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Shift Work and Clinical Applications of Time-Restricted Eating

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Abstract

Circadian rhythms refer to the oscillations of biological systems in synchrony with the 24-hour light/dark (LD) cycles of the earth. Mammalian circadian rhythms are coordinated by an array of endogenous "clocks" entrained by environmental inputs (zeitgebers), such as sunlight, locomotion, and food intake. Physiological states including energy balance, sleep-wake cycles, body temperature, and hormonal homeostasis, are all tightly regulated by endogenous circadian clocks. The primary controller of circadian rhythms is located centrally in the Suprachiasmatic Nuclei (SCN) of the hypothalamus, which is directly entrained by UV light signals coming from the sun. Peripheral circadian rhythms are directly modulated by behaviors such as locomotion and feeding behavior. A lack of coordination between the LD cycles of earth and behavioral activity results in systemic perturbations, ultimately resulting in metabolic dysfunction. This lack of coordination is likely responsible for the elevated prevalence of metabolic syndrome observed in night-shift workers, due to the misalignment of their activity patterns with the LD cycles of earth. The common trend of night-shift workers adopting a schedule of 3 days on, 4 days off followed by 4 days on, 3 days off may be the biggest driver of their increased risk of developing metabolic dysfunction. By constantly rotating between a nocturnal and diurnal sleeping pattern, their central and peripheral clocks fall into a state of perpetual arrhythmicity. While this type of schedule is provided to maintain social normalcy for the individual, it is detrimental to the functional rhythmicity of their circadian clocks. For this reason, night-shift workers may enact a time-restricted eating protocol in which food intake is restricted to a limited window of time every day. While disruption of the central circadian clock in the SCN is inevitable due to nighttime blue light exposure in these workers, maintaining a highly consistent feeding pattern may attenuate in part the negative consequences of such exposure by restoring rhythmicity in peripheral clocks. This type of feeding strategy may also be exploited by non-night shift workers, as the ubiquity of technology inevitably results in chronic blue light exposure during the intended dark phase of many humans in modern society. In doing so, circadian rhythmicity of key metabolic factors may be restored, thereby optimizing metabolic health and limiting the risk of developing chronic disease.

Keywords: Suprachiasmatic Nuclei (SCN); Food Intake; Time Restricted Eating

Introduction

The circadian rhythm refers to the cycling of biological processes in living organisms in response to environmental cues. While biological rhythms occur on various timescales, circadian rhythms occur on roughly 24-hour rhythms in synchrony with earth's light/dark (LD) cycle. Our physiology has adapted in such a way that processes of locomotion, metabolism, and feeding behavior are tightly coupled to the LD cycles of earth. Mammalian circadian rhythms are coordinated by an array endogenous "clocks" present in virtually all cells of the body. Physiological processes regulated by circadian rhythms include energy balance, metabolism, sleep-wake cycles, body temperature (Tb), and hormonal homeostasis.

The primary input of control for circadian rhythms comes from UV light signals emitted by the sun, which are relayed to the suprachiasmatic nuclei (SCN) in the hypothalamus. The SCN receives and processes light inputs from the external environment, thereafter relaying outputs to proximal central and distal peripheral clocks [1]. While central clocks are present only in the SCN of the hypothalamus, peripheral clocks azre ubiquitous across virtually every mammalian cell external to the brain. The molecular mechanism for both central and peripheral clocks involves positive and negative feedback loops of transcriptional elements. Clock-controlled gene (CCG) products display rhythmicity in their expression and functional activity over a roughly 24-hour period [2]. Disruption of primary clock genes critical to the function of positive and negative feedback loops can induce various disease phenotypes [3,4].

External to light-induced central regulation of circadian rhythms, locomotor activity (LA), food intake, & food availability all act as powerful *zeitgebers,* or entrainers, of peripheral circadian rhythms. Light signals have the capacity to alter the transcriptional activity of central clocks directly, thereafter influencing peripheral clocks indirectly, but the behavioral patterns of the organism alone drives direct entrainment of peripheral clocks [5-7]. A lack of coordination between central and peripheral clocks consequently results in, amongst other physiological perturbations, metabolic dysfunction. This review will focus on how shift work induces disruption of biological circadian rhythms, thereby driving metabolic syndrome. Additionally, it will explore the capacity of time-restricted eating (TRE) in restoring aberrant circadian rhythms and recovering the metabolic dysfunction phenotype commonly observed in shift workers and models of circadian disruption. By establishing mechanisms of circadian rhythm disruption and identifying possible behavioral modifications to restore it, clinicians may recommend proper lifestyle modifications to shift work patients struggling with metabolic disease.

