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Research report

Resveratrol limits diabetes-associated cognitive decline in rats by preventing oxidative stress and inflammation and modulating hippocampal structural synaptic plasticity

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ABSTRACT

Many patients with diabetes are at increased risk of cognitive dysfunction and dementia. Resveratrol, a polyphenol found mainly in grapes and red wine, has antioxidant, anti-inflammatory, and neuroprotective activities. Studies demonstrated that resveratrol could prevent memory deficits and the increase in acetylcholinesterase activity in streptozotocin-induced diabetic rats. However, whether administration of resveratrol could modulate the structural synaptic plasticity in diabetic rats remains unknown. Therefore, we tested its influence against cognitive dysfunction as well as on hippocampal structural synaptic plasticity in streptozotocin-induced diabetic rats. Our results showed that the cognitive performances in diabetic group were markedly deteriorated, accompanied by noticeable alterations in oxidative as well as inflammation parameters, SYN and GAP-43 expression were reduced in the hippocampus. In contrast, chronic treatment with resveratrol (10, 20 mg/kg) improved neuronal injury and cognitive performance by attenuating oxidative stress and inflammation as well as inhibiting synapse loss in diabetic rats. In conclusion, the present study suggested that oral supplementation of resveratrol might be a potential therapeutic strategy for the treatment and/or prevention of diabetic encephalopathy.

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1. Introduction

Diabetes mellitus is a common metabolic illness that is accompanied by high blood glucose concentration as a result of the lack of insulin or the presence of insulin resistance in peripheral tissues or both. DM impairs tissues and organs causing serious diseases such as diabetic retinopathy, diabetic nephropathy, and peripheral neuropathy. Besides the most common complications of the peripheral nervous system in diabetic patients, emerging evidences demonstrated that diabetes may also have negative impacts on the central nervous system (Mijnhout et al., 2006; Tuzcu and Baydas, 2006; McCrimmon et al., 2012; Ho et al., 2013; Thomas et al., 2013). Learning and memory deficits also occur in streptozotocin (STZ)-induced diabetic rats (Baydas et al., 2003; Stranahan et al., 2008; Tiwari et al., 2009; Wang and Jia, 2014), which have been partly associated with the structural and functional deficits in certain brain regions such as the hippocampus and cerebral cortex (Baydas et al., 2003; Hasanein and Shahidi, 2010).

The multifactorial pathogenesis of learning and memory impairments in diabetes has not been fully elucidated. Several factors such as chronic inflammation, vascular complications, metabolic disturbances, and the release of free radicals are implicated (Hasanein and Shahidi, 2010). Elevated blood glucose level stimulates pro-inflammatory cytokines, promotes lipid peroxidation, and further activates the apoptotic pathway which altogether contributes to the pathophysiology of various diabetic complications (Donath et al., 2008). Increased oxidative stress produces serious oxidative damage in the brain under diabetic conditions (Sharma and Singh, 2011; Wang and Jia, 2014). In addition, increased release of inflammatory cytokines and excessive inflammation are observed in diabetics (Kuhad et al., 2009; Wang and Jia, 2014). Activation of the nuclear transcription factor-κB (NF-κB) signaling pathway was shown to induce cognitive deficits (Kuhad et al., 2009; Wang and Jia, 2014) as well as neuronal apoptosis in diabetics. Previous study (Huang et al., 2009) confirmed that diabetic hyperglycemia indeed worsened seizure severity and status

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epilepticus-induced hippocampal neuron damage, and impaired hippocampus-dependent cognition and synaptic plasticity. Indeed, a complex pattern of changes in synaptic plasticity has been observed in hippocampal slices from STZ-diabetic rats (Chabot et al., 1997; Kamal et al., 1999). Synaptic plasticity includes the modifications of the structure and function of synapses, which are integral to learning and memory (Hasan et al., 2011). Cognitive decline associated with the progressive reduction of structural and functional plasticity in the brain regions that play key roles in cognitive functions (Bisaz et al., 2013).

Resveratrol (3,5,4-trihydroxy-trans-stilbene) is a polyphenol found mainly in grapes and red wine with diverse established biological activities, such as antioxidant, anti-inflammatory, cardioprotective and anti-apoptotic effects (Smoliga et al., 2011; Singh et al., 2013). Recently, a number of studies have focused on the neuroprotective effects of resveratrol, demonstrating that this compound attenuates amyloid β peptide-induced toxicity (Anekonda, 2006), protects against cerebral ischemic injury (Orsu et al., 2013) and prevents memory deficits against oxidative damage and the increase in acetylcholinesterase activity in streptozotocin-induced diabetic rats (Schmatz et al., 2009; Sadi and Konat, 2015). However, whether administration of resveratrol could modulate the structural synaptic plasticity in diabetic rats remains unknown. So the aim of this study was to investigate the effects of this compound on learning and memory as well as on hippocampal structural synaptic plasticity of STZ-induced diabetic rats. We chose two structural proteins involved in structural synaptic plasticity, SYN and GAP-43 as molecular targets.

