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Research Article

Abnormal Expression Level of BACE1 and RAGE of Hippocampus Related to Cognitive Impairment in SHR

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Abstract

More and more evidences suggest vascular risk factors such as hypertension, etc, are related to an increased risk and play an important role in the progression of Alzheimer disease (AD). Hypertension as the most common vascular risk factor, can promote AD occurrence and clinical deterioration. However, it is unknown whether the mechanism is involved in β-amyloid protein (Aβ) metabolic pathways. The study was carried out to reveal changes of Aβ metabolic pathways in SHR hippocampus and further to clarify mechanisms of AD occurrence in the development of hypertension. SHR and Wistar-Kyoto (WKY) rats were used in this experiment. The contents of $A\beta_{42}$ and $A\beta_{40}$ in hippocampus were measured with ABC - double antibody sandwich ELISA methods; The mRNA expression level of RAGE, LRP-1, APP and BACE1 in hippocampus were detected with RT-PCR; The expression levels of RAGE, LRP-1, APP and BACE1 were determined by Western-Blot. The contents of $A\beta_{42}$ in hippocampus of SHR were significantly higher than that of WKY groups, But the content of $A\beta_{40}$ have no significant difference between the SHR and WKY groups; Compared with WKY groups, the expression levels of RAGE mRNA and BACE1 mRNA in SHR hippocampus increased significant difference. The APPmRNA expression level relatively decreased and the LRP-1mRNA expression level relatively increased, but there is no statistically significant difference between the two groups; The RAGE and BACE1 expression level in SHR hippocampus increased obviously. The APP and LRP-1 expression level are relatively higher, but the difference was not statistically significant. So we can conclude that abnormal expression levels of mRNA and its protein of BACE1 and RAGE resulted in $A\beta_{42}$ increased in hippocampus may be associated with cognitive impairment in SHR.

ABBREVIATIONS

SHR: Spontaneously Hypertensive Rat; Aβ: β-amyloid protein; APP: Amyloid Precursor Protein; BACE1: β- Amyloid precursor protein Cleaving Enzyme; RAGE: Receptor for Advanced Glycation Endproducts; LRP-1: Low-density lipoprotein receptor-related protein-1; WKY: Wistar-Kyoto; AD: Alzheimer's Disease.

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by insidious onset and slowly progressive cognitive impairment. It is the most common form of dementia, accounting for 50–60% of all cases. The main pathological features include the hallmarks of the disease—ie, senile plaques, the deposition of β-amyloid (Aβ), and fiber tangles, composed of hyper phosphorylated tau [1-4]. The pathogenesis of AD is extremely complex, at present the pathogenic mechanisms are not fully known. Scholars have proposed many different theories to explain the pathogenesis of AD, "Aβ cascade theory" has been widely accepted among them. The central hypothesis for the cause of Alzheimer's disease is the amyloid cascade hypothesis which states that an imbalance between the production and clearance of Aβ in the brain is the initiating event, ultimately leading to neuronal degeneration and dementia [5].

Cognitive impairment can be caused by vascular risk factors in the elderly, but most investigators think it is closely related to occurrence of vascular dementia. However, there is also a changes related vascular disease in the clinical and pathological manifestations of AD. A large number of epidemiological evidence also shows that vascular risk factors play an important role in Alzheimer disease. It can hasten the occurrence of the AD and may accelerate deterioration of the clinical manifestation of the AD. Therefore the vascular hypothesis of Alzheimer disease was put forward [6]. Hypertension, as the most common form of cardio-cerebrovascular disease risk factors, is well known as a cause of cognitive dysfunction as well as vascular dementia. However, it remains uncertain whether hypertension plays a role in the progression of AD. It is not clear whether it leads to the development of cognitive impairment involved in the abnormal metabolism of Aβ. In addition, there is increasing evidence that spontaneously hypertensive rat SHR also show impairments in learning and memory. The SHR was developed by inbreeding rats of the Wistar-Kyoto (WKY) strain and is one of the best-studied animal models of cognitive impairment. To this end, we have taken SHR and WKY rats as the research objects to explore changes of Aβmetabolic pathways in hypertensive rats; it has important significance to clarify the mechanism of hypertension in the development of Alzheimer disease. This is the importance of prevention and treatment in AD patients.

