PIBB 生物化学与生物物理进展
Progress in Biochemistry and Biophysics
2021,48(11):1337~1347
www.pibb.ac.cn

Reversal of Memory Deficit Correlates to Formaldehyde Reduction in AβPP$^{Lon/Swe}$ Mice*

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Abstract The formation of plaques by the deposition of amyloid-β (Aβ) in the brain is a hallmark of Alzheimer's disease (AD). Transgenic mouse models based on amyloid-β precursor protein (AβPP) exhibited accelerated plaque formation and memory impairment. However, in some models, the correlation between memory loss and plaque formation is poor. Our lab has recently found a strong correlation between formaldehyde levels and cognitive impairment in AD patients and animal models. In the present study, we found that working memory was inversely correlated with formaldehyde levels in AβPP$^{Lon/Swe}$ transgenic mice, which showed memory deficiency at 3 months of age but normal memory at 6 months. Impaired memory in 3-month-old mice was accompanied by higher levels of formaldehyde and hyperphosphorylated tau than controls. Administration of resveratrol, which is a formaldehyde scavenger, rescued the cognitive deficits in these mice by reducing formaldehyde levels and attenuating tau hyperphosphorylation. With increased expression of formaldehyde catalytic enzymes such as aldehyde dehydrogenase 2 (ALDH2) and alcohol dehydrogenase III (ADH3), 6-month-old AβPP$^{Lon/Swe}$ mice displayed similar levels of formaldehyde and working memory as controls. We discovered that brain formaldehyde levels were significantly associated with the progression of memory deficit in AβPP$^{Lon/Swe}$ transgenic mice, and that recovery of memory was associated with formaldehyde reduction. Our findings provide valuable insights into the underlying mechanisms of AD.

Key words formaldehyde, resveratrol, Alzheimer's disease, amyloid-beta precursor protein, London/Swedish mutation, water maze
DOI: 10.16476/j.pibb.2020.0403

Alzheimer's disease (AD) is the most common type of dementia and accounts for 60%−70% of dementia cases worldwide[1]. However, the causes of AD are still unclear, and no effective approach is available to rescue the defects in patients with AD. Two highly recognized features of AD are the plaques formed by amyloid-β (Aβ) in the brain and neurofibrillary tangles composed of hyperphosphorylated tau protein[2-3]. Several other factors, such as presenilin 1/2[4] and apolipoprotein E (APOE)[5] are also important in the progression of AD. Patients with familial Alzheimer's disease (FAD) generally carry genetic mutations associated with these factors. FAD contributes to around 5%−10% of all AD cases[6]. Transgenic mice carrying mutations in amyloid-β precursor protein (AβPP), such as the London mutation (V717I)[7] and Swedish mutation

* This work was supported by grants from the Fundamental Research Funds for the Central Universities (2020-JYB-ZDGG-051), the National Basic Research Program of China (2012CB911004) and Natural Science Foundation of Inner Mongolia Autonomous Region (2021MS08040).
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Received: March 12, 2021 Accepted: April 25, 2021

(K670N/M671L)[8], with progressively increased plaque formation and learning and memory deficits, are the most commonly used animal models[9-10]. These models support the hypothesis that accumulation of Aβ (especially the oligomeric form) plays a key role in the neurodegenerative process and memory loss in AD[8, 11]. However, some studies have reported that plaque accumulation is not strictly associated with cognitive ability in mice. Similar cases have also been reported in humans who show plaques but have intact cognition[12-15]. Nevertheless, no single animal model can yet replicate all the features of AD seen in humans[16].

Formaldehyde, a small molecule that can penetrate the blood-brain barrier, was found to be related to AD in animal models and to clinical features of sporadic AD[17-18]. Formaldehyde can induce hyperphosphorylation and deposition of tau protein both *in vitro* and *in vivo*[19-20], as well as accelerate Aβ oligomerization[21]. The level of formaldehyde is elevated in the senescence accelerated mouse-prone 8 (SAMP8) mice, along with changes in metabolic enzymes including the upregulation of formaldehyde generation enzyme, semicarbazide sensitive amine oxidase (SSAO), and the downregulation of formaldehyde degradation enzymes such as alcohol dehydrogenase III (ADH3) and aldehyde dehydrogenase II (ALDH2)[18]. Rhesus macaques challenged with formaldehyde also show spatial working memory impairments and AD-like pathologies[22]. The above reports indicate that cognition levels are associated with formaldehyde metabolism. Resveratrol is a phytoalexin derived from grapes and other food products with antioxidant and chemopreventive activities. It has been reported to reduce formaldehyde levels and attenuate formaldehyde-induced tau hyperphosphorylation in Neuro-2a (N2a) cells[23]. Although administration of resveratrol has been shown to be beneficial in preventing AD progression in mouse models[24], the interplay of resveratrol and formaldehyde during pathogenesis in AD mouse models has not been well studied.

