

Chronopatterns of Metabolic Diseases : Trends & Challenges



Dr. Meenakshi Sinha
Additional Professor of Physiology
All India Institute of Medical Sciences,
Raipur, C.G.

Metabolic Syndrome :

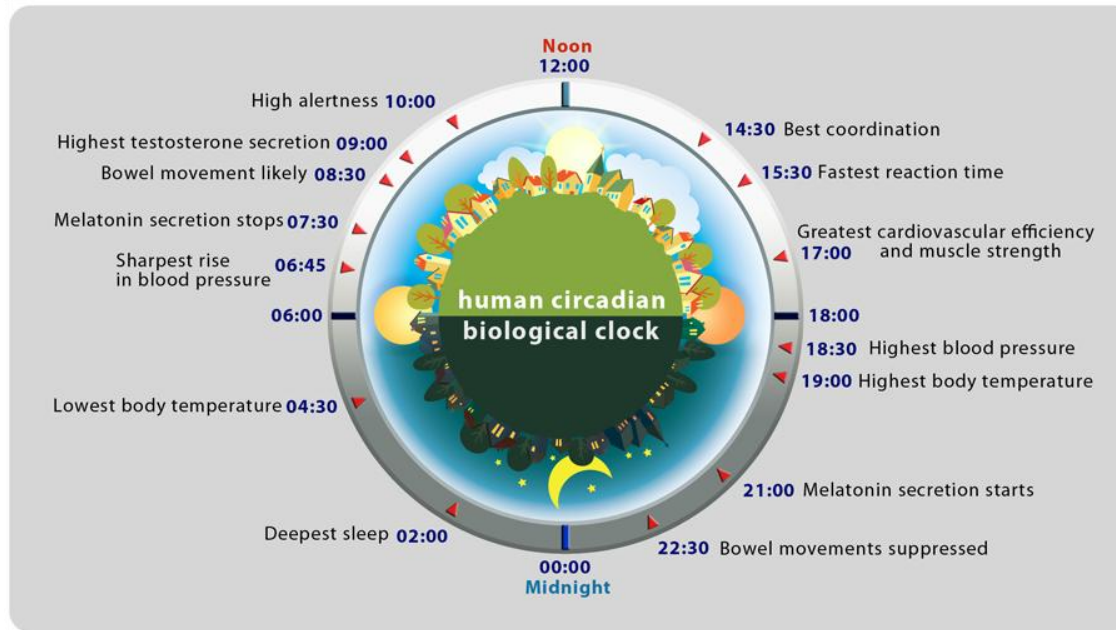
Cumulative cardio-metabolic risk exerted by abdominal obesity, hyperglycemia, high triglyceride, low HDL cholesterol, & hypertension, insulin resistance, and hepatic steatosis ---- risk for diabetes & cardiovascular disease

Management approaches : Diet, physical activity, stress management & pharmacological interventions

But, ROLE of TIMING.....??

LIGHT POLLUTION : *novel source of pollution and environmental risk factor*

Interruption of natural light/dark cycle (most reliable cue for entraining the biological clock) by introducing artificial light of short wavelengths..... public health problem



Biological rhythm

Periodic changes in the behaviour / physiology (eg sleep, hibernation and migration)

Chronobiology : 'the scientific discipline that quantifies & explores the mechanisms of biological time structure & their relationship to the rhythmic manifestations in living matter'

