Pineal Body(gland)
Circadian Rhythm Genes
and
Shiftwork

UIMC CONFERENCE 2026: Lisbon September 30- October 2

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Brain

- The brain is the intracranial part of the CNS

- Weighs between 1200–1500 grams

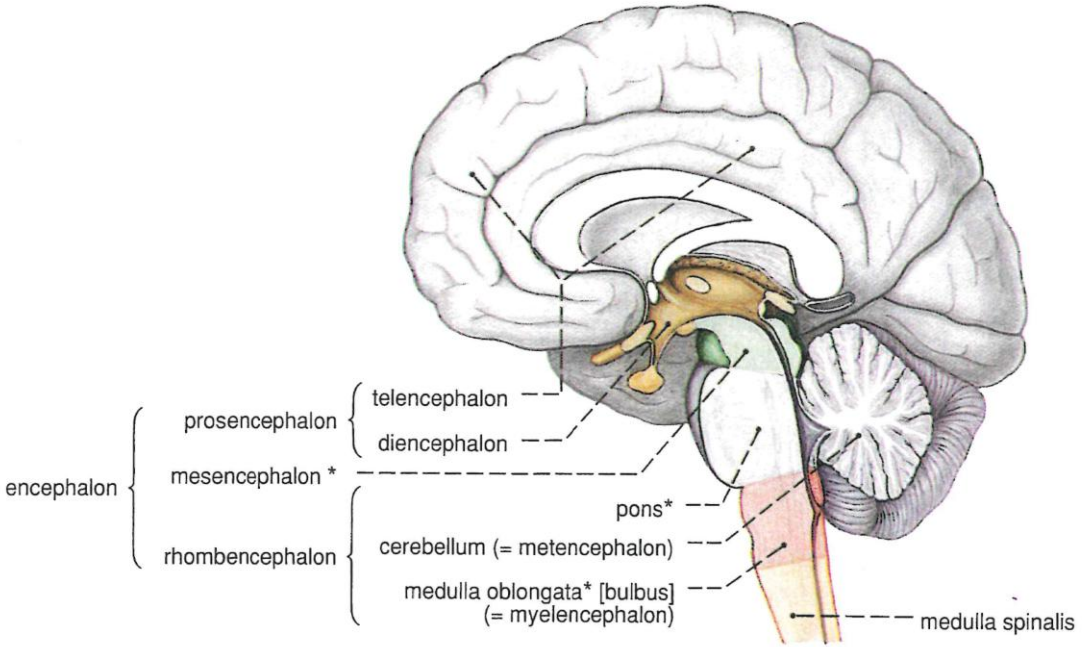
- Macroscopically, it is divided into three parts:

    1. Prosencephalon = telencephalon + diencephalon
    2. Midbrain= mesencephalon

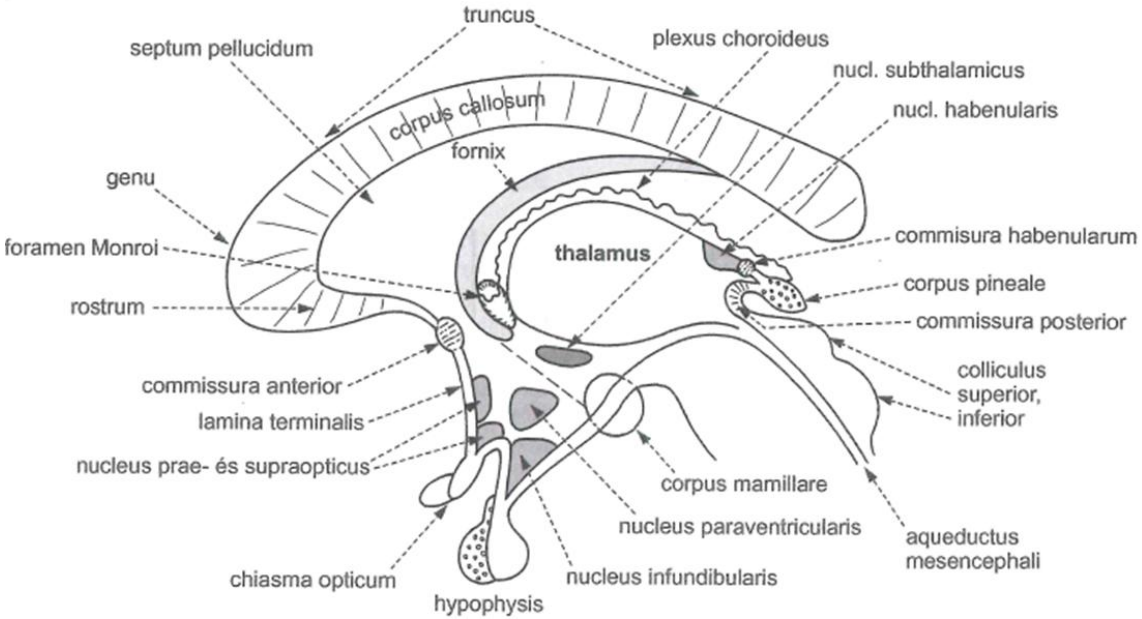
    (1 + 2 = cerebrum)