To determine the role of formaldehyde in the progression of memory impairment in AD, we used transgenic mice knocked in human AβPP695 with London (V717I)/Swedish (K670N/M671L) double mutations ($A\beta PP^{Lon/Swe}$) and a platelet-derived growth factor (PDGF) promoter[25]. Along with the formation of amyloid plaques, these mice exhibited learning and memory deficits as early as 3 months of age[25]. Interestingly, we found variable levels of formaldehyde in these mice between 3 and 6 months of age, which is similar to AβPP/PS1 mice[17]. To confirm the role of formaldehyde, we administrated resveratrol and formaldehyde to mice at 2 months and 5 months of age, respectively, in order to restore the levels of formaldehyde. Our results indicate memory reversal and formaldehyde correlation with memory progression in $A\beta PP^{Lon/Swe}$ mice, which has not been reported thus far.

1 Materials and Methods

1.1 Animals and treatment

All animal experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals from the National Institutes of Health, USA and were approved by the Biological Research Ethics Committee of Institute of Biophysics, Chinese Academy of Sciences (approval ID SYXK (SPF) 2007-141). The double-mutated transgenic $A\beta PP^{Lon/Swe}$ mice and wild-type (WT) C57BL/6 littermate mice were purchased from the Institute of Laboratory Animal Science, Chinese Academy of Medical Sciences (Beijing, China). All mice were maintained in animal facilities under specific-pathogen-free (SPF) conditions.

First, 80 $A\beta PP^{Lon/Swe}$ mice were randomly divided into five groups: $A\beta PP^{Lon/Swe}$ I to V; next, 48 WT mice were randomly divided into three groups: WT I to III. Each group included 8 males and 8 females. Two-month-old mice in the $A\beta PP^{Lon/Swe}$ I group were given intraperitoneal (IP) injection with resveratrol (0.6 mmol/L, 0.5 ml) everyday for 30 d (AβPP_Res). $A\beta PP^{Lon/Swe}$ II and WT I groups were IP injected with saline (0.5 ml) for 30 d as controls. After the 30-d treatment, the spatial learning and memory of these mice were tested with a water maze. Subsequently, the mice from all three groups were sacrificed for Western blotting and detection of brain formaldehyde concentrations. $A\beta PP^{Lon/Swe}$ III mice at 5 months of age were injected with resveratrol (0.6 mmol/L, 0.5 ml) (AβPP_Res), $A\beta PP^{Lon/Swe}$ IV and WT II mice were injected with formaldehyde (0.6 mmol/L, 0.5 ml) as AβPP_FA and WT_FA separately, and $A\beta PP^{Lon/Swe}$ V and WT III mice were injected with saline (0.5 ml) for 30 d as controls. All the treated

mice underwent a spatial learning and memory test with a water maze and were subsequently sacrificed for brain formaldehyde detection.

1.2 Behavior test with Morris water maze

Spatial learning and memory of mice were assessed using the Morris water maze, as described previously[26-27]. The water tank was separated into four quadrants, four predesigned cues were posted on the wall of the water tank in the middle of each quadrant, and an invisible platform was placed in the third quadrant. The animals were placed inside the pool from each quadrant. Each animal had four trials per day, with an inter-trial delay of 60 s. All trials had a maximum duration of 60 s unless the mouse found the platform, and the mouse was allowed to stay on the platform for 15 s at the end of each trial. Escape latency (time required to find the platform) was measured. After a 7-d training, the platform was removed from the tank. Each animal was then released into the quadrant, which was opposite to the previous platform. The capture camera recorded their tracks for 60 s. The retention time of the mice in each quadrant and their swimming speed were calculated.

1.3 Formaldehyde detection with HPLC

Supernatant fractions from whole brain homogenates (weight ratio of brain tissue∶ultrapure water 1∶4) were used for the detection of formaldehyde concentrations by high-performance liquid chromatography (HPLC) as previously described[26]. Briefly, 0.6 ml of the sample was mixed with 0.15 ml of 10% trichloroacetic acid *via* vigorous vortexing and then centrifuged at 12 000 r/min for 30 min at 4℃. 0.5 ml of the supernatant was mixed with 0.45 ml acetonitrile and 0.05 ml 2, 4-dinitrophenylhydrazine (DNPH, 0.1 g/L), and was then incubated in a 60℃ water bath for 30 min. The formaldehyde-DNPH derivative was detected using an HPLC system (LC-20A, Shimadzu, Japan) equipped with an ultraviolet detector and a C18 reversed-phase column (Agilent, US), using 65% acetonitrile/methanol as the mobile phase.

