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COMPARATIVE STUDIES ON THE AUTONOMIC NERVOUS REGULATION OF LIVER AND KIDNEY FUNCTIONS THAT CONTRIBUTE TO THE HOMEOSTASIS OF BLOOD GLUCOSE LEVEL IN RAT AND PIGEON: A REVIEW

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Abstract: In this review, a comparison was made between the effects of vagotomy and cisplatin treatment on the liver and kidney of rat and pigeon. The studies of the vagal ablation and cisplatin treatment have shown some similarities with respect to glucose homoeostasis. Transaction of vagal fibres can cause hyperglycaemia. A persistent hyperglycaemia was noticed in both vagotomized and CDDP treated rats and pigeons after glucose administration. Parasympathetic system is known to bring about reduction in glucose level in blood, through its action on glucose uptake by the liver as well as on the release of insulin from pancreas. Parasympathetic dysfunction through vagotomy as well as through cisplatin treatment (chemical parasympathectomy) also produced an increase in sympathetic tone. Sympathetic system has opposing or counter regulating actions. Liver, pancreas and kidney are also innervated by sympathetic nerves just as parasympathetic nerves. Chemical sympathectomy through 6-hydroxydopamine (6-OHDA) produced an increased vagal tone. The review, presents the highlights of several studies carried out on the role of autonomic nervous system in the regulation of glucose homeostasis through modulating the metabolic responses of tissues such as liver and kidney.

Key Words: Vagotomy, Cisplatin treatment, Hyperglycaemia, 6-Hydroxydopamine,

A discovery in the middle of nineteenth century by Claude Bernard [1] that the puncture in the floor of fourth ventricle results in hyperglycaemia was a major breakthrough in neuroendocrinology. The finding stimulated many endocrinologists to do further experiments on glucose balance in blood after the stimulation of various areas of diencephalon. A fair appreciation of Bernard's observation was made by Cannon et al. [2] who revealed that the sympathetic nervous system and adrenal glands are involved in glucose homoeostasis. Compelling evidences were also derived from the parallel studies by Britton [3] which implicated the involvement of parasympathetic nervous system, in particular the vagus nerve, in the control of insulin secretion. The autonomic nervous systems are credited with the power of controlling various physiological process including emergency mechanism, repair and preservation of constant internal milieu, and are thus likely to be important in modulating the metabolism of liver and kidney.

Maintenance of homoeostasis is the main function of hypothalamus. Hypothalamus monitors large number of physiological parameters and on the basis of the information it receives the regulation of body functions and metabolic reactions are carried out. The regulation of body functions by hypothalamus is done through both autonomic nervous and endocrine systems. The origin of autonomic nervous system, consisting of both parasympathetic and sympathetic divisions, is hypothalamus. Hypothalamus also regulates the release of several hormones through

the releasing hormones or through autonomic fibres that innervate the endocrines glands such as pancreas and adrenal.

Ban [4], on the basis of studies on evaluation of measurements of blood pressure, gastric motility, respiratory movement, milk ejection and urinary bladder function, described that hypothalamus has three distinct zones: (i) a parasympathetic zone involving the middle line periventricular stratum, (ii) a sympathetic zone located in the medial hypothalamus that included ventromedial nucleus and (iii) a parasympathetic zone corresponding to the lateral hypothalamic nucleus. These hypothalamic areas are in communication with metabolically important visceral organs through vagus (parasympathetic) and splanchnic (sympathetic) nerves. Preganglionic sympathetic fibres reach the coeliac ganglion through the bilateral greater and lesser splanchnic nerves. Postganglionic sympathetic fibres arise in the coeliac ganglion forming an extensive plexus, the coeliac plexus. Parasympathetic system also has preganglionic and postganglionic fibres that run directly to the visceral organs through right and left vagi which incidentally carry 75% of all parasympathetic fibres.

Parasympathetic system originates from lateral hypothalamic area (LHA) while sympathetic system originates from ventromedial hypothalamus (VMH). Thus LHA through parasympathetic nerve fibres and VMH through sympathetic fibres control the visceral functions including metabolic processes [5-8]. Gellhorn et al. [9] developed the concept of autonomic nervous control of blood sugar level through parasympatho-pancreo-insulin axis. Blood sugar regulation by autonomic nervous system was later recognized to be also through mechanizations of sympatho-adreno-catecholamine axis, sympatho-pancreo-glucagon axis.

Autonomic dysfunction is observed in many diseases affecting human beings. In diabetes mellitus, the incidence of autonomic neuropathy is as high as 20% to 40% of all patients. In most cases, the autonomic neuropathy can be a consequence of diabetic conditions. Shimazu [10] has investigated the relationship between changes in blood glucose level and the nuclei of the hypothalamus by selective stimulation of each nucleus in rabbits, and has shown that blood glucose increase after stimulation of the VMH (sympathetic area) while it decreases after stimulation of the LHA (parasympathetic area). In general, the roles of VMH and LHA in metabolic regulation as in other functions are reciprocal, particularly in the regulation of carbohydrate metabolism in the liver [11,12].

