Review Article

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Impression of the Clock Genes on Oral Health and Diseases: A Narrative Review

Dentistry Section

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ABSTRACT

The circadian clock helps organisms adapt their physiological processes to changing environmental conditions, including the adaptation of the 24-hour sleep-wake cycle in day and night. Circadian rhythms regulate the proper timing and synchronisation of various physiological and metabolic processes in our body by supporting 24-hour oscillations of master genes. At the molecular level, a family of transcription factors known as "clock genes" controls circadian oscillations in gene expression. Through this complex regulatory network, our brain communicates with several peripheral organs and tissues receive communication from our brain via this complex regulatory network. Dysregulation of the circadian rhythm can lead to multiple diseases, including cancer and autoimmune disorders. The circadian clock appears to significantly affect saliva production, salivary glands, oral epithelium, and tooth development. Therefore, the goal of this review is to provide a systematic and integrated perspective on the role and effects of the circadian clock and its genes on oral health and diseases, while briefly discussing their relation to systemic health and conditions.

Keywords: Ameloblasts, Autoimmune disease, Circadian rhythm, Malignancy, Salivary gland

INTRODUCTION

A circadian clock is a biological timekeeping system present in every cell and organ of mammals, animals, and plants [1-3]. It is suggested that circadian clocks evolved concurrently with the Earth's geological history and have been fine-tuned due to selection pressures brought on by cyclical environmental conditions [4].

The circadian clock drives the ability to synchronise with the changing environmental conditions at the molecular level. Biological clocks govern circadian rhythms. All living organisms, from bacteria to plants to humans, follow a circadian rhythm that lasts from a few seconds to several months. It is possible to induce a circadian rhythm within an organism through endogenous clocks or by cyclic events in the environment, such as light-dark cycles [5], but they can even be produced when there are no daylight-dark shifts [1].

Similar to mammals, birds have circadian cycles in behaviour and physiology. Even though they have similar genetic components birds and mammals appear to have distinct circadian clocks [6]. Bird migration is a prominently rhythmic phenomenon that typically exhibits approximately annual (circannual) and diurnal (circadian) rhythmicity at specific periods of the year and day. Both rhythms serve as biological clocks that allow organisms to adjust to seasonal and daily changes in the environment [7].

In humans, chronic inflammatory diseases are associated with disruptions in circadian rhythm entrainment and pathway functions [8-10]. The core clock genes that regulate the circadian rhythm are BMAL1, CLOCK, PER1, PER2, PER3, CRY1, and CRY2 [11,12]. Recently, research has demonstrated that the circadian rhythm influences various aspects of oral health and diseases, such as the coordination of the maxilla and mandible growth, remodelling of the alveolar bone, tooth development, oral epithelium homeostasis, salivary gland growth, and saliva production [9,13-15]. Any disturbance or deletion of the clock gene can lead to the incidence of diseases such as mandibular hypoplasia, Sjögren's syndrome, or oral carcinoma [2,9]. This review article focuses on how any alteration in the clock gene may have an adverse effect on the oral health and disease of an individual, with a brief description of the effects on general health and disease as well.

Circadian Rhythm and Clock Genes

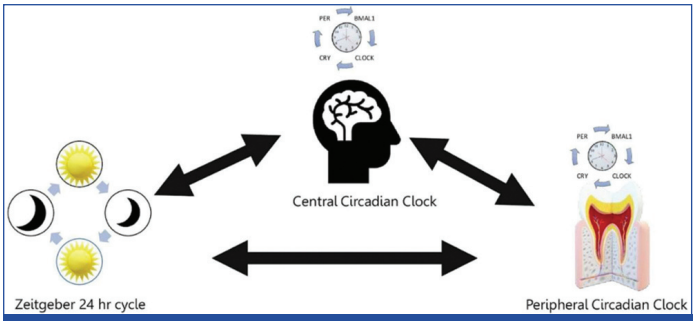
Circadian rhythms regulate the body's homeostasis through the temporal control of tissue-specific circadian rhythm control genes [2]. The circadian rhythm is controlled by "clock genes" [13]. The 20,000 neurons that make up the central clock, all express clock genes that oscillate in unison [14]. The main clock genes that maintain the biorhythm are Brain and Muscle Aryl Hydrocarbon Receptor Nuclear Translocation (ARNT) like (BMAL 1), Circadian Locomotor Output Cycles Kaput (CLOCK), Period homolog 1 (PER1), Period homolog 2 (PER2), PERiod homolog 3 (PER3), Cryptochromes (CRY 1) and (CRY 2) [13]. Additionally, RAR- Related Orphan Receptor Alpha (Rora), Nuclear Receptor Subfamily 1, Group D, member 1 and 2 (NRLD1 and NRLD2), and Albumin D-binding protein (Dbp) also play a key role in modifying the expression of the main clock genes [15].

