Journal of Applied Biomedicine
1: 77–84, 2003
ISSN 1214-0287

Why do circadian biorhythms age?

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Summary
Circadian biorhythms change with age and such changes are caused by the loss of both the time and the space structure. These alterations of biorhythms are associated with poor health and the end of life but we do not know the extent to which they represent cell clock system injury. It seems that ageing of biorhythms in mammals, i.e. including humans, is caused by the ability of suprachiasmatic nuclei to drive oscillations in other tissues. Social synchronization extending photic stimuli, which diminishes during degeneration of nerve and optic system, enhances the quality of life and therefore further studies of the influence of health and social care systems on circadian rhythms could contribute to the lengthening of life.

Key words: ageing – rhythm – regulation – synchronizer – quality of life

INTRODUCTION

Living systems have both a space and a time structure. The time structure is formed by the interactions between transient stages during development, and biorhythms. Biorhythms are regular incident phenomena in living organisms (chronobiology). Biorhythms can affect sensitivity to drugs (chronopharmacology, chronotoxicology), symptoms of various diseases (chronopathology) and many other interactions between an organism and its environment.

To measure biorhythms, we can use the equation $Y(t) = M + A \cos(\omega t + \Phi)$, where M is mesor, A is amplitude, ω is angle rate, t is time and Φ is the point of fiixed rhythm maximum, the so-called acrophase. This equation is frequently used, but real biorhythms are more or less irregular.

Biorhythms with a period of 22 to 26 hrs are called circadian (circa=about, dian=day), those with a period shorter than 22 hrs are ultradian, and those with a period longer than 26 hrs are infradian. Circannual rhythms have a period of 10–14 months. Circadian rhythms are an evolutionary adaptation to day/night alternations, that is, an adaptation to the environmental changes caused by the Earth‘s rotation. As circadian rhythms are frequently the object of study, we have concentrated on them in this article.

Ageing is a continuous process which starts at birth. The progressive decrease in physiological capacity and the reduced ability to respond to environmental stresses lead to increased susceptibility and vulnerability to diseases (see Troen 2003). Ageing is a multifold process involving many genes and many metabolic pathways.

Among a number of hypotheses, the theory of oxidative stress seems to be popular (cf. Miquel 2002, Hofhaus et al. 2003): radical oxygen species, which are by-products of oxidative phosphorylation in mitochondria, damage intracellular biopolymers including mtDNA; and damaged molecules of mtDNA can accumulate within cells. Since oxygen is both necessary for living cells and a source of free radicals, ageing is an unavoidable characteristic of living systems.

Telomeres, the non-coding sequences at the end of chromosomes, in the absence of telomerase shorten with each cell division and the percentage of short telomeres increases with age in many tissues except brain tissue (cf. Rensing et al. 2001, Cherif 2003). Telomere shortening in human beings contributes to mortality in many age-related diseases. Replicative senescence of cultured Werner syndrome fibroblasts is a telomere-induced event (Davis et al. 2003). Earlier ageing after telomere shortening, which is caused by an infection burden, could lead to the ageing of immune cells and

decreased immune surveillance and this predisposes to cancer (Sastry and Parikh 2003). The rate of telomere shortening can be modulated by oxidative stress (Saretzki and von Zglinicki 2002).

In human subjects and mammals, ageing may be the process which supports the prevention of malignant reversion and therefore paradoxically makes it possible to achieve maximal lifespan. Ageing can be influenced by many environmental factors, e.g. important nutritional factors (see Miquel 2002). The pioneer work of Pittendrigh and Minis (1972) discovered, that biorhythms could also influence lifespan: the lifespan of Drosophilas decreases when these insects are subjected to a 21- or a 27-h day instead a 24-h day (with light/dark cycle 12/12 h).

CIRCADIAN RHYTHMS IN HUMAN SUBJECTS AND THE ENVIRONMENT

As human physiology and behaviour can be modified by biorhythms, we can ask which environmental stimuli can influence our rhythms and benefit our health. It was thought for many years that social events are the most important synchronizers of human biorhythms. More recent findings have documented that the most important synchronizer of human circadian rhythms (i.e. rhythms with a period of about 24 hrs) is light, although there are many questions about this mechanism still to be answered (see Usui 2000).

