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Attenuation of streptozotocin-induced alterations in acetylcholinesterase and antioxidant system by S-allylcysteine in rats

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ABSTRACT

The present study was designed to investigate the effect of the administration of S-allylcysteine (SAC) (150 mg/kg body weight for 45 days) on acetylcholinesterase (AChE) activity and antioxidant levels in the brain tissues of streptozotocin-induced diabetic rats. The levels of glucose, TBARS, hydroperoxide and acetylcholinesterase were increased significantly whereas the levels of plasma insulin, reduced glutathione, superoxide dismutase and catalase were decreased in experimental diabetic rats. Administration of SAC to diabetic rats reverted all these parameters. The effect of SAC was compared with glyclazide, a well-known antioxidant and antihyperglycemic drug. In conclusion, the present findings showed that treatment with SAC prevents the increase in AChE activity, lipid peroxidation, and consequently improves the antioxidant system in diabetic rats, indicating that this compound can be considered as possible therapeutics to be investigated in brain disorders associated with the diabetes.

1. Introduction

Diabetes mellitus (DM) is known as a heterogeneous multi-organ metabolic disorder characterized by insulin insufficiency and hyperglycemia due to destruction of the pancreatic β cells (Norris & Wolfsdorf, 2005). Recent reports indicate that the number of adults with diabetes has risen from 135 million in 1995 and projected to be 300 million in 2025 (ADA, 2009). The disease becomes a real problem of public health in the developing countries like India, where its prevalence is increasing steadily. According to the International Diabetes Federation, 61.3 million people in India had diabetes in 2011. That figure is projected to rise to 101.2 million by 2030 (IDA, 2012).

It is suggested that oxidative stress impairs the brain due to the rapid oxidative metabolic activity, high polyunsaturated fatty acid content, relatively low antioxidant capacity, and inadequate neuronal cell repair activity of brain (Cassarino & Bennett, 1999). These effects of diabetes in the CNS are a series of neurochemical, neurophysiological and structural abnormalities (Biessels, Heide, & Kamal, 2002). Inhibition of acetylcholinesterase (AChE) serves as a strategy for the treatment of Alzheimer's disease (AD) which is characterized neurochemically by a consistent deficit in cholinergic neurotransmission, particularly affecting cholinergic neurons in the basal forebrain (Tuzcu & Baydas, 2006). Alterations in the activity of acetylcholinesterase, an enzyme

Abbreviations: SAC, S-allylcysteine; STZ, streptozotocin; kg, kilogram

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responsible for the hydrolysis of the neurotransmitter acetylcholine (ACh) in the synaptic cleft of cholinergic synapses and neuromuscular junctions leads to the modifications in cholinergic neurotransmission in this pathology (Sanchez-Chavez & Salceda, 2000). In addition, it has been established that hyperglycemia induces oxidative stress (Tuzcu & Baydas, 2006) in various brain regions and alters the activity of enzymes that are considered critical for normal CNS functioning, such as Na^+–K^+-ATPase, catalase, NTPDase and 5′-nucleotidase (Sanchez-Chavez & Salceda, 2000). Reports in humans and experimental models of diabetes have long-established that one of the most vital mechanisms responsible for correcting the cholinergic function is performed by AChE (Schmatz et al., 2009). In view of the fact that oxidative damage is concerned in the etiology of neurological complications treatment with antioxidants has been used as a therapeutic approach in various types of neurodegenerative disease. Plants and their metabolites play imperative role in neuroprotection in diabetes (Kuhad, Sethi, Kanwaljit, & Chopra, 2008).

