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ORIGINAL ARTICLE

Intracerebroventricular injection of resveratrol ameliorated Aβ-induced learning and cognitive decline in mice

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Abstract

Resveratrol (RSV) is a natural plant polyphenol compound which consists in red grape skins and wine in general. Plenty of previous studies have shown that resveratrol has neuroprotective effects. The primary object of this research was to study the effects of RSV on improving the cognitive function and neurodegeneration in the mouse model of Alzheimer's disease induced by $A\beta_{1-42}$, and the possible mechanism about targeting on Sirt1, which results in attenuating inflammatory response and mitochondrial dysfunction. We established the AD model of intracerebroventricular (i.c.v.) injection of $A\beta_{1-42}$ and it was observed that the significant decrease in alternately of Y Maze and the quadrant dwell time percentage of Morris water maze test. Furthermore, there were significant upregulations of AMPK/ PGC-1α and downregulations of NF-κB/ IL-1β/ NLRP3 signaling pathways in the hippocampus and prefrontal cortex in AD mice. The treatments with RSV and Donepezil could significantly ameliorate all the behavioral and biochemical changes induced by $A\beta_{1-42}$. It also noticeably improved the histopathological changes in the hippocampus and cortex. The results suggested that RSV might protect against cognitive deficits and neurodegeneration induced by $A\beta_{1-42}$, and serve as a potential agent in treatment of AD.

Keywords Resveratrol · Alzheimer's disease · Intracerebroventricular injection · Sirt1 · Inflammation · Mitochondrial dysfunction

Introduction

Alzheimer's disease (AD) regularly occurs to the aged and is one of the most common neurodegenerative diseases (Blennow et al. 2006). The number of patients with AD is increasing year by year. According to a survey, about 44 million people were suffering from AD by 2014 and it is even more shocking that the number will increase to 3-fold by 2050 (Prince et al. 2014). To date there is not an effective therapy yet to solve the conundrum of this devastating disease. Accordingly, it is a matter of the utmost urgency to find out what mechanisms are underlying the pathophysiology in AD.

Although some drugs are available on the market to ameliorate the symptoms such as dementia, none of them has sufficient capability toward Alzheimer's disease (AD) pathology (Zawia et al. 2009). Besides, certain drugs have severe side effects —Donepezil (DPZ), a recognized clinical drug used in the treatment of Alzheimer's disease but might at the same time brings nausea, gastrointestinal dysfunction and other side effects, for example. Resveratrol (RSV) —3, 5, 4′-trihydroxystilbene (Fig. 1) is a natural plant polyphenol compound which comes from red grape skin and wine mainly (Wan et al. 2016). A wealth of data provided strong evidence for its anti-aging (Hsu et al. 2014), anti-inflammatory (Csiszar 2011), antioxidant (Yousuf et al. 2009) and anti-apoptotic properties (Guo et al. 2016). Most studies have shown that the oral bioavailability of resveratrol was <1%, and

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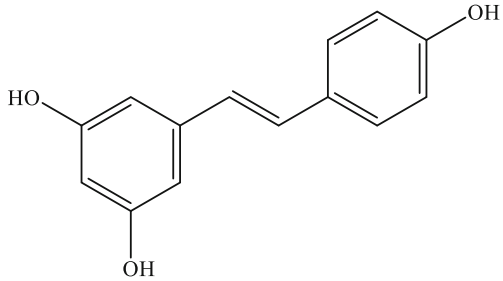

Fig. 1 Chemical structure of resveratrol ($C_{14}H_{12}O_3$, molecular weight = 228.24)

consequently, this may be the major reason for the discrepancies between in vitro/ in vivo studies (Francioso et al. 2014). The previous studies were administered by intragastric, and we took intracerebroventricular (i.c.v.) injection to see if resveratrol was effective through this administration route. In the present study we investigated the effect of RSV with successive i.c.v. administration of RSV on learning and memory deficits in the mouse control induced by $A\beta_{1-42}$ with behavioral studies.

Studies have demonstrated that RSV treatment exerted neuroprotective effects on Parkinson's disease (Gaballah et al. 2016) and Alzheimer's disease (Moussa et al. 2017). Sirtuin1 (Sirt1), one of the members of the mammalian proteins of the Sirtuin family of NAD^+ dependent deacetylases (Kumar et al. 2016) and it is considered a target for RSV treatment of AD. However, the exact mechanism of RSV exerting its therapeutical effect on AD by activating Sirt1 is unclear up to now.

The neuroinflammation which is associated with AD has been assumed to be a response to pathophysiological events and immune system-mediated actions in fact contributing to and driving AD pathogenesis. NF-κB is an extensive expressed dimeric molecule with posttranslationally regulated activity. The role of NF-κB in the immune system, defending inflammation has been well characterized. In the nervous system, NF-κB has been proposed to serve important function by acting as a transcription regulator that plays the role in inflammation, neuronal survival, differentiation, apoptosis, neurite outgrowth, and synaptic plasticity (Shi et al. 2016). RSV is a potent NF-κB inhibitor and several studies have highlighted its therapeutic effect against neuro-inflammation (Moussa et al. 2017). In the NF-κB signaling pathway, NLRP3 (NACHT, LRR and PYD domains-containing protein 3 inflammasome) can be activated and the processing and secretion of IL-1β are promoted at the same time. NLRP3 is involved in regulating thecatalytic activity of caspase 1, the enzyme that mediates the cleavage of the precursors of IL-1β and IL-18 into bioactive cytokines (Heppner et al. 2015).

