The pineal gland and Circadian rhythms
Press Release
2017-10-02

The Nobel Assembly at Karolinska Institutet has today decided to award
the 2017 Nobel Prize in Physiology or Medicine

jointly to

Jeffrey C. Hall, Michael Rosbash and Michael W. Young

for their discoveries of molecular mechanisms controlling the circadian rhythm
The diagram illustrates the circadian rhythm, showing different physiological states at different times of day:

- **06:00** - Cortisol release
- **12:00** - High alertness, Best coordination, Fastest reaction times
- **18:00** - Fastest increase in blood pressure
- **24:00** - Lowest body temperature, Melatonin secretion, Deep sleep
- **06:00** - Highest body temperature, Highest blood pressure

These changes help regulate various bodily functions throughout the day.
Summary

- The pineal gland
- Anatomical features of the pineal gland
- Circadian Rhythmicity
- Melatonin synthesis
- Melatonin’s functions
- Published data and clinical aspects
The Pineal Gland

• *epiphysis cerebri*
• unpaired organ
• “Seat of the soul”
• “Third Eye”
• circumventricular organ
• neuroendocrine gland
Similarities between the cross section of the brain showing the Pineal Gland and the "Eye of Ra".
Circumventricular organs

• midline structures around the third and fourth ventricles
• in contact with blood and cerebrospinal fluid, highly permeable microvasculature (BBB)
• the linkage between the central nervous system and peripheral blood
• Sensory or Secretory(?)
Neuroendocrine gland

• receives neuronal input (neurotransmitters released by nerve cells);
• as a consequence of this input, release message molecules (hormones) to the blood.
• MELATONIN
Anatomical features

- the midline of the brain
- attached by a short stalk to the roof of the third ventricle
- Part of the epithalamus, a component of the diencephalon
- pine-cone appearance
- 95% pinealocytes
Figure 16-1.
Anatomical relationships of the pineal gland. The pineal gland (green), named for its shape, which is similar to that of a pine cone, is attached to the posterior end of the roof of the third ventricle of the brain, here shown in sagittal section. This places it very near the midline of the brain. It is some distance from the suprachiasmatic nucleus and the hypothalamus, with which it has neuronal connections as shown in Figure 16-2.
• The gland tends to accumulate calcium deposits with age
• the effect of these deposits on pineal function is not known
• they provide an excellent imaging marker for the center of the brain.
Circadian Rhythmicity

- Connections of the pineal gland with the visual system
- Intrinsically photo-sensitive retinal ganglion cells, the ipRGCs
- The Suprachiasmatic Nucleus (SCN) acts as a central circadian clock/biological clock
- Informs the pineal gland whether it is light or dark
- Controls the melatonin synthesis in the pineal gland
• Light travels through the layer of **retinal ganglion cells** (RGC) and the neural cells in the inner retina to the rods and cones in the photoreceptor layer of the retina.

• A small number of the RGCs contain melanopsin and have intrinsic photoreceptor capability (**ipRGC**).

• The photic information from the retina is sent to the **suprachiasmatic nucleus (SCN)**/ biological clock

• **Paraventricular Nucleus (PVN)** of the hypothalamus

• **Superior Cervical Ganglion (SCGs)** which transmits the signal to the **pineal gland**.
This is what you get a Nobel Prize for!
Melatonin synthesis control

• The axon from the SCG releases norepinephrine (NE) which is the trigger for the pinealocyte to produce and secrete melatonin.

• Beta-adrenergic receptors – increased intracellular cyclic AMP levels

• increased synthesis and translation of mRNA encoding N-acetyltransferase (AANAT) required for the conversion of serotonin to N-acetylserotonin.
Pattern of synthesis

• The pineal conveys information about the light–dark cycle of the current day because melatonin is secreted only during darkness.

• Serum levels of melatonin rise several-fold to a peak (00:00 – 04:00 am) (?)