    3- Rhombencephalon = metencephalon (pons + cerebellum) +myelencephalon

Sagittal Section of the Brain

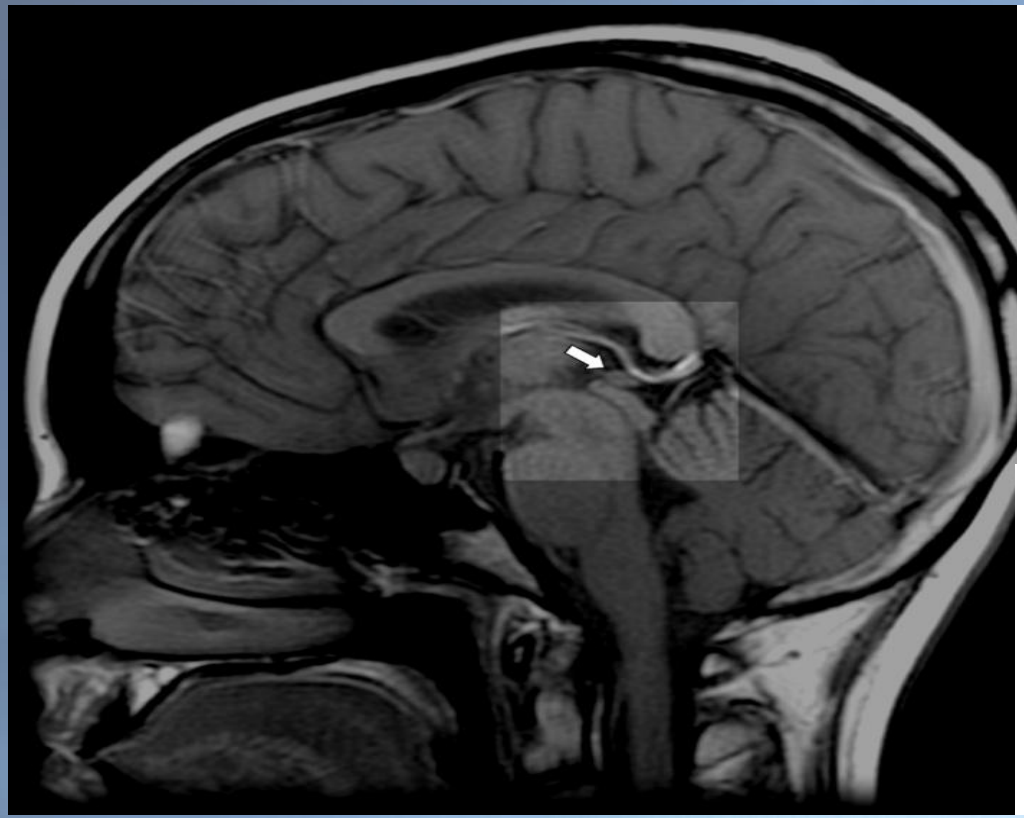


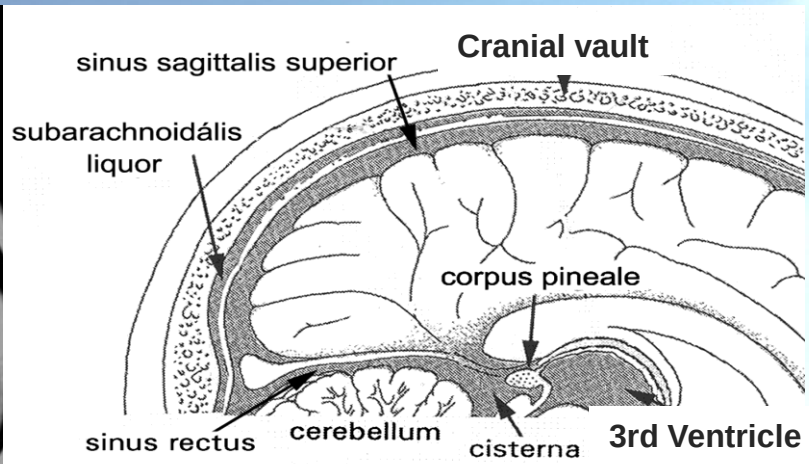
Diencephalon



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Location of the pineal gland







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Histology of the pineal gland



Pinealocytes non-visual photoreceptors (melatonin);

Neurons nerve cells – transmission of nerve impulses);

Glial tissue– support, nourishment and protection (e.g. astrocytes – macroglia);

Ependymal cells (e.g. microglia) production and circulation of CSF.

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Melatonin plays an important role in the regulation of circadian and circannual biorhythms

Suppression of melatonin leads to disruption of circadian rhythms

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CIRCADIAN AND CIRCANNUAL RHYTHMS

These are regular changes, involving both mental and physical characteristics.

Some are controlled by the suprachiasmatic nucleus, located in the hypothalamus (**master clock**),
but every organ has its own genetic clock (**slave clock**).

Circadian ⇨ (24 h) day / night — Throughout life

Circanual ⇨ throughout the year — A period of life

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CIRCADIAN RHYTHMS

Body temperature;

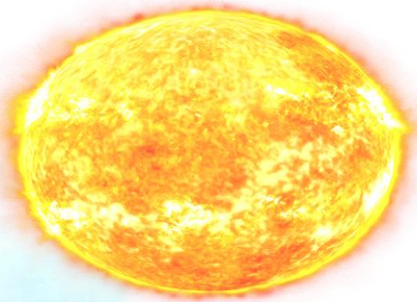
Heart rate;

Blood pressure;

Hormone secretion (adrenaline / cortisol / **melatonin**); Metabolism;

Cellular turnover ;

State of alertness / energy.



CIRCANNUAL RHYTHMS

Duration of daylight;

Ambient temperature;

Bird migration;

Hibernation / sleep requirements;

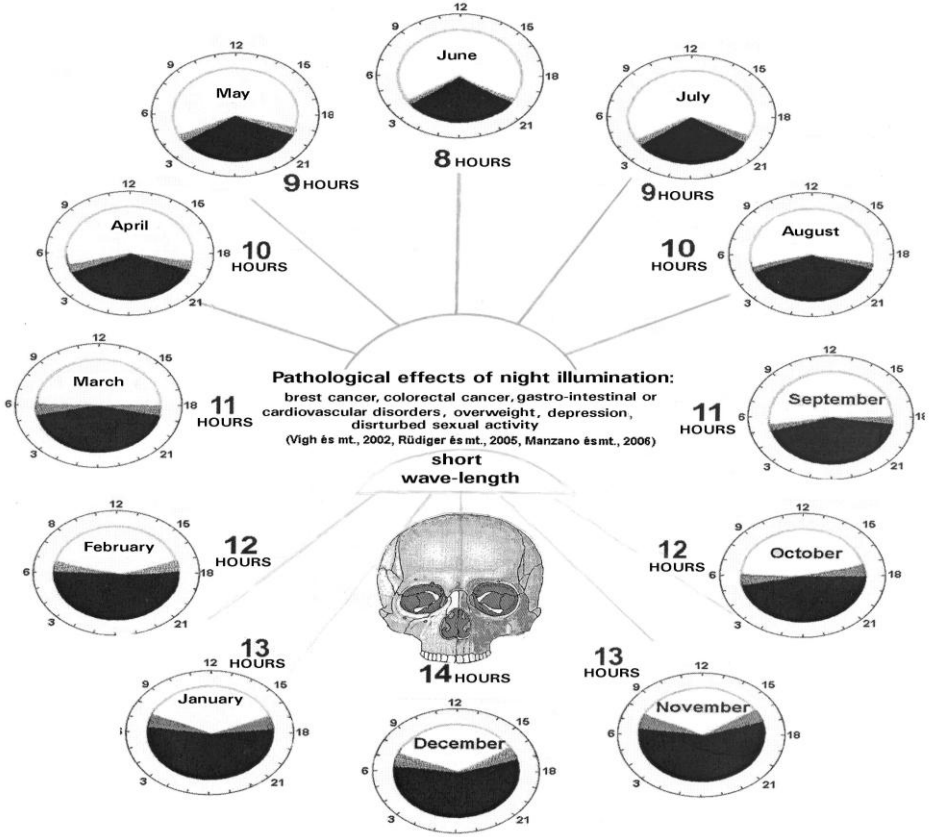
Annual cycles of reproductive activity.



