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ORIGINAL ARTICLE

Cerebroprotective effect of resveratrol through antioxidant and anti-inflammatory effects in diabetic rats

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Abstract Oxidative stress and inflammation have been implicated in cerebral ischemia/reperfusion injury and complication of diabetes. The present study was designed to evaluate whether resveratrol has cerebroprotective action through antioxidant and anti-inflammatory actions in diabetic rats. Bilateral common carotid artery occlusion (30 min) and reperfusion (4 h) was employed to induce cerebral infarction in diabetic Wistar rats. Diabetes was induced by streptozocine (50 mg/kg) intraperitoneally at once. Diabetic animals were divided into groups as: normal, sham, ischemia–reperfusion, and resveratrol-treated (5, 10, 20, and 30 mg/kg). These were used for estimation of cerebral infarction. Furthermore, 20 mg/kg dose was selected for estimation of oxidative stress markers (malondialdehyde, superoxide dismutase, and catalase). Inflammatory markers like TNF-α, IL-6, IL-10, and myeloperoxidase were estimated and histological characters were studied. Resveratrol produced dose-dependent reduction in percent cerebral infarction. With resveratrol of 20 mg/kg dose, levels of oxidative stress markers and inflammatory markers like malondialdehyde, TNF-α, IL-6, and myeloperoxidase were reduced and there was a significant increase in the levels of antioxidant and anti-inflammatory markers like catalase, superoxide dismutase, and IL-10. In the present study, we found that mechanism(s) responsible for the cerebroprotective effect of resveratrol in the diabetic rat brain involves antioxidant and anti-inflammatory actions.

Keywords Diabetes · Ischemia–reperfusion injury · Inflammation · Oxidative stress

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Introduction

Stroke is the second leading cause of long-term disability and death worldwide (Di Carlo 2009). Diabetes is an important risk factor for ischemic stroke. Diabetes augmented the response of inflammation and oxidative stress, which was induced by the ischemia–reperfusion (Tsuruta et al. 2010). The patients who suffered with ischemic stroke and intracerebral hemorrhage associated with diabetes had a higher mortality rate (Naylor 2011) and struggled with the risks of ischemic events and organ damage. Thrombolysis is an important therapy in acute ischemic stroke, which allocates reperfusion. During reperfusion, inflammation and reactive oxygen species were involved to cause further damage rather than beneficial effects. In the diabetic condition, this effect will be increased and caused severe damage to the injured tissue. Due to this undesirable effect, reperfusion injury has been paid further attention. Reperfusion injury encourages several pathological roles such as leukocyte infiltration, oxidative stress, inflammation, destruction of blood–brain barrier, platelet activation, nitric oxide release, and apoptosis (Kaste 1997; Kim 1997). Recent evidences showed that oxidative stress and inflammation were involved in ischemia–reperfusion injury, and in the presence of diabetes, the effect of inflammatory response was increased (Wang et al. 2005). Early reports demonstrated that diabetes increased ischemia–reperfusion injury and had worsened clinical and laboratory outcomes (Canbaz and Duran 2003). Therefore, potent antioxidant and anti-inflammatory agents' interference may be beneficial in the treatment of cerebral ischemia–reperfusion injury. Resveratrol is a polyphenol compound that can be extracted from grape's skin. Resveratrol was reported to have antioxidant, anti-inflammatory, antidiabetic, and antiaging, control of cell cycle, and apoptosis (Zhang et al. 2010; Mukherjee et al. 2007;

Dawn 2007; Juhasz et al. 2010). Earlier reports suggested that antioxidants and anti-inflammatory agents had potent role in treating the cerebral ischemia–reperfusion injury (Zhang et al. 2010; Del Zoppo 1997). In the present study, we employed bilateral common carotid artery occlusion for 30 min and reperfusion for 4 h in Wistar diabetic rats as a model of ischemia–reperfusion injury and an attempt was made to investigate possible protective role of resveratrol in cerebral ischemia–reperfusion injury in diabetic rats.

Material and methods

Chemicals

Rat TNF-α ELISA kit (Assaypro, USA), rat IL-10 ELISA kit (Assaypro, USA), rat IL-6 ELISA kit (Eaab, USA), phenazine methosulfate (Loba chemicals, India), thiobarbituric acid (Loba chemicals, India), nicotinamide adenine dinucleotide phosphate reduced form (Sisco chemicals, India), nitroblue tetrazolium (SD Fine Chemicals, India), O-dianisidine dihydrochloride (Sigma-Aldrich, India), 2,3,5-triphenyltetrazolium chloride (TTC) (Sigma-Aldrich, India), resveratrol (Sigma-Aldrich, India), and streptozocine (STZ) (Sigma-Aldrich, India) were used in the study. Other chemicals used were of analytical grade supplied from local agencies.