Criteria for defining clock genes include periodicity in activity or quantity, as well as molecular proof of a feedback mechanism [14]. The clock genes' oscillating transcription occurs over a roughly 24-hour period, and the output signals they produce cause rhythmic gene expression, which resulting in recurrent patterns in physiological processes [13]. Indirectly, clock genes may bind to intermediary clock-controlled genes, such as essential transcription factors, which subsequently affect the expression of downstream target genes involved in cell division or differentiation processes [13].

Mechanism of Action of the Circadian Clock

Generally referred to as the pacemaker of the circadian rhythm, the Central Circadian clock is located in the Suprachiasmatic Nucleus (SCN) [9]. The SCN is located in the anterior part of the hypothalamus [16,17], while peripheral or subordinate clocks are present in other body parts. The central clock is sensitive to light and driven by patterns of daylight/darkness. Although peripheral clocks cannot sense light, they are controlled by the central clock, or they can act independently based on other physiological stimuli, such as feeding. This suggests that cells do not need to be connected to the Central Circadian clock for the circadian mechanism to work see [Table/Fig-1].

At the molecular level, the circadian cycle works as a transcriptional-translational feedback loop. In mammals, there are two interlocking loops that coordinate together to produce a 24-hour rhythm of gene expression. The first transcription-translation feedback loop



[Table/Fig-1]: Mechanism of action of the central circadian clock.

is generated by the core genes BMAL1, CLOCK, CRY, and PER. In the Transcription-translation feedback loop, there is a positive and negative arm. The positive arm acts as an activator, while the negative arm acts as a repressor. In the positive arm of the loop, clock, and BMAL1 heterodimerise to activate transcription of circadian target genes, and in the negative arm of the loop, Per and CRY are thought to interact and inhibit the action of Bmal1 and Clock, thereby decreasing their own transcription. The second transcription-translation feedback loop is generated through transcriptional activation by the retinoid-ROR and repression by REV-ERBα/REVERBβ. The existence of cooperative, interlocking feedback loops allow the circadian system is able to maintain accurate and robust circadian timing regardless of noise or environmental factors [18-20].

ROLE OF CIRCADIAN RHYTHM IN HEALTH AND DISEASES

In humans, clock genes play an active role in cell proliferation and diseases. Numerous metabolic activities exhibit circadian rhythms, such as 24-hour variations in glucose, insulin, leptin, and cardiovascular functions [21,22]. Accumulating evidence suggests the role of clock genes in obesity, cancer, rheumatoid arthritis, and autoimmune diseases, and others.

Cardiovascular Health

The morning spike in Blood Pressure (BP) and heart rate is believed to coincide with the peak of cardiovascular events, including stroke, myocardial infarction, and thrombosis. The BP rises first thing in the morning, reaches a plateau during the day, and then falls as you sleep [23]. Patients who show the absence of normal nocturnal variations in BP are designated as "non dippers" [23,24]. These non dippers exhibit an increased risk of cardiovascular diseases such as myocardial infarction, congestive heart failure, left ventricular hypertrophy, microalbuminuria, vascular dementia, and stroke [21]. Studies have shown that the degree of artery wall lesions after endothelial injury also increases when Bmal1 is removed, indicating several mechanisms by which the clock gene may affect myocardial damage susceptibility [25-27].

Renal Diseases

Studies have reported that renal function plays a role in maintaining normal circadian changes in BP [23,28-30]. The connection between aldosterone signalling and fluctuations in circadian BP patterns is known [23]. In patients with aldosteronism, there is a non dippers pattern [23]. Molecular mechanisms are unclear, yet clinical observations are well-acknowledged. Renal blood flow, Glomerular Filtration Rate (GFR), and the excretion of electrolytes like sodium and potassium fluctuate on a daily basis, causing circadian oscillations in renal function [23].

