

Cracking the Code of the Circadian Clock: Nobel Prize in Physiology or Medicine 2017

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Abstract: The Nobel Prize in Physiology or Medicine in 2017 has been awarded for unraveling the mystery of the circadian rhythm. There are four main proteins involved: Period, Timeless, Cycle and Clock. Period was discovered by Jeffrey Hall and Michael Rosbash at Brandeis University (Boston, USA), Timeless by Michael Young at Rockefeller Institute (NY, USA); a Japanese scientist, Joseph Takahashi, discovered the Clock and and Cycle genes , which regulate the previous two. These findings will enable us to make future advancements in the treatment of sleep disorders. Melatonin is also currently being used for treating circadian rhythm disturbances. Now we know how it works ! [S Paralikar, Natl J Integr Res Med, 2018; 9(3):1-2]

Key Words: circadian rhythm, suprachiasmatic nucleus, melatonin, sleep-wake switch, zeitgebers, thalamus

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Introduction: I grew up in Karelbaug (Vadodara, Gujarat) in a bungalow, with a garden. The 'Touch Me Not' plant was a source of intrigue then: its leaves closed during the night and remained open during daylight. The riddle had been long solved by a Frenchman, Jean Jacques d Ortuos Marian, who deduced that it exhibited a 24- hour a day cycle irrespective of exposure to sunlight. Thus, the plant exhibited a circadian rhythm (circa= about, diem=day). Humans are known to adapt to the environment. The circadian rhythm plays a key role in this adaptation. It receives clues from the environment (called zeitgebers) and signals to the rest of the body to regulate its function.

Subsequent, studies in mutant fruitflies(*Drosophila*) – [one with a normal 24- hour rhythm, one with a 19- hour a day rhythm, and the other a 28-hour a day rhythm) led to a single gene called **PERIOD**.

[A gene is a part of a chromosome that codes for a protein; each human being having approximately 25,000 such genes]. The **Period protein** accumulates at night leading to sleep. Accumulation of the Period protein inhibits its synthesis leading to wakefulness. Jeffrey Hall, the senior most Nobel Laureate in Medicine in 2017, plied his trade at Brandeis University in Boston. With Michael Rosbash, also at Brandeis, he isolated the Period protein. It was only through advances in research techniques that such a breakthrough became possible. Then, Michael Young at the Rockefeller University in New York isolated the **Timeless gene**. The Timeless protein prevents the degradation of the period protein. This was followed by isolation of the **CLOCK** and **CYCLE** genes by a Japanese scientist, Joseph Takahashi, which stimulate **PERIOD** and **TIMELESS** synthesis¹

Thus, when the Period protein accumulates, its further production is inhibited by a negative feedback loop. Timeless regulates the Period protein. Clock and Cycle in turn, stimulate the synthesis of both Period and Timeless. Thus, four scientists at three different universities collaborated to crack the code of the circadian clock with the dutiful *Drosophila* at their disposal! Jeffrey Hall, Michael Rosbash and Michael Young were jointly awarded the Nobel Prize in Physiology or Medicine in 2017 (Fig.I,I,II,IV)

Fig.I. Accumulation of period promotes sleep; the former inhibits its own synthesis by a negative feedback loop which inhibits the Period gene

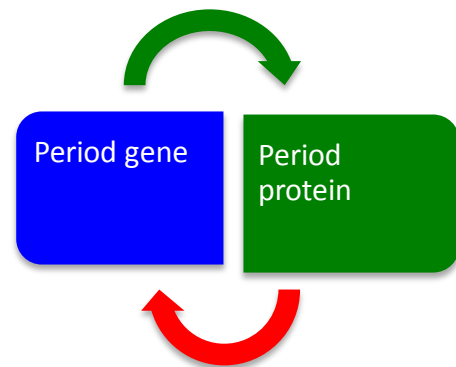


Fig. II Jeffrey Hall



Fig.III. Michael Roshbash



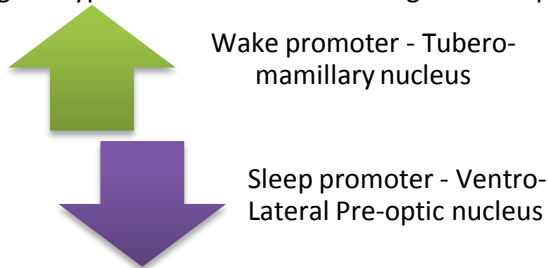
Fig. V. Michael Young



How does this discovery affect us in daily life? In humans, sleep is regulated by the hypothalamus. The tubero-mammillary nucleus, is the wake-promoter region. It enables a person to stay awake and alert by releasing the neurotransmitter histamine.

The neurotransmitters that enable us to put our HANDS up are – Histamine, Acetylcholine, Nor-epinephrine, Dopamine and Serotonin. On the contrary, increasing firing of the ventro-lateral pre-optic nucleus of the hypothalamus (VLPO) induces sleep. The latter is aptly called as the sleep-wake switch. Release of the inhibitory neurotransmitter GABA by VLPO ,is responsible for sleep.

Fig. V. Hypothalamic nuclei which regulate sleep



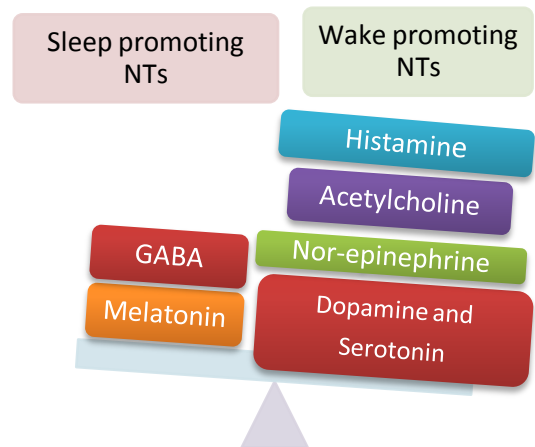
Wake promoting neurons in the tubero-mammillary nucleus are stimulated by the lateral hypothalamus. This area releases a substance called orexin/hypocretin; deficiency of which is responsible for narcolepsy (a condition characterized by increased sleepiness during daytime). The circadian clock is located in the supra-chiasmatic nucleus (SCN)of the hypothalamus. The latter releases melatonin. This neurotransmitter stimulates the accumulation of the Period protein, inducing sleep. The body also

possesses a homeostatic drive, which in turn is controlled by the level of fatigue, during daytime

Elderly persons and depressed individuals wake up early in the morning ; they are said to be phase-advanced. They would do well with a melatonin pill before 12 O'clock in the morning, and exposure to evening light. Adolescents particularly wake-up late. They are said to be phase-delayed. They would do well with exposure to light in the morning and a melatonin pill in the evening. Thus, work by the 2017 laureates has enabled us to demystify the mechanisms, through which the circadian clock can be re-set^[2]

I would like to conclude with a tribute to the humble fruit-fly (*Drosophila*), whom Jeffrey Hall humbly anointed as the fourth Nobel Laureate !!

Fig. VI. Neurotransmitters which regulate Wakefulness and sleep



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