Mitochondrial dysfunction is closely related to inflammation in the pathological activity of AD. AMP-activated protein kinase (AMPK) is a highly conserved cell energy receptor, in addition playing an important role in regulating the metabolism of glucose, fat and protein (Wang et al. 2017). Sirt1 and PGC-1α are the important downstream molecules of AMPK signaling pathway. Sirt1 is a kind of NAD+ dependent histone deacetylase not only regulated by AMPK but also sensitive to the energy state extremely. Sirt1 can also be activated by acetylating or promoting the expression of PGC-1 (Thirupathi and de Souza 2017).

In the current study, we evaluated the expression of AMPK, PGC-1α, Sirt1, NF-κB, NLRP3 and IL-1β in the cerebral cortex and hippocampus to validate the interaction between mitochondrial dysfunction and inflammatory responses. Our purpose of the present study was to evaluate the molecular changes in the brain that may contribute to the cognitive benefits provided by RSV treatment testify the possibility to improve the efficacy by changing the way of administration.

Materials and methods

Animals and drugs

All animal procedures were approved by the Animal Ethics Committee of the institution and were in accordance with the Guidelines for Animal Experimentation of Shenyang Pharmaceutical University. The experiments were performed with male Kunming mice, weighting 18–22 g were provided by the Central Animal House of Shenyang Pharmaceutical University (Shenyang, China), kept in plastic cages with standard laboratory conditions (temperature 23 ± 2 °C, 12 h:12 h light/ dark cycle, lights on 8 A.M.). The mice had free access to food and water and were allowed to adjust the environment for 7 d before the experiment.

RSV was purchased from National Institute for the Control of Pharmaceutical and Biological Products in China (Shenyang, China) with purity above 98% which was dissolved in PBS (1 mg/ml final concentration). The solution was diluted with physiological saline to 0.2 mg/ml, 0.02 mg/ml respectively; $A\beta_{1-42}$ (St Louis, MO, USA) peptide was dissolved and diluted in physiological saline to a stock concentration of 1.0 mg/ml. The solution was incubated at 37 °C for 5 days to obtain the fibrillized form.

Experimental design

The mice were divided into 6 groups randomly as Table 1 showed. Mice were anesthetized by intraperitoneal injection of 400 mg/kg chloral hydrate and then fixed in a stereotaxic apparatus as reported literature (Ji et al. 2013). The $A\beta_{1-42}$ group and drugs-treated groups were injected with $A\beta_{1-42}$ (3 μl) into the right lateral ventricle of AP, −0.5 mm; ML, −1.1 mm and DV, −3.0 mm within 1 min respect to the brain locator, while the sham group were injected with the same

Table 1 The groups of experimental design. The mice were divided into 6 groups randomly as Table 1 (n = 7 in each group) showed, the experimental operation was parallel

Group	Treatment
Control group	No treatment
Model group	$A\beta_{1-42}$-injection plus i.c.v. treatment with saline
Sham group	saline-injection plus i.c.v. treatment with saline
RSV(L) group	Aβ injection plus i.c.v. treatment with resveratrol (0.02 mg/kg/day)
RSV(H) group	Aβ injection plus i.c.v. treatment with resveratrol (0.2 mg/kg/day)
DPZ group	Aβ-injection plus i.c.v. treatment with donepezil (14 μg/kg/day)

amount of saline in the same area. The microsyringes were left in the injection site for 3 min to facilitate diffusion of the drugs, and all the mice with surgery received penicillin-G 200,000 IU/ml (0.2 ml/mouse) by intramuscular in the next two days. All mice were allowed to recover for 3 days before successive administration, and behavioral tests were performed from day 18 to day 24, and brain biochemical assessment was assessed on the following day. Animal experiments schedule was shown in Fig. 2.

Y-maze task

Y-maze is used as a measure of short-term memory by spontaneous alternation behavior. The Y-maze is consisted of three arms with equal angles and a central area (30 cm long × 5 cm wide × 25 cm high) which labeled A, B, C clockwise, and was placed in a room with no noise. Each mouse was initially placed at the end of one of the arms (facing the end of the arm), and was allowed to move freely enter the three arms within the 8 min testing period. The sequence and total number of through the arms were recorded manually by a trained observer. Spontaneous alternation behavior was defined as visits into all three arms on consecutive occasions with the following six cases: ABC, ACB, CAB, BCA, CBA and BAC (Murphy 2009). The number of maximum spontaneous alternation behaviors was defined as the total numbers of arms entered minus 2 and the percent alternation score (%) was calculated as (number of alternations/ total arms entries - 2) × 100.

Morris water maze test

The test of spatial learning and memory was performed by the Morris water maze, which is a circular water tank (150 cm diameter, 60 cm height) and filled to a depth of 40 cm with water of rendered opaque by adding ink at 27 ± 1 °C when the test was carried out (Nunez 2008). The tank was divided essentially into 4 quadrants and defined as south-west (SW), south-east (SE), north-east (NE) and north-west (NW). A platform (8 cm diameter and 10 cm height) was submerged 1 cm below the water surface and placed in the center of the SE quadrant of the tank. The tank was placed in a dimly lit, soundproof test room with various visual cues and the wall was surrounded with black curtain up to the camera, which was used to record the escape latencies and path length of each mouse. The Morris water maze test consisted of a place navigation test and a probe test. The place navigation test was performed as two trials daily for five consecutive days, and the mice were placed in the water facing the pool wall from the SW and NW quadrants as the different start points to start the two trials respectively and the two trials have 10 min interval. The mice were allowed to swim freely to explore the hidden platform positioned in the SE within 90s. If the mice succeed in finding the platform during the period and allowed stay on it for 3 s, then the time spent was recorded, but if the mice jumped into the water within 3 s, then the track was not terminated until the mice stayed on the platform for 3 s. If the mice failed to locate the platform within 90s, then the time was recorded 90s and the mice were guided to the platform for 20s. The escape latency was defined as the spent time to reach the

