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Progress in the Application of metabonomics in the intervention of traditional Chinese Medicine on Hypertension

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Abstract: *The incidence of hypertension is high in China, and the mortality and disability rate of its complications are high. Metabonomics can accurately reflect the real-time metabolism of organisms. The syndrome type of traditional Chinese medicine is a pathological summary of the development stage of the disease. The integrity, systematicness and dynamics of metabonomics are highly consistent with the holistic view and syndrome differentiation view of TCM theory. In recent years, the use of metabonomics technology in the research of TCM syndrome has achieved certain results, and the angle and depth of the research are constantly expanding. Therefore, the purpose of this paper is to explore the effect of traditional Chinese medicine on the metabolites of hypertension by metabonomics. With a view to more accurate clinical application of traditional Chinese medicine.*

Keywords: *metabonomics, Hypertension, Metabolic disorder, Traditional Chinese medicine Syndromes*

1. Introduction

Hypertension is a multifactorial disease, which involves the changes of nerves, kidneys and hormones, mainly due to the increase of systemic arterial pressure, that is, diastolic blood pressure ≥ 90mmHg and / or systolic blood pressure ≥ 140mmHg. Essential hypertension has become one of the most important public health problems, affecting more than 1.2 billion people worldwide every year and causing about 9.4 million deaths. The latest data show that the prevalence rate of hypertension in China is as high as 27.9%, and the treatment rate accounts for only 45.8% of the hypertensive population. The control rate is only 16.8% [1]. Although the diagnosis of hypertension is usually based on blood pressure measured by a sphygmomanometer, lesions in the body often precede elevated blood pressure. In view of the fact that hypertension is associated with an increased risk of coronary artery disease, stroke and end-stage renal disease, early diagnosis and early intervention are essential. In recent years, there have been many studies on the mechanism of hypertension and the metabolic pathway of drug treatment through metabonomics. Even before systolic blood pressure reached the defined high blood pressure value, blood pressure-related changes in serum metabolism were observed in the nuclear magnetic resonance map [2-3]. This finding indicates that the patient's actual blood pressure is higher than the current definition. Using metabonomics may have an updated understanding of hypertension in the future.

Hypertension belongs to the category of "vertigo" and "headache" in traditional Chinese medicine. It has the characteristics of slow onset, long course of disease, lingering and difficult to heal, due to internal injuries of seven emotions, improper diet, excessive work and rest and other factors. It leads to the imbalance of yin and yang, abnormal ascending and descending disorder, phlegm and blood stasis, blood stasis and other symptoms such as dizziness, tinnitus, blushing and so on.

2. Metabonomics and characteristic metabolites of hypertension

Metabonomics, as a new discipline, mainly uses systematic detection and analysis techniques to find small molecular metabolites in blood, urine and other biological samples [4]. Metabonomics can dynamically reflect the effects of cellular activity and external factors on the metabolic state of the body, such as the metabolic process of exercise, drugs, diet and so on in the human body [5]. The influencing factors of cardiovascular disease are complex, so metabonomics is used to explore the effects of single or multiple factors on cardiovascular disease, so as to provide ideas for prevention and intervention treatment. In particular, it is of great help to the treatment process and treatment targets of drugs. It has a unique advantage in the individualized treatment of diseases. Small molecular metabolites between different individuals can judge the internal performance of the same disease in different individuals through metabonomics analysis, so as to explore targeted treatment plans according to the basic metabolic changes of different bodies.

Metabonomics mainly includes magnetic resonance spectroscopy ((MR)), which is a fast, effective and repetitive non-targeted metabonomic monitoring technique. It distinguishes chemical and structural information according to the resonance frequency produced by each nucleus in a molecule. Mass spectrometry ((MS)) is often used in combination with liquid chromatography (LC) and gas chromatography (GC). According to the mass-charge ratio of ions and fragment ions, mass spectrometry (MS) is often used in combination with liquid chromatography (LC) and gas chromatography (GC) to obtain the information of tested substances according to the mass-charge ratio of ions and fragment ions. The former has low sensitivity and resolution, so its accuracy and certainty are low for a variety of metabolites, while the latter is unable to detect single-generation metabolites because of the diversity of physicochemical properties of metabolites. However, with the continuous progress of technology, the quantitative and qualitative detection of small molecular metabolites can be realized more sensitively, and a variety of different metabolites can be qualitatively and quantitatively analyzed at the same time [7]. The level of metabolites per unit time can also be observed by isotope tracking technique to understand the whole metabolic process of target small molecular metabolites [8].

