5. SUMMARY

Glucose homeostasis is a tightly regulated process by the two endocrine pancreatic hormones; insulin and glucagon. SST, the other endocrine pancreatic hormone inhibits both insulin and glucagon secretion via five known receptors (SSTR1-SSTR5). In rodents, SSTR2 inhibits glucagon secretion, whereas SSTR5 inhibits insulin secretion. Human pancreatic α and β cells express SSTR1-3 and SSTR5 but the role of individual SSTRs in regulation of insulin and glucagon secretion is not well understood. In the present study, isolated human pancreatic islets were used to analyze the role of SSTRs in regulation of human insulin and glucagon secretion. The present study demonstrates that in a system of isolated human pancreatic islets SST regulates both insulin and glucagon secretion mainly via SSTR2 receptor. In addition, data suggests that SSTR5 is an additional receptor subtype which is involved in the regulation of insulin secretion in humans although less potent inhibitor of glucagon secretion. Apart from SSTR2, SSTR1 potently inhibited glucagon secretion than compared to insulin secretion in humans.

Glucagon significantly contributes to hyperglycemia by stimulating hepatic glucose output in T2DM. SST inhibits glucagon secretion mainly via SSTR2. The present study characterizes the role of SSTR2 in the regulation of glucose homeostasis by using somatostatin receptor subtype 2 deficient $SSTR2^{-/-}$ mice with high fat diet induced obesity. Deletion of SSTR2 gene in mice with high fat diet leads to the symptoms which are the hallmarks of T2DM (e.g. obesity, insulin resistance, increase in postprandial glucagon secretion, hyperglycemia, impairment of glucose and SST-dependent inhibition of glucagon secretion etc). In brief, $SSTR2^{-/-}$ mice had increased postprandial levels of glucose, glucagon and fasting nonesterified fatty acids than compared to wild type mice. In addition, the inhibition of glucagon secretion was impaired by glucose and SST from the islets isolated from $SSTR2^{-/-}$ mice. Increase levels of glucose were observed in $SSTR2^{-/-}$ mice by the administration of exogenous SST. Furthermore, insulin less potently inhibited the blood glucose levels in $SSTR2^{-/-}$ mice than compared to wild type mice. Interestingly $SSTR2^{-/-}$ mice showed reduced levels of postprandial hepatic glycogen and lipid content. Simultaneously, expression and activity of enzymes regulating glycogen breakdown were increased whereas enzymes regulating glycogen

synthesis were decreased. In addition enzymes regulating glycogenolysis and lipolysis were increased in these $SSTR2^{-/-}$ mice.

All these data clearly suggest that SSTR2 has a very important role in the regulation of glucagon secretion. Increased levels of glucagon secretion in these mice was due to increased hepatic glycogen breakdown, less lipid accumulation and also impaired regulation by glucose.

By using permanent cell models of insulin- and glucagon secreting cells, data suggest that SSTR2 selective agonist potently inhibited insulin and glucagon secretion. Secretion of both insulin and glucagon is regulated by Ca^{2+} channels. Data of the present study shows that SNX-482, a highly selective R-type Ca^{2+} channel blocker prevents the inhibition of insulin secretion from INS-1-cells mainly via SSTR2.

In addition, at the intracellular signalling levels for insulin secretion, study suggests that SSTR2 inhibited the expression of forkhead transcription factors Foxo1 and Akt as well as their phosphorylation. These factors plays an important role in insulin secretion. Further work is required to identify the role of SSTR2 on nuclear translocation of Pdx1 and Akt.

Taken together, the present study clearly demonstrates the important role of SSTR2 in the regulation of glucose homeostasis. Deletion of SSTR2 gene and chronic feeding with high fat diet leads to obesity, insulin resistance and hyperglycemia. Our study sheds more light that SSTR2 is a strong regulator of glucagon secretion in both humans (*in vitro*) and in rodents (*in vivo* and *in vitro*). Further studies are required in humans by using highly selective SST2 selective agonist which can selectively inhibit glucagon secretion to unveil the crucial role of SSTR2 for its successful clinical use to treat T2DM.