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Curcumin enhances recovery of pancreatic islets from cellular stress induced inflammation and apoptosis in diabetic rats

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ABSTRACT

The phytochemical, curcumin, has been reported to play many beneficial roles. However, under diabetic conditions, the detail mechanism of its beneficial action in the glucose homeostasis regulatory organ, pancreas, is poorly understood. The present study has been designed and carried out to explore the role of curcumin in the pancreatic tissue of STZ induced and cellular stress mediated diabetes in eight weeks old male Wistar rats. Diabetes was induced with a single intraperitoneal dose of STZ (65 mg/kg body weight). Post to diabetes induction, animals were treated with curcumin at a dose of 100 mg/kg body weight for eight weeks. Underlying molecular and cellular mechanism was determined using various biochemical assays, DNA fragmentation, FACS, histology, immunoblotting and ELISA. Treatment with curcumin reduced blood glucose level, increased plasma insulin and mitigated oxidative stress related markers. In vivo and in vitro experimental results revealed increased levels of proinflammatory cytokines (TNF-α, IL1-β and IFN-γ), reduced level of cellular defense proteins (Nrf-2 and HO-1) and glucose transporter (GLUT-2) along with enhanced levels of signaling molecules of ER stress dependent and independent apoptosis (cleaved Caspase-12/9/8/3) in STZ administered group. Treatment with curcumin ameliorated all the adverse changes and helps the organ back to its normal physiology. Results suggest that curcumin protects pancreatic beta-cells by attenuating inflammatory responses, and inhibiting ER/mitochondrial dependent and independent pathways of apoptosis and crosstalk between them. This uniqueness and absence of any detectable adverse effect proposes the possibility of using this molecule as an effective protector in the cellular stress mediated diabetes mellitus.

Introduction

The life threatening disease, diabetes, increases the morbidity and mortality in the modern civilization. This disease arises due to impaired insulin secretion/resistance to insulin action or both in a biological system. It is associated with multiple organ dysfunctions due to persistent hyperglycemia and body's incapability of metabolizing biomolecules in the regulated manner (Baynes, 1991; Kim et al., 2006). Sustained hyperglycemia in the diabetic patient results in glucose autooxidation and protein glycosylation that in turn causes excessive production of reactive oxygen species (ROS). Earlier investigations suggest that the reduction in the pancreatic beta-cell mass, a characteristic of both type 1 and type 2 diabetes occurs due to the ill effect of oxidative stress (Rosenberg, 1995). Pancreatic cells are susceptible to oxidative damage because of the two reasons: one is their lower antioxidant defense machinery and other is the overproduction of ROS within the cell due to the exposition of general population to the toxic substances in daily life (Lenzen et al., 1996). Along with oxidative stress, endoplasmic reticulum (ER) stress also plays a vital role in diabetic pathophysiology (Marhfour et al., 2012). A well developed and active ER is present in the pancreatic beta-cells which play some important role in folding, export and processing of newly synthesized insulin (Oyadomari et al., 2002). ER homeostasis is disturbed by excessive Ca^{2+} release from ER stores, high lipid load, hyperglycemia, oxidative stress and/or misfolded mutant insulin proteins. This disturbance results in an adaptive unfolded protein response (UPR) and aimed to restore ER folding capacity and mitigate stress (Ozcan et al., 2004). However, if ER stress is severe and lasts for a long time, the UPR is unable to restore normal cellular function and ultimately triggers cell death. A monofunctional nitrosourea derivative, streptozotocin, is most frequently used to induce both kinds of diabetes in the experimental animals because of its ability to destroy pancreatic beta-cells (Szkudelski, 2001). Interaction of STZ with the pancreatic beta-cells via GLUT-2 receptors of the cells leads to the production of ROS (Schnedl et al., 1994) and induces oxidative stress which in turn enhances proinflammatory cytokines (TNF-α, IL-1β, IFN-γ, IL-6, IL-18, etc.) production that leads to inflammation (Esposito et al., 2006;

Abbreviations: ROS, reactive oxygen species; ER, endoplasmic reticulum; CUR, curcumin; NF-κB, nuclear factor kappa B; iNOS, inducible nitric oxide synthase; HO-1, heme oxygenase-1; Nrf-2, nuclear factor erythroid-2 related factor; STZ, streptozotocin; MMP, mitochondrial membrane potential; PARP, poly(ADP-ribose) polymerase; PI3K, phosphatidylinositide 3-kinase

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Alexandraki et al., 2008), and cytokine induced ER stress that further potentiates the machinery of the ROS production. Thus a number of signaling mechanisms and crosstalk between them are involved in diabetes. Therefore to protect cells from cellular stress induced cell death an antioxidant is required that has the ability to inhibit multiple checkpoints of the signaling mechanism. Use of naturally occurring antioxidants is drawing