Relationship between circadian disturbance and hypertension

Yinuo Cai *

Maple Leaf School, Grade 11, Tianjin, China

* Corresponding author: 21030008@students.mapleleafedu.com

Abstract. According to the largest survey of its kind to date, since 1990, the number of 30-to 79-year-olds with hypertension has increased rapidly from 650 million to 1.28 billion. Although this number is rising rapidly, no one knows what causes blood pressure to rise. The cause of hypertension is still unclear. The factors that contribute to elevated blood pressure are numerous and confusing. Studies have shown that abnormal biological rhythms can lead to hypertension. One of the key factors contributing to elevated blood pressure is an abnormal biorhythm. It has also been shown that abnormal biological rhythms can lead to hypertension. The nervous system, the renin-angiotensin-aldosterone pathway and melatonin secretion from the pineal gland may all be affected by circadian rhythm problems, which in turn affects glucocorticoid-mediated hypertension, and thus the development and progression of hypertension. The current intervention of it mainly based on pharmacological therapy, supplemented by improvement of lifestyle habits. Several new strategies for the treatment of hypertension have emerged in recent years. For example, acupuncture needle treatment, melatonin promotion treatment, RDN treatment hair etc. This study will present these methods and experiments to draw conclusions.

Keywords: Circadian disturbance, hypertension, RAAS, Acupuncture, Melatonin, RDN, blood pressure.

1. Introduction

Hypertension can harm the heart, brain, kidneys, and other systems organically or functionally. The most common persistent illness, hypertension plays a significant role in arterial and cerebrovascular disease. Blood pressure in healthy individuals fluctuates within a predetermined range in reaction to changes in the internal and exterior surroundings. Normally, systolic blood pressure generally increases with age, while after the age of 50, diastolic blood pressure starts to decline and pulse pressure increases. Recently, there has been a greater understanding of the numerous risk factors leading to cardiovascular disease and the diagnostic criteria for hypertension are being revised. The World Health Organization and Imperial College London led a comprehensive analysis of the prevalence of hypertension, which was published in the Lancet on 25 August 2020. In the last 30 years, according to the largest-ever study, the number of people aged 30-79 with hypertension has risen from 650 million to 1.28 billion. This number is rising rapidly, but it remains unclear what causes high blood pressure. Currently, medication is the main treatment for hypertension, and lifestyle changes to adjust the work and rest to obtain a good biological clock is a complementary measure [1]. But medical technology continues to innovate, and it has long been known that taking blood pressure drugs in concert with the body clock is more effective. Exogenous and endogenous rhythm systems make up the circadian system. Through neural or neuroendocrine pathways, the master clock of the endogenous rhythm system controls the typical circadian variation of it. Several new techniques for the management of hypertension have been developed, including autonomic modulation (vagus nerve stimulation, renal denervation, etc.), melatonin-assisted therapy and chronotherapy with anti-hypertensive drugs [1]. Thus, regulation of the body clock can be an effective treatment for hypertension. But how do circadian rhythm disturbances cause hypertension and what is the relationship between them? This is a topic worth exploring in terms of the etiology of hypertension.

In this article, we examine the relationship between circadian rhythm disturbances and hypertension. This article describes the causes of hypertension and some of the treatments available, thus examining the relationship between dysbiosis and hypertension.

2. The circadian rhythm of blood pressure

As the primary circadian controller in the biological clock, the suprachiasmatic nucleus not only generates an approximately 24-hour circadian cycle of endogenous molecules and behaviors, but also resets and synchronizes dormancy in response to the light-dark cycle of exogenous circadian rhythm changes [2]. The suprachiasmatic nucleus translates exogenous light and dark circadian signals transmitted via the retinohypothalamic tract into neural and/or humoral signals, thereby regulating the circadian rhythms of different physiologies and behaviors [2], and influences the blood pressure, which is 10% - 20% lower at night than the day. Factors that regulate blood pressure, such as melatonin, RAAS and autonomic god, have an endogenous circadian rhythm and are associated with this regulation. The lowest values of sympathetic tone in the autonomic nervous system occur between 2 and 4 o'clock, and the maximum occurs between 16 and 18 o'clock, showing resonant oscillations [3]. People with circadian disorders may experience an increase in blood pressure at 10 pm, for example, people who work night shifts may experience an increase in blood pressure at around 10 pm. Typically, healthy adults experience two blood pressure peaks during the day. The first peak may occur around 7-9am and the second peak may occur around 2-4pm. If blood pressure rises suddenly at around 10pm, it can generally be called nocturnal hypertension. People who have circadian disruptions are more likely to develop nighttime hypertension because their sympathetic nervous system may become overexcited at night, which would raise their blood pressure. To ascertain whether there is a rise in blood pressure at night, this set of individuals should undergo nocturnal sleep tracking and blood pressure monitoring. The scheduling and dose of antihypertensive medicine should be quickly changed if a person with hypertension develops nocturnal blood pressure rise to effectively reduce its recurrence.

