All scientists recognize that human knowledge is an entity and that sharp lines of demarcation cannot be drawn between various disciplines. Neurology and endocrinology developed as separate disciplines, but are not so divergent and sharply delimited as was formerly supposed. During recent decades it has been established that the nervous and endocrine systems are intricately interrelated and work together in many ways. Neuroendocrine mechanisms provide a major means by which environmental changes bring about appropriate and helpful adjustments in the body chemistry. These homeostatic responses help to preserve the life and well being of individual. A large part of the endocrine system is in fact an effector arm of nervous system, and changes in the rate of hormone secretion is one of the mechanisms by which the integrative function of the nervous system is affected.

Both neural and endocrine systems in conjunction regulate the metabolic functions of the body which have to be precisely controlled and balanced to achieve the homeostasis of blood sugar level. Glucose homeostasis is so important that the body has several mechanisms through which the production of glucose (from liver or gut) and the removal of glucose (utilization by various tissues) from the circulation are balanced. When either the rate of production or utilization exceeds the other, a state of glucose disequilibrium will exist, resulting in hyperglycemia or hypoglycemia either of which can be harmful. A regulatory system is present which stores glucose when it is in excess and releases it for combustion during fasting and other times of need (Liljenquist et al., 1979) This can be acquired through the co-ordination of both nervous and endocrine systems. Neural control is through
autonomic nervous system (ANS) and endocrine through the complicated interplay of multiple hormones such as insulin, glucagon, growth hormone, corticosteroid, catecholamine and thyroid hormones secreted by various endocrine glands. Not only that each hormone does not act alone but each one also does not act on single metabolite or single reaction.

Of the central neural structures, the hypothalamus has an influential role in controlling the glucoregulatory mechanisms (Shimazu, 1983). It has dual actions on the glucose homeostasis, one is the direct neurogenic effect in the liver and other organs (i.e. ventromedial hypothalamus (VMH), through the splanchnic nerves and lateral hypothalamus (LH), through the vagus nerves). The functions of sympathetic and parasympathetic nerves are concerned with emergency mechanisms, repair and preservation of a constant internal environment and are thus likely to be important in regulating the metabolism of the visceral organs including the liver in concert with hormonal regulation. The second, is by its control on the hormonal secretions from endocrine glands through the production of either hypothalamic releasing and inhibiting hormones or through the neural signals directly into the gland. This dual neural and hormonal regulation of metabolic pathways results in blood sugar homeostasis. Therefore, the hypothalamus is an important integrative station for metabolism (Shimazu, 1979; 1981).

**Neural Regulation**

As with many "new" ideas, when one searches the literature one finds that Claude Bernaud was there first. Bernaud (1854) punctured the floor of the fourth ventricle and produced hyperglycemia. He correctly concluded that hyperglycemia so induced resulted from nerve impulses passing via the splanchnic nerves and celiac plexus to the liver. The Cavazzani brothers much later (1893) stimulated the celiac plexus in dogs and produced hyperglycemia associated with a reduced hepatic glycogen content. Macleod (1907) stimulated the left splanchnic nerve and produced similar results. In spite of these observations the role of sympathetic nerves in releasing glucose from the liver was not accepted for many years.

However, some later studies have shown that the sympathetic nervous system acts in the genesis of hyperglycaemia by promoting mobilization of glycogen and by enhancing lipolysis and also by reducing insulin secretion (Wasserman et al., 1989a). This effect depends almost exclusively on neuroendocrine mechanisms with mediation of epinephrine released.
from the adrenal and of glucagon from pancreas (Cannon et al., 1924; Frohman and Bernardis, 1971). Besides the role of the sympathetic nerves in control of glycogen breakdown and glucose output, the role of the parasympathetic nerves in monitoring glucose balance (Lautt and Wong, 1978a) by regulating glycogen synthesis has also been elucidated (Shimazu, 1967; 1971; Shimazu and Fujimoto, 1971).

