1 INTRODUCTION

Diabetes Mellitus has shown to produce dysfunctions of the Autonomic Nervous System (ANS) contributing to alterations in cardiovascular, gastrointestinal and genitourinary functions [1, 2]. Abnormalities of Gastrointestinal (GI) emptying occur in patients with this disease [3, 4]. Although diabetes is associated with degenerative changes in the Peripheral Nervous System (PNS), there is conflicting information on the involvement of diabetic neuropathy in the pathogenesis of GI disorders [4].

Patients with diabetes mellitus can suffer a range of gastrointestinal symptoms including chronic diarrhea and gastroparesis diabeticorum, a term used to describe gastric atony associated with delayed gastric emptying and increased gastric residual volume [5]. There is a strong correlation between the development of diabetic autonomic neuropathy, a characteristic complication of diabetes, and that of diabetic diarrhea and delayed stomach to caecum transit time in the diabetic rats [6]. Alterations in the myogenic actions of different agonists in the intestinal smooth muscle from animal models with experimental diabetes have been found. Furthermore,
morphological and histochemical abnormalities occur in the intestinal myenteric neurons in the diabetic state, with alterations in the adrenergic, cholinergic, 5-hydroxytryptaminergic and peptidergic systems [7].

A crucial role for the orderly motor function of the stomach seems to be played by the blood glucose concentration. Acute hyperglycemia slows gastric emptying, reduces antral and stimulates pyloric contractile activity [8, 9]. Prolonged states of hyperglycemia such as prevail in diabetes mellitus may not only reduce gastric motility and slow down emptying for extended periods, but also alter nerve metabolism. Thus, the abnormally slow gastric emptying in diabetic patients may result from prolonged hyperglycemia states leading to neuropathy rather from neuropathy as such [8].

The propulsion of intestinal contents depends on peristaltic contraction and relaxation and the co-coordinated opening of tonically contracted sphincters. The spatial and temporal characteristics of gastropyloroduodenal contractions are controlled by a coordinated action of three mechanisms: myogenic, neural and chemical. The myogenic control regulates the timing, frequency,
distance and direction of propagation of contractions, whereas the neurochemical controls determine whether or not contractions will occur in a segment [10, 11]. Two types of postsynaptic enteric motor neurons innervate the muscle layers to regulate its contractions, motor excitatory and motor inhibitory. The established physiological neurotransmitter of the motor excitatory neurotransmitter is acetylcholine [12]. The physiological neurotransmitter/neurotransmitters of the enteric inhibitory motor neurons have been identified as non-adrenergic non cholinergic (NANC) [11, 12]. Three putative neurotransmitters of NANC nerves are adenosine triphosphate (ATP), vasoactive intestinal peptide (VIP) and nitric oxide (NO) [13, 14, 15].

The physiological role of enteric inhibitory motor neurons in the regulation of the spatial and temporal characteristics of postprandial gastropyloroduodenal contractions and gastric emptying is unknown. In fundus, the NANC inhibitory neurons relax the smooth muscle so that the fundus can expand in volume and accommodate a large meal without increasing intraluminal pressure [16]. NO is synthesized from l-arginine by calcium dependant constitutive Nitric oxide
synthase (NOS) in endothelial cells and neuronal tissue. NO derived from nitric oxide synthase (NOS) in NANC terminals have shown to impair the intestinal motility in experimental diabetes. This has been well demonstrated by the l-arginine: NO pathway. NOS are inhibited by \(\text{N}^\text{G}\)-nitro-l-arginine, \(\text{N}^\text{G}\)-nitro-l-arginine methyl ester, \(\text{N}^\text{G}\)-monomethyl-l-arginine. Inhibition of NOS has shown to delay the gastric emptying of solid meals [17, 18].

Elevated glucose levels as well as other hyperosmolar media impaired NO mediated transmission (nitrergic) and relaxation to field stimulation suggest elevated glucose levels \textit{in vivo} may contribute towards the development of impaired NO mediated neurotransmission in diabetes [19]. Diabetes mellitus has been shown to be associated with atherosclerosis and cardiovascular diseases with altered metabolism of cholesterol [20].

Insulin deficiency leads to various metabolic alterations in the animals with increase blood glucose, decrease protein content, increased cholesterol, increased alkaline phosphatases and increased level of transaminases [21, 22, 23]. Metformin, Phenformin (oral hypoglycemic agents) have shown to produce beneficial effects on
the lipid and amino acid metabolism mainly by correcting abnormal glucose metabolism [24]. Several herbal preparations containing shilajit, gymnema Sylvester, jambolan seeds, polygala arvensis have also shown to decrease the blood glucose level, amino acids and lipid levels. Co-administration of such herbal preparations with oral hypoglycemic agents has shown to be more effective in regulating the metabolism [25, 26, 27]. The effect of herbal preparations and oral hypoglycemic agents either alone or in combination with each other on GI emptying has not been well studied. Administration of L-arginine has shown to decrease the cholesterol level and has been reported to be effective in preventing cardiovascular diseases [28]. L-arginine has also shown to modulate the morphine-induced constipation via endogenous NO [29]. In order to investigate whether impaired NO neurotransmission plays a role in the hyperglycemia - induced inhibition / stimulation of the propulsive activity of the gut, we have studied the role NO, the NANC neurotransmitter in hyperglycemia and intestinal transit in chronic hyperglycemic rats.