1.4 Western blotting

For Western blotting, half of the mouse brain tissue was homogenized in radioimmunoprecipitation assay (RIPA) lysis buffer, and the proteins were extracted[27]. The proteins were separated using 10% SDS-PAGE and then transferred to polyvinylidene fluoride (PVDF) membranes (Millipore, USA). Membranes were blocked with 5% skimmed milk in tris-buffered saline (TBS) containing 0.1% Tween-20 (TBST) for 1 h at room temperature and then incubated with primary antibodies at 4℃ overnight. Antibodies for tau phosphorylated at pS396 and pT181 were purchased from Cell Signaling Technology, USA. ALDH2 and ADH3 primary antibodies were obtained from Sigma-Aldrich (USA). The membranes were washed with TBST and incubated with secondary antibodies (Zsbio Commerce, China) at room temperature for 1 h. Protein bands were visualized with an enhanced chemiluminescent reagent (Applygene, China). Images were documented and quantified using Quantity One software (Bio-Rad Laboratories, USA).

1.5 Data analysis

The statistical significance of all data was analyzed by analysis of variance (one-way ANOVA) followed by an unpaired Student's *t*-test. The statistical significance was set at $P < 0.05$. All data were expressed as $\bar{x} \pm s$, unless otherwise stated.

2 Results

2.1 Resveratrol rescued learning and memory deficits in 3−month−old AβPP$^{Lon/Swe}$ mice

In order to evaluate cognition deficit and the rescue effect of resveratrol in AβPP$^{Lon/Swe}$ mice, the three groups AβPP$^{Lon/Swe}$, AβPP$^{Lon/Swe}$_Res, and WT were subjected to the water maze test. The learning curve showed that AβPP$^{Lon/Swe}$ mice had difficulty in finding the platform, whereas mice administered with resveratrol performed as well as the control group (Figure 1a). There was a slight difference in day 5 training between AβPP$^{Lon/Swe}$ and AβPP$^{Lon/Swe}$_Res groups. When the platform was removed on the test day, the AβPP$^{Lon/Swe}$ group spent less time in the platform quadrant (~15 s), while mice in the other two groups searched in the quadrant for a longer duration (~22 s) (Figure 1b). Gender differences have been reported in animal models and patients with AD[9]. To assess the gender differences, we further separated the groups into male and female (n=8). Compared to the control group, the male AβPP$^{Lon/Swe}$ mice learned at a slow pace from day 1 to day 5 (significant at day 2), but showed accelerated learning on days 6 and 7; the female mice learned as fast as the controls at the

beginning but learned slowly after day 5 (significant compared to AβPP$^{Lon/Swe}$_Res at day 6) (Figure 1c, d). These results demonstrated that resveratrol rescued learning impairment in both male and female AβPP transgenic mice. The difference in the average swimming speed was insignificant among the three groups during the 60 s testing period (Figure 1e). During the 30-d injection period, the mass of mice increased steadily, and no significant difference was found among the three groups (Figure 1f). These results indicate that the AβPP$^{Lon/Swe}$ mice had deficits in learning and memory, while resveratrol improved learning abilities at 3 months of age.

