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# Inhibition of AGEs-RAGE-PP2A axis alleviates cognitive impairment after chronic heart failure

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**ABSTRACT**

To investigate the effect of the AGEs-RAGE-PP2A axis on cognitive impairment (CI) after chronic heart failure (CHF). Mice were divided into six groups: Sham, TAC, Sham+RAGE$^{-/-}$, TAC+RAGE$^{-/-}$, AG, and FTY720 group. AG mice and FTY720 mice were treated with AGEs inhibitor (aminoguanidine, AG) and PP2A activator (FTY720) respectively after TAC surgery. The cardiac function of AG and TAC+RAGE$^{-/-}$ mice was significantly better than that of TAC mice ($P<0.05$). However, the heart function of FTY720 mice were just improved a part of that. To behavioral function, the escape latency period of the TAC+RAGE$^{-/-}$, AG and FTY720 mice were significantly shorter ($P<0.05$), and the times of platform crossings and residence time of them were significantly improved ($P<0.05$). HE staining and silver staining show the structure of TAC+RAGE$^{-/-}$, AG and FTY720 mice were more complete. Also, in these three groups, the expression of Aβ and p-tau protein in the brain can be significantly down-regulated ($P<0.05$) and the PP2A protein expression level was up-regulated ($P<0.05$). And the expression of hippocampal Bax, Cyt-C, and Caspase-3 of that were all down-regulated ($P<0.05$), and Bcl-2 was up-regulated ($P<0.05$). Deficient of AGEs, RAGE and activating PP2A can significantly attenuate the cognitive impairment in CHF mice, and protect the brain structure. This mechanism seems via reducing the expression of Aβ, p-tau, and apoptotic protein.

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## Introduction

Chronic heart failure (CHF) is a common cardiovascular disease characterized by high mortality and morbidity. Globally, about 2% of patients have CHF, and the rate increases with age, which is one of the major causes of hospitalization. Cognitive impairment (CI) generally refers to damage to cognitive function, including memory, language and thinking, ranging from mild cognitive impairment to dementia (1). As the problem of aging become serious, CI is a worldwide health problem.

There is a close relationship between CHF and CI. It has been found that the incidence of cognitive impairment in CHF patients is four times higher than that in healthy controls. Up to 25% of patients with CHF have been found to have moderate to severe cognitive impairment (2). In addition, researchers made further discovered that most of patients with CHF have incomplete brain structures, especially brain structures related to learning and memory (3, 4). Patients with CHF are more prone to experiencing CI, potentially due to CHF's role in inducing abnormal cerebral structure, making it a central factor in CI development.

Patients with CHF CI generally have clinical symptoms: low memory, attention, execution and the disability to learn new things, resulting in a poor prognosis, low level of life quality and increased mortality in CHF patients (5). Therefore, the prevention and treatment of CHF CI should be a significant public health problem to be solved urgently. However, the mechanism of CHF CI is unclear and the therapy of that is resistant.

Current research revealed that advanced glycation end products (AGEs) and receptors for advanced glycation end products (RAGE) play an important role in the pathogenesis of CI (6)and CHF(7). It means that the AGE-RAGE axis might a central regulator of CHF CI. Recent research shows patients with CHF have a higher level of AGEs and RAGE protein in serum (8). It seems that CHF might accelerate the process of glycosylation in the human body and facilitate AGEs and RAGE production (8). Some neurological research revealed that AGE-RAGE axis stimulation can lead to tau hyperphosphorylation and Aβ deposition (9), which induce neurofibrillary tangles (NFTs) and senile plaques (SP), two characteristic pathologic changes of cognitive impairment. Thus, the AGEs-RAGE axis is a potentially important regulator of CHF CI.

Moreover, tau phosphorylation is mainly controlled by protein phosphatase 2A (PP2A). PP2A is the main protein phosphatase that regulates the dephosphorylation of tau protein, accounting for 70% of the total tau phosphatase activity. In patients with dementia, the activity of cerebral PP2A is significantly reduced, which aggravates the abnormal tau phosphorylation (10). After antagonizing tau hyperphosphorylation, patients with dementia can effecti-

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vely improve their clinical symptoms such as low memory. Therefore, PP2A is an important target for inhibiting the phosphorylation of tau protein and treating cognitive impairment. Therefore, our study hypothesized that the AGEs-RAGE-PP2A axis is a potentially crucial regulator that mediates the development of CI in CHF patients.

Our previous study reveal that the expression of cerebral AGEs and RAGE protein can be upregulated, and PP2A protein can be downregulated in CHF mice(11). Therefore, in this study, we further proved that the AGEs-RAGE-PP2A axis is a significant regulator of tau hyperphosphorylation and Aβ deposition in CHF CI mice. And we uncovered that inhibiting AGEs, knocking out RAGE and activating PP2A is a significant approach to reversing cognitive dysfunction induced by CHF.

