Agt Gene Rs5049 Locus in the Pathogenesis of Hypertension

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Abstract: Alcohol is a common addictive substance, which can lead to mental and physical dependence after long-term consumption. Large amounts of alcohol intake increase the risk of hypertension; some studies have shown that ethanol may activate renin-angiotensin- the aldosterone system raises hypertension; angiotensinogen (agt) is a rate-limiting substrate of the raas system, which is encoded by the agt gene, where the rs5049 site is the risk of essential hypertension (eh) genes; drinking may increase blood pressure by activating the raas system by altering the rs5049 locus of the agt gene.

1. Introduction

Primary hypertension is an important public health issue in both developing and developed countries. the prevalence of eh is high, and it is common with coronary heart disease, kidney disease, stroke, peripheral vascular disease, stress syndrome, etc the disease is closely related, and at the same time it is a risk factor for various cardiovascular and cerebrovascular diseases. Eh is a polygenic genetic disease caused by the combined effects of peripheral environment and genetic factors [1]. It is a complex trait disease with a combination of environment and genetics. It has a long course of disease, relatively slow disease progression, and morbidity is increasing year by year. It has long been the main cause of mortality and disease burden worldwide [2]. According to an epidemiological survey, 31% to 68% of patients with hypertension have a family genetic history [3]. Hypertension has a high degree of genetic heterogeneity. Since the first hypertension gene association study was reported in 1992, many susceptible gene researches on hypertension have been carried out successively [4]. This article makes a review of the pathogenesis of alcohol and hypertension.

2. Alcohol and Hypertension

2.1 Alcohol Intake Increases the Risk of Hypertension

Alcohol is a common addictive substance, which can lead to mental and physical dependence after long-term drinking in large quantities. In addition to alcohol, it can cause liver, cardiovascular disease and nutritional disorders, as well as damage to the nervous system. In recent years, with the increasing production and consumption of alcohol in our country, the health problems and social problems related to drinking are increasing, the incidence of alcohol abuse and dependence has been increasing significantly [5]. Studies at home and abroad have confirmed that alcohol dependence is the most serious public health problem that ranks third after cardiovascular disease and malignant tumors [6]. Studies have shown that there is a close relationship between drinking and blood pressure. Drinking and hypertension are linked in a dose-dependent manner. Moderate alcohol intake lowers blood pressure slightly, and large amounts of alcohol increase the risk of hypertension. [7] . Min-gyu yoo and other studies have shown that moderate to high alcohol consumption and the risk of hypertension are significantly increased. Drinking for more than 10 years has a positive correlation with the risk of hypertension [8]. Studies have shown that alcohol intake exceeding 30-50 g / d is responsible for hypertension risk factors [9]. Research by zhang

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yanmin et al. [10] showed that male alcohol consumption was positively correlated with systolic and diastolic blood pressure, that is, both systolic and diastolic blood pressure increased with the increase in alcohol consumption. After adjusting for factors such as age, body mass index, smoking, and education, there were significant differences in systolic and diastolic blood pressure among the drinking, non-drinking, and abstinence groups. After adjusting the effects of age, body mass index, smoking, education and other factors in the drinking group, there were significant differences between the systolic and diastolic blood pressure among the different drinking groups.with the increase in the amount of alcohol consumed, both the systolic and diastolic blood pressure there is an increase.

2.2 Possible Mechanisms of Alcohol-Induced Hypertension

Alcohol (ethanol) may increase blood plasma cortisol levels and lower aldosterone levels by inhibiting the catalytic activity of 11β-hydroxysteroid dehydrogenase type ii (11βhsd2), leading to increased blood pressure [11], the possible pathways are: ① similar to the mineralocorticoid excess pathway; ② “permissive effects” to strengthen the pathway. Possible mechanisms of increased blood pressure caused by drinking: (1) acetaldehyde, an alcohol metabolite, promotes the release of endogenous norepinephrine from the adrenal medulla; (2) ethanol can activate the renin-angiotensin-aldosterone system; (3) hypertension may be part of the alcohol withdrawal syndrome after the removal of ethanol, the content of catecholamines in plasma and urine increases, leading to increased blood pressure; long-term drinking causes intermittent alcohol removal, which will repeatedly increase blood pressure, eventually leading to persistent hypertension; (4) ethanol causes hypomagnesemia, which affects cells internal calcium concentration and blood potassium increase blood pressure; (5) ethanol can increase cortisol secretion; (6) ethanol can cause endothelial dysfunction and inhibit the synthesis of vasodilating substances such as nitric oxide [12]. Jia xueqin [13] and others reported that long-term drinking can cause left ventricular hypertrophy, leading to increased blood pressure. Patients with hypertension still have long-term alcohol abuse after diagnosis, which will cause serious damage to the organs such as heart, brain and liver [14]. In addition, the possible mechanism of alcohol-induced increase in blood pressure still cannot exclude inflammatory factors. There is clear evidence that some related inflammatory markers play a crucial role in different target organ damage (tod) mechanisms. And interventions targeting markers of inflammation will prevent and reduce tod and overall cardiovascular risk [15-16].

