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Yin and Yang: Why did evolution implement and preserve the circadian rhythmicity?

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A B S T R A C T

Yin and Yang concept emphasizes the reciprocal and interrelated nature; neither is sufficient, both are needed to sustain the overall balance of the living system. Changing the balance, by implementing deficiency or excess of one of them, upsets the equilibrium (homeostasis) of the whole system.

Purpose: In this opinion article intermittent exposure is presented as the stimulus for development and evolutionary conservation of circadian rhythm, an endogenous, entrainable oscillation of approximately 24 h, to counteract/balance the cells' natural tendency to attenuate their response during long-term exposure to different endogenous substances.

Results: The concept of Yin and Yang duality is an allegory on which the avoidance of attenuation of the cells' responses hypothesis is presented as an explanation for the circadian rhythmicity, which is integrated in all human cells, with the exception of stem and cancer cells.

Conclusions: We hypothesize, that circadian rhythmicity has evolved, during evolution, into a mechanism that prevents disruption of the organism's negative-feedback-loop homeostasis.

Introduction

Is the circadian rhythmicity/oscillation of the physiological processes observed in living cells/organisms similar to Yin and Yang/nigh day/activity rest cycle? What is the primary purpose of circadian rhythmicity/oscillation in the first place and why was this phenomenon developed in the early organisms and why it persisted during the evolution and is still functioning in cells until today? For example, the circadian rhythms of feeding, sleep, digestion, cardiac function, body temperature, immune system and many other processes have been observed in different organisms and conserved from the common ancestor during evolution [1–3].

The concentration of every substance of the body, e.g. hormone, enzyme, fat, electrolytes, minerals, etc., is maintained in a particular range and many substances have the tendency to slightly oscillate during a 24 h time period. Why do the concentrations of so many compounds in the cells of all organisms oscillate on a circadian level? Is the cell's circadian rhythm in multicellular organisms merely an adaptation to the 24 h Earth's day/night cycle with no fundamental physiological significance or is there another physiological reason, vital for the organism's survival? Did cellular timekeeping systems evolve due to Earth's 24-day/night cycle (daily fluctuations in energy availability) or did cells during the evolution just use/incorporate/adopt/integrate Earth's 24-day/night cycle to use it as oscillator or “clock” to counteract/balance the cells' natural tendency to attenuate their response during long-term exposure to different endogenous substances?

The mechanism which drives the circadian rhythmicity and the internal clock is summarized in Fig. 1. The central clock/master pacemaker is positioned in the hypothalamic suprachiasmatic nucleus (SCN) where it operates as a master pacemaker keeping phase alignment of autonomous cellular clocks [4,5]. It is synchronised by photonic inputs from photosensitive retinal ganglion cells. Information on the day/night cycle is passed on to brain regions and peripheral tissues through endocrine and neural signals [6]. Rhythms of different organs and tissues must be synchronized by the master pacemaker on a daily basis. Although the transcription-translation feedback loop related to the molecular timing mechanism was observed in all of the tested organisms, different »clock« elements and complexes evolved to regulate it [7].

At the individual cellular level, the circadian rhythms are regulated by proteins called »circadian clocks« which are regulated on a transcriptional negative feedback loop between transcriptional activators BMAL1 and CLOCK and repressors PER and CRY. Clock mutants of *Drosophila melanogaster* were first observed by Konopka and Benzer [8] almost half a century ago, when the circadian rhythm family of proteins in flies begun to be understood. Later the suprachiasmatic nucleus was identified as the master time keeper which transmitted the information of “time” to the rest of the body and synchronized cellular clocks

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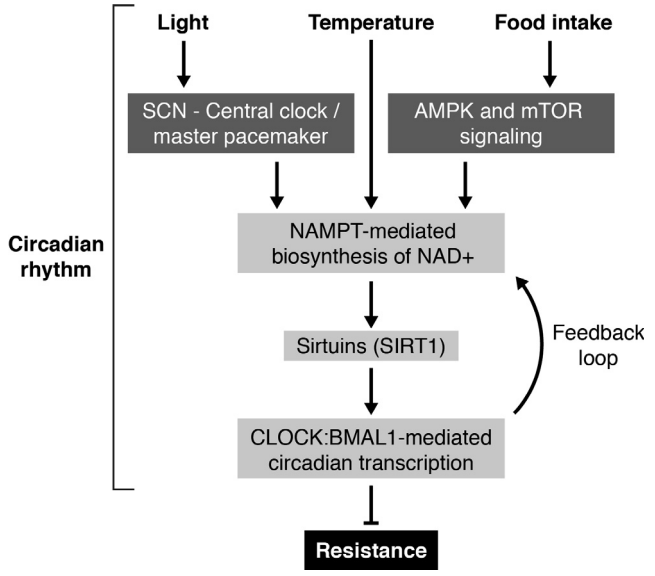