Molecular Mechanisms Driving the Circadian Clock

The mammalian circadian clock utilizes an autoregulatory feedback loop at the transcriptional level to exert its biological influence. Two sets of core clock genes exist: one of transcriptional activators, the other of repressors. The positive component of the transcriptional feedback loop includes transcription factors (TFs) *CLOCK* and *BMAL1*, while the negative component includes the Periods (*PER1 & PER2)* and Cryptochromes (*CRY1 & CRY2*). Belonging to the basic helix-loop-helix (bHLH) family of TFs, CLOCK and BMAL1 modulate the transcription of CCGs primarily through the CLOCK-BMAL1 heterodimer (Figure 1). This heterodimer binds to regulatory E-box elements in upstream promoter regions of CCGs, of which the primary binding targets are a set of rhythmically active genes encoding a set of PER & CRY repressor TFs. Mice studies have revealed CLOCK-BMAL1 transcriptional activation occurs during the inactive phase, leading to an accumulation of PER and CRY proteins. The PER-CRY heterodimer translocates to the nucleus during the active phase, interacting with promoter regions of CLOCK and BMAL1 genes to repress their own transcription. With a short nuclear half-life of PER and CRY proteins, the negative feedback component is attenuated upon turnover of the PER-CRY transcriptional repressor complex. This allows for a new circadian cycle of CLOCK-BMAL1 transcription to renew during the next inactive phase [8].

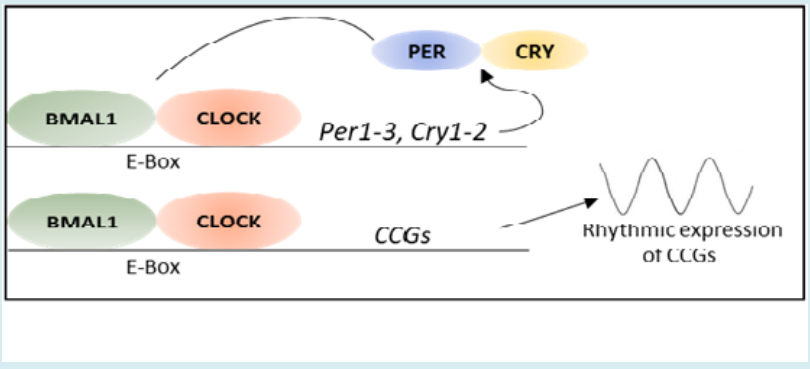

Figure 1: Basic Molecular Feedback Loop of Mammalian Circadian Clock [9].

The positive feedback loop is regulated primarily by the CLOCK-BMAL1 heterodimer binding to E-box elements of PER, CRY, & other Clock-Controlled Genes (CCGs). The negative feedback loop is regulated primarily by the PER-CRY heterodimer thereafter repressing transcription of CLOCK and BMAL. Proteolytic degradation of the PER and CRY

transcription factors ensures a rhythmic cycling of circadian clock genes.

Shift Work and Metabolic Disease

In line with the rhythms of the earth's rotation, the biological rhythms of humans are intended to align optimal physiological function with environmental inputs. Like many species on this planet, *homo sapiens* are diurnal; we are intened to be active during the day and inactive at night. Despite this, many occupations in modern society require night-shift work such as nurses, doctors, construction workers, and law enforcement. Shift work is commonly defined as work performed outside of standard daytime working hours, 7 a.m. to 6 p.m., Monday through Friday. The prevalence of shift workers across certain industries such as manufacturing has been reported to be as high as 25%, with increasing prevalence in both Europe and the U.S [10]. Many of these professions are vital to a functioning society, but the individuals performing them are required to regularly work and maintain activity during our biologically intended rest period. The uncoupling between physiological diurnal rhythms and behavioral patterns can produce metabolic complications. Shiftwork has been associated with an increased risk of a plethora of chronic diseases including obesity, diabetes, cardiovascular disease, and even cancer [11-13]. Recent literature has shown a significantly increased prevalence of overweight and obesity status in shift workers compared to day workers. These shift workers have additionally demonstrated a tendency to gain weight at a faster rate than daytime workers [14,15]. Esquirol, et al. [16] revealed that rotating shift work has a direct impact on every component of metabolic syndrome, including hypertension, fatty liver disease, cardiovascular disease, type 2 diabetes mellitus, hyperlipidemia, cancer, and even dementia.