The autonomic centres in the hypothalamus, not only receive the signals of glycaemic levels in the blood through gluco-sensitive neurons, but also receive a constant afferent influx of glucose related signals from liver and hepatic vein; on the basis of which hypothalamic controlling mechanisms centrifugally influence the hepatic carbohydrate metabolism. The afferent fibres also provide feed-backs for the maintenance of glucose homoeostasis. In maintaining glucose concentration, for instance, the liver plays a dominant role since it can vary the amount of glucose that is being pumped into the general circulation, and hormonal messengers are involved in this mechanism. The liver receives its innervation from the hepatic plexus, which is one of the subsidiaries of the celiac plexus. The hepatic plexus contains among other fibres, the sympathetic and parasympathetic efferent nerve fibres [13,14]. Lautt and Cote [15] showed that hyperglycaemia following surgical trauma occurs in the adrenalectomized rat in response to reflex activation of hepatic sympathetic nerves.

Since the early discovery of “puncture hyperglycaemia” by Claude Bernard, it has been assumed that the sympathetic nervous system participates in the genesis of hyperglycaemia by promoting mobilization of hepatic glycogen, and that its effects depends almost exclusively on neuroendocrine mechanisms through the mediation of epinephrine and glucagon [16]. Activation of principal sympathetic nerve innervating the liver resulted in a marked increase in the activity of glycogenolytic enzymes, G-6-Pase and phosphorylase within 30 seconds after the onset of stimulation [17,18]. Sympathetic nervous system can activate hepatic glycogenolysis and rapidly supply the circulating blood with glucose, first directly through the hepatic adrenergic innervation, second by the release of catecholamines from the adrenal medullary cells and third by the release of glucagon from the pancreatic islets. The role of parasympathetic system could be studied by either chemically sympathectomizing the animal or by electrically stimulating the branches of sympathetic system. Administration of 6-hydroxydopamine (6-OHDA) selectively promote acute degeneration of noradrenergic nerve terminals [19] and causes almost total depletion of adrenalin in sympathetically innervated tissues.

Direct stimulation of splanchnic nerves produced marked increase in blood glucose which was greatly reduced by cutting the hepatic nerves at the origin of the hepatic artery in adrenalectomized dogs [20]. Lautt and Wong [21] have shown that simultaneous action of sympathetic and parasympathetic fibres in the mixed hepatic nerve resulted in a complete domination by the sympathetic nerves. On the other hand, vagus plays an important role in the regulation of insulin secretion under physiological conditions [22-24]. Since acetylcholine (ACh) is released as a neurotransmitter from the nerve ending in the effecter cells upon physiological stimulation of the parasympathetic nervous system, the effects of vagus stimulation on insulin secretion would also be mimicked by exogenous ACh or the closely related cholinomimetic agents [25,26]. In the rat liver, stimulation of the parasympathetic nerves has direct effect on glucose metabolism synergic with insulin but antagonistic to glucagons [27]. Pilo and Patel [28] suggested that in birds, the parasympathetic nerves may be the predominant inducer of glucose uptake by liver cells. Avian liver has a rich cholinergic innervation and a high cholinergic activity [29]. Thus, parasympathetic system can influence the carbohydrate metabolism through its action on the release of insulin from pancreatic islets as well as through activation of hepatic enzymic machinery concerned with glucose uptake and glycogen formation. Parasympathetic system can also inhibit the action of glucagon and sympathetic neurotransmitters (norepinephrine and epinephrine) in the post-prandial condition thereby decreasing glucose output into the circulation.

Apart from liver, vagal parasympathetic fibres also innervate kidney, pancreas, adrenal and thyroid. Kidney is an organ which controls blood volume and plasma components through its excretory and reabsorptive capacity. Vagal cholinergic and adrenergic fibres are known to innervate kidney [30-32] and control the activity of kidney by counter regulation [33]. Kidney is also known to play an important role in general metabolism particularly in glucose homoeostasis [34-36]. It is reported that kidney takes a compensatory role of producing more glucose when liver functions are altered as in diabetes, because it is an important site for gluconeogenesis. The reaction rate of gluconeogenesis in kidney accelerates during times of food deprivation. As kidney is a principal site of glucagon degradation as indicated by the relatively high renal extraction rate and low urinary clearance of the hormone any renal pathologic condition could increase glucagon retention in blood and thereby producing hyperglycaemia.