The Main Bio-Rhythms

1. Ultradian Rhythm
(less than 24 hours)-
EEG during sleep

2. Circadian Rhythm
(24 hours)
*(term first coined by
F. Halberg in 1959)*

3. Infradian Rhythm
(less than 24 hours)

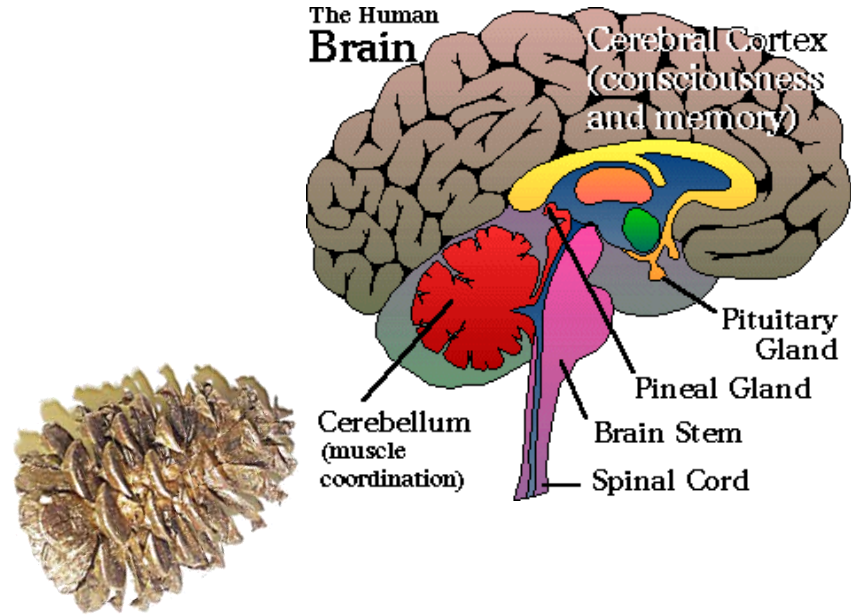
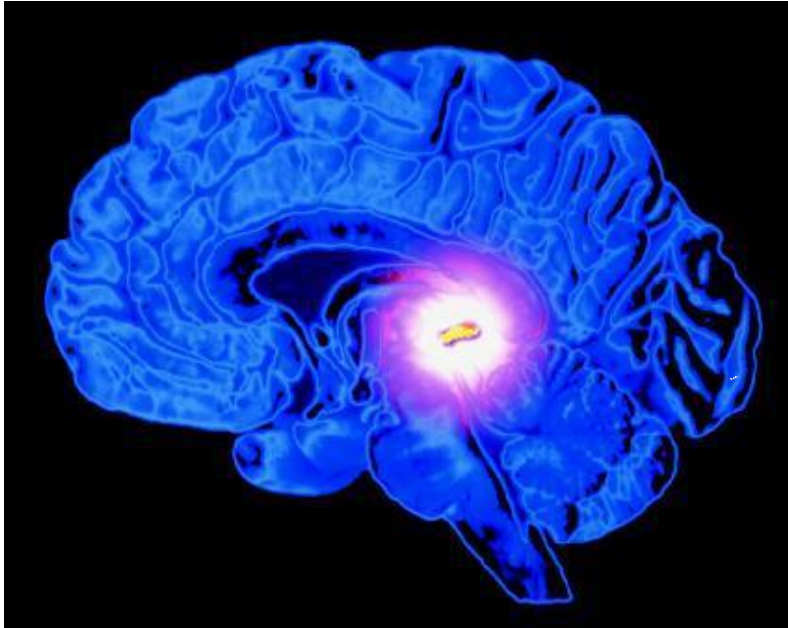
–
Menstrual cycle

4. Circannual Rhythms
(1 year)-
Seasonal breeders

Some Circadian Rhythms :

*Sleep/wake, Hormone release, Body temperature,
IOP, Sensitivity to drugs, Pain tolerance*