Night-shift healthcare workers in particular have the greatest risk of developing metabolic syndrome over other forms of shift work [17]. Night-shift workers typically perform work in a cycle of 3 days on, 4 days off (*3/4*) for one week followed by 4 days on, 3 days off (*4/3*) the following week. This schedule provides social normalcy for the shift worker while allowing for them to work the minimum required hours, but also places their circadian clocks into an unabating state of arrhythmicity. Disrupted central and peripheral circadian rhythms may be a driving force behind the increased prevalence of metabolic syndrome in this population.

Shift Work and Circadian Rhythm Disruption

Central and peripheral circadian rhythms may become dissociated when there is a lack of synchrony between UV light exposure and activity patterns. Nighttime activity ensures circadian rhythm disruption from multiple directions. First, light signals are the primary *zeitgebers* for the central circadian clocks located in the SCN [18]. Shift work ensures that light inputs will be uncoupled from the intended 12:12 LD cycles of the earth as artificial blue light relays signals to the SCN, providing light inputs during an expected dark phase. Second, the behavioral patterns of these individuals do not match up to the expected activity patterns of a 12:12 LD cycle. Activity during a time of day when sleep is expected [according to light cycles] provides an opportunity for activity- and nutrient-induced modulation of peripheral circadian clocks. Timing cues derived from LA and nutrient intake act as *zeitgebers* on peripheral clocks in key metabolic tissues such as the liver, heart, muscles, and kidneys. These *zeitgebers* act on peripheral tissues to entrain them to a given feeding schedule; metabolic complications may arise when our behavioral patterns do not match up with the entrained pattern of our endogenous clocks. While fuel utilization mechanisms involving substrate mobilization and oxidation are upregulated in the morning, fuel storage mechanisms involving adipogenesis and energy deposition are upregulated in the evening. Rodent studies have revealed diurnal variations in expression of key lipogenesis genes Fatty acid transport protein 1 (*Fatp1*), adipocyte differentiation-related protein (*Adrp)*, and fatty acyl-CoA synthetase 1 (*Acs1*). Nocturnal overexpression of clock-controlled proteins FATP1, ADRP, and ACS1 may promote elevated rates of adipogenesis [19].

Human physiology is not innately adapted to process and oxidize dietary nutrients in the nighttime, though in theory it could entrain under the proper conditions. Circadian rhythms may be entrained with consistent behavioral patterns over time, but the practical application of shift work, particularly in the third shift, prevents peripheral clock entrainment from ever taking place. The *3/4, 4/3* on/off cycle of night-shift workers is perhaps one of the most physiologically detrimental components of shift work. The circadian rhythms of shift workers could, in theory, be entrained over time with consistent eating and activity patterns during the evening, given they maintained this schedule every day. However, night-shift workers often adopt nocturnal patterns for 3-4 days out of the week, going back to a diurnal rhythm during their days off. Food intake and LA in the evening is not inherently damaging to circadian rhythmicity; it is the constant back-and-forth between their feeding and activity patterns which is likely responsible for the observed metabolic phenotype in shift workers. With both light-induced and diet-induced circadian rhythm disruption, the transcriptional activity of CCGs is altered [20]. The back-and-forth nature of this schedule of shift work leads to the transcriptional and functional activity of peripheral clocks being maintained in a constant state of misalignment with feeding and locomotive cues, resulting in metabolic dysfunction.

Although shift work likely induces the most potent disruption of circadian rhythms, the widespread use of blue lights and technology throughout the evening in the general population is likely to disrupt circadian rhythmicity through the same mechanism. Blue light emitted from lightbulbs and electronics in the evening relay light signals to the SCN, modulating central clock activity in a manner similar to UV sunlight, though perhaps to a lesser magnitude. Furthermore, there is often a disconnect between weekday and weekend sleep-wake cycles, aptly referred to as "social jet-lag", with individuals tending to stay and wake up later on weekends than weekdays. Differential sleep-wake cycles between weekdays and weekends have the potential to induce circadian disruption in a manner similar to shiftwork, resulting in a similar phenotype of metabolic dysfunction.