MATERIAL AND METHODS

The main reagents and instruments

The antibodies of rabbit anti-APP, anti-BACE1and anti-RAGE were purchased from Cell Siganling Technology. The antibodies of goat anti-LRP-1, mouse anti-GAPDH, HRP conjugated anti-rabbit IgG, anti-goat IgG and anti-mouse IgG were bought from Santa Cruz Biotechnology. ECL reagent for Western-Bolt assay was purchased from Hyclone. Trizol reagent was bought from the Invitrogen and RT-PCR kit was from TakaRa.

The main instruments included high speed freezing centrifuge (Sigma 3-30K), PCR Fluorescent Quantitative Machine (Biometra TG96), electrophoresis apparatus (Bio-Rad), horizontal strip electrophoresis apparatus (DYCP-31D from Beijing Liuyi instrument factory), Vertical Electrophoresis Tank (Bio-Rad Mini-P TET), Transfer Electrophoresis Tank (Bio-Rad Mini Trans-Blot), Puifed-water maker (ELGA Option-R7/15), Gel imaging and analysis system (Bio-Rad ChemiDocXRS), Super-micro Spectrophotometer (Bio-Tek Epoch), Dural Near Infrared fluorescenct Imaging System (Licor Odyssey), ELIASA detector (Bio-Rad iMark), ultra cold storage freezer (Thermo 8602), and liquid nitrogen utensils (MVE Cryosystem6000).

Experimental animals and sample collection

Experimental animals: 10 SHR (14-15 week old) and 10 WKY rats (8-10 week old) were bought from Beijing tong lihua experimental animal technical co. LTD, Which raised to 18-20 weeks in the Xi'an Jiaotong University medical experimental animal center under the condition of temperature (24±2) ℃, humidity (50±10) %, free access to food and water was permitted. One SHR rat died during the process of raising.

Animal euthanasia and sample collection: Experimental animals were anaesthetized by intraperitoneal injection of 10% chloral hydrate (3.5 ml/kg), A glass cannula was careful inserted to the aortic root from the left ventricle after rats were put on the operation panel and opened the chest to expose heart, by silk thread ligation in case of loss and eye camber of right atrium bloodletting, Aaline 100 ml were rapidly infused into intubation. Rats were decapitated and the brain were harvested. Both sides of the hippocampal tissue were separated, weighed, numbered and stored in liquid nitrogen tank respectively for further inspection.

Homogenated hippocampus tissue preparation

About 500ug hippocampus tissue weighted by analytical balance and was put into the glass homogenizer, adding 10% of the protein cracking fluid, grinding about 30 times repeatedly in the ice water bath. homogenated hippocampus tissue was put into 1.5 ml EP tube and separated by high-speed centrifuge at 15000 turn/min for 10 minutes. The supernatants were pipetted into another 1.5 ml EP for the testing immediately.

The $A\beta_{40}$ and $A\beta_{42}$ measures

$A\beta_{40}$ and $A\beta_{42}$ content in hippocampus were tested by ABC-double antibody sandwich ELISA method. $A\beta_{40}$ and $A\beta_{42}$ ELISA test kit were brought from the R&D Company, and specific experiment were performed according to the kit instructions.

