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The Evolution of Biochemical Storm of Circadian Rhythm and Circadian Dysfunction in Relation to Vascular Disease and Diabetes

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Abstract

The earth rotates around its axis (and around the sun); hence our physiology has adapted to coordinate functions according to circadian (and circannual) rhythms. Homo erectus used to go to river banks or lakesides in the forest in the early morning for hunting when animals emerged from the forest to drink water, which was associated with marked physical exertion and mental stress with underlying biochemical storm of increase in catecholamines, and cortisol. It is possible that this habit of the ancient men causing increased sympathetic activity in the morning (6.00-12.00 hours) became a circadian rhythm which has an adverse effects in modern men. The increased sympathetic activity may be also associated with rise in thyroid hormones which are known to cause increase in basal metabolic rate resulting in to increased energy expenditure in the morning compared to other times of the day. A disturbance in sleep wake cycles may cause increased cardiometabolic risk in the modern society. It is proposed that disturbances in circadian rhythms and diet and lifestyle factors may be associated with glucose variability disorder which may be the first event in the pathogenesis of diabetes. Halberg was first to propose circadian rhythm in biological functions and demonstrate vascular variability disorders. Guidelines from various agencies for the management of CVDs and diabetes emphasize that the necessity, choice and intensity of treatment should be determined by the individual's probability of an event (risk) within a given time span predisposing to complications. There is little consideration for chronotherapy, diet and exercise. Optimization of treatment by timing, however, in relation to the time of awakening, has already demonstrated that higher efficacy with fewer side effects can be reached with a reduced dosage, a practice that should enter mainstream medicine. Knowledge of circadian functions and utility of chronotherapy may be used in clinical trials, in reducing the dose of the agent as well as its adverse effects while providing several-fold greater benefit, thereby optimising therapeutic efficacy.

Keywords: Drug therapy; Lifestyle; Chronobiology; Circadian therapy

Introduction

Most biological rhythms are related to the movement of the earth around its axis (and around the sun). The day and night cycle follows the rotation of the earth on its axis and many "seasonal" variations can be linked to the movement of the earth around the sun. About-monthly cycles have been related to both a lunar influence and solar changes as the sun rotates around its axis. Many physiological functions have adapted to these external rhythms. Disruptions in these cycles have been linked to a host of disease conditions [1-4]. When the synchronization of biological rhythms to environmental cycles is disrupted, physiological and metabolic functions are impaired [1, 2]. Homo sapiens, along with their predecessors Homo habilis and Homo erectus, have been hunting for over a million years [1, 2]. Early humans were primarily vegetarians, but became omnivorous as they evolved away from other primates. In view of the influence of environmental factors, ancient men developed social groups which increased the demands for survival. The skills they developed influenced their lifestyle and longevity. Collection of food mainly via hunting was the most important activity of ancient men [3, 4]. They were killed due to traumatic accidents early in life; hence the life expectancy of early men is estimated to be less than 30 years [1-4] (Figure 1).

It has been proposed that to preserve their progeny, Homo sapiens mated early in the morning [3, 4]. This routine became the most important chronobiological adaptation of humans. An increased release of testosterone occurred in the morning [5] to coordinate sexual activity with the aim to impregnate. Throughout human history, there have been various attempts to establish the existence of a male cycle. The circadian testosterone cycle has been well studied and verified [5]. Testosterone is highest in the morning and lowest at bedtime, hence men's propensity for morning erections, which follows a 24-hour cycle. Circadian

Figure 1: Hunting by ancient men near a lake while animals came to drink water. Modified from [1,2].

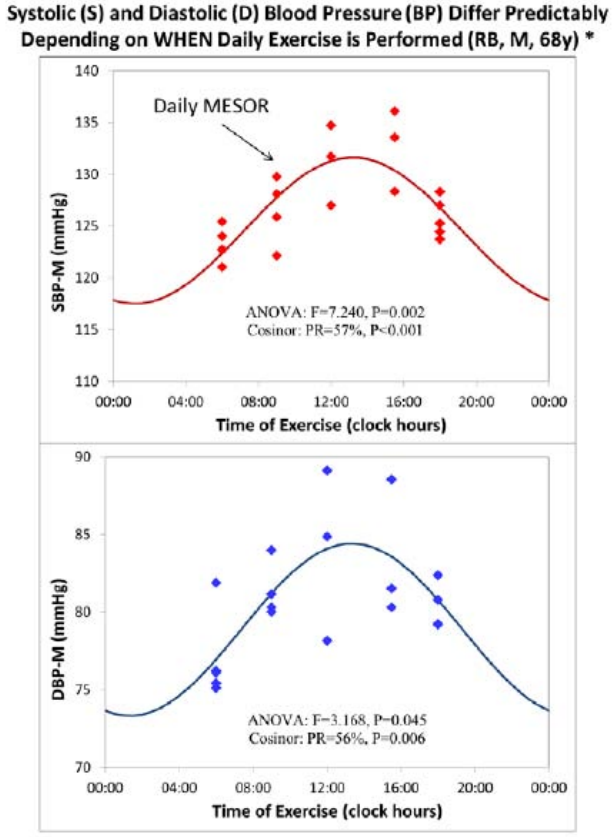

Figure 2: The same subject exercised at different times after awakening in a schedule of sleep/rest from 22:30 to 06:00, demonstrating a circadian rhythm in response to exercise validated by both cosinor and 1-way analysis of variance (ANOVA) [19].
* One shoe-size (one arbitrary time) does not fit all.