Vagus is known to be involved in several glucoregulatory processes, such as promotion of insulin secretion from B cells and inhibition of A cells by the efferent fibers and signaling the glycaemic state of the liver to hypothalamus by the efferent fibers (Lautt, 1980a; Lautt et al., 1983; Rohner-Jeanrenaud et al., 1983; Shimazu, 1983). Moreover, acetylcholine is now shown to act synergistically with insulin in the uptake of glucose by the target tissue such as liver cells (Nijima, 1969; Mondon and Burton, 1971; Pilo and Patel, 1978b; Beyner and Gelen, 1982). Apart from these actions acetylcholine secreted by the nerve endings may also counteract the action of catecholamine and other hormones such as glucagon and glucocorticoids. Thereby, parasympathetic system apparently has a definite influence on carbohydrate metabolism.

**Hormonal Regulation**

In addition to neural system, several endocrine glands function to a large extent to maintain relatively constant states of internal environment of the body. Almost every physiologic alteration is affected by a balance between some hormones acting together or in sequence. Therefore, the endocrine system is a highly integrated affair which generally collaborates with nervous system in affecting responses to a large variety of exteroceptive and interoceptive stimuli.

Of all the endocrine glands, adrenal and pancreas are involved in the regulation of blood sugar level in quite varied ways. In the mammals, the functional aspect of these endocrine glands are governed by direct neural innervation, by other hormones and also by the glycaemic status of the animal. By all accounts, the hypothalamo-pancreatic and hypothalamo-adrenal axis are responsible for the prolongation and consolidation of the metabolic changes in the body. Adrenocorticotropic hormone (ACTH), a major element of the hypothalamo-pituitary-adrenal axis, stimulates the adrenal gland steroidogenesis, leading
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to the production and release of glucocorticoids and mineralocorticoids, which in turn modulate a variety of important biological responses during stress.

The hormones of adrenal cortex are amongst the most potent and necessary chemical stimulants for the maintenance of life. They play a crucial role in facilitating the mobilization of amino acids. The role of glucocorticoid in maintaining the ability of the organism to carry out gluconeogenesis and glycogenesis is well explained by the studies of Long et al. (1940). Glucocorticoids govern gluconeogenesis in two ways: one by influencing extrahepatic tissues, furnishing gluconeogenic precursors to the liver and second by regulating hepatic metabolism.

Apart from the cortical hormones, the medullary hormones also profoundly involved in carbohydrate, protein and lipid metabolism. Catecholamine are involved in numerous intricated glucregulatory operations, thereby maintaining body homeostasis. The chief functions of the catecholamine are to maintain blood sugar level, to bring about alterations in carbohydrate metabolism and to assist in systemic adjustments from the medulla probably depending on the functional requirements of the organism.

Epinephrine exerts its hyperglycaemic action by increasing the rate of glycogenolysis (Hers, 1976; Hutson et al., 1976; Saiton, 1976) in the liver and muscles. It also causes hypoaminoacidemia (Shamoon et al., 1980) apparently by suppressing whole body proteolysis, an effect that resembles that of insulin on whole body protein metabolism (Fukagawa et al., 1986). Therefore, it is one of the most important factors in the normal organism for conterregulation of hypoglycaemic action of insulin (Goldfein et al., 1958).