According to the different objects of study, the metabolic group is currently divided into four levels: 1 target analysis of metabolites, 2 metabolic spectrum analysis, 3 metabonomics analysis, 4 fingerprint analysis [9]. At present, the metabonomic research of hypertension is mainly focused on the target analysis and metabonomic analysis of metabolites. The metabolites of hypertension are mainly abnormal in carbohydrate metabolism, amino acid metabolism, fatty acid metabolism and microbial metabolism [10-11].

2.1 Disorder of glucose metabolism

Insulin resistance and abnormal glucose metabolism are often associated with essential hypertension. Among the risk factors of hypertension, insulin resistance has long been regarded as one of the important risk factors. Liu et al. found that the contents of glucose, galactose, glucosamine, sorbose and inositol in plasma of patients with hypertension increased, while the contents of fructose, fiber pond and lactic acid decreased, suggesting that glucose metabolism disorders may occur in both monosaccharides and disaccharides in patients with hypertension. It was found that the metabolites of α-ketoglutaric acid, citric acid, pyruvate and fumaric acid involved in tricarboxylic acid cycle decreased in patients with essential hypertension [13].

2.2 Fat metabolism disorder

Abnormal lipid metabolism is also one of the characteristic changes of hypertension. A metabonomic study based on GC-TOF-MS analysis found that the contents of serum free fatty acids (oleic acid, nonanoic acid, heptanoic acid, morphinic acid, caproic acid) in elderly patients with hypertension were significantly higher than those in normotensive controls [14]. Liu [15] divided spontaneously hypertensive rats into exercise group and control group, and used metabonomics to study the effect of exercise on spontaneously hypertensive rats. The results showed that the level of serum free fatty acid (FFA) in exercise group was significantly lower than that in control group. This study suggests that FFA has the potential to become a new marker of hypertension. High FFA levels usually coexist with insulin resistance, both of which can affect blood pressure simultaneously or independently. FFA can also induce inflammatory state and oxidative stress, which can activate the classical pro-inflammatory NF- κ B pathway in vivo, resulting in excessive expression of pro-inflammatory factors in the body, causing inflammation, and activating NADH oxidase to induce the production of reactive oxygen species, reduce the production of NO in endothelial cells, cause oxidative stress and endoplasmic reticulum stress [16], resulting in endothelial dysfunction, abnormal vasodilation and elevated blood pressure.

2.3 Amino acid metabolism disorder

The disorder of amino acid metabolism has been proved to be common in patients with hypertension in recent years. Mahbub et al found that amino acids are related to hypertension, mainly methionine and tyrosine. In Wang [18], it was found that the contents of isoleucine, ornithine, aspartic acid, glutamine, lysine and tyrosine decreased. Glutamine has an effect on the vasomotor function of blood vessels, which increases blood pressure because it is the precursor of glutathione, which corrects vascular responses. A survey of 4680 people in four countries found that methyl acid, hippuric acid and alanine are highly associated with hypertension, while alanine is mostly derived from meat, so patients with hypertension should eat a light diet and avoid eating too much meat [19]. Through the above studies, it is found that there are abnormal metabolism of amino acids in patients with hypertension and prehypertension, which provides ideas for the prevention and intervention of hypertension.

