Food and Chemical Toxicology 71 (2014) 116–121

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Review

Taurine ameliorates neuropathy via regulating NF-κB and Nrf2/HO-1 signaling cascades in diabetic rats

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ARTICLE INFO

Article history:
Received 31 December 2013
Accepted 27 May 2014
Available online 4 June 2014

Keywords:
Diabetic neuropathy
Oxidative stress
Taurine
NF-κB
Nrf2
HO-1

ABSTRACT

Diabetic neuropathy is one of common complications of diabetes mellitus. Hyperglycemia induced oxidative stress involves in the development of diabetic neuropathy, which could be reversed by supplementation of taurine, an endogenous antioxidant. This experiment was conducted to evaluate alterations in the expressions of transcription factors [nuclear factor kappa B (NF-κB), nuclear factor-E2-related factor-2 (Nrf2), and heme oxygenase 1 (HO-1)] and glucose transporters and glucose metabolism in the brain of diabetic rats. In a 2 × 2 factorially arranged groups, taurine (2%) or water was administered per orally to healthy and streptozotocin (STZ)-induced diabetic rats ($n = 10$ per group) for 8 weeks. Diabetes was associated with weight loss, hyperglycemia, and oxidative stress as reflected by increased serum malondialdehyde (MDA) concentrations. Diabetic rat brains had increased the NF-κB expression and decreased the Nrf2, HO-1, GLUT1,3 expressions as compared to healthy rat brains. Supplemental taurine did not alter body weight and blood glucose concentration, but partially reduced serum MDA concentration in the diabetic rats. Taurine also partially alleviated neuroinflammation as reflected by suppressed the NF-κB expression and enhanced the Nrf2, HO-1, GLUT1,3 expressions in the diabetic rats. In conclusion, taurine reduces the severity of oxidative stress through activating antioxidative defense signaling pathway in diabetic rat brain.

Contents

Abbreviations: ARE, antioxidant response element; BW, body weight; GLUT1, glucose transporter protein 1; GLUT3, glucose transporter protein 3; HO-1, heme oxygenase 1; IR, insulin receptor; Keap1, Kelch-like ECH-associated protein; MDA, malondialdehyde; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor-E2-related factor-2; ROS, reactive oxygen species; STZ, streptozotocin.

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http://dx.doi.org/10.1016/j.fct.2014.05.023
0278-6915/

1. Introduction

Diabetes mellitus is a chronic metabolic disorder leading to serious complications, such as neuropathy, retinopathy, and autonomic dysfunctions. Neuropathy is one of the most common complications and its prevalence is more than 50% among diabetic patients (Sima and Sugimoto, 1999). Diabetes is associated with an increased oxidative stress due to excessive production of reactive oxygen species (ROS) and/or defects in antioxidant defense system, which lead to nerve hypoxia/ischemia, impaired nerve growth factor support (Van Dam, 2002; McCrimmon et al., 2012), and neuroinflammation (Vincent et al., 2008) as well as neuronal damage in the central and peripheral nervous systems (Little et al., 2007).

Nuclear factor-kappa B (NF-κB), a transcription factor, has complex roles in neuron survival and functions as well as cell cycle changes when cellular stress is provoked, ROS is produced and DNA damage is occurred (Massa et al., 2006; Mosley et al., 2006). It involves in the pathogenesis of several inflammatory diseases including diabetic neuropathy (Cameron and Cotter, 2008). The activation of NF-κB is extremely important for both oxidative stress and inflammatory signaling pathway in diabetic rat brain.

Nuclear factor erythroid 2-related factor 2 (Nrf2), another transcription factor, is considered the primary cellular defence against cytotoxicity caused by oxidative stress, through regulating induction of phase II detoxifying (glutathione S-transferases) or antioxidant enzymes (heme oxygenase-1, HO-1) (Jaiswal, 2004; Itoh et al., 2004). Nrf2 retains in the cytoplasm with Kelch-like ECH-associated protein (Keap1) under normal conditions and is separated from Keap1, and then is Nrf2 is translocated into the nucleus where it binds to antioxidant response element (ARE) to augment a number of antioxidative genes when severe oxidative stress occurs (Itoh et al., 1999; Li and Kong, 2009). Namely, Nrf2 is evaluated as the hub of defense against oxidative stress in the pathophysiology of diabetic neuropathy (Negi et al., 2011a).

Because glucose is a predominant fuel, its homeostasis is crucial to cerebral tissues. Insulin in the central nervous system is highly critical in terms of whole body metabolism and nutrient availability as well as uptake (Porte et al., 2005; Anitha et al., 2012). Insulin-stimulated glucose metabolism occurs in the brain-insulin receptors (IR). Glucose transporters (GLUTs) play essential functions in the delivery of glucose. GLUT1-3 are neuron-specific glucose transporter and responsible for neuronal glucose homeostasis (Duelli and Kuschinsky, 2001). Intracellular vesicles storing GLUTs are translocated to the plasma membrane and facilitate glucose uptake during insulin stimulation. Under diabetic conditions, reduced expression of GLUTs results in the disruption of insulin signaling and glucose uptake and utilization. Overall, these alterations favor hyperglycemia (Nizamutdinova et al., 2009).

