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Sleep and vascular disorders

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Abstract

It is not surprising that cardiovascular diseases such as congestive heart failure and coronary insufficiency can give rise to varying degrees of sleep impairment; it is less readily appreciated that certain physiologic events occurring during sleep—as well as long-term unsatisfactory sleep—may cause or increase the risk of cardiovascular conditions such as hypertension, atherosclerosis, stroke, and cardiac arrythmias. Heart rate abnormalities during sleep in normotensive subjects predict later cardiovascular disease, and their early identification alerts the physician to undertake preventive measures. Maneuvers, such as induction of hypoxia, can elicit abnormal blood pressure responses during sleep, and such responses have been used to identify impending cardiovascular problems that could become therapeutic targets. The spontaneously hypertensive rat has been used to examine the effect of sympathetic nervous system (SNS) activity on the heart under a variety of experimental conditions, including quiet and paradoxical sleep. The results have disclosed significant differences between the responses of spontaneously hypertensive rats and normal rats to SNS stimulation. Exploration of other pathophysiologic pathways affected by exposure to light and dark, including those responsive to the cyclic production of melatonin, will improve our understanding of the effect of disruptions of the circadian cycle on cardiovascular function. There is growing evidence that melatonin can influence important processes such as fluid, nitrogen, and acid-base balance. Human subjects whose nocturnal arterial blood pressure fails to show the "normal" decrement during sleep ("nondippers") are also prone to sleep poorly, exhibit increased SNS activity during sleep, and have an increased risk of total and cardiovascular disease mortality. Chronic sleep deficit is now known to be a risk factor for obesity and may contribute to the visceral form of obesity that underlies the metabolic syndrome. The rising prevalence of obstructive sleep apnea and central sleep apnea is linked to the modern-day epidemic of obesity. Obstructive sleep apnea is associated with an enhanced risk of having a new stroke or a transient ischemic attack.

1. Sleep-related animal and clinical observations

1.1. Experimental animal models

Several kinds of sleep-related vascular disorders have been studied in laboratory animals. Autonomic nervous system function was estimated from telemetrically transmitted electroencephalographic, electromyographic, and electrocardiographic data obtained across sleep-wake cycles in adult, spontaneously hypertensive rats (SHRs), control Wistar-Kyoto rats, and Sprague-Dawley rats [1]. During active wakefulness, as well as quiet and paradoxical sleep, high-frequency (HF) heart rate variability (HRV) was lower in SHR than in the control groups. Heart rate variability has been found to be a useful index for measuring sympathetic vs parasympathetic dominance during sleep. Increased HF and decreased low-frequency HRV indicate high cardiac and parasympathetic tone and low sympathetic tone, and are found in non–rapid eye movement (NREM) sleep. Decreased HF and increased low-frequency HRV activity indicate a low cardiac and parasympathetic tone and a high sympathetic tone, and are associated with REM sleep and wakefulness. Despite the higher blood pressure in the SHR, their R-R interval (heart rate) was similar to that in the control groups. These interesting in vivo findings led to the conclusion that significant cardiac sympathovagal imbalance, with increased sympathetic modulation, occurs in the SHR during sleep. This imbalance is less evident during the waking hours.

In another study, brain capillary perfusion was examined during the sleep-wake cycle in young (8-10 weeks) SHR before blood pressure became elevated [2]. The purpose of

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studying the brain microcirculation in these animals was to find out whether capillary rarefaction, reported by other investigators in extracerebral organs of the SHR, was also present in the brain. It was hypothesized that such rarefaction might be the underlying cause of the hypertension in these animals [3]. However, the study failed to demonstrate any abnormality in their brain microvasculature, and, therefore, did not support the notion that rarefaction of the brain microvasculature in the SHR either underlies the hypertension that evolves later or is responsible for the origin of sleep disturbances that might contribute to the hypertension.