2.4 metabolites of intestinal flora

Intestinal flora is inextricably linked with the occurrence and development of cardiovascular disease. In the study of hypertension, it is found that the intestinal flora of normal control group is significantly different from hypertension and prehypertension, and the ratio of pathogenic bacteria to beneficial bacteria is obviously out of balance [20]. The main metabolites of intestinal flora are short-chain fatty acid (SCFA) and trimethylamine-N-oxide (TMAO) [21]. In the study of metabonomics, the former found that there was a significant decrease in the body of animal models and people with hypertension, while the content of feces increased [22]. The latter will increase when the intestinal flora is maladjusted, which can cause inflammation, atherosclerotic plaque formation and changes in blood pressure [23]. UfnalMarcin et al. [24] the pressor effect of simple infusion of Ang-II, in mice was only about 5 days, while the pressor effect of infusion of Ang-II and TMAO was sustainable, which proved that TMAO had obvious pressor effect. In addition, in patients with salt-sensitive hypertension, it was found that the content of lactic acid bacteria in the intestine decreased significantly, indole production decreased, leading to inflammation [25]. It can also reduce the intestinal fragile Bacteroides and lead to a decrease in the level of arachidonic acid. The production of intestinal cortisol increased, which induced the occurrence of hypertension [26].

Although the pathogenesis of hypertension is not clear, many evidence suggests that hypertension is related to biological processes such as insulin resistance, inflammatory state, endothelial dysfunction and impaired nitric oxide production.

3. Application of metabonomics in Traditional Chinese medicine Syndromes

Traditional Chinese medicine carries on syndrome differentiation and treatment according to the different pathological characteristics of different patients or the pathological characteristics of different stages of the same patient. Therefore, the "syndrome type" includes the etiology, disease, location and the relationship between good and evil of the disease, so the syndrome type carries on the dynamic observation of the disease from the overall point of view, combined with a variety of factors. Metabonomics studies the human body as a whole, mainly through the changes of human metabolites and metabolic network under disease state and medical intervention [27]. Therefore, metabonomics and TCM syndrome types are highly consistent in the overall concept, which reflect the impact of pathogenic factors on the internal environment of the human body, or the overall pathological changes of the body at a certain stage of the disease.

3.1 Metabonomic characteristics of hyperactivity of liver fire (hyperactivity of liver yang) syndrome

Ning Cheng et al. [28] analyzed and compared the serum and urine metabolites of liver-fire hyperactive hypertension and healthy control group by gas chromatography / time-of-flight mass spectrometry. It was found that there were differences in serum 3-hydroxybutyric acid and glucose and glycine and phosphoric acid in urine between the two groups. Jiang Haiqiang et al. [29] explored the biomarkers of patients with liver fire hyperactivity hypertension by metabonomics, analyzed their data, constructed a metabolic network, and analyzed the key targets of the metabolic node analysis network. Epinephrine, hexose and metatetraenoic acid were obtained as the main targets. This provides an idea for TCM syndrome differentiation in the treatment of hypertension with hyperactivity of liver-yang.

3.2 Metabonomic characteristics of phlegm-dampness syndrome

Wu Tianmin et al. [30] compared with other syndrome types of hypertension with excessive phlegm-dampness by magnetic resonance hydrogen spectroscopy, compared with the healthy control group, the contents of acetone, very low density lipoprotein and low density lipoprotein increased, while the contents of lactic acid, serine, glucose, methionine and alanine decreased, and the contents of citric acid, alanine, low density lipoprotein and very low density lipoprotein increased compared with the liver fire hyperactivity group. Compared with the group of yin deficiency and yang hyperactivity, the content of creatinine increased.

3.3 Metabonomic characteristics of Yin deficiency and Yang hyperactivity Syndrome

Fan Qunli et al. [31] the metabolites of the normal healthy group with yin deficiency and yang hyperactivity were analyzed by gas chromatography-mass spectrometry (GC-MS). The contents of amino acids, small molecular organic acids, fatty acids, lipids, sugar alcohols and other small molecular compounds in the yin deficiency and yang hyperactivity group were significantly lower than those in the normal health group. Shao Ze et al. [32] found that there were differences between hypertensive patients with yin deficiency and yang hyperactivity syndrome and healthy people. 38 different metabolites were found in hypertensive patients with yin deficiency and yang hyperactivity.

