

Research progress on the correlation between sacubitril-valsartan and cognitive function in hypertensive patients

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Abstract. Sacubitril-valsartan can exert antihypertensive effects by blocking the effect of angiotensin II and inhibiting the activity of enkephalinase. As a currently common antihypertensive drug, sacubitril-valsartan's protective effects on target organs have been confirmed in more and more studies. Inhibition of enkephalinase can hinder the degradation and metabolism of beta-amyloid, deposition of which is a characteristic pathological feature of Alzheimer's disease. And hypertension itself is a risk factor for cognitive dysfunction, so long-term medications have the theoretical possibility to result in adverse effects on the cognitions of hypertensive patients. A review of various perspectives towards the effects of sacubitril-valsartan on cognitive function in patients with hypertension will be delivered.

Keywords: Sacubitril-valsartan, Hypertension, Cognitive function, Enkephalinase, Alzheimer's disease.

1. Introduction

At present, about 1 billion adults in the world suffer from hypertension, and it is expected that the number of patients will increase to 1.5 billion by 2025. According to statistics in 2020, there are 55 million people with dementia in the world, and it is foreseen to reach 139 million by 2050 [1]. Hypertension is an important risk factor for cardiovascular disease and cognitive impairment. A meta-analysis of middle-aged hypertension and Alzheimer's disease found that compared with normotensives, middle-aged patients with stage 1 and stage 2 systolic hypertension had an 18% and 25% increased risk of Alzheimer's disease, respectively [2]. A clinical trial of people over 50 years of age at high risk of hypertension showed that lowering blood pressure to 120 mmHg significantly reduced the risk of mild cognitive impairment and dementia in comparison with controlling blood pressure to 140 mmHg [3]. Results of another meta-analysis of 6 prospective studies showed that among hypertensive people, the ones used blood pressure-lowering drugs had a 16% lower risk of developing Alzheimer's disease than those who didn't, indicating that blood pressure levels regulation is of great significance for reducing the risk of cognitive impairment [4]. It can be seen that there is a close correlation between the occurrence of cognitive impairment and hypertension.

Sacubitril-valsartan (LCZ696), a class of dual-acting molecules consisting of the neprilysin inhibitor sacubitril and the angiotensin II receptor (AT1) blocker valsartan, has been approved by the FDA for the treatment of heart failure [5], many studies have shown that it also has a certain effect in the treatment of hypertension. As a novel antihypertensive drug, sacubitril-valsartan provides a complementary mechanism of action for other first-line antihypertensive treatments [6]. However, sacubitril-valsartan inhibits its enkephalinase activity, resulting in reduced β -amyloid degradation, and pathological amyloid deposition is a critical etiology of AD, so whether sacubitril-valsartan increased risk of developing AD-related diseases has raised concerns.

2. The mechanism of cognitive dysfunction in hypertensive patients

Alzheimer's disease (AD) is a devastating neurodegenerative disease that can lead to deficits in behaviors, cognitions and memories [7]. The deposition of A β amyloid, hyperphosphorylation of tau protein and neuronal dysfunction are the main reasons [8]. A β is a physiological polypeptide that is continuously synthesized and decomposed in the brain, and stable A β levels depend on the metabolic balance of synthesis and decomposition activities [9]. Over time, subtle changes in this metabolic

balance may lead to the emergence of pathogenic forms of A β that affect the pathological progression of the disease. In the brains of sporadic AD patients, elevation of A β anabolic activity is rarely observed, and thus the decrease in A β catabolic activity associated with A β catabolic enzymes is an important cause of amyloid deposition associated with the development of sporadic AD [10].

