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Review Article

CIRCADIAN RHYTHM AND CHRONOTHERAPEUTICS: ROLE IN DEPRESSION

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ABSTRACT

Chronotherapeutics is the branch concerned with the delivery of drugs in synchronization with the biological clock and the therapy may be helpful in pathological conditions where disturbance in the circadian rhythm and biological clock has been the underlaying cause. Depression is a disorder of major public health importance, in terms of its prevalence, suffering, morbidity and economic burden to society. Alterations in circadian rhythms play an important role in pathophysiology and the symptomatic expression of affective disorders particularly depression and this may be conclusive at least in a significant proportion of patients which profit from chronotherapeutic interventions. Rhythm abnormalities in depression include diurnal mood variation, elevated nocturnal body temperature, lower nocturnal TSH, overall increased cortisol secretion, phase advance of cortisol and melatonin secretion and sleep architecture abnormalities. The exact relationship of these abnormalities to etiopathogenesis of depression remains unclear yet the role of chornotherapeutics in depression has shown encouraging results. Future research should be aimed to explore the complex and multifaceted role of chronobiology and various mechanisms involved in the alleviation of the depression syndrome.

KEY WORDS: Chronobiology, Chronothreapeutics, Circadian Rhytham, Depression, Melatonin

INTRODUCTION

Each year at least 800,000 people commit suicide, 86% in developing countries.[1] The South Asian region has amongst the highest suicide rates in the world and suicide is one of the leading causes of death in young people.[2,3] Mental disorders are overwhelmingly the most important preventable factor for suicide, and depression is by far the most important mental disorder which predicts suicide.[4] In South Asia, 11% of Disability Adjusted Life Years and 27% of Years Lived with Disability are attributed to neuro-psychiatric diseases.[5]Depression is the single most important neuro-psychiatric contributor to years lived with disability.[4]Studies from India show that people with depression spend more days being unable to work as usual due to their illness.[6]

Depression is a disorder of major public health importance, in terms of its prevalence and the suffering, dysfunction, morbidity, and economic burden. Depression is more common in women than men. The report on Global Burden of Disease estimates the point prevalence of unipolar depressive episodes to be 1.9% for men and 3.2% for women, and the one-year prevalence has been estimated to be 5.8% for men and 9.5% for women. It is estimated that by the year 2020 if current trends for demographic and epidemiological transition continue, the burden of depression will increase to 5.7%

of the total burden of disease and it would be the second leading cause of disability-adjusted life years (DALYs), second only to ischemic heart disease.[7]

Depression is an affective disturbance with chronic sad mood state (dysthymia) and with a loss of interest in new or previously pleasant activities (anhedonia). Depression affects mood, mental and physical condition and behavioral performance. Approximately each year, 20 million people, one of ten adults, suffer from depression, and approximately 60% of these individuals do not receive the needed help, even though treatment diminishes symptoms in more than 80% of the cases. [8]

The etiology of depression is complex; it may have a genetic, physiological/biochemical or hormonal origin or be triggered by stressful conditions and/or psychological and social factors.[9] In addition, studies in chronobiology indicate that the disruption of circadian rhythms also contribute to the onset of depression.[10] Two factors leading to circadian disruption are the increase of nocturnal activity which is accompanied by a decrease in sleeping time and the extended exposure to artificial light at night.[8]

The circadian system

Rhythms that approximate the 24-hour dark-light cycle are called circadian (from *circa diem*) rhythms, whereas cycles that are shorter or longer that the 24-hour cycle are referred to ultradian and infradian rhythmicity, respectively. These biological cyclic processes are endogenously generated and maintained.[11] The rhythmic changes in metabolism and psychological activity of our body are under the control circadian clock; this ensures that our body is attuned to the level of mental and physical activity associated with a particular time of day or night.[12]

The internal body clock, which is responsible for generating 24-h rhythms, is located in the hypothalamic suprachiasmatic nuclei (SCN). The SCN receive light information from the retina via the retino-hypothalamictract and control most, if not all, peripheral rhythms (e.g., sleep/wake, hormones, body temperature).The main entraining, or synchronizing, agent of the SCN is the light-dark (LD) cycle. [13] However, several nonphotic stimuli have also been shown to alter clock function. Of particular interest is the role of activity or arousal, which may provide feedback to the clock. [14, 15]