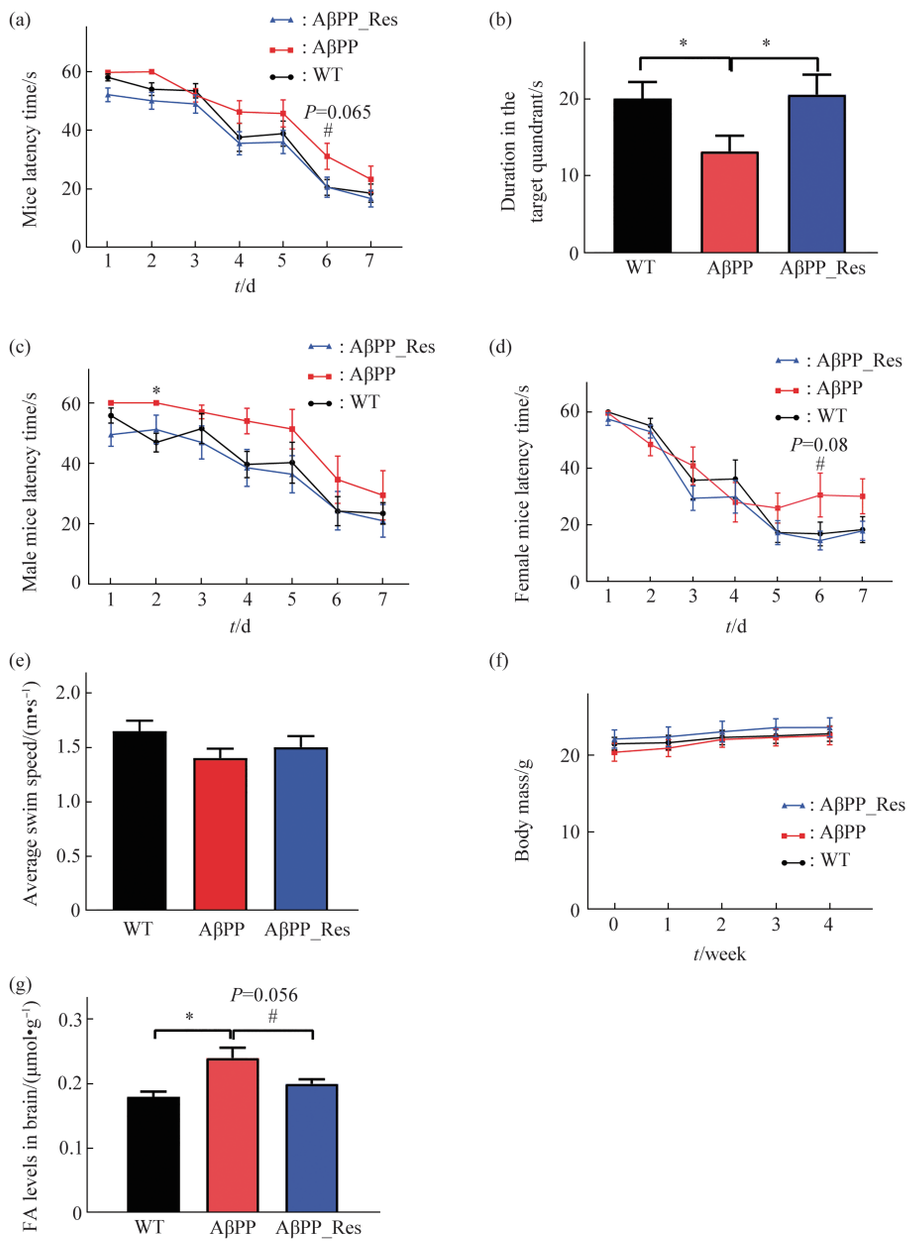

Fig. 1　Learning and memory of 3−month−old AβPP$^{Lon/Swe}$ mice tested with Morris water maze

(a) Escape latency of the AβPP$^{Lon/Swe}$ (AβPP), resveratrol injected (AβPP_Res) and littermate WT C57BL/6 mice that were trained for 7 days. n=16. (b) Retention time in target quadrant during the test. n=16. (c) Escape latency of male mice during training for 7 days period. n=8. (d) Escape latency of female mice during training for 7 days. n=8. (e) The average swimming speed of mice during the test. (f) Body mass of all the animals during drug administration period. n=16. (g) Formaldehyde (FA) levels in mouse brains among the groups. n=6. Data are expressed as $\bar{x} \pm s$. *P < 0.05, $^{\#}P$ < 0.1. n is the number of mice.

2.2 Resveratrol reduced formaldehyde levels in AβPP$^{Lon/Swe}$ mice at 3 months of age

To determine the changes in formaldehyde levels, the mice were sacrificed and their brains were used for detection. Formaldehyde levels were significantly higher in the AβPP$^{Lon/Swe}$ mice than in the littermate controls (Figure 1g). AβPP$^{Lon/Swe}$_Res mice showed a trend of reduction in formaldehyde level, which showed no significant difference compared to the WT control group (Figure 1g). Thus, resveratrol reduced the levels of formaldehyde and rescued learning and memory deficits; the formaldehyde levels were inversely correlated with learning and memory in these AβPP$^{Lon/Swe}$ mice.

2.3 Resveratrol attenuated tau hyperphosphorylation in 3−month−old AβPP$^{Lon/Swe}$ mice

When overloaded, formaldehyde induced tau hyperphosphorylation in mouse neuroblastoma N2a cells and mouse brains[20], while resveratrol reduced formaldehyde-induced tau hyperphosphorylation in N2a cells[23]. Western blotting results showed that tau phosphorylation at Ser396 and Thr181 drastically increased in both AβPP$^{Lon/Swe}$ groups regardless of resveratrol injection (Figure 2). However, in the presence of resveratrol, tau phosphorylation at both Ser396 and Thr181 was significantly reduced in AβPP$^{Lon/Swe}$ mice, though not to a level seen in the WT group. These results demonstrated that resveratrol significantly attenuated tau hyperphosphorylation in these transgenic mice. Tau hyperphosphorylation might play a second major role in learning and memory deficits in these mice.