Animals

Adult Wistar rats (220–310 g) were obtained from Gentox Bioservices Pvt. Ltd., Hyderabad, Andhra Pradesh, India. Animals were maintained under a 12/12-h light/dark cycle, in an ambient temperature (24±1 °C) colony room. Animals were provided with a constant supply of food and water. Animal care followed the official governmental guidelines in compliance with the CPCSEA, New Delhi, and experimental protocols were conducted at Srinivasarao College of Pharmacy with the approval of the Institutional Ethical Committee of Andhra University, Visakhapatnam, India.

Experimental procedure

Induction of diabetes

The rats were rendered diabetic by single injection of STZ (50 mg/kg, i.p.) and they were supplied with sucrose solution (50 % *w*/*v*); after 6 days, the animals were subjected to cerebral ischemia–reperfusion injury. Blood samples for glucose estimation were obtained from tail vein of the rats, 6 days after the administration of STZ. Rats with a blood glucose level of more than 250 mg/dl were considered to be diabetic and included in the study. Serum glucose was estimated spectrophotometrically by using commercially available kits (J. Mitra & Co. Pvt. Ltd. New Delhi, India).

Experimental induction of global cerebral infarction

Cerebral infarction was induced by bilateral common carotid artery occlusion method described by Iwasakhi et al. 1989. Briefly, rats were anesthetized with thiopental sodium (30 mg/kg). Cervical vertebrae and the common carotid arteries were then exposed and carefully separated from the vagus nerve. These arteries were occluded for 30 min followed by reperfusion for 4 h. The rectal temperature was maintained at 37±0.5 °C with a feedback-controlled heating pad. Animals which did not lose the righting reflex or which convulsed during the ischemic episode were excluded.

Measurement of percentage cerebral infarct volume

Resveratrol (RSV) was dissolved in 5 % DMSO. It was administered intraperitoneally 5 min before reperfusion. Diabetic rats were randomly divided into groups: sham, ischemia–reperfusion (I/R), I/R + vehicle, and I/R + RSV (resveratrol-treated) (5, 10, 20, 30 mg/kg). Each group consists of six animals.

After predetermined time point of ischemia–reperfusion, the brains were quickly removed and sliced into coronal sections of 2 mm thickness. Each slice was immersed in a 1.0 % solution of TTC for 30 min. Pale necrotic infarcted tissue was separated and weighed. Healthy, normal tissue was stained dark red and percent infarction was calculated (Orsu et al. 2013).

Histology

As previously stated, the brain tissues were obtained and prepared for histological examination. Each brain was postfixed in a 10 % formalin solution. After that, brain tissue was embedded with paraffin and coronal sections were made into 5-μm thickness. To assess the histopathological change, the sections were further subjected to hematoxylin and eosin staining.

Estimation of oxidative stress and inflammation markers

In selected group of animals, 20 mg/kg dose of resveratrol was used for estimation of oxidative inflammation parameters. Brain tissues were homogenized and the supernatant was used for the estimation of malondialdehyde (MDA) (Okhawa et al. 1979), superoxide dismutase (SOD) (Kakkar et al. 1984), catalase (CAT) (Aebi 1974), myeloperoxidase (MPO) (Mullane

and Bruce Smith 1985), IL-10 (Liu et al. 2009), IL-6 (Saito et al. 1996), and TNF-α (Liu et al. 2009).

Statistical analysis

All values were expressed as mean±SEM and analyzed by one-way analysis of variance followed by Tukey's *t* test ($P<0.05$) using Prism software 5.0.

Results

Effect of resveratrol on percentage cerebral infarction

There was a significant increase in percent cerebral infarction in I/R diabetic group compared to sham control group. A significant reduction in percent cerebral infarction was observed with resveratrol administration. Resveratrol produced dose-dependent effect by reducing percentage infarction. Results were shown in Table 1.

Histology

The histological changes of sham, I/R, and resveratrol-treated rats were shown in Fig. 1; there were abnormal changes like dens eosinophilic cytoplasm and triangular nucleus found in I/R diabetic rats. In contrast, these abnormalities were recovered in the resveratrol-treated diabetic rats.