The rhythms expressed by live organisms are not a passive consequence of the environmental conditions but rather have an endogenous origin. The circadian system is made up of an internal biological clock as the principal piece that has an intrinsic capacity to vary. In it, some entry pathways of information from the receptors that capture the signals from the environment and some exit pathways aimed at the physiological systems responsible for manifesting the biological rhythms of an individual function as a pacemaker. [16]

The circadian system is responsible for the generation and maintenance of the body's rhythms and for its synchronization with the environment. The characteristics of the circadian system are similar in all mammals, which are subjected to cyclic changes due to the rotation and transfer movements of the planet around the sun, must anticipate and improve their adaptation to these changes. Thus they have cyclic variations in several physiological and behavior functions that are called biological rhythms. [17]

The characteristics of the circadian system are remarkably similar in all mammalian species [18] and the biological clock in the suprachiasmatic nuclei is synchronized to the external light–dark cycle via retinal light input. Classic cones and rods participate in, but are not the major transducer of, 'non-visual' circadian photic input: the main photoreceptor pigment for circadian timing appears to be melanopsin in the retinal ganglion cells.[19] A specialized retino-hypothalamic tract provides direct neuronal connection to the SCN, which also receives indirect non-photic input (e.g. from the raphe´nuclei).[20] Nocturnal synthesis of the pineal hormone melatonin is driven by the SCN; melatonin also feed back on melatonin receptors in the SCN.[21] Furthermore, even though the SCN is the so-called master clock, circadian oscillators are found in every organ and, indeed, in every cell.[22]

Circadian rhythm and depression

Depression is a complex disorder whose clinical manifestations include affective, cognitive, somatic and behavior symptoms. Some core symptoms of depression show circadian rhythm in their clinical expression, such as diurnal mood variation, or are closely linked to the circadian system functioning, such as the sleep-wake cycle alterations. In addition, alterations have been described in the circadian rhythms of several biological markers in depressed patients. Thus, taking the neurobiological aspects of the circadian system into consideration is fundamental in the approach to the physiopathology and therapy of depressive conditions. [16]

The regular rhythm of night (dark) and day (light) regulates our life, as it does for most living organisms. Associated with this are regular changes in core body temperature, hormonal secretions, heart rate, renal output and gut motility. Our mental ability and energy levels are highest during daylight hours, when we engage in exercise and social interactions, with our metabolism and physiology adapted to this. During the night, when activity levels drop, core body temperature falls and reaches its nadir while cortisol levels rise before awakening. There are cyclic changes in the level of sleep (as shown by changes on an electroencephalogram [EEG] with hormonal release, such as the release of growth hormone linked to specific phases of the regular sleep cycle.[23-25]

The SCN coordinates daily sleep-wake cycles, metabolic processes, hormonal release, and in general the temporal order of all the body physiology. It also coordinates temporal oscillations of cells and organs, coupling the organs and systems to function in harmony.[26] The alteration of this temporal order causes sleep disturbances, irritability, lack of attention, gastrointestinal, or heart diseases as well as tendency to develop cancer, however, the mechanism by which circadian disruption leads to disease requires further studies.[27-29]

In humans, mood also exhibits changes across the 24-hour cycle and mood disorders, especially, are associated with changes in various circadian rhythms.[11] Disruptions to circadian rhythms have been found among patients with major depression.[30]

These occur in the form of disruptions of the sleep/wake cycle, changes in the pattern of several hormonal rhythms, and changes in the body temperature rhythm.[31] These rhythm disruptions suggest that the body's biological clock maybe malfunctioning in depressed patients. The disrupted rhythms may contribute to causing depression or

the depression may cause the rhythm disturbances. Alternatively third factor, such as a neuro-chemical or hormonal imbalance, may play an independent underlying role in the development of both.[32]

The phase-shift hypotheses of depression proposed that mood disturbances result from a phase advance or delay of the central pacemaker and related circadian rhythms that regulate temperature, cortisol, melatonin, and REM sleep relative to other circadian rhythms, and with a marked phase-shift relative to the sleep-wake rhythm. Findings indicative of advanced circadian phase such as early morning awakenings, earlier occurrence of REM sleep relative to sleep onset, and melatonin secretion shift in patients with depression compared to non-depressed subjects were thought to reflect a phase shift in the circadian oscillator that controls these parameters. Phase shift hypotheses have motivated therapeutic approaches with bright light exposure and melatonin to resynchronize the endogenous rhythms and the sleep-wake cycle and have yielded positive and encouraging findings mostly in patients with "winter depression".[33-35]

