

Editorial

Synchronize Your Biological Rhythm

“Rhythm is sound in motion. It is related to the pulse, the heartbeat, the way we breathe. It rises and falls. It takes us into ourselves; it takes us out of ourselves.”

Edward Hirsch

We all have an internal biological clock that coordinates our circadian rhythm. It operates on a roughly 24 hrs cycle and is calibrated by the appearance and disappearance of natural light. Sunlight teaches the master clock in the brain to keep on track. The rotation of our planet around its central axis creates daily rhythm in environment factors, light intensity, temperature and availability of food. Organisms adapt to the changes present in their environment to enhance their survival. Most of the living organisms, including humans have evolved a biological clock that can anticipate and adapt these 24 hrs changes in the environment. This internal clock in humans resides in the suprachiasmatic nucleus (SCN) in the ventral hypothalamus.¹ Besides light, exercise, hormones and medications affect the SCN and setting of circadian rhythm. The SCN has around 20,000 neurons responsible for generating the rhythm. The neurons receive signals from the eye using light information projected via retinohypothalamic tract (RHT), which is then passed on to other areas of the brain.^{2,3}

The nobel assembly at Karolinska Institute has awarded 2017 Nobel Prize in Physiology and Medicine jointly to Jeffrey C Hall, Michael Rosbach and Michael W Young for their discoveries of molecular mechanisms controlling the circadian rhythm. Hall and Rosbach both worked at Brandeis University in USA when they began their Nobel-winning work. Hall is presently associated with University of Maine. Michael Young is a faculty at Rockefeller University in USA. Their work explains how plants, animals and humans adapt their biological clock to synchronize with the Earth’s revolutions.

The Nobel laureates isolated a gene which controls the biological rhythm, using fruit flies (*Drosophila*) as their experimental organism. In 1984 Jeffrey C Hall and Michael Rosbach together and also Michael Young almost at the same time succeeded in isolating the period gene, they later discovered that PER – the protein coded by this gene accumulates at night and disintegrates during the day.^{4,5} The PER protein oscillate over a 24 hrs cycle in synchrony with the circadian rhythm. There is also an inhibitory feedback loop by which PER can regulate its own level throughout the day, therefore whenever PER levels increased in the cells its production decreased.⁶ But the question remained as to how PER protein formed in the cytoplasm reaches the nucleus.

In 1994 Michael Young discovered a second gene *timeless*, encoding the TIM protein required for circadian rhythm (Fig. 1) . When TIM was bound to PER, the two proteins were able to enter the nucleus where they blocked period gene activity to close the inhibitory feedback loop.⁷ These two proteins accumulate in the cytoplasm, but move into the nucleus of the cells if co-expressed. Regulation of cytoplasmic localization domains activity by assembly of PER/TIM complex is seen to be a key determinant of period length.⁸

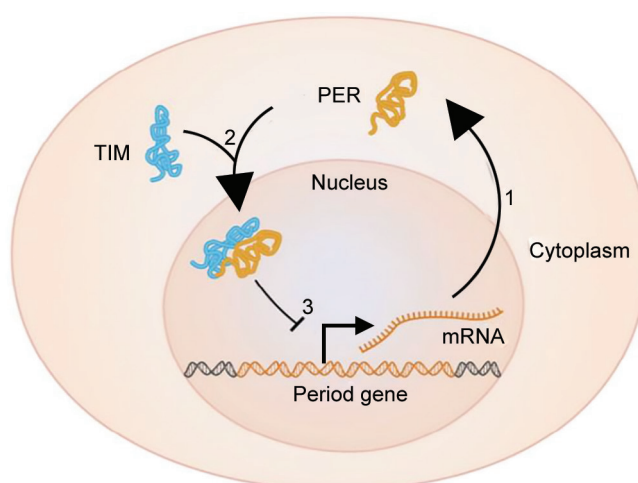


Fig. 1: Later work by the Nobel Laureates uncovered a second clock gene that encodes for a protein called TIM, which binds to PER and allows the duo to enter the cell nucleus (Credit: The Nobel Committee for Physiology and Medicine. Illustrator: Mattias Karlen)¹⁰

While these discoveries explained the phenomenon behind oscillations of cellular protein level, yet the unanswered question remained as to how the frequency of the oscillations is controlled. Yet another gene doubletime was identified by Michael Young which encoded the DBT protein that delayed the accumulation of the PER protein.⁹ This helped in explaining the reason behind oscillations adjusted to match 24 hour cycle. They also identified other protein components which contribute in maintaining the biological rhythm.

The press release from the Nobel Assembly at the Karolinska Institute, Stockholm, Sweden explains “With exquisite precision, our inner clock adapts our physiology to the dramatically different phases of the day. The clock regulates critical functions such as behavior, hormone levels, sleep, body temperature and metabolism. Since the seminal discoveries by the three laureates, circadian biology has developed into a vast and highly dynamic research field, with implications on our health and well-being.”¹⁰

The most significant part of their work rests on the aspect as to what happens when the clock runs either too fast or too slow. Young said ‘there is also growing research—mostly in animals — that supports the idea that maintaining a more regular schedule, including eating and sleeping may contribute to longevity’.¹¹

In fact modern world expectations are punishing for our bodies and brain – we have misaligned body clocks. Nature has been created to nurture all organisms and being the most intellectual of all organisms on this Earth, we need to learn that our lifestyle choices should be aligned to the Mother Nature. Our well-being is affected when there is a temporary mismatch between the environment and our internal biological clock. Our lifestyle choices sometimes cause misalignment of our biological clock opening doors to insomnia, anxiety, depression, increased blood pressure, stress and so on. But it is easy to align with the environment cues — getting a good night’s sleep, maintaining disciplined lifestyle, eating rich nutritious food, getting sun exposure and living a simple life close to mother nature.