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Circannual Rhythm

Hours of Sleep / Darkness Throughout the Year



B. Vigh (2006)

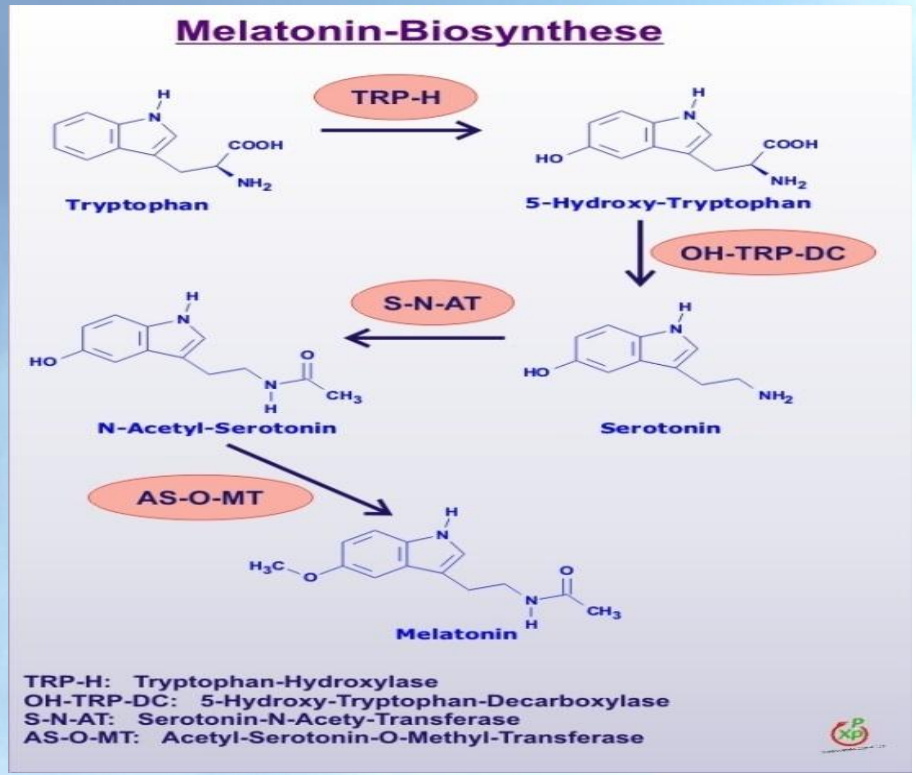
Melatonin

⇨**Sleep hormone**;

⇨Synthesised from tryptophan through serotonin ;

⇨Secreted mainly by the pineal body;

⇨ It is produced in the dark (higher levels at night and in winter!).



Functions of Melatonin

⇨Tells the body that it is night-time;

⇨Synchronises peripheral clocks;

⇨Reduces body temperature;

⇨ Plays a role in the onset and maintenance of sleep

⇨ Acts as an antioxidant and immunomodulator

BIOLOGICAL CLOCKS

⇨ ***Slave clocks:*** genetic and peripheral clocks;

⇨ ***Master clock*** **:** suprachiasmatic nucleus.



Clock genes

MORNING/DAYTIME

- **Clock**+**Bmal1** proteins bind to DNA—activate—**PER** and **CRY** ; by gene transcription enter the nucleus

- Desactivate Clock +Bmal 1

  EVENING/ NIGHTTIME

The relationship between melatonin and circadian genes

Melatonin influences the expression of:

-BMAL 1; PER 1/2; CRY 1/2;

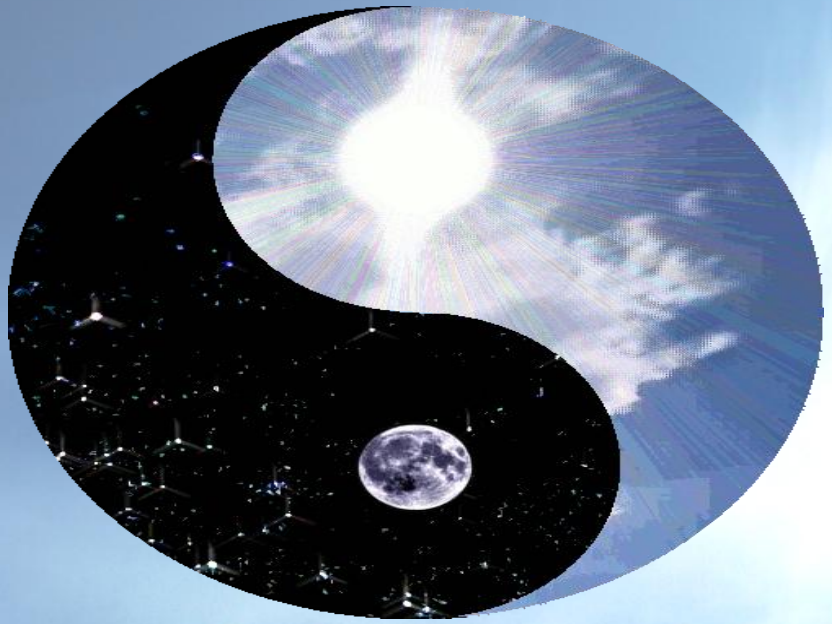
-Metabolic genes dependent on the biological clock;

-Individuals with mutations in CRY1, PER 2, etc., have altered responses to melatonin;

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PATHOLOGICAL EFFECTS OF EXPOSURE TO LIGHT DURING THE NIGHT

Disruption of circadian and circannual rhythms.