2.4 Recovered learning and memory in the 6−month−old AβPP$^{Lon/Swe}$ mice

At 6 months of age, the AβPP$^{Lon/Swe}$ mice that were injected with formaldehyde (AβPP_FA) performed as well as the littermate controls in the Morris water maze test (Figure 3a). However, the WT mice injected with formaldehyde (WT_FA) still showed significant learning and memory impairments (Figure 3a). On the test day, the WT_FA group spent less time in the target quadrant, while all the other four groups displayed similar search times in the quadrant (Figure 3b). Mice injected with resveratrol (AβPP_Res) did not show significantly improved learning through a better learning curve or longer retention time. No difference in the average swimming speed was observed among the groups, as shown in the 60 s recording (Figure 3c). No mass differences were observed in any of the groups (Figure 3d). These results show that the learning and memory deficits of AβPP$^{Lon/Swe}$ mice were reversed at 6 months of age, and these mice were more tolerant to formaldehyde overload than WT mice.

2.5 Reduced formaldehyde levels in 6−month−old AβPP$^{Lon/Swe}$ mice

To determine the correlation between learning ability and formaldehyde, we measured the formaldehyde levels in all the groups. Following formaldehyde injection, there was a significant increase in the formaldehyde level in WT mice although the formaldehyde levels were similar among the other groups, including WT, AβPP, AβPP_FA, and AβPP_Res (Figure 3e). Resveratrol injection did not further reduce the formaldehyde levels, nor did

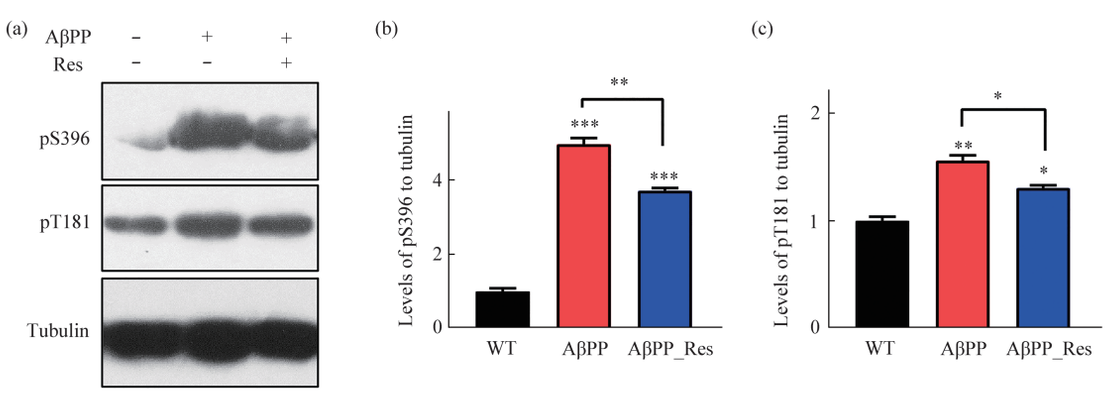

Fig. 2　Changes in tau phosphorylation in mice at 3 months of age

(a) Western blotting shows the levels of tau protein phosphorylated at pS396 and pT181 in the mice of WT, AβPP$^{Lon/Swe}$ and AβPP$^{Lon/Swe}$_Res groups. (b, c) Relative values show the levels of pS396 and pT181 in WT, AβPP$^{Lon/Swe}$ and AβPP$^{Lon/Swe}$_Res groups, respectively. Tubulin is used as an internal control. n= 4. Data are expressed as $\bar{x} \pm s$. *P < 0.05, **P < 0.01, ***P < 0.001. n is the number of mice.

formaldehyde injection increase the formaldehyde levels in AβPP$^{Lon/Swe}$ mice, which demonstrates that the AβPP$^{Lon/Swe}$ mice acquired formaldehyde resistance at 6 months of age. These data showed that formaldehyde levels were correlated with spatial learning and memory performance in all the five groups.

