Research progress on circadian rhythm-related Alzheimer's disease and Cancer

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Abstract. Endogenous oscillators include circadian oscillators, which control 24-hour physiological and behavioral processes. Nowadays, 7–16% of people with circadian sleep disorders are young adults or adolescents. On the other hand, there are in excess of six million Alzheimer's patients in the United States. By 2050, it is predicted that the population will nearly triple to 13 million. Numerous facets of mammals biology, such as the coordination of sleep and the immune respond are influenced by the central circadian clock. Unusual sleep-wake cycles and disrupted circadian rhythms are frequent symptoms of Alzheimer's disease (AD), which are typically seen as late effects of the neurodegenerative processes. Additionally, it appears that the amyloid-beta peptide, which is linked to AD, is regulated by the sleep-wake cycle and that altering sleep has a variety of effects on AD pathology in mouse models. Forthemore, cancer's pathophysiology has been clarified by new studies on circadian rhythms and the disease. The connections between irregularities in human circadian clocks and sleep disorders is disscused firstly in this paper. The most recent studies on the possible impact of sleep and circadian rhythms on AD pathogenesis and cancer are introduced. This article reviews the fundamentals of circadian rhythms before moving on to various forms of sleep disorders, cancer, and Alzheimer's disease. This review is significant because it compiles recent research on illnesses connected to the circadian rhythm, including Alzheimer's disease, cancer, and sleep disorders.

Keywords: Sleep disorder, Cancer, Alzheimer’s Disease.

1. Introduction

A 24-hour period for genetic networks is created by circadian rhythms (CR), which are controlled by an internal timing system. Suprachiasmatic nucleus (SCN) is situated in the brain's hypothalamus and controls CR in vertebrate animals, including humans. The master clock, known as SCN, controls and synchronizes all of the biological clocks present in every single cell. Along with sleep, metabolism, and the immune system, the circadian clock controls a variety of biological functions in mammals. The circadian clock regulates many aspects of mammalian physiology, together with sleep, metabolism, and the immune system.

CR allows procedures in biology and behavior to be synchronized with the outside dynamical surroundings. Ambient variables that affect the duration, phase, and intensity of these rhythms include contact with light, interactions with others, when to eat, and how much time is spent working. SCN receive imputs directly from light. Through conveying the pigment melanopsin, that renders those photosensitive to short-wavelength radiation, the retina's fundamentally photoreceptive retinal ganglion cells (ipRGC) primarily transmit photic details to regulate SCN timepieces. The secretion of excitatory amino acids, particularly glutamate, via this monosynaptic pathway transmits photic information. Light-induced SCN activation causes Ca2+ influx and intracellular signaling cascade activation, which in turn causes Period gene expression to increase and regulate the molecular clock. The photopigment ipRGCs are most generated by blue light with a wavelength of 480 nm, while red light with a wavelength of more than 600 nm possesses little impact. In general, during the day, sunlight has a higher concentration of short (blue) wavelengths and shifts to longer (red) wavelengths as dusk approaches. The properties of daylight shift throughout the day and in reaction to the conditions. Therefore, light–dark cycle could regulate circadian rhythms.

In every cell, including SCN neurons, a cycle of gene expression produces CR. Cell autonomous transcription-translation feedback loops (TTFLs) are the mechanisms sustaining the molecular clock

of the CR system. Period (Per1/2) and Cryptochrome (Cry1/2) are transcription determinants that mammals' CLOCK and BMAL1 stimulate the generation of, and their protein byproducts responses for inhibit CLOCK and BMAL1 (Fig.1). Circadian clock results have a significant impact on cell biology due to the fact that from 2 to 30% with regard to a single tissue's transcriptome displays a rhythm.

Additionally, additional levels of circadian clock regulating systems have been discovered through research. These extra layers of control over the circadian clock mechanism include polyamines, the NADP+: NADPH redox ratio, chromatin conformation and interactions, and even autophagy. There are biological cycles with shorter (ultradian) periods besides circadian rhythms. A 12-hour pacemaker that is cell-autonomous and crucial for preserving metabolic homeostasis has recently been proposed as the mechanism underlying these rhythms. It will be interesting to observe in the future what additional physiological processes are affected by ultradian rhythms and the way those processes interact with circadian physiology.