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Exposure to Night-time Light ➔ Suppression of melatonin

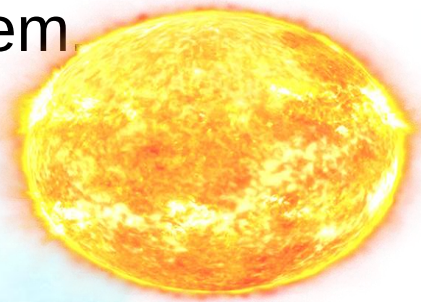
Sleep hormone



⇨Disruption of circadian rhythms;

⇨Anti-gonadotrofic action;

⇨ Negative effect on the immune system



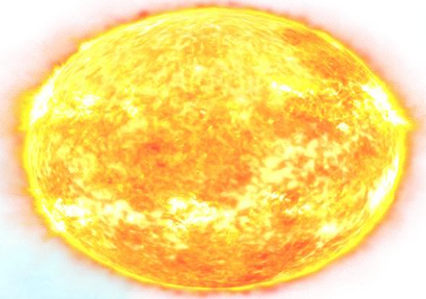
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NON-VISUAL PHOTORECEPTORS

Pineal Gland: Pinealocytes;

Retina: Ganglion cells;

***Deep Brain* Photoreceptors:** Preoptic nucleus.



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NON-VISUAL PHOTORECEPTORS

Contain sensitive molecules to blue light:

⇨ Photopigments: Opsin, Rhodopsin and

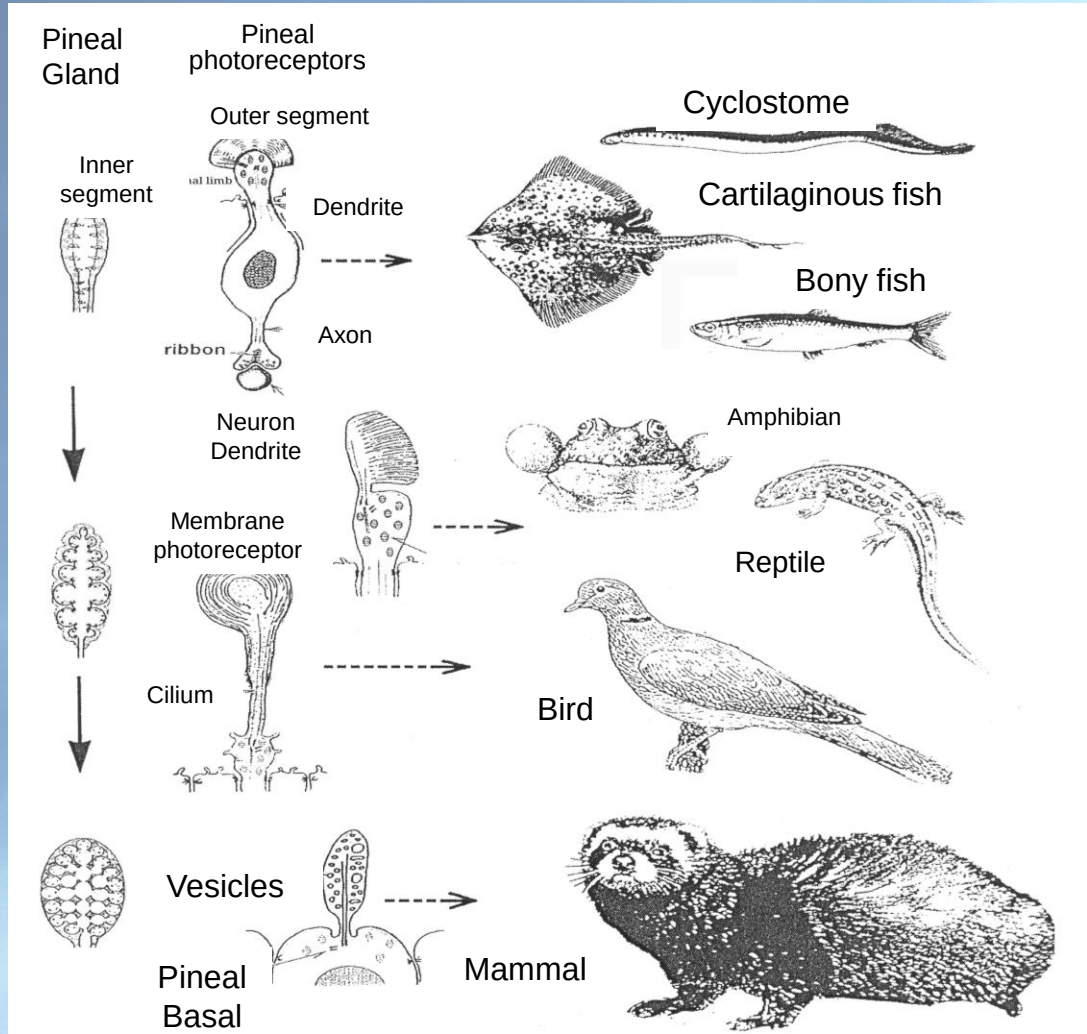
Iodopsin

Pinopsin and Melanopsin



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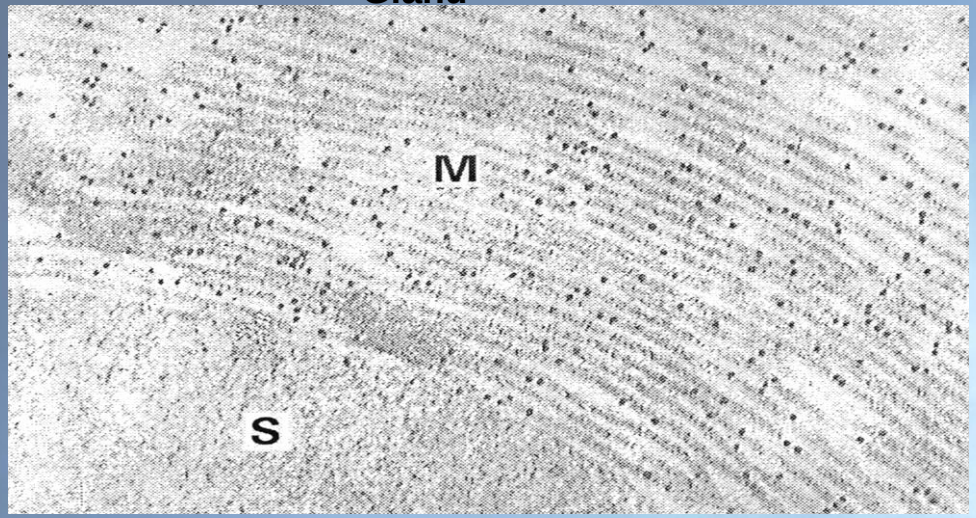
Development of the Pineal Gland



