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Aging-Related Circadian Disruption and Its Correction

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ABSTRACT

A gradual loss of synchrony between the factors modulating amplitude and phase of overt rhythms (physiological, biochemical processes, behavioral responses, etc.) occurs with age. These factors are of both central and peripheral origin and include molecular/genetic, tissue/organ and systemic links. The most typical manifestations are dampened amplitude and unstable phases of the circadian rhythms. Thereby aging per se leads to the circadian disruption and the loss of robustness in the circadian system. Dysfunction of the circadian system, in turn, accelerates the process of aging, initiating a vicious circle that affects health, fitness and causes sleep disturbances. Herein we discuss in brief the possible mechanisms and consequences of age-dependent circadian disruption, but also the ways to counteract such consequences: melatonin supplementation at night, bright blue light at daytime, optimal physical activity, maintenance of social contacts and regular feeding schedules.

INTRODUCTION

Increasing opportunities for unobtrusive monitoring of the clinically meaningful variables in regular, 24 h/7d life broaden boundaries for applying chronobiological approach into clinical medicine. Altered variability or compromised circadian rhythm parameters constitute alert signals that in nearby future should lay the groundwork for the personalized medicine with prevention and chronotherapy focused on an individual person.

Pleiotropic consequences of phase and amplitude disturbances in circadian expression of genome-transcriptome-proteome elements inevitably imply in desynchronized phenotypic functions. Causal factors include epigenetic, posttranscriptional and post-translational mechanisms of core clock and clock-controlled gene expression [1,2]. Age-dependent circadian disruption is an outcome of gradually misbalanced molecular, genetic, tissue, and systemic factors of the circadian system. These morphological and functional changes of the central oscillator and the cells of the peripheral tissues are heterochronic and sequential order of the particular derangements may dependent on individual gene polymorphism [3-6]. Feeding schedule [7,8], activity level [9] and photoperiodic environment [10,11] are also crucial. More specifically – on phenotypic level, aging is characterized by comprehensive changes in dynamics of physiological range and clinically meaningful functions (blood pressure, heart rate, body temperature, etc).

In general, dynamics of the physiological functions become more irregular due to the aging process. When single diurnal patterns are considered, the decrease in the amplitude and earlier peak time (phase advancement) are the most typical features. When data from longitudinal several-day long time series are considered, most common pattern is an Extra-Circadian Dissemination ECD [6,11-13]. ECD is an absolute or relative to overall variability reduction of the circadian amplitude, accompanied by the loss of its phase stability and an increase in variability in adjacent frequency domains (ultradian, $\tau<20$h; or infradian, $\tau>28$ h). Diminished day-to-day circadian phase stability are found in some individuals relatively early (already in the middle age of ~ 40-59 years). Phase scattering can be followed by a relative increase in distinct harmonics of infradian domain [11,14-15]. Vice versa, high amplitude robust circadian rhythms of numerous metabolic processes and temperature have been linked with both young, reproductive age and longevity but regularly is compromised s with age [16-20].

However, numerous recent studies suggested promising strategies to prevent and counteract aging-related circadian disruption. Herein we provide brief descriptions and outline the perspectives of these approaches.

PUTATIVE MECHANISMS OF AGE-DEPENDENT CIRCADIAN DISRUPTION

Following the multi oscillator model of the circadian system coordination, interplay of the several factors determines age-dependent circadian disruption:

1. Reduced amplitude of neuronal firing output from the central oscillator, suprachiastmatic nucleus **(SCN)**;
2. Compromised synchronization between the principal external zeitgeber, the light-dark cycle, and SCN;
3. Impaired signal transmission from the SCN to the peripheral oscillators;
4. Faded pacemaker function in the peripheral oscillators;
5. Reduced sensitivity of the peripheral organs to non-photoperiodic time cues;
6. Disabled circadian rhythms production in peripheral tissues/organs due to internal physiological causes;
7. Weakened internal synchronization between peripheral tissues and organs; and
8. Alteration of the feedback between the tissues and the central oscillator.

In a simplified model, the causes of age-related circadian rhythms disorders affect the afferent pathways to the SCN (the retina; the nerve pathways leading to SCN), the SCN themselves, and efferents from the SCN to the receptors of peripheral cells, tissues and organs.

FACTORS OF EXTERNAL DE-SYNCHRONIZATION

Reception of incoming entraining signals / synchronizing environmental periodicities deteriorates in the aging individuals. Main causes are pupillary miosis (constriction) and reduced transmission of light due to lens yellowing [21,22].

