Man In India, 97 (26) : 1-10

DESYNCHRONIZATION IN THE CONDITIONS OF THE NORTH AS PROFESSIONAL RISK FACTORS OF WORKERS OF THE MECHANICAL ENGINEERING, OIL AND GAS INDUSTRY

Alla G. Naymushina[*], Denis G. Gubin[**], Svetlana V. Solovieva[**], Alexei M. Durov[**] and Olga A. Dragich[***]

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. Major factors of risk of development of diseases is the climate of the North. Development desynchronization defines premature aging the person. 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

Age-dependent circadian disruption is an outcome of gradually misbalanced molecular, genetic, tissue, and systemic factors of the circadian system. Major factors-risk development diseases workers of technical specialties are bound to working conditions in the extreme climatic conditions the North. Development desynchronization defines premature aging the person. Signs of circadian disruption in variability/ECD manifestations of overt physiological, i.e. cardiovascular functions can also be even more pronounced in elder people, engaged in regular roundabouts to Far North/Artcic regions and back to their home cities [1, 2, 3, 15, 16].

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 [4,5]. Feeding schedule [6], activity level [7] and photoperiodic environment are also crucial. More specifically, aging is characterized by comprehensive changes in dynamics of physiological range and clinically meaningful functions (blood pressure, heart rate, body temperature, etc) in particular.

[*] *Corresponding author*, Department of Physical Education, Tyumen Industrial University, Volodarsky Str., 38, 625000 Tyumen. *Email: alla.naimuschina@yandex.ru*

[**] Department of Biology, Tyumen State Medical University, Tyumen, Russia

[***] Department of Physical Education, Tyumen Industrial University, Tyumen, Russia

PUTATIVE MECHANISMS OF AGE-DEPENDENT CIRCADIAN DISRUPTION: CENTRAL CAUSES

Following the multioscillator model of the circadian system coordination, interplay of the several factors determine 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 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. Impairment of the feedback between the tissues and the central oscillator.

In a simplified model, the causes of age-related circadian rhythms disorders may affect the afferent pathways to the SCN (the retina; the nerve pathways leading to SCN), the SCN themselves, or efferents from the SCN to the receptors of peripheral cells, tissues and organs. 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 make also make it less stable. Recent studies [8,9] 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 is fading with age. 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.

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 [10].

Another factor is to inappropriate 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 insufficient intensity. 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 [11,12]. 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 [13], supposing that processing of light information within the SCN is compromised.

SUPRACHIASMATIC NUCLEUS (SCN) WITH AGING PERIPHERAL FACTORS

Faded efferent signaling from master clock and unsustained melatonin production rhythm 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, 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 involution of circadian rhythms in different peripheral organs and tissues is not simultaneous. 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 [14].

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. 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. The initial signs of the reduced circadian phase stability can be accompanied by the relative increase in the infradian oscillations and are detected as early as after 40 years of age. To reveal such changes continuous monitoring for several days is required. Output of ultradian rhythms to 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. One of the most typical manifestation of the age-dependent frequency transformation is an increase of the amplitude ratio of 12-hour rhythm for 24-hour rhythm. The amplitude of the rhythms in the infradian frequency range ($\tau >$ 28 hours) further increases, and the entrainment of the rhythm by the secondary zeitgebers such as space, geomagnetic, and social factors is possible in some domains. 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 24 hours [15]. 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 circasemiseptan SBP component with T = 84 h was found in individuals over the age of 80 [16].

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

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. Continuous ambulatory monitoring of the physiologic functions in the different age groups helps to discover how its variability is changing during the lifetime. Age-dependent trends in the mean values of the different physiologic functions are well defined. For example, blood pressure tends to increase with age, whereas body temperature tends to decrease [15,16]. 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 [17]. 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) [15, 16]. 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).

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 [18,19]. Moreover, circadian disruption is regarded as the actual pathogenetic factor that aggravates cognitive impairment in Alzheimer's disease patients [20]. 5-year prospective epidemiological study [21] 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. 1.6 times increase in risk of dementia was associate with the reduced amplitude and robustness of the circadian rhythm of activity; and 1.8 increase was associated with the phase delay. Fragmented night sleep is also closely associated with 1.5 increasing risk of dementia over the next 6 years, partly due to the aggravated influence of apolipoprotein E4 on the formation of Aβ and Tau protein [22]. 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 Aβ deposits among persons of mature age without the presence of cognitive impairment [23].