In depressive patients, nocturnal melatonin release is often diminished, and this data may be related to sleep disturbances that depressive patients report. [36,37) Approximately, 90% of depressive patients complain about the low quality of their sleep. It is not surprising then that brain regions involved in depression are also implicated in the regulation of the sleep/wake cycle. One possible link for the narrow relationship between sleep disorders and depression is the onset of and anxious state that affects depressive patients when they wake up in the morning.[38] Actually, the therapy with antidepressant drugs improves the quality of sleep, although some of them display collateral effects that aggravate insomnia and cause sedation and sleepiness during the daytime.[39]

Depressive individuals also display increased levels of plasmatic cortisol, a hormone that is associated with stressful conditions. This constant hypercortisolemia has been reported to lead to an anhedonic behavior and metabolic alterations.[40] In depressive patients, the circadian rhythm of cortisol is disturbed, indicating that an alteration of the internal temporal order *per se* may trigger the depressive symptomatology.

Winter depression and circadian rhytham

In winter, when day is shorter and night is longer than in spring and summer, depression is developed as a consequence of a diminished sunlight exposure. Winter depression is characterized by the usual depressive anhedonic mood symptoms, but the vegetative symptoms are atypical hypersomnia, increased appetite (particularly for carbohydrates) and weight. This transient mood disorder has been denominated seasonal affective disorder (SAD). This type of depression is characterized by a regular, annual episode of major depression during autumn and/or winter, and remission or episode of mania/hypomania during spring and summer. [41] SAD affects 2–5% of general population in temperate weathers and generally is more common in the countries where seasonal changes are more noticeable, being days shorter than night and luminosity very low during the day in the winter time. In general, low luminosity in productive moments of the human life affects negatively mood state, especially if the individual remains in close spaces and without a sufficient illumination. Light deficiency can cause sleepiness in the day and insomnia at night, affecting people

performances and promoting fatigue during the day. Because of this light deficiency, several brain areas are not enough stimulated for releasing dopamine and serotonin, neurotransmitters that contribute to improved mood state.[42] Contrasting with major depression in SAD patient's melatonin is released in higher proportions.[43,44]

Chronotherapeutics in Depression

Chronotherapeutics is the branch concerned with the delivery of drugs in synchronization with the biological clock and the therapy may be helpful in pathological conditions where disturbance in the circadian rhythm and biological clock has been the underlaying cause like depression.

The main goal of chronotherapeutics is to match the timing of treatment with intrinsic time of illness. [45] Optimum therapy is given when the right amount of drug is delivered to the correct target organ at the most appropriate time.

Disruption of circadian rhythms is a relevant factor contributing to the pathogenesis of affective disorders, thus the recovery of correct internal-external circadian synchronization should be considered as a possible strategy for the therapy of depression. This implies that achieving a regular lifestyle may contribute to the stabilization of depressive patients, improving in this way the quality of their lives.[46]

Currently, the therapy of depression includes the pharmacological and different kinds of psychotherapy, cognitive behavioral therapy and interpersonal psychotherapy. Given the number of secondary effects that antidepressant drugs may cause, it is common that some depressed individuals prefer to quit the prescribed therapy. For this reason, an increasing amount of clinical studies supports the use of chronotherapy as an alternative for the treatment of mood disorders. This proposal requires that the administration of antidepressant drugs should occur in the moment and dosage when the beneficial effects on the neurochemical systems are maximal and the collateral consequences are the less annoying for the patient. [47,48]

Other "chronotherapeutical" strategies include strategies that modify the biological clock, like, light or dark therapy, sleep deprivation, or a phase advance in the sleeping time. All of these approaches are directed to modify and adjust the biological clock to the correct phase [49,50] and ameliorate light exposure.[51] Also, some pharmacological products that affect directly the function of the biological clock have been proposed for a chronotherapeutical use. Melatonin and melatonin agonists have chronobiotic effects, which mean that they can readjust the circadian system. Administration of melatonin at the start of the night can be used to resynchronize the biological clock, by providing time signals and entraining sleep and thus reduces circadian disruption and probably some of the sufferings that occur in depression.[52,53] Seasonal affective disorders and mood disturbances caused by circadian malfunction are theoretically treatable by manipulating the circadian system. In major unipolar depressive disorder, melatonin alone has no antidepressant action, but novel melatoninergic compounds demonstrate antidepressant properties. Agomelatine, for example, is a new melatonin agonist and antagonist of the 5HT2 serotonin receptors, with antidepressant properties and capacity to regulate and ameliorate the quality of sleep. Furthermore, melatonin is a potent antioxidant and a promoter of the immune function, which are excellent side effects in the therapy of depression. In

summary, antidepressants with intrinsic chronobiotic properties offer a novel approach to treatment of depression. [8]