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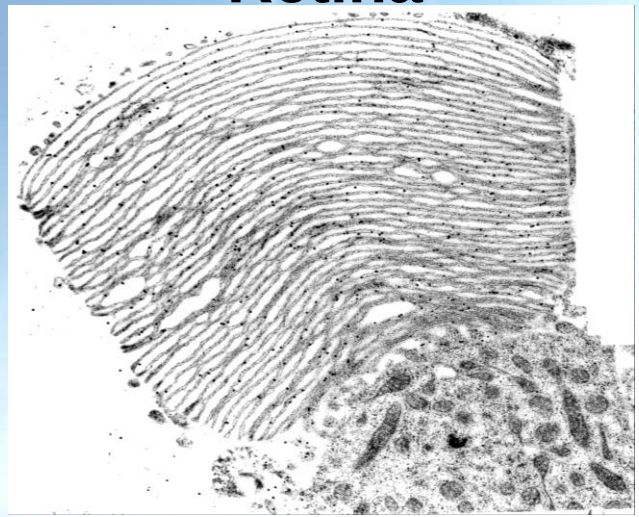
NON-VISUAL PHOTORECEPTORS

Pineal Gland



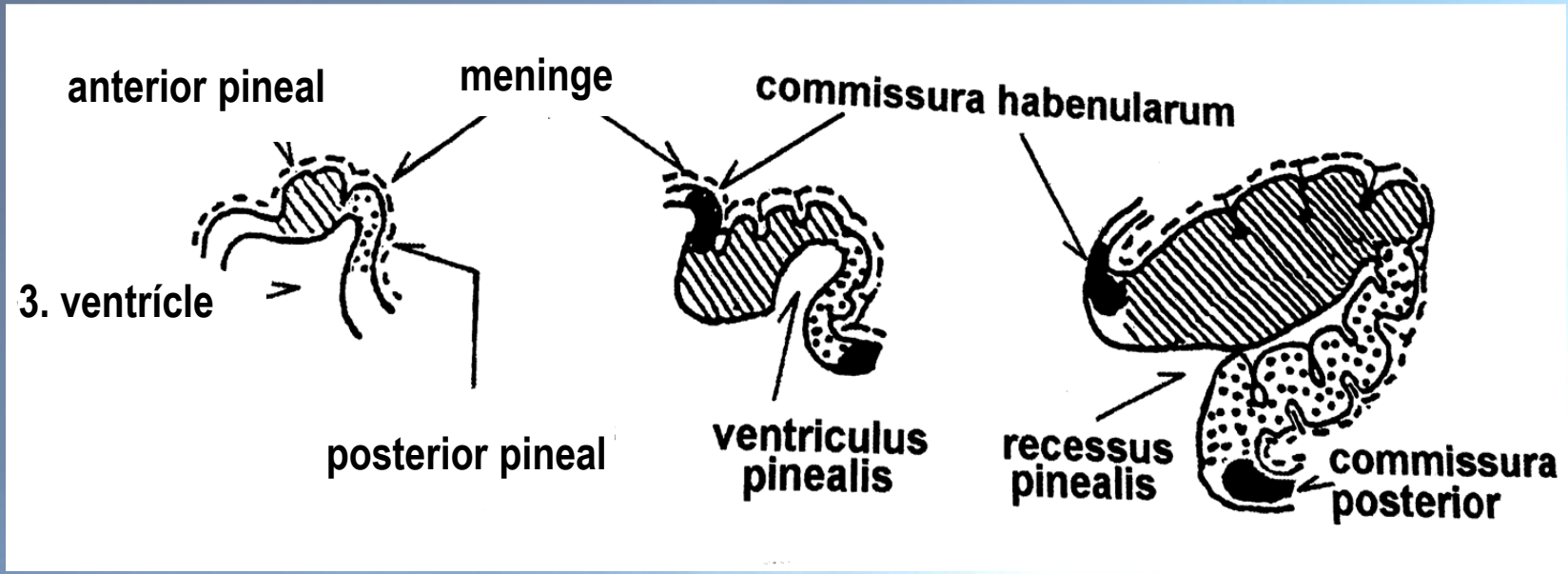
Pinopsin in a pinealocyte

Retina



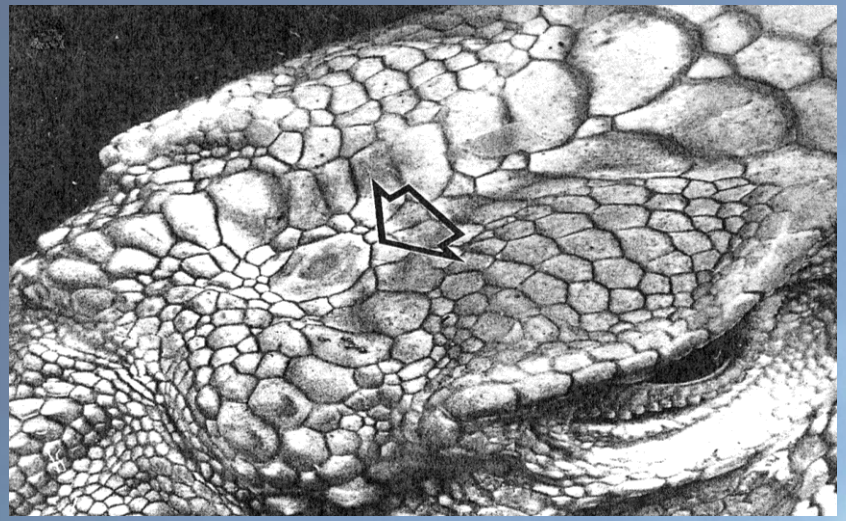
Opsin in a cone

Diagram of an 8 mm human embryo (2 months)