Furthermore, in patients with Alzheimer's disease signs of circadian disruption are even more prominent [24,25]. Intrinsic phase misalignment among core clock genes in brain regions (including SCN and pineal gland) of Alzheimer's disease patients have been repeatedly validated [26,27]. Impaired phase relationship between expression of Bmal1 and Per2 seem to be the principle finding. A recent study, performed on a mouse model of Alzheimer's disease [28], provides a possible mechanism for clock gene damage by beta-amyloid protein, Aβ. This study showed that Aβ 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

1. **Melatonin Supplementation:** Melatonin is the best studied substance with natural chronobiotic properties that is capable to ameliorate typical manifestations of circadian misbalance and age – related diseases [29]. For instance, melatonin reduces blood pressure insufficient nocturnal decline of heart rate, provides a gentler morning rise of heart rate. A pronounced nighttime blood pressure reduction by a low dose of melatonin taken for only 2 weeks in our study can be due to age-dependent deficits of melatonin. Another important issue was dependence of blood pressure reduction on initial values of blood pressure: the more blood pressure was before melatonin administration – the more it dropped by the end of the study [16].

It is likely that melatonin can gain more power in circumstances when its natural production is compromised.

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.

2. **Bright Light Therapy:** Aging is often accompanied by reduction in exposure to environmental blue light at daytime and compromised photoreception [16]. Reduced exposure to daytime bright light and decreased sensitivity of receptors of the circadian system to bright light may be among the causes of 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 as yet [30]. 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 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 [31].

3. **Chronodietology and Chrononutrition:** Another one promising approach is due timed nutrition. Food intake indeed is an important secondary synchronizer of the circadian system [32]. Chronodietology is focused on controlling circadian rhythms of metabolic processes and appeared to be relevant for the prevention of circadian disruption [33].

   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. [34].

4. **Regular Physical Activity:** To keep circadian rhythms robust and tuned-up secondary, synergistic zeitgebers can employed as well. Besides the already mentioned scheduled feeding and regimens, regular activity schedule, timed exercise and mainteained social contacts may be beneficial. Interestingly, aged people sometimes do this rather intuitively, by adopting a regular lifestyle. Individuals who keep established regular daily schedule enjoy reduced incidence of insominia [35,36].

   Regular physically activity upholds feedback back coupling with the central brain clock and helps to preserve synchronized circadian rhythms [37].

5. **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 peripheral circadian rhythms [38]. Thus, the significance of the 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. 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 all investigated variables and reduced nocturnal and morning blood pressure [16].

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. 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, including that used to fight seasonal affective disorders;
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.

References

Gubin D.G., Vetoshkin A.S., Bolotnova T.V., Danilova L.A. et. al., (2016). Arctic shift-workers blood pressure and heart rate circadian rhythms and variability depending on morningness/eveningness chronotype score//Medical science and education of Ural. 2015. N 2-1 (82). P. 108-113.

Soloviev VS, Naimushina AG, Solovieva SV (2013). Stratification of risk factors of stress induced conditions of Tyumen residents//Tyumen State University Herald. № 6. C. 79-85. http://elibrary.ru/item.asp?id=20182497.

Naimushina AG (2011). Stratification of risk factors stress-induced of conditions//Medical science and education of Ural. N 1. P. 69-71. http://elibrary.ru/item.asp?id=22783689.

Yu E, Weaver DR (2011). Disrupting the circadian clock: Gene-specific effects on aging, cancer and other phenotypes. Aging 3: 479–493 http://www.ncbi.nlm.nih.gov/pubmed/21566258.

Libert S, Bonkowski MS, Pointer K, Pletcher SD, Guarente L (2012). Deviation of innate circadian period from 24 h reduces longevity in mice. Aging Cell 11: 794–800 http://www.ncbi.nlm.nih.gov/pubmed/22702406.

Patel S, Velingkaar N, Makwana K, Chaudhari A, Kondratov R. (2016). Calorie restriction regulates circadian clock gene expression through BMAL1 dependent and independent mechanisms. Scientific Reports 6:25970 doi:10.1038/srep25970 http://www.ncbi.nlm.nih.gov/pubmed/27170536.

Leise TL, Harrington ME, Molyneux PC, Song I, Queenan H et. al., (2013). Voluntary exercise can strengthen the circadian system in aged mice. Age (Dordr) 35(6) :2137-52. doi: 10.1007/s11357-012-9502-y. Epub 2013 Jan 23. http://www.ncbi.nlm.nih.gov/pubmed/23340916.