Pineal Gland



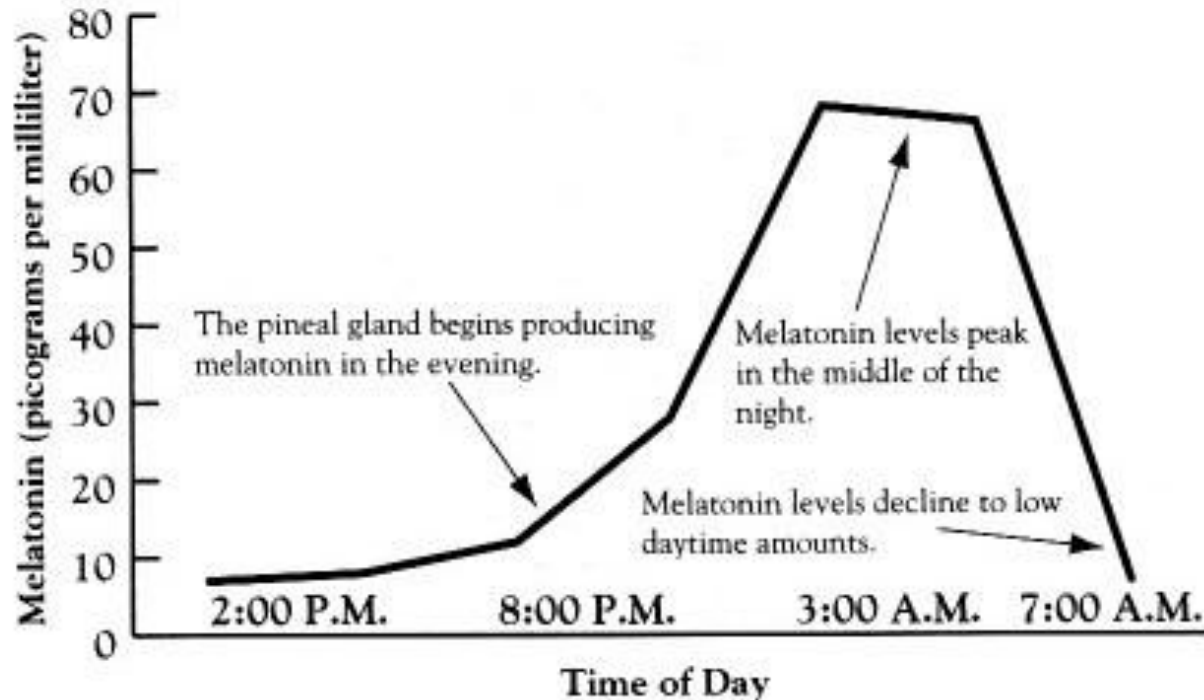
- ⊙ reddish gray, about the size of a pea, shaped like a pine cone
- ⊙ in vertebrate brain (between hemispheres; in a groove where two thalamic bodies join)
- ⊙ attached to posterior end of roof of 3rd ventricle
- ⊙ deeply situated in the midline of brain below corpus callosum.

“Ideally placed anatomically to collect, integrate and compare information from extra cranial sources & intracranial sites”

Melatonin

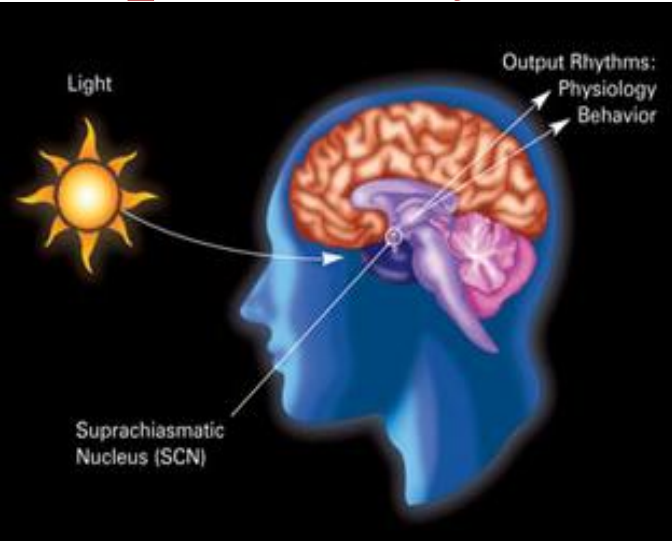
- **Secreted by pineal gland**

Exposure & duration of light at night (LAN).....powerful factor affecting melatonin level & its rhythm