## Materials and Methods

### Animal

Male, wild-type (WT) C57BL/6J mice, aged 8 weeks, were obtained from the Experimental Animal Center, Guangzhou University of Chinese Medicine. the receptor for AGE (RAGE) knockout ($RAGE^{-/-}$) mice was a gift from Kanazawa University, Japan. C57BL/6J male mice were randomly assigned to four groups: Sham, TAC, Aminoguanidine (AG), and Fingolimod (FTY720). $RAGE^{-/-}$ male mice were randomly assigned to two groups: Sham $RAGE^{-/-}$ or TAC+ $RAGE^{-/-}$. All animal studies were carried out with the approval of the Guangzhou University of Chinese Medicine Institutional Animal Care and followed the ethical code of animal use.

### Models and treatment

Transverse aortic constriction (TAC) surgery was performed to induce chronic heart failure in mice. Briefly, the mice were anesthetized with intraperitoneal (i.p.) injection of pentobarbital sodium (50 mg/kg, Sigma, St. Louis, MO, USA). While connected to a ventilator, a thoracotomy was conducted, and the aorta was ligated between the right innominate artery and the left common carotid artery using an 8-0 silk suture ligature against a 27G needle. This resulted in a narrowing of 25%–30% of the original cross-sectional area upon needle removal. Sham-operated mice underwent the same thoracotomy procedure without aortic constriction. In some experiments, mice received a single injection of either 1 mg/kg FTY720, 20 mg/kg aminoguanidine, or the vehicle (0.9% sodium chloride).

### Ultrasound echocardiography

Ultrasound echocardiogram was performed using a Vevo 2,100 Imaging System (VisualSonics Inc., Toronto, ON, Canada) in mice under anesthesia with isoflurane (RWD Life Science Co., Guangdong, China). Briefly, mice were anesthetized with 1.0–2.5% of isoflurane and the heart rate was maintained approximately between 450 and 550 beats/min. The heart was examined in the short-axis view at the papillary muscle level, and an M-mode echocardiogram of the mid-ventricle was recorded. Analysis of echocardiographic images was performed in a blinded manner.

### Morris water maze test

The Morris water maze test and DMS-2 water maze test system (RWD Life Science Co. Ltd., Shenzhen, China) were utilized to assess learning and memory in mice (12). The experiment commenced in week 13. Mice were positioned in water with their heads facing the pool wall, and one of the four starting positions (quadrants I, II, III, or IV) was randomly assigned. Test conditions ensured minimal background noise, and the water temperature was maintained between 22–25°C. The time taken by the animals to locate an underwater platform was recorded. During initial training sessions, if the time exceeded 60 s, the animal was guided to the platform and allowed to remain there for 10 s. Training was conducted four times daily at fixed intervals for 5 days. On the 6th day, the platform was removed, and the animal was placed in the water from the opposite side of the original platform quadrant. The time spent in the target quadrant (the quadrant where the platform was initially placed) and the number of times the animal entered that quadrant were recorded as indicators of spatial memory.

### Histological examination

Hippocampus tissue was isolated and rinsed with phosphate buffer saline (PBS) and fixed in 4% paraformaldehyde (PFA) for over 24 hours. The hippocampus was then dehydrated and paraffin-embedded. Next, 5 μm-thick slices were cut for hematoxylin-eosin (H&E) staining to explore changes in hippocampus neuron structure. After staining, all slices were completely scanned by using a Caseviewer 2.0 (Panoramic 250/MIDI, 3DHISTECH, Hungary).

### Silver staining

Brain tissue was isolated and rinsed with phosphate buffer saline (PBS) and fixed in 4% PFA for over 24 hours. Brain tissue was subsequently dehydrated and paraffin-embedded. Next, 5 μm-thick slices were cut for silver staining to observe changes in the structure of the axon. After staining, all slices were completely scanned using Caseviewer 2.0 (Panoramic 250/MIDI, 3DHISTECH, Hungary).

### Histological and immunochemical analysis

Cerebral cortex and hippocampus tissue were isolated and rinsed with PBS. The method of fixing and dehydration was the same as in the immunofluorescence analysis. An UltraSensitiveTM SP (Mouse/Rabbit) IHC Kit (KIT-9710, MXB Biotechnologies, Fuzhou, China) was used to complete the experiment. After blocking with 5% goat serum, samples were incubated with Aβ antibody (Abcam, ab201060, Cambridge, MA, USA) at room temperature for 60 min. Samples were then washed with PBS three times for 3 min each. Then, a secondary antibody was added followed by incubation at room temperature for 10 min. Samples were then washed with PBS three times for 3 min each. Streptomyces antibiotin protein-peroxidase reagent was added and incubated at room temperature for 10 min, then washed with PBS three times for 3 min each. Freshly prepared diaminobenzidine (DAB) reagent was then added to each section for color rendering, and PBS rinsing was used to stop the color development, hematoxylin redyeing, 1% hydrochloric acid ethanol differentiation, PBS rinsing cyanosis. Gradient dehydration and transparency with xylene. Sections were sealed with neutral gum and optical microscopy was used to observe and capture images.