Activation of the renin-angiotensin II-aldosterone (RAAS) system and reinforcing tension of vessels walls are the main pathophysiological features of hypertension, both of which may issue in brain amyloid deposition and neuronal dysfunction. Activation of the RAAS system in hypertensive patients induces oxidative stress on the one hand, and reduces the production of neuroprotective factors on the other. Angiotensin II (Ang II) can activate angiotensin receptor 1 (AT1R) on the surface of perivascular macrophages to induce oxidative stress [11], resulting in damages of blood-brain barrier disruption [12], thereby affecting the clearance of A β process [13] and cause neuroinflammation and myelin damage [14]. The cleavage of endogenous amyloid precursor protein (APP) by α -secretase can generate the neuroprotective factor APP α [15], while Ang II can activate AT2R and reduce the activity of α -secretase in human brain microvascular endothelial cells, resulting in decreased APP α production [16]. The increase of intravascular pressure in the cerebrovascular cavity of hypertensive patients can activate NADPH oxidase and promote the production of reactive oxygen species to induce oxidative stress [14], which activates the glycation end product receptor pathway on cerebral capillary endothelial cells, and then causes brain Amyloid deposition in cortex and hippocampus [17]. Long-term elevated intravascular pressure can damage vascular endothelial cells, causing atherosclerosis in cerebral blood vessels [18]. Hypoperfusion secondary to arterial stenosis can lead to reduced A β clearance, and cumulative A β can also promote atherosclerosis by inducing inflammation [19]. In addition, impaired neurovascular unit integrity results in insufficient oxygen and glucose supply leading to neuronal dysfunction [17].

Elevated intravascular pressure also does harm to cerebrospinal fluid drainage by the glial-lymphatic system, bringing about impaired lymphatic clearance of A β [14]. Studies have found that nocturnal systolic blood pressure decreases brain A β and tau protein clearance through the glial-lymphatic system, while nocturnal blood pressure increases brain lymphatic transport, which may be one of the mechanisms of AD in reverse dipper hypertension [20]. From the above, the pathophysiological characteristics of hypertensive patients are important mechanisms leading to the increased risk of AD.

3. Antihypertensive effect of sacubitril-valsartan

Sacubitril-valsartan (LCZ696) has been approved by the FDA for the treatment of heart failure [5], and a growing number of studies have shown that it also has a certain effect in the treatment of hypertension. A meta-analysis of five randomized controlled trials involving 1513 elderly hypertensive patients showed that sacubitril-valsartan played a essential role in reducing systolic hypertension [21]. A multicenter, double-blind, randomized controlled trial of 852 hypertensive patients found that sacubitril-valsartan reduced average office systolic blood pressure and day-to-day systolic blood pressure in the treatment of mild to moderate hypertension in Europe and the United States, the magnitude is significantly greater than that of valsartan [22]. The study carried out by Aaqib Malik et al. showed that sacubitril-valsartan is more effective in hypertensive patients than ARBs [23]. In the treatment of mild-to-moderate hypertension in Asia, a randomized controlled trial study conducted by Kario et al. included 362 hypertensive patients. Comparing with placebo, subjects taking different doses of LCZ696 within 24 hours, daytime and and nighttime dynamic systolic, diastolic, and pulse pressures were significantly reduced [24]. The results of the phase III clinical trial of sacubitril-valsartan in China also showed that its antihypertensive effect was better than that of single use of olmesartan, and had outstanding effects on the reduction of systolic blood pressure and nighttime blood pressure [25].

In addition, sacubitril-valsartan is more effective than ARBs in the treatment towards salt-sensitive hypertension [26] and elderly systolic hypertension [27]. Therefore, sacubitril-valsartan can provide

supplements for the clinical treatment of other first-line hypotensive drugs with its above-mentioned characteristics and advantages in antihypertension.

4. The antihypertensive mechanism of sacubitril-valsartan

Sacubitril-valsartan (LCZ696) is the first angiotensin receptor neprilysin inhibitor (ARNI) [7], which is composed of valsartan (ARB) and sacubitril (AHU377) according to 1: 1 molar ratio. After entering the body, LCZ696 will be decomposed into valsartan and the prodrug AHU377. Valsartan can directly exert its blocking effect on the angiotensin II type 1 receptor (AT1). AHU377 is hydrolyzed to generate its active component LBQ657, which contributes in inhibiting enkephalinase (NEP) [28].

