SUMMARY

Chapter I

This chapter deals with the materials and methods employed in present investigation.

Chapter II

The vagal afferent fibres from the liver are believed to play an important role in blood glucose homeostasis, both in mammals and birds. However, birds maintain a very high glucose level than mammals and it is reasonable to believe that avian kidney is also involved in glucose balance. Cisplatin (CDDP), a widely used anticancer drug has differential affinities for liver and kidney. Nephrotoxicity and peripheral neuropathy are the main side effects of this drug. These effects are similar to those in vagotomized animals. Hence, a comparative study of CDDP treatment and vagotomy was undertaken in rats and pigeons to elucidate the role of parasympathetic nervous system in regulating blood glucose homeostasis. Blood glucose levels and Acetylcholinesterase (AChE) activities were taken as indices to compare the effects of treatments. AChE activities tremendously declined in the liver and kidney of both the rats and pigeons after vagotomy. CDDP treatment also decreased AChE levels in both the organs of the pigeons while in the rats the kidney AChE level was the most affected. Both vagotomy and CDDP treatments elevated blood glucose levels in the rats and pigeons. The findings suggest that

both vagotomy and cisplatin treatment lead to parasympathetic dysfunction which in turn disrupt the fine control of blood glucose homeostasis in both the rats and pigeons.

Chapter III

Though a probable involvement of neural pathway in trophic stimulation of visceral organs is well-known, very little is known about such neural influence on adult liver and kidney although these organs constantly replace the worn out or damaged cells in large proportion. It is known that vagotomy and cisplatin treatment cause changes in nucleic acid and protein contents in tissues. Hence this study was aimed to compare the effects of vagotomy and CDDP treatment on nucleic acid and protein contents in the liver and kidney of rats and pigeons.

DNA content, after vagotomy and CDDP treatment decreased in the liver of rat and pigeon while the same remained unchanged in the kidneys of vagotomised animals. After vagotomy, the RNA content decreased in the liver of both the animals while it remained unchanged in their kidneys. RNA content, after cisplatin treatment, decreased in the liver and kidney of the pigeon while in the rat it remained unaltered in these organs. Cisplatin reduced the protein content in the kidneys of the rat and pigeon while no such changes were observed in vagotomised animals.

The reduced level of nucleic acids contents in the liver of CDDP treated and VgX animals could be due to the insufficiency of insulin resulted by the reduced neural stimulation. The reduction in RNA and DNA in the kidney may be also due the direct cytotoxic effects of CDDP on this organ. Altered insulin level and impaired glucose metabolism could be the causes of decreased protein content in the kidneys of both animals after CDDP treatment. Study concludes that the nucleic acid metabolism is greatly influenced by parasympathetic nerves and CDDP can inhibit the same through its cytotoxic action.

Chapter IV

Action of autonomic nerve fibres are under the control of hypothalamus where glucose level is monitored. Autonomic nerve fibres innervate liver and kidney and are credited with the power of controlling glucose uptake and output by these organs. Treatments with some drugs such as Cisplatin (CDDP) cause dysfunction of autonomic fibres and impairment of glucose homeostasis as in the case of bilateral vagotomy. A comparative study of the effects of CDDP and vagotomy by liver and kidney is manifested in CDDP treated and vagotomised rat and pigeon. As the mechanism of action of CDDP involves changes in intracellular Ca^{2+} or its redistribution, the effect of exogenous calcium on glucose metabolism was also determined in CDDP and VgX animals.

Experiment showed that both CDDP treatment and vagotomy could impair the glucose homeostasis in both the animals. A glucose load to CDDP treated animals produced a prolonged hyperglycaemic level indicating the dysfunction of vagal cholinergic fibres. Increased sympathetic tone and excess release of corticosterone could be the causes of hyperglycaemia in vagotomised animals. Similarly, CDDP treatment may be causing selective cholinergic neuropathy because of which glucose uptake by liver and insulin release by pancreas were severely affected. Calcium chloride infusion protected the tissues of treated animals from CDDP toxicity. Even in VgX animals calcium infusion evoked partial recovery from the adverse effects of vagotomy on glucose tolerance.