4. Metabolic Mechanism of traditional Chinese Medicine in reducing Blood pressure

4.1 Antihypertensive metabolic mechanism of single drug and drug pair

The study of single drug is mostly based on animal experiments, through different methods to model different syndrome types of spontaneously hypertensive rats ((SHR),) to explore the effects of single drug on metabolites or metabolic pathways in SHR rats by metabonomics method. Yu Ruixue et al. [33] Ultra high performance liquid chromatography-quadrupole-electrostatic field orbital trap ultra-high resolution mass spectrometry was used to analyze the effects of Uncaria on hypertensive rats with liver-yang hyperactivity. It was found that Uncaria could regulate the synthesis of metabolites in metabolic pathways such as linoleic acid metabolism, sterol hormone biosynthesis metabolism, arachidonic acid, glycine, serine and threonine metabolism in hypertensive rats. Improve the facial temperature, dizziness and other symptoms of hypertensive rats. Rhizoma Alismatis et al. [34] using ultra-high performance liquid chromatography-quadrupole time-of-flight mass spectrometry, it was found that alisma alisma could interfere with the pathway of aromatic amino acids and fat metabolism such as tryptophan metabolism and tyrosine metabolism in SHR rats. Feng Health et al. [35] analyzed the effects of Gardenia jasminoides on urine metabolism in spontaneously hypertensive rats by ultra high performance liquid chromatography-quadrupole tandem time-of-flight mass spectrometry. It was found that Gardenia jasminoides could significantly reduce blood pressure in spontaneously hypertensive rats. And the level of biomarkers in urine changed, mainly related to arginine and proline metabolism, epinephrine, taurine and sub-taurine metabolic pathway. Through metabonomics technology, we also studied some drug pairs commonly used in the treatment of cardiovascular and cerebrovascular diseases such as hypertension, such as Radix Astragali-Salvia miltiorrhiza and Han Cong, which have anti-inflammatory, anticoagulant and antioxidant stress. It was found that it had a certain antihypertensive effect, and the ultra-high liquid chromatography system-quadrupole-orbital ion trap combined mass spectrometry technique was used. The effects of Radix Astragali and Salvia miltiorrhiza on tryptophan metabolism, arachidonic acid metabolism and steroid hormone biosynthesis pathway in SHR rats were analyzed. Another drug has antihypertensive and anti-atherosclerotic effects on Eucommia ulmoides-Tribulus terrestris. [37] non-targeted gas chromatography-mass spectrometry metabolites were detected in the feces of SHR rats. It was found that Eucommia ulmoides-Tribulus terrestris had a good antihypertensive effect on rats and could increase the metabolic levels of glycolic acid, guanine, ethylene glycol and tryptamine.

4.2 Antihypertensive metabolic mechanism of compound preparation

Through the method of metabonomics to find the iconic metabolites or metabolic pathways of different syndrome types, in order to identify the differences of related metabolites in healthy people and different syndrome types, and monitor the changes of metabolites or metabolic pathways again after symptomatic drug intervention. In order to clarify the action mechanism of traditional Chinese medicine in different syndrome types, and provide strong evidence for the development of traditional Chinese medicine. After the intervention of compound preparation in SHR rats or patients with hypertension, the serum or urine of the compound preparation was analyzed in order to clarify the action pathway of the compound preparation. Wang Yulong et al. [38] using hydrogen magnetic resonance spectroscopy, it was found that the metabolism of amino acids such as alanine, lysine, phenylacetylglycine and phenylalanine and glucose metabolism such as β-glucose in urine of SHR rats interfered with Danqi tablets changed. Jian Weixiong et al. [39] using gas chromatography-mass spectrometry detection technique, it was found that compound Gouteng Jiangya tablet had certain effects on the metabolites of xylitol, sorbitol, ribose, lactic acid and other metabolites in the left ventricle of spontaneously hypertensive rats. It was found that it may have characteristics on cell structure adjustment, energy optimization and the mechanism of oxidative stress. Wu Guixia et al. [40] the urinary metabolites of SHR rats treated with Danhong injection were analyzed by magnetic resonance hydrogen spectroscopy. It was found that the metabolites such as acetic acid, N-acetyl glycoprotein and citrate were abnormal, which were mainly related to glycolysis, fatty acid metabolic pathway and amino acid metabolic pathway. Gu Ping [41] and other high performance liquid chromatography-mass spectrometry (HPLC-MS) were used to analyze the plasma metabolites of hypertensive patients with yin deficiency and yang hyperactivity. Zhengan Xifeng decoction can significantly change the disorder of amino acid metabolism in hypertensive patients with yin deficiency and yang hyperactivity.