Valsartan can antagonize the activation of the RASS system by retarding the effect of Ang II and AT1, and resist the AngII-induced vasoconstriction, increased aldosterone release and sympathetic nervous system excitation. In addition, inhibiting the binding of Ang II to AT1 will lead to enhanced binding of Ang II to AT2 [29], thereby exerting protective effects such as vasodilation and inflammation suppression [30]. LBQ657 can reduce the degradation of natriuretic peptides by inhibiting the activity of enkephalinase, thus increasing the level of endogenous natriuretic peptides, and facilitating natriuretic excretion and vasodilation [31]. The two synergistically play a beneficial role in lowering blood pressure and preventing cardiovascular.

NEP is widely expressed in a variety of tissues throughout the body, including the central and peripheral nervous system, kidney, heart, lung, adrenal gland, intestinal mucosal epithelial cells, thyroid, placenta, and the cell surface of fibroblasts and neutrophils. Soluble NEP has also been detected in blood, cerebrospinal fluid (CSF), urine, and synovial fluid [32]. NEP is responsible for the degradation of various polypeptide substances in the body, such as enkephalin, B-type natriuretic peptide, atrial natriuretic peptide, bradykinin, adrenomedullin, endothelin, angiotensin and beta-amyloid [33]. Vitro experiments have shown that NEP has an important effect on the degradation of amyloid A β , with the most rapid and effective degradation of A β 1-42 and A β 1-40 [34], and the NEP gene dosage is significantly negatively correlated with A β levels [35]. Therefore, inhibition of NEP may lead to impairment of cognitive function [36, 37], and whether NEP inhibitor drugs increase the risk of AD-related diseases remains to be elucidated [38].

5. Effects of sacubitril-valsartan on cognitive function in patients with hypertension

5.1. The impairment of cognitive function by sacubitril-valsartan

The US FDA Adverse Event Reporting System (FAERS) included 9004 unique adverse reaction cases involving sacubitril-valsartan, 459 (5.1%) reports described cognitive and/or dementia-related adverse reactions, of which 96% directly attributable to the patient's use of sacubitril-valsartan. In cases where sacubitril-valsartan was discontinued, 85 percent reported a reduction in cognitive and dementia-related adverse effects [39].

Elevated levels of A β 1-42 and A β 1-40 have toxic effects on neurons and cerebral vascular endothelial cells [40]. LBQ657 inhibits the degradation of β -amyloid by enkephalinase, which may lead to increased A β levels. It has also been demonstrated that mice lacking enkephalinase can show symptoms similar to Alzheimer's disease [41]. Therefore, long-term administration of sacubitril-valsartan may theoretically increase the risk of AD.

Cerebrovascular amyloidosis, a chronic potential side effect of sacubitril-valsartan (ARNI), is associated with deposition of A β in the media and adventitia of meningeal arterioles, capillaries, and cerebral cortex, and is a major cause of cerebral microbleeds and cognitive impairment in elderly patients [42]. Cerebral amyloidosis (CAA) leads to dysfunction of the blood-brain barrier [7], which is a key factor in the accumulation of A β in brain tissue or cerebrospinal fluid [43]. Therefore,

sacubitril-valsartan accelerates the pathological progression of AD by causing cerebral vascular amyloidosis to exacerbate the deposition of β -amyloid after damaging the blood-brain barrier.

5.2. Protection of cognitive function by sacubitril-valsartan

Hypertension and cardiovascular disease are established risk factors for AD [44], so lowering blood pressure and the occurrence of cardiovascular diseases can reduce the risk of cognitive impairment.