Several studies suggest that some micronutrient including taurine can prevent or reverse the hyperglycemia-induced cerebral and neuronal dysfunctions (Obrosova et al., 2001; Terada et al., 2011; Ito et al., 2012). Taurine, a free sulfonic acid, is synthesized from the metabolism of methionine and cysteine mainly in the liver and brain (Jacobsen and Smith, 1968; Tappaz et al., 1992). Meat, seafood, and milk are rich in taurine (Huxtable, 1992). Taurine is abundantly found in a variety of organs of most mammals, including brain, heart, and kidney, but it is essential nutrient in cats (Hansen, 2001). It acts as a neuromodulator, a neuroprotector, an antioxidant, and an anti-inflammatory agent (Hagar, 2004; Banerjee et al., 2008; Pan et al., 2010, 2011; Sun et al., 2011). It has been reported that insulin dependent and non-insulin dependent diabetic patients had low plasma taurine concentrations (Franconi et al., 2004, 2006; Schaffer et al., 2009). The hippocampus and hypothalamus taurine contents were shown to increase by taurine supplementation (Dawson et al., 1999) because exogenous taurine could pass blood–brain barrier upon ingestion (Huxtable, 1992). Taurine supplementation has been shown to have rewarding effects on reducing the severity of diabetes mellitus and diabetic complications through ameliorating oxidative stress (Obrosova and Stevens, 1999; Obrosova et al., 2001; Franconi et al., 2004; Ito et al., 2012) and enhancing insulin secretion (Chang and Kwon, 2000; Pandya et al., 2010). However, the exact mechanism by which supplemental taurine exerts hypoglycemic action in diabetic subjects has not been fully elucidated. Therefore, this experiment was conducted to evaluate alterations in the transcription factors and GLUTs and glucose metabolism in the cerebrum of diabetic rats.

2. Materials and methods

2.1. Animals, experimental design, and diabetes induction

Forty male Wistar rats (8 weeks old; 180–200 g) were obtained from the Animal Experimental Unit, Firat University. Rats were kept in a room with a temperature of 22 ± 3 °C and relative humidity of 55 ± 5% and subjected to 12 h light:12 h dark cycle. The animals were on a standard diet with tap water available *ad libitum*. All animal procedures were in accordance with the guidelines for care and use of laboratory animals and were approved by the Animal Experimentation Ethics Committee of Firat University (Elazig, Turkey).

After providing compliance with the conditions the rats were randomly divided into 4 groups, each containing 10 animals. The groups were as follows: (i) Control group: Rats administered with water as placebo, (ii) Taurine group: Rats administered with 2% taurine orally (w/v in water), (iii) STZ group: Rats administered with single dose of streptozotocin (STZ) to induce diabetes, and (iv) STZ + taurine group: Diabetic rats treated with taurine orally (2% w/v in water) starting from day 4 relative to STZ injection. The experiment lasted for 8 weeks.

Diabetes was induced by a single intraperitoneal injection of STZ after overnight fasting [60 mg/kg body weight (BW) in 0.1 M cold citrate buffer (pH 4.5), (Sigma, St. Louis, MO, USA)]. The positive control group was given single dose citrate buffer within water via intraperitoneal injection. Taurine (Carl Roth GmbH, Karlsruhe, Germany) was dissolved in water (2%, w/v) (Yao et al., 2009).

2.2. Laboratory analyses

2.2.1. Blood glucose and serum malondialdehyde (MDA) concentrations

Fasting blood glucose concentration was measured using a portable glucometer (Accu-Check Active, Roche Diagnostics, Mannheim, Germany) on days 2, 28, and 56 relative to the experiment.

Blood samples were centrifuged at 3000*g* for 10 min and sera were separated for analysis of MDA using a fully automatic HPLC (Shimadzu, Kyoto, Japan), consisting of a pump (LC-20AD), a UV–visible detector (SPD-20A), an inertsil ODS-3 C18 column (250 × 4.6 mm, 5 m), a column oven (CTO-10ASVP), an autosampler (SIL-20A), a degasser unit (DGU-20A5), and a computer system with LC solution Software (Shimadzu) (Barim and Karatepe, 2010).

2.2.2. Western blot analysis

Rats were sacrificed by cervical dislocations and brains were promptly removed at the end of the experiment. Prior to protein isolation, the brain sample was homogenized (10% w/v) in an ice-cold 1 ml of hypotonic buffer A containing 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES, pH 7.8), 10 mM KCl, 2 mM $MgCl_2$, 1 mM dithiothreitol (DTT), 0.1 mM ethylene diaminetetraacetic acid (EDTA), and 0.1 mM phenylmethylsulfonyl fluoride (PMSF). The homogenates were added with 80 μl of 10% Nonidet P-40 (NP-40) solution and then centrifuged at 14,000*g* for 2 min. The supernatant was collected as a cytosolic