RT-PCR detection

The total RNA in 50~100 mg hippocampus were extracted by Trizol one-step method according to TRizol reagent kit from the Cell signal company. The determination of purity RNA samples by RNA A260 / A280 values. 5 pair of primers of APPmRNA, BACE1mRNA, RAGEmRNA, LRP-1mRNA and GAPDHmRNA(glyceraldehyde-3- phosphate dehydrogenase) were synthesized by Shanghai jie rui biotechnology company. APPmRNA upstream primer: 5 '- GGATGCGGAGTTCGGACATG - 3', downstream primer:5'-GTTCTGACTCTGCTCAAAG-3'; BACE1mRNA upstream primer: 5'- GATGGTGATGCGGAAGGACTGATT-3', downstream primers: 5'-CCGGCGGGAGTGGTATTATGAAGT- 3'); RAGEmRNA upstream primer: 5'-CAGGGTCACAGAAACCGG-3' and downstream primers: 5'- ATTCAGCTCTGCACGTTCC-3'); LRP-1mRNA upstream primer:5'-GAGTGTTCCGTGTATGGCAC-3', downstream primers: 5'-GATGCCTTGGATGATGGTC-3'; GAPDHmRNA upstream primer:5'- GGCATGGGTCAGAAGGATTCC-3', downstream primers: 5'-ATGTCACGCACGATTTCCCGC-3'. The reverse transcribed cDNA and PCR amplification were done according to the manual operation.The amplification of targe was taken in 25μL PCR reaction system from 2μL cDNA. (1) Reverse transcription: according to Lithuania Fermentas company kit instructions: reverse transcription condition is: 25℃ for 10min;42 ℃ for 60min;70 ℃ for 10min; (2) the PCR conditions are: APP: 94℃ modified 5min, denaturation, 94℃ for 30s; annealing, 52℃ for 45s;extension,72℃ for 45 s; 30 cycle, ultimate extension at 72℃ for 7 min. BACE1: 94℃ modified 5min, denaturation, 94℃ for 30s; annealing, 60℃ for 45s; extension, 72℃ for 45 s; 30 cycles; ultimate extension at 72℃ for 7 min. RAGE: 94 ℃ modified 5 min, denaturation, 94 ℃ for 30s, annealing, 53 ℃ for 45s, extension, 72 ℃ for 45s, 30 cycle , ultimate extension 72℃ for 7min. LRP-1:9 4℃ modified 5min, denaturation, 94℃ for 30s, annealing, 51℃ for 45s, extension, 72℃ for 45s, 35 cycles , ultimate extension 72℃ for 7min.The fragment length of end products were 298,

322, 214, 768 and 500 bp respectively. PCR products were conducted on 2% agarose gel electrophoresis in the total sample of 15 ul (10 ul amplification products and 5 ul DNA Marker), it was analysised by the Bio-RAD gel imaging analyzer. The ratio value of grey of APP/GAPDH, BACE1/GAPDH, RAGE/GAPDH and LRP-1 / GAPDH is representative of the expression level of APPmRNA, BACE1mRNA, mRNA and LRP-1mRNA respectively.

Western-blot assay

The proteins were extracted from 50 ~ 100 mg hippocampus tissues and the protein concentration was determinate according to the Bradford kit. After the amount of 30ug protein samples were conducted on SDS-PAGE electrophoresis, the proteins in the gel was transferred to the PVDF membrane, blocked with 5% skimmed milk powder TBST, and incubated with primary mouse anti-APP, BACE1, RAGE, LRP - 1 and GAPDH antibodies (diluted based on antibody manual) respectively, incubated 1.5 h at 4°C. Then the membrane were incubated with the specific second antibodies (HRP conjugated anti rabbit IgG and anti-mouse IgG, 1:3000) after washing, then incubated for 1 h at room temperature, exposure imaging after ECL chemiluminescence chromogenic substrate analyzed by Scannerk708 BenQ scanner imaging system. The OD value of APP/GAPDH, BACE1/GAPDH, RAGE/GAPDH and LRP-1 / GAPDH was represented for the expression level of APP BACE1 RAGE and LRP-1 respectively.

Statistical analysis

Normal distributed continuous variables are demonstrated as means ± standard deviations. A database was set up according to the Excel by computer. Normal test and homogeneity test of variance with groups are tested; differences are compared between groups by t- test. Statistical analyses were made by using SPSS13.0 for Windows program. A P-value of less than 0.05 was considered to indicate a statistically significant difference.

RESULTS AND DISCUSSION

Result

The content of $A\beta_{40}$ and $A\beta_{42}$ in hippocampus of SHR and WKY groups: At the study, a abnormal changes of Aβ were found .The content of $A\beta_{42}$ in hippocampus of SHR groups increased significantly than that in the WKY groups (1.583±0.085 vs 1.438±0.112 pg/mg, P <.05). The content of $A\beta_{40}$ in hippocampus of SHR groups less increased than that in WKY groups, but there was no significant statistically difference (P > .05) (See Table 1).