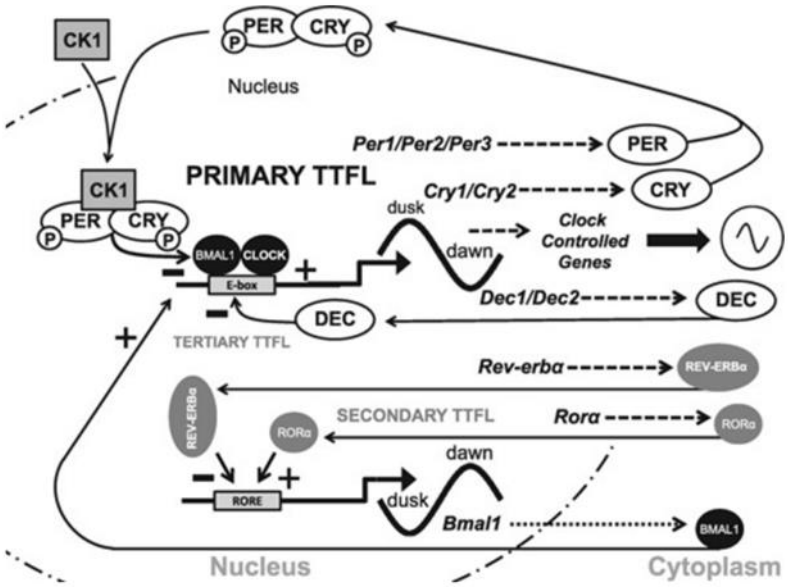

Fig 1. The molluscan biological clock. Circadian Locomotor Output Cycles Kaput (CLOCK) is a name for two proteins that interact alongside BMAL1, provide the transcriptional drive for the mammalian molecular clockwork [2].

2. Sleep disorder

A collection of sleep disorders is called Circadian Rhythm Sleep Disorders (CRSDs) have been characterized by erratic sleep patterns. They have a close association with other mental health conditions like schizophrenia, bipolar disorder, and others. When the internal timing mechanism is disrupted, such as by a clock gene mutation, or when there is an imbalance among sleep and the constantly changing social and physical surroundings, CRSDs develop. The circadian phenotypes or chronotypes of the human population range widely, from larks, the early types, to owls, the late types. Typically, different chronotypes can change their sleep habits to complement their social needs and circadian rhythms and at the same being influence by factors such as genetics, and encounters with dawn and dusk light. Nonetheless, severe interference with the outer periodicity of light and darkness causes grave sleep-wake cycle disruption, tiredness, and exhaustion.

CRSDs mainly contain delayed sleep phase disorder (DSPD), advanced sleep phase disorder (ASPD), non-24-hour circadian rhythm disorder (N24WSD), irregular sleep-wake disorder (ISWRD), shift work sleep disorder (SWSD) and jet lag disorder. Familial advanced sleep phase syndrome (FAFPS), known to be associate with changes in Per2, and familial delayed sleep phase syndrome, which is linked with variations of the casein protein kinase 1 delta, are the first categories that

included the disorders of the delayed or advanced sleep phases. Changes within Cry1 are found to be associated with Familial Delayed Sleep Phase syndrome, affecting sleep in quite a few in human beings, with a strikingly significant incidence of 0.6% in the population.

The basic principles that support CRSDs are able to be separated into two distinct groups: Intrinsic type disorders, those in which the endogenous oscillator has been changed. Extrinsic type CRSDs, in which the internal circadian clock and the outside world are out of sync, make up the second classification of CRSDs.

2.1. Intrinsic type disorders

DSPD, ASPD, ISWRD, N24SWD belongs to the intrinsic type. When compared to people who are functioning normally, Individuals in delayed sleep phase disorder have delayed sleep-wake cycles. When people with DSPD try to fall asleep during typical sleeping hours, they frequently experience very long periods of sleep latency. They also struggle to wake up at regular times, in a similar manner. An alteration to CRY1 that skips exon 11 along with eventually results to the elimination of twenty-four remains in the C-terminal area on CRY1 has been linked with a hereditary form called DSPD, according to Patke et al. By strengthening this repressor's affinity towards the circadian protein activators CLOCK and BMAL1, these modifications lengthen circadian cellular rhythms duration.

Patients with advanced sleep phase disorders display contrasting traits from those in delayed sleep phase disorder. These people typically fall asleep and wake up earlier than the average person because they have advanced sleep-wake cycles. A lesser-known disorder in elderly individuals than DSPD is ASPD.