In terms of blood pressure reduction, sacubitril-valsartan, as a new type of antihypertensive drug, can reduce central aortic systolic blood pressure, pulse pressure and nocturnal blood pressure [45], and in comparison with singly using ARB, the incidence of adverse events is same. The former one has a more obvious antihypertensive effect under the same adverse events occurrence rates [46]. Bhat SA et al. found that the use of low-dose ARB could prevent the activation of astrocytes and microglia, as well as the occurrence of neuroinflammation in the brain of hypertensive rats [47], which shows that ARB has neuroprotection in the hypertension models. In hypertensive patients with chronic kidney disease, the use of ARNI can reduce the risk of cognitive dysfunction by delaying the progression of CKD [48].

In terms of reducing the incidence of cardiovascular diseases, studies have shown that enkephalinase inhibitors can not only reduce myocardial fibrosis and improve cardiac remodeling, but also increase the antiarrhythmic effects of enkephalin, endorphin and bradykinin [49], reduce the incidence of cardiovascular disease and thus prevent the occurrence of cognitive impairment. In addition, chronic hyperglycemia is also a crucial risk factor for cognitive impairment [50], and sacubitril-valsartan can improve glycemic control [51], so the use of ARNI can reduce cognitive impairment in hypertensive patients with diabetes, which has considerable guiding significance.

In conclusion, long-term administration of sacubitril-valsartan may have beneficial effects on cognitive function by lowering blood pressure, reducing the incidence of cardiovascular disease, and improving glycemic control.

5.3. There is no correlation between sacubitril-valsartan and the occurrence of Alzheimer's disease

Animal experiments have found that compensatory mechanisms may reduce the concentration of sacubitril-valsartan in the brain to a certain extent [52]. A clinical study in healthy volunteers showed that after taking sacubitril-valsartan Increased concentrations of A β 1-40 and A β 1-42 aggregated isoforms did not result in severe neuronal injury toxicity [53]. Other studies have shown that the concentration of LBQ657 in plasma and cerebrospinal fluid has no significant effect on the level of A β 1-38 [54, 55], and there is currently no evidence that a simple increase in the concentration of A β 1-38 in cerebrospinal fluid causes or promotes the formation of A β plaques in the brain or cognitive decline, and whether it alters the propensity of other A β isoforms to form oligomers in the body [56]. In vitro experiments have shown that sacubitril and its active metabolite are selective for human NEP and do not inhibit other metalloproteases known to degrade A β , such as ACE-1 [52]. Therefore, sacubitril-valsartan may not inhibit the degradation of β -amyloid protein with neuronal toxicity due to the selective inhibition of NEP in different species and the difference in the type of substrate A β , and will not cause Alzheimer's disease related pathological changes.

In addition, whether sacubitril-valsartan causes A β accumulation in brain tissue or cerebrospinal fluid depends on whether LCZ696 can cross the blood-brain barrier [43, 52, 57]. After signal detection and analysis of the FAERS data, it was found that due to the poor penetration of the blood-brain barrier of sacubitril-valsartan, it is difficult to enter the brain tissue to inhibit enkephalinase, so there is no risk of cognitive impairment in patients [58, 59]. However, at the same time, changes in the permeability of the blood-brain barrier also need to consider the influence of the primary disease. A β accumulation occurs decades before clinical symptoms appear in patients with AD and cerebral amyloid angiopathy, which means that the patient may already have blood-brain barrier dysfunction at the time of clinical symptoms. Therefore, ARNI may not play a direct role in the occurrence of AD.

In conclusion, whether sacubitril-valsartan causes Alzheimer's disease is related to whether it can pass through the blood-brain barrier, and whether it leads to neurotoxic A β amyloid deposition, and the integrity of the blood-brain barrier may be in the Cognitive dysfunction-related symptoms have been damaged by chronic cardiovascular and cerebrovascular diseases.