### Western blotting analysis

Hippocampal tissue was isolated, rinsed with PBS, and lysed using a Minute™ Total Protein Extraction Kit for Animal Cultured Cells and Tissues (Ca. SD-001/SN-002, Invent Biotechnologies, USA). Protein content was measured via a bicinchoninic acid (BCA) Kit (Ca. P0012, Beyotime, Shanghai, China). Samples were heated at 95°C with 2×Loading Buffer (Ca. FD003, Hangzhou Fode Biological technology co., LTD, Hangzhou, China) for 5 min to fully denature the protein. Next, lysates were subjected to sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) gel electrophoresis and transferred to 0.45-μm polyvinylidene fluoride (PVDF) membranes (Ca. 1620260, Bio-Rad Laboratories, Inc., Hercules, CA, USA). The membranes were blocked with 5% skim milk (Ca. 9999, CST, Danvers, MA, USA) at room temperature for 1 hour and incubated overnight at 4°C with 1:1000 GAPDH (CST, 2118, Danvers, MA, USA), 1:10000 phospho S396-tau (Abcam, ab109390, Cambridge, MA, USA), 1:100 tau (Abcam, ab64193, Cambridge, MA, USA), 1:500 beta Amyloid 1-42 (Aβ, Abcam, ab201060, Cambridge, MA, USA), 1:5000 PP2A (Abcam, ab32104, Cambridge, MA, USA), 1:5000 Bax (Proteintech, 50599-2-Ig, Rosemont, IL, USA), 1:1000 Cytochrome C (Cyt-c, Proteintech, 10993-1-AP, Rosemont, IL, USA), 1:1000 caspase3 (Proteintech, 19677-1-AP, Rosemont, IL, USA), and 1:1000 Bcl-2 (Proteintech, 12789-1-AP, Rosemont, IL, USA). The membranes were washed with TBST three times for 10 min each. Samples were then incubated with HRP-conjugated secondary antibody (CST 7074 or 7076, Danvers, MA, USA) at room temperature for 1 hour and washed with TBST. Lastly, proteins were visualized using a chemiluminescence system (Bio-Rad, Hercules, CA, USA).

### Statistical analysis

Data are represented as mean ± standard deviation. Statistical analyses between the two groups were done using the Student's t-test. For multiple comparisons, the P-value was determined by one-way ANOVA. Analyses were carried out with Prism 7 (GraphPad, San Diego, CA, USA) and Statistical Product and Service Solutions (SPSS) 20.0 (IBM, Armonk, NY, USA). $P<0.05$ was considered significant.

## Results

### Inhibition of AGEs-RAGE-PP2A axis attenuates cardiac dysfunction after TAC

To determine whether RAGE knockout or inhibition of AGEs expression or activated PP2A protein improved cardiac function in TAC mice, we examined the changes in cardiac function after TAC at 14 weeks. Compared to sham mice, echocardiography showed a significant reduction of left ventricular ejection fraction (LVEF) and left ventricular fractional shortening (LVFS), and a significant increase of end-diastolic left ventricular internal dimension (LVID; d), end-systolic left ventricular internal dimension (LVID; s), left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV) in TAC mice. Compared to TAC mice, echocardiography showed significant improvement in LVEF, LVFS, LVID; d, LVID; s, LVEDV, LVESV and LV mass at 14 weeks in TAC+RAGE$^{-/-}$ and AG mice. Furthermore, FTY720 mice had better cardiac function than TAC mice at 14 weeks (Figure 1).

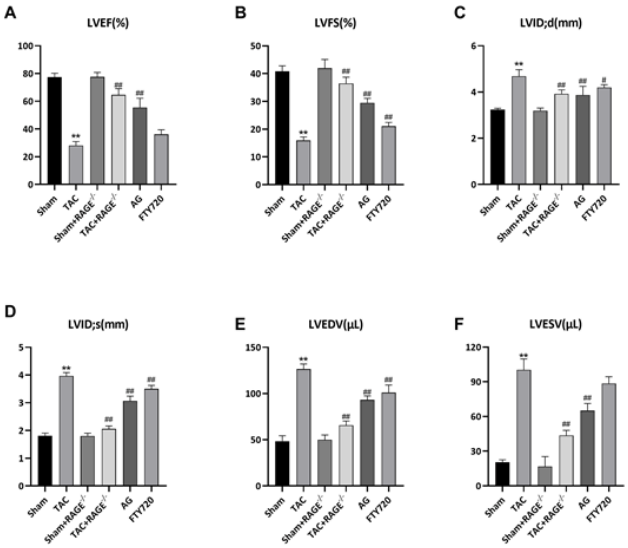


**Figure 1.** RAGE Knockout and the AGEs Inhibitor Aminoguanidine Attenuates Cardiac Dysfunction After TAC. Echocardiographic parameters: LVEF (A), LVFS (B), LVID; d (C), LVID; s (D), LVEDV (E), and LVESV (F). Mean±SEM, n = 5 biologically independent samples, $^{**}P < 0.01$, vs. Sham and $^{\#\#}P < 0.01$ by one-way ANOVA followed by Tukey's multiple comparisons test.