In a rat model of secondary arterial hypertension (renal artery clamping), intermittent elevation of systemic blood pressure during sleeping hours was found to be associated with early left ventricular hypertrophy. Subsequent cessation of renal artery clamping, with consequent blood pressure normalization, was followed by a reduction in the left ventricular hypertrophy [4].

Finally, the role of nitric oxide (NO) synthase inhibition on sleep responses was examined in normotensive Sprague-Dawley rats. The purpose of the study was to obtain information about the potential role of this vasoactive gas in sleep regulation [5]. Brain slow-wave activity (associated with non–rapid eye movement [NREM] sleep) was monitored by electroencephalography in both normal and vagotomized rats. Administration of a nitric oxide synthase inhibitor (an NO synthase inhibitor) suppressed slow-wave activity at light onset and during darkness in both control and vagotomized rats. These findings indicate that the sleep effects of NO inhibition are not mediated through sensory vagal mechanisms.

1.2. Clinical studies

Numerous clinical studies of the relationship between sleep disorders, arterial hypertension, and cardiovascular events (such as myocardial infarction and stroke) have been published during the past decade. A recent editorial review [6] addresses the ongoing debate about the mechanisms that connect central nervous/autonomic system perturbations with disturbances of the central and peripheral vasculature. The review examines the "nondipping" blood pressure profile in patients who exhibit abnormal variations of diurnal blood pressure in response to physical activity—including a reduced response to physical and/or mental activity during daytime. "Nondippers" are hypertensive patients whose nighttime arterial pressure goes down by less than 10% from day to night. Such patients are at high risk of total and cardiovascular mortality. The cause of the elevation of arterial blood pressure in these hypertensive patients may be faulty baroreceptor activation. The patients also exhibit elevated central sympathetic nervous system (SNS) activity, increased numbers of arousals during sleep, reduced length and depth of NREM sleep, and shortened REM sleep latency. Endothelium-dependent vasodilation in these individuals is less active.

The author concludes that "...a better understanding of the mechanisms that underlie the altered diurnal blood pressure rhythm in hypertensive 'non-dippers' would help establish how a non-dipping pattern should be treated.... "

1.3. Ambulatory blood pressure

In a clinical study in which ambulatory blood pressure was monitored in borderline and normotensive Norwegian subjects, it was shown that, in the borderline group, systolic blood pressure values were higher than in the normotensive subjects for the entire 24-hour period, as well as during the four 6-hour periods [7]. These findings support the notion that isolated, elevated systolic blood pressure values measured in borderline subjects may prove to be harbingers of later, established hypertension.

Interestingly, the abnormal sleep pattern exhibited by nondipper hypertensive patients was also found to be present in some of their normotensive children—another indication that an abnormal sleep-wake hemodynamic profile can be identified before systemic peripheral resistance actually becomes established [8].

A clinical study of Chinese subjects revealed that, among individuals with an isolated elevation of systolic blood pressure, systolic pressures increased during the day and fell significantly during periods of sleep [9]. According to the authors, the circadian diastolic blood pressure rhythm in these individuals was attenuated in the isolated systolic group, giving rise to potentially enhanced pulse pressure values, and—perhaps—a disposition to ischemia-related cerebral damage.

A large study performed in Japan that used 24-hour ambulatory blood pressure measurements disclosed that the impacts of pulse pressure and mean blood pressure values on stroke risk are different during the sleep and wake periods of the day [10]. Sleep pulse pressure and wake mean blood pressure values were both predictors of stroke events, independently of silent cerebral infarcts carefully evaluated by magnetic resonance imaging in more than 500 patients.

1.4. Heart rate

Heart rate, a basic physiologic component of cardiovascular function, has not been extensively studied in sleep-wake circadian phenomena. Nevertheless, resting heart rate is intimately related to prognosis in patients with cardiovascular diseases. The waking state is, of course, influenced by psychologic and physical activity—which makes it difficult to reproduce physiologic variations in a given individual. Wristwatch-type recording instruments are now available to record and evaluate the heart rate in normotensive as well as hypertensive subjects receiving no medication [11]. Validation of this approach to measurement of heart rate throughout the day and night was accomplished by simultaneous use of the Holter electrocardiographic monitor, yielding an extremely high correlation coefficient (r = 0.98). Findings obtained in more than 350 subjects revealed that there is a close relation between heart rate and

changes in cardiac function brought about by hypertension and aging. A statistically significant correlation was found between heart rate and stroke volume index during sleep in hypertensive subjects. However, the relationship between these parameters during awake periods—although in the same direction—was not statistically significant.