The islets of Langerhans are richly vascularized and both the islet cells and blood vessels are intimately associated with the autonomic nerves. Lesions of the ventromedial nuclei or stimulation of the lateral hypothalamus within the diencephalon were found to increase plasma insulin concentration; most probably by influencing neural outflow from the vagal nuclei to the pancreatic islets [37]. Nerve to the pancreas contains preganglionic parasympathetic fibres from the dorsal trunk of the vagus and postganglionic sympathetic fibres from the greater and middle splanchnic nerves which originate in the celiac and superior mesenteric plexus [38,39]. The presence of both cholinergic and adrenergic fibres within the islets has been established by fluorescence microscopy and enzymatic histochemistry [40,41]. VMH lesion brought about alterations in the central nervous system (CNS) controlled homoeostasis that was responsible for the increase in the activity of the efferent vagus nerve that influence the endocrine pancreas [42,43]. It is well-known that electrical stimulation of vagus nerve of normal rats favours not only insulin but also glucagons secretion; both processes are inhibited by the cholinergic antagonist atropine [44,37]. In view of all these observations, it seems clear that hypothalamus controls both liver glycogen metabolism and glucose homoeostasis. The liver glycogen metabolism is controlled by direct innervation of the liver, via the VMH-splanchnic and LH-vagus nerve pathways (hypothalamo-hepatic axis) which directly controls the enzymes metabolizing glycogen in the liver and thus, is responsible for the initial and fine regulation of metabolic changes. Other mechanism is the hormonal regulation of glycogen breakdown and synthesis, which involves neural stimulation of the release of pancreatic hormones (hypothalamo-pancreatic axis) and adrenal hormones (hypothalomo-adrenal axis), which are responsible for the prolongation or consolidation of metabolic changes rather than their initiation. Because of the operation of hypothalamo-hepatic, hypothalamo-pancreatic axis and hypothalamo-adrenal axis, glucose homoeostasis could be severely affected if there are hypothalamic lesions especially in VMH and LHA or if the autonomic nervous system is not functioning properly (neuropathy).

Autonomic nervous control of metabolism and glucose homoeostasis:

Modulation of glucose homeostasis in blood, one of the important roles of the autonomic nervous system, is performed through regulating the functions of liver,

kidney and adipose tissue, endocrine pancreas and adrenal gland. Both liver and kidney have substantial role in controlling blood glucose level through their ability to take up, store and release glucose and these organs are innervated by both the Parasympathetic Nervous System (PNS) and Sympathetic Nervous System (SNS). Stimulation of parasympathetic nerves to the liver or administration of acetylcholine produced a rapid and dramatic decrease in hepatic glucose output and activated glycogen synthetase enzyme which resulted in rapid glycogen deposition [26,45,46]. Stimulation of sympathetic nerves to the liver, on the other hand, leads to the activation of phosphorylase and G-6-Pase and release of glucose [17,18]. Both sympathetic and parasympathetic systems have their controlling centres in the hypothalamus. Hypothalamus receives information about glucose concentration in blood through its own glucose receptors as well as through (afferent) fibres coming from hepatic blood vessels (mainly portal vessels). According to the signal regarding the glycaemic level, ventromedial hypothalamus – VMH (the sympathetic centre) and or LHA (the parasympathetic centre) get activated. VMH through sympathetic nervous system can increase blood sugar level while lateral hypothalamic area (LHA) through PNS can decrease the blood sugar level. Lesions of VMH have been reported to produce hyperinsulinemia whereas electrical stimulation of this nucleus decreased the release of glucagons [47]. The stimulation of LHA- (parasympathetic centre), on the other hand, will increase insulin release, glycogenesis in the liver and a fall in glycaemia as well as reduced glucose uptake by liver.

Hypoinsulinemia and the inability of the tissues to absorb glucose are the two main abnormalities in diabetes mellitus. These two conditions are found in vagotomized pigeons [48]. Vagotomized pigeons also failed to bring about normoglycaemia within 60-90 minutes when challenged with a glucose load [48]. Thus vagal denervation can bring about hyperglycaemia. It is now recognized that many complications found in diabetes mellitus could be due to vagal cholinergic dysfunction [13,49]. In some cases, vagal neuropathy could also be considered as a reason for the manifestation of diabetes mellitus, especially insulin dependent diabetes mellitus (IDDM).

Although diabetic condition could be experimentally produced by alloxan and streptozotocin, which are selective B cell cytotoxic agents, it is difficult to produce experimentally a selective neuropathic condition. Lack of such experimental models where autonomic neuropathy could be induced has created a real vacuum in the knowledge of autonomic dysfunction as a causative factor for the development of IDDM.