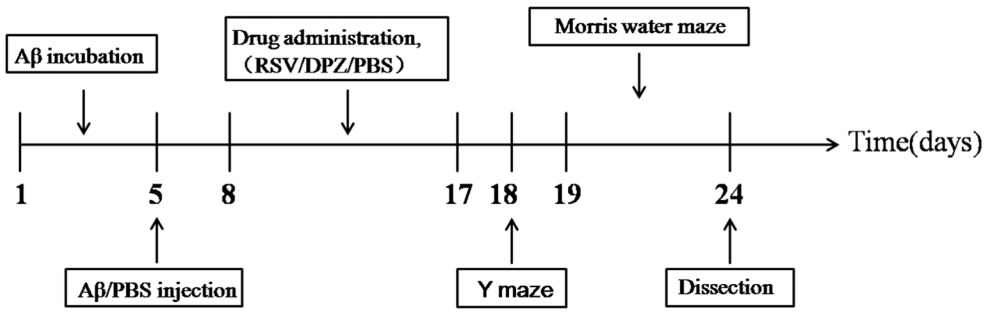

Fig. 2 The experiment schedule. After $A\beta_{1-42}$ incubation, mice were i.c.v. $A\beta_{1-42,}$ and then mice were i.c.v. treatment with RSV or daily for 10 days. On day 18, mice were tested for spontaneous alternation in the Y-maze test. Behavioral testing in the Morris water maze began on day 19 and lasted until day 24. Animals were euthanized on day 24; the brain tissue was collected and stored in the −80 °C freezer

platform and the total distance of swimming was record by the camera (Devan et al. 1996). 24 h after the last training session, the platform was removed and took out the probe trial. The mice were allowed to look for the removed platform freely for 90s without inference. In this part, the number of crossing platform and the percentage of time spent in the target quadrant were recorded (D'Hooge and De Deyn 2001).

Brain sample collection

After behavioral tests described above, the animals were sacrificed by decapitation and the hippocampus and the cortex were stripped out quickly, rinsed with physiological saline quickly frozen in a freezer (−80 °C) until used for biochemical analysis. Two entire brains in each group were removed, immersion by 10% formalin solution at 4 °C subsequently until histopathologicaltrial. The brain tissues were weighted, and rapidly homogenized in ice-cold saline ($w/v = 1{:}1$) and the homogenates were centrifuged at 3500 rpm at 4 °C for 15 min, after which supernatants were transferred to another centrifuge tube for assay (Liu et al. 2014a).

ELISA assay kits

The supernatant of hippocampus and cerebral cortex tissue obtained was used to measure the levels of Sirt1, anti-inflammatory enzyme activities including NF-κB as well as its downstream molecules NLRP3, IL-1β and the level of AMPK/ PGC-1α by means of the ELISA assay kits from Nanjing Jiancheng Bioengineering Institute (Nanjing, China) (Shi et al. 2014).

Histopathological examination

For histopathology, the entire brains were soaked in 4% paraformaldehyde (PFA) solution for 48 h and then transferred to 30% sucrose in 0.1 mol/l PBS (pH 7.4) for at least 16 h until they sank for cryoprotection. Tissues were kept in the final sucrose solution then stained with hematoxylin and eosin (H.E.) and examined under a lightmicroscope (Ahmad et al. 2005).

Statiscal analysis

The results are expressed as the mean ± SD ($n = 6$–7). All statistical analyses were performed using the SPSS software, version 16.0. Data were analyzed by one-way or two-way analysis of variance (ANOVA) followed by Turkey post hoc test; $^{*}p \leq 0.05$ was considered significant.

Results

RSV ameliorates Aβ-induced learning and memory impairment in the Y-maze test

Y- Maze is widely used in research fields such as hypofunction, tendency and spatial working memory. It is mainly used to study the rodent dynamic spatial working memory, which is completely the use of experimental animal to explore the natural instincts of the new environment. In the Y-maze test, there was no significant difference in the arm entries among 6 groups ($P > 0.05$, Fig. 3a), suggesting that the locomotor activity or motivation to explore was not affected by successive i.c.v. administration of RSV. However, the decreased spontaneous alternation behaviors induced by $A\beta_{1-42}$ were significantly improved by donepezil ($p < 0.001$, Fig. 3b), RSV (L) ($p < 0.001$, Fig. 3b) and RSV (H) ($p < 0.01$, Fig. 3b).