Autoimmune Diseases

Clock gene transcription controls cells, including eosinophils, macrophages, synovial fibroblasts, and CD4+T-cells [31]. Abnormal circadian rhythm leads to chronic fatigue, which is a common feature of autoimmune diseases like rheumatoid arthritis, Sjögren's syndrome, and systemic lupus erythematosus. Future research can provide insight into the treatment of autoimmune diseases by investigating the effect of circadian rhythm on the immune system [31].

Relation between Shift Workers and Circadian Rhythm

Shift workers tend to show a higher incidence of impaired glucose tolerance, cardiovascular diseases and obesity, and breast cancer [21,32,33]. The International Agency for Research on Cancer (IARC) concluded that "shift work involving circadian disruption is probably carcinogenic to humans" [32]. Investigations suggest low levels of CLOCK methylation and high levels of CRY2 methylation were demonstrated in breast cancer patients. Therefore, the epigenetic effects of shift work on the activity and functionality of circadian regulators may fill in the gap in the association between breast cancer and night shift work [32].

Others

The circadian clock is also linked with winter depression, also called Seasonal Affective Disorder (SAD) [34].

Role of Clock Genes in the Development of Craniofacial Structure

There are three different mineralised substances that make up the teeth: enamel, dentin, and cementum. Teeth develop in increments, and previous research suggests that the odontoblasts, which form the dentin, and the ameloblasts, which form the enamel, are under the influence of molecular clocks [13]. Understanding the circadian rhythm that regulates tooth shape can help characterise and identify the biological regulatory pathways that govern the development of dental cells [33]. However, there is no concrete evidence of the expression or probable function of clock genes (the genes that control circadian rhythm) in teeth [14].

Ameloblasts and Odontoblasts

Enamel and dentin are mineralised tissues formed during amelogenesis and odontogenesis, respectively. Evidence indicates that the circadian clock affects bone remodeling as also controls the homeostasis of other mineralised tissues [5]. It has been suggested that the circadian clock controls ameloblasts and odontoblasts [13].

Amelogenin (AMELX), kallikrein-related peptides 4 (KLK4), and MMP20 are the key markers in the process of amelogenesis. These proteases degrade the organic materials present in the matrix, and secondary crystal growth and mineralisation occur in the remaining fluid-filled tissue, leading to mature enamel production [5,15]. AMELX and MMP20 are found during the secretory phase of amelogenesis and odontogenesis, while KLK4 is found during the maturation phase of amelogenesis [15]. It has been found that these markers are stimulated by the Bmal1 gene in rat cells [5]. Patients with Amelogenesis Imperfecta exhibit abnormalities in the formation of enamel, and mutations in the above markers (AMELX, ENAM, KLK4, MMP20) have been linked to the cause of Amelogenesis Imperfecta [15].

Studies have shown that RunX2 plays a vital role in regulating ameloblast differentiation by upregulating the genes of the maturation stage, such as KLK4, and downregulating the genes that express during the secretory stage, like ENAM and AMELX [13,16,35,36]. Similarly, Dlx3 upregulates AMELX, ENAM, and KLK4. Runx2, a crucial transcription factor highly expressed in maturing ameloblasts, is upregulated due to excessive Nr1dl expression. Therefore, it is postulated that clock genes may control the daily fluctuations in ameloblast gene expression either directly by controlling the transcriptional rates of these genes or indirectly by controlling the expression of important transcription factors (like Runx2) [15].

Another hard tissue that makes up teeth is dentin. Odontoblasts parallel the actions of clock elements in ameloblasts during tooth development. Incremental lines are another characteristic of dentin development, and mammals show a circadian pattern for these incremental lines. Collagen secretion and production in odontoblasts exhibit a circadian control, which may be playing a role in the rhythmicity of incremental dentinal lines. Another study that supporting this conclusion, suggested that incremental lines are controlled by the SCN, which is the site of the main circadian clock [5].

Although the aforementioned observation strongly suggests that the creation of dentinal tissue is under circadian regulation, there is no concrete proof of the circadian clock of teeth. Furthermore, it is still unknown how the circadian clock affects the activities of ameloblasts and odontoblasts, resulting in the full mineralisation of enamel and dentin [13].

Oral Epithelium

Numerous epithelial craniofacial tissues have been found to express the clock gene, primarily in the basal cells of the oral epithelium. These include the palatal and junctional epithelia and the cell rests of Malassez, which surround the tooth roots. The expression of clock genes in oral epithelia is yet to be understood [13,31].

