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Review

The clock is ticking. Ageing of the circadian system: From physiology to cell cycle

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ABSTRACT

The circadian system is the responsible to organise the internal temporal order in relation to the environment of every process of the organisms producing the circadian rhythms. These rhythms have a fixed phase relationship among them and with the environment in order to optimise the available energy and resources. From a cellular level, circadian rhythms are controlled by genetic positive and negative auto-regulated transcriptional and translational feedback loops, which generate 24 h rhythms in mRNA and protein levels of the clock components. It has been described about 10% of the genome is controlled by clock genes, with special relevance, due to its implications, to the cell cycle. Ageing is a deleterious process which affects all the organisms' structures including circadian system. The circadian system's ageing may produce a disorganisation among the circadian rhythms, arrhythmicity and, even, disconnection from the environment, resulting in a detrimental situation to the organism. In addition, some environmental conditions can produce circadian disruption, also called chronodisruption, which may produce many pathologies including accelerated ageing. Finally, some strategies to prevent, palliate or counteract chronodisruption effects have been proposed to enhance the circadian system, also called chronoenhancement. This review tries to gather recent advances in the chronobiology of the ageing process, including cell cycle, neurogenesis process and physiology.

Contents

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1. Introduction

From the life's origin, Earth has been rounding on its axis and around the sun, generating daily and annual cycles. Under these conditions, organisms evolved a biological clock as an adaptation to anticipate the predictable periodical environmental changes. Thus, possible damage to biomolecules produced by the most energetic electromagnetic waves could be diminished by predicting the daytime, metabolic processes could be scheduled improving their efficiency and cyclic events like breeding, hibernation or predator/prey antagonism can be prepared in advance.

Almost all living beings have a biological clock, which predicts, adapts and prepares the organism to the cyclical environment changes. The circadian timekeeping system (from Latin *circa* and *diem*, means approximately one day) is responsible for predicting environmental cyclical cues, also called *zeitgebers* ("time giver" in German), and organising the internal temporal order of physiological processes. The circadian system is constituted by a series of structures hierarchically organised like a clock with inputs to wind-up the clock, the main pacemaker as the central machinery, and the circadian rhythms as the clock hands.

2. Structure and organisation

The circadian system differs in its cellular and molecular organization among species. However, its general structure is very similar and consists of: 1) inputs, i.e. sensors that receive and process the information from the main *zeitgebers* such as light, environmental temperature or food availability; 2) a central pacemaker, which is in charge of keeping the temporal structure of the organism at pace with the inputs, of its integration in useful information and of the transmission of this information to the organism; 3) outputs, which transmit temporal signal transmission from the main clock to every cell of the organism (Fig. 1A). In addition to the central pacemaker, in mammals there are additional oscillators in brain and other organs such as kidney, liver, intestine or adipose tissue, whose function is to sustain the central clock. Some of the outputs present also a synchronizer effect such as scheduled sleep, activity and feeding time [1–3]. These overt rhythms with both components (synchroniser(s) and rhythmic physiological outputs) are known as *zeitnehmer* ("time taker" in German), which is defined as an input pathway that is itself rhythmically regulated by feedback from an oscillator [4].

2.1. Inputs

Living beings appeared and evolved in a cyclic environment with the light-dark cycle as the most important environmental cue and, thus, the organisms used light information as the main *zeitgeber*. However, there are non-photic synchronisers that send information to the main clock in order to maintain the organism synchronisation [5].

In mammals, circadian photoreception occurs mainly by a subgroup of intrinsically photosensitive ganglion cells in the retina (ipRGCs) due to the presence of melanopsin [6,7], which shows a maximum sensitivity *in vivo* from 440 to 480 nanometres [8]. In addition, these ipRGCs receive also information from rods and cones [9,10], integrating different information sources to provide a unique input for the central pacemaker [11–13]. This information is transmitted to the master clock in the hypothalamus by the retinohypothalamic tract [14–16].

Thermocycle is also an important *zeitgeber* to the circadian system, which is capable to entrain cellular cultures *in vitro* [17], core body temperature of mice *in vivo* [18] and ectotherm organisms [19]. In addition, some overt rhythms present also a synchroniser effect such as feeding time, scheduled sleep and activity [4]. Food availability has an important role in the circadian physiology, since digestion, motility, nutrient absorption and mobilisation are organised around the feeding schedule to improve the efficiency of the processes. Regular exercise exerts a synchronising effect on the human circadian system improving physical health and affective disorders [1], while sleep habits are a weak synchroniser probably due to their ability to determine light exposure and to drift melatonin secretion and core body temperature by a fixed schedule [20]. Although social contacts have been considered for a long time as a synchroniser [21], recent reports failed to confirm the existence of this effect [3,22].

2.2. Central pacemaker

The master clock is embedded in specialised neural structures with specific anatomical organisation in different organisms: for example, the optic and cerebral lobes in insects; the eyes in certain invertebrates and vertebrates; the pineal gland in low vertebrates (several fish, amphibians, and reptiles). In mammals, the master clock is located in the suprachiasmatic nucleus of the hypothalamus (SCN), consisting of two small groups of around 20,000 heterogeneous neurons with small somata together with glial cells. Each single suprachiasmatic nucleus consists of two regions in terms of anatomical and physiological differences, the dorsomedial "shell" and the ventrolateral "core" [23–25]. The dorsomedial area has low neuronal density and expresses arginine-vasopressin (AVP) as its main neurotransmitter. The ventrolateral area is highly packed and expresses the vasoactive intestinal polypeptide (VIP) as its main neurotransmitter [24]. The light information from the retina via the retinohypothalamic tract to the SCN is mainly received in the ventrolateral region, where expression of immediate genes is induced by light, synchronising the dorsomedial region. Therefore, it is the place of reception of ventral projections and the origin of projections to other brain nuclei [26]. Thus, ventrolateral area is the responsible for light synchronisation, while output regulation is mediated by dorsomedial area [13,24].

At cellular level, each neuron is able to act as an independent oscillator with a cell-autonomous period, however, the neuronal ensemble is synchronised to produce a common periodicity [27,28]. The nature of the molecular clock residing in each neuron is a series of genetic positive and negative auto regulated transcriptional and translational feedback loops (TTFL), evolutionarily conserved in metazoans [29], showing 24 h rhythms in mRNA and protein levels of key clock components, even in the absence of external rhythmic inputs [30]. The transcription factors BMAL1 and CLOCK (alternatively NPAS2 in the SCN) constitute a heterodimer, which activates the expression of the clock genes *Period*, *Cryptochromes* (*Per* and *Cry*, respectively) *Rev-Erbα* and *Ror*, as well as other clock controlled genes (CCGs, representing approximately a 10% of the complete genome), by binding to E-box enhancement elements [29]. PER and CRY dimerize and inhibit their own expression by translocation into the nucleus, and also acting as repressor of the CLOCK:BMAL1 heterodimer with a delay of several hours [31]. A second regula-