RSV ameliorates Aβ-induced learning and memory impairment in the Morris water maze test

In the Morris water maze test, the model group exhibited longer escape latency on day 4 and 5 compared with the control group in the place navigation test ($P < 0.01$, Table 2). No significant difference was observed among all the groups in

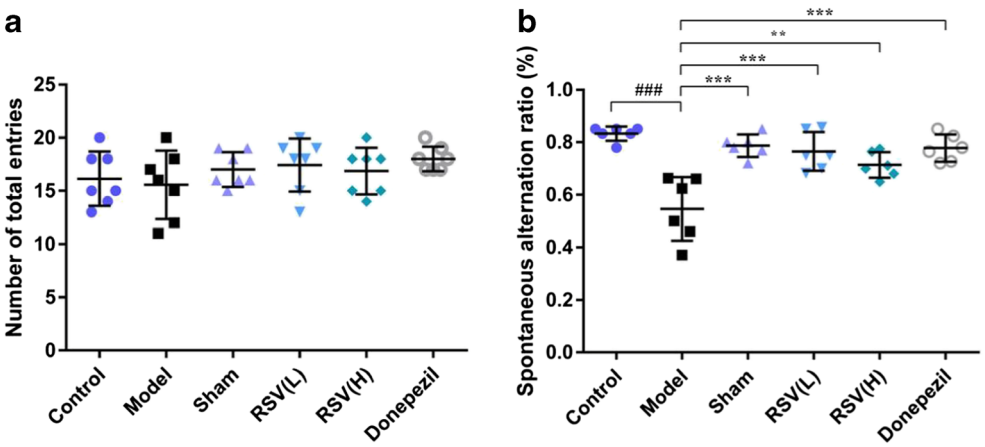

Fig. 3 Effects of RSV on open arm entries number (**a**) and spontaneous alternation ratio (**b**) in the Y-maze task were evaluated. The values represent the mean ± SD ($n = 6$–7 in each group), $^{**}p < 0.01$ and $^{***}p < 0.001$ versus the model group; $^{###}p < 0.001$ versus the control group

Table 2 Effects of RSV on escape latency in the Morris water maze

Group	Day1	Day2	Day3	Day4	Day5
Control	64.86 ± 27.58	52.92 ± 14.77	42.78 ± 17.51	26.51 ± 13.14	20.72 ± 6.73
Model	76.55 ± 17.41	64.12 ± 26.65	59.67 ± 23.19	58.23 ± 7.92$^{\#\#}$	49.94 ± 5.47$^{\#\#}$
Sham	70.47 ± 22.42	57.46 ± 18.35	57.35 ± 16.99	32.09 ± 10.48	25.13 ± 9.44*
RSV(L)	73.38 ± 26.16	63.92 ± 17.66	48.17 ± 22.71	34.13 ± 6.85*	24.08 ± 5.76**
RSV(H)	80.94 ± 12.81	62.40 ± 24.78	54.08 ± 27.15	39.41 ± 11.15	31.95 ± 13.88*
Donepezil	63.37 ± 16.10	58.68 ± 23.31	51.34 ± 8.43	33.88 ± 10.72*	21.22 ± 12.23**

Data are shown as mean ± SD (n = 7 per group). $^{\#}$p < 0.05 and $^{\#\#}$p < 0.01 versus the control group; * p < 0.05 and ** p < 0.01versus the model group

swimming speed throughout the test (P > 0.05, Fig. 4a). However, the RSV (L) group and the donepezil treated group significantly ameliorated the effects of $A\beta_{1-42}$ on escape latency ($p < 0.05$ and $p < 0.01$ for the 4th and the 5th day, respectively) and the RSV (H) group only had significant effect on day 5. On the day of the spatial probe test, we assessed memory retention of the platform location performed on the day following the place navigation test. Mice in the model group spent less time in the target quadrant than the control group ($P < 0.001$), as well as the in cross platform times were significantly decreased (P < 0.001) (Fig. 4b and c). However, donepezil, RSV (L) and RSV (H) significantly increased the decreased swimming time in the target quadrant (P < 0.001, Fig. 4b). Stated thus, in all these experiments in the Morris water maze, RSV showed the ability of reversing cognitive impairment.

Effects of RSV on the level of Sirt1 in hippocampus and cerebral cortex

The amount of Sirt1 in the model group was decreased significantly in hippocampus and prefrontal cortex in comparison with the control group (p < 0.01) as shown in Fig. 5. However, RSV (L) group and RSV (H) group (p < 0.05) ameliorated this $A\beta_{1-42}$-induced decrease. There was no significant difference between sham group and control group as well.