• Cortisol

• The highest cortisol secretion happens in the second half of the night with peak cortisol production occurring in the early morning.
Melatonin’s functions

Clock genes expression control (circadian rhythm)

Oxidative stress

Immune system

Cardiovascular system

Brain functions

Reproductive functions

Folliculogenesis and spermatogenesis

Ovulation

Sperm activation

Gametal production and fertility modulation

Oocyte maturation

Sexual maturation

Puberty onset
Melatonin Receptors

• MT1 and MT2 receptors
• **G protein-coupled receptors**
• About 60% amino acid homology
• MT1 receptor’s melatonin affinity is approximately five-fold greater than that of the MT2 receptor.
<table>
<thead>
<tr>
<th>LOCATION</th>
<th>RECEPTOR TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovary</td>
<td>MT1</td>
</tr>
<tr>
<td>Uterus (myometrium)</td>
<td>MT1</td>
</tr>
<tr>
<td>Adrenal cortex</td>
<td>MT1</td>
</tr>
<tr>
<td>Liver</td>
<td>MT1</td>
</tr>
<tr>
<td>Pancreas</td>
<td>MT1</td>
</tr>
<tr>
<td>Spleen</td>
<td>MT1</td>
</tr>
<tr>
<td>Brain</td>
<td>MT1</td>
</tr>
<tr>
<td>Cerebellum, Hippocampus,</td>
<td>MT1</td>
</tr>
<tr>
<td>Ventral Tegmental Area,</td>
<td></td>
</tr>
<tr>
<td>Substantia Nigra</td>
<td></td>
</tr>
<tr>
<td>SCN and Hypothalamus</td>
<td>MT1, MT2</td>
</tr>
<tr>
<td>Placenta</td>
<td>MT1, MT2</td>
</tr>
<tr>
<td>Testis</td>
<td>MT1, MT2</td>
</tr>
<tr>
<td>Breast</td>
<td>MT1, MT2</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>MT1, MT2</td>
</tr>
<tr>
<td>(heart and blood vessels)</td>
<td></td>
</tr>
<tr>
<td>Immune system</td>
<td>MT1, MT2</td>
</tr>
<tr>
<td>Retina</td>
<td>MT1, MT2</td>
</tr>
<tr>
<td>Kidney</td>
<td>MT1, MT2</td>
</tr>
<tr>
<td>Pituitary</td>
<td>MT2</td>
</tr>
<tr>
<td>Gastrointestinal system</td>
<td>MT2</td>
</tr>
<tr>
<td>Adipose Tissue</td>
<td>MT2</td>
</tr>
</tbody>
</table>
In Sync

• The central clock in the SCN has an **autonomous** period of slightly longer than 24 hours
• **Feedback effect** of melatonin on SCN helps maintain entrainment of the central clock to the external light/dark cycle
• Melatonin synchronizes the **peripheral clocks**.
Jet Lag/Shift Workers

- Disruption of the normal circadian rhythm
- Fatigue, sleep problems, and reduced performance are common symptoms of jet lag
- **Exogenous melatonin** can be effective in accelerating the phase shift if given at the appropriate time prior to bedtime.
Optimising sleep for night shifts

Helen McKenna intensive care research fellow¹, Matt Wilkes specialty registrar²

¹Royal Free Intensive Care Unit, London, UK; ²Department of Anaesthesia, Critical Care and Pain Medicine, Royal Infirmary of Edinburgh, Edinburgh, UK

What you need to know

- Working at night disrupts the circadian rhythm and can lead to the accumulation of a sleep debt, impairing performance and health
- Full circadian adaptation to night shift work is not possible in the short term

What evidence is available regarding strategies for workers on night shifts?
Sleep Phase Syndrome

• In advanced (ASPS) or delayed (DSPS) sleep phase syndrome, patients either sleep during the day and wake in the middle of the night or do not sleep until the middle of the night.