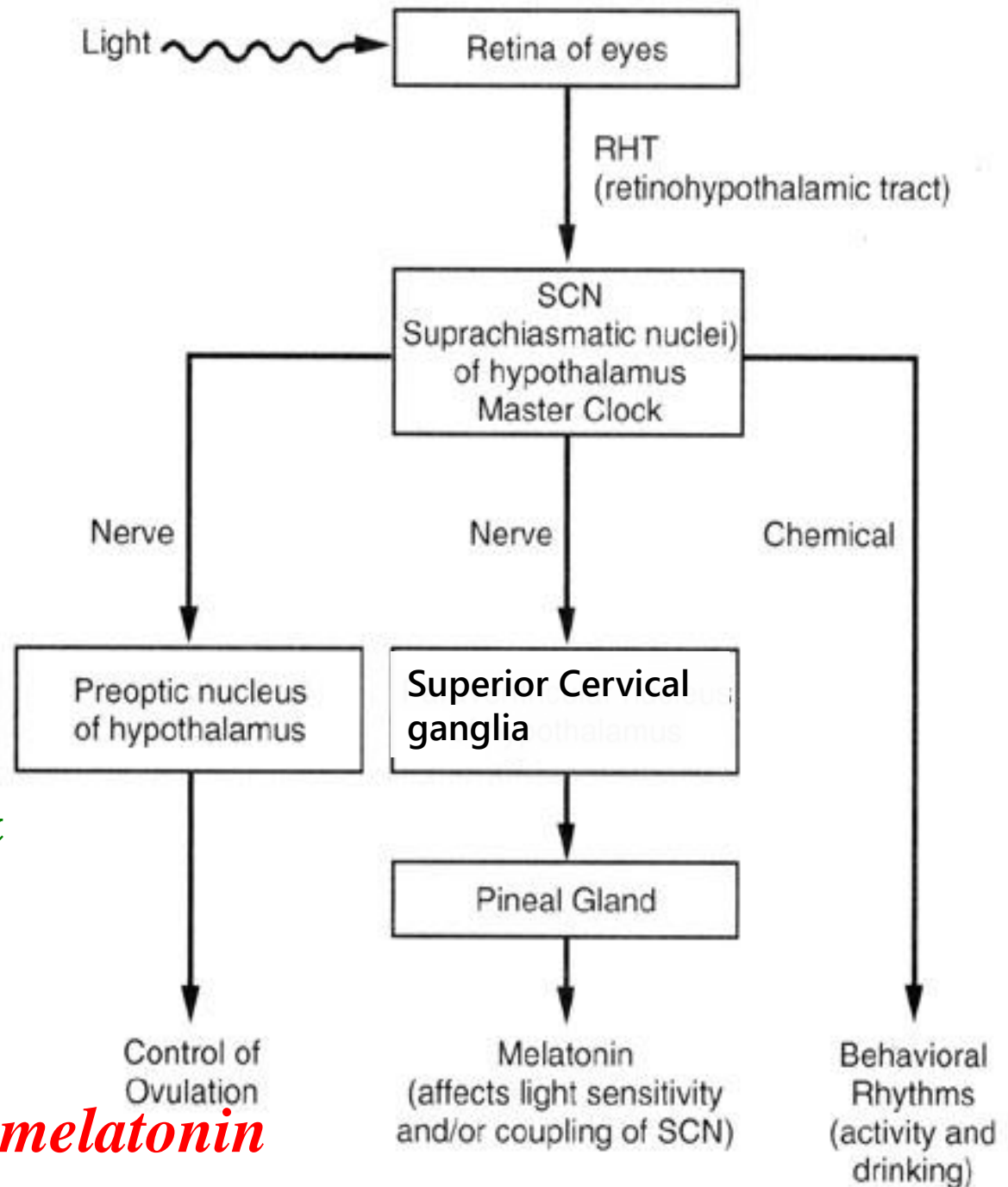
*“Hormone of darkness” /
chronobiotic &
Dim-Light Melatonin Onset (DLMO)*

Mammalian clock pathways



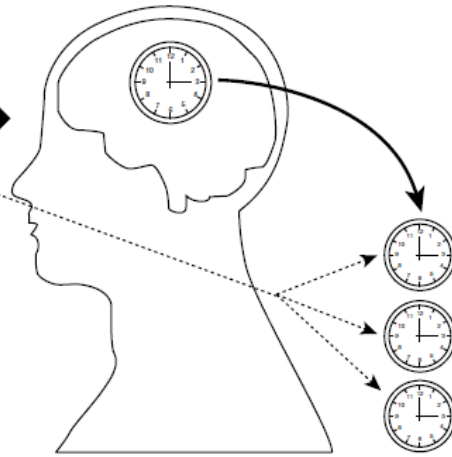
Light entrains SCN & pineal cells

*Also,
extra retinal source of melatonin*



A**Environmental Input**

Light/Darkness
Social
Meal time



Central
Clock

Peripheral
Clocks

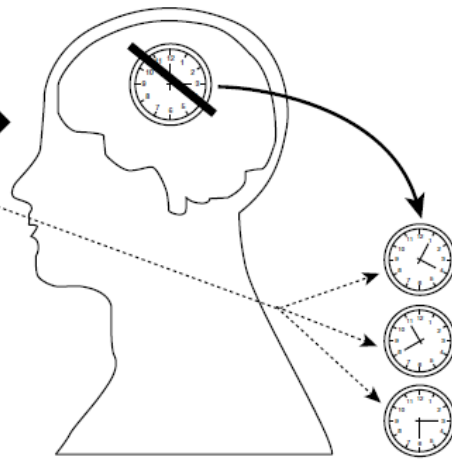
Effect

Sleep/wakefulness
Hormonal rhythms
Metabolic rhythms

Immune response
Airflow dynamics
Upper airway
collapsibility
Cell cycle, DNA repair