6. Discussion

In conclusion, sacubitril-valsartan has a significant effect in the treatment of hypertension, and has now become the first-line antihypertensive drug. However, since its main component contains an enkephalinase inhibitor, which theoretically affects the degradation and metabolism of amyloid A β , long-term medication in hypertensive patients may increase the risk of cognitive decline. However, the current clinical trials have not found the neurotoxic effect of sacubitril-valsartan, and some researchers believe that sacubitril-valsartan can reduce blood pressure, reduce the occurrence of cardiovascular events and improve blood sugar control. cognitive function has a beneficial effect.

The current clinical trial subjects are mostly elderly people, and the study time is limited, so long-term conclusions on the effects of sacubitril-valsartan on cognitive function cannot be drawn. In addition, it is not clear whether sacubitril-valsartan can pass through the blood-brain barrier, and hypertension itself can cause damage to the blood-brain barrier and impairment of cognitive function. Therefore, the adverse effects on cognitive function of hypertensive patients cannot be ruled out. At present, more clinical trials and experimental studies are needed to explore the effects of sacubitril-valsartan on cognitive function, so as to guide the medication of clinical hypertension treatment and achieve a win-win effect.

References

- [1] Tarawneh HY, Menegola HK, Peou A, et al. Central Auditory Functions of Alzheimer's Disease and Its Preclinical Stages: A Systematic Review and Meta-Analysis [J]. *Cells*, 2022, 11 (6).
- [2] Lennon MJ, Makkar SR, Crawford JD, et al. Midlife Hypertension and Alzheimer's Disease: A Systematic Review and Meta-Analysis [J]. *J Alzheimers Dis*, 2019, 71 (1): 307 - 16.
- [3] Group SMIfSR, Williamson JD, Pajewski NM, et al. Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia: A Randomized Clinical Trial [J]. *JAMA*, 2019, 321 (6): 553 - 61.
- [4] Ding J, Davis-Plourde KL, Sedaghat S, et al. Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies [J]. *Lancet Neurol*, 2020, 19 (1): 61 - 70.
- [5] Wehland M, Simonsen U, Buus NH, et al. An evaluation of the fixed-dose combination sacubitril/valsartan for the treatment of arterial hypertension [J]. *Expert Opin Pharmacother*, 2020, 21 (10): 1133 - 43.
- [6] PharmD SLA, PharmD JCM. Sacubitril/valsartan: evaluation of safety and efficacy as an antihypertensive treatment. *Drugs in Context* 2018.
- [7] Wang Shuang, Feng Jinghui, Wu Lixin, et al. Research progress of enkephalinase inhibitors on cognitive function in patients with heart failure [J]. *Advances in Cardiovascular Diseases*, 2019, 40 (09): 1253 - 6.
- [8] Forman MS, Trojanowski JQ, Lee VM. Neurodegenerative diseases: a decade of discoveries paves the way for therapeutic breakthroughs[J]. *Nat Med*, 2004, 10 (10): 1055 - 63.
- [9] Saido T. Overview-A β metabolism: from Alzheimer research to brain aging control [J]. *A β metabolism and Alzheimer's disease*, 2003.
- [10] Iwata N, Higuchi M, Saido TC. Metabolism of amyloid-beta peptide and Alzheimer's disease[J]. *Pharmacol Ther*, 2005, 108 (2): 129 - 48.
- [11] Santisteban MM, Ahn SJ, Lane D, et al. Endothelium-Macrophage Crosstalk Mediates Blood-Brain Barrier Dysfunction in Hypertension [J]. *Hypertension*, 2020, 76 (3): 795 - 807.
- [12] Walker KA, Power MC, Gottesman RF. Defining the Relationship Between Hypertension, Cognitive Decline, and Dementia: A Review [J]. *Curr Hypertens Rep*, 2017, 19 (3): 24.