Fig. 1. External environmental cues such as light, temperature and food intake directly or indirectly influence NAMPT-mediated biosynthesis of NAD+. The molecular clock directly regulates transcription of nicotinamide phosphoribosyltransferase (NAMPT). Through oscillating NAD+ concentration, the circadian clock modulates SIRT1 (a class III protein deacetylase) activity and targets several transcription factors associated in conservation of nutrient flux. Homeostatic control mechanisms operate through interconnected, negative feedback loops, to maintain coordination of anabolic and catabolic processes between various tissues in the organism and to prevent the onset of chronic diseases, like diabetes, hypertension and cancer, the risk of which is increased in sleep disorders.

through all peripheral tissues [4,5]. Internal, cell-specific clocks were discovered in 1998 by Balsalobre et al. [4] when it was observed that cells did not need a stimulus from the remote suprachiasmatic nucleus. The exceptions to this rule are stem and cancer cells, which do not have an endogenous circadian time keeper [9]. Cell-specific clocks (peripheral clocks) produce two transcription factors CLOCK and BMAL1 which regulate the daily cellular work by triggering transcription of required genes (e.g. Period (Per) genes), which are regulated by a negative transcription-translation feedback loop. The clock contains four genes/proteins: Clock, BMal1, CRYs (Cryptochrome 1 and 2), and Per 1 and 2 [10]. A histone acetyltransferase, CLOCK, is the core circadian regulator, whose activity is outweighed by the nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylase SIRT1 [11]. BMAL1 and CLOCK stimulate the expression of Per and Cryptochrome (Cry) genes. When PER and CRYs proteins gather to a critical level they make complexes with BMAL1-CLOCK heterodimers, thus repressing the transcription of their own genes [12]. CLOCK:BMAL1 heterodimer balances the circadian expression of the nicotinamide phosphoribosyltransferase (NAMPT). NAMPT mediates a rate-limiting step in the NAD + salvage pathway. Therefore, NAD + displays a circadian rhythmicity as a result of a direct clock transcriptional control of the rate-limiting enzyme in NAD + biosynthesis, NAMPT [13]. NAMPT regulates the cellular metabolism in the circadian oscillation. SIRT1 regulates the duration and amplitude of circadian gene expression by the interaction and deacetylation of BMAL1 and PER2 [14]. SIRT1 is transferred to the Nampt promoter and modulates the circadian-regulated synthesis of its own coenzyme [11].

It is believed that the circadian clocks developed as an adaptation to the 24 h Earth rotation cycle. The leading hypothesis "escape from the light" explains the development of circadian rhythms during early evolution in primitive life forms, such as cyanobacteria (Synechococcus elongates), to enable these organisms to sense daylight and to divide during the night when the UVR damage to their DNA was the least [15–17], with some exceptions reported. For example, in cyanobacterium *Synechococcus elongates* cell division peaks during day time [18]. Namely, the DNA molecule is most susceptible for the effect of mutagenic agents during its division process. Even today, in many mammal tissues, the cellular division peaks at around nighttime [19–22].

Two approaches have been used to explain the evolution of circadian rhythms. The first, emphasizes the "escape from the light induced DNA damage" strategy in living organisms where cellular division is higher during the night than during daytime. The second approach highlights the significance of co-evolution of redox proteins with circadian oscillators succeeding the Great Oxidation Event which happened approximately 2.3 billion years ago [7,23,24]. Both explanations are supported by examples in different life forms. Therefore, different life forms may have evolved their circadian rhythms by preferentially adopting the "escape from the light" strategy or not. What unites both explanations is the central premise that variations in the production of DNA damaging reactive oxygen species (ROS) elicited the development of endogenous, entrainable oscillations in cell metabolic processes, i.e. the circadian rhythms.