Another factor is inadequate lighting conditions that became typical for the modern human societies. It includes inappropriate timing of light exposure, exposure to light of sub-optimal wavelengths and its insufficient intensity [21]. Lack of exposure to daytime blue light and a sedentary life style that are typical for the elderly people might further worsen the ability to maintain due phasing of the circadian rhythms and thus contribute to its instability.

In addition, the number of photoreceptors, especially photosensitive retinal ganglion cells **(pRGCs)** decreases with age [23,24]. Finally, impaired sensitivity of the SCN itself may affect photic synchronization. Indeed, photic phase responses are diminished despite a normal photoreception and c-fos expression [25], supposing that processing of light information within the SCN is compromised.

SUPRACHIASMATIC NUCLEUS (SCN) WITH AGING

Weakened rhythms generated by individual neurons, decreased number of fully functional neurons and an altered coupling between them are the main causes of faded output signaling from the SCN that also make it less stable. Recent studies [26,27] reported a profound 25% decrease in the circadian amplitude of the multineuronal oscillations, caused mainly by the lower daytime activity of neurons in old animals. In younger age, daytime oscillatory activity of

neurons predominates and the number of active neurons has a Gaussian distribution near the time of maximum activity. Such synchrony attenuates due to the aging process. Gradual loss of synchrony of interneuron interactions in the SCN appeared to be a principal factor for the circadian deterioration in mammal's master brain clock. Though core clock genes functioning in the aged SCN is largely preserved [28,29], the number of neurotransmitters producing neurons **(AVP,VIP)** that are involved in circadian rhythm maintenance also decreases with age [20,30].

PERIPHERAL FACTORS

Faded efferent signaling from the master clock and un sustained melatonin production rhythm [31,32] are principle but not exclusive causes for misalignment of due timing in the vast network of physiologic processes at the periphery. Besides feasible alterations in core clock gene and clock-controlled gene expression pathways [rev. in 2,5,6,13], phase discordance among circadian rhythms of acting substrates, its receptors and substrate converting enzymes are putative rationale for intrinsic causes of circadian disruption at the cell level. Age-dependent peripheral causes include rhythm generation and rate of resynchronization after a zeitgeber shift.

Age-dependent involution of circadian rhythms in different peripheral organs and tissues is not simultaneous and affects both primary and secondary clock loop genes and clock-controlled genes. For example, circadian expression of the core clock gene Per1 is significantly phase advanced or even absent, though only in the distinct tissues [29]. Aging as well has tissue-dependent effects on Bmal1 expression, the amplitude / phase relations between Clock and Bmal1 expression in different brain areas, alters Cry1 mRNA expression in adipose tissue [2,5,6,13]. Gene polymorphism may determine individual patterns of the decline in the rate of re-entrainment in peripheral tissues that is accompanied by increased response lability in the SCN neurons [33]. However, as a result of such enhanced excitability, the amplitude of circadian rhythm oscillations in the SCN dampens. Elimination of the leading entraining factor (light/ dark signaling) may cause tissue-specific adjusting of the phase of a rhythm towards the secondary zeitgebers [34].

Younger individuals usually exhibit higher plasticity of circadian rhythm parameters that enables faster re-synchronization and re-adaptation to abrupt phase shifts; i.e. circadian rhythms are restored faster in young and adult rats that were given a single dose of 40% ethanol than in old rats that were given the same treatment [16]. Circadian activity rhythm disturbed by light regimen inversion is also restored faster in juvenile mice than in adult animals [35], in contrast to the slower recovery of this circadian rhythm in juvenile animals after alcohol administration.

OVERT RHYTHMS WITH AGE

Cardiovascular dynamics is possibly the best studied among overt rhythmic functions. Without applying a chronobiologic approach, though, it is rather difficult to discern specific cardiovascular risk factors in the subjects over 70 years of age [36,37], whereas there are numerous variability disorders and anomalies that take place and can be found only with continuous several-day monitoring [11].

Nonlinear analysis of cardiovascular functions variability that is routinely performed on databases of ambulatory blood pressure monitoring records usually reveals rhythms with different frequencies. The relative output of the distinct amplitudes and changes in phase stability under different physiologic conditions throughout ontogeny may help discriminate between health and certain diseases.