Biological Time keeping and therapeutic strategies:

The pair of supra chiasmatic nuclei are situated in the hypothalamus and the pineal gland controls the circadian rhythms and master clock network. [45,54,55] The rhythmic activities of specific, so-called, clock genes, like per1, per2, per3 and their gene products are the cyclic or nocturnal secretion of melatonin from the pineal gland that comprises the central timekeeping mechanism.

Wake therapy

Light therapy was specifically developed as a 'zeitgeber' treatment for SAD patients, who become depressed as the days shorten and spontaneously remit during the longer days in spring and summer.[56] Bright light has three major effects on the circadian system: it increases circadian amplitude, shifts circadian phase (depending on the time of application) and thereby modifies the phase relationships between the internal clock and sleep, and the external light–dark cycle.[57] Any of these might alone suffice for the mood-elevating effects.[58] It has been found clinically that light therapy combined with an SSRI leads to more rapid (within 1 week) and more profound (by approximately 30%) improvement in patients with non-seasonal major depression.[59,60]

The slow response to most antidepressants is a big problem for psychiatrists and their depressed patients. In remarkable contrast is the improvement within hours afforded by staying awake all night. This apparently paradoxical behavioral treatment of major depression—a night of total sleep deprivation—was first scientifically studied 40 years ago. It is the most rapid antidepressant we know: approximately 60% of patients respond with marked improvement within hours, a finding that has been replicated in thousands of cases. Timing the sleep deprivation to the second half of the night, with equivalent effects, suggests a circadian component in the response—and not just that of being awake. A third sleep manipulation that supports this interpretation is that when sleep is shifted a few hours earlier—without deprivation—a slower, but longer-lasting antidepressant effect is induced.

Several combination strategies have been used to maintain the rapid response after wake therapy. The most studied protocol has added daily morning light therapy to concomitant administration of antidepressants or lithium.[59,60] In patients with bipolar I disorder, 70% with no history of drug resistance improved rapidly with the brief intervention and 57% remained euthymic at 9-month follow-up. The rate was lower in drug-resistant patients; however, the 44% response in these patients is still remarkable when compared with standard antidepressant drug response rates.[61] Thus, a short-term chronotherapeutic protocol can induce long-term remission. Adding sleep phase advance for 3 days after sleep deprivation to regular light therapy also results in long-term maintenance of response.[62,63] For patients who relapse, further sessions can be used. Wake and light therapy may also reduce duration of hospitalization. In a general psychiatric hospital setting, the combination of wake therapy (3 sessions over a week) with antidepressants resulted in discharge 3 days sooner than drug treatment alone. Furthermore, retrospective analyses have revealed a 3-day advantage for patients exposed to more natural light in sunny hospital rooms than those staying in dimmer rooms.[64,65]

Dark therapy

Another chronotherapeutic element, dark therapy, focuses on darkness, particularly in bipolar patients. Keeping acutely manic patients in dark rooms during the night has been shown to improve symptoms and immediately stop rapid cycling.[66,67] Dark therapy is interesting because the response to it is so rapid, but it is not very practical. One alternative being investigated is the use of blue-blocking sunglasses to induce "circadian darkness" while not impairing the patient's vision. [68]

CONCLUSION

In conclusion, it appears that there is an intricate and complex network linking circadian rhythms and depression. The circadian rhythm disturbances described in depressive states as well as the efficacy and fast onset of action of chronobiological based treatments point out the circadian system as an important therapeutic target in the treatment of depression. However, the development and application of therapies aimed at correcting circadian system alterations present in the clinical depression has been given little thought up to now. The rapid increase of knowledge on the molecular substrate of the circadian system that has occurred in recent years offers new and promising opportunities for the development of therapeutic alternatives to cope with the challenges that continue to occur at present in the treatment of depression, including agents that act by modifying the expression of genes belonging to the circadian molecular machinery.

Thus future research efforts may be directed and unified to understand chronobiological aspects in pathology of depression.

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