testosterone variation indicates that concentrations peak between 05:30 and 08:00, with trough concentrations occurring approximately 12 hours later. In several studies, the amplitude of variation of total testosterone concentrations, which is usually estimated as the difference between peak and mean hormone concentrations of a fitted 24-hour cosine function, was 6–12% of the 24-hour average concentration [5]. The suprachiasmatic circadian clock (SC) coordinates the circadian release of hormones from the pituitary gland in men, releasing follicular stimulating hormone (FSH) and luteinizing hormone (LH) in response to low concentrations of serum testosterone at night. FSH stimulates the formation of sperm (Sertoli cells), and LH stimulates the formation of testosterone (interstitial cells). If the testosterone inventories are high enough, such as in the morning, the pituitary quiets down and serum concentration gradually decreases until late night, until the whole process begins again, sometime in the early hours of the morning the following day [5]. The circadian rhythm of testosterone may have evolved to support the sexual activity of *Homo sapiens.*

Hypothesis; The evolution of circadian rhythm

Homo erectus used to go to river banks or lakesides in the forest in the early morning for hunting when animals emerged from the forest to drink water [3, 4]. Singh et al. proposed that since hunting started just before sunrise, bringing enormous excitement, physical and mental exertion and increased sympathetic activity with a biochemical storm of marked releases of cortisol, catecholamines, aldosterone, angiotensin, renin, glucocorticoids and thyroid hormone occurred at a circadian stage when melatonin is low. The circadian clock of the suprachismatic nucleus may have evolved to coordinate circadian physiological functions in association with clock genes [1, 2]. Palaeolithic men had enormous physical activity. Eating Palaeolithic foods, they were able to fight the adverse effects of the morning rise in testosterone, cortisol, thyroid hormones and catecholamines and the evening decline in thyroid hormones [1-6]. Thus, the circadian restriction of feeding may have protected against this biochemical storm in the morning and lowered hormonal concentrations in the evening [7, 8]. Increased concentrations of catecholamines and cortisol are associated with increased heart rate, blood pressure, endothelial dysfunction and coronary artery constriction, with underlying increased oxidative stress, pro-inflammatory cytokines, increased free-fatty acids, and deficiency of antioxidant vitamins and endogenous antioxidants [9-12]. Ancient men possibly had no time for breakfast due to their involvement in hunting, but modern men consume a heavy breakfast which may predispose to athero-thrombosis [12]. Hence modern men with their altered diet and lifestyle and the presence of other risk factors experience circadian rhythm dysfunctions, resulting in increased risk of cardiac events which tend to preferentially occur in the second quarter of the day from 06:00 to 12:00 [9-12]. Late night sleep, late awakening, heavy breakfasts rich in processed Western foods, psychosocial stress, lack of physical activity and meditation in the morning, and excitement for going to work, all contribute to triggering a biochemical and biological milieu in the body that may account for a greater prevalence of incidence of cardiovascular events and deaths between 08:00 and 11:00 [1-4, 12]. Late night eating and sleep and late awakening have also been associated with obesity and the metabolic syndrome [8].

Hypothesis of increased energy metabolism in the morning.

Physical activity (running and riding for hunting) in the

morning may have increased basal metabolic rate in association with a burst of thyroid hormones. We propose that these clinical and biochemical factors, under or without the influence of the circadian clock, may have become circadian rhythms during the evolution of biological and metabolic functions which are also observed in modern men [3, 4]. Thus thyroid hormones peaking in the morning may have developed as a circadian rhythm triggered by the suprachiasmatic circadian clock, as a result of evolution in ancient times [6]. The higher concentrations of thyroid hormones released in the morning may be related to higher basal metabolic rate, associated with greater energy expenditure in the morning compared to the evening. Thus, eating the same meal in the morning or evening can be expected to relate to less or more weight gain, respectively, as first documented by Halberg et al. [for review see 7]. Halberg was also the first to report the circadian variability in eosinophil counts [13], and he is also known for coining the words chronobiology, circadian and chronotherapy (optimization of treatment by timing its administration according to body rhythms) [14-16]. Time structures, including circadian rhythms characterizing metabolic and physiological functions, may be influenced by magnetic storms and space weather more generally [16, 17]. Modifications in lifestyle and meal timing may also influence these functions [7, 8, 18-20].