A phase shift or an abrupt change in the circadian amplitude of one or more coordinated functions may lead to the emergence of internal desynchronization of overt variables that are actually monitored. The initial signs of the reduced circadian phase stability are followed by the relative increase in the infradian oscillations and in some individuals are detected as early as after 40 years of age [11,12]. To reveal such changes, however, continuous monitoring for the several days is required. Output of ultradian rhythms to the overall variability significantly increases at the age over 60 years. A decrease in the circadian amplitude per se occurs even later; and is evident only in some elderly persons and involves only certain physiologic functions. The amplitude of the rhythms in the infradian frequency range ($\tau > 28$ hours) further increases in the seniors, and the entrainment of the rhythm by the secondary zeitgebers such as space, geomagnetic, and social factors is possible in some domains [14,15]. This is particularly plausible, since the effect of the main synchronizing factor—photoperiodism—weakens. Amplification of the infradian phenotypic rhythms may also be the result of modulation of the rhythmic factors with τ that are not exactly 24 hours [12]. In a number of our studies, we revealed the emergence of some previously less pronounced rhythms later in the ontogenesis. A significant increase in the amplitude of the circaseptan (near-weekly) and circasemiseptan (near-half-weekly) systolic blood pressure component was found in individuals over the age of 80 [14,15]. Amplitude increase of the circaseptan rhythm in the elderly was also found in the melatonin production [38].

AGE-DEPENDENT FREQUENCY TRANSFORMATION: EXTRA-CIRCADIAN DISSEMINATION (ECD)

Age-dependent trends in the mean values of the different physiologic functions are well defined. For example, blood pressure tends to increase with age [14,15], whereas body temperature tends to decrease [39]. However, such changes are not equally distributed throughout 24-hour scale and within distinct spectral frequencies. Knowledge of nighttime values are often most important for due control of the functions that is the case for the blood pressure [40]. Another interesting feature is the change of the variability spectrum. The typical attribute of aging is a variance transposition: decline of the circadian amplitudes and rise of the amplitudes of the adjacent ultradian and infradian (i.e. "extracircadian") frequencies. We defined this consistent pattern as ECD (for Extra-Circadian Dissemination) [11-13]. ECD was further classified into 4 types in terms of modifications in the (a) overall variability, gauged by standard deviation of the mean **(SD),** and in the (b) circadian and (c) pooled extracircadian variability, gauged by the amplitudes of the respective spectral harmonics. These 4 types are: I. True hypervariable ECD: upward trends in certain frequencies of ultradian and infradian variability prevailing over downward trends in

circadian amplitude, leading to an increase in overall variability with age (described for systolic BP, pulse BP and vascular resistance); II. True euvariable ECD: upward trends in ultradian and infradian variability are counterbalanced by proportional downward trends in the circadian amplitude, resulting in no significant trend with age in overall variability (diastolic BP, mean BP, cardiac output); III. True hypovariable ECD: downward trend in the circadian amplitude prevails over upward trends in ultradian and infradian variability, leading to a decrease in overall variability with age (body temperature); IV. Relative ECD: downward trends in all frequency domains are found, predominantly in the circadian amplitude and PR, leading to a drastic decrease with age in overall variability (heart rate, blood flow).

Signs of circadian disruption in variability / ECD manifestations of overt physiological, i.e. cardiovascular functions can also be even more pronounced in individuals over 50 years of age, engaged in regular roundabouts to Far North / Artcic regions and back to their home cities [11,41,42]. One of the most typical manifestations of the age-dependent frequency transformation is an increase of the amplitude ratio of 12-hour rhythm for 24-hour rhythm.

CIRCADIAN DISRUPTION IN ALZHEIMER'S DISEASE

According to the recent research, manifestation of the circadian disruption and sleep disorders are the early signs of Alzheimer's disease that precede cognitive dysfunction [43,44]. Moreover, circadian disruption is likely an actual pathogenic factor that aggravates cognitive impairment in Alzheimer's disease patients [45]. Animal experiments demonstrated that SCN modulates circadian rhythms, cognitive functions and memory, whereas the loss of the circadian rhythms in SCN entails complex cognitive disorders [46].

5-year prospective epidemiological study [47] found that the decrease in the amplitude and robustness of the circadian rhythm of activity and its phase delay is an independent predictor of the development of cognitive impairment and dementia. The 1.6 increase in risk of dementia associates with the reduced amplitude and robustness of the circadian rhythm of activity and 1.8 increase associates with the phase delay. Fragmented night sleep is also closely associates with 1.5-increase risk of dementia over the next 6 years [48], partly due to the aggravated influence of apolipoprotein E4 on the formation of Aß and Tau protein [49]. Monitoring of the activity rhythm and sleep characteristics in conjunction with positron emission tomography revealed correlation between the increase in the frequency of daytime sleeping time, decreased quality of nighttime sleep and the presence of Aß deposits among persons of mature age without the presence of cognitive impairment [50].

