INTRODUCTION

Diabetes Mellitus is a metabolic disorder associated with insulin deficiency, which not only affects the carbohydrate metabolism but also is associated with various central and peripheral complications. Chronic hyperglycemia during diabetes mellitus is a major initiator of diabetic microvascular complications like retinopathy, neuropathy, nephropathy (Sheetz & King, 2002). Glucose processing uses a variety of diverse metabolic pathways. Chronic hyperglycemia can induce multiple cellular changes leading to metabolic disorders. The central nervous system (CNS) neurotransmitters play an important role in the regulation of glucose homeostasis. These neurotransmitters mediate rapid intracellular communications not only within the central nervous system but also in the peripheral tissues. They exert their function through receptors present in both neuronal and non neuronal cell surface that trigger second messenger signaling pathways (Julius, et al., 1989).

Neurotransmitters have been reported to show significant alterations during hyperglycemia resulting in altered functions causing neuronal degeneration (Kaur, et al., 1999). Neurochemical and neuro-imaging evidences have been reported to show regionally selective sympathetic denervation in diabetic neuropathy (Goldstein, et al., 2002). The changes in the brain monoamines during experimental diabetes have been reported. The serotonin content is doubled in the hypothalamus with no apparent alteration of its metabolite 5-hydroxy indole acetic acid (5-HIAA) levels, suggesting a reduced release. In the brain stem, serotonin and dopamine with the relative metabolites 5-HIAA and dihydroxyphenylacetic acid (DOPAC) are significantly reduced whereas noradrenaline is markedly increased (Chen, 1992). Insulin deficiency is the major factor involved as a trigger of the monoaminergic changes in the diabetic brain. Streptozotocin-induced diabetes produced marked alterations of monoamine concentrations in the brain regions of rats (Shimzu, 1991; Chen & Yang, 1991). The effects of streptozotocin (STZ)-induced diabetes on dopamine and serotonin release in striatum revealed that striatal dopamine release increased in acute diabetic state and this release depleted during the chronic state. The progression of diabetes is associated with an impaired ability of
the neurons in the CNS to release neurotransmitters resulting in behavioral changes (Broderick & Jacoby, 1989).

Hypothalamus epinephrine content increased in the suprachiasmatic nuclei but was decreased in the arcuate nucleus while dopamine decreased in the ventromedial nucleus during STZ induced diabetes (Linnoila, et al., 1986). Experimental diabetes resulting in acute insulin deficiency (Onegova, et al., 1980) causes a rapid onset of detectable alterations in epinephrine and dopamine activity in specific hypothalamic nuclei, which may contribute to the development of secondary neuroendocrine abnormalities known to occur in this condition. Insulin treatment partially normalised the altered neurotransmitter levels in streptozotocin induced diabetic rats.

Brain tissues absorb excessive glucose during hyperglycaemia due to abundance in the brain glucose I transporter. The brain interface for glucose transport is at the brain capillary endothelial cells which comprise the blood-brain barrier (BBB). Glucose transport across these barriers is mediated exclusively by the sodium-independent glucose transporter GLUT1. Changes in endothelial glucose transport and GLUT1 abundance in the barriers of the brain have profound consequences on glucose delivery to these tissues and major implications in the development of two major diabetic complications, namely insulin-induced hypoglycemia and diabetic retinopathy. The hyperglycaemic state is accompanied by increased metabolic activity in some specific brain regions and decreased metabolic activity in others. This regional variation is due to the distribution of glucose transporter sites within the brain. Hyperglycaemia is reported to be associated with hyperactivity of dopaminergic system.

Dopamine is a neurotransmitter that has been implicated in various central neuronal degenerative disorders like Parkinson's disease and behavioral diseases like Schizophrenia. Dopamine is synthesised from tyrosine, stored in vesicles in axon terminals and released when the neuron is depolarised. Dopamine interacts with specific membrane receptors to produce its effects. These effects are terminated by re-uptake of dopamine into the presynaptic neuron by a dopamine transporter or by metabolic inactivation by monoamine oxidase B (MAO-B) or catechol-0-methyltransferase.
Dopamine plays an important role both centrally and peripherally. The recent identification of five dopamine receptor subtypes provides a basis for understanding dopamine's central and peripheral actions. Dopamine receptors are classified into two major groups: DA D_1 like and DA D_2 like. Dopamine D_1 like receptors consists of DA D_1 and DA D_3 receptors. Dopamine D_2 like receptors consists of DA D_2, DA D_3 and DA D_4 receptors. Stimulation of the DA D_1 receptor gives rise to increased production of cAMP. Dopamine D_2 receptors inhibit cAMP production, but activate the inositol phosphate second messenger system. Impairment of central dopamine neurotransmission causes muscle rigidity, hormonal regulation, thought disorder and cocaine addiction. Peripheral dopamine receptors mediate changes in blood flow, glomerular filtration rate, sodium excretion and catecholamine release.