Meal timing, food content, physical activity, intercourse and all other lifestyle-related functions may be under the influence of the circadian clock present in the suprachiasmatic nucleus which coordinates peripheral clocks [3, 4]. In an earlier study involving 17 subjects, the profiles of plasma cortisol, thyrotropin (TSH), melatonin and body temperature were monitored continuously to derive estimations of circadian phase position. Exercise at night was associated with 1- to 2-hour phase delays of both melatonin and TSH, with the extent of the delays tending to be smaller when exercise was presented in the latter part of the night or in the early morning. These data demonstrate that nonphotic stimuli may exert phase-shifting effects on the human circadian pacemaker.

Variability as a circadian dysfunction

Guidelines from various agencies for the management of cardiovascular diseases (CVDs) and diabetes emphasize that the necessity, choice and intensity of treatment should be determined by the individual's probability of an event (risk) within a given time span which predisposes to complications and death [21-23]. Disruption of circadian rhythms associated with changes in diet and lifestyle factors can predispose to psychological stress, as well as to CVDs and diabetes, whereas eating and exercising patterns can be optimized for health maintenance [21-23].

Blood pressure variability

Abnormal circadian patterns of blood pressure and heart rate predict cardiovascular disease risk and can be treated. The circadian rhythms in blood pressures and heart rate can be studied by ambulatory blood pressure (ABPM) monitoring by recording blood pressures and heart rate every half hourly for 3-7 days. In a recent sub-study from India involving 209 subjects (142 men and 67 women) aged 42.4 ± 18.0 years, in which blood pressure records were collected for 3-7 days by ambulatory monitoring, anticipated relationships were found [9]. The MESOR of heart rate decreased with increased activity ($F=5.558$, $P=0.001$). The MESOR of systolic blood pressure decreased slightly with increased activity, but the relationship was not statistically significant. Interestingly, the beneficial effect of eating fruits, vegetables and legumes (FVL) on the MESOR of heart rate was significant ($r=-0.192$, $P=0.011$). The circadian double amplitude of heart rate was also found to be higher among Hindus who prayed (11.7 beats/min) as compared to Hindus who did not pray (8.1 beats/min) (Student $t=2.137$, $P=0.035$), indicating that prayer may have beneficial effects on parasympathetic activity. In a clinical study, blood pressure and heart rate were monitored for 4-7 days while regular physical activity was done at different circadian stages -- morning, midday, afternoon and night -- to assess any circadian stage-dependent effects of exercise [19]. The MESOR of blood pressure and heart rate showed minimal adverse effects after exercise in the morning as compared to the evening or other circadian stages. Effects of autogenic training and antihypertensive agents on the circadian and circaseptan variations of blood pressure were also observed in Japan [20].

Halberg et al. were the first to propose an extended consensus on the need and means to detect vascular variability disorders (VVDs) and vascular variability syndromes (VVSs) [21-23]. Among such known vascular variability disorders (VVDs) are MESOR-hypertension, that is an elevated blood pressure MESOR (Midline Estimating Statistic of Rhythm, a rhythm-adjusted mean value which is usually more precise and more accurate than the arithmetic mean), an excessive circadian amplitude of blood pressure (CHAT, brief for Circadian Hyper-Amplitude-Tension), and circadian blood pressure ecphasia, characterized by an odd timing of the overall high values of blood pressure – but not heart rate – recurring each day. These VVDs can be diagnosed based on around-the-clock measurements, preferably by ambulatory monitoring, for at least 7 days at the outset [21, 22].

Blood glucose variability

Since variability in blood glucose concentrations has also been found to be associated with increased risk of target organ damage, it is logical to propose that glycemia be measured around the clock to find out mean glucose concentration and glycemia lability index. ABPM in subjects with diabetes mellitus may be a powerful tool for a better stratification of the risk of vascular disease in presence of glucose variability [24]. The risk related to elevated blood pressure may be a substantial contributor to morbidity and mortality due to CVDs in diabetes. ABPM may also be helpful in detecting alterations in autonomic control of the cardiovascular system, reflected by the absence of nocturnal blood pressure fall or by a reduced 24-hour heart rate variability and an increased 24-hour BPV as well as in the diagnosis of VVDs [21-24]. The extent of variations in blood pressure over time may provide additional, independent prognostic information and information about chronotherapy with drugs. It has been suggested that in order to achieve the highest CV protection in hypertensive patients, anti- hypertensive treatment should be targeted at normalizing 24-hour as well as 7-day VVDs in addition to reducing

absolute 7-day MESOR of blood pressure [21-24]. In the majority of studies, 24-hour or 7-day ABPM has not been routinely used in large-scale trials on anti- hypertensive treatment. Hence, the protective effect of treatment-induced changes with respect to the concomitant changes in mean blood pressure and blood glucose values still needs to be properly documented. Recent meta-analyses of clinical trials on hypertension have shown an increased visit-to-visit blood pressure variability or lack of blood pressure control at any given visit to be associated with an adverse CV prognosis [24]. Therefore, the evidence for such recommendations is still limited regarding the targets of blood pressure variability to achieve with antihypertensive treatment, particularly in presence of glucose variability.