5. Discussion and prospect

Pyruvate is produced in glucose metabolism, and pyruvate, as the hub of the three major nutrients, plays an important role in glucose metabolism in the body. Pyruvate has antioxidant and anti-inflammatory effects, which can not only eliminate excessive reactive oxygen species ((ROS),) in the body, but also inhibit TNF- α and NF- pathway. These two pathways are classical inflammatory pathways [42]. It was also found that the contents of α-ketoglutaric acid, citric acid, pyruvate and fumaric acid in tricarboxylic acid cycle metabolites decreased, while the contents of lactic acid and glucose increased [43]. These metabolites affect the production of NO in many ways. It has been reported that NO deficiency is related to the pathogenesis of hypertension. NO is produced by the combination of the isoenzyme of endothelial nitric oxide synthase (eNOS) with arginine. NO has the effect of relaxing vascular smooth muscle, thus reducing vascular resistance and lowering blood pressure. Another disorder of glucose metabolism is insulin resistance, which can activate the sympathetic nervous system, increase the calcium concentration of vascular smooth muscle cells and the reabsorption of sodium in renal tubules, and increase vascular resistance and blood volume. In turn, it increases blood pressure [44].

Insulin resistance can also affect the metabolism of very low density lipoprotein and high density lipoprotein, which leads to dyslipidemia and the increase of plasma free fatty acids, which can act directly on vascular endothelial cells. As second messengers, they can enter the cell and change the function of the cell membrane through phospholipids to produce vasoactive eicosanes to affect the cell function [16].

Isoleucine has the effect of regulating blood glucose and may have the effect of insulin sensitization and hypoglycemia. Metabonomics studies also found that the content of inositol in patients with hypertension decreased, which can improve insulin sensitivity [45]. In addition, the contents of phenylalanine and tyrosine are considered to be closely related to insulin resistance [46]. Phenylalanine is hydroxylated by phenylalanine hydroxylase to form tyrosine, which produces dopa in adrenal medulla and nerve tissue under the catalysis of tyrosine hydroxylase. Dopamine is produced by dopa decarboxylase. Dopamine enters the adrenal medulla and is hydroxylated again to produce norepinephrine. Norepinephrine is demethylated to produce epinephrine. Dopamine, epinephrine and norepinephrine are collectively known as catecholamines, which have been shown to be related to the occurrence and development of blood pressure. Taurine is the most abundant free amino acid in cardiomyocytes and central nervous system, which can regulate cell Ca2+ stability, scavenge free radicals and stabilize cell membrane. Taurine also has anti-heart failure, anti-myocardial ischemia and anti-arrhythmic effects [47]. Taurine is also one of the end products of Hcy metabolism and the biological effect antagonist of Hcy. Zulli [48] and other studies found that Hcy can damage vascular endothelial cells through oxidative stress and other mechanisms, so that vascular elasticity decreases, leading to hypertension.

In both human and animal metabonomic studies, some metabolites with the same trend have been found, which may become biomarkers of hypertension, which provides a direction for the mechanism of hypertension. After the intervention of traditional Chinese medicine, it was found that the metabolites of hypertension patients and animals also changed to some extent, and it was found that there were different metabolites in patients with different syndrome types of hypertension, which provided a basis for the use of traditional Chinese medicine in the treatment of hypertension. However, the current metabonomics research uses different samples, analysis platforms and parameter settings, which makes the data results uneven, which hinders the current research. Therefore, researchers need to make continuous efforts to identify special metabolites as soon as possible, which can be used to distinguish between patients with hypertension and people with normal blood pressure. This is very useful for the early detection, diagnosis and treatment of hypertension and other complications that may be caused by it.

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