Diabetology

Extended Abstract

Renoprotective Effect of Co-Enzyme Q10 and N-Acetylcysteine on Streptozotocin-Induced Diabetic Nephropathy in Rats - Manojkumar S Mahajan - Savitribai Phule Pune University, India

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Abstract

Background

Persistent chronic hyperglycemia is an important player in the development and progression of diabetic nephropathy (DN) due to generation of oxidative stress (OS) which is at the center in the pathophysiology of DN and underlying kidney damage. The present study was aimed to evaluate the effect of antioxidants like Co-enzyme Q10 (CoQ10) and N-acetylcysteine (NAC) either alone or in combination in streptozotocin (STZ) induced diabetic nephropathy (DN) in rats. Type 1 DM which occurs due to autoimmune destruction of pancreatic β-cells or absolute deficiency of insulin is also known as insulin dependent diabetes mellitus (IDDM). There is considerable evidence indicating that the chronic hyperglycemia causes many of the chronic complications of DM. There are several macrovascular complications like coronary artery, cerebrovascular and peripheral vascular disease arising due to damaged blood vessels. The primary microvascular manifestations of DM include diabetic nephropathy (DN), diabetic neuropathy and diabetic retinopathy [2,3].

DN is a leading reason for chronic kidney disease (CKD) and end-stage renal disease (ESRD). It is traditionally defined as a glomerular disease inclusive of five distinct stages: Glomerular hyperfiltration, incipient nephropathy, microalbuminuria, overt proteinuria and end-stage renal disease [4]. It is a progressive and irreversible loss of renal function characterized by initial hyperfiltration, albuminuria, glomerular mesangium expansion, accumulation of extracellular matrix, interstitial fibrosis, thickening of basement membranes and renal cell damage. This means, DN leads to structural changes and functional abnormalities in the kidneys [5].

Hyperglycemia is the key player in the development of DN. Recent clinical studies have shown that persistent hyperglycemia in DM can induce oxidative stress through diverse mechanisms including glucose auto-oxidation, protein glycation through non-enzymatic means, polyol pathway activation and acceleration, and reduced antioxidant defense system. Hyperglycemia may act through PKC activation, acceleration of the polyol pathway, production of reactive oxygen species (ROS) and over-expression of transforming growth factor-β (TGF-β) [6].

The normal kidney due to its high metabolic activity is capable of generating a considerable oxidative stress that is balanced by an extensive antioxidant system. Accumulating research showed that the significant contributor to the diabetic complications is chronic hyperglycemia that shifts this balance to a pro-oxidant state leading to tissue damage and vascular injury [7]. It is shown that almost all pathways contributing to the DN induce oxidative stress by one or other mechanism.

Methods

Type-1 diabetes mellitus (T1DM) was induced in male Sprague-Dawley rats by intraperitoneal (i.p.) administration of 55 mg/kg STZ. DN was confirmed by assessment of renal function tests. Blood glucose level, glycated hemoglobin (HbA1c), serum and urinary total protein, albumin, creatinine, urea, blood urea nitrogen (BUN) and uric acid were determined. Markers of oxidative stress including superoxide dismutase (SOD), catalase (CAT), malondialdehyde (MDA), glutathione (GSH), myeloperoxidase (MPO) and nitrite content in renal homogenate were measured. Histopathological evaluation of kidney was carried to assess renal damage. The rats were treated with CoQ10 (10 mg/kg, p.o.) alone or in combination with NAC (300 mg/kg, p.o.) for 8 weeks after confirmation of DN. Drugs and chemicals

Coenzyme Q10, as a gift sample was obtained from Zydus Cadila, Ahmedabad, India. N-acetylcysteine was procured from Loba Chemie (Mumbai, India). STZ was purchased from Sigma (USA). Spectrophotometric kits for assessment of superoxide dismutase (SOD), malondialdehyde (MDA), reduced glutathione (GSH), catalase (CAT), myeloperoxidase (MPO) and nitric oxide (NO) were purchased from Elabscience Biotechnology Inc., USA. All other Biochemical kits for estimation of total protein, albumin, creatinine, urea, BUN and uric acid, used in the study were procured from SPAN Diagnostics, India. All other chemicals and reagents used in the study were of analytical grade.

Experimental animals

Study was conducted using adult male Sprague-Dawley rats (8-weeks-old, weighing 220-250 g). Animals were procured from the National Institute of Bioscience, Pune and housed under

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standard conditions in polypropylene cages. Rats were housed in a controlled environment of temperature (18-22 °C) and light (12-hr light/dark cycle, lights on 07:00-19:00). All animals were given ad libitum access to standard food and water and were acclimated for 1 week prior to the beginning of the study. All the procedures which applied to rats in this work were performed in accordance with ethical guidelines on the care and use of animals issued by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). The protocol of the study was approved by Institutional Animal Ethics Committee (IAEC).

Induction of diabetic nephropathy

T1DM was induced in overnight fasted 40 adult male Sprague-Dawley rats (220-250 g). The rats received 55 mg/kg streptozotocin as a single intraperitoneal (i.p.) injection. STZ was administered immediately after dissolving it in freshly prepared cold citrate buffer, (pH 4.5). Hyperglycemia was assessed at 72 h and then on day 7 post-STZ injection by determination of blood glucose using glucometer (AlereG1, Korea) in samples gathered from the end part of tails. Animals with blood glucose level greater than 280 mg/dL were considered as diabetic and included in the DN studies.

Results

Renal function of diabetic rats was significantly impaired as indicated by renal function tests than control rats. Renal damage caused due to STZ was identified by means of increased MDA, depleted SOD and CAT activities and reduced GSH. MPO activity and nitrite content in rats with DN increased significantly. Treatment with CoQ10 or NAC and their combined treatment improved STZ induced renal damage as reflected by reduced oxidative stress. Also, the combined treatment protected renal structural damage as seen in histopathological assessment.

Conclusion

The present research suggests that oxidative stress due to persistent hyperglycemia causes development and progression of DN whereas combined administration of antioxidants used in the current investigation i.e. CoQ10 and NAC has better renoprotective effect by attenuation of DN than coenzyme Q10 or NAC alone.

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