Rhythmicity seems to be essential in controlling and harmonizing internal metabolic processes and also coordinating these processes with the daily environmental changes [25]. It has been experimentally observed that circadian clock provides competitive selective advantages [26,27] and afford organisms to anticipate and 'prepare for' environmental changes, with increasing their fitness [28]. For example, circadian timekeeping offers a selective benefit when it promotes anticipation of environmental adjustment in energy supply and oxidative stress [7]. An interplay between the clock and energy metabolism is through expression modulation of redox- and/or temperature-dependent transcription factors (e.g. CLOCK, HSF1), nutrient-sensing transcriptional regulatory proteins (e.g. FOXO-p300, CREB-CBP-CRCT2), nuclear receptors, PGC-1α, NAD + -dependent enzymes, like Sirtuins and poly [ADP-ribose] polymerases and protein kinases (e.g. AMPK) [29,30]. This crosstalk between the two systems seems extensive; about 50% of metabolites oscillate in mouse liver, while knockdown of core clock components altered metabolite cycling in the cell model [31].

Hypothesis

We present an alternative explanation for the etiology of circadian rhythmicity in multicellular organisms – the so-called avoidance of attenuation (loss of effect) hypothesis; circadian rhythmicity prevents the development of cellular attenuation to different hormones, compounds that regulate gene expression and other intracellular vital compounds that form the basis for single cell and whole organism, negative-feedback-loop based homeostasis.

Explanation

It is estimated that the expression of one in ten genes is under circadian control, either as a result of circadian initiation of transcription or through circadian control of post-transcriptional processes [32,33]. In order to explain the hypothesis, examples will be presented where circadian rhythmicity inhibits cell's resistance development, formed by a sustained stimulus.

Nampt gene expression is controlled in a circadian manner and NAMPT protein displays a robust diurnal oscillation pattern [13,34,35], with high values (acrophase) at the start of the dark period [36]. The circadian rhythmicity in the expression of nicotinamide phosphoribosyltransferase which drives the oscillation in NAD^+ levels might prevent the development of resistance. Namely, NAMPT modulates processes associated in the pathogenesis of type 2 diabetes mellitus (T2DM) and obesity by affecting the oxidative stress response, lipid and glucose metabolism, apoptosis, inflammation, and insulin resistance [37]. With advancing age NAMPT activity and consequently

NAD + level decline and NADH level increases [38,39]. Could impaired NAMPT-mediated NAD + biosynthesis observed during human aging [40] be a consequence of impaired circadian rhythm which regulates NAMPT activity [34]? The circadian rhythm, and with it the homeostasis at the single cell and whole-body level, deteriorates with age (change in period, amplitude, and phase); the exact mechanism(s) responsible for the age-related dysregulation have not been completely elucidated yet and might be a consequence of decreased SIRT1 levels in the suprachiasmatic nucleus, as well as decreased levels of BMAL1 and PER2 [41]. By increasing the NAD + levels with genetic or pharmacologic approaches in mature individuals different health-related parameters that promote longevity could be restored (reviewed in) [42].

Many endogenous antioxidant defense systems are oxidized during active/day/feeding period and are reduced back during the night [43]. It was observed in eukaryotes (humans, mice), as well as in bacteria, algae, and archaea that the ratio of oxidized/reduced form of antioxidant protein peroxiredoxin oscillates in a circadian manner [7,43–45]. By examining peroxiredoxins in red blood cells, it was discovered that transcription is not mandatory for circadian oscillations and that non-transcriptional events are enough to preserve cellular circadian rhythms [44].

The circadian rhythms and the pulsatile release were observed also in hormone synthesis, e.g. in prolactin, testosterone, luteinizing hormone, cortisol, catecholamines, melatonin and aldosterone, as well as in ACTH (adrenocortical tropic hormone); ANP (atrial natriuretic peptide); BDNF (brain-derived neurotrophic factor); FSH (follicle-stimulating hormone); GH (growth hormone); LH (luteinizing hormone); NGF (nerve growth factor); TSH (thyroid-stimulating hormone) [46–50].

Since the continuous exposure creates resistance, the dynamic pulsatile nature and circadian rhythmicity of hormone release prevents its development. For example, cortisol is secreted roughly every 60–90 min with the highest amplitude and frequency just prior to awakening [51,52]; the pulse duration of leptin (the hormone that reduces appetite and shows its acrophase during the night) was relatively shorter (32.8 min) [53,54]. Additionally, melatonin (N-acetyl-5-methoxytryptamine) is delivered into circulation in a pulsatile way with the highest peaks in the early morning [55]. Melatonin is synthesized from tryptophan and primarily released by pineal gland, which is controlled by the suprachiasmatic (SCN) clock. The endogenous rhythm of secretion is generated by the SCN nuclei and entrained to the light/dark cycle [56]. Melatonin has a crucial role in regulation of circadian rhythm since it is both a master clock output and an internal time-giver [57]. Melatonin is a strong natural antioxidant and a circadian phase regulatory agent; its signals are used for synchronization of central and peripheral oscillators, as well as for readjustment of circadian rhythms including sleep-wake timing, blood pressure regulation, and seasonal reproduction [58–60]. As humans age, melatonin production decreases [61] disabling the adaptation of the individual to their internal and external environments [62].

