Review Article

Chronobiology and chronotherapy of allergic diseases

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Background

Birds migrate to warmer climates at colder times of the year. Mammals sleep during the night and are more active during daytime. Asthmatics tend to have more bronchospasm early in the morning. These are examples of chronobiology; the term originated from the Greek 'kronos' (time), 'bios' (life) and 'logos' (study). It is defined as the science of time and internal biological clocks or the study of the effect of timing on biological events, especially repetitive or cyclic phenomena in individuals[1]. Though scientific research on chronobiology began in the 20th century, an astronomer, Jean Jacques d'Ortous de Mairan, who lived in the 18th century, had investigated daily leaf movements of the Mimosa[2]. He showed that the leaves continue to swing in a circadian manner even in permanent darkness. Charles Darwin reported similar rhythmic phenomena.

There are several terms in relation to chronobiology such as chrono-pharmacology and chrono-therapeutics. Variation in the pharmacological actions of various drugs during different time periods of the day is known as chrono-pharmacology[3]. Similarly, drug delivery based on the inherent activity of a disease over a time period is chrono-therapeutics[3]. There are three basic cycles of chronobiology; infradian rhythms, ultradian rhythms and circadian rhythms[4]. Infradian rhythm lasts more than 24 hours and is repeated every few days, weeks, months, or yearly[4]. Seasonal rhythms like bird migration and female menstrual cycles follow the infradian rhythm. Ultradian rhythms last less than 24-hours. They regulate physical, emotional, and spiritual functions[4].

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Many physiological functions of the human body, including food ingestion, blood circulation, hormone excretion, different sleep stages and the human performance curve have multiple cycles in one day.

A circadian rhythm is a biological process displaying an endogenous oscillation lasting for around 24 hours[5]. Usually, circadian rhythms synchronize with the internal biologic clocks associated with the sleep-wake cycle[5]. These circadian rhythms may influence sleep-wake cycles, hormone release and body temperature. Jet lag, which is commonly experienced by many travelers, has associated symptoms of fatigue, disorientation and insomnia[6]. Obesity, diabetes and psychiatric disorders, including depression and bipolar disorders are among many other disease states associated with abnormal circadian rhythms[7]. Of the three, circadian rhythm is the one which has been most extensively studied. Understanding the inner clock of the human body which controls circadian rhythm is incomplete. Light and darkness have a great impact on the human body, and this fundamental rhythm is controlled by genetically manifested timers that reside deep within our bodies. The circadian rhythms are closely associated with the sleep-wake cycle.

Physiology of the sleep-wake cycle

Swiss sleep researcher Alexander Borbély[8] described a two process sleep-wake cycle. These determine the sleep-wake status and related activities of the body.

- *Process S - Sleep-wake homeostasis:* The accumulation of melatonin in the brain induces sleep. The secretion of melatonin stops in the morning and the person starts to wake up. During daytime the tendency to sleep increases but is overridden by the circadian drive to remain awake.

- *Process C - The circadian process:* This regulates sleep patterns, feeding patterns, core body temperature, brain wave activity, and hormone production over a 24-hour period and thus controls the sleep rhythm.

Regulation of circadian rhythm

Studies have shown that a specific retinal group of photoreceptors connected to the central supra-chiasmatic neuronal clock, 'the master clock' in the brain, is activated by light[9]. This consists of a group of nerve cells, supra-chiasmatic nucleus (SCN), which is thought to be located in the hypothalamus. SCN acts on peripheral circadian clocks via neural and endocrine pathways to coordinate all the body clocks, so that they are in synchronization.

Circadian regulation via gene expression

The functional rates of the biological processes of our body function at different rates at different times of the day. This includes brain activity, digestion and absorption, endocrine function, bronchiolar size etc. Microarray studies have revealed that 2–25% of total genes expressed have significant changes in their expression levels during the course of the day depending on the tissue[10]. Gene expression of many genes has been shown to be influenced by circadian rhythm. Studies have found that this occurs through changes in translational efficiency, changes in chromatin conformation in response to distal gene porters, and changes in the rates of translation and protein synthesis[10]. Rhythm generated by the brain is carried to the organs via about 150 messengers to update and to prescribe specific consequences. Molecular mechanisms of rhythm generation are cell autonomous and highly conserved in the SCN and peripheral cells[11]. These rhythms are created and maintained by transcriptional and translational feedback networks comprising several 'clock genes', including Clock, Bmal1, Period and Cryptochrome[10,12]. Orexin/hypocretin-producing neurons are a crucial component for maintenance of wakefulness and it`s hypofunction results in narcolepsy[13].

Chronobiology and chronotherapy

Synchronization of timing of therapy with the intrinsic timing of illness is the main objective of chrono-therapeutics. Theoretically, delivery of the precise quantity of drug to the correct target organ at the most suitable time results in optimal therapy. Although many drugs have reproducible daily variations, researchers have identified over 100 drugs with significant variations in concentrations or effects, or both, over 24 hours[14].

Understanding of chronobiology has led to attempts at using them in treatment of diseases. Chrono-therapeutics makes use of synchronization of medication levels in a timely manner according to need, taking into account biologic rhythms in the pathophysiology of medical conditions, and/or rhythm-dependencies in patient tolerance for given chemical interventions. Advances in chrono-therapeutics have led to the production of pulsatile drug delivery systems taking the required drug concentrations at the required time to different organs needing them[15].