The mRNA expression level of RAGE, LRP-1, APP and BACE1 in hippocampus of SHR and WKY groups: Adopting the method of RT-PCR, there was a significant difference between SHR and WKY groups (see figure 1). Compared with WKY groups, the expression level of AGEmRNA (1.020 ± 0.084 vs 0.768 ± 0.300) and BACE1mRNA (1.361 ± 0.257 vs 1.085 ± 0.237) in hippocampus of SHR increased significantly (p<.05). But the expression level of APP mRNA (1.024 ± 0.083 vs 1.078 ± 0.100) relatively decrease (***p***>.05); And the expression level of LRP-1 mRNA (1.022 ± 0.083 vs 0.816 ± 0.348) is relatively higher (*p*>.05).

The expression levels of BACE1, RAGE, LRP-1 and APP in the hippocampus of SHR and WKY groups: Using western -blot method, we can find a significant difference in SHR compared with WKY rats (see Figure 2). The expression level of RAGE and BACE1 in hippocampus of SHR increased significantly (*p*<.05). While the expression level of APP and LRP -1 are relatively higher, but there is no statistically significant difference between the two groups (*p*>.05).

DISCUSSION

Aβ is a major component of senile plaques in the pathogenesis

Table 1: The content of $A\beta_{40}$ and $A\beta_{42}$ in hippocampus (pg/mg).

Group	n	$A\beta_{42}$	$A\beta_{40}$
SHR	9	1.583±0.085	0.119±0.064
WKY	10	1.438±0.112**	0.118±0.079$^{\Delta}$

Numeric variables are presented as mean ±SD. SHR: Spontaneously hypertensive rat; WKY: Wistar-Kyoto rat; Aβ: β-amyloid protein. Compared with WKYgroups:* *p<.01 $^{\Delta}$p>.05

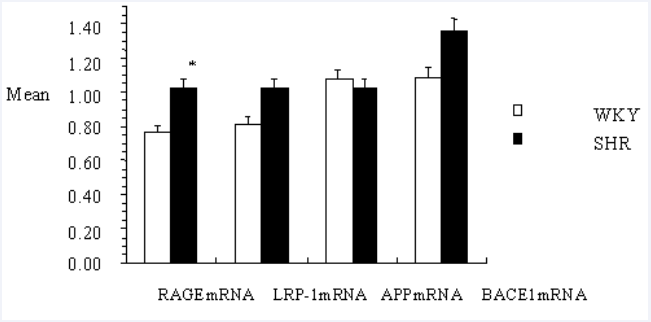

Figure 1 The mRNA expression level of RAGE, LRP-1, APP and BACE1 in hippocampus of SHR and WKY groups. The numerical value in figure is mean of grey in agarose gel electrophoresis. RAGE: receptor for advanced glycation end products; LRP-1: low-density lipoprotein receptor-related protein-1; APP: amyloid precusor protein; BACE1: β-amyloid precusor cleaving enzyme. Compared with WKY groups, p<.05

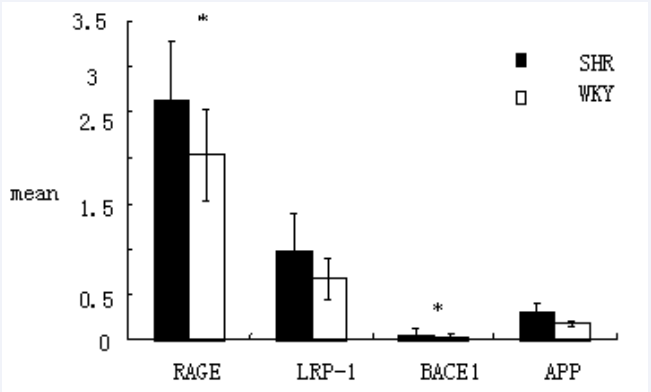

Figure 2 The expression levels of BACE1, RAGE, LRP-1 and APP in hippocampus of SHR and WKY groups. The numerical value in figure is mean of OD value in SDS-PAGE electrophoresis. RAGE: receptor for advanced glycation end products; LRP-1: low-density lipoprotein receptor-related protein-1; APP: amyloid precusor protein; BACE1: β-amyloid precusor cleaving enzyme. Compared with WKY groups, *p<.05