Reports that several antitumour drugs cause autonomic neural dysfunction that disturbed metabolic regulations, especially in liver and kidney, attracted attention in our laboratory. Cisplatin (CDDP), a widely used chemotherapeutic agent, belongs to this category [50]. Patients who have undergone cisplatin therapy have developed side effects very similar to that seen in diabetic autonomic neuropathy. Cisplatin can influence carbohydrate metabolism by their ability to alter insulin secretion [51]. Nephrotoxicity has also been reported in many cases as one of the side effects of this drug [52]. In animals, CDDP induces toxic side effects mainly in kidney, intestine and bone marrow. Cisplatin has differential affinities for kidney and liver. It shows preferential localizations within the subcellular sites in the kidney. Kidney not only retains a great concentration of CDDP than liver, but the biological half-life of this drug is also longer in the kidney [53]. The fact that CDDP administration has resulted in hyperglucagonemia and impaired the insulin secretion [51] can be shown as an evidence of cisplatin's selective side effect on autonomic nervous system.

There are several clinical reports at hand that show peripheral neuropathy after high dose of CDDP. Richardson and Cantwell [54] observed that some patients with metastatic germ-cell cancer have autonomic neuropathy based on CDDP. Thus, CDDP was found to cause (1) neuropathy, especially that of autonomic nervous system and (2) hyperglycemia. A natural sequel to this contention is that CDDP can be considered as chemical agent that causes selective autonomic neuropathy. So far there is no concentrated research that relates to the autonomic neuropathy and glucose homeostatic mechanisms. Most of the work was based on vagal transection and chemical sympathetectomy.

The role of parasympathetic nervous system (PNS) in glucose homoeostasis:

An effective way to study the role of PNS in blood sugar regulation is to perform vagal ablation and study

the response of the animals to glucose load. The effect of vagotomy on glucose homeostasis has been extensively done in our laboratory. Vagotomy in pigeon has been shown to cause:

- Decreased hepatic phosphorylase [55]
- Increased hepatic glycogen synthetase activity [56]
- Increased gluconeogenesis in liver [55]
- Decreased gluconeogenesis in kidney [57]
- Increased glucose uptake by liver [48]
- Hyperglycaemia [58]

In general, bird's response to hyperglycaemia and hypoglycaemia are similar to that of mammals, at the molecular level but the temporal correlates of these responses and the degree of tolerance to hypo- and hyperglycaemia are different in birds and mammals [59]. The basic difference is that birds tolerate hyperglycaemia much more than hypoglycaemia. In fact, in birds the pancreatic islets contain more A cells than B cells; reverse is true for mammals as they are less tolerant to hyperglycaemia and release insulin more quickly and in larger amounts than glucagon. It was thus indeed deemed worth while to compare mammalian response to vagotomy and CDDP treatment with that of avian response. In this light, a series of experiments were designed to get comprehensive and comparative information about glycaemic response in animals in which cholinergic action is completely removed (surgically vagotomized) or chemically parasympathectomized (cisplain-CDDP treated) rats and pigeons.

Vagotomy (VgX) caused hyperglycaemia in rats which is indicative of the fact that parasympathetic afferents and efferents are necessary for maintaining blood sugar level. CDDP treatment also elevated the blood glucose level in rat [60]. A possibility of cholinergic dysfunction as the cause for the hyperglycaemia in CDDP treated rat could be envisaged as both vagotomy and CDDP treatment reduced the AChE activity in liver and kidney [61] (Figs.1,2). Absence of acetylcholine secretion from vagal fibres in VgX and CDDP treated animals could be the reason for the reduced AChE activity in the liver and kidney. Experiments on smooth muscle strips from CDDP treated rats exhibited hypersensitivity to Ach. The muscle is hypercontractile to ACh because less of the neurotransmitter is hydrolysed due to the presence of less active AChE [61]. Response of pigeon to vagotomy and CDDP treatment is also similar to that of rat. Hyperglycaemia was accompanied by a decreased AChE activity in the liver and kidney of pigeon [60].

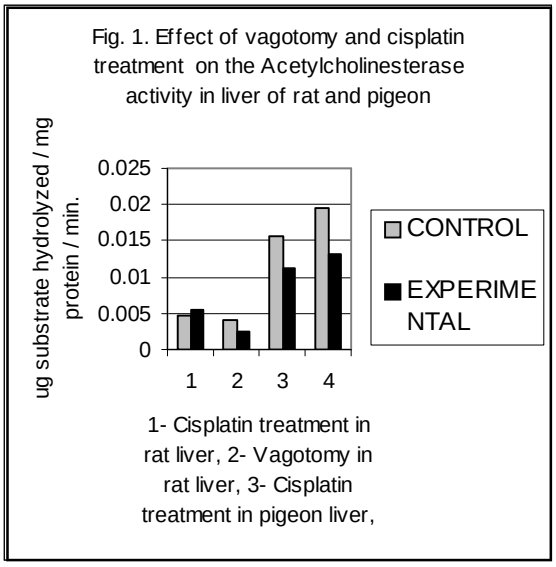
The hyperglycaemic response of VgX and CDDP treated rat and pigeon (Fig. 3) could be either due to increased glucose output by liver and kidney or due to decreased uptake of glucose by these tissues. It has been shown in our laboratory that the liver glycogen and glycogen synthetase activity levels decreased in VgX and CDDP treated rats and at the same time phosphorylase enzyme was very active [62].