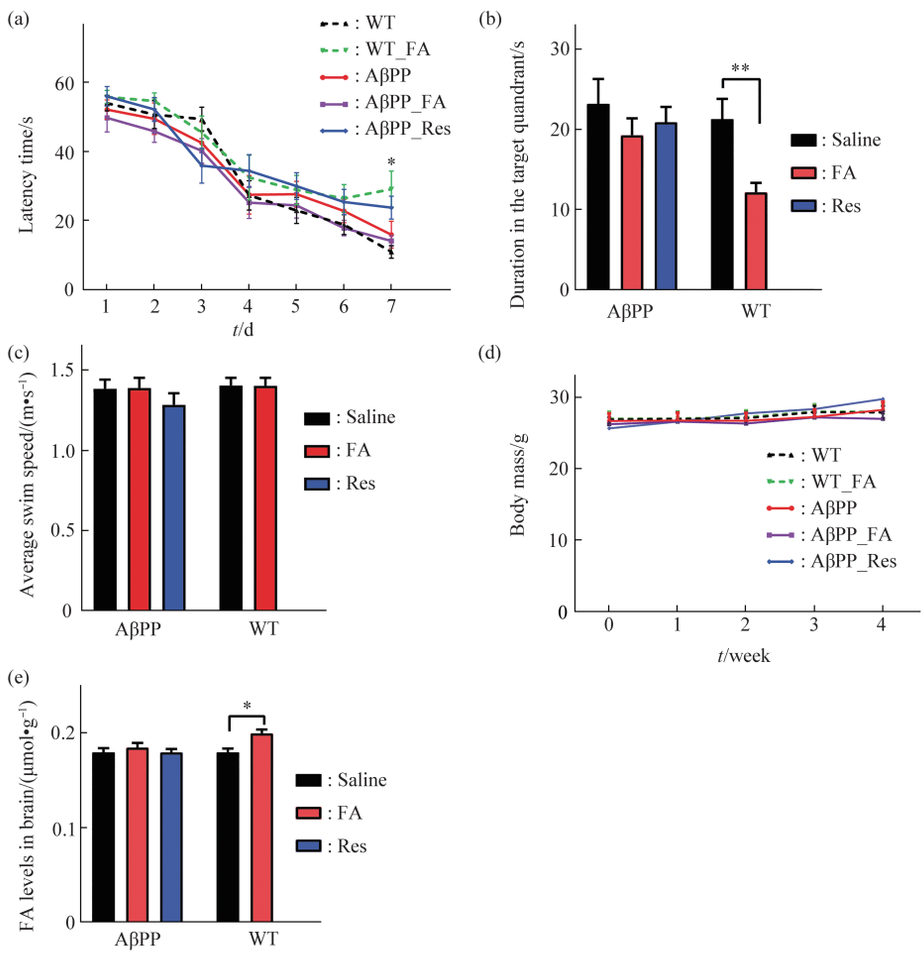

Fig. 3 Learning and memory of AβPP $^{Lon/Swe}$ mice tested with water maze at 6 month of age

(a) Escape latency (with training for 7 days) of the AβPP$^{Lon/Swe}$ (AβPP) mice administrated with formaldehyde (FA) or resveratrol (Res). n=16. *, WT_FA *v.s.* WT. (b) Retention time in target quadrant during the test. n=16. (c) The average swimming speed of mice during the test. (d) Body mass of all the groups of animals during the drug administration period. n=16. (e) FA concentrations in brains among different groups. n=6. Data are expressed as $\bar{x} \pm s$. *P < 0.05, **P < 0.01. n is the number of mice.

2.6 Increased formaldehyde degradation enzymes, ALDH2 and ADH3, in the AβPP$^{Lon/Swe}$ mice

To determine the metabolic changes of formaldehyde in this mouse model, we performed Western blotting to measure the levels of formaldehyde catalytic enzymes, ALDH2 and ADH3. Interestingly, both enzymes were upregulated in the AβPP$^{Lon/Swe}$ brains with or without resveratrol injection (Figure 4). Resveratrol injection did not significantly change the expression levels of either dehydrogenases in AβPP$^{Lon/Swe}$ mice.

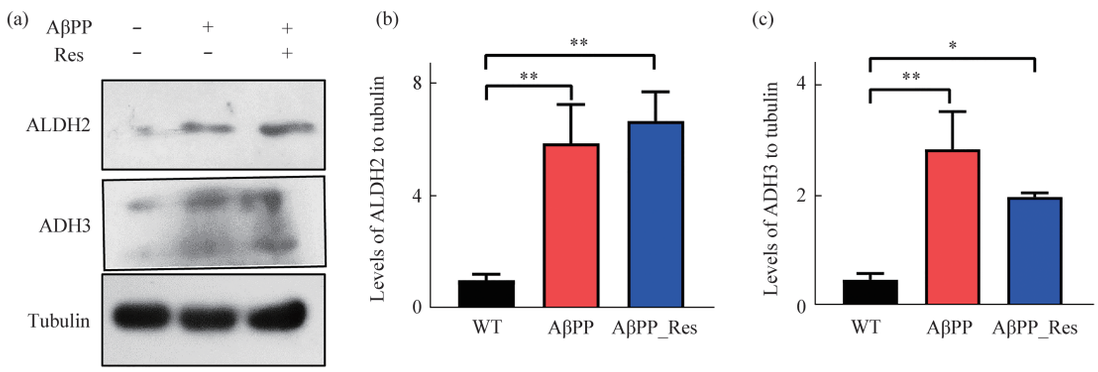

Fig. 4　Changes in the expression levels of ALDH2 and ADH3

(a) Western blotting shows the expression levels of ALDH2 and ADH3 in WT, AβPP$^{Lon/Swe}$ and AβPP$^{Lon/Swe}$_Res groups. (b, c) Relative values indicate the expression levels of ALDH2 and ADH3 in AβPP$^{Lon/Swe}$ and AβPP$^{Lon/Swe}$_Res groups, respectively. Tubulin is used as an internal control. n=4. Data are expressed as $\bar{x} \pm s$. *P < 0.05, **P < 0.01. n is the number of mice.