Furthermore, in patients with Alzheimer's disease signs of circadian disruption are even more prominent than in the elderly individuals without Alzheimer's disease [44,51,52]. Intrinsic phase misalignment among core clock genes in brain regions (including SCN and pineal gland) of Alzheimer's disease patients have been repeatedly validated [53-55]. Impaired phase relationship between expression of Bmal1 and Per2 seems to be the principle finding. A recent

study, performed on a mouse model of Alzheimer's disease [56], provides a possible mechanism for clock gene damage by beta-amyloid protein, Aß. This study showed that Aß could cause the destruction of two key factors of cellular biological clock: BMAL1 protein and factor of perception of light signals, CREB with consequent impairment of the production of the PER2 protein.

CORRECTION

Melatonin Supplementation

Melatonin is the best-studied substance with natural chronobiotic properties that is capable to ameliorate typical manifestations of circadian misbalance and ageing – related diseases [13,39,57,58]. For instance, melatonin reduces blood pressure [57-60]; compensates insufficient nocturnal decline of heart rate [11,57,61], provides a gentler morning rise of heart rate [57]. A pronounced nighttime blood pressure reduction by a low dose of melatonin taken for only 2 weeks [57] can be due to age-dependent deficits of melatonin. Another important issue is dependence of blood pressure reduction on initial values of blood pressure: the more blood pressure is before melatonin administration – the more it drops after 2 weeks of melatonin treatment. It is likely that melatonin can gain more power in circumstances when its natural production is compromised.

Furthermore, specific effects of exogenous melatonin may critically depend on time. In part, due to the circadian rhythm of MT receptors density, in part due to the circadian rhythms of the intracellular mechanisms involved in melatonin post-translational actions on biological clock in peripheral cells [reviewed in 2]. Notably, circadian dynamics of MT2 receptors concentration in SCN and melatonin plasma concentration may generate feedback loop with each other: pretreatment with melatonin causes decrease of MT2 receptors in a time and concentration-dependent manner [62]. As melatonin desensitizes endogenous MT2 melatonin receptors, it prompts an assumption that individuals with relatively low endogenous melatonin production would benefit more from low doses of exogenous melatonin. Moreover, desensitization caused by exposure to concentrations of exogenous melatonin equal to physiological is reversible and it takes 8 hours for full recovery, while exposure to the doses higher than physiological may cause desensitization that still not recovers after more than 24 hours. These data counsels a rationale why high doses of exogenous melatonin may be less effective or even deleterious while low doses – more effective.

MT2 receptor gene polymorphism, particularly SNP rs10830963, associates with the increased risk of impaired fasting glucose and diabetes mellitus [63,64] and higher systolic blood pressure in hypertensive patients [65]. On the other hand, lower mean and nocturnal melatonin levels associate with higher nocturnal systolic blood pressure and diabetes [66]; "non-dipper" blood pressure profiles, caused by elevated nocturnal blood pressure – inversely correlate with urinary melatonin excretion [67]. Also melatonin was effective in combating metabolic dysfunction in obese patients, improving lipid profile [68,69]. More pronounced effects of melatonin in the elderly seem to be due to deficit in its production. However, melatonin is not necessarily lowers

with age. In some seniors, high nocturnal melatonin values are preserved. We suppose that those with deficit will benefit most, and low, physiological, doses can be more effective than higher, pharmacological due to the discussed above reasons.

Bright Light Therapy

Aging is often accompanied by the reduction in exposure to environmental blue light at daytime and compromised photoreception [13]. As above mentioned, reduced exposure to daytime bright light and decreased sensitivity of receptors of the circadian system to bright light are among the causes of the disrupted circadian rhythms in the aged population. Thus, likewise exogenous melatonin renders numerous positive effects during nocturnal phase – the more effectively – the more it is lacking; bright light therapy exerts beneficial effects on circadian rhythms and sleep quality via compensating deficits of its circadian effects during daylight phase.

However, optimal timing, duration, and intensity of bright light therapy for the treatment of the age-related circadian disruption are not well established yet [70]. Timing, number of sessions, light intensity (amount of lx) that will yield an optimal result in terms of the correction of sleep disorders and manifestations of the circadian disruption vary considerably between aged individuals. The efficiency of bright light therapy depends on correct diagnosis of the major disorder that underlies the onset of circadian disruption, as well as on the mechanisms that underlie sleep disorders and individual chronotype features [71].