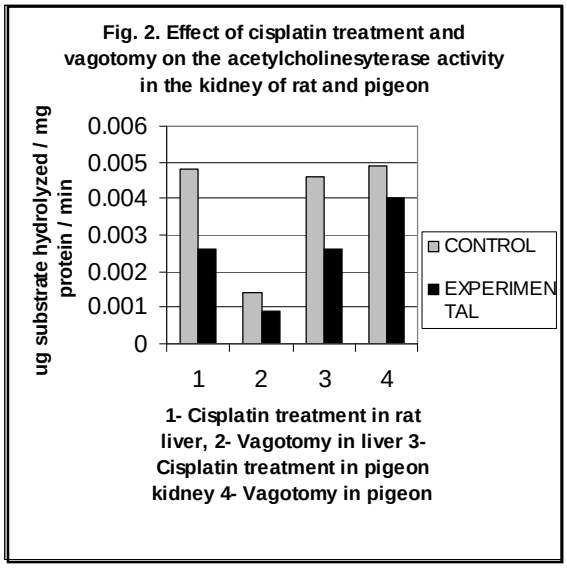
Gluconeogenesis and lactate utilization was also more in VgX and CDDP treated rat and pigeon livers [62]. Gluconeogenesis was not at the expense of labile proteins in the liver which was evident from the fact that protein content did not decrease in the liver of both rat and pigeon after VgX or CDDP treatment [63].

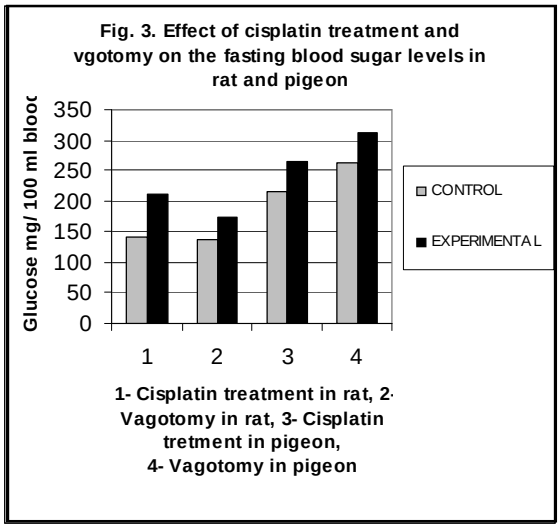
Protein and nucleic acid concentration also reflect on the overall state of multiplication of cells and maintenance of cell mass in any tissue. Hormones and nerves are equally involved in this tropic action. It has been suggested that insulin plays a major role during cholinergic differentiation [66]. Hence, the reduced level of DNA and RNA content in the liver of CDDP treated or VgX animals could be due to insufficiency of insulin as well as due to the lack of trophic action because of decreased neural activity [63] (Figs.9,10). The major effect of cisplatin in tumour cells is to inhibit DNA synthesis by cross linking the complimentary strands of nucleic acids. Moreover, like CDDP, vagal denervation also resulted in causing an impediment in DNA synthesis [8]. Cellular toxicity of CDDP in pigeon was more than that of rat. Administration of CDDP reduced the DNA content in the kidney of both the rat and pigeon while DNA content did not alter in the kidney after vagotomy. Cisplatin treatment produced a drastic reduction in RNA content in the kidney of pigeons. Bilateral vagotomy inhibited DNA synthesis during regeneration after partial hepatectomy [67].

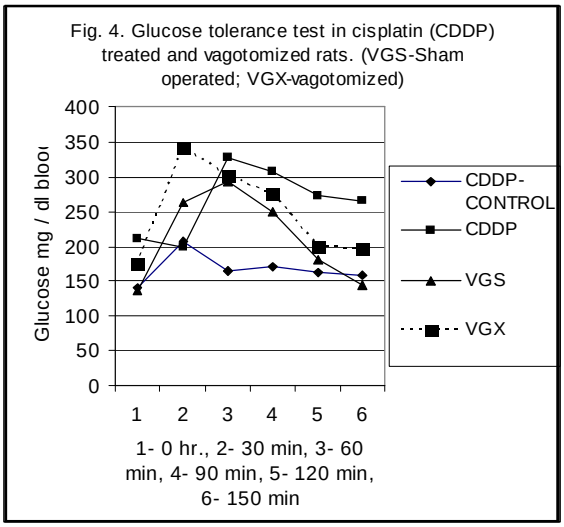
The decreased trophic action in the VgX and CDDP treated animals may be manifesting through two ways. Vagal denervation removes the direct trophic action of cholinergic fibres on one hand, and on the other hand, reduces the release of insulin and increases the release of glucocorticoids. Cisplatin has direct cytotoxic action as well as neurotoxicity, by which it reduces the neural stimulation of secretion of various hormones.