Dopamine itself has a regulatory effect on the synthesis of post-synaptic receptors. Dopamine D_2 receptors decreases when there is an increased dopaminergic transmission, while a decrease in the transmission has an opposite effect. Schizophrenia causes an increased dopamine D_2 receptor synthesis due to dopaminergic blockade by neuroleptics. In Parkinson's disease dopamine deficiency causes an increase in DA D_2 receptors.

Diabetes causes an increase in striatal dopamine with a decrease in its metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) (Lim & Lee, 1995; Saller, 1984; Kwok & Juorio, 1986). The central vagal connection with dopaminergic innervation is reported to reach the pancreatic islets through the parahypothalamic ventricular (PHV) nucleus while adrenergic and serotonergic innervations reach the pancreas through the brain stem (Smith and Davis, 1983, Lowey et al., 1994). Substantia nigra is an important autonomic area involved in controlling islet growth and development. It plays a role in modulating the outflow of both sympathetic and parasympathetic signals which ultimately reach the islets (Smith and Davis, 1983). In obese (ob/ob) diabetic rats activation of dopamine receptors reduce glucose, insulin resistance, obesity and certain lipids associated with cardiovascular risk. A series of studies conducted in ob/ob mice demonstrated that dopamine agonist therapy concurrently reduced elevated levels of chemical messengers in hypothalamus like
corticotropin releasing factor (CRF) and neuropeptide Y (NPY). Dopamine agonist combination treatment normalized the increased circadian organisation of the suprachiasmatic nuclei (SCN) to normal in obese animals. Blood glucose is regulated by the ventromedial hypothalamus (VMH) and changes in SCN temporal organization during diabetes are believed to influence the VMH affecting its function (Cincotta, et al., 1998, 1999). Dopamine agonist treatment was also associated with changes in VMH activity known to improve hyperglycemia (Cincotta, et al., 1998).

The central dopaminergic postsynaptic receptor supersensitivity due to decreased dopamine release is reported to decrease locomotor activity in STZ-induced diabetic rats (Kobayashi, et al., 1990). The metabolic abnormalities during diabetes in the striatum cause alterations in dopaminergic neurons by decreasing their firing rate (Saller, 1984; Saller, & Chiodo, 1980). Streptozotocin induced diabetic rats are reported to be associated with decreased ambulatory activity (Shimomura, et al., 1990). Striatal DA D1 receptors affinity decreased while there was an increase in number of DA D2 receptors during diabetes (Trulson & Himmel, 1983; Salkovic & Lackovic, 1992).

Streptozotocin induced diabetes in rats is reported to cause peripheral neuropathy. The autonomic and enteric innervation of the gut were denervated and hyperinnervated in the small intestine of diabetic animals (Di Giulio, et al., 1989; Gario, et al., 1989). It was previously reported that the cholinergic parasympathetic innervation of the intestine was markedly reduced and noradrenergic sympathetic axons hyperinnervate the duodenum of diabetic rats. Also, noradrenaline levels were reported to be high in the duodenum of diabetic rats (Gorio, et al., 1989). The intrinsic serotonergic innervation was not affected in the gut (Di Giulio, et al., 1989).

Dopamine exerts its inhibitory effect through the DA D1 receptors in the pancreatic exocrine secretion of conscious rats (Miyasaka, et al., 1998). Pancreatic β-cell secretory granules have the ability to store substantial amounts of calcium, dopamine and serotonin. Dopamine plays an important role in the modulation of the glucose-induced insulin secretion. L-3, 4-dihydroxyphenylalanine (L-DOPA) is rapidly converted to dopamine in islet β-cells. Dopamine accumulation in pancreatic islets is accompanied by
an increase in MAO activity which has an inhibitory effect on glucose-stimulated insulin response (Ahren & Lundquist, 1985). It is suggested that increased hydrogen peroxide production, following increased MAO activity augments the inhibitory effect of dopamine accumulation on insulin release.

The reports so far stated did not attempt to emphasize the functional correlation of dopaminergic receptors during diabetes. In the present study a detailed investigation on the alterations of dopamine and its receptors in the brain and pancreatic islets of streptozotocin induced diabetic rats were carried out. Our studies confirmed the stimulatory role of dopamine through dopamine D₂ receptors in glucose induced insulin secretion.