Chronodietology and Chrononutrition

Another one promising approach is due timed nutrition. Food intake is an important secondary synchronizer of the circadian system [72]. Chronodietology, focused on controlling circadian rhythms of metabolic processes, is another promising strategy for the prevention of the circadian disruption [73].

Certain gene polymorphism may predispose a kind of “natural born healthy constitution” in terms of food intake regimen. α MUPA mice that spontaneously consume 20-30% less calories than wild type mice are long-lived and exhibit high-amplitude circadian rhythms in the expression of number of clock genes in the liver. It coincides with higher amplitude rhythms of food intake and body temperature of these mice [74]. α MUPA mice also enjoy healthier cardiac system and slower cardiac aging due to increased ischemic tolerance mediated through circadian coordination of endogenous leptin metabolism [75]. Calorie restriction per se can modulate expression of circadian core clock genes, i.e. BMAL1 affecting their mRNA and protein levels via transcriptional and post-transcriptional mechanisms [8]. Targeted use of specific nutrients based on individual chronotype has the potential for immense clinical utility in the future. Certain nutrients may act as zeitgebers regulating clock genes and clock-controlled genes at different tissues and organs. Such circadian clock control by distinct nutrients can as well be tissue-specific. Optimization of the nutritional regimens for treatment of metabolic disorders and counterbalance age-related circadian disruption should be incorporated into strategy of personalized medicine in the recent future [76].

Regular Physical Activity

To keep circadian rhythms robust and tuned-up, secondary, synergistic zeitgebers are as well crucial. Besides the already mentioned feeding regimens, regular activity schedule, timed exercise and maintained social contacts may as well be beneficial. Interestingly, aged people sometimes do this rather intuitively, by adopting a regular lifestyle [77]. Individuals who follow and keep established daily schedule enjoy reduced incidence of insomnia [78, 79].

Regular physically activity upholds feedback coupling with the central brain clock and helps to preserve synchronized circadian rhythms [80]. In rodents, voluntary access to a running wheel can attenuate some age-related changes in the circadian system, helps to keep high-amplitude circadian rhythms in peripheral tissues and SCN and reduce time required for resynchronization after inducing experimental jet lag [81,82].

Body Temperature Rhythm Maintenance

Another important agenda is preservation of the robust temperature rhythm that is considered the "third signaling pathway" in the circadian control of sleep, in addition to the synaptic and neurohormonal pathways. It helps to modulate the activity of neurons and serves as an internal zeitgeber, providing synchronization of the peripheral circadian rhythms [83]. Furthermore, sensitivity of tissues to temperature fluctuations increases when impairment of interactions between SCN neurons is present [84]. Thus, the significance of the robust temperature circadian rhythm for the maintenance of harmony of other rhythms increases with age.

We have shown that most typical age-dependent changes such as diminished rhythm stability and synchronization with the 24 h regimen can be partially ameliorated with low dose exogenous melatonin taken by night [39]. A single daily melatonin dose stabilized and synchronized the body temperature rhythm via hypothermic and sleep-improving effects. Melatonin improved not only body temperature circadian rhythm but also cardiovascular (blood pressure and heart rate) rhythms; partly attenuated intrinsic phase misalignment between these variables and reduced nocturnal and morning blood pressure [57].

CONCLUDING REMARKS

De-coordinated temporal sequence of the physiological processes entails untimely events at multiple levels of life; triggering a vicious circle of disturbances and progressive disharmony in functioning of the circadian system [85]. The prevention and correction of the disturbances of circadian coordination of physiologic processes can be undertaken using at least several different strategies:

(1) Chronobiotics (i.e. melatonin) that help to maintain circadian rhythms, including that of the secondary synchronizers (i.e. body temperature and hormone levels); (2) Bright light therapy; (3) A due timed nutrition; (4) Maintaining social contacts; (5) Optimal and regular physical activity; (6) Keeping scheduled sleep–wake regimen.

Optimization of these strategies is in incorporation of the personalized approach. Further progress should rely on development of argumentation for choosing optimal timing or time windows in consent with individual chronotype, region of residence, and gender-related aspects. Correction of concomitant chronic diseases that underlie aging-related circadian disruption, i.e. Alzheimer disease and type 2 diabetes mellitus should imply personalized chrono therapeutic approaches as well (Figure 1).