3　Discussion

The widely recognized mechanisms for AD onset are pathology-based amyloid hypothesis and tau hypothesis[28]; other significant hypotheses based on other clues in the AD pathology, include oxidative stress hypothesis[29], iron hypothesis[30], and inflammation hypothesis[31]. There is evidence to show that metabolite formaldehyde is involved in AD progression[32]. Human AβPP transgenic mice are commonly employed animal models featuring progressive amyloid formation and memory loss[33]. In this study, we observed: (1) AβPP$^{Lon/Swe}$ transgenic mice with increased formaldehyde in the brain displayed learning and memory impairment at 3 months of age; however, a reversal of memory deficit at 6 months of age correlated with reduced formaldehyde levels. (2) Administration of formaldehyde scavenger, resveratrol, rescued the cognitive deficits in 3-month-old mice by reducing formaldehyde levels and attenuating tau hyperphosphorylation. (3) The increased expression of formaldehyde catalytic enzymes, ALDH2 and ADH3, was associated with formaldehyde reduction and reversal of memory deficit at 6 months of age.

AβPP transgenic mice are useful models to study the behavior and pathology of AD. Compared to working memory, robust cognition memory is not well established in the AβPP (Tg [AβPPV717F]) model[34]. In TG2576 mice, working memory deficit was not detected through the Morris water maze, but was however detected through the circular platform, visible platform, Y-maze, and active avoidance tests[14]. Most current models are inconsistent in cognition memory test during the test period of 3−19 months[35]. Amyloid formation progressively increased in AβPP$^{Lon/Swe}$ mice[25]. After learning and memory impairment at 3 months of age, a reversal of memory deficit occurred at 6 months without any treatment. These mice could be used as a new model to study the key factors affecting the Aβ burden.

In addition, we found that administration of resveratrol rescued learning impairment in these transgenic mice at 3 months of age when the mice had higher levels of brain formaldehyde. When injected with exogenous formaldehyde at 5 months of age, the AβPP$^{Lon/Swe}$ mice did not show increased formaldehyde levels, or learning and memory deficits. Conversely, the injection of formaldehyde resulted in higher formaldehyde concentration and learning and memory impairment in WT mice (Figure 3). We have shown that formaldehyde levels in plasma were relatively stable, but the brain formaldehyde levels correlated with AD severity[17]. Therefore, we detected brain formaldehyde levels, because it directly reflects the association between formaldehyde and learning and memory in these mice. Thus, formaldehyde levels were correlated with learning and memory ability in the AβPP$^{Lon/Swe}$ mice, which is consistent with clinical reports[17].

As an air pollutant, formaldehyde has been widely reported for its neurotoxicity and carcinogenicity[36]. Formaldehyde is metabolized inside our body through metabolic systems[32] such as

ribose degradation[37-38]. The intestinal length of 129S2/SvPasCrl mouse became longer from adult to agedness[39] and Liu *et al.* detected a higher level of formaldehyde in the digestion contents of the cecum of AβPP/PS1 mice, suggesting that intestinal microbiota is a source of formaldehyde[40]. As a by-product of metabolism, formaldehyde levels are in homeostasis[40-41]. Formaldehyde can penetrate the blood-brain barrier[41] and its exposure can cause severe neurological symptoms in occupational workers[42]. Similar to the current study, earlier reports have shown impaired cognition and damaged neurological system in animal experiments[43-44]. Recently, higher levels of endogenous formaldehyde were reported to be associated with chronic neurological diseases such as AD, amyotrophic lateral sclerosis (ALS), and post-operative cognitive dysfunction[31, 45-46]. Furthermore, formaldehyde promoted tau hyperphosphorylation by activating glycogen synthase kinase-3β (GSK-3β) and decreasing protein phosphatase 2A (PP2A) in N2a cells and in mouse brains[20, 23]. Meanwhile, formaldehyde was shown to accelerate the formation of Aβ aggregates *in vitro*[47]. Amyloid oligomers related to dementia were also associated with a decline in global DNA methylation; overloading formaldehyde reduces DNA methylation by interfering with DNA methyltransferase (DNMT) [48]. Formaldehyde was also elevated in the brains of AD model AβPP/PS1 and SAMP8 mice with memory impairment[17-18]. Therefore, high levels of formaldehyde are associated with the progress of AD-like memory impairment, either directly or indirectly. In our study, along with memory impairment in the 3-month-old AβPP$^{Lon/Swe}$ mice, we found a rarely reported reversal of both the memory deficit and formaldehyde levels in 6-month-old AβPP$^{Lon/Swe}$ mice, even when challenged with an extra injection of formaldehyde. This implies the activation of intrinsic regulation of formaldehyde homeostasis, which is supported by the upregulation of formaldehyde degradation enzymes, ALDH2 and ADH3.