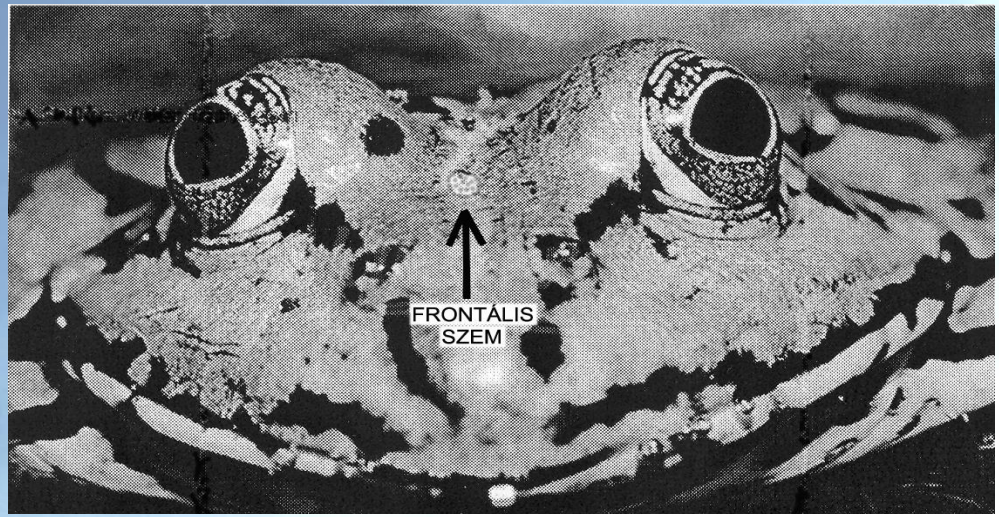


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Evolution of the Pineal Gland



Iguana
Parietal eye

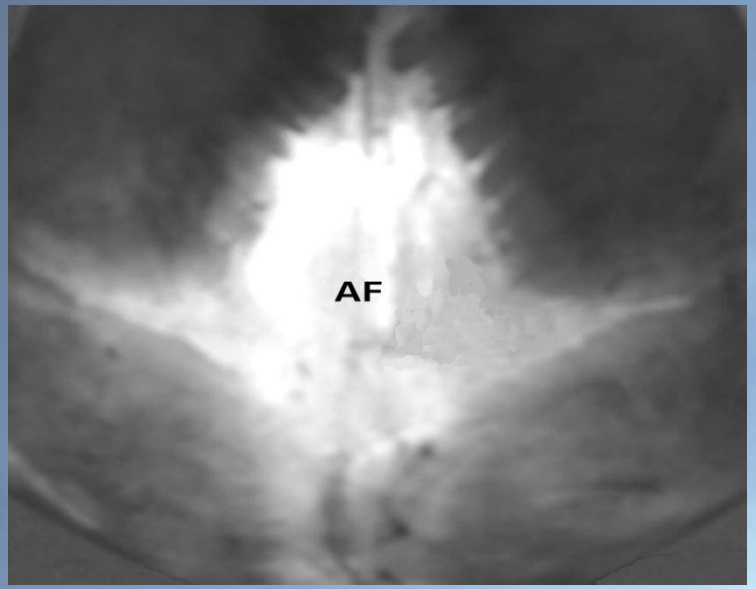


Frog
Frontal eye outside the skull

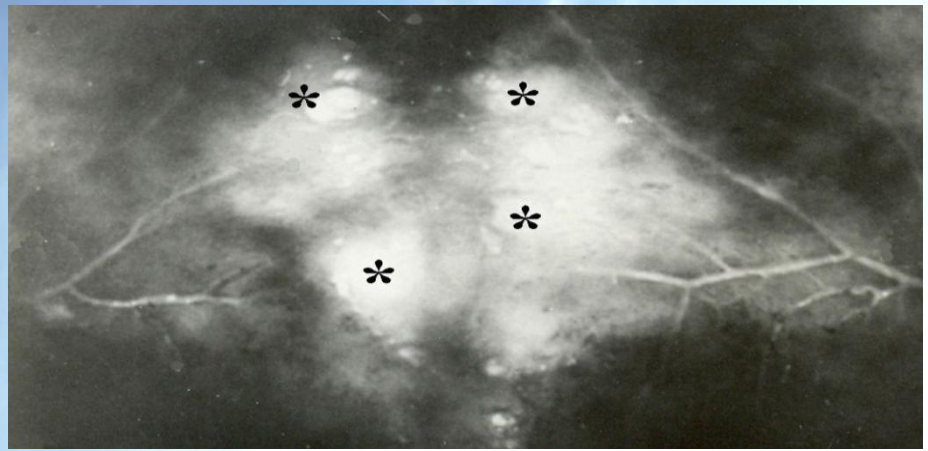
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Direct Light Afferents of the Pineal Gland

Light transmission (60W bulb) through the human skull.