Peripheral Clock Entrainment *Via* Feed-Fast Cycle: Time-Restricted Eating

Time-restricted eating, or TRE, is when food intake is limited to a given window of time in the day. TRE has been shown to powerfully entrain both behavioral patterns and transcriptional activity of circadian clocks in peripheral tissues [21]. Diet-induced obesity (DIO) through *ad lib* high-fat feeding is often performed when examining possible diet-induced restoration of circadian rhythms. Kohsaka, et al. [20] revealed a dampening of circadian metabolic regulators in response to an *ad lib* high-fat DIO model. However, when mice under the same DIO model were provided with the same caloric intake as the *ad lib* mice in a restricted availability time period of 8-12 hours, rhythmicity was maintained in expression of both core transcriptional clock components and metabolic parameters. Although TRE may not manipulate expression of CCGs in the central clocks of the SCN directly, it has been shown to induce an anticipatory elevation of LA and T_b in the 2-3h prior to the entrained feeding time. Even though clock gene expression in the SCN is dictated by the LD cycles, feedback signals regarding the nutrient status of the body may be relayed to the SCN, inducing behavioral modifications thereafter [22].

Clock mutant mouse models of peripheral (hepatic) circadian clock disruption have been utilized in research to determine the effects of TRF protocols on metabolic parameters. Chaix, et al. [23] revealed TRF may protect *Bmal1*^{LKO} [liver clock mutant] mice on a high-fat diet against body weight gain, hepatosteatosis, hypertriglyceridemia, hypercholesterolemia, and even *Bmal1*^{LKO}-induced decrease in locomotor activity, compared with *ad lib* fed experimental counterparts. Independent of clock mutant models, TRF has the capacity to prevent and potentially reverse metabolic dysfunction incurred through DIO [24]. Collectively, these findings reveal that the protective effects of TRE against a phenotype of metabolic dysfunction may be due to the restoration of rhythmicity in peripheral circadian clocks.

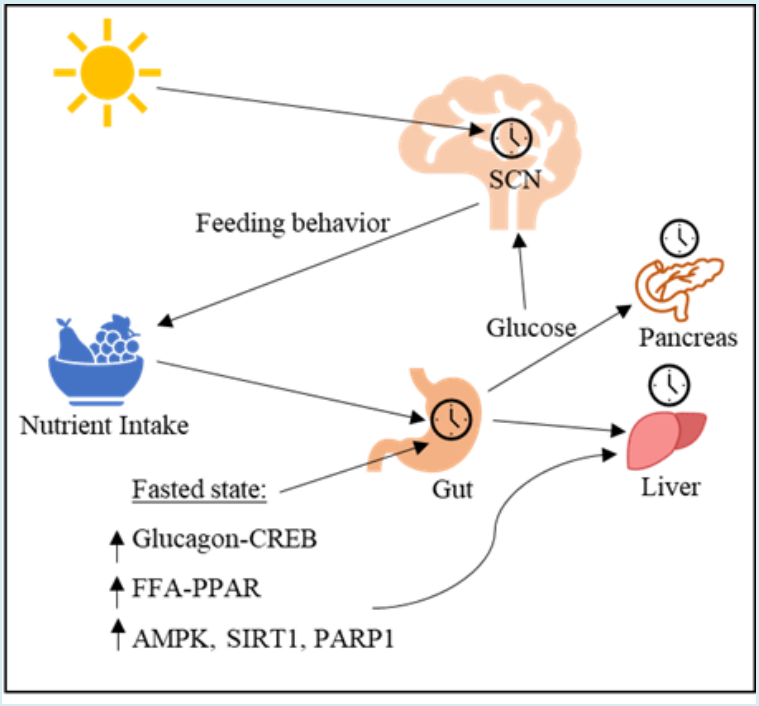

Figure 2: Feed-Fast Cycle and Peripheral Circadian Clock Entrainment [9].