### Inhibition of AGEs-RAGE-PP2A axis reverses TAC-induced behavioral disorder

To determine whether TAC induces cognitive impairment and behavioral disorder and whether inhibition of the AGEs-RAGE-PP2A axis could improve cognitive function, Morris water maze testing was performed. Our results show that compared to the sham group, the navigation route was significantly complex (Figure 2A-B), the escape latent period time was significantly prolonged (Figure 2G-H) and the time of crossing the platform was significantly decreased (Figure 2I-J) in TAC mice. Compared to TAC mice, the navigation route was significantly simplified (Figure 2B-F), the escape latent period time was significantly decreased (Figure 2G-H) and the times of crossing the platform significantly increased (Figure 2I-J) in TAC+RAGE$^{-/-}$, AG and FTY720 mice.

### Inhibition of the AGEs-RAGE-PP2A axis protects against TAC-induced the damage of neurons

To determine whether TAC damaged the structure of neurons or reduced the number of neurons and dendritic cells and whether inhibition of the AGEs-RAGE-PP2A axis could reverse the changes, H&E straining in hippocampus CA1 area were performed. The results showed that compared to sham mice, the structure of the hippocampus was incomplete and disordered in TAC mice. The nucleus is constricted and deeply stained, and some neurons nucleolus disappeared, and the number of hippocampal neurons was significantly decreased (Figure 3A-B). Compared to TAC mice, the structure of the hippocampus was more complete and the number of hippocampal neurons was significantly increased in TAC+RAGE$^{-/-}$, AG, and FTY720 mice. (Figure 3B-F).

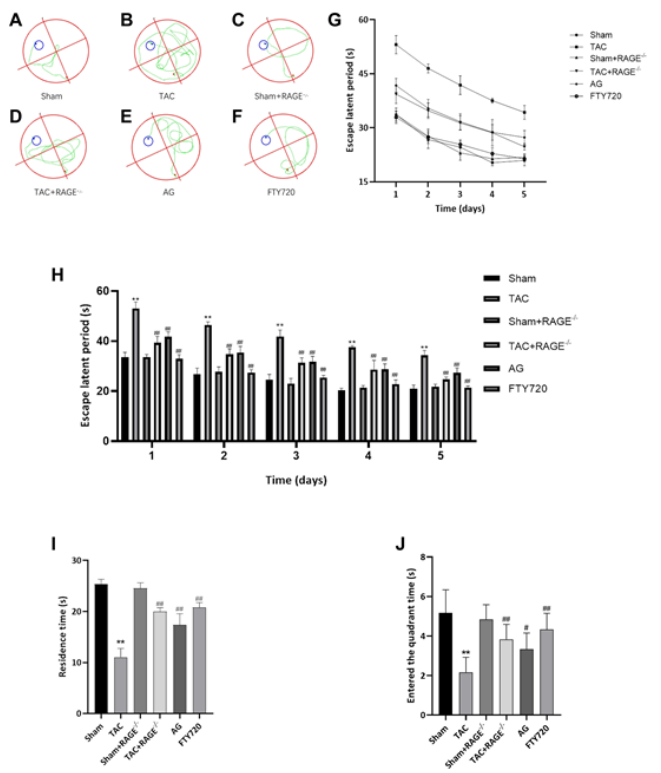


**Figure 2.** Inhibition of AGEs-RAGE-PP2A Axis reverses TAC-Induced Behavioral Disorder. Morris water maze test: mouse navigation route map (A-F), line chat of escape latent period (G), bar graph of escape latent period (H), residence time (I), entered the quadrant time (J). Mean±SEM, n = 6 biologically independent samples, $^{**}P < 0.01$ vs. Sham, and $^{\#\#}P < 0.01$ by one-way ANOVA followed by Tukey's multiple comparisons test.

## Inhibition of the AGEs-RAGE-PP2A axis protects the structure of axon from damage

To determine whether TAC damages the structure of axon cells and whether inhibition of the AGEs-RAGE-PP2A axis could reverse this damage, sliver straining was performed. As results showed, the axon structure of sham mice was normal and complete (Figure 3G). The axon structure of TAC mice was abnormal, and a large number of punctate dark brown neural tangles were scattered at the brain tissue (Figure 3H). Compared to the TAC mice, the axon structure of TAC+RAGE$^{-/-}$, AG and FTY720 mice were more complete, and the neural tangles were less than that of the TAC mice (Figure 3I-L).