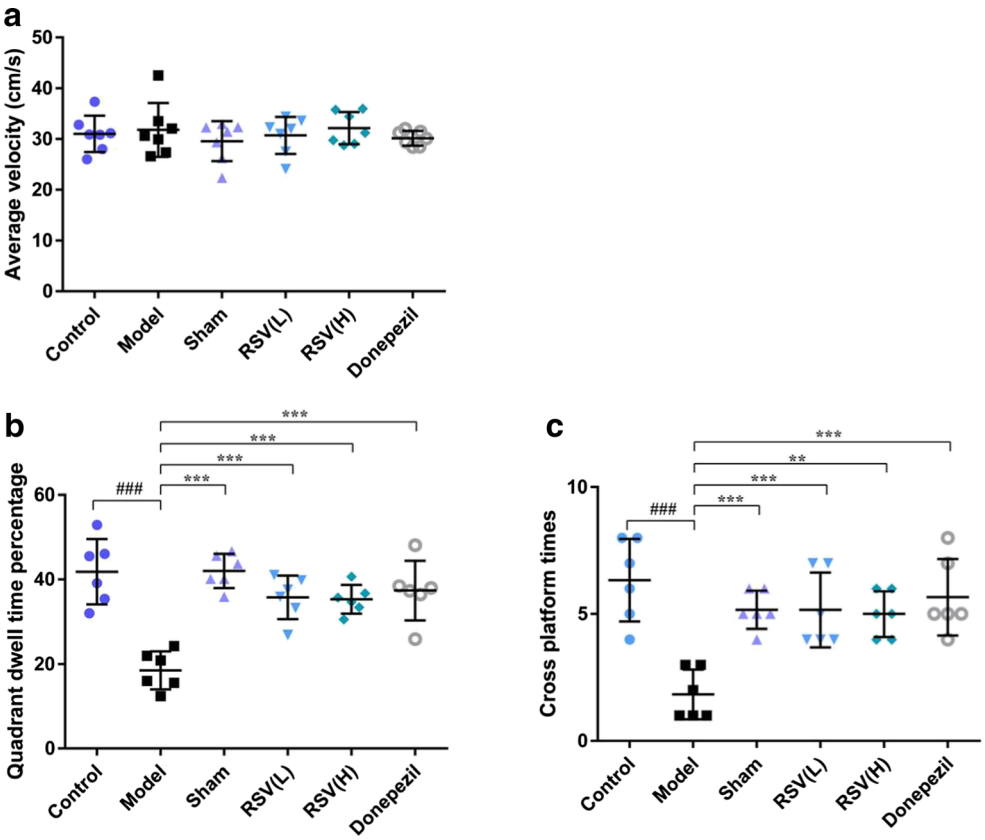

Fig. 4 Effects of RSV on The average velocity of mice (**a**), Quadrant dwell time percentage (**b**) and the cross platform times (**c**) in the Morris water maze test. The values represent the mean ± SD (n = 6–7 in each group), **p < 0.01 and ***p < 0.001 versus the model group; $^{\#\#\#}$p < 0.001 versus the control group

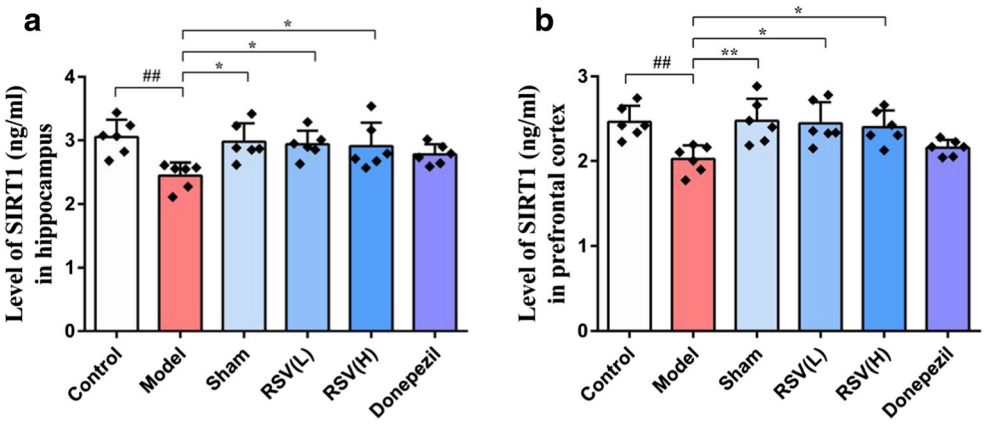

Fig. 5 Effects of RSV on Sirt1 level in the hippocampus (**a**) and prefrontal cortex (**b**) of Aβ-injected mice. The values represent the mean ± SD (n = 6 in each group), $^{\#\#}p < 0.01$ versus the control group; $^{*}p < 0.05$, $^{**}p < 0.01$ versus the model group

Effects of RSV on the level of AMPK and PGC-1α in hippocampus and cerebral cortex

As shown in Fig. 6, the activities of AMPK and PGC-1α in the model group were the lowest among all the groups both in the hippocampus and cerebral cortex. However, RSV (L) and donepezil group generated a dramatic increase in the activity of AMPK and PGC-1α.

Effects of RSV on the level of NF-κB, IL-1β and NLRP3 in hippocampus and cerebral cortex

In order to elucidate the biochemical mechanism of anti-dementia effects of RSV in brain tissue, the anti-inflammatory enzyme activities including NF-κB, IL-1β and NLRP3 were determined. As shown in Fig. 7, we can see the level of NF-κB, IL-1β and NLRP3 in

