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THE CIRCADIAN SYSTEM AND THE VARIATION OF BLOOD PRESSURE THROUGHOUT DAY AND NIGHT

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ABSTRACT

The biological processes and functions fluctuate at regular intervals in time which is known as the circadian rhythm of the body, such as the sleep wake cycle, the circadian rhythm of blood pressure (BP), the body temperature cycle, etc. These circadian rhythms are under direct control of the bilateral paired suprachiasmatic nuclei (SCN) which are situated in the hypothalamus. There are various peripheral clocks which work in coordination with the central clock for maintaining and regulating the normal circadian timing of the body. These peripheral clocks comprise of the peripheral tissues and some organs and these in turn are regulated by the central circadian clock, i.e., the SCN. At the molecular level, there is presence of clock genes which are involved in mediating the final output of both of these central and peripheral circadian clocks. These circadian rhythms have accuracy in their timing and the factors promoting this accuracy are the various environmental time signals, the most important of which is the normal light dark cycle or the day night cycle. These circadian rhythms are very important for the normal functioning of all the bodily processes. The blood pressure also varies and follows a certain characteristic pattern during the twenty four hour period which is very essential for the normal cardiovascular health.

INTRODUCTION

The various biological rhythms are classified into three types based on the length of their cycles. First is the circadian rhythm in which the length of the cycle is nearly 24 hours. Second is the ultradian rhythm in which the length of the cycle is less than 24 hours, i.e., hours, minutes or seconds. An important example of this ultradian rhythm is the electrical activity of the brain which keeps on changing every minute. Third is the infradian rhythm in which the length of the cycle is more than 24 hours, i.e., days or months. An important example of this infradian rhythm is the menstrual cycle. Among these three, the most common is the circadian rhythms. These are most commonly associated with the cardiovascular system.[1,2]

The Circadian System

All the living organisms, whether it is unicellular, plants, insects or humans, possess an intrinsic timing system which fluctuates throughout day and night and affects various physiological functions. This system is known as circadian system. It comprises of two words: "circa" meaning around and "dies" meaning day.

There are two basic properties of this circadian system[3]

1. There is presence of an endogenous rhythmicity which has a time length of about twenty four hours. This rhythmicity is not lost by the fluctuations in external environment. For example, by the light dark cycle.
2. There may be phase shifting because of external factors. For example, due to light or intake of nutrients, phase shifting of circadian system can occur.

Mechanisms behind the Circadian Rhythm

It can be endogenous mechanism, exogenous mechanism, or combination of both endogenous and exogenous. Examples include:

1. Exogenous rhythm: The rhythm of growth hormone secretion is affected by sleep. So, sleep is an exogenous factor here.
2. Endogenous rhythm: Example is the respiratory rhythm which is regulated by internal mechanisms.
3. Majority of the circadian rhythms, including the cardiovascular rhythms, are influenced by both endogenous and exogenous factors.[4]

The Central Circadian Clock

The SCN is the central circadian clock and is located bilaterally in the anterior hypothalamus over the optic chiasm.[5]

There are various experimental evidences which indicates that the circadian rhythms are regulated by the SCN:

1. Any lesion of the SCN results in alteration of circadian rhythms.[6]
2. If a donor SCN is transplanted into a previously SCN lesioned rodent, then it leads to restoration of circadian rhythms.[7]
3. After transplantation of the donor SCN, the circadian rhythm in the recipient resembles that of donor's circadian rhythm.[8]
4. The circadian rhythmicity in firing rate of neurons of SCN is seen in vivo as well as in vitro.[9]

The circadian system also consists of the peripheral clocks such as cells, tissues and organs that are under control of the SCN.[10]

Inputs to the Scn

There are two types of inputs to the SCN

1. Photic signals: light
2. Non photic signals

The SCN receives light signals via two pathways[11]

1. Directly via the retinohypothalamic tract (RHT)
2. Indirectly via the geniculohypothalamic tract (GHT).

Lesions of these pathways leads to loss of synchronisation of circadian system with respect to light and dark cycle.[12] There are various other inputs also to the SCN, but their exact role in circadian system is not yet known.

