EDITORIAL

Circadian rhythm in health and disease

Ahmed Badar

The Nobel Prize in Physiology or Medicine for 2017 was awarded on October 02, 2017 to Jeffrey C. Hall, Michael Rosbash and Michael W. Young "for their discoveries of molecular mechanisms controlling the circadian rhythm." The Nobel Assembly declared on October 02, 2017 that the winners "were able to peek inside our biological clock and elucidate its inner workings".[1]

Konopka and Benzer reported in 1971 that mutations in an unknown gene disrupted the circadian clock of fruit flies. This gene was named "period".[2] In 1984, Hall and Rosbash, in collaboration with Michael Young isolated the 'period' gene. They later discovered that the protein encoded by the 'period' gene named 'PER', accumulated during the night and was degraded during the day. They then demonstrated that 'PER' protein prevents its own synthesis by a negative feedback system. Accumulation of 'PER' protein in the nucleus of cell blocks the activity of 'period' gene, thus giving rise to the inhibitory feedback loop that controls the 24 hours biological oscillation. This discovery was supplemented by discovery of another clock gene called 'timeless' in 1994 by Michael Young. This gene was found to encode a protein called 'TIM'. It was reported that when 'TIM' binds to 'PER', both can get into the cell nucleus to block the 'period' gene to complete the inhibitory feedback loop. Later Young identified another gene named "doubletime", that was found to encode a protein named 'DBT' that delayed the accumulation of the 'PER' protein. This provided insight into how an oscillation is adjusted to more closely match a 24-hour cycle.[1]

Our ancient ancestors knew about the behavioural changes in relation to the day and night cycle. Keeping the criminals in dark cells of prisons even in very old times was meant to disturb their biological clocks. The ancient observers noticed that plants, animals and humans had a biological clock that adjusted them for the fluctuations of the day. This daily adjustment of body functions was named 'circadian rhythm', Circa' (about, around) and 'Diem' (Day). This term is now used for the biological events that are repeated once every 24 hours.

Department of Physiology, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.
Correspondence: Email: absheikh@iau.edu.sa

The first written material about biological clock is attributed to 'Jean Jacques d'Ortous de Mairan'. The leaves of the plant 'Mimosa pudica' open towards the sun during day but close in the evening. Around the year 1729 de Mairan placed the plant in constant darkness. He observed that the opening and closing of leaves continued irrespective of the plants being deprived of sunlight. He concluded that something other than light and dark was responsible for this phenomenon. The published accounts of de Mairan's work stimulated further research in the field of chronobiology.[3]

Chronobiology is the branch of biology that studies adjustments of numerous cyclical phenomena seen in living organisms with environmental signals like movements of earth around the sun (solar) or movement of moon around the earth (lunar).[4] "Entrainment" is the word used for synchronization or adjustment of these cyclical biochemical, physiological or behavioural processes to the environmental signals. These environmental influences lead to a 'phase shift' (crudely defined as change in biological rhythm), but the entrainment helps in adaptation of our biological clock to the environmental signals.

The biological clock in a normal person oscillates with an endogenously adjusted period of 24 hours. This clock entrains (modifies phase) with the help of daily environmental corrective signals, mainly daylight and darkness. This biological clock has three parts. First, a central biochemical oscillator with a phase adjustment of 24 hours. Second, input pathways from sensors of environmental signals that help in entrainment (phase adjustments) of the central oscillator. Third, the output circuits that regulate biochemical, physiological as well as behavioural rhythms in our bodies. Some of the typical cyclical phenomenon that are tied to this clock are body temperature, blood pressure, coordination, reaction time, alertness, hormone release (particularly melatonin and cortisol), feeding behaviour, sleep pattern, ability to respond to infectious disease cycles and control of blood glucose concentrations, to name just a few. The diversity and importance of these processes indicate the relation of circadian rhythm with our health and disease. As quoted by a recent editorial in Lancet, one of the above three Nobel laureates said, "It is hard to find things that are not rhythmically fluctuating".[5]

Circadian rhythm is controlled by a 'pacemaker' located in the suprachiasmatic nuclei of anterior hypothalamus. The "clock genes" present all over the body regulate this pacemaker. There are now many known genes that switch on and off according to the likely pattern of daily routine of an organism. This internal clock and its adjustment with changing environmental signals works with an astonishing precision. Whenever there is a temporary mismatch our wellbeing is affected. An example is the 'jet lag' while travelling across many time zones.

Several studies have concluded that a chronic mismatch between our life style and our biological clock leads to increased risk of various diseases like cardiovascular disease,[6] inflammatory bowel disease,[7] psychiatric disorders and neurodegenerative diseases,[8] amongst many others. Parkinson's disease is known to have diurnal fluctuations. Circadian dysfunction observed in the Parkinson's disease patients may exacerbate the disease progression.[9] Similar patterns have been reported in other neurodegenerative disorders like Huntigton disease and Alzheimer's disease. Therefore, circadian therapies, including light stimulation, physical activity, dietary and social schedules are thought to be helpful for these patients.

Disruption of the circadian rhythm has been associated with sleep and mood disorders, and there is growing evidence of the harmful consequences of shift work. Working in the night-shifts has become a norm of the modern societies. In these night shift workers, the normal circadian rhythm as well as melatonin synthesis is interrupted. Evidence suggests that this might lead to oxidative stress that can lead to neural and other tissue damage. Therefore, long term night-shift work must be avoided.[10]

It is required that we keep ourselves abreast with the fast pace of work on circadian rhythm and its applications in health and disease for better understanding of disease and patient management.

References

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