Photons are absorbed by retina photopigments and neural signals are generated in the retinohypothalamic tract. Photic stimuli are projected into the mammalian suprachiasmatic nucleus of the hypothalamus (cf. Ibata et al. 1999). Surgical destruction of suprachiasmatic nuclei aborts many circadian rhythms in mammals (cf. Meyer-Bernstein et al. 1999). This nucleus regulates the synthesis of the melatonin, a hormone produced by the pineal gland; photic stimuli suppress melatonin synthesis (Brainard et al.1997). The endogenous rhythm of melatonin synchronizes light/dark regime dependent circadian rhythms (Illnerova and Sumova1997, Shanahan et al.1997).

Although the causes are different, totally blind people and night shift workers have in common recurrent bouts of insomnia and wake-time sleepiness that cause asynchrony of sleep and wake times with their endogenous circadian rhythms. Exogenous melatonin given at the optimal circadian time can synchronize several biorhythms (Sack and Lewy 1997).

Thus, both a good light regime and intensity are necessary for human health including adaptation to night work and subsequent recovery (Bougrine et al. 1995). Morning bright light is a powerful synchronizer, it also reduces the frequency of behaviour disorders in elderly men with dementia (Mishuma et al. 1994). Nevertheless, non-photic stimuli play their role in the synchronization of rhythms, too (cf. Mrosovsky 1996).

SENESCENCE IN PHYSIOLOGICAL RHYTHMS

Biorhythms change during ontogenesis; they can be modified in both children and the elderly. Older individuals have higher scores for their activity in the morning than young men (Atkinson et al. 1992). A growing number of published papers indicate that one of the important changes in both older men and animals is the loss of function of the circadian clock. In this part of our article, we concentrate on a discussion of the general features of "old" rhythms and age-related changes in wake-rest activity that can be a prognostic factor of life span in older human subjects.

An increased tendency to low amplitude, loose internal synchronization and poor response to external environmental time queues are documented for many characteristics of both human subjects and animals (Richardson et al. 1982, Brock 1991, Vansomeren et al. 1993, Atkinson et al. 1994, Garciapatterson et al. 1996, Forsling 1998, Driver 2000, Weinert 2000, Van Someren et al. 2002). A shortened period of circadian rhythms was observed sometimes in old laboratory animals and elderly humans (Witting et al. 1994, Deuschle 1997, Weinert 2000).

Although the tendency to alteration of the circadian rhythm, mentioned above, has been documented in many publications, several physiological rhythms change in the elderly in different ways. For example, the mesor of circulating neutrophils is higher in old men than in young men with unchanged amplitude (Swoyer et al. 1989). As neutrophils play a critical role in the inflammation process, which is more frequent in the elderly, such observations seem to be logical in the framework of physiological regulations. Circadian variations in many other haematological characteristics are also evident (cf. Berger 1987) and these rhythms originate in both the circadian rhythm of physiological needs (Sletvold et al. 1988) and in blood cell production. Although the mechanism of many age-related changes in the circadian rhythm of haemopietic and blood cell numbers remains unknown, it seems that these variations are of a physiologic rather than a genetic origin.

Sleep disruption is common in the elderly and it has been suggested that these age-related alterations

could reflect fundamental changes in the circadian system (cf. Billiard 1993). Various types of sleep disorders are associated with ageing (irregular sleep-wake rhythms, insomnia etc.) and affect the elderly. Sleep disturbance is associated with impaired quality of waking life and it is a risk factor for institutionalization and mortality (cf. Pollak et al. 1992, Mishima et al. 1994).

Less distinction between day and night with unwanted sleeps during the day and unwanted wakefulness in the night was shown when comparing old with young people. (cf. Monk et al. 1991). The loss of the circadian system in the central nervous system results in impaired timing and quality of sleep with consequent behaviour problems (Driver 2000).