1.5. Vascular diseases

Among vascular diseases where sleep blood pressure abnormalities have been reported, diabetes mellitus and chronic renal failure are examples of morbid disorders in which imbalance of the autonomic nervous system is a central manifestation of circadian rhythm disorganization. In type 2 diabetic patients with nephropathy, extracellular volume, fluid shift from the interstitial to the vascular compartment, sympathetic activity (catecholamines), and plasma melatonin values were examined [12]. Patients were divided into 2 groups according to the magnitude of nocturnal blood pressure decrements (high/low). Hemodilution was more evident in those patients with the large reduction in pressure at night, as opposed to those with small night reduction. Plasma noradrenaline changed in the same direction in both groups, which led to a significant correlation between changes in hematocrit and noradrenaline—interpreted by the authors as representing a lack of peripheral vasodilation in the group exhibiting the abnormal nocturnal blood pressure profile. Surprisingly, there was no difference between groups in extracellular volume distribution and melatonin blood levels, suggesting no impact of these variables on the diabetic vascular system. Unfortunately, the potential contribution of intracellular fluid movements, as well as endothelial permeability dysfunction, on the nocturnal blood pressure changes was not discussed by the authors.

In a subsequently reported study, nighttime blood pressure fall in patients with renal disease was examined by 24-hour monitoring [13]. Notably, systolic—but not diastolic—blood pressure was higher in the patients with renal disease: the nocturnal systolic and diastolic pressure decrements averaged 5.8% and 11.1% ($P < .001$), respectively. The frequency of nondipper status was higher in patients with renal disease than in control subjects. The authors suggested that chronopharmacologic factors might be responsible for the differences observed in the renal patients.

2. Pathophysiology of sleep-related vascular disorders

2.1. Nocturnal hypoxia/anoxia

Maintenance of adequate oxygen delivery to the body cell mass requires appropriate day and night adjustments of the vascular system. The reverse phenomenon, far less popular as a subject for scientific investigation, is transport of the carbon dioxide produced by the body's working cells to sites (notably the lungs) that enable its excretion into the ambient atmosphere. The vascular consequences of hypoxia and hypercapnia are well known, having been studied in animal models as well as in humans. Experimental obstructive sleep apnea and repetitive episodic hypoxia cause sustained elevation of blood pressure [14]. In humans, epidemiologic studies have shown an increased prevalence of hypertension in patients with sleep-disordered breathing (see below). These findings provide additional support for the existence of a causal relationship between the 2 conditions [15].

In carefully designed experiments performed in normal nonsmoking, nonobese, normotensive volunteers exposed to hypobaric hypoxia and normobaric normoxia, a distinct pattern of diastolic blood pressure elevation was observed after the hypoxia night, but not after the normoxia night [16]. Interestingly, there was no evidence of fluid retention to explain changes in blood pressure profile in these subjects, but an increase in plasma viscosity as well as a lower urine osmolality in the hypoxic subjects suggested hemoconcentration as a potential causative mechanism.