Anterior fontanelle

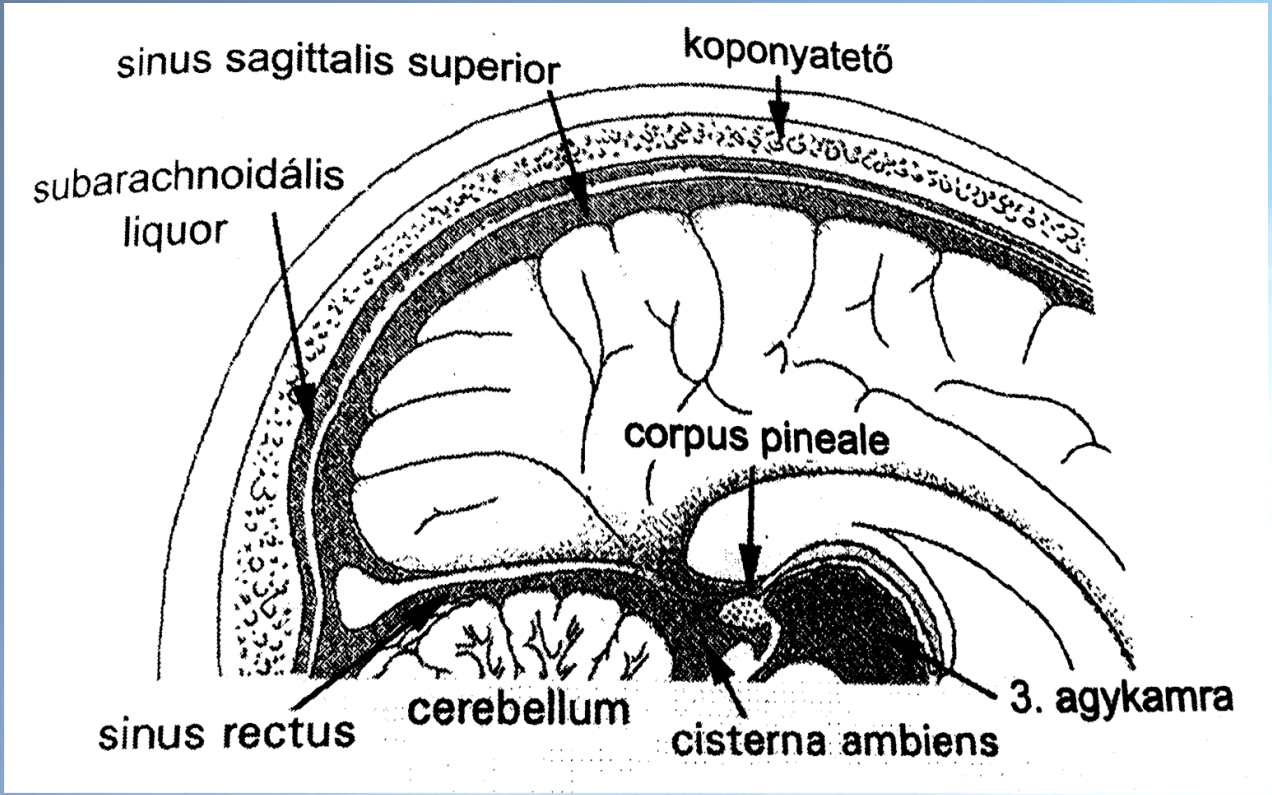


Adult skull

* Granular foveolae and sulcus arteriae meningeae mediae

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The Role of Cerebrospinal Fluid in Light Propagation



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Retina-Pineal Body Connections



Neuroscience Letters 588 (2015) 1–6

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Is a neuronal chain between the pineal body and the retina in rats and hamsters? Transneural tracing studies

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Neuroscience Letters 665 (2018) 189–194

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Ontogenesis of the pinealo-retinal neuronal connection in albino rats

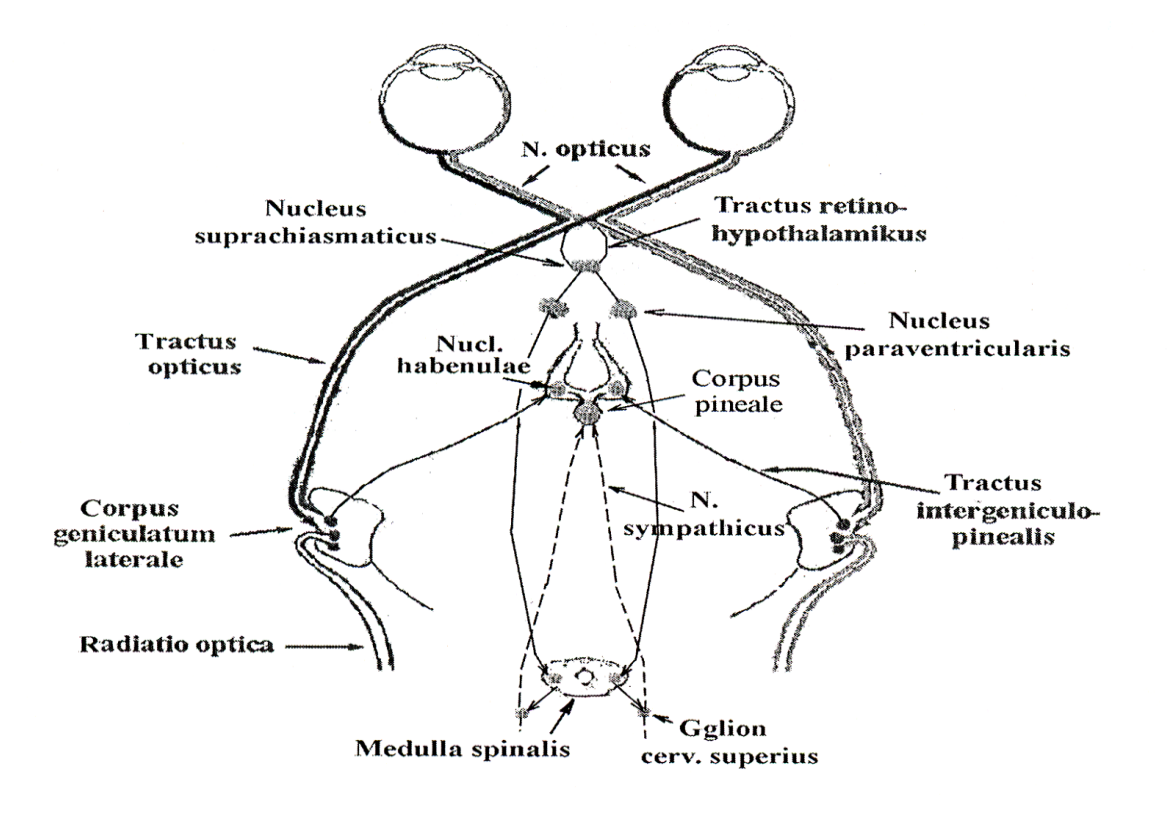
Ágnes Csáki[a], Viktória Vereczki[a], Ákos Lukáts[a], Zsolt Boldogkői[b], Anna Sebestyén[c], Zita Puskár[a], Katalin Köves[a,*]

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2 October 2026

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Retino-Pineal Neural Connections



Light—Circadian System

- **Non-visual photoreceptors** detect light via their photopigments (opsin, rhodopsin, iodopsin, pinopsin, melanopsin)

- and send direct signals, via nerve tracts, to the **suprachiasmatic nucleus** (**SCN**) in the hypothalamus, the master clock

Interaction between Light, Melatonin and Metabolism

- Circadian rhythms are linked to light, melatonin and metabolism – CHRONOBIOLOGY – integrating the brain, hormones and cells throughout the body.

- Light is the main synchroniser (“zeitgeber”) of the biological clock

Suprachiasmatic Nucleus – SCN

- Resets and synchronises the expression of the CLOCK, BMAL1, PER and CRY genes

- adjusting all peripheral clocks (liver, pancreas kidneys, skin, gut,…)

- The SCN sends information directly to the pineal gland or activates sympathetic fibres that stimulate the **pineal body/gland** to produce melatonin.

Biological Effects of Light

- **Morning light**:

increases cortisol; wakes up the brain; advances the body clock (it becomes ‘earlier’)

. **Light at night**:

suppresses melatonin; delays the body clock (makes it harder to fall asleep); affects the liver and metabolism

Interaction with melatonin

- Melatonin is the ‘dark hormone’, produced by the pinealocytes of the pineal gland
- How is it regulated?