3. Circadian rhythm disturbance promotes the occurrence and development of hypertension

Individuals with jet lag, night work or shift work may be stimulated by irregular or prolonged changes in the light-dark cycle, causing circadian rhythm disturbances that cause the blood pressure to rise and deterioration of cardiac function, promoting the development and progression of hypertension [4]. Healthy adults were placed in a light-dark cycle for 28h to develop a pattern of circadian rhythm disturbance. After 7 days of intervention, mean pulse pressure was found to be 3% higher than baseline levels [1]. Researchers looked at clinical data and discovered that systolic and diastolic blood pressure both rose, over the course of a day, in the long-term shift work group compared to the normal working hours group [5]. Blood pressure and heart rate continued to rise after 12 hours of night work and remained elevated after 36 hours of rest. In one experiment, a 24-hour-a-day light intervention for 6 weeks not only caused increasing blood pressure of model animals, but also promoted left ventricular fibrillation and left ventricular hypertrophy [6], which caused the blood pressure to rise. Most normal people have lower blood pressure than the nighttime working group relative to the group that has a nighttime job. These studies suggest that circadian rhythm disturbances induced by night work can not only elevate blood pressure and delay its return to normal levels, but also promote left ventricular hypertrophy and fibrosis, worsening cardiac function and promoting the development of hypertension. It is also evident that circadian clock disturbances can promote the development and progression of hypertension. These experiments can also provide evidence for the conclusion.

4. The mechanism of Circadian rhythm and hypertension

4.1. Inhibition of melatonin synthesis and secretion leads to the formation and progression of hypertension

The exact mechanisms of blood pressure affected by melatonin are not fully understood and further research is necessary to elucidate this relationship. This area has great potential for research as it has the potential to identify new therapeutic strategies for hypertension and improve public health outcomes. Melatonin, also known as melatonin, is a chemical compound that is present in microbes, fungus, plants, and mammals. Melatonin controls the biological cycle of animals; its effects may vary in other creatures, and animals' melatonin synthesis varies from that of other species. Melatonin is an over-the-counter drug in the United States, Canada and some European countries, and is mostly used as a health food in mainland China (for example, Nao Platinum contains melatonin as one of the main active ingredients). It is a neuroendocrine hormone produced by the pineal gland. Projection of the supraspinal nucleus to the pineal gland via autonomic neurons in the paraventricular nucleus, Sympathetic preganglionic neurons neurons in the first thoracic segment of the spinal cord and multilevel adrenal sympathetic pathways in the superior cervical ganglion. Norepinephrine released from sympathetic nerve terminals binds to beta and alpha-adrenergic receptors on the pineal cell membrane. In addition, the cyclic adenylate protein kinase A-cyclic adenylate reaction activates the protein and phospholipase C-CA2 +-protein kinase C signaling pathways, thereby promoting melatonin synthesis [7]. Continuous light or nocturnal light inhibits melatonin synthesis and secretion [8]. Circadian rhythm disturbances can increase blood pressure by inhibiting melatonin synthesis and secretion, which may be caused by reduced melatonin binding to vascular receptors, increased cyclic adenosine water levels and decreased intracellular Ca2 + levels. Studies have shown that rats with melatonin deficiency induced by excision of the pineal gland or continuous light exposure will develop hypertension [9]. To prevent nitric oxide from constricting blood vessels and increasing peripheral resistance to hypertension, it is necessary to increase the production of phospholipase C, diacylglycerol and phosphatidylinositol. Melatonin supplementation can significantly lower blood pressure and inhibit the onset and progression of hypertension. One can work out more solutions from the point of how to promote melatonin. In conclusion, disturbances in circadian rhythms can prevent the production and secretion of melatonin, prevent the production of NO in blood vessels, lead to vasoconstriction and increase peripheral resistance, all of which leading to the hypertension.