B**Environmental Input**

Shift work
Hospital setting
Cigarette smoke
Genetic
Behavioral



Central
Clock

Peripheral
Clocks

Effect

Sleep disorders
Inflammation
Metabolic abnormalities
Mood disorders

Increased sepsis risk
Increased asthma/COPD
exacerbation risk
Increased cancer risk

CHRONOPATHOLOGY

Changes in an individual's biologic time structure preceding, coincident or following functional disorders or organic disease

&/or

Time dependent manifestation of disease

leading to

Temporal gates of susceptibility

Due to.....

- ***Age or blindness related chronopathologies***
- ***Modern era & our lifestyle serious threat of circadian disruption***

Rhythmicity of disease manifestation

Circadian desynchrony, characteristic of shift work, jet lag, &/or sleep disruption, have profound effects on both normal body weight regulation & glucose/lipid homoeostasis

Obesity---imbalance between energy uptake & expenditure----the global epidemic

Difficult to tackle with only dietary changes & physical exercise.

Increased risk of obesity in shift workers compared with day workers (Keith C. Summa et al 2010)

Crucial role of the circadian clock in the regulation of metabolic processes, thereby, body weight ---bidirectional interactions.

*Extensive chronobiological researchpivotal role played by circadian system in the development & exacerbation of obesity.....***CHRONOBESITY**

Modern man

victim of disturbed sleep habits or a short sleeper

Another linkage between clock-regulated sleep & insulin resistance/type 2 diabetes is association between short sleep duration & risk of obesity & diabetes

- Chronic sleep curtailment → insulin-resistant adipocytes → inadequate pancreatic insulin secretion & increased plasma glucose conc.
- Short sleep duration → increased ghrelin & decreased leptin → obesity & diabetes

Cardio-vascular chronorisk

- **CR of BP in HTN either disappears /inverted** (Jonas, 2003)
- **Non-dippers— coincides with less melatonin level & Melatonin supplement effective** (Simko, 2007)
- **MI more frequent in late night/early morning**
(Manfredini R 2013)
- **Chronotherapy very effective of anti hypertensive drugs** (Hermida 2007, 2013; Farah R 2013)
- **Efficacy of morning vs evening statin in hyperlipidemia**
(Kim SH et al, 2013)

Type 2 diabetes

Lower melatonin secretion associated with increased risk of development

Women with low levels of ML found to be more likely to develop (JAMA, 2013)

Mutation of gene encoding for ML receptors – elevated risk (Prokopenko I, 2009)



CHRONOTYPE

LARK Type

Intermediate



OWL Type

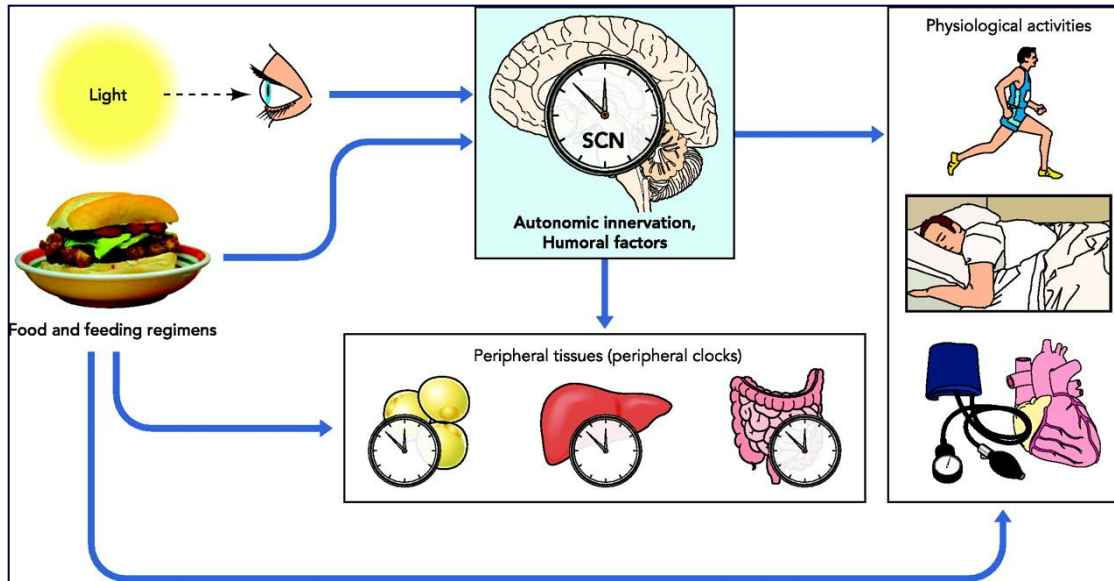
People with evening chronotype (i.e. owl type) tend to exhibit much higher potential of metabolic deregulations