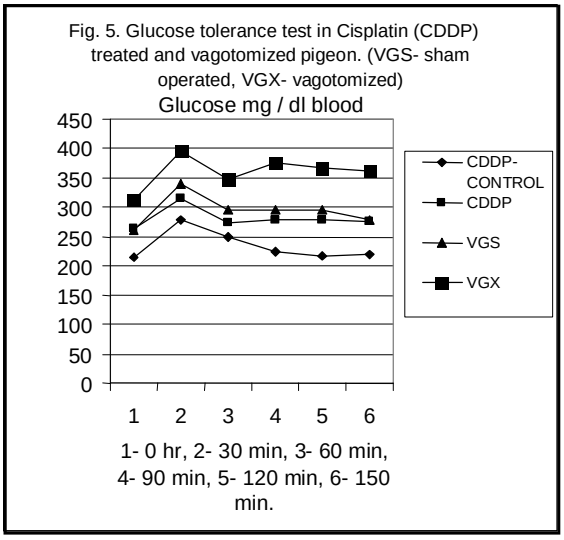
Vagotomy caused an increase in serum free fatty acid and blood sugar level in pigeon [58] which was attributed to an increased release of corticosteroids and norepinephrine (NE) [68]. The glucocorticoids

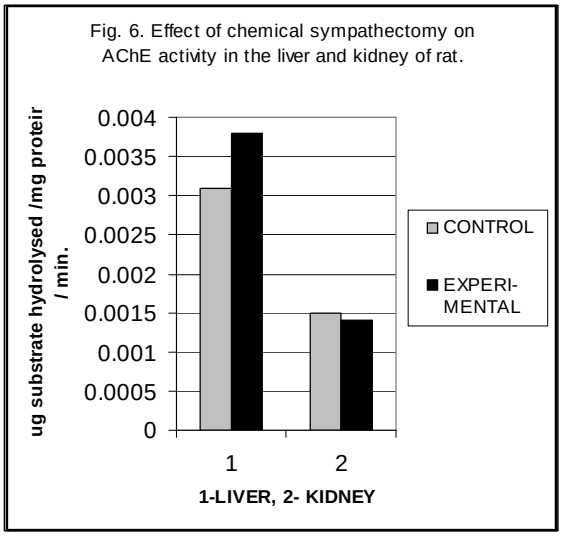




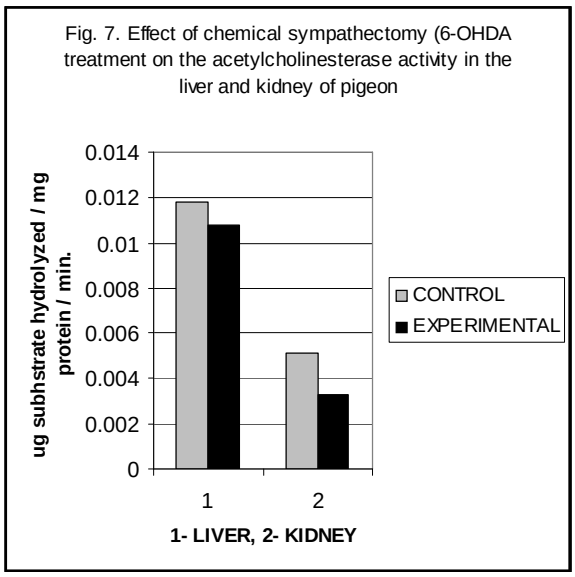


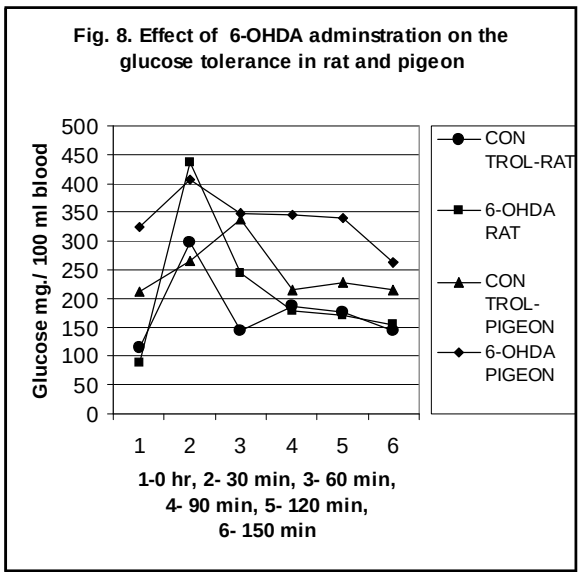


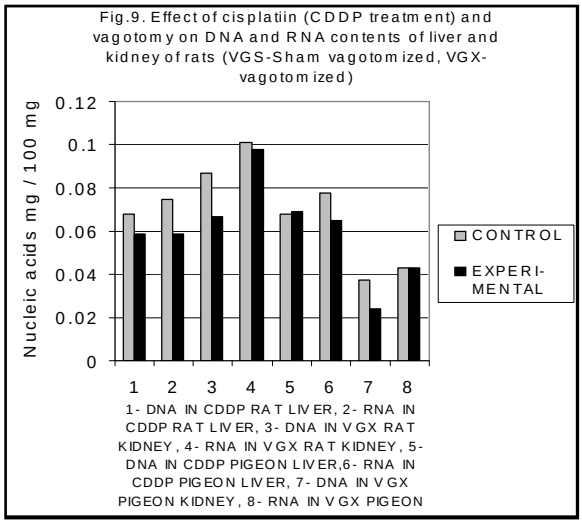


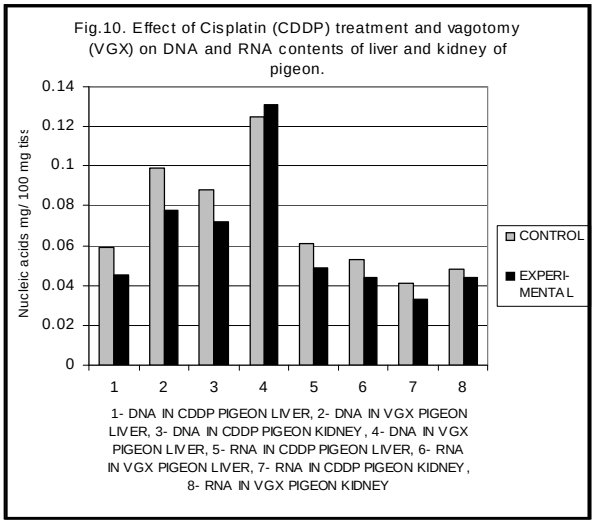


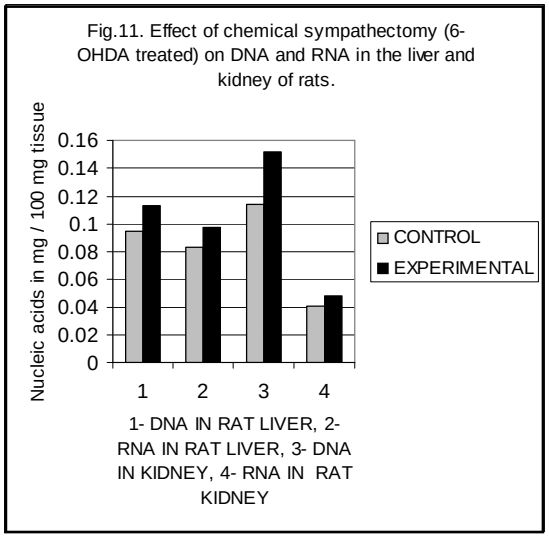
Figs. 1, 2 and 3: Adapted from Pilo and Oommen [64]. Figs. 4 and 5. Adapted from Pilo and Oommen [71].Fig. 6. Adapted from Pilo and Oommen [60].

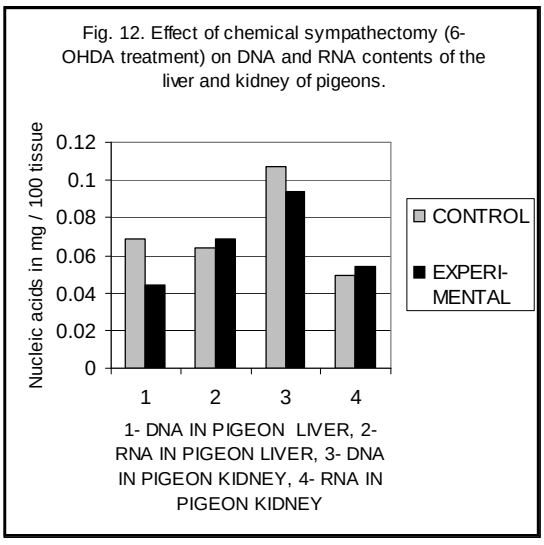












Figs. 7 and 8. Adapted from Oommen and Pilo [64]. Figs. 9-12. Adapted from Oommen and Pilo [63].

exert a very profound inhibitory effect on DNA synthesis [66] (Figs. 9, 10). Thus it is possible to conclude that in both rat and pigeon, nucleic acid metabolism was adversely affected under the influence of glucocorticoids that might have been released in greater amounts in VgX and CDDP treated animals.

Usually, hyperglycaemia is a result of several factors that operate differently depending on the physiological state of the animal. During post-prandial conditions increased level of glucose in blood is effectively absorbed by tissues through the influence of insulin. If insulin deficiency or disruption of glucose uptake mechanism takes place, then hyperglycaemia lasts more than the usual period. Hyperglycaemia can also occur when excess release of glucose manifests. This latter process found in stress, starvation or during exercise, is initiated by glucagon, NE and GH. Sustained glucose release under such conditions required gluconeogenesis which is stimulated by glucagon and glucocorticoids, in organs such as liver and kidney [69,70].