In addition to adrenal, the pancreatic islets are known to have an authenticated role in maintaining glucose homeostasis (Smith and Davis, 1983). An alternate control of insulin and glucagon levels regulated by several nonpancreatic hormones and also via direct actions of the autonomic nerves which adequately supply the hormone producing islet cells (Woods and Porte, 1974; Gerich et al., 1976; Smith et al., 1979; Woods et al., 1980; Miller, 1981). Sympathetic influence results in decreased insulin secretion and decreased glucose induced secretion (Girardier et al., 1976). Parasympathetic effects on the pancreas results in elevated glucose induced secretion of insulin (Bloom et al., 1974; Kaneto et al., 1974). Therefore, parasympathetic nerves act synergistically with insulin (Lautt, 1980b).
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Insulin an anabolic hormone, has broad influence within the body and acts directly or indirectly to affect many kinds of biochemical processes. It plays a major role in the regulation of gluconeogenic hormones, glucagon and adrenaline (Pilkis et al., 1975). Insulin deficiency is expected to enhance glycogenolysis from the target organs (Whitton and Hems, 1975; Van de Werve et al., 1984) whereas plasma glucagon has a reverse effect (Ercan et al., 1995). Glucagon plays major role in gluconeogenesis, glycogenolysis and lipolysis in the liver (Cherrington et al., 1979). However, glucagon secretion is modified by the combined suppressive effects of glucose and insulin. It is mainly glucose that mediates glucagon secretion in response to physiological changes in glucose concentration, but this modulatory effect might be impressive without an adequate quantity of ambient insulin. Glucagon secretion decreases in response to high glucose stimulation and increases in response to low glucose stimulation, as in the perfused rat pancreas, just as it does in vivo (Gerich et al., 1974; Weir et al., 1974). Therefore, islets contain an endogenous pacemaker responsible for the oscillatory release of hormones, seemingly independent of other signals (Miller, 1981; Samols et al., 1981) and are important regulators of carbohydrate metabolism (Smith and Davis, 1983).

Moreover, in addition to above mentioned endocrine glands thyroid also regulate carbohydrate metabolism. To maintain a normal basal metabolic rate, precisely the right amount of thyroid hormone (T_3 and T_4), must be secreted all the time. To provide for this, specific feedback mechanism operates through the hypothalamus (TRF) and anterior pituitary gland (TSH) to control the rate of thyroid secretion. Thyroid hormones stimulates the oxygen consumption of most of the cells in the body, helps to regulate lipid and carbohydrate metabolism and is necessary for normal growth and maturation. They also regulates the metabolic reactions concerned with glycogenolysis and gluconeogenesis (Pilo et al., 1984a).

Importance Of Liver In Glucose Metabolism

Glucose is the major substrate for brain energy metabolism (Lund-Andersen, 1979). Therefore the brain is dependent on a constant supply of glucose from circulation to maintain its normal function. Thus, maintenance of plasma glucose within narrow limit is one of the most tightly regulated functions in mammalian body. Apart from contribution by kidney, the liver alone is responsible for meeting the major demands for glucose by other tissues. A major role of liver in maintaining a constant glycemic level is ensured by its large size, synthetic
capacity and privileged position. It plays a prime role in assimilating ingested carbohydrate, particularly glucose and fructose. As a major carbohydrate, liver also plays an equally important role in releasing glucose into blood stream whenever there is a heavy demand. The blood sugar level at which this output or uptake of sugar by the liver occurs seems to be influenced by nervous and endocrine mechanisms to ensure that glucose concentration is maintained in a homeostatic range.

The rich innervation of the liver includes sympathetic, parasympathetic and afferent component of autonomic nervous system (Lautt, 1980a; Mc Cuskey, 1980; De Wulf and Carton, 1981). Sympathetic nerve stimulation results in increased glycogenolysis (Shimazu, 1981) and rapidly increases the circulating blood glucose which in turn corollates into hyperglycaemia. The parasympathetic nerves to the liver stimulate the enzymatic activation of glycogen synthesis and decrease hepatic glucose output favouring low blood sugar level. Therefore, liver executes the neural and hormonal signals by adjusting the metabolism in such a way that glucose is released into or taken up from blood. Over and above, the liver has an intrinsic ability to serve as glucostat which is also present in isolation, free of neural and hormonal influences (Glinsman et al., 1969; Bucolo et al., 1974).

The first evidence that hepatic glycogenolysis is under direct control of hepatic sympathetic innervation was obtained by Shimazu and Fukuda (1965), who demonstrated rapid and marked increases in the activities of liver enzymes that catalyze the rate-limiting steps in glycogen breakdown i.e. glycogen phosphorylase and G-6-Pase, with a concomitant decrease in the liver glycogen content after electrical stimulation of peripheral nerve stimulation of the left splanchnic nerve of rabbits.