4.2. Circadian clock gene mediators for hypertension

With the continuous research on diseases caused by hypertension, it has been found that different cardiovascular diseases, such as myocardial ischemia and myocardial infarction, occur mostly in the early morning and have a rhythmic onset. Various cardiovascular physiological functions, such as blood pressure, have distinct circadian rhythms. This not only suggests a close relationship between cardiovascular physiological functions, cardiovascular disease and circadian rhythms. It also suggests that an increase in the activity of endocrine vasoactive factors such as norepinephrine and the RAS can lead to a higher myocardial oxygen demand, which may be one of the reasons why ischemic heart disease tends to occur in the morning [10]. Short-term administration of angiotensin II induces strong expression of the mPer2 gene, followed by synchronous periodic oscillations of other components of the biological clock. This effect is mediated by the angiotensin II receptor, as blocking this receptor eliminates the high expression of mPer2. This suggests that angiotensin II may be involved in target organs such as the aorta, adjusting clock gene expression of the cell in heart and kidney in response to environmental changes these may cause cardiovascular disease. Blood pressure variations show circadian rhythms and abnormal changes in blood pressure rhythms are a risk factor for many cardiovascular diseases. In a study of Dahl salt-sensitive rats, it was found that after 6 weeks of hypertension induced by salt, the amplitude of daily blood pressure rhythm fluctuations increased in rats, while the amplitude of circadian oscillations of mPer2, Bmal1 and dbp in peripheral organs such as heart, liver and kidney decreased compared to controls on a conventional diet, except for Bmal1

in the liver [11]. In spontaneously hypertensive rodents, recent study discovered that the blood production of PAI-1 was increased in rats with spontaneous hypertension due to greater clock gene expression [12]. A rise in the blood concentration of PAI-1, an inhibitor of plasminogen activator, causes a hypercoagulable condition that may be related to a higher risk of myocardial infarction and early hypertension.

4.3. Activation of renal sympathetic nerves and RAAS leads to fluid retention mediators hypertension

The kidney is the most critical organ in the body for the metabolism of water and sodium, and it controls changes in blood pressure as well as sympathetic and RAAS activity throughout the day and night. Rats exposed to daylight have higher blood pressure and pulse, as well as higher renal efferent sympathetic activity and lower gastric vagal tone [13]. Circadian rhythm disturbances may raise blood pressure by increasing renal sympathetic activity, as renal sympathetic activation promotes constriction of the renal arterial inlet, decreases effective renal filtration rate, and increases effective circulating blood volume. Studies have further demonstrated that the rate of epinephrine excretion in the 24-hour urine of shift workers is greatly reduced [5]. In addition, it has been shown that under typical light-dark cycle conditions, urinary output and sodium excretion in dogs peaks during the day, while their osmolality and potassium excretion peaks at night. This is associated with a marked increase in the activity of hormones such as pressin, aldosterone and renin at night [14]. After 5 weeks of reversal of the light-dark cycle, it was completely reversed that the circadian rhythms of renin activity and aldosterone levels in rat plasma [15], and the continuous light intervention inhibited water consumption and reduced urine volume and sodium excretion [16], suggesting that circadian rhythm disturbances caused by changes in the light-dark cycle can promote renal reabsorption of water and salt through the RAAS. This increases the effective circulating blood volume, which in turn raises blood pressure. In conclusion, circadian rhythm disturbances can lead to renal sympathetic activation, increased plasma renin and activation of the RAAS, which causes peripheral arterial vasoconstriction, increases peripheral circulatory resistance and promotes renal reabsorption of water and sodium, leading to hypertension. Anti-hypertensive drugs such as beta-blockers, diuretics and RDN may be effective strategies to reduce hypertension in circadian rhythm disorders. In conclusion, circadian rhythm disturbances can lead to renal sympathetic activation and plasma.

5. Reduces hypertension due to circadian rhythm disturbance

5.1. Acupuncture treatment intervention

The systolic blood pressure of rats decreased obviously in the acupuncture group at 14 and 21 hours, according to studies on rat models of acupuncture treatment [17]. At 14 hours, the acupuncture group's systolic blood pressure was considerably lower. After treatment, compared with before treatment, the pressure in acupuncture group decreased significantly at 21 o 'clock Low. mRNA expression levels of Bmal1, Clock and Per2 in myocardial tissue of rats in the 14:00 and 21:00 acupuncture groups were significantly down-regulated compared with the SHR model group, It can be seen that simulated acupuncture can reduce systolic blood pressure of SHR, down-regulate mRNA and protein expression of Bmal1, clock and Per2, and the antihypertensive effect of simulated acupuncture at 21h is better than that at 14h. Wang Yanjun et al. [18,19] found that acupuncture at different time points can reduce the total systolic and diastolic blood pressure of SHR, suggesting that the intervention time of acupuncture is one of the factors affecting the antihypertensive effect.This could demonstrate that artificial interventions in the timing of hypertension treatment can lead to better outcomes and that research in this area is significant.

