INTRODUCTION

Diabetes mellitus (DM) is one of the most common serious metabolic disease that has spread all over the world, and the number of people with diabetes has continued to grow in recent years. DM is a group of metabolic endocrine disorder resulting from defects in insulin secretion, insulin action, or both (Kumar and Clark, 2002). In type 2 diabetes, there is a progressive deterioration of β-cell function due to impaired glucose tolerance (Weyer et al. 1999). Patients with long term hyperglycemia experience brain complications which include increased risk of brain atrophy, lacunar infarcts and white matter lesions (van Harten et al. 2006). The functional and behavioural consequences of diabetic brain complications also include cognitive dysfunction like dementia and movement disorders (Biessels et al. 2006; van Elderen et al. 2010). These pathologies emerge from changes in cerebral metabolism, vascular reactivity and increased oxidative stress (Mankovsky et al. 1996; Manschot et al. 2007; Valko et al. 2007). Several studies also suggested that long term diabetes affects astrocytic function, which may also contribute to oxidative damage associated with diabetes (Mastrocola et al. 2005).

In addition to oxidative stress, nitrosative stress is also involved in many pathologies including diabetes. Nitric oxide (NO) is an important physiological signalling molecule which performs an array of functions. NO becomes noxious if it is produced in excess and displays cytotoxicity. It can undergo oxidative–reductive reactions to form reactive nitrogen species (RNS) which cause cellular damage (Guix et al. 2005; Pacher et al. 2007). Under pathological conditions such as Parkinsonism (Hirsch and Hunot, 2000) and ischemic brain injury (Iadecola, 1997), a high concentration of NO is synthesized by neurons or activated glial cells which could...
induce apoptotic cell death in neuronal cells. High NO level as well as i-NOS activity plays a deleterious effect on CNS following pathological events such as trauma and inflammation (Bredt, 1999; Calabrese et al. 2006). NO has also been implicated as the effector molecule responsible for the selective destruction of β-cells of the pancreatic islet (Kroncke et al. 1991) and alters pancreatic architecture via oxidative stress (Richa and Chaturvedi, 2015). Excessive NO production is an important contributing factor which augmented increased expression of glucose-stimulated insulin release in the diabetic condition (Salehi et al. 2008). Numerous studies report the occurrence of a constitutive NO synthase (cNOS) activity in both endocrine cells and nerves of the pancreatic islet tissue (Panagiotidis et al. 1994). Effects of NO on insulin secretion from the β-cells of pancreatic islets are not conclusive due to contradictory reports that NO may increase, (Schmidt et al. 1992) or decrease insulin secretion (Henningsson and Lundquist, 1998). Experimental evidences also indicate a correlation between diabetes and NO. In Type 2 diabetes, nitric oxide synthase (NOS) inhibition reduces glucose uptake during exercise (Kingwell et al. 2002). It was also reported that in type 2 diabetic patients with nephropathy, intravascular NO synthesis is decreased under both basal and hyperinsulinemic states (Tessari et al. 2010).

In view of our interest in the different aspects of NO and its possible correlation with diabetes, present study was undertaken to investigate the interrelation of hyperglycemia and nitrosative stress with following specific objectives:

**Objective 1:** To evaluate and compare the effects of Streptozotocin and Alloxan induced Diabetes mellitus on the brain and pancreas of female laboratory mouse, *Mus musculus.*

**Objective 2:** To assess the effects of hyperglycemia and NO on glial cells (microglia and astrocytes) with reference to neuroinflammation.
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**Objective 3:** To correlate the effects of hyperglycemia and NO modulators on pancreatic pathophysiology.

**Objective 4:** To study the effects of altered glucose and NO on hypothalamic glucose sensing neurons.

To undertake this research study, many experiments were performed which have been compiled into four chapters each dealing with one objective. These chapters preceded by general introduction, extensive review of literature and general materials and method, are followed by summary and conclusions as well as reference section. Present thesis is focused on wide spread disease occurring throughout the world but situation is more alarming in India which is predicted to be the “Capital of Diabetes”. It is presumed that outcome of this experimental study; on diabetes- its mechanism and complications, will have applied significance in addition to its importance in basic science.

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