Melatonin and Hypertensive Disorders of Pregnancy: A Narrative Review

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ABSTRACT

Hypertensive disorder complicating pregnancy (HDP) is a common pregnancy complication that seriously threatens the safety of mother and baby. The current antihypertensive drugs have safety limitations and often fail to protect placenta well, which shows that we really need new, safer and more effective treatment strategies. In this paper, we use the methods of literature review and content analysis to collect recent research on melatonin and its role in hypertensive disorder complicating pregnancy. Oxidative stress plays a very important role in HDP. Endogenous melatonin has the characteristics of antioxidation and vascular protection, and has become a promising supplementary intervention strategy for HDP in recent years. By summarizing and analyzing the effects of melatonin and its mechanism, we hope to provide theoretical basis for the safe and accurate clinical use of melatonin to manage HDP. The current evidence shows that melatonin has potential value for HDP. However, its optimal dosage, correct time and long-term safety have not been confirmed. In addition, melatonin with different curative effects is an area to be explored in the future according to the clinical subtypes and age groups of patients.

Keywords: Melatonin, Hypertensive Disorders of Pregnancy, Antioxidant, Placenta, Vascular Endotheliam.

1. INTRODUCTION

Hypertensive disorder complicating pregnancy (HDP) means that pregnant women have high blood pressure, which is a common complication during pregnancy. According to the guidelines for diagnosis and treatment of hypertension in China in 2015, HDP can be divided into four categories: pregnancy-induced hypertension, preeclampsia, chronic hypertension complications and chronic hypertension complications [1]. With the implementation of the two-child policy, the proportion of HDP has steadily increased, and the proportion in China is about 5.22% [2]. Blood pressure management deserves close attention. A study comparing HDP patients with normal pregnant women shows that ADHD during pregnancy is related to higher caesarean section rate and bleeding rate. After delivery, the baby has abdominal pain, neonatal asphyxia and low birth weight-which poses serious risks to the mother and baby [3].

Therefore, the safety of drugs during pregnancy is very important for mother and fetus. However, there are few drugs to treat hypertension, so it is difficult to evaluate its clinical safety [4]. Commonly used antihypertensive drugs are mainly used to control the blood pressure of pregnant women, but they cannot cure the basic diseases. In addition, they often ignore the potential impact on the placenta, which may further reduce blood flow, thus causing harm to the fetus [5,6]. At present, no antihypertensive drugs have been proved to be absolutely safe for HDP patients. Therefore, when choosing treatment, priority should be given to the safest and most reliable drugs known at present [6].

In 2012, the Hypertension Expert Committee of China Medical Association reported that the emergence of hypertension disease. Inpregnance is related to factors such as immune problems, placental ischemia, heredity and oxidative stress. Among them, oxidative stress is a key pathogenic mechanism, which provides a theoretical basis for antioxidant intervention [7]. Therefore, the use of antioxidants to reduce oxidative stress-a key factor in the development of HDP-may be a good strategy to protect placenta and maternal endothelium. Melatonin, as a safe endogenous hormone, shows important antioxidant and antihypertensive effects. Studies have shown that although the effect of melatonin on blood vessels may vary from animal species to animal species, in humans, it can lower the blood pressure of mothers and safely delay delivery [5]. Although it is not clear how melatonin lowers blood pressure, its protective effect on placenta and endothelial cells has been confirmed by many studies, which leads to its introduction into the treatment of HDP [8].

This review will use the methods of literature review and content analysis to collect the latest and highly appreciated research on melatonin and hypertension in recent years. It will summarize and generalize the influence of melatonin on HDP and its potential mechanism, and provide the basis and direction for safe and accurate treatment of hypertension.

2. MELATONIN

Melatonin (n-acetyl-5-methoxytryptamine) is a metabolite of L-tryptophan. It is mainly produced by the pineal gland in the brain and is the central regulator of our body's circadian rhythm. In addition, melatonin can also be produced locally in different peripheral tissues, such as retina, heart, abdominal cavity, placenta, skin, kidney and intestine [8, 9]. Melatonin is soluble in fat and water, which makes it easy to cross the physiological barrier. It has many biological effects-such as anti-oxidation and anti-inflammation, regulating circadian rhythm, maintaining the steady state of pregnancy, and promoting the neural development of fetus-by eliminating reactive oxygen species, activating antioxidant enzymes, and combining with MT1 and MT2 receptors [10].

Melatonin has a short half-life, about 40 minutes, and it is metabolized quickly in the body. Studies have shown that its secretion is light-dependent and follows the circadian rhythm. During the day, the secretion of melatonin is inhibited, resulting in a very low level; At night, secretion gradually increases, and then returns to a low level in the morning. Exogenous melatonin intake may help to maintain the hormonal balance of the body and effectively improve sleep disorders [11]. In addition to regulating sleep, exogenous melatonin has the advantages of low effective dose, mild pharmacological action and no toxic and side effects, which deserves great attention from French and foreign medical circles. Many clinical trials show that melatonin has a variety of pharmacological activities, including anti-oxidation, free radical capture, immune system enhancement and anti-tumor, and is expected to be used in the clinical treatment of cancer and hypertension [12].