Hypertension, myocardial infarction, cerebrovascular accidents, bronchial asthma, peptic ulcer, arthritis, hypercholesterolaemia, allergic diseases, cancer, diabetes and some psychiatric illnesses are examples where chrono-therapeutics has been made use of. Chrono-therapeutic preparations consider the effect of therapeutic influences in accordance with the body's inner clock. Effects and side-effects of medications may vary according to the time of consumption. When making use of chrono-therapeutics the questions one should ask are: What is most effective when taken in the morning? What does the body need in the evening? Which substances have a mutually-potentiating effect?[15]

Chrono-therapeutics and allergic diseases

Allergic rhinitis

The major symptoms of allergic rhinitis (AR) are nasal discharge, sneezing, nasal congestion and nasal pruritus. Many studies have identified that symptoms of AR such as nasal itchiness, sneezing and rhinorrhoea are common around breakfast time and symptoms such as nasal congestion and nasal block are common during early morning[16]. The main pathological process behind AR is an acute type I hypersensitivity reaction releasing histamines, leukotrienes and tumour necrosis factor (TNF) alpha etc. on exposure to allergens. The late reactions occur 12-16 hours later from acute exposure of the allergen and occur through eosinophils and lymphocytes. These cells when stimulated release histamine, prostaglandins and leukotrienes leading to local vasomotor changes manifesting as nasal congestion and nasal obstruction. Early response is known to be associated more with sneezing and rhinorrhoea and late response with more of nasal congestion and nasal obstruction[16]. The observation of diurnal variation of symptoms observed in patients with AR can be due to exposure to allergens like pollen in the morning to cause symptoms of type 1 hypersensitivity reaction and symptoms of late reactions towards early morning or night[17].

Studies have shown that the above phenomenon gets influenced by circadian rhythm of hormones as well[16,17]. It is established that cortisol, which has the highest concentration in the morning, can modulate inflammation of the nasal mucosa[5]. Adrenaline and noradrenaline are found in the lowest concentrations during early morning, when histamine levels in plasma are found to be at the highest. Adrenaline and noradrenaline are involved in stabilisation of eosinophil membranes so that their release is minimised. The severity of AR symptoms becomes worse at night and early morning in the majority of patients which indicates a prominent 24-hour variation. This can compromise night-time sleep which disturbs the quality of life in the daytime, inducing irritability and moodiness. In addition, studies have shown that it has a negative impact on school and work performance[16,17]. Chrono-pharmacotherapy has been attempted in allergic rhinitis. H1-antagonist, decongestant, and anti-inflammatory (glucocorticoid and leukotriene receptor antagonist and modifier) medications are being frequently used to treat AR. Among them, only H1-antagonists have been studied for their chrono-pharmacology and as potential chronotherapy[18]. Many studies have assessed the efficacy of different antihistamines at different times of the day to maximize the effect. The H1 antagonist mequitazine, when administered in the evening compared with morning dosing has exhibited improved efficacy in AR[17]. Other studies using long-acting antihistamines cetrizine and loratidine have failed to show a benefit[19].

Bronchial asthma

Bronchial asthma (BA) is a disease associated with reversible bronchial obstruction characterized by exacerbations manifesting as cough, wheezing and /or shortness of breath. Asthma exacerbations are common towards late night and early morning. The bronchiolar luminal diameter becomes progressively smaller across the night. This effect is more when the person is asleep[20]. An increased responsiveness of allergen has also been observed at night. A study using house-dust-mite challenge found that the greatest decrease in FEV_1 occurred after a late-evening (11 PM) challenge[21]. Medications used in bronchial asthma include preventers and relievers. The preventers include inhaled corticosteroids and long-acting theophylline. The relievers include short acting beta 2 agonists and cholinergic antagonists. The chrono-pharmacology and chronotherapy of many classes of BA medications have been explored[22,23].

Chrono-therapeutics has been used with certain SR formulations of theophylline. They have been administered in the evening so that the highest blood levels are achieved when the limitation to airflow is at the highest and the adverse effect are also better tolerated[24]. Long-acting inhaled β_2-agonists salmeterol and formoterol have been studied for nocturnal asthma therapy and twice daily use has been shown to improve bronchoconstriction in asthmatics. In patients with nocturnal asthma, optimal timing of steroid therapy is shown to be early evening when there is a significant increase in forced expiratory volume in one second (FEV1) and a decrease in airway inflammatory cells relative to control[18]. Similarly, evening dosing of long-acting bronchodilators in nocturnal asthma achieves maximum efficacy at night[25].

Many other classes of medications too have been explored for chronotherapy of allergic diseases. Studies on gastro-oesophageal reflux (GOR) and bronchoconstriction have not shown conclusive evidence whether GOR makes asthma symptoms worse[26].

Chrono-disruption (CD)

It is the disturbance of the internal temporal order of physiological and behavioural circadian rhythms. In modern society, CD can be seen in conditions like jet lag, shift work or social jet lag. Furthermore, clock gene polymorphisms and aging can have chrono-disruptive effects. Garaulet M, *et al* have shown that obesity and CD are highly interconnected[27].

Some of our inner clocks are ticking slower while others are ticking more rapidly with aging. Further, they tend to go out of tune, and some stop ticking altogether over time. One good example is the melatonin surge. Around 11 pm, there is usually a sudden surge in melatonin levels in the human body. This nocturnal melatonin surge has been diminished in most elderly people[28]. Thus, many rhythms, including sleep, blood pressure, body temperature and hormones remain uncontrolled, resulting in the development of their own rhythm by the organs and disturbances occur.

Conclusion

Most of our bodily functions are controlled by a biological clock coordinated by SCN in the hypothalamus. Chronotherapy remains a potential science to make use of potentiate therapeutic options in the management of disease conditions including asthma and allergic rhinitis. Future studies should aim at determining suitable drugs and discovering the right time of their administration in order to achieve maximum benefit and minimizing the side effects by understanding chronobiology.

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