The mechanism by which TRE restores circadian rhythmicity to disrupted peripheral clocks is primarily exerted through the fasting segment of the feed-fast cycle. TRE protocols commonly initiate with an overnight fast; under fasting conditions, an upregulation of glucagon secretion occurs. The fasting-induced secretion of this peptide hormone results in an activation of cAMP response element binding protein (CREB). CREB-activated signaling pathways in hepatic tissues activate *Per1/Per2* expression through CRE binding in the promoter region (Figure 2). Additionally, lipolysis and free fatty acid (FFA) synthesis is increased under fasting conditions. Fasting-induced elevations in FFA concentrations increases peroxisome proliferator activated receptorα (PPARα) signaling, leading to an upregulation of hepatic *Rev-erbα* expression, one of the major CCGs [9,25]. An additional explanation for fasting-induced restoration of arrhythmic circadian CCGs relates to the cellular nutrient status. The metabolic status of a cell can induce alterations in NAD^+/NADH concentrations, potentially inducing NAD^+-dependent alterations in peripheral circadian clocks through SIRT1 and PARP1 activity. SIRT1 acts as a histone deacetylase (HDAC) on histone lysine residues associated with *CLOCK* and *BMAL1* promoter regions, downregulating transcriptional activity of these genes in peripheral tissues. PARP1 acts as an ADP-ribosyltransferase which modulates DNA binding of the CLOCK-BMAL1 heterodimer. PARP-$1^{-/-}$ mice exhibit a slower rate of entrainment to TRF in hepatic circadian clock gene expression compared to their wild-type counterparts [9,26,27]. The positive effects of TRE on circadian entrainment and recovery of metabolic disease is likely a result of increased time spent in the fasting phase of the feed-fast cycle. Given these findings, it may be beneficial for clinicians to advise TRE protocols to shift work patients, particularly those with the greatest genetic and behavioral predisposition of developing metabolic syndrome.

Fasting-induced increases in Glucagon & FFA lead to increased CREB and PPARα activity, respectively. CREB and PPARα signaling on hepatic & pancreatic tissues entrain rhythmicity in CCG expression. Afferent signals regarding energy status may be relayed to the SCN through glycemic alterations.

Conclusion

Approaching this quandary from an evolutionary perspective, it is reasonable to predict that TRE may be beneficial in recovering a healthy metabolic phenotype. Our physiology and genetics have adapted to the behavioral patterns of our hunter-gatherer ancestors roughly 10,000 years ago. Food sources were highly sparse thousands of years ago; it would not have been uncommon for *homo sapiens* during that time to undergo fasting periods greater than 24 hours. With respect to energy balance, these humans were very rarely in a caloric surplus. Contrasting this against modern conditions in which the general population is in a constant state of caloric surplus, it should come as no surprise that restricting the time under which one consumes food would reduce the time under positive energy balance, attenuating excess energy storage.

The effect of being in a perpetual caloric surplus is amplified even further when you consider the variance in disrupted light patterns between our distant ancestors and modern-day humans. The central circadian rhythms of our hunter-gatherer ancestors were likely to be powerfully intact, while modern-day society is in a constant state of central circadian clock disruption due to chronic nighttime blue-light exposure. Night-shift workers seem to be the population most powerfully affected by this coupling of a chronic energy surplus with circadian rhythm disruption, displaying an increased risk of developing metabolic syndrome compared to normal shift workers.

Even though shift work-induced circadian disruption is a significant risk factor for developing metabolic syndrome, the around-the-clock lifestyle of modern society may be responsible in part for the increasing rates of obesity and metabolic syndrome observed in the general population. While regularly staying awake into the late evening is not likely to induce central and peripheral circadian clock disruption as potently as night-shift work, minor yet chronic disruption of circadian rhythmicity is likely detrimental to metabolic function. For this reason, TRE protocols to restore circadian rhythmicity may be effective clinical interventions for attenuating the negative consequences of metabolic diseases observed in both shift workers and the general population.

References

1. Yamazaki S, Numano R, Abe M, Hida A, Takahashi R, et al. (2000) Resetting central and peripheral circadian oscillators in transgenic rats. Science 288(5466): 682-685.

2. Reppert SM, Weaver DR (2001) Coordination of circadian timing in mammals. Nature 418: 935-941.

3. Hastings MH, Reddy AB, Maywood ES (2003) A clockwork web: circadian timing in brain and periphery, in health and disease. Nat Rev Neurosci 4(8): 649-661.