Other hormones also display circadian variations of secretion, eg. thyroid-stimulating hormone levels peak in the middle of biological night [63], growth hormone is secreted during deep sleep and peaks immediately after the sleep onset [64,65]. Insulin sensitivity and action vary during the day with minimum secretion during the nigh time. Also, glucose levels display circadian oscillations with peak at the beginning of the active period [66,67]. Leptin levels are highest at night, while ghrelin level increases before meal times in human [68].

While the circadian rhythmicity inhibits the cell's resistance development (e.g. loss of cell's response to different endogenous substances), the constant stimulus (i.e. constant concentration of endogenous substances) promotes it. For example, the circadian pulses of insulin prevent the development of insulin resistance. On the other hand, the situation changes during the constant exposure to insulin due to the circadian misalignment. Indeed, healthy young men developed insulin resistance in response to the constant exposure to insulin at levels normally seen in the human body by insulin infusions (insulin was constantly infused over 96 h) [69]. Similarly, the insulinoma patients develop insulin resistance due to constant exposure, which is reversed when the tumor is surgically removed [70]. Additionally, hepatic insulin sensitivity is regulated via CLOCK/BMAL1-dependent SIRT1 expression. Consequently, the circadian change of insulin sensitivity is impaired in Clock mutant, liver-specific Bmal1 knockout (KO) or Sirt1 KO mice [71]. Perturbation of circadian oscillator components leads to obesity and diabetes [72].

Time-restricted (intermittent) feeding (8 h per day feeding/16 h per day fasting) improved robustness of circadian and metabolic rhythms and prevented obesity, diabetes, and liver diseases in mice on a high-fat diet [72]. Also, resveratrol (3,5,4′-trihydroxystilbene, a potent natural sirtuin activator) extends lifespan in mice when given to animals on a high-fat diet [73] and in combination with standard chow but only when fed every other day (intermitted exposure) [73–75]. Such intermitted exposure seems to be necessary to prevent the development of resistance. Presumably, also other caloric restriction mimetics like astaxanthin, curcumin, catechins, etc., and other ageing preventive compounds might work better if taken intermitted. Future experiments will prove/disprove this assumption.

There are many examples where the body develops resistance/tolerance after persistent exposure to physical agents. For example, it is much easier to get used to continuous and constant (although loud) noise than to the intermitted one. Varying the levels of light intensity can prevent the development of ocular resistance to darkness or bright light. In passing from dark to light, the eye develops adaptation to the light. In passing from light to dark, the body develops adaptation to the dark. Similarly, constant daylight or darkness “dysregulates” the coordinated timing of BMAL1 and SIRT1. Accordingly, BMAL1 and SIRT1 expression diminishes with constant darkness and hepatic insulin resistance is induced. NAMPT is primarily up-regulated at night and its activity is constrained by light or sleep deprivation [13]. NAMPT gene expression is down-regulated also by over-eating and sedentary lifestyle [76]. Thus, the balance between darkness/light as well as the balance between feeding/fasting intervals is needed for appropriate NAMPT expression, as well as for many other gene expressions.

Besides an increased risk of diabetes development, disrupted circadian rhythms might be involved in many pathological processes including accelerated ageing, increased incidence of cardiovascular diseases and cancer. On the other hand, matching the innate circadian period with the environmental photoperiod could be favorable. Actually, mice with innate circadian periods close to 24 h had shorter or longer innate circadian periods and showed approximately 20% longer life spans compared to littermates [77]. In mice, mutations in circadian clock gene BMAL1 have been associated with premature aging [78]. Additionally, in different circadian gene knockout mice accelerated aging and increased incidence of age-related diseases [11] was observed. Three possible ways to disrupt the clock are to change either period, phase, or amplitude [79]; each can trigger disorders of metabolism. In transgenic mice with increased SIRT1 levels in the brain, the intrinsic period is shortened, and the period is elongated in brain-specific SIRT1 knockout mice [41]. Transgenic mice bearing an extra copy of the Sirt1 gene were put on the cholesterol-rich (Western-type) diet and the SIRT1 gain of function resulted in harmful (proatherogenic) effects on lipid metabolism, even though its salutary effects on glucose metabolism [80]. Additionally, mice with constantly increased brain SIRT1 show increased anxiety; variations in the SIRT1 gene resulted with risk of anxiety in human population samples [81,82], too. The circadian rhythm deteriorates with age (change in period, amplitude, and phase) and aged model organisms; dysregulated circadian system (duration and amplitude) is a consequence of decreased SIRT1 levels in the suprachiasmatic nucleus, as well as BMAL1 and PER2 [41]. Similarly, age-related changes in NAD + levels and the melatonin synthesis decline have been reported in different organs and organisms, including