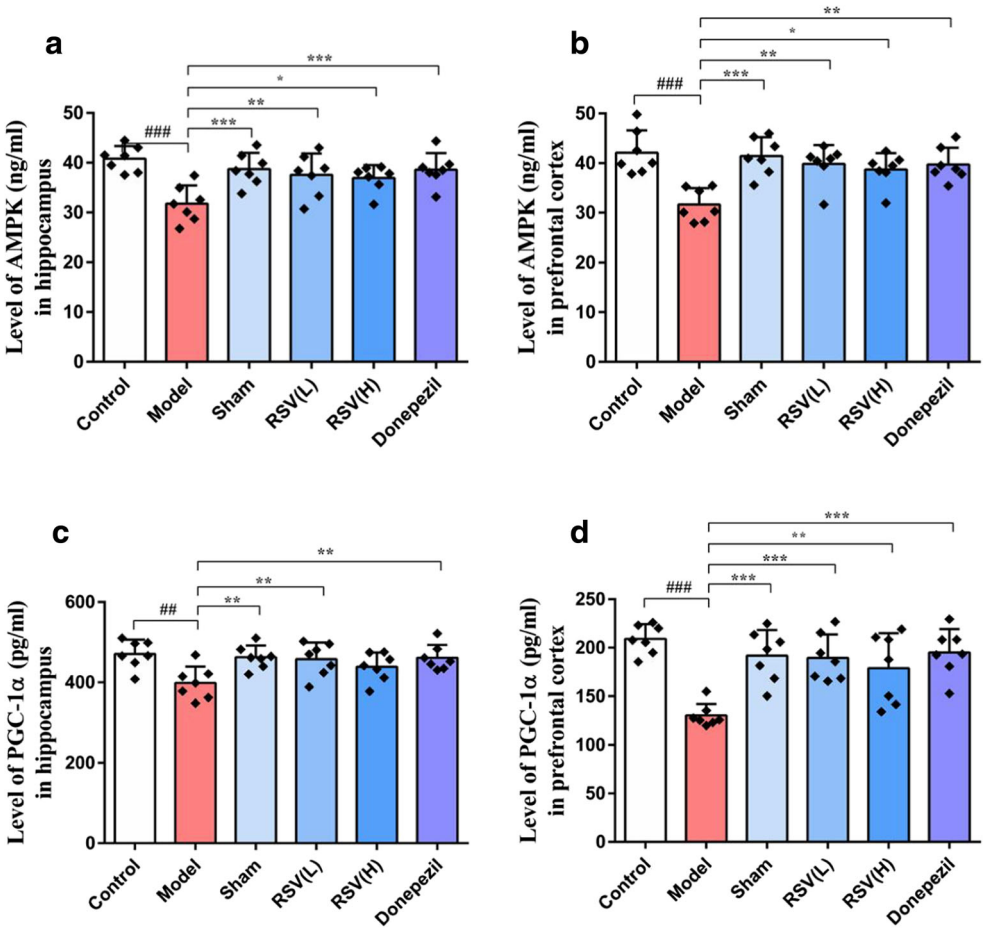

Fig. 6 Effects of RSV on AMPK and PGC-1α level in the hippocampus (**a**, **c**) and prefrontal cortex (**b**, **d**) of Aβ-injected mice. The values represent the mean ± SD ($n = 7$ in each group), $^{\#\#\#}p < 0.001$ versus the control group; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus the model group

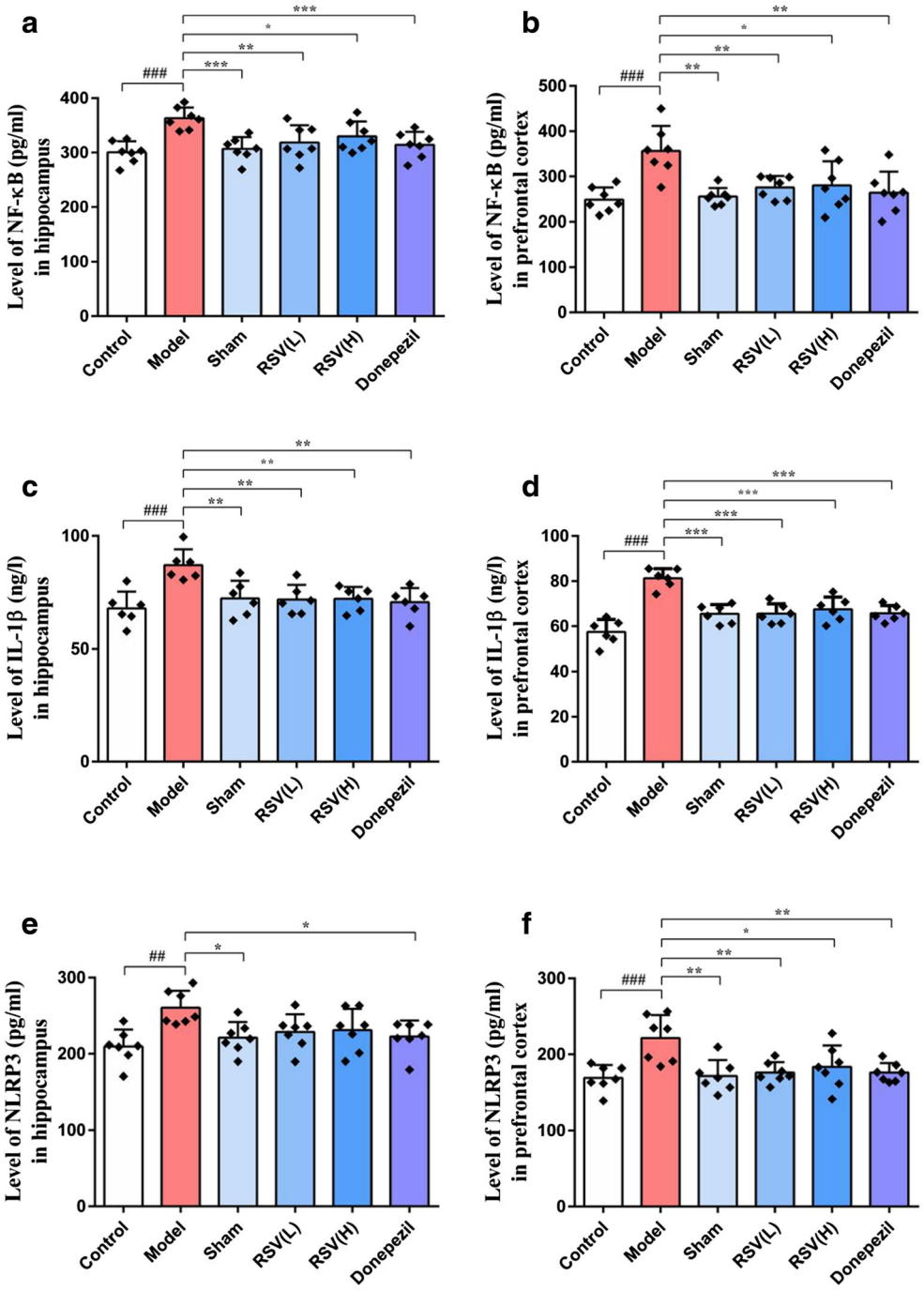

Fig. 7 Effects of RSV on NF-κB, IL-1β and NLRP3 level in the hippocampus (**a**, **c**, **e**) and prefrontal cortex (**b**, **d**, **f**) of Aβ-injected mice. The values represent the mean ± SD (n = 6–7 in each group), $^{###}p < 0.001$ versus the control group; $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ versus the model group

model group were remarkable high among all groups whether in the hippocampus or the prefrontal cortex in relation to the control group. With regard to the result of NF-κB level, compared with cerebral cortex, the changes of biochemistry were obvious in hippocampus. The figures showed that in the hippocampus, donepezil and RSV treated groups regulated three inflammatory markers significantly compared with the model group.