Nakamura TJ, Nakamura W, Yamazaki S, Kudo T, Cutler T (2011). Age-related decline in circadian output. J Neurosci 2011 31(28): 10201-5. http://www.ncbi.nlm.nih.gov/pubmed/21752996.

Farajnia S., Michel S, Deboer T, vanderLeest HT, Houben T et. al., (2012). Evidence for neuronal desynchrony in the aged suprachiasmatic nucleus clock. J. Neurosci. 32: 5891–5899. http://www.ncbi.nlm.nih.gov/pubmed/22539850.

Kessel L, Lundeman JH, Herbst K, Andersen TV, Larsen M. (2010). Age-related changes in the transmission properties of the human lens and their relevance to circadian entrainment. J Cataract Refract Surg. 36(2): 308-12 http://www.ncbi.nlm.nih.gov/pubmed/20152615.

La Morgia C, Ross-Cisneros FN, Sadun AA, Hannibal J, Munarini A, et. al., (2010). Melanopsin retinal ganglion cells are resistant to neurodegeneration in mitochondrial optic neuropathies. Brain. 133(Pt 8): 2426-38. http://www.ncbi.nlm.nih.gov/pubmed/20659957.

Lupi D, Semo M, Foster RG. (2012). Impact of age and retinal degeneration on the light input to circadian brain structures. Neurobiol Aging. 33(2): 383-92. http://www.ncbi.nlm.nih.gov/pubmed/20409612.

Schöttner K, Vuillez P, Challet E, Pévet P, Weinert D. (2015). Light-induced c-Fos expression in the SCN and behavioural phase shifts of Djungarian hamsters with a delayed activity onset. Chronobiol Int. 32(5):596-607. doi: 10.3109/07420528.2015.1018422. Epub 2015 May 4. http://www.ncbi.nlm.nih.gov/pubmed/25938796.

Sellix MT, Evans JA, Leise TL, Castanon-Cervantes O, Hill DD et. al., (2012). Aging differentially affects the re-entrainment response of central and peripheral circadian oscillators. J. Neurosci. 32(46): 16193–16202 http://www.ncbi.nlm.nih.gov/pubmed/23152603.

Agadzhanian NA, Gubin DG (2004). [Desynchronization: mechanisms of development from molecular to systemic levels]. Uspekhi fiziologicheskikh nauk 35 (2): 57-72 http://www.ncbi.nlm.nih.gov/pubmed/15174296.

Aging-related circadian disruption and its correction (2016). Gubin D., Bolotnova T., Solovieva S., Naymushina A., Platitsyna N., Okonechnikova N., Kuimova J., Pustovit E.Dover, DE, USA, 2016. Treatment Options for Aging. http://elibrary.ru/item.asp?id=26790063.

Hermida RC, Ayala DE, Mojon A, Fernandez JR. (2010). Influence of circadian time of hypertension treatment on cardiovascular risk: results of the MAPEC study. Chronobiol Int. 27(1): 629-651 http://www.ncbi.nlm.nih.gov/pubmed/20854139.

Bedrosian TA, Nelson RJ (2012). Pro: Alzheimer's disease and circadian dysfunction: chicken or egg? Alzheimer's Research & Therapy. 4(4): 25. doi: 10.1186/alzrt128. eCollection 2012. http://www.ncbi.nlm.nih.gov/pubmed/22883711.

Musiek ES, Xiong DD, Holtzman DM (2015). Sleep, circadian rhythms, and the pathogenesis of Alzheimer Disease. Experimental & Molecular Medicine 47(3):e148-. doi:10.1038/emm.2014.121 http://www.ncbi.nlm.nih.gov/pubmed/25766617.

Krishnan HC, Lyons LC. (2015). Synchrony and desynchrony in circadian clocks: impacts on learning and memory. Learn Mem. 22(9): 426-37. doi: 10.1101/lm.038877.115. Print 2015 Sep. http://www.ncbi.nlm.nih.gov/pubmed/26286653.

Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, et. al., (2011). Circadian activity rhythms and risk of incident dementia and MCI in older women. Annals of neurology. 70 (5): 722-732. doi:10.1002/ana.22468. http://www.ncbi.nlm.nih.gov/pubmed/22162057.

Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. (2013). Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. Sleep. 36:1027–1032 http://www.ncbi.nlm.nih.gov/pubmed/23814339.

Ju YE, McLeland JS, Toedebusch CD, Xiong C, Fagan AM, et. al., (2013). Sleep quality and preclinical Alzheimer disease. JAMA Neurol. 70:587–593. http://www.ncbi.nlm.nih.gov/pubmed/23479184.