Effect of resveratrol on cerebral oxidative stress parameters

MDA levels were significantly increased and SOD and CAT levels were significantly decreased in I/R group of diabetic rats as compared to sham control group. In resveratrol-treated groups, MDA levels were significantly reduced and SOD and CAT levels were increased significantly. Results were shown in Table 2.

Table 1 Effect of resveratrol on percentage cerebral infarction in diabetic rats

Groups ($n=6$)	Percentage cerebral infarction
Normal	0
Sham control	7.337±0.596
I/R	60.07±0.8671*
Vehicle treated	60.32±0.8057
Resveratrol (5 mg/kg, i.p.)	34.49±1.186*
Resveratrol (10 mg/kg, i.p.)	26.72±1.226*
Resveratrol (20 mg/kg, i.p.)	13.84±0.8122*
Resveratrol (30 mg/kg, i.p.)	11.87±0.9807*

Data represent the mean±SEM. Number of animals used in each group = 6

I/R ischemia and reperfusion

*$P\leq0.05$ (statistically, significantly different from control group)

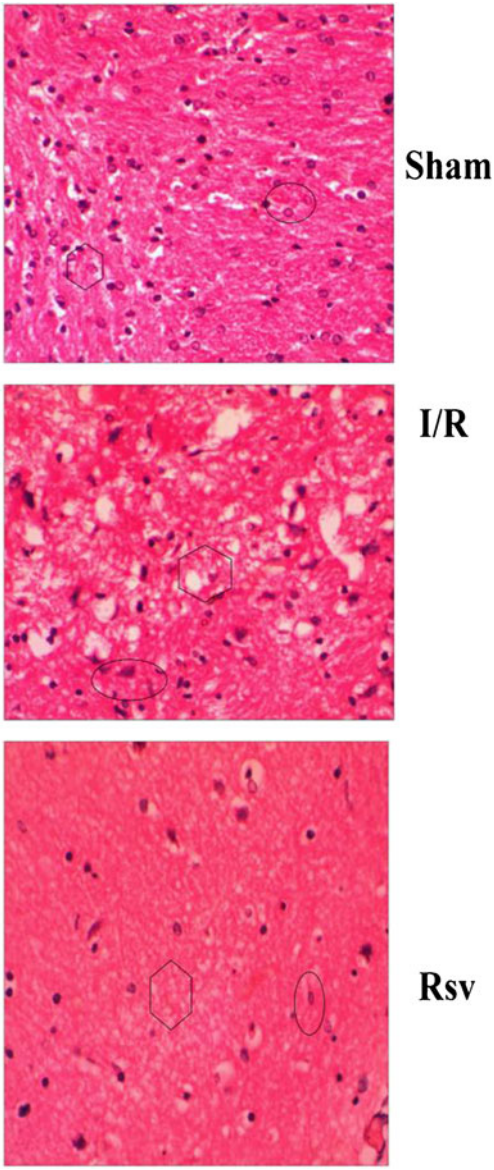

Fig. 1 Histology of coronal sections of rat brain: *hexagon* = eosinophilic cytoplasm and *oval* = neuron nucleus. *I/R*, ischemia and reperfusion; *Rsv*, resveratrol-treated (20 mg/kg, i.p.). In I/R, appearance of triangular nucleus and dense eosinophilic cytoplasm and significant recovery from formation of dense eosinophilic and triangular nucleus in resveratrol-treated group

Effect of resveratrol on cerebral inflammatory parameters

TNF-alpha, IL-6, and MPO levels were significantly increased and IL-10 levels were significantly decreased in I/R diabetic rats as compared to sham. In resveratrol-treated diabetic rats, TNF-alpha, IL-6, and MPO levels were significantly reduced and IL-10 levels were significantly increased. Results shown in Table 3.