2.2. Body temperature, fluid, electrolyte, and nitrogen homeostasis

During the dark portion of each day, body temperature and fluid and electrolyte homeostasis are rigorously controlled. Of equal importance, carbon dioxide and nitrogen elimination are ensured in normal, nonhibernating mammals through complex and coordinated autonomic nervous system and metabolic adjustments. The circadian factors involved in maintenance of these variables have been carefully examined in normal human subjects [17]. From midnight to sunrise (ca 06:00 AM), body temperature falls by 0.4°C, heat production by 418.4 kJ (100 kcal), and heart rate by 6 beats per minute—small but physiologically important changes. These variations are followed by 6 hours (06:00 AM to noon) of marked elevation in renal parameters: a 3-fold increase in urine flow, sodium, potassium, and urea excretion. Urinary creatinine excretion, a rough measure of glomerular filtration rate, remains relatively constant. Significant correlations between heat production and loss, mainly through sudation, heat production, and heart rate, have been observed in these carefully designed experiments. Of course, any dissociation between the timing profile of systemic vascular parameters (heat production and loss, heart rate, etc) and renal responses (urine flow, electrolytes and urea) could give rise to pathophysiologic consequences, particularly if amplified by disruption of normal circadian cycles. Adverse results also could result from changes in the normal circadian pattern of release of hormones that affect vascular behavior; for example, plasma kallikrein is normally elevated during daylight and reduced at night, whereas plasma vasoactive intestinal peptide varies in the opposite direction [18].

2.3. Melatonin

Identified almost half a century ago by Lerner et al [19], melatonin (5-methoxy-*N*-acetyltryptamine) is an important biologic modulator of nycthemeral cycles in living organisms. This compound is derived from tryptophan, an essential

amino acid in humans. Its production in the pineal gland involves 3 biochemical steps, including the intermediate formation of serotonin by an aromatic decarboxylase reaction. Melatonin has been identified in extracts of several plant species, suggesting that it may contribute to physiologic processes in such organisms [20]. Surprisingly, however, there is no satisfactory evidence, based on recent analytic studies, that any actual foods contain more than trace amounts of melatonin [21]. Significant interest has developed during the past decade in the potential value of melatonin in the treatment of insomnia and/or other sleep disorders. In the United States (in contrast to the rest of the world), melatonin is sold as an over-the-counter dietary supplement [22]. In healthy young and middle-aged human subjects, plasma concentrations of melatonin exhibit a 6-fold increase during the first 6 hours after bedtime, and the measured plasma melatonin profile is often used as a marker of physiologic events that take place during the sleeping hours [23]. An enormous number of psychologic, metabolic, and vascular effects have been attributed to variations in endogenous melatonin, and any physiopathologic consequences of such variations remain to be sorted out. So far, observations in human subjects have revealed close relationships between plasma melatonin values and the day/night cycle, as well as core body temperature. Since its discovery and the development of knowledge of its role in the regulation of sleep, melatonin has been implicated in numerous other physiologic functions—some of which are difficult to connect to our subject of sleep-related vascular disorders.

In vitro studies have shown that melatonin increases gluconeogenesis in primary cultures of rabbit kidney-cortex tubules, suggesting that this hormone might be able to protect animal species at risk against hypoglycemia [24]. In addition, melatonin is capable of enhancing glucose metabolism through the pentose phosphate shunt pathway, increasing production of nicotinamide adenine dinucleotide phosphate hydrogen (NADPH), and thereby influencing the cellular redox potential [25]. Finally, melatonin stimulates production of glutathione—a metabolite that helps to protect cells from oxidative stress [26]. Via this metabolic pathway, melatonin also may contribute to the protection of blood vessels—an action demonstrated experimentally in the kidney [27]. In the same protective manner, melatonin has been shown to protect blood vessels (including the aorta and corpus cavernosum) from the adverse effects of nicotine [28] and, by extension, against atherogenesis. Finally, among other unexpected beneficial effects of melatonin, this hormone was shown to reduce interstitial renal inflammation and improve blood pressure in the spontaneously hypertensive rat [29]. Some of these findings are summarized in Fig. 1.

2.4. Metabolic syndrome and sleep apnea

The metabolic syndrome is an increasingly common obesity-associated entity, characterized by visceral adiposity, fasting hyperglycemia, insulin resistance, arterial hypertension, a prothrombotic state, a proinflammatory state, and dyslipidemia (high triglyceride and low high-density lipoprotein cholesterol level) [30-32]. In individuals who exhibit a preponderance of the features of this constellation, the risk of developing cardiovascular disease doubles, and, eventually, the risk of sudden death also increases substantially [31]. Based on information presently available, the metabolic syndrome appears to arise primarily from an excess of energy intake over energy expenditure—ordinarily because of excessive energy intake or insufficient physical activity, or some combination of the two.

