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Chronic treatment with taurine after intracerebroventricular streptozotocin injection improves cognitive dysfunction in rats by modulating oxidative stress, cholinergic functions and neuroinflammation

K.H. Reeta*, Devendra Singh, Y.K. Gupta

Department of Pharmacology, All India Institute of Medical Sciences, New Delhi, India

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ABSTRACT

The present study investigated the neuroprotective effects of taurine, an essential amino acid for growth and development of central nervous system. Intracerebroventricular streptozotocin (ICV-STZ) model of cognitive impairment was used in male Wistar rats (270 ± 20 g). Morris water maze, elevated plus maze and passive avoidance paradigm were used to assess cognitive performance. Taurine (40, 60 and 120 mg/kg) was administered orally for 28 days following STZ administration on day 1. Oxidative stress parameters (malondialdehyde, glutathione, nitric oxide and superoxide dismutase) and cholinesterases (acetylcholinesterase and butyrylcholinesterase) activity were measured at end of the study in the cortex and hippocampus. Levels of TNF-α, IL-1β, expression of rho kinase-II (ROCK-II), glycogen synthase kinase-3β (GSK-3β) and choline acetyltransferase (ChAT) were studied in cortex and hippocampus. STZ caused significant cognitive impairment as compared to normal control. Chronic administration of taurine attenuated STZ-induced cognitive impairment. Increased oxidative stress and increased levels of TNF-α, IL-1β induced by STZ were also significantly attenuated by taurine. Taurine significantly ($p < 0.05$) decreased the STZ-induced increased expression of ROCK-II in cortex and hippocampus. Further, STZ-induced increased activity of cholinesterases was significantly ($p < 0.001$) mitigated by taurine. STZ decreased the expression of ChAT in hippocampus which was significantly ($p < 0.05$) reversed by taurine. However, GSK-3β expression was not altered by either STZ or taurine. The present study indicates that taurine exerts a neuroprotective role against STZ-induced cognitive impairment in rats. This effect is probably mediated by modulating oxidative stress, cholinesterases, inflammatory cytokines and expression of ROCK-II. Thus, this study suggests a potential of chronic taurine administration in cognitive impairment of Alzheimer's type.

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1. Introduction

Alzheimer's disease (AD) is a chronic, debilitating neurodegenerative disorder of aged brain, characterized by a general and progressive loss of mental, behavioural, functional decline and ability to learn (Anand et al., 2014). Cognitive impairment is associated pathologically with extracellular deposition of amyloid-β peptide contributing to senile plaque and intracellular aggregation of neurofibrillary tangles formed of hyper phosphorylated tau protein, mainly in hippocampus and cerebral cortex. These lead to cholinergic dysfunction, generation of free radicals, neuroinflammation and finally neuronal loss (Hardy and Selkoe, 2002; Perl, 2010; Stuchbury and Münch, 2005). Evidences suggest association of impaired memory function with disturbances in cholinergic system synthase such as choline acetyltransferase (ChAT), hydrolytic enzymes cholinesterases [acetylchoinesterases (AChE) & butyryl cholinesterases (BuChE)], glycogen synthase kinase-3β (GSK-3β) and rho kinase (ROCK-II) (Huang et al., 2008; Ishrat et al., 2006; Mehla et al., 2012; Salminen et al., 2008). ChAT and cholinesterases play a crucial role in maintenance of acetylcholine levels, essential for learning and memory. Increased GSK-3β activity in AD brain favours hyperphosphorylation of tau and NFTs formation (Forlenza et al., 2011). Rho-kinase/ROCK, a serine threonine kinase,

* Corresponding author.
E-mail address: reetakh@gmail.com (K.H. Reeta).

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has pleiotropic functions including the regulation of cellular contraction, motility, polarity, cell division, morphology gene expression (Amano et al., 2010).

Intracerebroventricular streptozotocin (ICV-STZ) is a commonly used model of AD as it demonstrates metabolic changes very similar to those found in the sporadic form of AD (Knezovic et al., 2015; Lannert and Hoyer, 1998; Paidi et al., 2015; Salkovic-Petrisic et al., 2013). It is postulated that the impairment of glucose and energy metabolism caused by STZ may be a potential source of oxidative stress, neuro-inflammation, cholinergic damage and neuronal cell death (Ishrat et al., 2006; Lannert and Hoyer, 1998; Sharma and Gupta, 2001). These finally lead to progressive loss of memory. Additionally increased levels of ROCK-II and decreased levels of ChAT were also observed following administration of ICV-STZ (Blokland and Jolles, 1993; Mehla et al., 2012).