3. THE CORRELATION BETWEEN MELATONIN AND HDP

In recent years, although great progress has been made in the treatment of antihypertensive drugs, these treatments still cannot cure or slow down the progress of the disease, and may even affect the health of mothers and fetuses. During pregnancy, melatonin is mainly secreted by placenta, and its level changes with pregnancy age and fetal development. Melatonin can cross the placental barrier, help the circadian rhythm and nerve development of the fetus, and maintain the balance of pregnancy through its anti-inflammatory and antioxidant effects [13]. Studies have shown that there is an important relationship between melatonin levels and blood pressure. Abnormal changes in blood pressure will disrupt the rhythmic secretion of melatonin. Studies have shown that pregnant women's blood pressure at night is higher than that of non-pregnant women, and with the increase of blood pressure, melatonin levels tend to decrease. When pregnant women suffer from hypertension, the melatonin level is significantly lower than that of normal pregnant women, and this decline will become stronger if the condition worsens [14, 15]. This shows that the lower melatonin level is related to the severity of HDP.

Because of the complex etiology and the mechanism of HDP that has not been fully explained, taking melatonin from outside has become a promising new method to help treat HDP. A study in 2022 found that melatonin can cross the placenta and exist in breast milk, which plays an important role in mother and fetus: in mother, melatonin can have anti-inflammatory effect during high-risk pregnancy and start and promote delivery, which is helpful for downstream delivery; In the fetus and newborn, melatonin not only regulates the circadian rhythm and ensures the normal neural development of the fetus, but also reduces the oxidative stress of the newborn and continues to support the establishment of the circadian rhythm and the growth after birth[16]. Although the current research is still insufficient, people can usually conclude that there is a functional relationship between melatonin and HDP, which works together at three levels: concentration, rhythm and receptor.

4. MECHANISM OF MELATONIN'S EFFECT ON HDP

The pathogenesis of hypertensive diseases (HDP) is very complicated. The imbalance of oxidative stress and the loss of function of placenta and vascular endothelial cells are the main pathological mechanisms. Melatonin is an important endogenous bioactive substance with strong antioxidant effect. It eliminates excess reactive oxygen species and reduces the damage caused by oxidative stress. At the same time, melatonin can protect the normal structure and physiological function of placenta, thus improving placental perfusion. In addition, melatonin can also regulate the homeostasis of

vascular endothelial cells. This improved vascular dysfunction and restored normal vascular tone. Based on these various regulatory mechanisms, this paper will discuss the role of melatonin in the following three aspects of HDP.

4.1 Antioxidant

Melatonin was originally known for its antioxidant properties. It is considered as a safe endogenous antioxidant hormone. Many studies have confirmed that melatonin can reduce the damage of oxidative stress, eliminate oxygen free radicals and reduce the level of reactive oxygen species [17, 18]. In vitro and in vitro studies show that melatonin plays a beneficial role in optimizing placental function and reproductive microenvironment. For example, Milczarek et al. The first experimental evidence is given that melatonin, depending on its concentration, inhibits coenzyme II-dependent lipid peroxidation in human placenta mitochondria. This provides a direct mechanical basis for its potential application in HDP [19]. In addition, studies have shown that melatonin reduces oxidative damage during follicular development and improves uterine receptivity. This thus improves the success rate of implantation, both in vivo and in vitro [20].

In animal experiments, melatonin shows the protective effect and long-term preventive effect on the fetus. Evidence shows that it reduces the oxidative stress damage in the mitochondria of rat fetal brain during ischemia reperfusion. It achieves this through its antioxidant properties, thus improving mitochondrial respiration [21]. In addition, in the rat model exposed to lipopolysaccharide before birth, it has been found that melatonin can effectively prevent hypertension in infant rats. This protective effect works by calming the renal-angiotensin system (RAS) and sympathetic nervous system (SNS), which are too active in the paraventricular nucleus. This subsequently reduces the level of reactive oxygen species [22].

On the basis of these basic research results, recent theoretical comments have further expanded its potential in clinical translation. A review in 2024 pointed out that melatonin can effectively prevent and treat cardiovascular Kideney metabolic syndrome (CKM) by regulating oxidative stress [17]. In view of the common pathophysiological basis of CKM syndrome and hypertension, and melatonin has a positive impact on fetal programming and pregnancy outcome, it seems promising as a powerful reprogramming intervention. However, at present, the evidence about melatonin preventing HDP mainly comes from mechanical exploration in vitro and animal experiments. Therefore, its clinical efficacy in humans and the exact mechanism of its role in CKM and pregnancy complications need to be further clarified.