Effect of RSV on the histopathological changes in the hippocampus and cortex of $Aβ_{1–42}$-treated mice

Hematoxylin-eosin (HE) staining is one of the most commonly used staining methods in paraffin sectioning which is performed to detect the neuronal integrity and orderliness in the hippocampus and cortex. The neuronal layers both in the CA1 region of the hippocampus and

cortex have shown disordered, rarefaction, pronounced shrinkage nuclei and swollen neuronal bodies in the model group (Fig. 8b and 9b) compared with the control group (Fig. 8a and 9a) and sham group (Fig.8c and 9c). RSV (L) and donepezil group significantly inhibited the histopathological damage following 10 days treatment (Fig. 8d, f, 9d and f).

Discussion

The increasingly high prevalence rate of Alzheimer's disease currently is the reason that we put more attention on the treatment of Alzheimer's disease (Association 2017). There are a number of hypotheses about the pathogenesis of AD, the most noted of which is the hypothesis of Aβ. Aβ aggregation in the brain leads to the formation of senile plaques, giving rise to neuronal degeneration that is an initiation factor for the onset of Alzheimer's disease (Kummer and Heneka 2014). Hence in our current research we have adopted the model of $A\beta_{1-42}$. The number of people suffering from AD increases year by year, however, it is a pity that the drugs curing the disease have not emerged so far. Just because most of the drugs delaying the symptoms of AD carry a lot of side effects, we transfer our attention to resveratrol— which is so widely found in grapes and wine that there is increasing interest in producing wines with higher contents of this compound and a higher nutritional value (Luigi et al. 2016).

We adopted i.c.v. injection of RSV as a result of its low biological availability. In our research group, i.c.v. injection is a highly mature technique and we had already published several papers about it (Li et al. 2014; Liu et al. 2014b). The present study provided further evidence that RSV can significantly ameliorate the pathological changes induced by i.c.v. injection of $A\beta_{1-42}$ and improved both learning and memory in AD model mice. The model group showed an obvious decrease of alternately in Y maze and a significantly increase of quadrant dwell time percentage. Administration of RSV could changeover this phenomenon that it indicated RSV could ameliorate the symptoms of AD. The data obtained appear to be similar to those reported earlier by Wang (Gang et al. 2016). Moreover the results of histopathological examination suggested that RSV significantly restored the neural injury induced by $A\beta_{1-42}$ in the hippocampus. Based on the above results, we explored the mechanism of resveratrol in the treatment of AD.

Previous studies have also shown that RSV had effect on cerebral ischemia/ reperfusion injury (He et al. 2017), cardiovascular diseases (Dominique 2016) and neurodegenerative diseases (Yang et al. 2017). The most famous target which RSV plays a role in nervous system diseases such as AD is Sirt1. The research we have done suggested an increase in Sirt1 level of RSV group while there was a decrease in model group.

Activation of AMPK signaling pathway resulted in upregulation of Sirt1 and PGC-1α, by promoting mitochondrial biogenesis via AMPK/ Sirt1/ PGC-1α pathway, thereby playing a role in delaying skeletal muscle aging. AMPK is a conserved heterologous protein kinase, which is distributed in all tissues. AMPK is called intracellular 'energy receptor', which can inhibit the synthesis and secretion of proinflammatory cytokines in various types of cells, such as IL-1β and IL-6 in macrophages with its activation (Galic et al. 2011). PGC-