Taurine, 2-aminoethanesulfonic acid, is the second most abundant amino acid after glutamate in the central nervous system of mammals. Taurine is synthesised from the metabolism of methionine and cysteine mainly in liver and brain (Tappaz et al., 1992. In the brain, metabolic cooperation between astrocytes and neurons is required for biosynthesis of taurine. Cysteine sulfinic acid decarboxylase is not present in neurons and hence is thought to either rely on astrocytes for providing hypotaurine or to acquire taurine through active transport (Brand et al., 1997; Tappaz et al., 1992; Vitvitsky et al., 2011). Taurine has been reported to produce plethora of functions such as anti-inflammatory effect (Miao et al., 2012; Sun et al., 2012), antioxidant property (Huxtable, 1992; Pushpakiran et al., 2004), as a neurotransmitter (Lin et al., 1985; Okamoto et al., 1983), in osmoregulation (Wade et al., 1988), as a neuroprotector against L-glutamate induced toxicity (El Idrissi and Trenkner, 1999), in maintaining structural integrity of membrane (Moran et al., 1987), in calcium homeostasis and CNS development (Lazarewicz et al., 1985). Furthermore, taurine administration has shown functional improvement in traumatic brain injury in rats (Su et al., 2014), hypoxia induced learning impairment (Malcangio et al., 1989) and excess manganese exposure-induced cognitive deficits (Lu et al., 2014). Taurine pre-treatment was also found to improve cognitive deficits induced by streptozotocin in rats (Javed et al., 2013). Based on these earlier findings, we propose that taurine administration post ICV-STZ injection may attenuate cognitive impairment in rats. To test our hypothesis, we evaluated the effect of chronic taurine treatment using a battery of behavioural parameters, oxidative stress markers, cholinergic activity status, inflammatory cytokines and expression of ROCK-II, GSK-3β and ChAT in ICV-STZ administered rats.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 270 ± 20 g were obtained from central animal facility of All India Institute of Medical Sciences, New Delhi, India. Prior ethical permission for experimentation was taken from the Institutional Animal Ethics Committee (682/IAEC/12). All efforts were made to minimize animal suffering, to reduce the number of animals used, and to utilize alternatives to *in vivo* techniques, if available. All experimental protocols were performed in compliance with the National Institute of Health (NIH) Guidelines for the Care and Use of the Laboratory Animals (NIH Publication no. 85 723, revised 1996). For acclimatisation in departmental animal house, rats were group housed (four rats each) in polyacrylic cages (38 × 23 × 10 cm) for ten days and gently handled to reduce the stress. The animals were maintained under standard laboratory conditions with natural light–dark cycle. Rats were allowed standard dry pellet diet and tap water *ad libitum*.

2.2. Chemicals and drugs

Streptozotocin, taurine, 5,5′-dithiobis (2-nitrobenzoic acid) (DTNB), reduced glutathione, sodium dodecyl sulphate (SDS), tetra ethoxy propane (TEP), phenylmethylsulphonylfloride (PMSF), dithiothreitol (DTT), acetylthiocholine iodide and butyrylthiocholine iodide were purchased from Sigma–Aldrich, USA. Western blot antibodies were procured from Abcam Plc, UK. Chemiluminescent reagent (Luminata Forte) was procured from Millipore, Germany. ELISA kits for the assay of inflammatory biomarkers were obtained from Diaclone, France. All other reagents were of analytical grade and were obtained from Merck Millipore, USA.

2.3. Experimental protocol

After acclimatization, the rats were randomly divided into 7 groups (n = 6): Group 1 - normal control (no surgery/treatment was given), Group 2 - Sham (artificial CSF administered ICV), Group 3 - STZ (STZ 3 mg/kg administered once intracerebroventricularly), Group 4- STZ + Taur 40 (STZ + taurine 40 mg/kg), Group 5 - STZ + Taur 60 (STZ + taurine 60 mg/kg), Group 6-STZ + Taur 120 (STZ + taurine 120 mg/kg) and Group 7 − Taur *per se* (Taurine 120 mg/kg). Taurine was administered orally by gavage from day 1 (of ICV- STZ injection) and continued for next 28 days (Fig. 1).

Morris water maze (escape latency and time spent in target quadrant), elevated plus maze and passive avoidance paradigm were done before STZ administration at baseline and repeated on 14th and 28th days of ICV-STZ. On 29th day, animals were decapitated under overdose of anaesthesia and brains were taken out; hippocampus and cortex were separated for estimation of oxidative stress as well as cholinergic markers. The levels of inflammatory cytokines were estimated by ELISA. ROCK-II, GSK-3β and ChAT protein expressions were studied by western blot.

2.4. Intracerebroventricular injection of streptozotocin

STZ was injected intracerebroventricularly as described previously (Mehla et al., 2012). Briefly, the animals were anesthetized with chloral hydrate, 400 mg/kg of body weight, intraperitoneally. Animals were placed on stereotaxic frame and a midline sagittal incision was made on the scalp. All surgicals were sterilised prior to use. The surface of rat brain was disinfected with 10% povidone iodine solution followed by 70% isopropyl alcohol twice. Bilateral burr holes were drilled in the skull over lateral ventricles using the following coordinates: 0.8 mm posterior to bregma, 1.5 mm lateral to sagittal suture and 3.6 mm beneath the surface of brain. STZ was injected slowly (2 μl/min), bilaterally at a dose of 3 mg/kg. Fresh STZ solution was prepared by dissolving in artificial cerebrospinal fluid (aCSF) immediately before administration. 41 mg/ml of STZ solution was prepared and a constant volume (10 μl) of STZ solution was injected slowly on both sides in each rat. Hamilton syringe was made to remain in place for 5 min to allow diffusion of STZ and prevent back flow. In the sham group, aCSF (147 mM NaCl; 2.9 mM KCl; 1.6 mM $MgCl_2$; 1.7 mM $CaCl_2$ and 2.2 mM dextrose) was injected on the same days as in STZ group. After injection, the burr holes were blocked with bone wax. Post-surgery, animals were kept separately in individual cages with free access to food and water.

2.5. Behavioural assessment

Battery of behavioural parameters were carried out before (day 0) and on 14th and 28th days after STZ injection.

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