## Inhibition of the AGEs-RAGE-PP2A axis Ppevents tau protein phosphorylation and Aβ protein deposition

To determine whether inhibition of the AGEs-RAGE-PP2A axis could protect against tau protein phosphorylation and Aβ deposition caused by TAC, we detected the levels of Aβ, p-tau and PP2Aprotein in brain tissue. Histological and immunochemical analysis showed that compared to sham mice, the deposition of Aβ was significantly increased in the cerebral cortex and hippocampus in TAC mice. Compared to TAC mice, the deposition of Aβ was significantly decreased in TAC+RAGE$^{-/-}$, AG, and FTY720 mice (Figure 4A-N). Western blotting analysis showed that compared to sham mice, tau protein phosphorylation and Aβ expression were significantly increased while PP2A expression was significantly decreased in TAC mice. Compared to TAC mice, tau protein phospho-

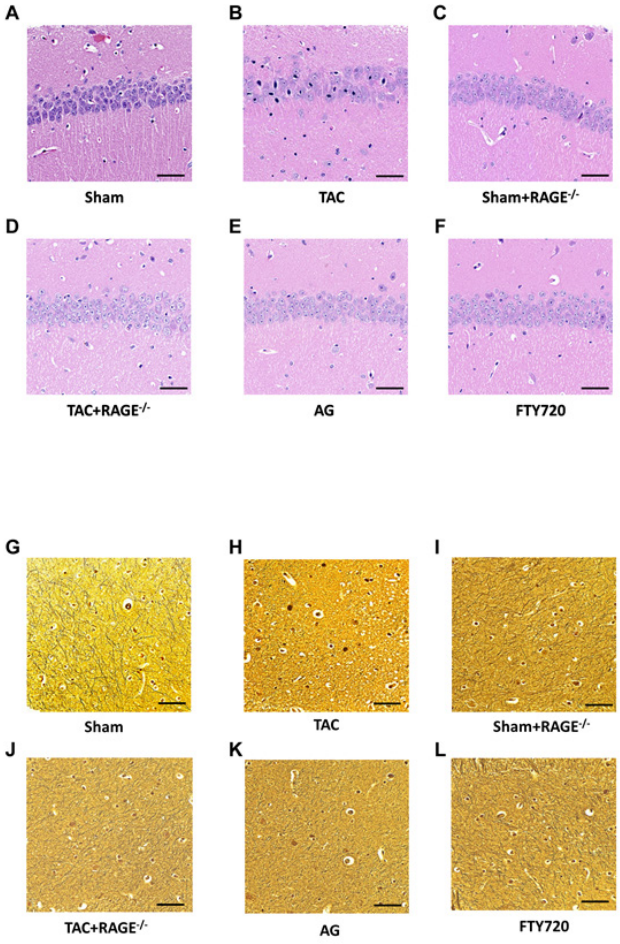


**Figure 3.** Inhibition of the AGEs-RAGE-PP2A Axis Protects Against TAC-Induced the Damage of Neurons. H&E staining of hippocampal CA1 area in Sham group (A), TAC group (B), Sham+RAGE$^{-/-}$ group (C), TAC+RAGE$^{-/-}$ group (D), AG group (E) and FTY720 group (F). Silver staining of brain axon in Sham group (G), TAC group (H), Sham+RAGE$^{-/-}$ group (I), TAC+RAGE$^{-/-}$ group (J), AG group (K) and FTY720 group (L).

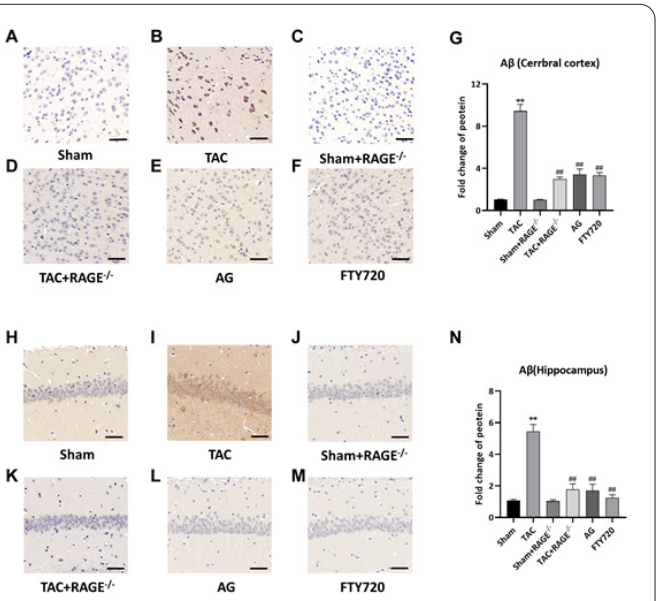


**Figure 4.** Inhibition of the AGEs-RAGE-PP2A Axis Protects Against Aβ Deposition. Immunohistochemical staining of Aβ in the cerebral cortex (A-F) and hippocampus (H-M). Quantitative analysis of Aβ protein levels in the cerebral cortex (G) and hippocampus (N), n = 3 biologically independent samples, $^{**}P < 0.01$, vs. Sham and $^{\#\#}P < 0.01$ by one-way ANOVA followed by Tukey's multiple comparisons test.