The balance between process involving uptake of glucose by tissues or supply of glucose by the liver through gluconeogenesis and glycogenolysis will depend on the balance of hormones at that time and this in turn apparently influences the enzyme activities of tissues. Hormonal control of gluconeogenesis occurs at three levels. The first involves regulation of substrate supply (Scrutton and Utter, 1968; Exton, 1972). The second levels deals with very significant but relatively slow adaptive changes in enzyme activity due to regulation of protein synthesis and /or degradation. The third level is concerned with the minute-to-minute regulation of gluconeogenesis by glucagon, insulin and catecholamine. Catecholamine and
Glucagon have been reported to regulate gluconeogenesis at same enzymatic sites (Kraus-Friedmann, 1984). Thereby, emphasizing the role of hormone in liver glucostatic activities.

Glycolytic and gluconeogenic pathways have most of their enzymes common which catalyze reversible reactions and their rates are mainly controlled by the concentration of substrates and products. Metabolic fluxes mediated through the enzymes of these cycles are modulated by short term (phosphorylation state and/or allosteric effectors) and long term (changes in enzyme activity) regulatory mechanisms. Hormones are involved in these regulatory mechanisms and the key regulators are glucagon and insulin (Vaulont and Kahn, 1994). Glucagon stimulates glycogenolysis (Bergstrom et al., 1972; Exton, 1980; Kraus-Friedmann, 1984), gluconeogenesis (Ercan et al., 1995) and lipolysis and inhibits glycogen synthesis, glycolysis and lipogenesis whereas insulin has reverse effects.

Glycogenesis in the liver is also enhanced by the direct action of parasympathetic nerves through the activation of glycogen synthetase, while glycogenolysis in the liver is stimulated by sympathetic nerves through activation of phosphorylase and glucose-6-phosphatase. Glucose-6-phosphatase occupies a strategic position in the maintenance of glucose homeostasis. It is the substrate or product of several major metabolic pathways, including glycolysis, gluconeogenesis, glycogen synthesis and degradation and the pentose phosphate pathway.

Hence, both neural and hormonal control monitor the complex physiological processes occurring in the body in such a way that a constant blood sugar level is maintained.

Clinical Manifestation Of Diabetes
From several decades, diabetes mellitus is a serious problem that gathered the immense attention of neuroendocrinologists. Most commonly, diabetes manifests in hyperglycaemia. Physiologically, an increase in blood glucose is the main signal for insulin secretion by pancreatic beta cells (Taylor et al., 1988; Unger, 1991; McGarry, 1992). But in diabetic condition secretion and/or action of insulin is hampered or impaired (Unger and Grundy, 1985; Valera et al., 1994). Glucose transport and metabolism in the beta cells are necessary for both prestored insulin release and insulin synthesis de novo (Meglasson et al., 1986; Unger, 1991).
Moreover, during hyperglycaemic (diabetic) condition the alpha cells of the pancreatic islets secrete glucagon as a response to falling insulin levels (Unger and Orci, 1983; McGarry et al., 1989). The rise in the glucagon/insulin ratio leads to metabolic alterations (Taylor et al., 1988; McGarry, 1992). Therefore, it is apparent that the ratio of these two hormones are important in the homeostatic regulation of blood sugar level.

Diabetic hyperglycaemia results both from the impairment of glucose uptake by the liver and peripheral tissue and from the over production of glucose through activation of liver gluconeogenesis (Taylor et al., 1988; McGarry, 1992). A variety of neurologic disturbances are known to occur in diabetes mellitus, producing multiple signs and symptoms referable to different segments of the nervous system.

**Diabetic Neuropathy**

Scanty knowledge in neuropathology have elicited much attention on the relationship between metabolic abnormalities associated with diabetes mellitus and structural and functional changes in the peripheral nervous systems. In diabetic neuropathy, local functional and anatomical features interact with systemic abnormalities to produce the complex neurologic disturbances. The pathogenesis of diabetic neuropathy is not explainable by single mechanism and development of neural lesions is linked to extraneural systemic complications.

