7. CONCLUSION

The adrenergic system regulates the insulin secretion and islet cell proliferation. The regulation is suggested to be mediated through the central nervous system directly and/or indirectly affecting the peripheral adrenergic system at the pancreatic level. The DNA synthesis was peaked at 72 hrs and started decreasing at 7 days after partial pancreatectomy as observed by the \[^{3}H\]thymidine incorporation studies. There was a significant elevation in the circulating insulin and T\textsubscript{3} levels during active DNA synthesis in the pancreatic islets. The EPI and NE contents were significantly decreased in the cerebral cortex, brain stem and hypothalamus as well as in the pancreatic islets during active pancreatic islet regeneration. Circulating NE and EPI levels were found to decrease at the time of active regeneration of pancreatic islets. The decreased brain EPI content lead to a decreased receptor function in the brain as well as in the pancreatic islets. The \(\alpha\)- and \(\alpha\text{-}2\)-adrenergic receptors were down regulated in the brain regions and pancreatic islets during pancreatic regeneration. The \(\beta\)-adrenergic receptors were up regulated in the brain regions and islets at 72 hrs after partial pancreatectomy. RT-PCR studies confirmed the receptor data. The decreased \(\alpha\text{-}2\)-adrenergic and increased \(\beta\)-adrenergic receptor function will lead to an increase in the insulin secretion and DNA synthesis in the pancreatic islets.

\textit{In vitro} studies of pancreatic islets showed that EPI 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. The \(\alpha\text{-}1\)-adrenergic receptors act both stimulatory and inhibitory depending upon the EPI concentration. \(\alpha\text{-}2\)-adrenergic receptors are inhibitory and \(\beta\)-adrenergic receptors are stimulatory to insulin secretion in both 1 hr and 24 hrs islet cell cultures. Peripherally the EPI uptake by the islets is time-dependent irrespective of the glucose concentration. EPI is able to bind with a novel 70-kDa nuclear protein within the islets. During regeneration, this protein was found to be up regulated and in diabetic condition it was down regulated. It is clear from our results that the 70-kDa EPI-binding nuclear protein is acting as an enhancer of insulin synthesis thereby promoting the islet cell regeneration. The \textit{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 and \(\beta\)-adrenergic receptors stimulated the DNA synthesis in the islet cell cultures.

Thus we conclude that EPI can regulate the pancreatic islet cell proliferation by controlling the insulin synthesis and secretion. The brain adrenergic receptor gene expression and functional correlation regulate the pancreatic adrenergic receptors. The functional balance of \(\alpha\)- and \(\beta\)-adrenergic receptors controls the insulin secretion and pancreatic \(\beta\)-cell proliferation, which will have immense clinical significance in the treatment of Diabetes mellitus.