Interrelation of master and peripheral clocks

*SCNx → clock disruption → weight gain and insulin resistance
(Coomans CP et al; Diabetes 2013)*

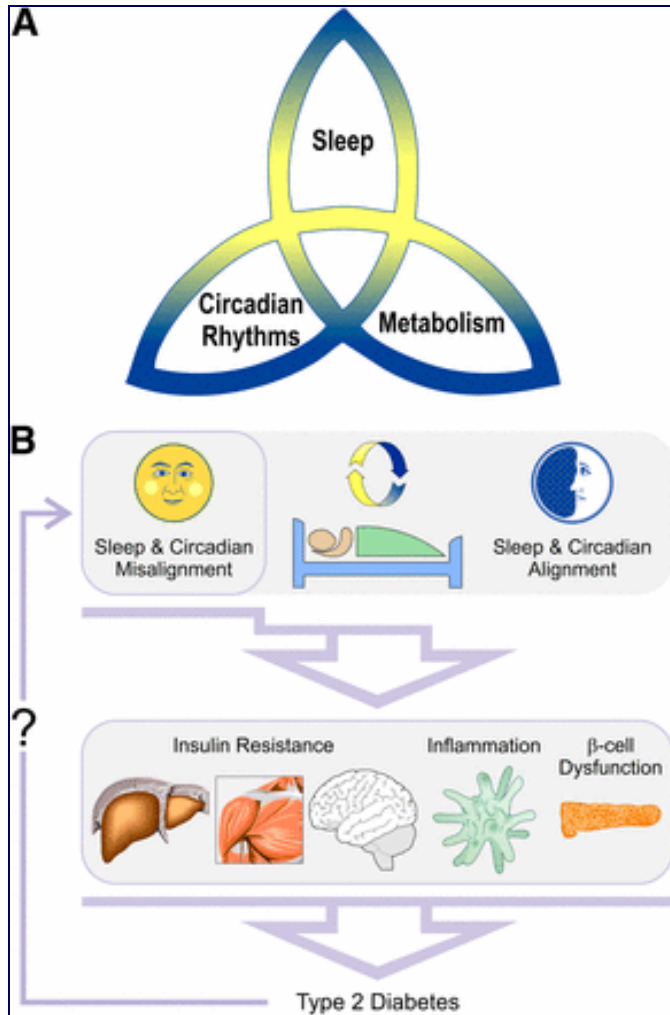
Clock in liver--critical role in regulating diurnal cycle of blood glucose conc. during feeding & fasting (Lamia KA et al; 2008)

Robust CR of metabolic hormones eg. insulin, glucagon, cortisol, leptin and ghrelin (Sato et al 2014)



& Enzymes + transport systems of metabolic pathways eg. glycogen, glucose, cholesterol, amino acid, drug and toxin metabolism as well as ligands/receptors of dietary nutrients

“Inseparable triad”-- interconnections between disrupted sleep, circadian rhythms & metabolic dysfunction



Environmental perturbations of circadian timing impair insulin sensitivity & promote obesity (Shi SQ et al; Curr Biol 2013)

Significant association of short sleep with mortality outcome, DM, hypertension, CV diseases, CAD & obesity