The biggest circadian rhythm in our lives will always be the big yellow source of light, heat and energy which is at the center of our solar system. This justifies that even after millions of years of messing around with the sun’s influence by lighting care fires; the human race remains prepensely diurnal from physiological, evolutionary and genetic point of view.¹²

The modern human race however is in confrontation with the rhythms. People keep watching TV, working on computer and mobile phones late into the night. This mismatch is increasingly responsible for the increased incidences of headaches, lack of concentration and mood disorders. People keep sitting indoors to enjoy the modern amenities, missing the immense benefits of sunlight which is the pivot of circadian rhythm.

Many of the health promoting benefits of sun’s exposure are linked to Vitamin D synthesis. Many studies have also demonstrated a strong link between Vitamin D3 which we get from the sun and chronic diseases often associated changing including cognitive decline, osteoporosis, diabetes and cancer.^{13,14} Even small increases in sleep have shown to improve our concentration, memory and mood. In addition to well documented impact on age related diseases sunlight is associated with stronger immunity, reduced depression, and reduced stress even in small closes.¹⁵

We must endeavor to strike a balance between modern lives and some real ancient wisdom – fusion of reality and wisdom. In fact maintaining our body’s biological rhythm on an even keel may be one of the best things to improve our overall health and reverse aging. This way we can better relish the time we have on this planet.

REFERENCES

1. Abrahamson EE, Moore RY. Suprachiasmatic nucleus in the mouse: retinal innervation, intrinsic organization and efferent projections. *Brain Res* 2001; 916:172–91.
2. Kalsbeek A, Palm IF, La Fleur SE, Scheer FA, Perreau-Lenz S, Ruiters M, et al. SCN outputs and the hypothalamic balance of life. *J Biol Rhythms*. 2006; 21:458–69.
3. Morin LP, Allen CN. The circadian visual system, 2005. *Brain Res Rev*. 2006; 51(1):1-60. <https://doi.org/10.1016/j.brainresrev.2005.08.003>
4. Zehring, W.A., Wheeler, D.A., Reddy, P., Konopka, R.J., Kyriacou, C.P., Rosbash, M., and Hall, J.C. P-element transformation with period locus DNA restores rhythmicity to mutant, arrhythmic *Drosophila melanogaster*. *Cell*. 1984; 39, 369–376.
5. Bargiello, T. A., Jackson, F. R. & Young, M. W. Restoration of circadian behavioural rhythms by gene transfer in *Drosophila*. *Nature*. 1984; 312, 752–754.
6. Hardin, P. E., Hall, J. C. & Rosbash, M. Feedback of the *Drosophila* Period gene product on circadian cycling of its messenger mRNA. *Nature* 1990; 343, 536–540.
7. Vosshall, L.B., Price JL, Sehgal A, Saez L, Young MW. Block in nuclear localization of period protein by a second clock mutation, timeless. *Science*. 1994; 263: 1606-09.
8. Lino S, Young M W, Regulation of Nuclear Entry of the *Drosophila* Clock Oroteins Period and Timeless. *Neuron* 1996; Vol. 17: 979-990

9. Price JL, Blau J, Rothenfluh A, Abodeely M, Kloss B and Young MW. Doubletime is a novel *Drosophila* clock gene that regulates PERIOD protein accumulation. *Cell* 1998; 94:83-95.
10. The Nobel Assembly. The 2017 Nobel Prize in Physiology and Medicine (press release). Karolinska Institute, Stockholm, Sweden; 2017 Oct 2. http://www.nobelprize.org/nobel_prizes/medicine/laureates/2017/press.html
11. Cha A E. Nobel in Physiology, Medicine awarded to three Americans for discovery of 'clock gene'. *The Washington Post*. 2017 Oct 2.
12. Day JD, Day JN. *The Longevity Plan – Seven life transforming lessons from Ancient China*. New York. Harper Collins 2017.
13. Meehan M and Penckofer S. The role of vitamin D in the aging adult. *Journal of Aging and Gerontology*. 2014; 2(2):60-71.
14. Mead M. Benefits of sunlight: A bright spot for human health. *Environment Health Perspective*. 2008; 116(4):160-7.
15. Moller –Levet C, Archer Sn, Bucca G, Laing EE, Slak A, Kabiljo R et al. Effects of insufficient sleep on circadian rhythmicity and expression amplitude on the human blood transcriptome. *Proceedings of the National Academy of Sciences of United States of America*. 2013; 110(12): E1132-E1141; published feb 25, 2013 doi:10.1073/pnas.1217154110

Richa Ghay Thaman

Editor

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