of Azheimer's disease and derive from amyloid precursor protein (APP). BACE1 is main rate-limiting enzyme of APP cleaving process to generate Aβ . APP can be processed along two main pathways. In the α-secretase pathway, α-secretase cleaves APP within the Aβ domain; this pathway does not produce Aβ. In the β-secretase pathway, β-secretase cleaves APP just before the Aβ domain, releasing soluble βsAPP. The remaining is cleaved by the γ-secretase complex releasing the free 40 or 42 aminoacid Aβ peptide. In pathological situation, APP can be cleaved by the β-secretase pathway which generating a small amount of $Aβ_{42}$ and a large number of $Aβ_{40}$. $Aβ_{40}$ is chiefly deposited in the vessel wall and $Aβ_{42}$ is one of the major components of senile plaques. Under normal conditions, Aβ is also cleared from the brain in a process balanced by the efflux, mediated by LRP-1, and the influx, mediated by the RAGE, of Aβ across the blood–brain barrier. Such the net content Aβ of the brain cells, not only depends on the APP via BACE1 cracking generation, also is affected at transfer balance by RAGE and LRP-1 across the blood brain barrier .In Familial Alzheimer's disease, it is key to excess Aβ cleaving from APP. By contrast with familial disease, the existing research data show that sporadic Alzheimer's disease may not be the increase generated Aβ and is mainly due to Aβ reduce cross the blood brain barrier transport imbalance [1,6].

Vascular risk factors are the main cause of vascular dementia. With the deepening of the research on AD. Epidemiological survey found that traditional risk factors for stroke, such as hypertension, diabetes, and hypercholesterolemia, increase the risk not only of vascular cognitive impairment but also of AD [7-25], but the mechanism is not fully clear, that it is mostly speculation that cerebrovascular damage lead to secondary cerebral ischemic damage. SHR is an ideal animal model to research Cognitive impairment due to hypertension and to screen cognitive dysfunction drugs [26]. Early study had showed that there were learning and memory ability damage in SHR [27]. And the mechanism of cognitive impairment was due to the low expression of nicotinic acetylcholine receptor and reduces of nicotine stimulation function [28]. Some studies have confirmed that there was a functional disorder of the hippocampus at the early stage of hypertension formation in SHR. With further increased blood pressure, the volumes of local brain such as hippocampus dentate gyruscorpus callosum have dropped gradually and the loss range of hippocampal neuron have expanded gradually [29-30]; Another study found that the density of nicotinic acetylcholine receptor of the hypothalamus and cerebral cortex in the young and aged SHR decreased obviously than that in the same age normotensive WKY rats [31]. The recent study show that modest, sustained levels of hypertension are sufficient to cause cerebrovascular alterations accompanied by endothelial and inflammatory changes [32].These hanges caused by abnormalities of cerebrovascular, brain morphological structure and the cerebral blood flow from long-term high blood pressure. These brain areas are the first involvement place closely associated with learning and memory function in AD patients.

Our study found that the content of $Aβ_{42}$ in hippocampus tissue of SHR increased obviously, compared with normal blood pressure of WKY rats, and the expression levels of APP mRNA and APP changed little, while the expression levels of BACE1 mRNA and BACE1 were further increased. The overexpression levels of BACE1 accelerated to generate increasing Aβ cleaving from APP. Meanwhile it found that the expression levels of RAGE mRNA and RAGE in hippocampus in SHR significantly higher and the expression levels of LRP-1mRNA and LRP 1 expression changed little in hippocampus in SHR, Which disturbed transport balance of Aβ through blood brain barrie to transport more Aβ into the brain, thereby increasing the net content Aβ in brain . Therefore abnormal expression levels of mRNA and its protein of BACE1 and RAGE resulted in $Aβ_{42}$ increased in hippocampus may be involved in the cognitive impairment of SHR.