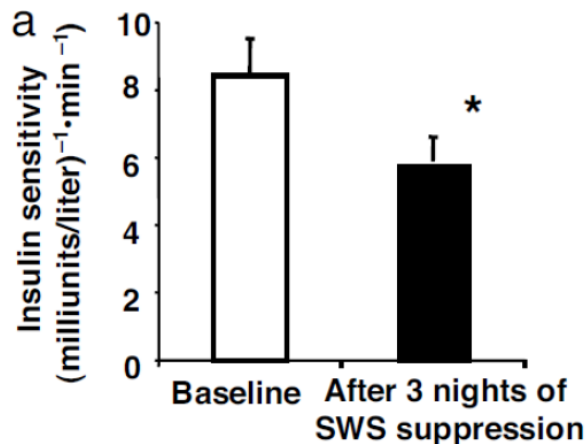
Osamu Itani et al. Short sleep duration and health outcomes: a systematic review, meta-analysis & meta-regression.

Sleep Medicine 2017

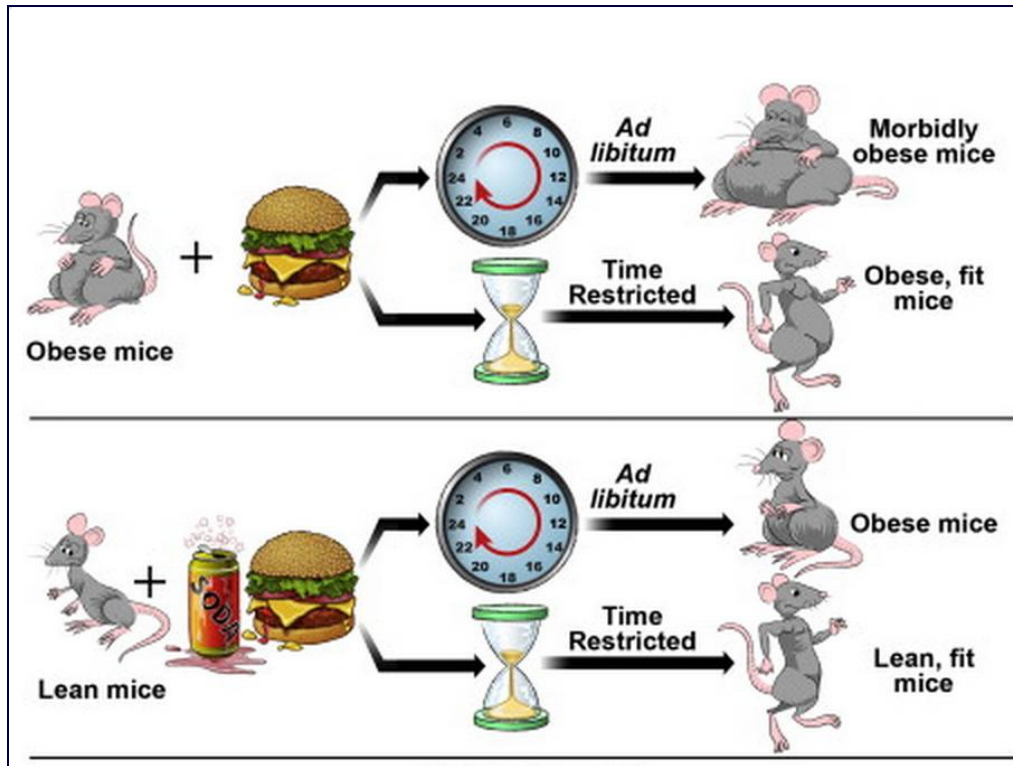
Slow-wave sleep and the risk of type 2 diabetes in humans

Esra Tasali*, Rachel Leproult, David A. Ehrmann, and Eve Van Cauter

1044–1049 | PNAS | January 22, 2008 | vol. 105 | no. 3



Do age related changes in sleep structure contribute to metabolic dysregulation?