When glucose tolerance test (GTT) was undertaken after administration of glucose intraperitoneally, both VgX and CDDP treated rats and pigeons (Figs.4,5) showed persisting hyperglycaemia during the period of tests indicating that glucose uptake is very much reduced due to vagotomy and cisplatin treatment [71]. It has been reported that vagotomy produced a decrease in insulin level and impaired response to glucose load [22]. Even oral glucose loading in vagotomized rats did not elicit a proper insulin release response [72]. Impairment of glucose uptake mechanism was reported in vagotomized rats by Parikh [62] in liver and Pillai [73] in kidney. In both these organs a decreased glycogen synthetase and glycogen depositions was noticed following vagotomy and CDDP treatment. Moreover, there were increased activities of phosphorylase, G-6-Pase and LDH in these organs which explain the increased glucose release and the resultant hyperglycaemia. An overall decline in the activity of Na^+K^+-ATPase and other phosphatases observed in the liver and kidney of VgX and CDDP treated rats [62,73] also indicated the decreased transport activities.

Role of sympathetic nervous system (SNS) in glucose homoeostasis:

Some of the metabolic effects caused by ablation of vagus nerve and CDDP treatment seem to be correlated with activation of sympathetic nervous system (SNS) and release of glucagons, catecholamines and thyroid hormones. Reduction of parasympathetic tone (due to vagotomy and cisplatin treatment) as such can cause sympathetic adrenergic tone to assume a dominant role. Glucose homoeostasis is modulated by a coefficient correlation of these two opposing autonomic divisions. Activation of PNS or inhibition of SNS could bring the same set of response in many tissues. As mentioned earlier, hyperglycaemia in VgX and CDDP treated rats and pigeons could be due to increased sympathetic activity (tone).

The role of SNS can not be studied by surgical ablation unlike with PNS. Chemical sympathetectomy with 6-hydroxydomanie (6-OHDA) is method of choice. Administration of 6-OHDA selectively disturbs the hepatic sympathetic nerve and also restrains the neuronal stimulation of glucose release [21]. A comparative study was undertaken to understand the role of SNS in blood sugar regulation in birds and mammals [64]. Chemical sympathetectomy resulted in hypoglycaemia in rats while pigeons showed hyperglycaemia. Both parasympathetic and sympathetic nervous systems may be intimately involved in the control of home secretion. In mammals, insulin, glucagon and catecholamines play major role in the minute to minute regulation of hepatic glucose output under *in vivo* condition [74]. Increased vagal cholinergic action could be deduced by the increased AChE activity in the liver of sympathectomized rat [65] (Figs.6,7). The decreased blood sugar level in rat could be thus due to the increased vagal tone as well as due to increased insulin secretion after sympathetctomy. These two will lead to an increased operation of glucose-uptake mechanism in the rat liver resulting in a lower glycaemic level. In contrast, chemical sympathectomy produced hyperglycaemia in pigeon. Unlike in rat, there was no increased AChE activity in the liver of pigeon after sympathectomy. Lack of activation of PNS could be taken as a reason why there was no increased glucose uptake and a resultant hypoglycaemia one would rather expect. GTT in 6-OHDA treated pigeons showed that glucose uptake mechanism is not at all affected by sympathectomy as a normal glucose curve was noted in the experimental birds (Fig.8). The increased glucose level in the pigeon treated with 6-OHDA could be due to increased glucocorticoids released under stress.

Similar to vagotomy, sympathectomy also did affect the DNA and RNA contents in the liver and kidney of rat; while in pigeon it was not much affected [64] (Figs. 11,12). Enhanced content of nucleic acids in the liver and kidney of rat could be due to the increased insulin release after 6-OHDA treatment. The major influence

of insulin in the liver on protein synthesis is attributed to the augmentation of RNA synthesis [75,76]. The insignificant role of insulin in maintaining glucose level in pigeons was also reflected in nucleic acid metabolism. The decrease in DNA content in the liver and kidney of pigeon after sympathectomy could be primarily due to the elevated release of glucocorticoids. The high dose of corticoids injection in rats produced an inhibitory effect on protein synthesis [77,78]

In conclusion it could be stated that interplay of parasympathetic and sympathetic nervous systems are important in glucose homeostasis along with neuroendocrine regulations. The dysfunction of these two opposing autonomous nervous systems could pave way for the development of diabetic conditions. Studies on glucose homoeostasis with chemical vagotomy through the action of cisplatin or chemical sympatectomy by the action of 6-OHDA are useful in understanding the role of efferent fibres of these two nervous systems in conditions that cause autonomic neuropathy.

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