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Review

Antidepressant Drugs, Biological Clocks, and Cancer: Is There a Relation?

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ABSTRACT

Depressive disorders are associated with abnormalities in circadian rhythms, leading to disruptions in the sleep cycle, mood, and hormonal levels. However, damage to the circadian rhythm increases the risk of some health problems and is considered a factor in triggering depression. Examining this situation plays an important role in understanding the causes of depression in living things. In conclusion, molecular biology needs to investigate the effects of antidepressants used in the treatment of depression on the biological clock. Despite this close relationship between depression and the biological clock, the lack of studies at the molecular level makes it difficult to understand the molecular mechanism of antidepressants on the biological clock. On the other hand, some disorders such as panic and depression, which often accompany cancer patients, make it necessary to use antidepressant derivatives in addition to the use of chemotherapy drugs in these patients. Therefore, the effects of antidepressant drugs on cancer cells are extremely interesting. Some studies have reported that antidepressant drugs cause loss of function and apoptosis in cancer cells. This review was conducted to analyze the molecular connection of the biological clock with paroxetine in cancer cells and to include the effect of antidepressant drugs in the relationship between cancer and the biological clock.

Keywords: Antidepressants, biological clock, cancer, depression

The biological clock is an internal system that regulates physiological functions, metabolism, and behavioral rhythm according to adaptation to the internal and external environment in most organisms living in the universe, and is controlled by the day-night cycle and seasonal cycles, which is approximately 24 hours.[1] The biological clock mechanism that has been studied in many model organisms goes back to very ancient times to evolve. For instance, as a result of studies, it was discovered that the circadian mechanism in cyanobacteria, which are prokaryotic, is very similar to the eukaryotic cellular organization.[2] After this research, it was suggested that the bacterium Synechococcus elongatus is a useful model for understanding the prokaryotic circadian mechanism. In research on Drosophila, it was found that first, the period gene is a mammalian homolog, and then it is highly parallel to the mammalian circadian rhythm.[3] The main control center of the biological clock in mammals is the suprachiasmatic nucleus (SCN), which consists of many nerve cells, positioned near the anterior hypothalamus in the brain. This region is closely concerned with optic chiasma. The light signal detected by the photoreceptors in the cone and rod cells of the eye is transmitted directly to this region, and for the SCN, the light acts as an important synchronization regulator. The SCN uses a variety of neural and endocrine stimuli to synchronize the clocks of many peripheral organs. Therefore, the master clock is reset and it stimulates the reset of the clock in the peripheral tissues by inducing the hormone center. In addition, many tissues and organs can generate circadian rhythms in vitro. Peripheral tissues have distinctive circadian oscillations but rely on the central clock and tissue-specific factors for synchronization.[4] Many of the mammalian biological clock genes were first identified by mutagenic studies in fruit flies (*Drosophila pseudoobscura*). The core molecular clock generates oscillations at the protein level via some autoregulatory transcriptional/

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translational feedback loops (TTFL).[5] Some biological clock genes encode transcription factors for the expression of clock-controlled genes located in the downstream pathways of major biological clock genes.[6] Looking at the cellular biological clock system, CLOCK (circadian locomotor output cycles kaput) and BMAL1 (brain and muscle Arnt-like protein-1) are seen as transcriptional activators. Of the other main components, those that produce the negative arm of the feedback loop (repressors) are known as Period (Per1 and Per2) and Cryptochrome (Cry1 and Cry2). At the beginning of the day, the expression of BMAL1 driven by RORα (retinoic acid receptor-related receptor α) which activates nuclear receptor pathways in cancer cells begins and forms a heterodimer with BMAL1 CLOCK. Positive transcription factors (BMAL1:CLOCK heterodimer) which belong to the bHLH (basic helix-loop-helix) class bind to regulatory sequences (E-boxes) located in the promoters of Per and Cry genes and increase the expression of related genes. This increase in expression causes the accumulation of PER in the cell cytoplasm. PER is degraded intracellularly by phosphorylation and ubiquitination, but a stable complex containing PER and CRY is formed with the accumulation of CRY. This complex inhibits the transcriptional capacity of BMAL1 and CLOCK, thereby preventing further expression of the Per and Cry genes. The phosphorylation and gradual reduction of negative factors (CRY and PER) allow re-initiation of BMAL1 expression. In this way, the first half of the circadian rhythm, which includes the negative feedback loop, and the second half with the removal of negative factors are done. This phenomenon is also referred to as the TTFL.[7] Clock genes and proteins not only promote their transcription, but also regulate the transcription of target genes and/or modulate key molecular pathways through protein-protein interactions such as the monoaminergic system, hypothalamic-pituitary-adrenal (HPA) axis, or neurogenic pathways.[8,9]