In AD patients and APP transgenic animal model, the expression level of RAGE in BBB make up-regulaiton significantly, while the expression level LRP-1 make down regulation, which is associated with the aggregation of Aβ [33-34]. Abnormal expression of LRP-1 and RAGE in BBB, leading to Aβ transport function imbalance resulting in Aβ level abnormally elevated in the brain and Aβ aggregation and deposited in senile plaques [35]. RAGE combining with Aβ across BBB transport into the brain, then is taken in microglial cells and neurons inducing oxidative stress response, which promotes the release of inflammatory factors and activates the NF-κB signal transduction pathway, further strengthens the inflammatory reaction. At the same time, the RAGE combining with Aβ can promote the expression of endothelin increased, thus induce ischemia response, further a vicious cycle, increase the damage of brain cells. Animal studies have shown that the expression level BACE1 mRNA increase of nearly 100% after cerebral ischemia model of rats caused by ligation of bilateral common carotid artery. The activity of BACE11 in ischemia cerebral cortex was increased by 30% and the content of BACE11 was increased by 67% after unilateral cerebral ischemia model of rats [36]. It was found that deposition of Aβ increased in microvascular wall and hippocampus in chronic hypertension model rats caused by aortic coarctation and subcutaneous injection of angiotensin. Further studies have found that this may be related to the blood-brain barrier damage and increase of the expression of RAGE in cerebrovascular [37-38]. It is similar to our results. Therefore cerebral ischemia can induce Aβ metabolic disorders, which imply the expression level of BACE1 mRNA and BACE1 due to cerebral ischemia caused by hypertension in SHR increased and then increased formation of Aβ. So we can be sure that there is similar to abnormal changes of Aβ metabolic pathways among the AD animal models, SHR and patients with AD, but it is not quite the same.

Our study found the expression level of LRP-1 in hippocampus in SHR increased slightly than that in WKY, but the difference did not reach statistical significance The expression level of LRP-1 in BBB AD patients and animal models with AD significantly reduce [39]. There is also evidence that there are negatively correlations between the expression level of LRP-1 and Aβ deposition in brain capillaries in AD model [40-41]. While another study found that the IgG against RAGE antibody can block Aβ to the influence of RAGE, and the expression level of LRP-1 increased in brain microvascular endothelial cells under the region of enrichment of Aβ. Thus there is a negative correlation between RAGE and LRP -1 in Aβ enrichment area [42].So it is possible that the expression level of LRP-1 in the brain was mainly affected by the local microenvironment of the brain. The expression level of LRP-1 in the different stages of disease may vary.

The change of structure and function of neurovascular unit is the key to study relationship between AD and vascular risk factors. It is necessary to be further explored to Alzheimer disease onset and clinical deterioration due to the change of Aβ metabolic pathway in neurons and BBB and different vascular risk factors and the influence of their exposure time. Our preliminary research found abnormal changes of Aβ metabolic pathways in SHR, but the specific parts of abnormal expression of those proteins still need to be further studied. Therefore based on our preliminary study, it may be think that hypertension play important role in the occurrence of AD, Which the mechanisms were not only involved in the cerebral ischemia damage due to hypertension, but also associated with abnormal Aβ metabolic pathways. The occurrence of AD was widely accepted in addition to Aβ deposition cascade theory, the vascular hypothesis is also worthy of attention and research. The relationships of the two hypothesis are inseparable, but the causal relationships or synergistic effects between them are still not very clear. The hypertension can affect cerebral blood flow CBF and neurovascular coupling .Based on theoretical system of "neurovascular unit", the uncoupling theory of nervous vascularis can be better explain the internal mechanism between vascular risk factors and Alzheimer disease onset [6,43-44]. The relationships among Aβ, RAGE and BACE1 are focus in the role of vascular risk factors in the occurrence of AD. It is also a notable potential target of treatment patients with AD.

It should be noted that our study has some limitations. It needs to be considered when interpreting the present findings and that should be addressed in future research. First, age is one of most important influence factors of cognitive impairment, our design do not consider the effect of age, that is, does not have a control group of different ages. Second, there are lacks of intervention measures to reduce high blood pressure. How changes will be taken in the index of Aβ metabolic pathways when administering different drugs. In addition, Aβ transshipment dysfunction in nerve cells or the vascular endothelial cells need to be study. Despite these limitations, the present study has several notable findings that there are abnormal changes of Aβ metabolic pathways in SHR compared with the normal blood pressure of WKY rats.

CONCLUSION

Abnormal expression levels of mRNA and its protein of BACE1 and RAGE resulted in $A\beta_{42}$ increased in hippocampus may be associated with cognitive impairment in SHR.

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