People who are blind and unable to see light are more likely to have N24WSD, who do not adhere to cycle of day and night. This results in a slow yet foreseeable delay in the beginning of awakening and sleeping times for those who have this disorder. Patients with DSPD run the risk of developing this disorder if their condition is not treated.

A typical 24-hour sleeping cycle is a defining characteristic of ISWRD. However, people who have this disorder have fragmented and terribly disorganized sleep, which can show up as frequent nighttime awakenings and daytime naps despite still getting enough sleep overall. Insomnia and excessive daytime sleepiness are just two of the symptoms that ISWRD patients frequently experience.

2.2. Extrinsic type CRSDs

Working shifts other than the usual 800-1700 h shifts has been linked to SWSD, a circadian rhythm sleep disorder. Shift work sleep disorder is thought to affect 9% of Americans employed on shift nights or other erratic shifts. Because working overnight shifts closely interacts conflicts with the external stimuli which enter our physiological clocks, this illness develops while a person's biological clock fails to adapt to the accepted operate timetable. Severe cases of insomnia and excessive daytime sleepiness may be simultaneously brought on by shift work sleep disorder.

A person who travels across several time zones may experience jet lag, also known as jet lag disorder. The need for advancement of the body's biological clock makes discomfort more severe for passengers traveling from an eastern direction than those traveling in the western direction, and they typically get worse with the numerous time zones journeyed. International flight crews and others who frequently travel throughout time zones say they experience ongoing jet lag symptoms quite frequently. The difficulty falling or staying asleep due to an imbalance between one's inside circadian system and external stimuli is the most obvious symptom of jet lag.

3. Cancer

In all major organ systems, epidemiological research has connected circadian interruptions to increased cancer vulnerability. There is strong evidence that oncogenic MYC reduces the clock and that cancers in people frequently contain variations within central circadian genes Per1, 2, and 3, which results to decreased expression of these genes. Mice with genetic defects in Per2 or Bmal1

develop lung tumors more frequently, which results in elevated c-Myc activity, increased growth, and metabolism instability. Similar to what is seen in obese people, chronic jet lag causes hepatocellular carcinoma (HCC) within mice, which starts as non-alcoholic fatty liver disease, later progresses into HCC. Consequently, both of these investigations have effectively established an explanation within clock disturbance and the development of malignancies. The microRNA miR-211, that inhibits Clock and Bmal1, also aids in the development of tumors. It is possible to effectively treat cancer while preserving the viability of healthy cells and tissues by targeting REV-ERBs. Sulli et al. were capable of interfering with a minimum of one cancer hallmarks, newly generated lipogenesis and autophagy, two processes that are crucial in satisfying the nutritional requirements of cells with cancer, by applying REV-ERBs (SR9009 and SR9011).

Low oxygen levels stabilize hypoxia-inducible factors (HIFs), the transcription variables offering acclimate the cancerous microcosm to an acidic state. Studies have demonstrated that HIFs can affect different clock transcripts. Additionally, Walton et al. evidenced that when tumor-specific dehydrated cells acidify the surrounding conditions, the clock and rhythmic collection of all the messenger RNA in particular cells are disrupted. This explained how low pH inhibits translation by mTORC1 transmitting signals. In order for complete rescue translation and clock oscillations, researchers also discovered mTORC1 signals must be brought back either by preventing a rise in acid or by preventing the production of lactic acid from occurring.

Cancers like breast, ovarian, brain, kidney, lung, liver, and colorectal are all strongly correlated with circadian rhythms. Circulating hormone concentrations impact circadian rhythms reciprocally. While further study has demonstrated that disruption of the circadian rhythm has a strong connection with malignant growth of the endocrine system, such as breast cancer, it is crucial for normal physiology that there is a bidirectional information flow. One illustration is the tendency for overnight shift workers to experience a higher incidence of malignancies in general as well as hormone-related breast cancer. Recent molecular research findings demonstrate that key clock genes oscillate rhythmically within human mammary epithelial cells, maintaining an inner circadian oscillator. Both estrogen receptor-positive (ER-positive) and ER-negative breast cancers have a malfunctioning internal clock. Former examinations showed a strong correspondence among the development of breast cancer and the disruption of the circadian rhythm. Breast cancer risk is significantly reduced by NPAS2, a key circadian gene and transcription regulator. In normal NPAS2 expression, mutagen-treated MCF-7 cells are more likely to be in the G1 or G2 phases, which correspond to the primary phases of cell cycle for DNA damage repair, while the relative cells number in the S phase is substantially reduced. Nevertheless, there is no apparent distinction among cells treated with or without MMS within cells that have decreased NPAS2 expression by siRNA, pointing to an aberrant reaction to DNA damage. A missense polymorphism (Ala394Thr) in NPAS2 is likewise become correlated to a significant boost in the danger of developing tumors like breast cancer and prostate cancer, according to some earlier genetic epidemiological studies. As a result, even though CLOCK and NPAS2 serve similar roles in terms of circadian rhythm regulation, their impacts on onsets and development of breast cancer are distinct.

