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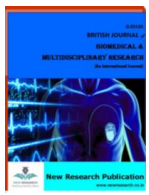

How circadian cycle is related to learning and memory?

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Abstract
Circadian rhythm (CR) is an endogenous biological process, which happens every 12 hours. This oscillation (day-night cycle) is found in behavior and biological progressions in all kingdoms of life. It also controls a wide variety of physiological events, including metabolism, sleep, body homeostasis, learning and memory in all organisms. CR is also known as the internal body clock, which allows an organism to adjust its physiology in the alterations between night and day. It also regulates a wide variety of body's natural processes, including body temperature, blood pressure, sleep, locomotor activity, and blood hormone levels. In mammals, this rhythmic expression of circadian clock has been regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus but also in multiple non-SCN regions in the brain. Disturbance of normal CR leads to commotion in normal body physiology leading to diseases including neurodegeneration, dementia and metabolic disorders. The aim of the report is to know the mechanism by which circadian clock can cope with biological process and feedback into the circadian system and dysregulation of circadian cycle leading to human diseases and how it can apply in the management of diseases.

Keywords: Circadian clock, neuroscience, learning and memomry.

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1. Introduction

Biological rhythms or the circadian cycles are the episodic arrangements of body's physiological, behavioral and metabolic activities by which our bodies are cope with to the nature. In mammals, circadian rhythm is most crucial to maintain body's normal physiological functions like sleeping and waking, heart rate, body temperature, hormone secretion and mental alertness in response to 24-h episodic variations of a day. In the traditional model, it has been well demonstrated that the circadian rhythm of the mammals are controlled by a single dominant "circadian pacemaker", situated in the suprachiasmatic nucleus (SCN) of the hypothalamus.

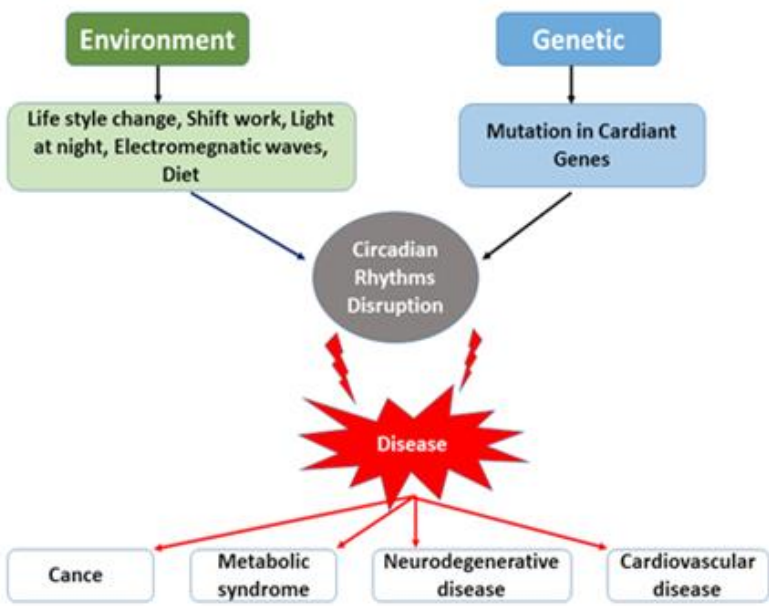

Fig. 1. Basic mechanism of circadian rhythm disruption. Several environmental and genetic factors can cause disruption of the circadian rhythms, which may lead to cancer, cardiovascular disease, and metabolic syndrome. (Adapted from Ruger and Scheer 2009)

Recently, it has been postulated that circadian pacemaker is not only one clock within the body to maintain function but clock-like activities also have been found in many tissues, both neural and non-neural. Almost every cell in the body has at least one circadian clock. These finding challenges the uniclock model and suggesting that the mammalian circadian system encompasses multiple pace making nuclei. But SCN plays the central roles and controls other circadian nuclei activity to regulate normal body function in response to diurnal rhythms. It has been well demonstrated that, pharmacological inactivation of SCN may cause complete absence of sleep-wake rhythm in rats and confirming the roles of SCN in regulating the body's rhythms.