In addition to the metabolic defects traditionally implicated in the metabolic syndrome, it is important to note that hyperuricemia is becoming another potential marker of the syndrome. Hyperuricemia may arise from a diversion of carbohydrate metabolism to the pentose phosphate shunt and purine synthesis pathways. In a recent study in rats, a high-fructose diet was reported to induce important features of the metabolic syndrome, including hyperuricemia. Interestingly, administration of allopurinol, a xanthine oxidase inhibitor, was able to prevent or reverse the syndrome [33].

There is no doubt that many of the illnesses associated with obesity and the metabolic syndrome can, and do, interfere with normal sleep. Moreover, chronic sleep deficit is now known to be an independent risk factor for obesity [34]. However, from the perspective of the sleep disorders, the complication of obesity that has attracted the greatest attention is sleep apnea. It is important to be reminded that there are 2 forms of sleep apnea, central sleep apnea and obstructive sleep apnea. In central sleep apnea, there is an intermittent loss of respiratory drive, resulting in apnea that is then followed by compensatory periods of hyperventilation. In Somers' words [35], "Obstructive sleep apnea occurs when mechanisms that maintain upper-airway tone

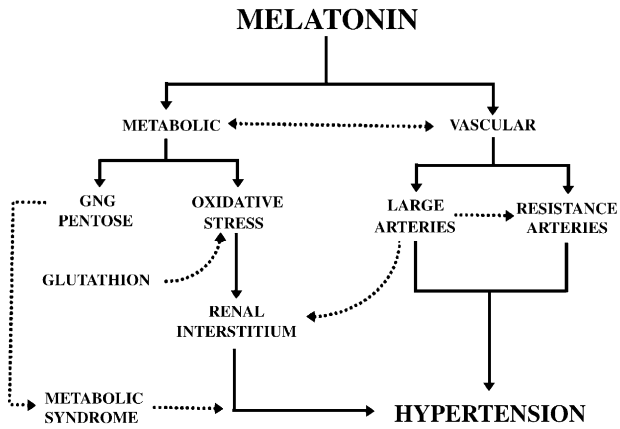

Fig. 1. Some documented physiologic effects of melatonin that may be involved in the development of vascular disorders. Metabolic actions (left side) may influence glucose metabolism via stimulation of gluconeogenesis (GNG) and increased activity of the pentose phosphate shunt (PENTOSE), leading to enhanced purine synthesis and uric acid production. Melatonin also promotes glutathione production, a potential protector against oxidative stress and damage to the renal interstitium. The vascular actions of melatonin (right side) may also modulate large-artery rigidity, an important contributor to arterial hypertension.

during sleep are dysfunctional, resulting in a narrowing or collapse of the airway . . .. Although obstructive sleep apnea and central sleep apnea differ in many respects, they are both linked to the modern-day epidemics of obesity, cardiovascular disease, and heart failure."

According to Shamsuzzaman and associates [36], nighttime obstructive apneas activate a number of cardiovascular disease mechanisms. However, because of its association with a variety of existing illnesses such as hypertension, insulin resistance, and obesity, the evidence that implicates sleep apnea as a causal factor in a range of cardiovascular disease disorders is mostly circumstantial and difficult to interpret.

Acknowledgment

In our preoccupation with light/darkness-related events in various animal species, we often overlook the remarkable photosynthetic plasticity of plants (such as orchids) in response to different light environments. Also, we need to learn more about the physiology of plants that contain varying amounts of melatonin. I should like to acknowledge our scientific debt to the botanists and their objects of study, and do so in lyrical fashion, "Who is your best friend capable of adapting to a day and night existence: *Cattleya*, my faithful orchid companion."

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