Slats D, Claassen JA, Verbeek MM, Overeem S. (2013). Reciprocal interactions between sleep, circadian rhythms and Alzheimer's disease: focus on the role of hypocretin and melatonin. Ageing Res Rev. 12(1):188-200 http://www.ncbi.nlm.nih.gov/pubmed/22575905.

Coogan AN, Schutova B, Husung S, Furczyk K, Baune BT et. al., (2013). The Circadian System in Alzheimer's Disease: Disturbances, Mechanisms, and Opportunities. Biol. Psychiatry. 2013. 74(5): 333–339. http://www.ncbi.nlm.nih.gov/pubmed/23273723.

Wu YH, Fischer DF, Kalsbeek A, Garidou-Boof ML, van der Vliet J et. al., (2006). Pineal clock gene oscillation is disturbed in Alzheimer's disease, due to functional disconnection from the "master clock". Faseb J. 20(11): 1874–6. http://www.ncbi.nlm.nih.gov/pubmed/16818472.

Cermakian N, Lamont EW, Boudreau P, Boivin DB (2011). Circadian clock gene expression in brain regions of Alzheimer ‘s disease patients and control subjects//J. Biol. Rhythms. 2011 26: 160–170 http://www.ncbi.nlm.nih.gov/pubmed/21454296.

Song H, Moon M, Choe HK, Han DH, Jang C. et. al., (2015). Aβ-induced degradation of BMAL1 and CBP leads to circadian rhythm disruption in Alzheimer’s disease. Molecular Neurodegeneration 10:13 DOI: 10.1186/s13024-015-0007-x http://www.ncbi.nlm.nih.gov/pubmed/25888034.

Cardinali DP, Hardeland R. (2016). Inflammaging, Metabolic Syndrome and Melatonin: A Call for Treatment Studies. Neuroendocrinology. May 11. [Epub ahead of print]. http://www.ncbi.nlm.nih.gov/pubmed/27165273.

Campos Costa I, Nogueira Carvalho H, and Fernandes L. (2013). Aging, circadian rhythms, and depressive disorders: a review. Am. J. Neurodegener. Dis. 2(4):228–246. http://www.ncbi.nlm.nih.gov/pubmed/24319642.

Münch M, Linhart F, Borisuit A, Jaeggi SM, Scartezzini JL. (2012). Effects of prior light exposure on early evening performance, subjective sleepiness, and hormonal secretion. Behav. Neurosci. 126(1): 196–203. http://www.ncbi.nlm.nih.gov/pubmed/22201280.

Kent B.A. (2014). Synchronizing an aging brain: can entraining circadian clocks by food slow Alzheimer’s disease? Front Aging Neurosci. 6(234): doi 10.3389/fnagi.2014.00234 http://www.ncbi.nlm.nih.gov/pubmed/25225484.

Albrecht U. (2012). Timing to perfection: the biology of central and peripheral circadian clocks. Neuron 74(2): 246–260. http://www.ncbi.nlm.nih.gov/pubmed/22542179.

Ribas-Latre A, Eckel-Mahan K. (2016). Interdependence of nutrient metabolism and the circadian clock system: Importance for metabolic health. Molecular Metabolism. 5(3):133-152. doi:10.1016/j.molmet.2015.12.006. http://www.ncbi.nlm.nih.gov/pubmed/26977390.

Zisberg A, Gur-Yaish N, Shochat T. (2010). Contribution of routine to sleep quality in community elderly. Sleep. 33(4): 509-14. http://www.ncbi.nlm.nih.gov/pubmed/20394320.

Moss TG, Carney CE, Haynes P, Harris al., (2015). Is daily routine important for sleep? An Investigation of social rhythms in a clinical insomnia population. Chronobiol Int. 32(1): 92-102 http://www.ncbi.nlm.nih.gov/pubmed/25187987.

Weinert D, Waterhouse J. (2007). The circadian rhythm of core temperature: Effects of physical activity and aging. Physiol Behav. 90: 246-56. http://www.ncbi.nlm.nih.gov/pubmed/17069866.

Weinert D. (2005). The temporal order of mammals. Evidence for multiple central and peripheral control mechanisms and for endogenous and exogenous components: some implications for research on aging. Biol. Rhythm Res. 36(4): 293–308. http://www.tandfonline.com/doi/abs/10.1080/09291010500079759?journalCode=nbrr20.