There is evidence that management of hyperglycemia may be protective for subjects with sepsis. In critically ill patients, blood glucose variability, rather than the glucose concentration, has also been shown to be an important factor associated with in-hospital mortality [25]. In a recent study, glucose variability was calculated for all subjects as the average and standard deviation of glucose, the mean amplitude of glycemic excursions, and the glycemic lability index. This study revealed that the glycemic lability index had the best discrimination for mortality (area under the curve = 0.67, $p < 0.001$). Subjects with increased glycemic lability index, but lower average glucose values had almost five-fold increased odds of hospital mortality (odds ratio = 4.73, 95% confidence interval = 2.6 – 8.7) compared with those with lower glycemic lability index after adjustment for confounders, including the number of organ failures and the occurrence of hypoglycemia. In septic patients, glucose variability may be independently associated with hospital mortality. Chronotherapy may be studied to reduce glucose variability to determine whether it can improve the outcomes of these patients. In a further study, among 294 patients with 34,796 glucose measurements, mean glucose concentrations and glycemic lability index were measured [26].The time-weighted mean blood glucose concentration was 9.31 ± 1.91 mmol/L, and the median of glycemic lability index was 55.27 (mmol/L) (2) h-(1) wk-(1). Intensive care unit(ICU) mortality was 43.5% and increased progressively as glycemic lability index increased, reaching 62.5% of patients with index above 115.89 (mmol/L) (2) h-(1) wk-(1). The highest odds ratio for ICU mortality was found in patients with the highest quartile of glycemic lability index: odds ratio, 3.47 (95% confidence interval, 1.76-6.86; P < .000). No such relationship could be found with mean glucose concentration. The logistic regression analysis showed that glycemic lability index was a better predictor of ICU and hospital mortality than was mean glucose concentration. Together with the second 24-hour APACHE II score and the number of organ failures upon ICU admission, glucose lability index appear to be an independent predictor of mortality in patients with acute pancreatitis.

Hypothesis; Glycemia variability disorders

It seems that variability in blood glucose may be the first and earliest event in the pathogenesis of diabetes which may occur due to entrainment of the circadian clock. It is possible that glucose lability index and 24-hour APACHEII score may have limitations because these scores give little consider to amplitude and peaks of hyper and hypoglycaemia burden, which may be covered by measuring glucose/glycemia variability disorders (GVDs).It is proposed that estimation of the circadian MESOR, amplitude and acrophase (phase of maximum of 24-hour cosine curve fitted to the data) and GVDs, 7-day blood glucose concentrations measured at 15 min to 60 min interval may be important. Deviations from reference values for these parameters, derived as 90% prediction limits on data collected from clinically healthy peers, could then be similarly defined as MESOR-Hyperglycemia/hypoglycemia, Circadian Hyper-Amplitude Glycemia (CHAG), and ecphasia of glycemia which may be called Glycemia Variability Disorders (GVDs). The extent to which these abnormal patterns of GVDs, particularly in relation to hypoglycaemia load, relate to complications of diabetes and adverse outcomes warrants more studies. Clinical trials with drugs via chronotherapy may be useful in reducing toxicity and providing better efficacy of the same agent.

Further studies showed that circadian physiology and metabolism as well as blood pressure and blood glucose variations are influenced by clock genes [27, 28]. Recently, unexpected features of Drosophila circadian behavioral rhythms under natural conditions have been reported which are different compared to those observed in the laboratory [29]. Also note from in-vitro experiments that yeast and cardiomyocytes share ultradian oscillatory redox mechanisms of cellular coherence and survival [30]. Further studies are required to understand the circadian physiology and metabolism of humans under natural conditions compared to effects of urbanization or in a metabolic ward.

In brief, circadian rhythms evolved possibly in ancient times as physiology and metabolism adapted to the rotation of the earth around its axis, currently in about 24 hours. Circadian rhythms account for increased sympathetic activity with marked releases of cortisol, catecholamines and thyroid hormones occurring at a circadian stage when melatonin decreases to low values in the morning. We propose that these patterns may have come about in ancient times in response to marked physical and mental exertion during morning hunting. An increase in thyroid hormones with increased physical activity while hunting in the morning may have brought about an increase in basal metabolic rate resulting in greater energy expenditure in the morning as compared to the evening. Further studies are necessary to confirm our hypothesis.

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