- [13] Huang Y, Zheng H, Tan K, et al. Circulating metabolomics profiling reveals novel pathways associated with cognitive decline in patients with hypertension [J]. *Ther Adv Neurol Disord*, 2020, 13: 1756286420947973.
- [14] Ungvari Z, Toth P, Tarantini S, et al. Hypertension-induced cognitive impairment: from pathophysiology to public health [J]. *Nat Rev Nephrol*, 2021, 17 (10): 639 - 54.
- [15] d'Uscio LV, He T, Katusic ZS. Expression and Processing of Amyloid Precursor Protein in Vascular Endothelium[J]. *Physiology (Bethesda)*, 2017, 32 (1): 20 - 32.
- [16] Sun R, He T, Pan Y, et al. Effects of senescence and angiotensin II on expression and processing of amyloid precursor protein in human cerebral microvascular endothelial cells [J]. *Aging (Albany NY)*, 2018, 10 (1): 100 - 14.
- [17] Yao Miaomiao, Qin Hongyun, Hu Chengping. Research progress on the influence of hypertension on cognitive function [J]. *Advances in Cardiovascular Diseases*, 2020, 41 (03): 284 - 7.
- [18] Eglit GML, Weigand AJ, Nation DA, et al. Hypertension and Alzheimer's disease: indirect effects through circle of Willis atherosclerosis [J]. *Brain Commun*, 2020, 2 (2): fcaa114.
- [19] Jordan JD, Powers WJ. Cerebral autoregulation and acute ischemic stroke [J]. *Am J Hypertens*, 2012, 25 (9): 946 - 50.
- [20] Tan X, Sundström J, Lind L, et al. Reverse Dipping of Systolic Blood Pressure Is Associated with Increased Dementia Risk in Older Men: A Longitudinal Study Over 24 Years [J]. *Hypertension*, 2021, 77 (4): 1383 - 90.
- [21] De Vecchis R, Soreca S, Ariano C. Anti-Hypertensive Effect of Sacubitril/Valsartan: A Meta-Analysis of Randomized Controlled Trials [J]. *Cardiol Res*, 2019, 10 (1): 24 - 33.
- [22] Izzo JL, Jr., Zappe DH, Jia Y, et al. Efficacy and Safety of Crystalline Valsartan/Sacubitril (LCZ696) Compared with Placebo and Combinations of Free Valsartan and Sacubitril in Patients with Systolic Hypertension: The RATIO Study [J]. *J Cardiovasc Pharmacol*, 2017, 69 (6): 374 - 81.
- [23] Malik A, Malik S, Aronow W. SACUBITRIL/VALSARTAN BETTER THAN ANGIOTENSIN-RECEPTOR BLOCKERS FOR HYPERTENSION? [J]. *Journal of the American College of Cardiology*, 2019, 73 (9S1): 1825-.
- [24] Kario K, Sun N, Chiang FT, et al. Efficacy and safety of LCZ696, a first-in-class angiotensin receptor neprilysin inhibitor, in Asian patients with hypertension: a randomized, double-blind, placebo-controlled study [J]. *Hypertension*, 2014, 63 (4): 698 - 705.
- [25] Huo Y, Li W, Webb R, et al. Efficacy and safety of sacubitril/valsartan compared with olmesartan in Asian patients with essential hypertension: A randomized, double-blind, 8-week study [J]. *J Clin Hypertens (Greenwich)*, 2019, 21 (1): 67 - 76.
- [26] Wang TD, Tan RS, Lee HY, et al. Effects of Sacubitril/Valsartan (LCZ696) on Natriuresis, Diuresis, Blood Pressures, and NT-proBNP in Salt-Sensitive Hypertension [J]. *Hypertension*, 2017, 69 (1): 32 - 41.
- [27] Supasyndh O, Wang J, Hafeez K, et al. Efficacy and Safety of Sacubitril/Valsartan (LCZ696) Compared with Olmesartan in Elderly Asian Patients (≥ 65 Years) With Systolic Hypertension [J]. *Am J Hypertens*, 2017, 30 (12): 1163 - 9.
- [28] Uijl E, Roksnoer LC, Hoorn EJ, et al. From ARB to ARNI in Cardiovascular Control [J]. *Curr Hypertens Rep*, 2016, 18 (12): 86.
- [29] Qin Mengyun, Yang Wei, Lv Yuanyuan, et al. Research progress of multi-target intervention of renin-angiotensin-aldosterone system inhibitors in the treatment of hypertension [J]. *Modern Medicine and Clinic*, 2022, 37 (02): 439 - 44.
- [30] Verdonk K, Danser AH, van Esch JH. Angiotensin II type 2 receptor agonists: where should they be applied? [J]. *Expert Opin Investig Drugs*, 2012, 21 (4): 501 - 13.
- [31] Singh JSS, Burrell LM, Cherif M, et al. Sacubitril/valsartan: beyond natriuretic peptides [J]. *Heart*, 2017, 103 (20): 1569 - 77.
- [32] Aubignat M. Long-term use of neprilysin inhibitor: Should we fear development of neurological diseases? [J]. *Rev Neurol (Paris)*, 2020, 176 (7-8): 529 - 30.
- [33] Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician [J]. *J Psychiatr Res*, 1975, 12 (3): 189 - 98.