• ASPS is often seen in elderly individuals and DSPS in children with some neurodevelopmental disorders.
History

An historical view of the pineal gland and mental disorders

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ABSTRACT

Since Classical Antiquity numerous authors have linked the origin of some mental disorders to physical and functional changes in the pineal gland because of its attributed role in humans as the connection between the material and the spiritual world. The pineal organ was seen as a valve-like structure that regulated the flow of animal spirits through the ventricular system, a hypothesis that took on more vigour during the Middle Ages and the Renaissance. The framework for this theory was “the three cells of the brain”, in which the pineal gland was even called the “appendix of thought”. The pineal gland could also be associated with the boom, during this period, of certain legends about the “stone of folly”. But the most relevant psychopathological role of this organ arrived with Descartes, who proposed that it was the seat of the human soul and controlled communications between the physical body and its surroundings, including emotions. After a period of decline during which it was considered as a mere vestigial remnant of evolution, the link between the pineal gland and psychiatric disorders was definitively highlighted in the 20th century, first with the use of glandular extracts in patients with mental deficiency, and finally with the discovery of melatonin in 1958. The physiological properties of melatonin reawakened
Melatonin as an antioxidant

• Free-radical scavenging properties
• Highly lipophilic molecule
• Promotes the expression of antioxidant enzymes (glutathione peroxidase, glutathione reductase, superoxide dismutase, catalase)
• Melatonin is four times as effective as glutathione as an antioxidant.
Melatonin and the reproductive function

• Maternal melatonin may have a major role in influencing the development of the fetus
• It readily crosses the placenta
• Entraining the circadian rhythm of the fetal hypothalamus
Maternal Chronodisruption

• Programming adult health: from embryo to adult life
• Elevated systolic blood pressure
• Glucose intolerance
• Metabolic syndrome
• Anxiety, depression and memory impairment
Light travels fast in Australia

**REVIEW** | *Model Systems for the Study of Integrative Physiology: The Rebirth of Translational Biology*

Maternal circadian rhythms and the programming of adult health and disease

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**Varcoe TJ, Gatford KL, Kennaway DJ.** Maternal circadian rhythms and the programming of adult health and disease. *Am J Physiol Regul Integr Comp Physiol* 314: R231–R241, 2018. First published December 4, 2017; doi:10.1152/ajpregu.00248.2017.—The in utero environment is inherently rhythmic, with the fetus subjected to circadian changes in temperature, substrates, and various maternal hormones. Meanwhile, the fetus is developing an endogenous circadian timing system, preparing for life in an external environment where light, food availability, and other environmental factors change predictably and repeatedly every 24 h. In humans, there are many situations that can disrupt circadian rhythms, including shift work, international travel, insomniás, and circadian rhythm disorders (e.g., advanced/delayed sleep phase disorder), with a growing consensus that this chronodisruption can have deleterious consequences for an individual’s health and well-being. However, the impact of chronodisruption during pregnancy on the health of both the mother and fetus is not well understood. In this review, we outline circadian timing system ontogeny in mammals and examine emerging research from animal models demonstrating long-term negative implications for progeny health following maternal chronodisruption during pregnancy.
ANIMAL MODELS OF MATERNAL CIRCADIAN RHYTHM DISRUPTION

• Functional pinealectomy
• Chronic Phase Shift (CPS)
• Surgical removal of the pineal gland
And so does in Romania

Research report

Behavioral and molecular effects of prenatal continuous light exposure in the adult rat

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Our results

• Anxiety behavior, Short-term memory impairment but normal long-term memory
• Depressive behavior
• Increased ROS concentration in the offspring and adult brains
• RORa and Serotonin Reuptaker modified gene expression
Conclusions

• The pineal gland is a neuroendocrine gland that produces melatonin
• Melatonin is essential for dark/light synchronization
• SCN is the central biological clock (Nobel prize material!)
• Melatonin is also involved in reducing oxidative stress and modulating the immune response
• Chronodisruption is probably the next Nobel prize material!