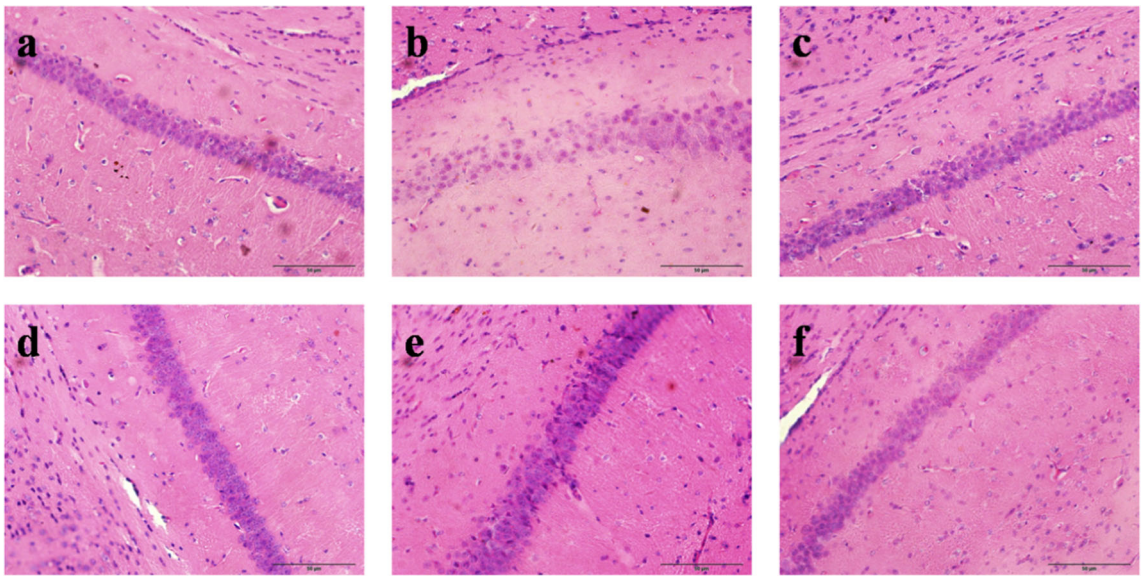

Fig. 8 Effects of RSV on the morphology and the number of neurons in an Aβ-induced AD mouse model. Light micrographs of hippocampal neurons from the CA1 region of control group (**a**), model group (**b**), sham group (**c**), RSV at doses of 0.02 mg/kg group (**d**) and 0.20 mg/kg group (**e**), donepezil group (**f**)

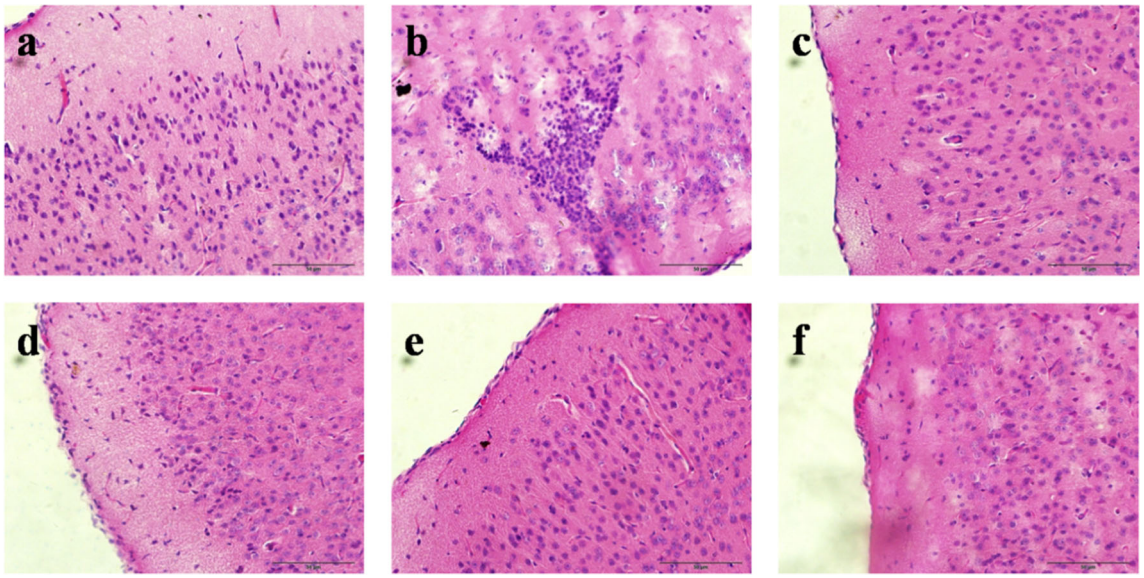

Fig. 9 Effects of RSV on the morphology and the number of neurons in an Aβ-induced AD mouse model. Light micrographs of hippocampal neurons from the prefrontal cortex region of control group (**a**), model group (**b**), sham group (**c**), RSV at doses of 0.02 mg/kg group (**d**) and 0.20 mg/kg group (**e**), donepezil group (**f**)

1α is a downstream molecule of AMPK, which regulates the expression of mitochondrial genes in brain tissue (Kim et al. 2013). Our data therefore suggested RSV can enhance the level of AMPK and Sirt1 significantly. During our study, in accordance with the behavioral deficits, we observed that the levels of AMPK and PGC-1α in hippocampus and prefrontal cortex showed significant decreases in the model mice which is in line with the published research (Anderson and Prolla 2009). Therefore, RSV significantly increased the expression of AMPK and PGC-1α.

In the pathology of AD, amyloid-β (Aβ) protein is a major component of plaques in the brain of AD patients which causes neurodegeneration and activates inflammatory response (Pallo et al. 2016; Villemagne et al. 2017). Nuclear factor κB (NF-κB) is a rapid response factor involved in immune and inflammatory response of the body. In the process of Aβ formation, various AD high-risk factors cause large numbers of inflammatory factors by inducing dissociate activation of NF-κB and these over producing inflammatory factors play an important role in the formation of Aβ plaques (Li et al. 2015). Microglias are recruited around Aβ, engulfing it and activating NLRP3 inflammatory bodies, releasing IL-1β to extracellular inflammatory response. IL-1β, other proinflammatory factors and cytotoxic factors may cause loss to the surrounding neurons and then expand the pathogenic role of Aβ. We have demonstrated in this paper that the increased level of the three inflammatory factors mentioned above including NF-κB, IL-1β and NLRP3 induced by $A\beta_{1-42}$ was reversed when give RSV treated. Thus it can be seen, RSV significantly decreased the expression of NF-κB/ IL-1β/ NLRP3 which indicating this pathway might be involved in the anti-dementia effects.

Conclusion

On the basis of the results above, the following conclusion can be made that RSV could not only improve the learning and cognitive disorder behaviors but also reverse the Aβ-induced changes of inflammatory response and mitochondrial dysfunction. These findings may indicate a beneficial therapeutic target in pathogenesis of Alzheimer disease.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest to declare.

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