- [34] Shirotani K, Tsubuki S, Iwata N, et al. Neprilysin degrades both amyloid beta peptides 1-40 and 1-42 most rapidly and efficiently among thiorphan- and phosphoramidon-sensitive endopeptidases [J]. *J Biol Chem*, 2001, 276 (24): 21895 - 901.
- [35] Iwata N, Tsubuki S, Takaki Y, et al. Metabolic regulation of brain Aβ by neprilysin [J]. *Science*, 2001, 292 (5521): 1550 - 2.
- [36] Mouri A, Zou LB, Iwata N, et al. Inhibition of neprilysin by thiorphan (i.c.v.) causes an accumulation of amyloid beta and impairment of learning and memory [J]. *Behav Brain Res*, 2006, 168 (1): 83 - 91.
- [37] Dubrovskaya NM, Nalivaeva NN, Plesneva SA, et al. [Changes in the activity of amyloid-degrading metalloproteinases leads to disruption of memory in rats] [J]. *Zh Vyssh Nerv Dej Im I P Pavlova*, 2009, 59 (5): 630 - 8.
- [38] Campbell DJ. Long-term neprilysin inhibition - implications for ARNIs [J]. *Nat Rev Cardiol*, 2017, 14 (3): 171 - 86.
- [39] Perlman A, Hirsh Raccach B, Matok I, et al. Cognition- and Dementia-Related Adverse Effects with Sacubitril-Valsartan: Analysis of the FDA Adverse Event Report System Database [J]. *J Card Fail*, 2018, 24 (8): 533 - 6.
- [40] Govindpani K, McNamara LG, Smith NR, et al. Vascular Dysfunction in Alzheimer's Disease: A Prelude to the Pathological Process or a Consequence of It? [J]. *J Clin Med*, 2019, 8 (5).
- [41] Chen Qiyang, Li Yimin, Chen Wenfa. Analysis of the adverse reactions of sacubitril-valsartan based on FAERS [J]. *Chinese Journal of Hospital Pharmacy*, 2021, 41 (03): 264 - 8.
- [42] Krittanawong C, Kitai T. Pharmacogenomics of angiotensin receptor/neprilysin inhibitor and its long-term side effects [J]. *Cardiovasc Ther*, 2017, 35 (4).
- [43] Poorgolizadeh E, Homayouni Moghadam F, Dormiani K, et al. Do neprilysin inhibitors walk the line? Heart ameliorative but brain threatening! [J]. *Eur J Pharmacol*, 2021, 894: 173851.
- [44] Thorin E. Hypertension and Alzheimer disease: another brick in the wall of awareness [J]. *Hypertension*, 2015, 65 (1): 36 - 8.
- [45] Kario K. The Sacubitril/Valsartan, a First-in-Class, Angiotensin Receptor Neprilysin Inhibitor (ARNI): Potential Uses in Hypertension, Heart Failure, and Beyond [J]. *Curr Cardiol Rep*, 2018, 20 (1): 5.
- [46] Sutanto H, Dobrev D, Heijman J. Angiotensin Receptor-Neprilysin Inhibitor (ARNI) and Cardiac Arrhythmias [J]. *Int J Mol Sci*, 2021, 22 (16).