Effects of Clock Genes on Salivary Glands and Salivary Flow

Studies suggest that salivary flow rate follows a circadian rhythm [31,33,37]. Circadian rhythms influence salivary secretions, which are vital for nutrition and immunity. There is been evidence of circadian clock mechanisms in vital organs such as the kidneys. Additionally, there is also evidence of circadian clocks in the salivary gland, which regulates the amount, type, and content of saliva. Genes are responsible for regulating fluid movement in the salivary gland and kidney. Aquaporin-5 (Aqp5) plays a crucial part in saliva fluid secretion (Ishikawa and Ishida 2000) [38]. It is known through experiments that the clock gene controls this water channel gene AqP 5 [31,39]. Consequently, any abnormal changes in clock genes will affect saliva's secretion level. Further investigation is required for better diagnosis and treatment of salivary disorders [31,34,37].

Effect of Clock Genes on Oral Diseases

Pulp and pulpal diseases: Although it has been suggested that the circadian clock is involved in the formation of teeth, the function of key circadian clock genes and their regulation in the dental pulp is not widely understood [11]. A study on the circadian rhythm of pulp sensitivity found that early afternoon and early morning had the highest and lowest pain thresholds, respectively [40]. Another recent study discovered that ageing affected the circadian cycle of individuals' pulp sensitivities [40]. These findings may be helpful in identifying pulpal diseases and determining the appropriate timing for treatment [14].

The downregulation of PER2 and PER3 in the dental pulp of carious teeth is well-known. An altered pulp sensibility rhythm has been identified in geriatric patients with diabetes and hypertension. Even in healthy individuals, pulp sensibility appears to follow diurnal rhythms [5]. Tests conducted at 4:00 and 16:00 in diabetic or male hypertensive patients showed that the dental pulp is at its bluntest and most sensitive state. The bathyphase and acrophase of aged female hypertensive patients have a comparable circadian pattern to that of elderly individuals in good health, which appear at 12:00 and 0:00, respectively. It was proposed that pain perception and the use of analgesics in oral regions correlated with circadian phases. Further investigation is needed to understand the function of the circadian clock on pain perception in teeth in order to design effective treatment methods [40].

Relation of Clock Gene and Oral Malignancies

Cancer is characterised by uncontrolled cell proliferation, deregulated DNA damage, dysregulation of angiogenesis, and neoplastic growth [5,31]. Variations in lifestyle and industrialisation can disrupt the endogenous circadian rhythm in about half of the human population, contributing to the increased incidence of cancer worldwide [33]. The diurnal rhythms of PER1 have been found to correspond with carcinogenesis. Increased downregulation of PER1 is associated with tumour progression, while a decrease in PER1 is related to later stages of cancer and lymph node metastasis [5,41]. Both PER1 and BMAL1 play a tumour suppressor role, and mutations or alterations in these genes are associated with tumour progression and poor patient outcomes [31]. Downregulation of PER3 is associated with deeper tumour invasion, and upregulation of TIMILESS (TIM) and downregulation of PER3 are indicative of larger tumours. Poor patient survival is correlated with the downregulation of PER1 and PER3. Disruption of clock components like BMAL1, CRY1, CRY2, PER1, PER2, PER3, and Casein Kinase 1 (epsilon) {CK1(epsilon)} has been observed in patients with head and neck squamous cell carcinoma [5]. However, the direct relationship between the expression of circadian clock genes and cancer, including oral and head and neck carcinoma, is not yet fully understood.

Understanding the mechanism of the circadian clock can be beneficial in developing therapeutic strategies that can interact at more complex levels. Studies have demonstrated a link between the cell cycle phases in oral mucosa cells and clock gene expression [5,31]. This supports the use of chronotherapy for cancer treatment, where chemotherapeutics are administered at specific times based on the patient's circadian rhythm. Chronochemotherapy has shown to have fewer adverse effects when applied at a lower dose over a specified period of time. Research has shown that the use of chronochemotherapy resulted in reduced adverse effects, reduced stomatitis, improved treatment tolerance, and increased survival time in patients with oral squamous cell carcinoma and nasopharyngeal carcinoma [5].

CONCLUSION(S)

A deeper understanding of the circadian clock and its relation to general and oral health will provide new dimensions in dentistry. Chronotherapy will open up new areas for diagnosis and treatment plans for clock-related diseases. This information will benefit healthcare providers in understanding the influence of time on disease mechanisms and formulating customised treatment plans for individuals in need. Although the evidence related to this is not conclusive, further research in this field will help enhance knowledge and develop better clinical strategies.

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