It is concluded that both CDDP treatment and vagotomy could affect the glucose tolerance level adversely and these effects could be reversed to some extent if the animals are given exogenous calcium.

Chapter V

The divalent cation Ca^{2+} has a multitude of functions in all living systems. The level of intracellular Ca^{2+} is critical for activation and inactivation of several enzymes and hormones. Evidence exist for the involvement of cholinergic system in membrane calcium permeability. Calcium influx and efflux in cells greatly affects cell functions and calcium

channel blockers elevate the cytoxicity of the antitumor drug through blockade of these mechanisms. The antitumor drug cisplatin is believed to evoke its cytotoxic effects on the kidney through alterations in cellular calcium pool. This investigation focused on the protective effects, if any, of exogenous administration of calcium chloride, on CDDP treated and vagotomised animals. The activity of the enzyme acetylcholineesterase (AChE) and nucleic acid contents were estimated to correlate the effects of calcium loading.

The results have shown that calcium supplementation to CDDP treated and vagotomised rats reversed the decreasing trends of AChE level and nucleic acid contents to normalcy. On the contrary, in pigeon calcium loading could not elicit any beneficial effects either in AChE level or in nucleic acid contents. Thus the present study has shown that calcium supplementation has some protective role in CDDP induced cytotoxicity and in adverse effects of vagotomy in the liver and kidney of mammals but not in birds.

Chapter VI

The antitumour drug carboplatin (CBDCA) is less toxic than cisplatin (CDDP), but its anti-metastatic actions are similar to that of CDDP. This chapter deals with the effect CBDCA treatment on glucose metabolism, AChE, protein and nucleic acid contents in the liver and kidney of rat and pigeon.

Glucose tolerance curve of CBDCA treated rat and pigeons were similar to that of control animals. CBDCA treatment caused a decrease in AChE level in the kidney of rats and the liver of pigeons. This reduction in AChE could be considered as an index of reduced parasympathetic stimulation due to the treatment, since cholinergic parasympathetic stimulation is found both in liver and kidney. The DNA content decreased in the kidney of both animals after the treatment indicating that the drug is inducing some cellular toxicity in the kidney but at a lesser level in comparison to that of pigeon while it remained unchanged in rat liver after the treatment reveals that an altogether different pattern of toxicity of the drug is resulted in birds and mammals. The findings suggest that CBDCA, by and large, is a promising drug with respect to the decreased toxicity in rats and it can be successfully used as an alternative to CDDP in circumstance where neural and renal toxicities are of dose limiting considerations.

Chapter VII

The carbohydrate metabolism in metabolically active organs like liver and kidney are influenced by autonomic nerve fibres. The autonomic centres in the hypothalamus control the secretion of pancreatic hormones through the parasympathetic and sympathetic fibres. Chemical sympathectomy using 6-Hydroxydopamine (6-OHDA), a catecholamine neurotoxin, is a novel method to study the

adrenergic functions in animals. In the present study the rats and pigeons were chemically sympathectomised with 6-OHDA. Glucose Tolerence Test was carried out to study the glucose homeostasis. Protein and nucleic acid contents were also determined to correlate the trophic functions of sympathetic fibres.

Chemical sympathectomy evoked a high glucose levels in pigeons while in rats a decrease was noted. Glucose loading produced an increase in the level of glucose which started declining by 30 minutes. However, in pigeons, peak hyperglycemia was noted by 30 minutes which declined thereafter, but remained at a higher level compared to that in rats. Acetylcholineesterase (AChE) activity was reduced in the liver of rats and in the kidney of pigeons while rat kidney and pigeon liver did not show any significant alterations. 6-OHDA treatment increased the protein, DNA and RNA content in rats. In pigeons these parameters were decreased. As a result of sympathetic denervation, the vagal tone increased in rats which might have released more of insulin to the circulation and resulted in hypoglycemia. The increased protein, DNA and RNA levels could be due to the insulin action. Persistance of hyperglycemia which was noticed in pigeons after 6-OHDA treatment may be related to the increased glucocorticoid and growth hormone levels which also in excess supress protein and nucleic acid levels.