Nobel Prize in Physiology/Medicine- 2017

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Chronobiology is the study of molecular basis of the internal biological rhythms and their impact on the functioning of an organism. There are three basic cycles of chronobiology. The names of cycles were derived from latin words.

i. Infradian rhythms (Infra- under, dies- day): Rhythms lasting for more than 24 hours. These cycles are repeated only weekly, monthly or yearly.

ii. Ultradian rhythms (Ultra- over, dies- day): Rhythms lasting for less than 24 hours. These have multiple cycles within a day.

iii.Circadian rhythms (Circa- around, dies- day): Rhythms that last for approximately 24 hours i.e., the human sleep-wake cycle. This rhythm has multiple effects in human health.[1]

The circadian rhythm is regulated at the central and peripheral levels. The central pacemaker is the suprachiasmatic nucleus (SCN) located in the anterior hypothalamus, which plays the role of the master circadian clock. The SCN receives information from the photic input of the retina relayed through the retinohypothalamic tract. The SCN regulates the rhythm throughout the body through the humoral factors and the peripheral autonomic nervous system. Apart from this, the circadian genes are expressed throughout the body in various peripheral organs and tissues, hence, circadian oscillations in isolation can also be expressed.[2] The peripheral clocks are synchronized by SCN and external environmental stimuli known as zeitgebers (timekeepers), such as light, physical activity and temperature. Depending on the situation of the peripheral clocks, the physiological outputs are controlled, such as production of hormone, glucose and fat storage.[3] These, in turn functions as cues sending feedbacks to SCN.

Clock genes also influence metabolism by their action on gluconeogenesis, insulin sensitivity and the systemic oscillation of blood glucose.[3] Circadian clocks regulate sleep pattern, feeding behaviour, body temperature, blood pressure and hormone release (Figure 1). The most commonly studied rhythms are sleep wake cycle, melatonin, cortisol and temperature.[4] Misalignment of our lifestyle and the rhythm may be associated with risk of diseases such as cancer, metabolic disorders, neurodegenerative diseases and inflammation. Sleep is essential for normal brain functioning and circadian dysfunction has been associated with mental health problems such as depression, bipolar disorder, sleep disorders, cognitive function (including memory formation) and few neurological diseases.[5]

The nobel prize in physiology or medicine for the year 2017, was awarded to Jeffrey C. Hall, Michael Rosbash and Michael W. Young for their invention of molecular mechanisms which control the circadian rhythms. They isolated the clock genes, "period" and "timeless" from fruit flies (Drosophila) in 1984 and 1994 respectively.[6,7] Subsequently, they discovered the Transcription- Translation Feedback loop (TTFL), in which the transcription of period and timeless genes is repressed by their gene products, the PERIOD (PER) and TIMELESS (TIM) proteins (Figure 2A). Young also discovered the doubletime gene, which encodes a kinase DOUBLETIME (DBT) which phosphorylates PER, increasing its degradation (Figure 2B). This, in turn generates an autonomous oscillation.[8] The discovery of the self-sustained TTFL as the molecular mechanism behind the circadian oscillations in cells and tissues by the clock genes, has added a new understanding about organisms adapting to their regular daily environmental cues such as light.

About the nobel laureates (Adapted from the press release - The Nobel Assembly at Karolinska Institute)

Jeffrey C. Hall was born in 1945 in New York, USA. At the time of the award, he was affiliated to the University of Maine, Maine, USA

Michael Rosbash was born in 1944 in Kansas City, MO, USA. At the time of the award, he was affiliated to the Brandeis University, Waltham, MA, USA, Howard Hughes Medical Institute

Michael W. Young was born in 1949, Miami, FL, USA. At the time of the award, he was affiliated to the Rockefeller University, New York, NY, USA

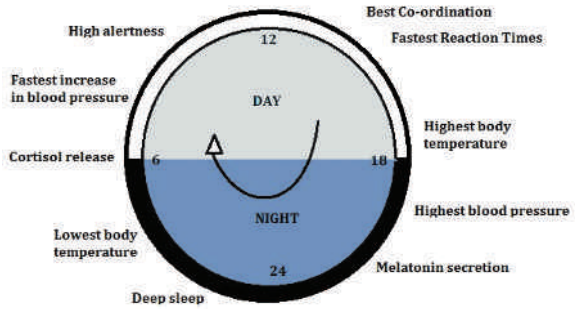

Figure 1 Impact of circadian clock on various aspects of physiology.

Source : The 2017 Nobel Prize in Physiology or Medicine - Press Release. 2017 Oct.

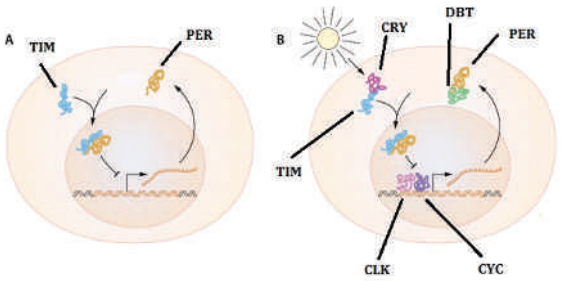

Figure 2 Feedback regulation of the period gene.

A) Period mRNA and PER protein oscillate, followed by accumulation of PER protein many hours after a peak in period mRNA. There is localization of PER protein in the nucleus, and feedback inhibition of its own gene which results in oscillation of period gene activity. B) Oscillation of the period gene requires additional proteins. Timeless gene, which encodes the TIM protein oscillates and interacts with PER protein, which leads to nuclear accumulation of PER protein and repression of the period gene. The doubletime gene encodes the DBT protein. The protein kinase DBT phosphorylates PER, leading to degradation of PER protein. DBT-mediated PER protein degradation contributes to the delay between period mRNA and PER protein accumulation. The clock and cycle genes encode the CLK and CYC proteins, which are two transcription factors that activate the period gene.

Source : The 2017 Nobel Prize in Physiology or Medicine - Press Release. 2017 Oct.

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