Table 2 Effect of resveratrol on cerebral oxidative stress markers in diabetic rats

Assessments	Normal	Sham control	I/R	Vehicle treated	Resveratrol (20 mg/kg, i.p.) treated
MDA (nMol/g of wet tissue)	159.5±0.6925	188.4±2.85	645.4±3.002*	649.8±3.822	278.3±4.362*
SOD (units/mg of protein)	9.072±0.2216	7.367±0.4421	4.582±0.409*	4.092±0.2621	8.49±0.6783*
CAT (units/mg of protein)	114.5±1.807	86.37±2.675	46.23±1.426*	45.22±2.068	107.7±2.807*

Data represent the mean±SEM. Number of animals used in each group = 6

I/R ischemia and reperfusion, *MDA* malondialdehyde, *SOD* superoxide dismutase, *CAT* catalase

*$P \leq 0.05$ (statistically, significantly different from control group)

Discussion

The present study was conducted to investigate the potential mechanisms of resveratrol against diabetes-associated acute ischemia–reperfusion injury. The clinical outcomes of cerebral ischemia with diabetes worsened. Reactive oxygen species (ROS) and inflammation play a key role in ischemic tissue injury and reperfusion. The effect of reperfusion injury will become worse when associated with diabetes because diabetes also releases ROS and inflammation. The effect causes more disgusting pathological events in ischemic injury. Some of the researchers suggest that antioxidant and anti-inflammatory agents may be useful to limit the reperfusion injury (Khan et al. 2004; Lakhan et al. 2009). Recently, resveratrol showed neuroprotective role in rats (Wong and Crack 2008; Sinha et al. 2002).

Recent researchers suggested that bilateral common carotid arteries occlusion (BCCA) causes cerebral ischemia in rats (Tosaki et al. 1994). After BCCA occlusion and reperfusion, the pathological events such as free radicals and inflammation cause tissue apoptosis in diabetic rats. Resveratrol can prevent a wide variety of conditions including cancer, cardiovascular, diabetes, and neurological disorders (Aggarwal et al. 2004; Markus and Morris 2008). Resveratrol exerts multiple biological effects, including anti-inflammatory, antiproliferative, antiplatelet, and potent antioxidant effects (de la Lastra and Villegas 2007; Dawn 2007; Juhasz et al. 2010). Recent studies have identified that administration of resveratrol caused activation of adenosine receptors $A_1$and A_2, activation of the mitogen-activated protein kinase pathway, and myocardial induction of vascular endothelial growth factor, Flk-1, endothelial nitric oxide synthase, thioredoxin-1, and hemeoxigenase-1 (Dawn 2007). According to supported evidence, resveratrol activates multitudes of cytoprotective signaling pathways in the tissues like cerebrum and myocardium thereby affording considerable protection against ischemic injury (Dawn 2007; Juhasz et al. 2010). Resveratrol imparts several beneficial effects on the cardiovascular system by reducing infarct size and improving left ventricular functions after global ischemia and reperfusion injury. It also reduced blood glucose level and cardiomyocyte cell death in conjunction with increased Mn-SOD activity in diabetic rat myocardium (Thirunavukkarasu et al. 2007; Juhasz et al. 2010).

Cerebral damage was assessed by the examination of percentage of infarction in the injured brain, an important determinant in assessing the consequences of cerebral ischemia which leads to neurological impairment. The infarct size was determined by staining the coronal sections with TTC. The TTC highlights the viable cells as deep red color, whereas the unstained cells (pale whitish tissue) represent the infarct tissue. In the present study, we noticed a significant increase in percentage of infarction in I/R diabetic rats. In contrast, significant decreased infarction percent was noticed in resveratrol-

Table 3 Effect of resveratrol on cerebral inflammatory markers in diabetic rats

Assessments	Normal	Sham control	I/R control	Vehicle control	Resveratrol-treated (20 mg/kg, i.p.)
MPO (units/g of wet tissue)	4.603±0.205	8.812±0.555	84.84±0.688*	83.42±1.310	6.256±1.110*
TNF-α (ng/mg of tissue)	0.095±0.0043	0.1983±0.018	0.3117±0.025*	0.2983±0.021	0.03333±0.0084*
IL-6 (ng/mg of tissue)	0.1883±0.020	0.295±0.021	0.7067±0.025*	0.6517±0.036	0.2067±0.018*
IL-10 (ng/mg of tissue)	1.485±0.096	1.447±0.090	0.635±0.046*	0.62±0.040	1.412±0.14*

Data represent the mean±SEM. Number of animals used in each group = 6

I/R ischemia and reperfusion, *MPO* myeloperoxidase, *TNF-α* tumor necrosis factor-alpha, *IL-6* interleukin-6, *IL-10* interleukin-10

*$P \leq 0.05$ (statistically, significantly different from control group)

treated diabetic rats. Resveratrol (5, 10, 20, 30 mg/kg)-treated rats showed dose-dependent reduction in percent infarction. These results were in accordance with the earlier reports (Orsu et al. 2013). In the histological examination, ischemic cells were identified by the presence of dense eosinophilic cytoplasm and dark-stained triangular nuclei (Della-Morte et al. 2009). These changes were diminished in resveratrol-treated rats as shown in Fig. 1. These results suggest that resveratrol has cerebroprotection by limiting the cerebral infarction. Therefore, we assumed that resveratrol has cerebroprotective effect.