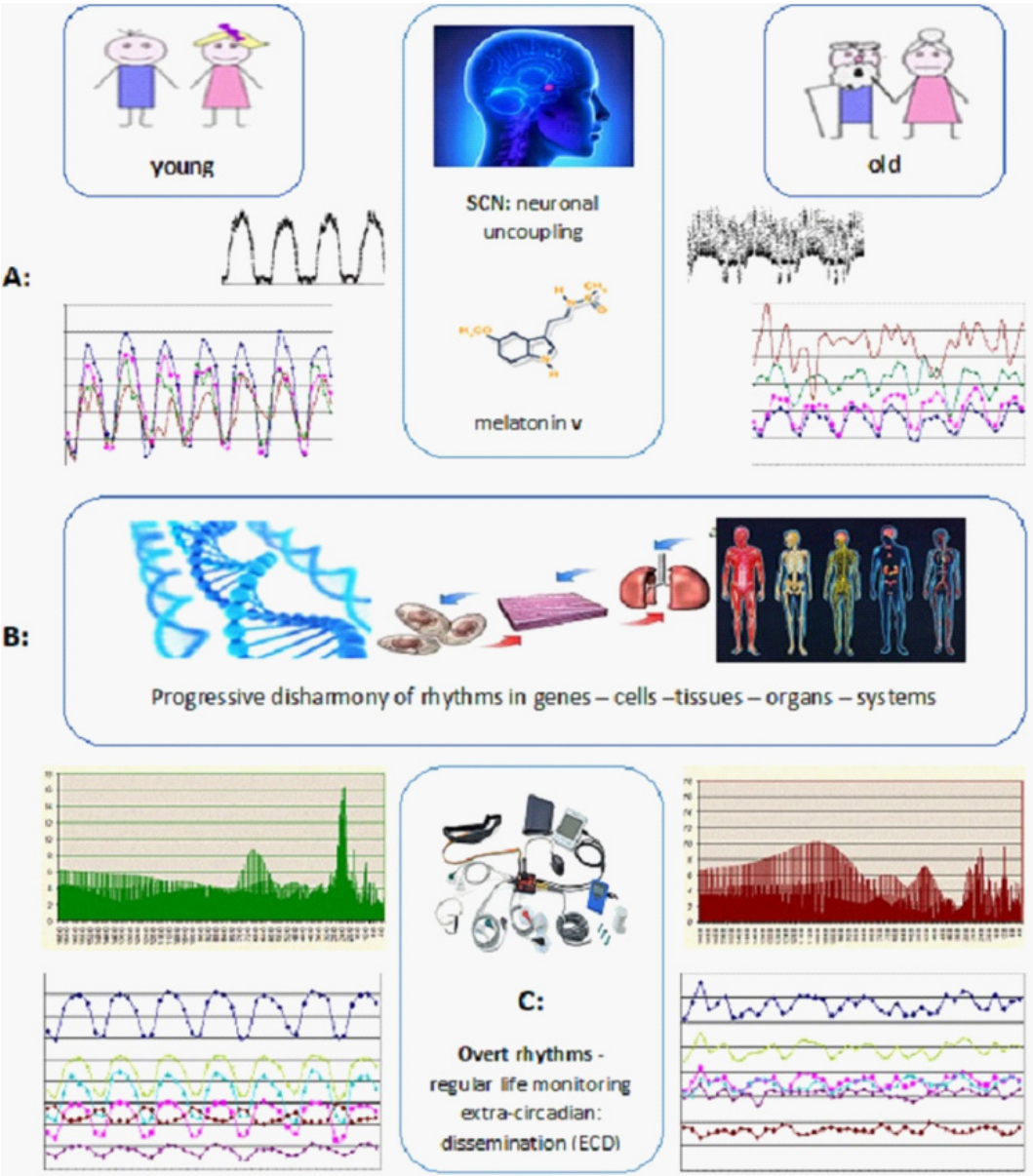

Figure 1: The putative causes, mechanisms and manifestations of age-related circadian disruption.

A: Central factors / afferent link: compromised synchrony among neurons of the master clock in SCN and decline of nocturnal melatonin production causes fading of downstream entraining signaling.

B: Deterioration of the circadian rhythmicity at peripheral cells – a consequence of a gradual loss of the synchrony at molecular/genetic, tissue/organ and systemic levels due to both intrinsic and extrinsic (faded downstream central signaling/ efferent link) factors.

C: Extra-circadian dissemination of overall variability, dampened circadian amplitudes and unstable phases are manifestations of irregular dynamics of the physiologic functions (overt circadian rhythms) with age.

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