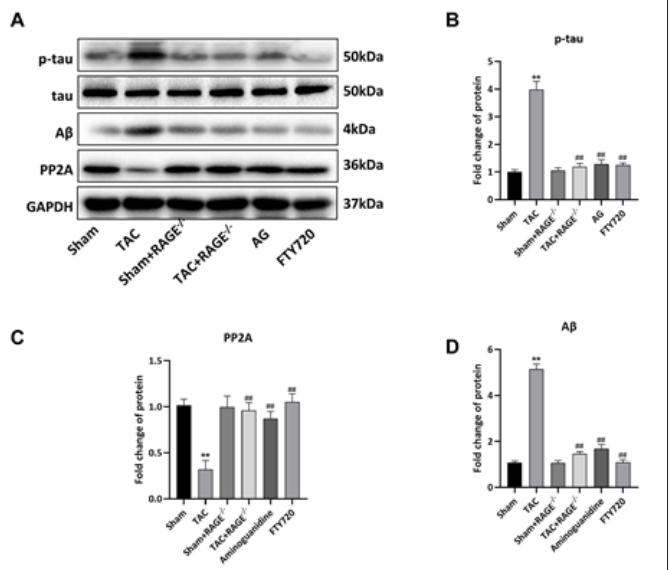


**Figure 5.** Inhibition of the AGEs-RAGE-PP2A Axis Protects Against Tau Phosphorylation, Aβ upregulating and PP2A downregulating. Representative western blotting of p-tau, Aβ, and PP2A protein in the hippocampus (A). Quantitative analysis of protein levels of p-tau (B), Aβ (D), and PP2A (C) in the hippocampus. GAPDH was used as the internal control. n = 4 biologically independent samples, **P < 0.01 vs. Sham, and ##P < 0.01 by one-way ANOVA followed by Tukey's multiple comparisons test.

rylation and Aβ expression were significantly decreased while PP2A expression was significantly increased in TAC+RAGE$^{-/-}$, AG, and FTY720 mice (Figure 5A-D).

### Inhibition of the AGEs-RAGE-PP2A axis prevents apoptosis in the hippocampus

In order to further clarify the mechanism by which inhibition of the AGEs-RAGE-PP2A axis affects cognitive impairment induced by heart failure, we assessed apoptosis in the hippocampus. Compared to sham mice, the expression of Bax, Cyt-c, and caspase3 proteins was significantly increased in TAC mice while the expression of Bcl-2 protein was significantly decreased. Compared to TAC mice, the expression of Bax, Cyt-c, and caspase3 proteins were significantly decreased while the expression of Bcl-2 protein was significantly increased in TAC+RAGE$^{-/-}$, AG and FTY720 mice (Figure 6A-E)

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## Discussion

In this study, we found that inhibition of the AGEs-RAGE-PP2A axis (inhibit AGEs-RAGE and activate PP2A) can effectively improve the mouse cognitive dysfunction induced by chronic heart failure, elevate the learning and memory ability of mice, resist neuronal apoptosis, protect the structure of the neuronal cell, and reduce the damage of axonal structural. Moreover, we elucidate p-tau and Aβ proteins are the targets of the AGEs-RAGE-PP2A axis. Inhibition of the AGEs-RAGE-PP2A axis can down-regulate the expression of p-tau protein and reduce Aβ deposition in the hippocampus of CHF CI mice.

Our findings have significant implications in three aspects. Firstly, we demonstrate that chronic heart failure induced by TAC leads to memory deterioration in the MWM test, which assesses cognitive functions. Secondly, we observe damage to neuronal structure in the HE staining, specifically in the hippocampal neuron structure. Thirdly, we observe the formation of neurofibrillary tangles in the silver staining, which indicates alterations in synaptic structure. Additionally, we observe an up-regulation of p-tau, Aβ, and apoptosis-related proteins. Cognitive impairment in this context is characterized by memory loss, damage to neuronal structure, formation of neurofibrillary tangles, hyperphosphorylation of tau, deposition of Aβ, and neuronal apoptosis. Consequently, we have successfully established a mouse model for CI induced by CHF, which will be valuable for future studies on CI associated with CHF.