Leukemia is a collective noun for a range of diverse malignant diseases that affect the bone marrow and lymphatic system among other blood-producing organs. Leukemia is characterized by an explosive growth of abnormal cells in these tissues. Leukemia is primarily categorized by how the illness is serious or long-term and whether it arises in lymphoid (cells that develop into to lymphocytes and NK cells) or myeloid (cells that provide increase to platelets, monocytes, neutrophils and so on) cells. Leukemia affects 350,000 people worldwide annually, and 250,000 of them pass away from it. Leukemia possesses a complicated etiology, wherein several genetic, dietary, and exterior factors—collectively referred to as risk factors—affect the disease's development. In this regard, circadian rhythm disruption and within circadian clock genes possess endured linked with all four of the major types in leukemia (AML, ALL, CML, and CLL). There is evidence that whereas the circadian gene oscillations are partially retained in peripheral blood mononuclear cells (PBMC) from AML, ALL, and CLL patients but absent in CML patients. A small cohort analysis revealed that

the hypermethylation of BMAL1's promoter resulted in decreased expression of the gene in 33% of ALL patients. Notably, the proliferation, function, differentiation, and discharge of blood cells both in circulation and in the bone, marrow exhibit circadian rhythms. As a result, it's possible that when these rhythms are off, leukemia may develop more easily. It is unlikely that changes in the genes which regulate circadian rhythms, when brought on by shifted gene expression, mutations, epigenetic changes, or other processes, will cause leukemia on their own, but they could have an important part in predisposing people to the disease, according to the data presented here.

As a whole, circadian rhythms and cancer: recent studies have shed significant light on the disease's pathophysiology, which should lead to more effective treatments that may take circadian factors into account.

4. Alzheimer's Disease

Alzheimer Disease (AD) frequently manifests as irregular sleep-wake cycles and circadian rhythms, which are typically viewed as late effects of the neurodegenerative processes. The frequent association of CRSD accompanied by excessive napping during the day and insomnia in people with AD serves as both a characteristic of AD patients and a risk factor for functional decline that gets worse over time. According to some, the sleep-wake cycle disrupted in AD patients due to altered melatonin levels along with elevated concentrations of circadian rhythm irregularity. The damage to the hypothalamic SCN regions, which is frequently observed in AD, is most likely to blame for this. On the other hand, a decline in the mental abilities, mood, and standard of life of AD patients has been associated with disturbed sleep and sleep patterns states. Correspondingly, the disease's abnormal behavioral symptoms make it difficult for the patient's family members and caregivers to cope.

However, it is still unclear how sleep-wake disturbances affect an AD patient's subjective experience. Because of the importance of neurodegenerative disorders in medical settings and the rising lifespan, it is highly recommended that more research be done in this area.

5. Summary

As a matter of fact, in the exciting recent years of circadian research, circadian biology has emerged as the key to understanding the biology of animals. The regulation for biological processes like immune regulation, cell cycle progression, hormone secretion, sleep and wakefulness, etc. depends on the circadian rhythm network. Chronobiology research is currently a major focus in the biological and medical fields due to the growing body of evidence showing that numerous systemic diseases are intimately linked to circadian rhythm disorders. These years have seen the development of chronobiology and, along with it, the slow identification of environmental cues that could synchronize the circadian oscillators of living things or individual cells. It is possible to better understand the pathogenesis of diseases that are connected to the circadian cycle by shedding light on the relationships between circadian rhythm and human diseases. This opens up new possibilities for disease prevention and treatment.

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