Medicinal plants and their bioactive constituents have been extensively used as an alternative medicine for a better control and management of diabetes mellitus (Saravanan, Ponmurugan, Senthil Kumar, & Rajarajan, 2009a). Garlic, a member of the Liliaceae family, is a rich source of bioactive compounds and is used in folk medicine for the treatment of various diseases (Block, 1992). Actually, garlic contains a variety of effective compounds that exhibit more medicinal properties (Martha Thomson, Al-Amin, Khaled, & Al-Qattan, 2007). S-allylcysteine (SAC) is a sulfur containing amino acid, derived from garlic and has been reported to have antioxidant activity (Numagami & Ohnishi, 2001). In our previous report, the efficacy of SAC in treating diabetes, we investigated the antihyperglycemic, lipid modulating and antioxidant effects of SAC (Saravanan & Ponmurugan, 2011, 2012). SAC also reverses the changes in the levels of the carbohydrate metabolizing enzymes (Saravanan, Ponmurugan, Senthil Kumar, & Rajarajan, 2009b). SAC reduces the formation of edema in the brain of ischemic rats through a mechanism involving the inhibition of lipid peroxidation and also and exhibits neurotrophic actions in cultured hippocampal neurons. Thus, our hypothesis is that the administration of SAC leads to reducing acetylcholinesterase level and improving antioxidant system in STZ induced diabetic rats. To test this hypothesis, we investigated whether SAC reduced acetylcholinesterase level and improved antioxidant system in the brain of STZ induced diabetic rats. The effect of SAC on blood glucose, plasma insulin and the level of acetylcholinesterase and antioxidant profile in the brain were measured to determine the role of SAC in altering the oxidative mediated acetylcholinesterase activity.

2. Materials and methods

2.1. Animals

Male Wistar rats of body weight 150–180 g were obtained from Nandha College of Pharmacy, Erode, India. The animals were maintained in The Animal house, Sastra University, Thanjavore, India and fed on standard pellet diet (AMRUT, Pune, India) and water ad libitum. Before the initiation of the experiment, the rats were accustomed for seven days to the laboratory circumstances. They were maintained in polycarbonate cages, under restrained temperature ($20\pm2^{\circ}$ C) and 12 h light/12 h dark rhythm. The protocol of this study was approved by Institutional Ethical Committee of Sastra University.

2.2. Chemicals

SAC (99%) was purchased from LGC Prochem, Bangalore, India. Streptozotocin was purchased from Himedia, Bangalore, India. Acetylthiocholine iodide, 5,5,-dithio-bis(2-nitrobenzoic acid) (DTNB) and all the drugs and biochemicals used in this experiment were purchased from Sigma Chemical Company Inc., St. Louis, MO, USA. All other chemicals used were of analytical grade.

2.3. Induction of diabetes

The overnight fasted rats were made diabetic by a single intraperitoneal injection of freshly prepared STZ (55 mg/kg body weight) in citrate buffer (0.1 M, pH 4.5) in a volume of 1 ml kg^{-1} (Kaleem, Asif, Ahmed, & Bano, 2006). Hyperglycemia was confirmed by the elevated glucose levels (above 250 mg/dl) in blood, determined at 72 h and then on day 7 after injection.

2.4. Experimental design

After the successful induction of experimental diabetes, the rats were divided into four groups each comprising a minimum of six rats.

Group 1: Control rats.
Group 2: Diabetic control rats.
Group 3: Diabetic rats administered with SAC (150 mg/kg body weight/rat) in aqueous solution orally for 45 days (Saravanan et al., 2009a).
Group 4: Diabetic rats administered with glyclazide (5 mg/kg body weight/rat) in aqueous solution orally for 45 days (Pulido, Suarez, & Casanova, 1997).

Body weight and blood glucose level measurements were conducted periodically. At the end of the experimental period, the animals were submitted to euthanasia being previously anesthetized with ketamine (50 mg/kg body weight, i.p.) and brain structures were removed and separated into cerebral cortex and hippo campus. The blood was collected with or without anticoagulant for plasma or serum separation, respectively.

2.5. Acetylcholinesterase activity

Cholinergic dysfunction was assessed by measuring acetylcholinesterase levels in cerebral cortex and hippo campus according to the method of Ellman, Courtney, Andres, and