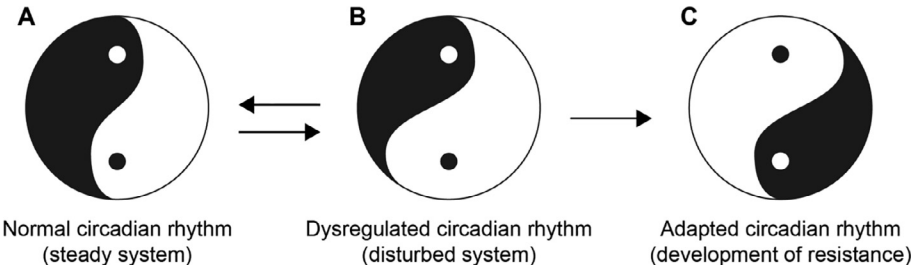

Fig. 2. Yin and Yang disruption.

humans [83,84]. Consistent with experimental results, there is a wide range of health problems related to irregular shift workers and their sleep disturbances and sleep loss. Many epidemiological surveys found a correlation between circadian disruption in humans and in metabolic disorders, in cardiovascular disease and in cancer [85]. Contrary, the sleeping routine i.e., consistent, and constant sleeping pattern without sleep disturbances during the night is a strategy that helps to prevent the disruption of the circadian rhythms.

As nicotinamide mononucleotide (NMN) is the "product" of the NAMPT enzyme (NAMPT converts nicotinamide into a key NAD + intermediate), high levels of NMN may induce a "feedback inhibition effect" on NAMPT, thus inhibiting NAD + formation; similar to nicotinamide "feedback inhibition effect" on SIRTs and PARPs. Nicotinamide phosphoribosyltransferase (NAMPT)-mediated nicotinamide adenine dinucleotide (NAD+) levels are controlled by the circadian clock and might be disrupted by changes in circadian mechanisms or by changes in NAD + metabolism. Although treatment with NAD + precursors nicotinamide mononucleotide (NMN) and nicotinamide riboside (NR) was beneficial and increased longevity in different organisms [86–89] the question arises whether there might be even greater beneficial effect if NMN and NR would be administered in an intermitted way (e.g. on each second day). Namely, the continued supplementation of NMN or NR might suppress the enzyme NAD(P)H dehydrogenase, quinone 1, which regulates the NAD/NADH ratio by oxidizing NADH to generate NAD+ [90]. Thus, each extreme in Yin and Yang imbalance is not beneficial since even too much of "good" is "bad" as shown in Fig. 2.

Conclusion

The Yin and Yang (i.e. *organism's* homeostasis) is the tendency of a physiological system to follow and preserve a condition of equilibrium within its internal environment. A constant stimulus, a constant concentration exposure of the organism to a particular compound, produces attenuation or loss of the organism's response. We hypothesize, that circadian rhythmicity has evolved, during evolution, into a mechanism that prevents disruption of the organism's negative-feedback-loop homeostasis (Fig. 1). BMAL1, CLOCK, and SIRT1 "turn on" and "turn off" daily 15% of the genome in human cells, thus their synchronization and intermittent activity is vital for normal organism function [11,12,71]. In this opinion article we highlight the physiological significance of circadian rhythms, that prevent the attenuation or loss of response of cells to different endogenous compounds, by cycling the levels of endogenous substances to which the cells are exposed. Disruption of the circadian and other biological rhythms affects multiple interacting feedback loops, which operate to sustain the organism's homeostasis (Fig. 1). The cycling between low and high levels of endogenous substances sustains homeostasis at the whole body, organ, and cellular level. Our hypothesis is supported by research reports of many authors, who describe how disruption of the homeostasis (Yin and Yang) of circadian rhythms and other biological (e.g. antioxidant and drug resistance) systems precipitates the attenuation or loss of organism's response with detrimental effects at the whole body, organ, or cellular level.

Declaration of Competing Interest

None.

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