Findings of other studies indicates that apart from light, synchronisation of circadian clock can occur from non photic signals also. Examples of non photic signals are melatonin, temperature, exercise and feeding.[13] If melatonin is administered daily to blind individuals, it synchronises with their circadian rhythm. Melatonin receptors are present in abundance in the SCN.[14] Temperature variations can affect the peripheral circadian clocks but it does not have an effect on the central circadian clock.[15]

Outputs of the Scn

The output of the SCN occurs via two pathways:

1. Endocrine or hormonal pathway: This includes various hormones like melatonin, cortisol, thyroid, epinephrine and norepinephrine. The levels of these hormones also varies throughout day and night and have a characteristic pattern. They have an endogenous rhythmicity.[16]
2. Neural pathway: It occurs through autonomic nervous system (ANS). There are projections to heart, liver, adipose tissue, kidneys, pancreas and adrenal cortex.[17]

Because of the influence of SCN on the ANS, there is presence of circadian variation in heart rate (HR) and blood pressure (BP) also.[18] As a result, the incidence of many adverse cardiovascular events peaks at a certain time of the day, particularly in the early morning hours.[19]

Circadian Variation of Blood Pressure

The circadian rhythm of BP follows the same pattern as of the autonomic nervous system which are under the influence of the SCN. Normally, there is a distinctive increase in the BP levels which occurs in the early morning time. This increase is known as morning surge of BP. After this, the BP level rises to high values during the daytime and the peak value is seen between 10 AM and noon. Then, the BP level falls in the afternoon which is known as siesta, and finally during the night time, BP falls to lower values and reaches its lowest value from 3 to 6 AM, or 1 to 3 hours before awakening. This is known as nocturnal dipping of BP.[20]

So, on the basis of this dipping pattern of BP, individuals are classified into two categories: dippers and non dippers. The dippers and non-dippers classification was first introduced by O'Brien E et al. in 1988. In dippers, the sleep time mean BP is less than the daytime mean BP by 10-20%. In non dippers, there is <10% reduction in sleep time mean BP as compared to daytime mean BP. In some cases of non dippers, night time mean BP may be even more than the day time mean BP.[21]

This diurnal variation of BP has got a prognostic value because it has been found that the individuals who show this non dipping pattern of BP are at high risk of cardiovascular diseases.[22]

Recently, one more circadian type of BP has been reported which is known as extreme dippers or over dippers. In over dippers, there is more than 20% fall in night time BP as compared to day time BP. This pattern of BP is also associated with higher risk of cardiovascular complications.[2]

Factors Affecting the Circadian Rhythm of Blood Pressure

Following are the factors which affect the rhythmicity of BP

1. Age: Nocturnal fall in BP is inversely related to age.
2. Sex: Hypertensive women have lower night time BP values than men.
3. Race: African Americans are more frequently non dippers than the whites.[23]
4. Physical activity: SBP is directly related to physical activity. So, increase in physical activity leads to increase in SBP also. If a person is active during night time, then his nocturnal BP fall is blunted. Lack of physical activity, for example, in case of astronauts, leads to loss of circadian variation of SBP.[24]
5. Autonomic function: Mainly the sympathetic nervous system and its markers epinephrine and norepinephrine are responsible for the circadian variation of BP. When a person awakes from sleep,

there is release of sympathetic markers, which causes the BP to increase. If the resting levels of these sympathetic markers are high in an individual, then there will be greater variability in day time BP and also more fall in nocturnal BP.[25]

6. Diet: Sodium is an important component of our daily diet. If sodium intake is restricted, then it leads to restoration of dipping in patients of hypertension who were earlier non dippers. [26]
7. Posture: There is change in BP levels when a person changes his posture, i.e., from supine to sitting or standing. So, the change of posture throughout day and night is also a contributing factor for the BP variability.

Pathophysiology of Non Dippers

Any abnormality in the intrinsic circadian cycle can lead to absennce of nocturnal dip in BP. Non dipping of Bp is seen in following conditions:

1. Essential hypertension,
2. Secondary hypertension
3. Diseases involving ANS like autonomic failure

The cause of non dipping in patients of hypertension[27]

1. Increase in the level of sympathetic activity
2. Sympathetic activity fails to decrease in night.

There are various findings in non dippers which suggests that there is sympathetic over activation in them [28,29]:

1. Non dippers have impairment in excretion of sodium through kidneys in standing posture.
2. In supine position, norepinephrine is released inappropriately in non dippers.
3. In night time, there is no fall in rate of urinary excretion of epinephrine and norepinephrine.
4. There is increased sensitivity of adrenergic receptors

CONCLUSIONS

The proper functioning of the circadian system is very important because the disruption of circadian timing can result in various disorders including disorders of sleep, metabolism, obesity and even decrease in life expectancy. So, extensive research is required in this field of circadian rhythms and the factors causing its disruption so that the risk factors can be modified.

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