Interactions between the circadian system and sleep timing and consolidation, which are very important for the process of ageing, are altered in the elderly (Duffy and Czeisler 2002). Nevertheless, circadian periods of the melatonin, core body temperature, and cortisol are essentially identical in young and elderly subjects (Czeisler et al. 1999). There are some significant changes in humans older than 50 years (cf. Lunenfeld 2002), and other significant changes were documented for men older than 65 years (e.g. Blanker et. al. 2002).

The susceptibility to photic and nonphotic cues is decreased, and the number of functioning neurons in the suprachiasmatic nucleus is also lowered with advancing age (Weinert 2000). Photic stimuli can be also slightly eliminated by the degeneration of the optic system in senescence (cf. Hinton et al. 1986). But also, several rhythms do not change during senescence, for example circadian rhythms in erythropoietin serum levels were found unchanged in elder healthy peoples (Pasqualetti and Casale 1997).

The role of gender in the age-dependent changes of rhythms seems to be important. In evaluating temperature rhythm, which is relatively stable (Weitzman and Kripke 1981), it was found that elderly women have significantly higher amplitude (0.23 ^{o}C) than older men (0.17 ^{o}C) (Czeisler et al. 1992); the amplitude in young men is higher (0.28 ^{o}C) than the amplitude in older men, also. The objective sleep quality of women is better than that of men (Reynolds et al. 1991). However, a lower amplitude of circadian rhythms seems to be a good marker of poorer tolerance to the stress of night work (Reinberg at al. 1984). Older men (more than 50) poorly resynchronize their biorhythms following long distance flight involving a change of time zone (Gander et al. 1993).

We can summarize by saying that biorhythms in the elderly change simultaneously with degeneration of the part of the nervous system which synchronizes peripheral oscillators and such changes are individually specific.

REGULATION OF BIORHYTHMS AND AGEING

It has been shown that there are several intracellular molecules which are important in both the ageing process and biorhythms notwithstanding our incomplete knowledge of ageing mechanisms.

Melatonin, an antioxidant and a hormone of the pineal gland, is (i) the synchronizer of many circadian rhythms and seasonal adaptations, (ii) a free-radical scavenger, (iii) an endogenous sleep-inducer, and (iv) an anti-ageing agent (Olde Rikert and Rigaud 2001, Pandi-Perumal et al. 2002). Melatonin also influences reproduction, carcinogenesis and ageing (cf. Edmunds Jr 1994, Blask et al. 2002, Bubenik 2002, Mayo et al. 2002, Winczyk et al. 2002, Collins et al. 2003). Melatonin production can decline with age (Garciapatterson et al. 1996. Terron et al. 2002) but this phenomenon seems to be very individual for different human subjects (Zeitzer et al. 1999). The higher age is also associated with a shift in the acrophase (Sharma et al. 1989, Thomas and Miles 1989). Exogenous melatonin can prevent some undesirable ageing effects (Lunenfeld 2002). A decline in the superoxide anion, among others in relation to oxidative metabolism, was observed simultaneously with the increase in phagocytic function (Terron et al. 2002), and an increase in IgG_1 and IgM responses (Akbulut et al. 2001). There is evidence of the therapeutic effects of melatonin, but further clinical trials are necessary as the mechanisms of melatonin effects remain to be determined.

Nitric oxide seems to be also involved in the regulatory events of the circadian rhythm. Its release from the hyxpothalamus and anterior pituitary gland is apparently induced by leptins (Mastronardi et al. 2002). This is very interestig as leptins are produced by adipocytes, the number and size of which are influenced by age (Rozman et al. 1989) and nutrition (cf. Vidal-Puig et al. 1997).

Nucleolar size in neurons is related to the circadian rhythms (Pébusque et al. 1981) as well as in human lymphocyte (Berger and Berger 2002). Age-dependent changes in nucleoli (Dayan 2002) reflect metabolic activity in cells. Thus, the alternations in nucleoli rhythms can be a marker of senescence, but the regulation of rRNA synthesis does not seem to be the primary source of biorhythm alterations.