2. Results

2.1. Effects of resveratrol on body weight and the fasting blood glucose levels

As shown in Table 1, eight weeks after streptozotocin injection, diabetic rats exhibit significantly increased (20.97 ± 0.685 mmol/L) fasting blood glucose (FBG) levels as compared to the control rats (4.33 ± 0.158 mmol/L) ($P < 0.001$). Also, there was a marked decline in the body weights of streptozotocin-treated rats as compared to age matched control rats ($P < 0.001$). One-way ANOVA revealed that chronic treatment with resveratrol (10, 20 mg/kg) significantly reduced the FBG levels [$F(4, 45) = 178.602$, $P < 0.05$] and increased body weights [$F(4, 45) = 260.995$, $P < 0.05$] in diabetic rats. Whereas resveratrol per se had no influence on FBG levels and body weight.

Table 1
(Results 2.1). Effect of resveratrol on body weight and blood glucose levels (mean ± S.E.M. of 10 observations) in the groups of rats at the onset and the end of the experiments.

Treatment	Body weight (g)		Plasma glucose (mmol/L)	
	Onset of study	End of study	Onset of study	End of study
Control	220.6 ± 4.12	364.6 ± 5.34	4.18 ± 0.207	4.33 ± 0.158
Diabetic	215.1 ± 3.41	175.8 ± 5.82[a]	4.21 ± 0.150	20.97 ± 0.685[a]
Diabetic/ RV 10 mg/kg	215.0 ± 3.62	197.3 ± 6.74[a]	4.45 ± 0.177	18.22 ± 0.762[ab]
Diabetic/ RV 20 mg/kg	219.4 ± 3.92	212.9 ± 4.67[ac]	4.38 ± 0.139	15.20 ± 0.796[ac]
RV 20 mg/kg	210.4 ± 1.64	361.8 ± 5.97	4.34 ± 0.183	4.08 ± 0.192

[a] $P < 0.001$, compared to the control group
[b] $P < 0.05$, compared to the diabetic group.
[c] $P < 0.01$, compared to the diabetic group.

2.2. Effect of chronic resveratrol treatment on diabetes-induced cognitive deficit

To examine whether resveratrol could attenuate the diabetes-induced cognitive impairments, we tested the learning and memory using the MWM test and the results are shown in Fig. 1. The mean escape latency for the trained rats was decreased over the course of the learning trials in the all groups (Fig. 1A). From the third day onwards there was a significant difference in transfer latency between the diabetic and the non-diabetes control rats [$F(4,45) = 11.545$, ($P < 0.01$)], while treatment with resveratrol at doses of the 10 mg/kg and 20 mg/kg ($P < 0.01$) significantly decreased the transfer latency as compared to the diabetic rats. However, there was no significant difference in escape latency between the resveratrol (20 mg/kg) control group and the non-diabetes control group.

In the probe trial of the MWM test, which assesses how well the animals have learned and consolidated the platform location during the four days of training, the animals showed a significant difference. The percentage of time spent in the target quadrant (Fig. 1C) and the number of crossings of the platform area (Fig. 1D) were significantly [$F(4,45) = 23.495$, ($P < 0.01$); $F(4,45) = 17.844$, ($P < 0.01$)] lower in diabetic group as compared to the non-diabetes control group, reflecting impairment in memory. The percentage of time spent in the target quadrant and the number of crossings of the platform area significantly increased by resveratrol (10 mg/kg, 20 mg/kg) treatment ($P < 0.01$). Resveratrol (20 mg/kg) control rats exhibited performance similar to that of the control rats in the MWM test, indicating that resveratrol per se had no effect on the learning and memory in the control group ($P > 0.05$). No significant difference was observed in the swimming speed among the five groups during the 5-day period of the MWM test ($P > 0.05$; Fig. 1B), indicating that motor deficits in the rats did no contribute to the differences in escape latencies, numbers of crossings, and time spent in the target quadrant.

2.3. Effects of resveratrol on parameters of oxidative stress in the hippocampus

2.3.1. Effects of resveratrol on diabetes-induced changes in lipid peroxidation

Effects of chronic treatment with resveratrol on lipid peroxidation (LPO) are depicted in Fig. 2A. Malondialdehyde (MDA) levels were significantly increased in the hippocampus [$F(4,25) = 45.318$, $P < 0.001$] of diabetic rats as compared to the non-diabetic control animals. However, 8-week resveratrol (10, 20 mg/kg) treatment significantly inhibited the elevation of MDA levels as compared to diabetic rats in the hippocampus ($P < 0.05$, $P < 0.001$). However, resveratrol per se did not alter MDA levels in different brain areas of control rats.

2.3.2. Effects of resveratrol on diabetes-induced changes in the antioxidant profile

The reduced glutathione (GSH) levels [$F(4,25) = 39.475$, $P < 0.001$, Fig. 2B] and enzyme activities of superoxide dismutase (SOD) [$F(4,25) = 29.875$, $P < 0.001$, Fig. 2C] and catalase (CAT) [$F(4,25) = 45.473$, $P < 0.001$, Fig. 2D] significantly decreased in the hippocampus of diabetic rats as compared to the non-diabetic control group. This reduction was significantly improved by the treatment with resveratrol in the hippocampus of diabetic rats. However, resveratrol per se did not influence the endogenous antioxidant profile.

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