5.2. Melatonin improves circadian rhythm disruption

Melatonin alleviates blood pressure problems associated with the circadian cycle Melatonin is a potential natural anti-hypertensive agent that serves a significant part in controlling blood pressure. Melatonin supplementation improves ventricle fibrosis and left ventricular enlargement and reduces oxidative stress damage to the left ventricle and aorta of chronic light-induced hypertension [6]. Melatonin lowers blood pressure, plasma catecholamine levels, and arterial reactions in healthy people, according to clinical studies [20]. The mechanism is that melatonin inhibits the release of 5-hydroxytryptamine in the brain and suppresses sympathetic nerves or activates parasympathetic nerves [21], thereby initiating the anti-hypertensive effect. Melatonin supplementation can act on blood vessels to increase nitric oxide production, dilate blood vessels and reduce peripheral vascular resistance. At the same time, it can enter the brain, inhibit central sympathetic output, reduce hypertension caused by circadian rhythm disturbances, improve the long-term prognosis of the cardiovascular system and is also effective in other types of hypertensions [1].

5.3. RDN treats hypertension

Renal denervation (RDN) is a novel hypertension treatment method that can achieve continuous blood pressure reduction by destroying the afferent and efferent sympathetic nerves in the kidney and blocking sympathetic overexcitation therapy is regarded as a successful non-drug approach to treating intractable hypertension. By increasing the activity of gamma-aminobutyric neurons in the paraventricular nucleus, RDN may lower the level of dopamine and sympathetic tone in the brain stem. RDN can also restore normal circadian rhythm changes of metabolism-related hypertension, improve vascular endothelial function, and reduce the damage of oxidative stress on the cardiovascular system [22]. Clinical trials have shown that after 3 months of transcranial RDN treatment in hypertensive patients, the blood pressure decreased, without the occurrence of adverse events [23]. Due to its destructiveness, RDNs are currently only used to treat drug-resistant hypertension. Ablation methods for RDN include cry balloon ablation and radiofrequency catheter ablation. However, which RDN ablation method can effectively reduce sympathetic activity caused by circadian rhythm disturbance is worth further exploration.

5.4. Time therapy to control antihypertensive drugs

As previously mentioned in the introduction, better treatment results can be obtained by controlling the treatment time, which has a complex mechanism. Antihypertensive drugs like calcium channel blockers and diuretics are commonly used in the therapeutic therapy of hypertension. varying dosage periods result in varying antihypertensive effects. [Anti-hypertensive drugs have been shown to greatly decrease the frequency of adverse events]. When compared to taking antihypertensive medications while conscious, the utilization of antagonists of the angiotensin-converting enzyme or angiotensin receptor blockers at night also returns the non-arterial blood pressure pattern to a normal blood pressure circadian rhythm pattern [24]. This suggests that the antihypertensive effect of antihypertensive drugs taken at different times of day may be related to age, gender, and drug dose. Although circadian rhythm disturbances mainly affect blood pressure regulatory factors through changes in the temporal phase of light to raise blood pressure, drug treatment can achieve more satisfactory results. However, the effect of circadian rhythm disorders on hypertension is still worth exploring as the effect of anti-hypertensive drugs on chronotherapy is controversial.

6. Conclusion

Hypertension is a common disease of the cardiovascular system, which is influenced by a variety of lifestyle and genetic factors. Night shifts, shift work, or jet lag can cause disruptions in circadian rhythms that increase central and renal sympathetic outflow, activate RAAS, inhibit melatonin production and secretion, and increase blood pressure. There are many ways to reduce hypertension caused by circadian rhythm disturbance. Here, acupuncture therapy, RDN therapy, control of

medication time and melatonin can improve circadian rhythm disturbance, but these methods are not all. These methods are related to circadian rhythm and affect hypertension. Through this study, the logical closed loop between hypertension and circadian rhythm disturbance can be generally understand, which can help to study other aspects of this field. For example, circadian rhythm disturbance leads to hormone secretion imbalance in the body, which contributes to the production and development of hypertension. Why a disrupted body clock has a complicated effect on hypertension is a question for future research.

References

[1] Chen Hu, et al. Research progress of circadian rhythm disturbance and hypertension [J]. Medical Review, 201, 27 (08): 1567 - 1573.

[2] Park J, et al. Effect of night shift work on the control of hypertension and diabetes in workers taking medication [J]. Ann Occup Environ Med, 2019, 31: e27.

[3] Linsell CR, et al. Circadian rhythms of epinephrine and norepinephrine in man [J]. J Clin Endocrinol Metab, 1985, 60 (6): 1210 - 1215.