3. Renin-Angiotensin-Aldosterone System and Hypertension

The renin-angiotensin-aldosterone system (raas) is an important body fluid regulation system in the human body.raas exists in both the circulatory system and the blood vessel wall, heart, center, kidney and adrenal gland. China and china participate in the regulation of target organs. Under normal circumstances, raas plays an important role in the normal development of the cardiovascular system, homeostasis of cardiovascular function, maintenance of electrolyte and body fluid balance, and regulation of blood pressure. Renin is an acidic protease that is synthesized and secreted by the parabulbar cells of the glomerulus into the arterial artery, and is an important part of raas. The release of renin is the primary activation signal of raas, and it is also the key to determine the level of angiotensin (angiotensin, ang) in the plasma. 17]. Angiotensinogen (agt) is a rate-limiting substrate of the raas system, which is encoded by the agt gene and is catalyzed by reninase to produce angI, which is catalyzed by angiotensin-converting enzyme (ace). AngII, angII can regulate blood pressure [18].

4. Rass System Genes and Hypertension

Many studies have shown that the rass system gene polymorphisms are closely related to the occurrence of hypertension. There are more than 200 candidate gene loci for hypertension that have been discovered. Relevance is considered a research hotspot [19]. The agt gene is located at 1q42-43, is 13kb long, has 5 exons and 4 introns, and is a single copy gene. So far, more than 50 agt

gene polymorphism sites have been found, but the most studied about the coding region polymorphism are m235t and t174m. The correlation between eh and m235t locus of agt gene has been confirmed, so m235t is also considered as one of the important candidate loci for eh [20]. In addition, agt core promoter element 1 can bind to the transcription factor agcf1 and affect its transcription rate by interacting with the ale sequence and enhancer elements, while the -6a / g and -20a / c mutations in this region can affect the agt gene transcriptional activity, which in turn affects its physiological function. Agt is a substrate of renin. The amino terminus contains angI. Under the action of renin and angiotensin-converting enzyme, angII is formed. When it binds to the receptor, vascular resistance increases on the one hand, and the blood output of the heart also increases. Increasing it stimulates the release of aldosterone, and sodium water retention increases blood pressure. It is the earliest discovery and the most studied eh candidate gene so far. A large number of studies have shown that agt single nucleotide polymorphisms (snps) are related to eh, but the research results are not consistent [21].

5. Rass System Genes and Drinking

In recent years, the effects of each snp of the agt gene on the pathogenesis of eh have been most fully studied by mutations in the promoters g217a (rs5049), a20g, and a6g. The g217a (rs5049) primer sequence is f: caggctgtcacacaccta; r: gagaggagggttacatcacttg. Related studies have confirmed that promoter mutations can affect agt transcription and affect the pathogenesis of eh [22]. Furusawa t [23] pointed out that the linkage of agt genes rs699, rs5051, and rs5049 was imbalanced in the study of eh susceptibility genes, in which rs5049 was a risk gene for eh ($p = 0.025$). Bruggs jj [24] also pointed out that rs4291, rs5049, rs2968915, and rs5981008 are closely related to blood pressure in the occurrence of cardiovascular disease, which will increase the prevalence of eh by 2-3 times. In the study of the incidence of snp and eh in pacific island populations, it was found that rs5049 aa is a risk factor for hypertension ($p = 0.025$) [25]. Song tingting [26] and others used logistic analysis. The final results showed that the agt gene rs5049 locus would interact with diet and drinking. The rs5049 locus cc type was wild-type, and tt type was mutant. It was speculated that the gene had a mutation it may be related to the onset of eh and lead to the onset of essential hypertension. The or value of eh caused by the interaction between the three is 1.46 (95% ci: 1.08, 1.96).

To sum up: at present, the incidence of hypertension in china is high and the control rate is low. The mechanism of alcohol-induced hypertension is not clear. The activation of the raas system may be one of the possible mechanisms of alcohol-induced hypertension. Among the many possible mechanisms of alcohol-induced hypertension, it seems that the sympathetic nervous system and / or cell membrane electrolyte transport changes play a role in it, but it is difficult to determine [27]. Drinking may increase blood pressure by activating the raas system by altering the rs5049 locus of the agt gene, but it remains to be experimentally confirmed that revealing the relationship between alcohol consumption in patients with hypertension and the rs5049 locus of the agt gene will help further reveal the effects of drinking on hypertension and its mechanism, improve the awareness of hypertension among alcohol drinkers, and provide better clinical guidance for patients with hypertension. To provide scientific basis for the prevention and control of alcohol-related hypertension.

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