As the characteristics of suprachismatic nuclei alter in the aged (both humans and animals) and because this structure is a pacemaker of many

circadian oscillations, such age-related changes could be the source of biorhythm ageing in mammals including human subjects. Histological and anatomical changes were reported in old animals and men (Hofman et al. 1988, 1996, Woods et al. 1993, Zhou and Swaab 1999), electrical activity of suprachiasmatic nucleus neurons taken from old animals have a lower amplitude(cf. Aujard et al. 2001), and suprachismatic nuclei transplants from young animals restore circadian behavioral rhythms in aged animals (Hurd et al. 1995, Cai et al. 1997, Ki and Satinoff 1998).

Clock genes are expressed in cells of suprachiasmatic nuclei and also many peripheral tissues. The mammalian circadian clock has a central pacemaker in suprachiasmatic nuclei which coordinates tissue - specific rhythms according to light input (Reppert and Weaver 2002). Products of the clock gene fall with age (Driver 2000). Circadian rhythms in mRNAs of per1, per2 and rCry1 are similar in several tissues of young and old organisms but expression of Per1 and Per2 in the suprachiasmatic nucleus, which is induced by photic stimuli, is reduced with ageing; these and similar findings suggest that the molecular mechanisms of regulation of circadian rhythms are not altered by aging (Asai et al. 2001). The only difference documented for in vitro cultivated suprachiasmatic nucleus cells from an old laboratory rat was shortening of the free-running period as compared with those from young animals; circadian oscillations in some peripheral tissues were unaffected by ageing (Yamazaki et al. 2002).

Based on this observation, the genetic basis of circadian clocks seems to be unaffected by the process of ageing; the loss of biorhythms is on the cellular level. Pharmacological intervention is efficient when the exogenous substance (e.g. melatonin) is a substitute for a lower level of synthetic activity of old cells.

Table 1. **Circadian rhythms during the human life**

Age (years)	Number of circadian cycles
10	3652
50	18262
60	21915
70	25567
80	29220
90	32872
100	36500

BIORHYTHMS IN THE ELDERLY AND QUALITY OF LIFE

The source of age-dependent changes of biorhythms can be the consequence of age-dependent impairment of light stimuli perception including diminution of retina cells and neurons in the suprachiasmatic nucleus but experiments on the effects of nursing mothers on young animals have reported that non-photic stimuli on rPer circadian expression in suprachiasmatic nuclei (Ohta et al. 2002) could play a role. Could non-photic stimuli substitute photic-stimuli and, therefore, improve the quality of life of older humans?

The organism of a 80-year man has passed through 29 thousand circadian cycles (Table 1) and, therefore, we can expect certain changes in this system and cannot be surprised at findings which tell us that poorly developed circadian rhythms are often associated with poor health (Watershouse and Minors 1996). As various published data demonstrate individual differences in age-related changes, circadian rhythms may be dependent on the

quality of life of the investigated persons who are near the end of their life.

We can expect that the quality of biorhythms is a prognostic factor of years remaining as the loss of temporal structure in elderly is associated with a poor health state and decreased longevity and it is characterized by a decrease in circadian amplitude (Duffy and Feuers 1991). Increased circadian amplitude, which has been induced by food stimuli in experimental animals, is connected to prolonged healthful life span (Nelson and Halberg 1986, Nelson 1988). Similarly, the pharmacological effect of estrogen therapy in postmenopausal women leads to higher amplitude in certain biorhythms and enhance longevity but the mechanism of such effects is not known (Gudmundsson et al. 1999).

Although the process of ageing is a necessary characteristic of human life, we might view as slightly optimistic the findings of Mormount and Watershouse (2002), that the rest-activity circadian rhythm is independent of sex or that the type of primary tumour in cancer patients is independent of age. The quality of these circadian rhythms is positively correlated with physical, emotional and social functioning. Thus, we conclude that further studies on the health and social care systems, could benefit human healthy longevity.

Received 26th February 2003.
Published online 19th March 2003.

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