Reducing amyloid-associated beta-cell death during islet culture in diabetic conditions by targeting GLP-1 receptor

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Aim of the study

To study the effect of treatment with exenatide (Byetta), a GLP-1 receptor agonist on amyloid-induced beta-cell death in cultured human islets.

Methods and Materials

- Diabetes mellitus (DM) belongs to a group of metabolic disorders characterized by chronic hyperglycemia, and is broadly categorized into two categories: Type 1 diabetes (T1D) and Type 2 diabetes (T2D).
- Progressive insulin resistance and islet beta-cell failure are thought to play major roles in pathogenesis of T2D.
- Islet amyloid polypeptide (IAPP, amylin) is a normal beta-cell hormone that is co-secreted with insulin by pancreatic beta cells.
- IAPP has amyloidogenic sequence and forms amyloid plaques in the islets of Langerhans in T2D patients that are toxic to islet beta cells and contribute to progressive beta-cell dysfunction and death in T2D.
- Exenatide (Byetta) is a glucagon-like peptide-1 (GLP-1) receptor agonist that mimics incretin action to enhance beta-cell function.

Results

- The majority of islets formed amyloid during 7 days culture in elevated glucose.
- Treatment with exenatide reduced amyloid formation in cultured islets.
- The proportion of TUNEL-positive beta cells in isolated islets (day 0) was low suggesting good quality of isolated islets. More than half of the islets in Day 0 had no TUNEL-positive beta-cell (Figure 2).
- Islets treated with exenatide for 7 days had improved beta-cell survival than non-treated 7-day cultured islets. The maximum proportion of TUNEL-positive beta-cells in non-treated and treated 7-day cultured islets was 5.19% and 5.71%, respectively (Figure 3).
- The mean percentage of TUNEL-positive beta cells for day 0, day 7 with exenatide and day 7 non-treated were 1.32% ± 0.37%, 1.56% ± 0.42% and 1.81% ± 0.50%, respectively (Figure 4).
- The mean percentage of the TUNEL positive to beta cell ratio for Day 7 treated with exenatide was lower than Day 7 non treated. However, this difference was not statistically significant due to small sample size in this pilot study.
- ANOVA single factor statistical test was performed. (p-value = 0.72, p > 0.05). A set of student t-tests were done to confirm statistical significance. (p-values = 0.73, 0.43 and 0.70, p > 0.05).

Conclusion

- Treatment with exenatide reduced amyloid formation in cultured islets.
- The number of TUNEL-positive beta cells were lower in 7-day cultured islet treated with exenatide as compared to non-treated cultured islets. Further studies are in-progress to validate findings of this pilot study with larger sample size.
- Treatment with GLP-1 receptor analogues may provide a new strategy to reduce amyloid-induced beta cell death.