6. SUMMARY

Partial pancreatectomised (60%) rats were used as the model for studying the pancreatic regeneration in rats.
Suspension cultures of pancreatic islets were used as the in vitro model system to study the insulin secretion and DNA synthesis.
[^3H]Thymidine incorporation into the pancreatic islets was used as the index to study the DNA synthesis after partial pancreatectomy and in cultured pancreatic islets.
The DNA synthesis was peaked at 72 hrs and started decreasing at 7 days after partial pancreatectomy.
The circulating insulin and T₃ levels were significantly elevated during active DNA synthesis in the pancreatic islets.
The EPI and NE contents were significantly decreased in the cerebral cortex, brain stem and hypothalamus during active pancreatic islet regeneration. EPI and NE contents in the pancreatic islets also decreased at the peak of DNA synthesis.
Circulating NE and EPI levels were decreased at the time of active regeneration in pancreatic islets
The brain adrenergic activity is reduced. The α₁-adrenergic receptors are decreased significantly in all brain regions. The α₂-adrenergic receptors were down regulated in the cerebral cortex and brain stem during pancreatic regeneration. The hypothalamic α₂-adrenergic receptor affinity was increased at the period of peak DNA synthesis. In all brain regions, the β-adrenergic receptors were up regulated at 72 hrs after partial pancreatectomy.
RT-PCR studies confirmed the decreased α₂A-adrenergic receptors in the cerebral cortex and brain stem and the increased β-adrenergic receptors in the cerebral cortex, brain stem and hypothalamus.
The decreased α₂-adrenergic and increased β-adrenergic receptor function will lead to an increase in the insulin secretion and DNA synthesis in the pancreatic islets.
In the pancreatic islets, the α₂-adrenergic receptors were down regulated and β-adrenergic receptors were up regulated which lead to an increase in the insulin secretion as well as DNA synthesis.
In vitro studies of pancreatic islets with EPI showed that it regulates the insulin secretion in a concentration-dependent manner. Higher concentrations of EPI inhibited the glucose-mediated insulin secretion and lower concentrations stimulated the glucose-mediated insulin secretion from the islets. Insulin secretion studies in the presence of different adrenergic antagonists revealed that $\alpha_1$-adrenergic receptor can act both as stimulatory and inhibitory depending upon the EPI concentration. $\alpha_2$-adrenergic receptors are purely inhibitory and $\beta$-adrenergic receptors are stimulatory to insulin secretion in both 1 hr and 24 hrs islet cell cultures.

In vitro incubation of pancreatic islets with $[^3]$H]EPI showed that EPI uptake by the islets is time-dependent irrespective of the glucose concentration. It is also found out that EPI can bind to a specific nuclear protein. By using ligand blotting method the protein was identified as a 70-kDa protein. The amino acid analysis showed that this protein is rich in Hisitdine. The homology search in SWISS-PROT revealed that it has a homology to a mouse zinc-finger protein, which may act as a transcriptional activator. During regeneration the 70-kDa EPI-binding nuclear protein was up regulated and in insulin-deficiency it was down regulated. From our data it is clear that the 70-kDa EPI-binding nuclear protein is acting as an enhancer of insulin synthesis thereby promoting the islet cell regeneration. The in vitro DNA synthesis studies showed that EPI at low concentrations could enhance the EGF-induced DNA synthesis and at high concentrations inhibit the EGF-induced DNA synthesis in the pancreatic islets. $\alpha_1$-adrenergic receptors act both as stimulatory and inhibitory according to the EPI concentration. $\alpha_2$-adrenergic receptors inhibited the DNA synthesis while the $\beta$-adrenergic receptors stimulated the DNA synthesis in the islet cell cultures. Thus from our results it is evident that $\alpha$- and $\beta$-adrenergic receptors regulate the insulin secretion and islet cell proliferation. The changes in the brain adrenergic receptors were similar to the islet receptor changes. This suggests that the brain adrenergic receptor gene expression alters the pancreatic adrenergic receptor function. The balance between $\alpha$- and $\beta$-adrenergic receptor functional correlation controls the insulin secretion and pancreatic $\beta$-cell proliferation in diabetes.