[4] Scheer FA, et al. Adverse metabolic and cardiovascular consequences of circadian misalignment [J]. Proc Natl Acad Sci U S A, 2009, 106 (11): 4453 - 4458.

[5] Morris CJ, et al. Circadian misalignment increa ses cardiovascular disease risk factors in humans [J]. Proc Natl Acad Sci U S A, 2016, 113 (10): E1402 - 1411.

[6] Simko F, et al. Hypertension and cardiovascular remodeling in rats exposed to continuous light: Protection by ACE-inhibition and melatonin [J]. Mediators Inflamm, 2014, 2014: 703175.

[7] Amaral FGD, et al. A brief review about melatonin, a pineal hormone [J]. Arch Endocrinol Metab, 2018, 62 (4): 472 - 479.

[8] Smolensky MH, et al. Nocturnal light pollution and underexposure to daytime sunlight: Comple mentary mechanisms of circadian disruption and related diseases [J]. Chronobiol Int, 2015, 32 (8): 1029 - 1048.

[9] Simko F, et al. Experimental models of melatonin-deficient hypertension [J]. Front Biosci (Landmark Ed), 2013, 18: 616 - 625.

[10] Li JJ. C ircadian variation in myocardial ischem ia: the possible mechanism s involving in this phenom enon [J]. Med Hypotheses 2003 61 (2): 240 - 243.

[11] M ohri T, Emoto N, Nnaka H, et al. A lternation ofcirca-dian expression of clock genes in Dahl salt - sensitive rats fed a high - salt diet [J]. H ypertension, 2002, 42 (2): 189 - 194.

[12] Naito Y, et al.C ircadian expres-sion of clock genes and plasminogen activator inhibitor-1 in heartand aorty of spontaneously hypertensive and Wistar-Kyoto rats [J]. J H ypertens, 2003, 21 6): 1107 - 1115.

[13] Mutoh T, et al. Melatonin modulates the light-induced sympathoexcitation and vagal suppression with par ticipation of the suprachiasmatic nucleus in mice [J]. J Physiol, 2003, 547 (Pt 1): 317 - 332.

[14] Gordon CR, et al. Day-night variations in urine excretions and hormones in dogs: Role of autonomic innervation [J]. Physiol Behav, 1985, 35 (2): 175 - 181.

[15] Hilfenhaus M. Circadian rhythm of the renin-angiotensin-aldoste rone system in the rat [J]. Arch Toxicol, 1976, 36 (3/4): 305 - 316.

[16] Stoynev AG, et al. Effect of constant light and darkness on the circadian rhythms in rats: I. Food and water intake, urine output and electrolyte excretion [J]. Acta Physiol Pharmacol Bulg, 1983, 9 (3): 58 - 64.

[17] SHU Ya, et al. Effects of simulated acupuncture on the expression of Bmal1, Clock and Per2 in myocardial clock genes in rats with spontaneous hypertension [J]. Journal of Shanghai University of Traditional Chinese Medicine, 2021, 35 (04): 89 - 93.

[18] Wang Yanjun, et al. Different effects of Chen hour acupuncture on Chen hour and Youhour Blood pressure of spontaneous hypertension rats [J]. Chinese Journal of Traditional Chinese Medicine, 2018, 33 (1): 362 - 365.

[19] Wang Yanjun, et al. Chen hour acupuncture on SHR noon and noon blood pressure data analysis of repeated Measurement of Change [J]. Chinese Journal of Basic Medicine of Traditional Chinese Medicine, 2018, 24 (11): 1589 - 1591.

[20] Pandi-Perumal SR, et al. Melatonin and human cardiovascular disease [J]. J Cardiovasc Pharmacol Ther, 2017, 22 (2): 122 - 132.

[21] Chuang JI, et al. Melatonin decreases brain serotonin release, arterial pressure and heart rate in rats [J]. Pharmacology, 1993, 47 (2): 91 - 97.

[22] Katayama T, et al. Long-term renal denerva tion normalizes disrupted blood pressure circadian rhythm and ameliorates cardiovascular injury in a rat model of metabolic syn drome [J]. J Am Heart Assoc, 2013, 2 (4): e000197.

[23] Townsend R R, et al. Catheter-based renal denervation in patients with uncontrolled hypertension in the absence of antihypertensive medications (SPYRAL HTN-OFF MED): A randomized, sham-controlled, proof-of-concept trial [J]. Lancet, 2017, 390 (10108): 2160 - 2170.

[24] HermidaRC, et al. Chronotherapy with val sartan/hydrochlorothiazide combination in essential hypertension: Improved sleep-time blood pressure control with bedtime dosing [J]. Chronobiol Int, 2011, 28 (7): 601 - 610.