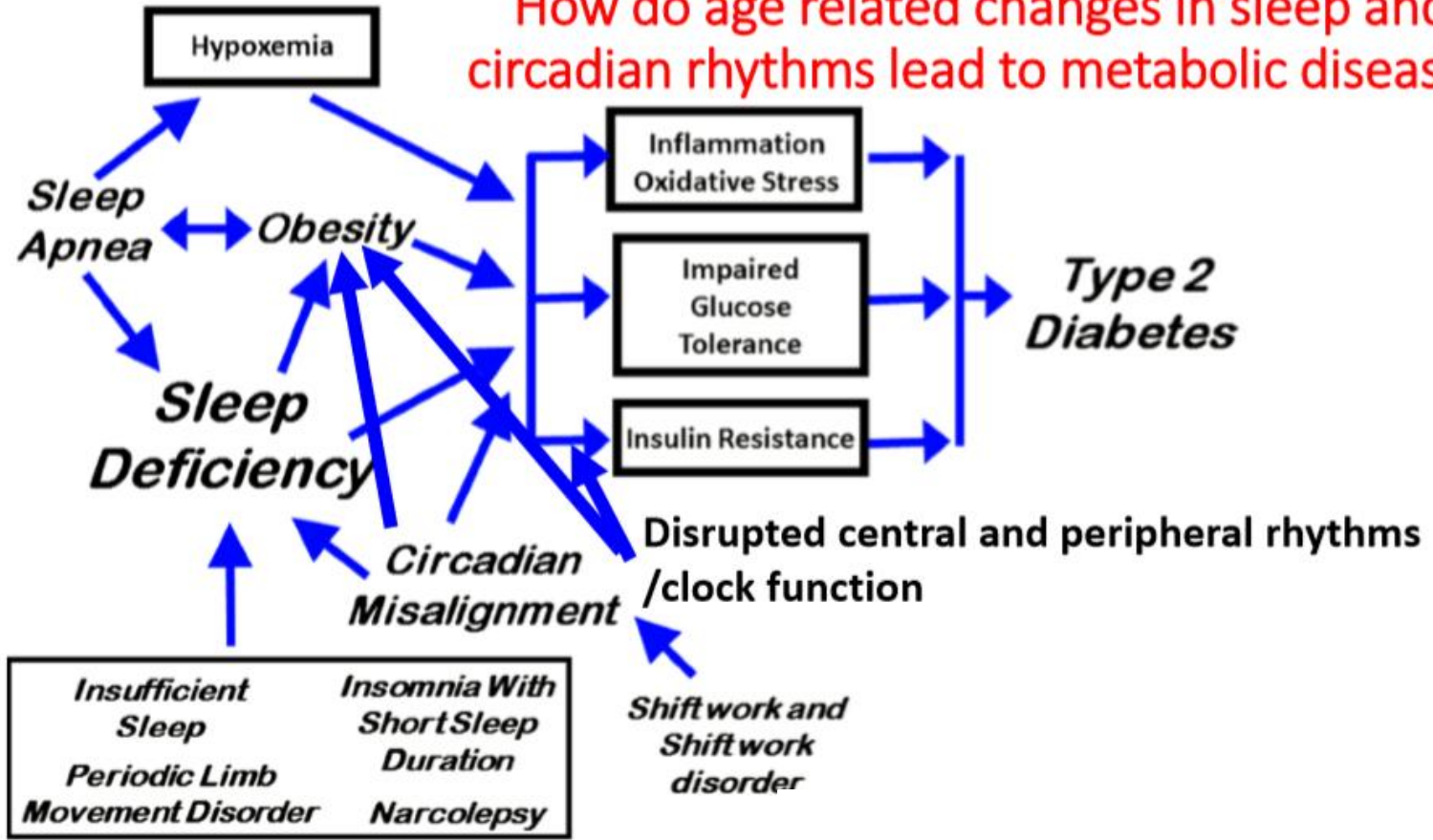


Need for greater attention on the timing (Leproult et al)..... more so because of modern lifestyle of living and working in temporally disrupted environments

(Social Jetlag)

For a healthy lifestyle, it's not only important what & how much you eat, but also when you eat.....

How do age related changes in sleep and circadian rhythms lead to metabolic disease?



Depner et al, Curr Diab Rep. 2014

Indication for significant effects of noninvasive manipulations of the circadian patterns of activity and feeding on body weight & metabolism

Circadian-based interventions eg. light therapy, melatonin supplementation (&/or physical activity, diet and social schedules) --- favorable effects on sleep-wake cycles →

very useful for the management of patients with circadian rhythm related metabolic disorders

(Videnovic A, 2017).

Complex link between circadian rhythms & metabolic disturbances → options for interventions on sleep quality & circadian rhythm regularity → reduce/tackle cardiovascular risks & metabolic disorders