In ischemia–reperfusion injury, brain cells are continuously exposed to free radicals by oxidative metabolism and inflammation. This injury will become worse with diabetes. Lipid peroxidation release free radicals and the end product of which is MDA which determines the oxidative stress. The most important of the endogenous antioxidative enzymes are SOD and CAT. They play a key role to scavenging the free radicals. In the ischemic condition, the excess free radicals limit the levels of SOD and CAT that alter the antioxidative defensive mechanism. Increased levels of free radicals were involved in diabetes associated with ischemia. Therefore, oxidative stress is greater in ischemic rats associated with diabetes compared to normal rats. In the present study, we identified remarkable reduction of SOD and CAT and significant increase in levels of MDA in I/R diabetic rats. In contrast, SOD and CAT levels were increased significantly and MDA levels were decreased significantly in resveratrol-treated diabetic rats. Thus, these results show that resveratrol strengthened the oxidative defense mechanisms and reduced lipid peroxidation. Several researchers also demonstrated the modulatory effect of resveratrol on lipid peroxidation and antioxidant enzymes following injuries such as ischemia/hypoxia and CNS injuries (Yousuf et al. 2007; Andrabi et al. 2004). These results were in accordance to our results. Therefore, we suggest that resveratrol has cerebroprotective action against cerebral ischemia and reperfusion injury through antioxidative mechanism.

Accumulating evidence suggested that post-ischemic inflammation contributes to the development of neuronal injury and cerebral infarction. In the inflammation, endogenous mediators (cytokine and chemokines) and recruitment of circulating leukocytes are involved. Cytokines play a key role in the attraction of leukocytes as potent inducers of chemokines. Therefore, cytokines act as primary mediators and chemokines act as secondary mediators to attract leucocytes in the condition of inflammation (Gouwy et al. 2005). In addition, activated astrocytes and microglia produced cytokines and chemokines (Rock et al. 2004). These molecules appear to be responsible for the accumulation of inflammatory cells in injured brain tissue. TNF-α, IL-1β, and IL-6 are the impotent cytokines which initiate inflammatory mediator and inflammatory reactions and induce expression of other cytokines after ischemia–reperfusion injury (Yasuda et al. 2011; Lakhan et al. 2009). The ischemic brain was observed with increased levels of TNF-α, IL-6, and IL-1β. They are considered as a part of tissue damaging response in ischemia and reperfusion injury (Yasuda et al. 2011; Lakhan et al. 2009). IL-10 is the main cytokine which inhibit expression of TNF-α and IL-1β activity in the injured brain tissues (Lakhan et al. 2009). Several reports suggested that IL-10 acts as an anti-inflammatory cytokine in cerebral ischemia (Liu et al. 2009). In the present study, we noticed that the MPO, IL-6, and TNF-α levels were significantly increased and IL-10 levels were significantly decreased in I/R diabetic rats. In contrast, the levels of TNF-α, IL-6, and MPO were significantly decreased and IL-10 levels significantly increased in resveratrol-treated diabetic rats. These results were in accordance with the earlier reports (Yasuda et al. 2011; Yousuf et al. 2007; Zhang et al. 2010). Significantly attenuated MPO, IL-6, and TNF-α levels and increased IL-10 levels in ischemia–reperfusion injury indicate potent anti-inflammatory effect. Therefore, resveratrol may be having cerebroprotective action through anti-inflammatory effect.

Conclusion

The present study results constituted the evidence that resveratrol has significant cerebroprotective activity by reducing percentage of infarction and abnormal histological modification. Resveratrol showed inhibitory effects against oxidative stress (MDA) and inflammation (MPO, TNF-alpha, IL-6, and IL-10) caused by cerebral ischemia and reperfusion injury in diabetic rats. The present study suggests that the protective effect of resveratrol against cerebral infarction was mediated by antioxidant and anti-inflammatory mechanisms. This study further supports the possible use of resveratrol as a therapeutic agent to ameliorate cerebral infarction.

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Conflict of interest None

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