4. Rana S, Mahmood S (2010) Circadian rhythm and its role in malignancy. J Circadian Rhythm 8: 3.

5. Holmes MM, Mistlberger RE (2000) Food anticipatory activity and photic entrainment in food-restricted BALB/c mice. Physiol Behav 68(5): 655-666.

6. Marchant EG, Mistlberger RE (1997) Anticipation and entrainment to feeding time in intact and SCN-ablated C57BL/6j mice. Brain Res 765(2): 273-282.

7. Mrosovsky N (1996) Locomotor activity and non-photic influences on circadian clocks. Biol Rev Camb Philos Soc 71: 343-372.

8. Takahashi JS (2016) Transcriptional architecture of the mammalian circadian clock. Nature Reviews Genetics 18(3): 164-179.

9. Tahara Y, Shibata S (2017) Entrainment of the mouse circadian clock: Effects of stress, exercise, and nutrition. Free Radical Biology and Medicine 119: 129-138.

10. Szosland D (2010) Shift work and metabolic syndrome, diabetes mellitus and ischaemic heart disease. International Journal of Occupational Medicine and Environmental Health 23(3).

11. Moore-Ede MC, Richardson GS (1985) Medical implications of shift-work. Annu Rev Med 36: 607-617.

12. Rajaratnam SM, Arendt J (2001) Health in a 24-h society. Lancet 358: 999-1005.

13. Stevens RG (2005) Circadian disruption and breast cancer: from melatonin to clock genes. Epidemiology 16(2): 254-258.

14. Di Lorenzo L, De Pergola G, Zocchetti C, L Abbate N, Basso AZ, et al. (2003) Effect of shift work on body mass index: results of a study performed in 319 glucose-tolerant men working in a Southern Italian industry. Int J Obes Relat Metab Disord 27(11): 1353-1358.

15. Ostry AS, Radi S, Louie AM, D La Montagne A (2006) Psychosocial and other working conditions in relation to body mass index in a representative sample of Australian workers. BMC Public Health 6: 53.

16. Esquirol J, Bongard V, Mabile L, Jonnier B, Soulat JM, et al. (2009) Shift work and metabolic syndrome: Impact of job strain, physical activity, and dietary rhythms. Chronobiol Int 26: 544-59.

17. Pietroiusti A, Neri A, Somma G, Coppeta L, Iavicoli I, et al. (2010) Incidence of metabolic syndrome among night-shift healthcare workers. Occup Environ Med 67(1): 54-57.

18. Roenneberg T, Daan S, Merrow M (2003) The art of entrainment. J Biol Rhythms 18(3):183-194.

19. Bray MS, Young ME (2007) Circadian rhythms in the development of obesity: potential role for the circadian clock within the adipocyte. Obes Rev 8: 169-181.

20. Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, et al. (2007) High-fat diet disrupts behavioral and molecular circadian rhythms in mice. Cell Metab 6(5): 414-421.

21. Tahara Y, Shibata S (2013) Chronobiology and nutrition. Neuroscience 253: 78-88.

22. Yang JJ, Cheng RC, Cheng PC, Wang YC, Huang RC (2017) KATP channels mediate differential metabolic responses to glucose shortage of the dorsomedial and ventrolateral oscillators in the central clock. Sci Rep 7(1): 640.

23. Chaix A, Lin T, Le HD, Chang MW, Panda S (2018) Time-Restricted Feeding Prevents Obesity and Metabolic Syndrome in Mice Lacking a Circadian Clock. Cell Metabolism 29(2): 303-319.

24. Chaix A, Zarrinpar A, Miu P, Panda S (2014) Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. Cell Metab 20(6): 991-1005.

25. Mistlberger RE (2009) Food-anticipatory circadian rhythms: concepts and methods. Eur J Neurosci 30: 1718-1729.

26. Asher GH, Reinke M, Altmeyer M, Gutierrez-Arcelus MO, Hottiger U, et al. (2010) (ADP-ribose) polymerase 1 participates in the phase entrainment of circadian clocks to feeding. Cell 142(6): 943-953.

27. Akerstedt T, Ingre M, Broman JE, Kecklund G (2008) Disturbed sleep in shift workers, day workers, and insomniacs. Chronobiol Int 25: 333-348.