On the other hand, we have found the mechanism of CHF and how to induce CI. After TCA surgery, cerebral PP2A protein is significantly downregulated. However, this can be reversed by inhibition of RAGE and AGEs proteins. This means that RAGE and AGEs are the upstream of PP2A. Previous studies showed AGEs is one of the important ligands of RAGE. In other words, the axis regulating mechanism of CHF CI should be AGE-RAGE-

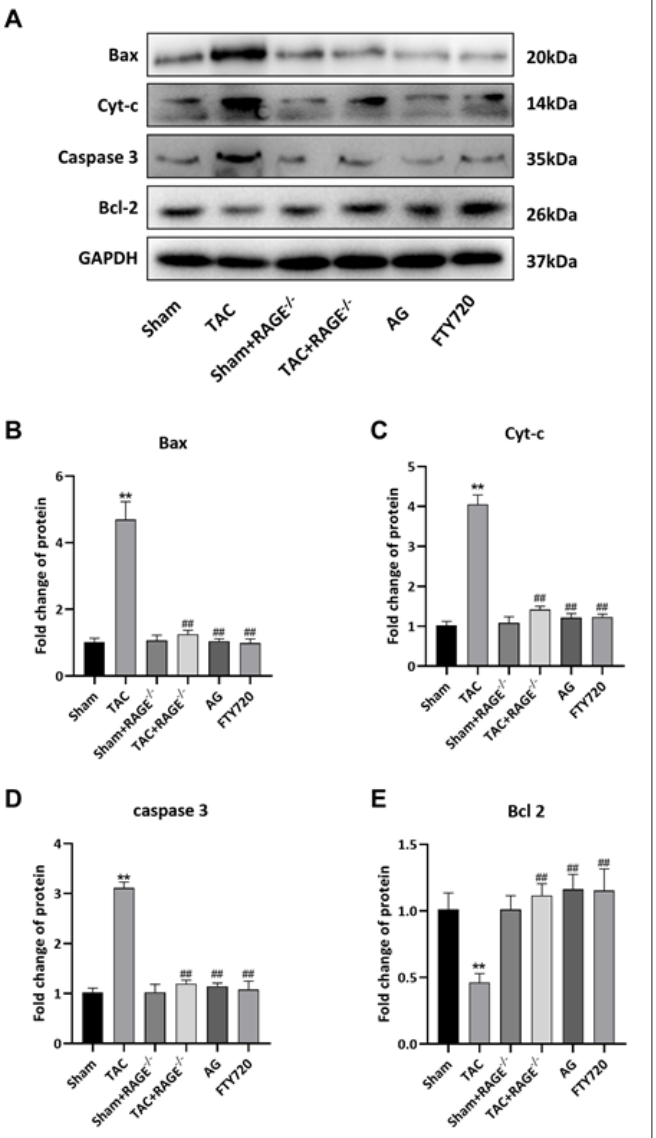


**Figure 6.** Inhibition of AGEs-RAGE-PP2A Axis Prevents Apoptosis in the Hippocampus. (A). Representative western blotting of Bax, Cyt-c, caspase3 and Bcl-2 proteins in the hippocampus. Quantitative analysis of Bax (B), Cyt-c (C), caspase3 (D) and Bcl-2 (E) protein levels. GAPDH was used as the internal control. n = 4 biologically independent samples, **P < 0.01 vs. Sham, and ##P < 0.01 by one-way ANOVA followed by Tukey's multiple comparisons test.

PP2A. To further explain how the axis regulates CHF CI, we use RAGE KO mice, AGEs inhibitor (AG) and PP2A activator (FTY720) to modify the axis.

When the expression of RAGE and AGEs were inhibited and PP2A activated, the cardiac function of mice subjected to TAC was significantly improved. TAC mice also showed cognitive impairment, tau protein phosphorylation, and Aβ deposition, which was significantly improved after inhibition of the AGEs or RAGE, and activation of-PP2A axis. In order to further clarify the mechanism of inhibition of the AGEs-RAGE-PP2A axis on cognitive impairment induced by HF, we determined that the inhibition of the AGEs-RAGE-PP2A axis can efficiently prevent apoptosis in the hippocampus. In summary, phosphorylation of tau protein mediated by the AGEs-RAGE-PP2A axis activated by HF may be an important mechanism of cognitive impairment caused by HF.