As a direct formaldehyde scavenger, resveratrol can reduce formaldehyde concentration both *in vitro* and *in vivo*[23]. Therefore, resveratrol could directly react with extra formaldehyde in 3-month-old AβPP$^{Lon/Swe}$ mice and reduce formaldehyde concentrations. We detected an increase in reactive oxygen species (ROS) when formaldehyde was added to the cells[49]; an earlier study has shown that ROS is found in formaldehyde-exposed animals[50]. Resveratrol is an efficient antioxidant that reduces ROS level *in vivo*[51]. Therein resveratrol could have improved the learning and memory of these mice. Tau hyperphosphorylation as a downstream effect of formaldehyde overload is also a cause of impaired learning and memory[20]. Resveratrol may affect tau acetylation and phosphorylation by activating sirtuin 1 (SIRT1), leading to further oxidative stress[52]. Resveratrol attenuates formaldehyde-induced tau hyperphosphorylation in N2a cells[23]. Here, we provide further evidence that resveratrol attenuates hyperphosphorylated tau in AβPP$^{Lon/Swe}$ mice brains (Figure 2). However, tau hyperphosphorylation did not completely recover to the control level after resveratrol treatment, which might play a second major role in reduced learning and memory deficiency.

Learning and memory deficits occurred in both male and female AβPP$^{Lon/Swe}$ mice, although the learning patterns were marginally different. Resveratrol rescued the learning and memory deficits in both male and female mice with no significant bias, which suggests that it is a good candidate to antagonize early defects. As the formaldehyde level is associated with cognitive dysfunction and recovery in both 3- and 6-month-old AβPP$^{Lon/Swe}$ mice, it could be an additional indicator and target in mice with Aβ burden.

4 Conclusion

This study revealed that changes in the formaldehyde levels were negatively related to learning and memory in AβPP$^{Lon/Swe}$ mice. Formaldehyde could therefore be used as a biomarker to monitor the effects of AD treatment. Resveratrol improves learning and memory by reducing formaldehyde levels at the early stages of AD in transgenic mouse model and could be considered as a supplement for elderly individuals at the early stages of AD.

Acknowledgments We acknowledge Dr. HE Zhi-Yong (Monash University, Australia) and Dr. CUI Yan-Fang (Central China Normal University, China) for their critical reading of this manuscript. We thank Hindawi to offer the Editing Services.

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AβPP$^{Lon/Swe}$转基因小鼠记忆缺陷逆转与甲醛水平降低相关*

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摘要　β淀粉样蛋白（Aβ）沉积形成斑块是阿尔茨海默病（AD）的病理标志之一. 以β淀粉样前体蛋白（AβPP）为基础的转基因小鼠模型表现出斑块形成加速和记忆损伤. 然而，在一些模型中，记忆丧失与斑块形成的相关性较差. 我们实验室最近报道了AD患者和动物模型的认知障碍与其体内甲醛水平有很强的相关性. 本研究发现，AβPP$^{Lon/Swe}$转基因小鼠3月龄时表现出记忆缺陷，而在6月龄时记忆正常，其工作记忆与甲醛水平变化相反. 与对照组相比，3月龄小鼠记忆受损伴随着甲醛水平的增高和过度磷酸化tau的增加. 腹腔注射甲醛清除剂白藜芦醇可通过降低甲醛水平和tau蛋白的过度磷酸化，挽回小鼠的记忆损伤. 6月龄AβPP$^{Lon/Swe}$小鼠甲醛水平和工作记忆与对照组相似，伴随甲醛降解酶ALDH2和ADH3表达增加. 结果显示，在AβPP$^{Lon/Swe}$转基因小鼠中，大脑甲醛水平与记忆变化进程显著相关，且记忆的恢复与甲醛水平下降相关. 该研究为揭示阿尔茨海默病机制研究提供了新视角.

关键词　甲醛，白藜芦醇，阿尔茨海默病，淀粉样前体蛋白，London/Swedish突变，水迷宫
中图分类号　Q189，Q5　　**DOI**：10.16476/j.pibb.2020.0403

* 中央高校基本科研业务费专项资金（2020-JYB-ZDGG-051），科技部国家重点基础研究发展计划（2012CB911004）和内蒙古自治区自然科学基金（2021MS08040）资助项目.
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收稿日期：2021-03-12，接受日期：2021-04-25