THE RELATIONSHIP BETWEEN BIOLOGICAL CLOCKS AND MAJOR DEPRESSIVE DISORDER

Major depressive disorder is a common and serious disorder that negatively affects the mood and behavior of the individual. It causes various emotional and physical problems and reduces the quality of daily activity of the patient.[10,11] Depressive disorders are associated with many illnesses and moods because of their effects on brain function and the body's overall chemistry. It has been suggested that the abnormal circadian rhythm is somehow related to the development of certain diseases, such as depression and bipolar disorder.[12-14] Although this relationship has not been resolved yet, circadian rhythm disturbances are frequently observed in major depressive disorder, and therefore it is predicted that circadian rhythm will play an important role in depressive disorders.[15-17] However, investigating the repair of circadian disorders in depression would allow the treatment of depressive illnesses to change direction. It is known that many metabolic, physiological, and hormonal rhythms are damaged in patients with depression. For example, it has been found that the cortisol level secreted from the shell region of the adrenal gland and the prolactin level secreted from the pituitary gland, which provides milk production in women, is different from the normal profile in healthy individuals in case of stress in patients with depression.[18,19] Since the mechanisms in the examples given are regulated by the biological clock, it is thought that the biological clock causes some biochemical changes during the depression. Disrupted circadian rhythm is generally not specific, but is directly related to the disruption of the central clock, but any damage that may occur in the SCN directly affects specific (peripheral) circadian rhythms.

EFFICACY OF ANTIDEPRESSANT DRUGS

Antidepressants are in the drug class used in the treatment of many depressive disorders such as depression, anxiety disorder, and bipolar disorder. Antidepressant treatment aims to eliminate depressive symptoms and minimize the risk of recurrence of the disease.[20-22] Antidepressants help correct dysfunction by making changes in the nervous system that transmits signals along the nerve pathways to the brain and in the chemicals secreted in the body. These drugs are divided into five main classes according to how they affect chemical events in the brain and their targets: selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and atypical antidepressants. There are three basic molecules known as monoamines (serotonin, norepinephrine, and dopamine) in the chemical regulation in the human body and known to be involved in the psychological mechanism. The most important function of monoamines is their work as neurotransmitters,

transmitting neural signals to receptors in the brain. Most antidepressants function by preventing the reuptake of these neurotransmitters into the body and increasing the number of available substances.[23,24] Although the general working mechanism of antidepressants is neuron-related, how they have an effect at the cellular level is a subject that has been researched. The effects of antidepressants, especially on cancer cells, are very important. Using NG108-15 neuronal cells, Bellet et al.[25] modulate CLOCK: BMAL1-mediated travnscriptional activation of ketamine when CLOCK and BMAL1 are expressed ectopically. In addition, the effect of ketamine on circadian gene expression was analyzed, and they reported that it caused a dose-dependent decrease in the amplitude of circadian transcription of bmal1, per2, and cry1 genes.

A ROLE FOR THE BIOLOGICAL CLOCK IN CANCER

The human body converts timing signals into molecular oscillations in individual cells and then creates 24-hour rhythms in cellular processes in nearly every tissue in the body. The damaged circadian clock can alter or directly manage susceptibility to certain diseases. Another situation that can be encountered is the damage to the circadian mechanism due to some diseases. One of the events regulated by the circadian clock is the cell cycle. Disruption of circadian rhythms may therefore be associated with abnormal cell divisions that occur in cancer.[26,27] Impaired expression of biological clock genes can alter cell biology and promote cancer. However, the levels of biological clock gene expression are also controlled by the microtissue environment and may differ in the stage of tissue development. For example, a hardened extracellular matrix caused by aging and cancer leads to suppression of core clock rhythms.[28] On the other hand, disruption of clock gene expression also increases the risk of cancer.[26] In general, the circadian clock mechanism is preserved in low-grade and non-metastatic tumor cells compared to high-grade and metastatic tumor cells. In addition, it has been explained that high expression of clock, Per, and Cry extend the life span by reducing the production of metastasis in cells.[29] On the other hand, Bmal1 is the only gene that spoils rhythmicity when silenced alone.[30] In a study by Korkmaz et al.[31],it was determined that the mechanism of action of the Bmal1 in cancer cells depends on the stage of cancer.

DEPRESSION IN CANCER PATIENTS

In addition to the difficulty of cancer treatment, patients often experience depression. In a clinical study, it was reported that women with cancer mostly used antidepressants.[32,33] Depression may not be easily realized in cancer patients, as some physiological symptoms brought on by cancer can be confused with the symptoms of depression. Untreated depression progresses with an increase in psychological symptoms. This situation affects the quality of life, decreases motivation, and may complicate the adaptation process to cancer treatment.[34,35] Cancer patients are keen on negative behaviors as a result of chemotherapy treatment and the large amounts of the disease. Therefore, antidepressants with high tolerability should be selected for cancer patients, and it is recommended that these drugs be used in appropriate doses.[36,37]

In conclusion, cancer treatment not only wears outpatients physiologically but also weakens them psychologically. For this reason, patients may need antidepressant medication before and during cancer treatment. Regardless of the class of antidepressant drugs used in psychotherapy, it is thought to have a positive or negative regulation mechanism on the biological clock, but there are not enough studies on the action of such drugs on the biological clock and cancer development and treatment. In addition, the relationship between antidepressant drugs and the biological clock at the molecular level is open to research. At the same time, this review interprets how paroxetine, which is frequently used in psychotherapy, affects the presence and destruction of the biological clock at the cellular level. In this context, examining the relationship between depression-biological clock-cancer will contribute significantly to the literature. The review helps to understand the apoptotic effect of an antidepressant drug on cancer cells, in particular paroxetine. In this context, the fact that correlation will be obtained at the molecular level, unlike previous physiological and mostly clinical experiments, will present a different approach to the connection of drugs used in psychological disorders with cancer.

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