Heart failure (HF) is a group of clinical syndromes caused by ventricular filling and impaired ejection due to structural or functional disorders of the heart, such as myocardial infarction, hypertension, cardiomyopathy, or degenerative valvular heart disease. Many clinical and experimental results have shown that HF can lead to the occurrence of different degrees of cognitive impairment (13). Moreover, HF imposes a huge economic burden on society, and to individuals. Cognitive impairment refers to the impairment of aspects of mental and intellectual activities of the brain, such as feeling, memory, speech, abstract thinking, and other higher functions. The severity of cognitive impairment can range from mild cognitive impairment to dementia. Currently, the etiology of cognitive impairment is unclear. The pathogenesis is complex and involves multiple links, such as decreases in neuron nutrition, changes in neurotransmitters, and the abnormal modification or deposition of proteins, ultimately leading to the deformation and death of neurons (14). A growing number of studies have shown that HF is an important risk factor for Alzheimer's disease (15, 16). Clinical studies have found that, compared to healthy individuals, people with CHF have significantly reduced gray matter volume, which is mainly concentrated in the insular cortex, frontal cortex, hippocampal gyrus, cingulate gyrus, cerebellar cortex, and deep cerebellar nucleus (17). Furthermore, studies have revealed a significant reduction in the volume of key brain regions, including the hippocampus, caudate nucleus, corpus callosum, and papillary muscles, in individuals with CHF (18). This evidence indicates that CHF contributes to the acceleration of cognitive impairment. However, the precise mechanism by which this occurs remains unclear.

Tau protein is a microtubule-related protein widely expressed in the nervous system. Its main physiological function is to catalyze microscopic assembly and to maintain the stability of the neuroskeletal system. Highly phosphorylated tau protein aggregates to form NFTs in the brains of those with senile dementia and is believed to be a key cause of the degeneration of nerve fibers and the death of neurons, leading to cognitive impairment (19). Inhibition of tau hyperphosphorylation can effectively improve the clinical symptoms of senile dementia and is thus considered to be an important therapeutic strategy for the prevention and treatment of senile dementia. Epidemiological and basic research evidence shows that CHF is closely related to the occurrence of senile dementia and is one of the important causes of the onset of senile dementia (16). Therefore, the abnormally high phosphorylation of tau-related protein may be an important cause of the occurrence and development of CHF-related senile dementia. An in-depth study of the upstream mechanism regulating tau phosphorylation in CHF-related senile dementia will help to elucidate the pathogenesis of CHF-related senile dementia and reveal targets for intervention.

AGEs are nonenzymatic glycation end products resulting from the reaction between the amino group of protein lysine and the aldehyde group of reducing sugars. Initially, a reversible Schiff base is formed, which then undergoes structural rearrangement to yield stable ketamine compounds known as Amadori products. Through dehydration, oxidation, and condensation reactions, stable and irreversible AGEs are then formed. The role of AGEs in diabetic microangiopathy and other complications has attracted wide attention. Recent research suggests that AGEs may also play an important role in the development of CHF, aging, and cognitive impairment. AGEs can lead to decreased cardiac compliance, increased stiffness, limited myocardial relaxation, and vascular endothelial dysfunction, thus causing serious damage to the heart (20). Increased AGEs levels in vivo can also inhibit the proliferation and differentiation of neural stem cells by peroxidase-activated receptor (PPAR). A positive correlation between AGEs level and the wall of plaque forming element A has been observed in vivo, suggesting that there may be an internal correlation. At the same time, AGEs colocalize with NFTs and senile plaques, which are the two characteristic lesions found in AD. This further suggests that AGEs may be directly involved in the formation of NFTs and senile plaques (21).

RAGE is a member of the immunoglobulin superfamily of cell surface molecules, and through interaction with different ligands leads to a series of proinflammatory, coagulant, oxidative, and apoptotic cascades that damage myocardial mitochondria. This process is involved in vascular remodeling and cardiac function room wall reconstruction, which are different degrees of damage to the heart (22). Studies have shown that in vitro AGEs stimulation can upregulate the expression of RAGE in nerve cells, resulting in highly phosphorylated tau protein in Alzheimer's neurons. Aβ, a component of senile plaques, is one of the ligands of RAGE. The interaction between Aβ and RAGE after AGEs glycation can activate and induce microglia cells to move to the deposition, aggravating brain injury and cognitive impairment. The above studies suggest that the AGEs-RAGE axis is closely related to the occurrence of tau protein phosphorylation and Aβ deposition (23). Studies have shown that AGEs can induce tau hyperphosphorylation and impair synapses and memory through RAGE-mediated GSK-3 or PP2A activation (24, 25). There are many genetic, biochemical, physiological, and epigenetic findings related to Cardiopulmonary Function (25-27).

In this study, we found that HF induced by TAC caused high expression of RAGE protein. When the expression of RAGE and AGEs were inhibited and PP2A activated, the cardiac function of mice subjected to TAC was significantly improved. TAC mice also showed cognitive impairment, tau protein phosphorylation, and Aβ deposition, which was significantly improved after inhibition of the AGEs-RAGE-PP2A axis. In order to further clarify the

mechanism of inhibition of the AGEs-RAGE-PP2A axis on cognitive impairment induced by HF, we determined that the inhibition of the AGEs-RAGE-PP2A axis can efficiently prevent apoptosis in the hippocampus. In summary, phosphorylation of tau protein mediated by the AGEs-RAGE-PP2A axis activated by HF may be an important mechanism of cognitive impairment caused by HF.

## Data Availability

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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## Conflict of interest

The authors declare that they have no conflict of interest.

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