1. Darkness – the SCN activates sympathetic fibres that stimulate the pineal gland/body
2. Light – via non-visual photoreceptors – retinal ganglion cells – SCN – inhibits its production

Circadian Rhythm Genes

- In mammals (including humans), more than 100 circadian rhythm genes are known.
- They form the molecular ‘gearwork’ of the circadian rhythm

Key genes of the circadian clock

- 1.**CLOCK**- activates the transcription of the various clock genes
- 2.**BMAL1**- essential partner of the CLOCK dimer – the most indispensable gene in the circadian clock
- 3.**PER1**,**PER2**,**PER3** (Period genes)

Negative feedback loop

maintenance of stable rhythms (PER2!)

. 4. **CRY1** and **CRY2**(cryptochrome genes)

inhibit Clock/Bmal1 activity

Affect the duration of the cycle

Positive and negative feedback loops

- The circadian system consists of positive and negative feedback loops that generate a cycle of approximately 24 hours
- Positive loop – activation of the Clock/Bmal1 genes –dimer; DNA E-boxes (activating various genes – Per1, Per2, Per3)
- Negative loop – after a few hours, the Per and Cry proteins accumulate in the cytoplasm, forming Per/Cry complexes which migrate to the nucleus. Within the nucleus, Per/Cry inhibit Clock/Bmal1, bringing the active phase to an end

This ***delay between activation and inhibition generates a cycle of approximately 24 hours***

- secondary loop— regulates Bmal1 levels throughout the day, reinforcing the rhythm (VER-ERB repressor and RORs, which activate Bmal1)

Output genes—***DBP***,***TEF***,***HLF***

These are activated via Clock/Bmal1 transcription

regulating physiological processes:energy metabolism; hormones (melatonin, cortisol, GH, etc.);

sleep/wakefulness; body temperature; the immune system; hepatic detoxification.

All tissues have peripheral clocks controlled by these genes!

Human mutations and their effects

- CRY1 mutation – delayed sleep (Delayed Sleep Phase Disorder)
- PER2 mutation – advanced sleep phase (Familial Advanced Sleep Phase Syndrome)
- CK1delta – also causes an advanced sleep phase
- PER3 – variant associated with being more of a ‘morning person’ or an ‘evening person’

How it all fits together:**light–melatonin–metabolism–genes**

1.**Morning light** resets the NSQ-activated CLOCK/BMAL

2. **Darkness**- increases melatonin

3. **Melatonin** – sends a ‘night-time’ signal to the organs – regulates PER/CRY

4. In the **liver**, **pancreas** and **muscles**, **circadian genes** determine: whether it is time to eat, burn or store energy

5. What we eat and when we eat also send signals back to the clock via SIRT1, AMPK and mTOR (cellular sensor genes)

In summary: the body only functions properly when light, sleep and food are in synchronization with the biological clock

Epigenetics, our hope!

Our DNA doesn’t change, but the way it is used throughout our lives does!

The environment; lifestyle; diet and sleep;

We can create markers or ‘switches’ that block genes, for better or for worse

(DNA methylation – switches off certain genes; histone modification – the way DNA winds itself; non-coding RNA – gene activation)

NIGHT-TIME WORK

Some people adapt less well to night work than others (morningness).

DISRUPTION OF THE CIRCADIAN RHYTHM!!

MELATONIN

may be a biological indicator

(6-sulphatoxymelatonin in urine/saliva;Questionnaires)



The health consequences of exposure to night-time light can manifest as:

- Sleep disturbances (insomnia); daytime sleep may not be as restorative due to various external factors (mobile phones, noise e.g. cleaning, cars…);
- Changes in eating habits (weight changes) – increased food intake in the evening, gastrointestinal disturbances;
- Changes to biological balance, resulting in:
- Increased cardiovascular risk (hypertension); metabolic disorders (diabetes, obesity); breast cancer (prostate cancer, endometrial cancer, colorectal cancer, non-Hodgkin's lymphoma); neuropsychological changes (irritability, depression);
- Loss of concentration, increased fatigue;
- Increased number of accidents and accumulation of errors: *Three Mile Island (1979), which occurred at 4.00 am; Chernobyl (1986), which occurred at 1.25 am; and the Bhopal chemical disaster (1984), which occurred at 0.57 am*

INDIVIDUAL VULNERABILITY

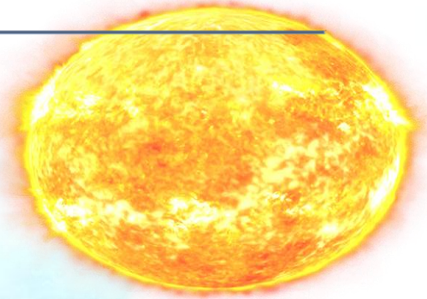
- Age;
- Early circadian phase ("*morningness*" / morning);
- Research into "*clock genes*";
- Behaviour and lifestyle;
- Risk of carcinoma.



IARC (2007) – Classified night work as **Group 2A** (probably carcinogenic to humans) **for breast cancer**, based on experimental animal studies and epidemiological studies.

International Agency for Research on Cancer

World Health Organization



CONTROL OF AMBIENT LIGHT

***Clock* physiological** (suprachiasmatic nucleus) operates on a cycle of approximately 24 hours;

1 day of adaptation to adjust **1 hour** time difference (jet lag);

Rotations are easier: M→A→N and travelling westwards;

12-hour shifts: showed less disruption to the circadian rhythm /melatonin secretion:

M → M (8 am–8 pm) → A → A (8 pm–8 am)

→TO→TO→TO→TO



MEDICAL EVALUATIONS

⇨ **Admission /**

⇨ **Pre-existing conditions**

Digestive disorders (ulcers);
Heart problems – hypertension;
Diabetes, **Epilepsy**;
Neoplasm.

⇨ **Melatonin test** (?)

⇨ Questionnaires(?)



Night Work

Consensus Report – Conclusions and Recommendations

- Significant/high risk; *Include in the list of occupational diseases (?);*
- Restrict the number of years of service (to 20 or 15 years);
- Implement short rotations (1 to 2 nights); Rotation schedule (Morning – Afternoon – Night);
- Limit the number of consecutive nights (4 nights per month);
- Melatonin secretion is a good marker of the circadian rhythm *(melatonin supplement?);*
- The light should be red in colour and of reduced intensity;
- Women with breast tumours should be advised not to work night shifts.

Ref: Bond et al. (2011), "Scand J Work Environ Health" – online first: doi:105271/sjwek.3282

Naps during the night Shift, if possible !



No Light at Night!



Thank You for being here!