods and Findings: We followed 69,269 women aged 42–67 in Nurses' Health Study I (NHS I, 1988–2008), and 107,915 women aged 25–42 in NHS II (1989–2007) without diabetes, cardiovascular disease, and cancer at baseline. Participants were asked how long they had worked rotating night shifts (defined as at least three nights/month in addition to days and evenings in that month) at baseline. This information was updated every 2–4 years in NHS II. Self-reported type 2 diabetes was confirmed by a validated supplementary questionnaire. We documented 6,165 (NHS I) and 3,961 (NHS II) incident type 2 diabetes cases during the 18–20 years of follow-up. In the Cox proportional models adjusted for diabetes risk factors, duration of shift work was monotonically associated with an increased risk of type 2 diabetes in both cohorts. Compared with women who reported no shift work, the pooled hazard ratios (95% confidence intervals) for participants with 1–2, 3–9, 10–19, and ≥20 years of shift work were 1.05 (1.00–1.11), 1.20 (1.14–1.26), 1.40 (1.30–1.51), and 1.58 (1.43–1.74, *p*-value for trend <0.001), respectively. Further adjustment for updated body mass index attenuated the association, and the pooled hazard ratios were 1.03 (0.98–1.08), 1.06 (1.01–1.11), 1.10 (1.02–1.18), and 1.24 (1.13–1.37, *p*-value for trend <0.001).

Conclusions: Our results suggest that an extended period of rotating night shift work is associated with a modestly increased risk of type 2 diabetes in women, which appears to be partly mediated through body weight. Proper screening and intervention strategies in rotating night shift workers are needed for prevention of diabetes.

Shift work, and sub fertility among Swedish midwives.
Ahlborg G et al Int J Epidemiol. 1996;25:783–790.

Molecules with potential role in Disorders of Sleep

Nocturnal Peak of Melatonin at 2.00 am in normal
Primarily a circadian rhythm and very little change in day
Promotes sleep and decrease wakefulness

Use of Melatonin particularly sustained release might be of help to Night shift workers

GHRH for obvious reasons is not a viablr option but GH scretagoglues need evaluation

CRG anatgonist (astressin) and CRG receptor antagonist are viable options

Thank You

Different phase of Airway obstruction

- **Phase I:** Increased collapse of airway, turbulent flow & fluttering of soft palate leading to snoring

- **Pahse II:** Increased airway resistance, respiratory efforts & short arousals noticed in sleep analyses

- **Phase III:** Apnoea/Hyponea episodes > 5/hr
  Apnea = Interruption of breathing > 10 sec
  Hypopnea = (a) fall in inspiratory flow to 50% for 10 sec
  (b) 4% fall in O2 saturation

Diagnostic Procedures for OSA

- Gold standard : polysomography in sleep Laboratory
- History of snoring, disturbances in sleep
- Nocturnal oximetry during sleep
- Assessment of airway by optic procedure
- Video-endoscopy under sedation
- Measurement of pharyngeal pressure in sleep

Neurocognitive consequences of OSA

- Neurocognitive
  Day time sleep slow reactions, oor memory, irritability and quality of life, road accidents

CVS- consequences

- HT risk increased by 3 fold in AHI of> 15
- Drug resistant hypertension.
- Higher sympathetic tone & plasma aldosterone

- Higher CVS mortality. Cardiac pre & after load increased due to –ve intrathoracic pressure during breathing with narrow UA.

- Hypoxemia induced reactive O_2 species, free radicals, endothelial dysfunction & atheraosclerosis

CVS-Consequences of OSA

- OSA is an independent risk for arrhythmia, heart failure & stroke in epidemiological studies.

- RCT of CPAP showed lowering of HT, improved Left ventricular systolic function, Ventricular premature contractions and reduced sympathetic activity in patients with heart failure

(Bradley TD, Lancet 2009 373: 82-93)