2. Regulation of Biological clocks, in mammals

In mammals, the central clock (CC) is located in the SCN of hypothalamus but interconnected with the other neuronal and peripheral clock and control body function. Light activate the SCN through retina, then the photosensitive specialized types of ganglion cells within the retina (other than rod and cones) can activated and then stimuli transfer to the SCN and synchronize the activities of master clock with others. Research found that genetically knock outing this gene in to the mice have normal vision but impairment in day-night variation in response to light. These cells contain photo pigment protein called melanose that follows the retinohypothelamic pathway directed to the SCN. After getting the day light, the SCN interprets it and convey it to the pineal gland, which secretes melatonin. Melatonin secrets highly in the night and lower concentration in the day and which provide the information for night length. Other than this, SCN also secrets some neurochemicals in response to light such as glutamate, dopamine, GABA, AVP, cytokine, VIP, PK2 and transforming growth factor α to maintain the body homeostasis by regulating the oscillatory rhythms.

3. Ageing and the circadian system

There are close relation in between aging process and circadian system. Researcher found that there are close relation between neuroendocrine and circadian system and postulated that, SCN function declines with progression of age, but the underpinning of molecular mechanism of this still unclear. The clock protein, BMAL1 is responsible for maintaining SCN activities and adapt with circadian rhythms. Growing evidence found that, mice knocking out with BMAL1 showing early death compare with control related to accumulation of ROS, which confirming the close relationship between age and clock protein. Though epidemiological evidences suggesting close relationship between defective circadian system and cancer risk, but the role of circadian system in tumorigenesis is still unclear.

4. Molecular and biochemical links of circadian clock

A complex molecular mechanism is involving in to the Body's circadian rhythms that can control the circadian clock function of the SCN pacemaker that maintaining coherent rhythms. In molecular level, mammalian circadian systems are encompassed with a set of interconnecting transcriptional–translational feedback loops that control rhythmic, ~24 h expression arrangements of central clock factors. CLOCK and BMAL1 are the main transcriptional factor protein from the primary loop, stimulating transcription of Period (Per) and Cryptochrome (Cry) genes, are known as the circadian gene, are crucial for creation and instruction of circadian rhythms inside the body. Transcription of CLOCK: BMAL1 complex is repressed and translocate back to nucleus by the negative feedback of Per: Cry heterodimers. Another regulatory loop can trigger retinoic acid-related orphan nuclear receptors transcription. Transcription of BMAL1 facilitated by RORs and inhibited by REV-ERBs. This complex auto-regulatory molecular mechanism can complete a cycle by ~24 h and institute a molecular clock, which is directed by post translational modification including phosphorylation and ubiquitination and play a key role to the development of the mammalian clock by upsetting the steadiness and nuclear translocation of core clock proteins. Casein kinase 1 epsilon and delta (CK1a and CK1d) are the most crucial factors that regulate the circadian protein. Research found that, mutations in CK11 and CK1d result in distorted kinase activities and trigger shorter circadian timing in mammals.

5. Genetic link of circadian clock

It has been well established that the circadian genes are not only centered in circadian pacemaker (SCN) but also concentrated to other organs that controlled this specific organ physiology in response to diurnal variation. For developing the atlas of central clock and the distinct biological activities it synchronizes, researcher used RNA-sequencing (RNA-seq) and DNA arrays to identify the transcriptomes of different organ. By using this resource, they assessed the genomic characteristics of the rhythmic coding and noncoding transcriptomes on the basis of rhythmic variation in timing, variation in oscillation, and response in environmental variation and build an ontogenic tree that represent organ variation in related to circadian gene.

6. Circadian clock may be critical for learning and memory

Circadian system has noticeable influence on learning and memory, showing as distinct variations in memory acquisition and recall over the day and night. In mammals, the circadian timing system controlled the sleep and wake process. Research has found that, sleep is one of the most important components for memory consolidation at the system and cellular level. The hippocampus plays a major role in learning and one of the key brain parts to assimilate circadian information by updating information from local independent oscillators, synaptic remodeling, neurogenesis and epigenetic regulation of gene expression. Hippocampus-dependent learning and memory is initiated by a calcium influx mediated NMDA receptors and other signaling

pathways, including the cAMP and Erk1, 2 MAP kinase MAPK pathways. CRE-mediated transcription is instigated by the stimulation of CaM-stimulated adenylyl cyclase and MAPK that is responsible for learning and memory. Perturbing any of these signaling pathways disrupts memory consolidation.

