PHYSIOLOGY OF CIRCADIAN RHYTHM

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The word 'circadian' is derived from Latin language- 'circa diem', meaning 'about a day'[1]. Basically, circadian rhythm means endogenous 'daily biological rhythm'. Study of such biological rhythm is called as chronobiology.

Circadian rhythm includes behavioral and physical changes occurring in living organisms over a 24-hour day night cycle. They are present in animals, plants, fungi, cynobacteria and other living beings. These changes may be in sleep patterns, body temperature, hormonal changes, emotional changes, digestive changes and other body processes.

Circadian rhythm develops during first four months of life, as the child gets adapted to normal physiological and environmental changes.

History:

History and evolution of circadian rhythm is in parallel to earth's geological history

History of biological rhythms dates back to 1700'- daily leaf movements of plants was published by a French Scientist de Mairan. More formal studies were conducted in 1950's in fruit flies by Colin Pittendrigh. In humans, Jurgen Aschoff studied biological rhythm initially and variations in sleep according to day and night cycle were studied by Nathaniel Kleitman[1]. In 1959, Franz Halberg introduced the term, 'circadian' from the Latin 'circa', describing 24-hour biological rhythms in the body. In 1977, International Committee on Nomenclature of the International Society for Chronobiology, recognized definition of circadian rhythm as:

Circadian: relating to biologic variations or rhythms with a frequency of 1 cycle in 24 ± 4 hours; circa (about, approximately) and dies (day or 24 h)[2].

In 2017, Nobel Prize in *Physiology or Medicine* was awarded to three researchers- Jeffrey C. Hall, Michael Rosbash, and Michael W. Young, for molecular studies on controlling circadian rhythms in fruit flies[3].

First mammalian circadian clock mutation was first discovered in mice by Joseph Takahashi in 1994[4]. Till date, many studies are going on to understand molecular and genetic mechanisms related to circadian rhythms like post transcriptional modifications and role of RNA methylation.

Circadian rhythm in mammals:

The main switch for circadian rhythm in mammals is present in the suprachiasmatic nucleus of the hypothalamus, which is responsible for sleep wakefulness cycle.

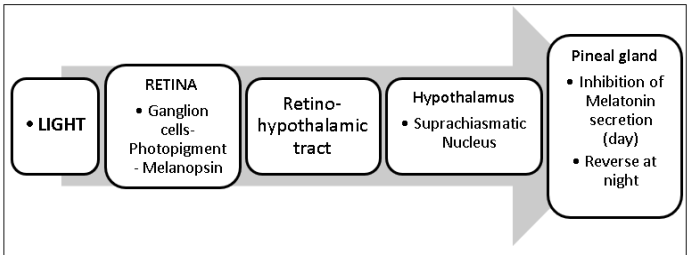

Figure 1: Circadian rhythm via suprachiasmatic nucleus of hypothalamus.

When light enters the eyes during day (Figure 1), photo pigment called melanopsin present in

ganglionic cells of retina get stimulated. These signals are passed to suprachiasmatic nucleus or hypothalamus via the retino-hypothalamic tract. This information is processed and sent to pineal gland which in turn reduces the secretion of melatonin leading to wakefulness. Reverse happens at night; melatonin secretion is increased leading to sleep. This is how suprachiasmatic nucleus plays am important role in circadian patterns of day and light, in turn, affecting various activities of the body. In humans, natural rhythm is approximately 24 hours and 11 minutes, with circadian rhythm for women being shorter than men. Women- 24.09 hrs and men 24.19 hrs[5].
Biological markers of circadian rhythm are melatonin secreted by pineal gland, core body temperature, cortisol plasma level.

Genetic basis of circadian rhythm[6].

The circadian rhythm is regulated by interplay of interconnected cellular pathways, proteins and genes. Genetic basis of circadian rhythm are special 'clock genes'.

Auto regulatory transcription-translation feedback loops (TTFLs) are present which form basis of circadian clock. There is heterodimeric interaction between protein factors-brain and muscle Arnt-like protein 1 (ARNTL, also known as BMAL1) and the circadian locomotor output cycles kaput (CLOCK), period (*Per1, Per2 and Per3*), and cryptochrome (*Cry1* and *Cry2*). Protein products and transcripts of these genes produce 24 hour oscillations in cells. Many post-translational regulatory processes like ubiquitination, acetylation, phosphorylation help in above processes. Clock genes integrate temporal information outside vs inside the body.

Mutations in clock genes can cause disorders like Familial Advanced Sleep Phase Syndrome (FASPS). Clock genes are present in all cells; however, the master clock of circadian rhythm is the suprachaismatic nucleus in the hypothalamus.

Factors affecting circadian rhythm:
Many factors affect circadian rhythm like light and dark environment, mental status, trave, temperature, sleep habits, physical activity, many diseases, medications etc.

Importance of circadian rhythm:
Normal circadian rhythm is absolutely required for restful sleep. Metabolic regulation, memory consolidation, healing etc occur during sleep. All these get negatively affected if circadian rhythm becomes abnormal.
At cellular level, normal rhythm allows the cells to recognize time of the day to function normally. Core clock genes expression acts as signals for circadian rhythm. These core clock genes- BMAL1/BMAL2, CLOCK, CRY1/CRY2, and PER1/PER2/PER3, regulate and control transcription and translation[7]. Expression of these core clock genes inside the cell influence many signaling pathways affecting function of cells.

Circadian rhythm disorders:
Circadian rhythm is crucial for maintenance of homeostasis of the body. Disruption of circadian rhythm can lead to following disorders:[8]

- Delayed sleep-wake phase disorder: As name suggest, such people have delayed sleep, interfering in day-to-day activities. This is most common disorder related to circadian rhythm.

- Advanced sleep-wake phase disorder (ASWPD): The person has severe urge of sleeping early in evening, leading to early rise in morning.
- Jet lag disorder: This occurs if one travels across at least two time zones in very short time. The sleep wakefulness cycle gets disrupted due to difference in time zones of destination. It is temporary and if precautions are taken, can be avoided and recovery is very fast.
- Non–24-hour sleep-wake rhythm disorder: This occurs when light exposure is minimum. Sleep time is too delayed. This is very common in blind people.
- Circadian rhythm disruptions have been associated with cardiovascular disorders, obesity, mental disorders and other metabolic disorders.

Since circadian rhythm is directly related to light, artificial illumination form screens of computers, laptops, mobiles and other electronic devices can lead to disrupted circadian rhythm.

References and further reading:

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