Peripheral neuropathy is the most common complication in diabetes (Ellenberg, 1976). It is generally believed that autonomic neuropathy accompanies peripheral neuropathy and does not become apparent until later stages of diabetes (Niakan, 1986). Dysfunction of autonomic nervous system is reported to occur at an incidence of 20% to 40% in diabetes (Sharey-shafer et al., 1960; Hilsted et al., 1979). Diabetic patients with autonomic neuropathy have subnormal level of catecholamine, glucagon and somatostatin responses to insulin induced hypoglycaemia (Hoeldtke et al., 1982; Polonsky et al., 1982; Bolli et al., 1983). Therefore, diabetic autonomic neuropathy is a pathological state of variable severity and extent which can vary from asymptomatic anomalies of a parasympathetic test to a severe symptoms, with abnormal sympathetic and parasympathetic tests (Clarke et al., 1979).
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Hypoglycaemia is a potent activator of sympathetic nervous system which in turn increases plasma epinephrine and norepinephrine levels (Katagiri et al., 1982; Vinik et al., 1982). But, this response is hampered in diabetic patients with sympathetic neuropathy (Polinsky et al., 1980; Hoeldtke et al., 1982).

Parasympathetic neuropathy is seen very early on in diabetes and this has been considered an effect of diabetes, it may in some diabetes, be the cause itself. Parasympathetic neuropathy may result in reduced ability to rapidly activate glycogen synthetase via a gut-liver reflex and also a reduced effect of insulin on the liver. Such a neuropathy could therefore produce symptoms common in the non-obese, maturity onset diabetics.

Previous Findings
Substantial amount of research has been done in the field of neuroendocrinology in our laboratory. Comprehensive studies were carried out on the avian and mammalian glucoregulatory mechanisms by Pilo and his co-workers. The role of sympathetic and parasympathetic components of autonomic nervous system on the carbohydrate metabolism was emphasized in various previous studies (Pilo et al., 1984c; Verma et al., 1984; Parikh et al., 1992; Pillai et al., 1993). Several reviews are at hand regarding the effect of sympathetic and parasympathetic innervation on the structural and functional aspects of adrenal gland (Pilo and Patel, 19778a).

Studies by Parikh (1992), Oommen (1992), Pillai (1993) have accentuated the role of sympathetic innervation on glucose homeostasis using 6-OHDA, an antisypathetic drug. 6-OHDA is specific catecholamine neurotoxin which destroys the adrenergic nerve terminals leaving the cell bodies intact (Theonen and Tranzer, 1973; Oommen, 1992). It has been proved that autonomic nervous system plays a significant role in rationing the blood sugar level and liver is the target organ for the action of various hormones.

Theme Of The Present Study
Apart from a detailed analysis on the regulation of metabolic activities of various visceral organs through autonomic nervous system, the effect of each component individually and in co-ordination with adrenal and pancreatic hormones is to be elucidated. Hence, the present
research work was undertaken, for interpreting the interaction between hypothalamo-hepatic, hypothalamo-adrenal and hypothalamo-pancreatic axis.

Vagotomy leads to the suppression of parasympathetic component of autonomic nervous system. By sectioning vagus nerves subdiaphragmatically, the parasympathetic supply to the liver was abolished and the regulatory effect of sympathetic nerves and adrenal hormones were featured.

Sympathectomy was performed chemically using guanethidine sulphate. Guanethidine causes more specific and permanent destruction of adrenergic neurons in sympathetic ganglia compared to 6-OHDA. Guanethidine, an adrenergic neuron blocking agent employed clinically as an antihypertensive agent. This drug primarily influences cell bodies rather than the axons (Heath and Burnstock, 1977) through an immunologically mediated mechanism. Thus, the role sympathetic system in regulating carbohydrate metabolism has been highlighted.

Apart from neural control, the hormonal influence was examined by performing bilateral adrenalectomy. Effect of obliteration of adrenal medullary and cortical hormones on carbohydrate metabolism of liver and in turn, on glucose homeostasis has been elaborated.

In addition to this, effect of parasympatho and sympathoadrenal manipulation on insulin and thyroid hormone profile and their influence on liver metabolism has also been elucidated. Moreover, the glucose tolerance and insulin response after autonomic manipulation has been illustrated through Glucose Tolerance Test.