Circadian cycle also influence learning and memory by the hormonal signaling pathway. In rats, melatonin secretes from SCN, modulates memory in a phase-specific method. It has been found that, omissions of melatonin receptors in mice leading to cognitive deficit. Research has found that, high glucocorticoid levels increase learning-induced spine formation, while low glucocorticoid levels do not.

7. Circadian cycle and disease

Circadian cycle regulate body's normal physiology and homeostasis. Changes in this cycle may lead to disease condition such as metabolic disorder like type II diabetics, obesity, dementia, cancer and neurodegenerative disorders like Alzheimer's and Parkinson's'. Disorders in the sleep–wake cycle and circadian rhythms are common symptoms of Alzheimer Disease (AD). Mutation of circadian gene may cause modification or disruption of circadian oscillation that facilitate many disease conditions.

8. Chronobiology and health

Chronobiology is the wing of biology that studies the relationship between the periodic (cyclic) fact in living organism and their adaptation to solar and lunar rhythm. Chronobiology includes the comparative studies of anatomy, physiology, genetics, molecular biology of organisms and the relation with the circadian rhythms. Research on "Monogenic disorders" have stipulated suggestion that clock genes have an influence not only on choronotype, but also on neurological alleyways that adjust sleep in humans.

9. Chronobiology and cancer treatment

The body's Circadian timing system (CTS) is the collection of molecular clocks, that make the correlation of 24-h cycle and alterations in xenobiotic metabolism and detoxification, cell cycle events, DNA repair, apoptosis, and angiogenesis. To reduce the effects of anticancer agent, the cellular circadian clocks can maintain it by endogenous physiological rhythms and can adopt it. By this way, it's possible to identify the most toxic and safest time of drug administration. By applying this concept it has been found that, cancer patients could increase the tolerability of anticancer drug 2- to 10-fold of the normal level which can helps in reducing less side effects. On the other hand, host clocks are interrupted when anticancer drugs are administered at their most toxic time and displaying more side effects.

10. Scientific dissemination

Recently a lot of research has conducted to identify the role of circadian protein in human diseases and the relationship between chronobiology and disease management. Clinical investigations have found that there is a close association between labor shifting and metabolic disease. For example, people work with stress, has connected sleep time and circadian interruption showing a broad range of health conditions - including type II diabetes, gastrointestinal disorders and cancer. Research has found that chronobiology also related to disease and its management. Recently drugs are developed in considering this idea and relation to diseased and cyclic regularities. Recent notion found that, circadian cycle could play a vital role for controlling sleep and facilitate memory consolidation and in fact manipulation of circadian protein either by genetically or pharmacologically may enhance or interfere learning and memory.

11. Question to be answer

Although lot of studies have been conducted but there are some more question need to be answered. How molecular clocks could relate to molecular pathogenesis of metabolic disorder mainly type II diabetics and neurological disorder like Alzheimer's? Though circadian cycle, aging and neurodegenerative are closely related but the underlying mechanism that aggravate sleeping disorder leading to Alzheimer's disease.

12. Conclusion

In a nutshell, circadian rhythmicity in cell physiology is observed almost in all organisms and is the most crucial biological process within the body to confront with external environmental rhythmicity and can maintain body physiology. Disruption of this rhythm leads to dysfunction of normal body physiology and cause diseases. The presence of circadian variants in gene expression and synaptic plasticity in hippocampal cells is accountable for learning and memory, directs an inherent link among cellular activities and phenotypes of the whole animal. Disruption of this link may lead to dementia and other neurological disorder and in consequence memory loss, sleepless and mode dysfunction may occur. However, the mechanism by which the pacemaker cells are translated into behavioral responses is still unclear. Although many researches have been conducted to elucidate the relationship between circadian rhythms and learning-memory, but no precise animal model exists for this study that warrants further research. The discovery of circadian gene and its function arise the possibility that pharmacological modification of molecular clock function may have therapeutic paybacks.

Conflicts of interest

The author declares no conflicts of interest.

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