4.2 The protective effect on the placenta

Placenta is a very important organ during pregnancy. It works a lot and has a lot of oxidative stress. It must balance oxidation and antioxidant defense to maintain health and good function.

A study published in 2022 found that in pregnant women with placental insufficiency, the mother's oxidative stress is higher, but the production of melatonin is lower. This leads to lower melatonin levels in the whole body and placenta, and fewer melatonin receptors [23].

Another study measured the levels of melatonin in the blood of normal pregnant women and pregnant women with problems in different pregnancy periods. It shows that the slow increase of melatonin in the mother's blood during the whole pregnancy can objectively tell us the condition of the fetus and placenta [15].

In addition, the experiment shows that the effect of melatonin is mainly through eliminating free radicals and preventing lipid peroxidation in human placenta mitochondria in a way dependent on its concentration. This effect is helpful to reduce the over-saturation of oxidative stress in placenta, and brings hope for the antioxidant treatment of preeclampsia [24].

In addition, a study in 2022 showed that melatonin can prevent trophoblast death through secretion, paracrine or endocrine mechanisms through MT1 and MT2 receptors in placenta, which is helpful for the growth of syncytiotrophoblast [16]. In fact, the placenta is the source of melatonin and contains melatonin receptors. In addition to relying on trophoblasts to produce melatonin, a study in 2023 reported for the first time that placental macrophages can also produce melatonin. The experiment also found that in women with preeclampsia, the production of melatonin and the oscillation mode of macrophages changed, which indicated the importance of studying the synthesis of placental melatonin during normal pregnancy and preeclampsia [25]. Another controlled trial showed that pregnant women with preeclampsia had much less melatonin and placental growth factor in venous blood than pregnant women with normal pregnancy. According to the experimental results, it is considered that the poor placental function of these patients may prevent the production of antioxidant hormones melatonin and pro-angiogenic placenta growth factor, which will help to raise blood pressure [26].

4.3 Regulation of vascular endothelial function

Endothelial dysfunction is the core pathological mechanism of hypertension. Melatonin can protect vascular endothelium by acting on a variety of signal pathways, and effectively improve endothelial cell dysfunction. Its protective effect is mainly manifested in reducing oxidative stress, inhibiting cell proliferation and inhibiting inflammatory reaction, which is closely related to the regulation of NLRP3 inflammatory corpuscle pathway.

The protective effect of melatonin on vascular endothelial cell injury induced by lipopolysaccharide was studied in vitro. The results showed that melatonin significantly reduced the injury of endothelial cells induced by lipopolysaccharide and effectively increased the cell viability. It is speculated that the protective mechanism of melatonin may be related to inhibiting cell production, reducing oxidative stress damage and maintaining the migration ability of endothelial cells, thus promoting the repair and protection of damaged vascular endothelial cells [27]. A study confirmed by a clinical trial in 2018 shows that melatonin has the potential to reduce the oxidative damage of pregnant women's endothelium, and can be used as a supplementary treatment of antihypertensive drugs to improve HDP. Although the sample size of this small-scale study is limited and may be biased, it is the first report on the use of melatonin in the treatment of pre-eclampsia [28]. In addition, a review in 2025 showed that melatonin can reduce the inflammatory reaction by preventing the formation and activation of NLRP3 inflammasome, which makes it have the potential to treat various diseases. This mechanism makes melatonin a promising candidate for the treatment of preeclampsia and provides a new scientific direction for the treatment of hypertension. However, the specific mechanism of melatonin inhibiting the activity of inflammatory corpuscles of NLRP3 and its therapeutic effect need further study [29].

5. CONCLUSION

This review examines the mechanism of melatonin in HDP. It shows that taking melatonin not only contributes to the natural defense of placenta, but also precisely protects placenta and blood vessels in many ways because of its main antioxidant activity. This ranges from the survival of placental cells (trophoblasts) and the formation of new blood vessels (angiogenesis) to the reduction of inflammation. Therefore, it can prevent and treat hypertension (hypertension disorder) during pregnancy.

A study (2019) shows that taking melatonin can prolong pregnancy time and reduce the demand for hypertension drugs, which provides new insights for the diagnosis and treatment of pregnancy-related diseases. Because of its antioxidant and hormonal properties, melatonin has the potential to treat and prevent gynecological diseases. Importantly, short-term administration has been proved to improve egg quality and fertility [30].

The level of melatonin in human body is quite low. When our bodies don't produce enough, we often need to get it from the outside. Some studies have shown that taking melatonin is safe for people who are not pregnant in a short time. However, if we eat too much, it may interfere with the way our body produces melatonin [31,32]. At present, there is not much research on the long-term safety or optimal dosage of melatonin. There are also few double-blind, randomized and placebo studies to see their effects on pregnancy [18,23,30]. In addition, more research is needed to understand how melatonin affects women with different types of clinical problems and women of different ages. In the future, more clinical studies are needed to determine the best time to start treatment, which dose is safe, and the long-term effects of melatonin on mothers and babies.

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