- [47] Bhat SA, Goel R, Shukla S, et al. Angiotensin Receptor Blockade by Inhibiting Glial Activation Promotes Hippocampal Neurogenesis Via Activation of Wnt/β-Catenin Signaling in Hypertension [J]. *Mol Neurobiol*, 2018, 55 (6): 5282-98. Epub 2017 Sep 7. PMID: 28884281.
- [48] Judge P, Haynes R, Landray MJ, et al. Neprilysin inhibition in chronic kidney disease [J]. *Nephrol Dial Transplant*, 2015, 30 (5): 738 - 43.
- [49] Pascual-Figal D, Bayés-Genis A, Beltrán-Troncoso P, et al. Sacubitril-Valsartan, Clinical Benefits and Related Mechanisms of Action in Heart Failure with Reduced Ejection Fraction. A Review [J]. *Front Cardiovasc Med*, 2021, 8: 754499.
- [50] McCrimmon RJ, Ryan CM, Frier BM. Diabetes and cognitive dysfunction [J]. *Lancet*, 2012, 379 (9833): 2291 - 9.
- [51] Seferovic JP, Solomon SD, Seely EW. Potential mechanisms of beneficial effect of sacubitril/valsartan on glycemic control [J]. *Ther Adv Endocrinol Metab*, 2020, 11: 2042018820970444.
- [52] Schoenfeld HA, West T, Vergheze PB, et al. The effect of angiotensin receptor neprilysin inhibitor, sacubitril/valsartan, on central nervous system amyloid-β concentrations and clearance in the cynomolgus monkey [J]. *Toxicol Appl Pharmacol*, 2017, 323: 53 - 65.
- [53] Čelutkienė J, Vaitkevičius A, Jakštienė S, et al. Expert Opinion-Cognitive Decline in Heart Failure: More Attention is Needed [J]. *Card Fail Rev*, 2016, 2 (2): 106 - 9.
- [54] Gaudoux F, Boileau G, Crine P. Localization of neprilysin (EC 3.4.24.11) mRNA in rat brain by in situ hybridization [J]. *J Neurosci Res*, 1993, 34 (4): 426 - 33.
- [55] Ji Y, Permanne B, Sigurdsson EM, et al. Amyloid beta40/42 clearance across the blood-brain barrier following intra-ventricular injections in wild-type, apoE knock-out and human apoE3 or E4 expressing transgenic mice [J]. *J Alzheimers Dis*, 2001, 3 (1): 23 - 30.

- [56] Langenickel TH, Tsubouchi C, Ayalasomayajula S, et al. The effect of LCZ696 (sacubitril/valsartan) on amyloid- β concentrations in cerebrospinal fluid in healthy subjects [J]. *Br J Clin Pharmacol*, 2016, 81 (5): 878 - 90.
- [57] Tyler JM, Teerlink JR. The safety of sacubitril-valsartan for the treatment of chronic heart failure [J]. *Expert Opin Drug Saf*, 2017, 16 (2): 257 - 63.
- [58] Xiao Jie, Liu Yige, Fu Fang, et al. Risk analysis of cognitive impairment induced by sacubitril-valsartan-a study based on the US FDA Adverse Event Reporting System (FAERS) database [J]. *Practical Medicine and Clinical*, 2019, 22 (11): 1134 - 9.
- [59] Bai Yujia, Xu Dingli. Safety review of sacubitril-valsartan [J]. *China Circulation Journal*, 2018, 33 (02): 206 - 8.