INTRODUCTION:

A recent clinical evidence suggests a potential synergistic effect between first generation insulin sensitizers and GLP1 in the clinic when given as an early treatment (6). Here we have asked whether the combination of GLP1 treatment with an mTOT modulator currently in clinical trials might function to prevent loss of functional beta cells in the ZDSD/PCO rat. We have previously shown MSDC-0602 and GLP1 to synergistically increase glucose tolerance in vivo (4). This mechanism appears to involve alteration in nutrient sensing pathways that favor the differentiated state of the beta cells, at least in vitro (4).

RATIONALE:

The ZDSD/PCO rat is a new rat model of type 2 diabetes that undergoes beta cell dysfunction in response to a high fat diet. There is an apparent synergism between GLP1 and MSDC-0602, a new insulin sensitizing agent designed to act on the mitochondrial target, mTOT. We have previously shown that MSDC-0602 and GLP1 increase insulin secretion by human beta cells in vitro (1). We have also shown that combining mTOT modulators with GLP1 agonists to preserve functional beta cells.

METHODS:

Most ZDSD/PCO rats were maintained on standard chow diet (Purina) until treatment (6 weeks at 21 weeks of age). PDX1 and insulin stained islets were prepared for Ki67 and CD3 positivity as described (1). Sample size was determined based on the anticipated effect size and variability of the parameter. Briefly, in all cases the insulin positive islet cells were counted, Ki67 positivity was assessed, and cells were stained for Ki67, insulin, and Bcl2. An Image Pro Plus system was used with Image J to quantify the number of Ki67 positive cells and the combination with MSDC-0602 increased this further. Interestingly, however, individual cells were either positive for Ki67 or insulin and/or PDX1 but not both, indicating that the individual islet cells were at different stages of proliferation. Both treatments increased the number of Ki67 positive cells and insulin staining, but the largest increase was group 5 where both treatments were combined. Experiments included: (1) A 4 week period of daily subcutaneous injection of vehicle or 1 µg oral dose of vehicle (1% SCMC/0.1% Tween 80) or MSDC-0602 5SCA (Purina) high fat diet and then given either oral vehicle and saline injection (group 2), or MSDC-0602 5SCA (Purina) and saline injection (group 2). Experiments included: (2) A 6 week period of daily subcutaneous injection of vehicle or 1 µg oral dose of vehicle (1% SCMC/0.1% Tween 80) or MSDC-0602 5SCA (Purina) high fat diet and then given either vehicle and exenatide s.q. (group 3), or MSDC-0602 5SCA (Purina) and exenatide s.q. (group 4), or oral MSDC-0602 and exenatide s.q. (group 5).

REFERENCES:


Conclusion:

These results suggest that there could be a therapeutic value to combining mTOT modulators with GLP1 agonists to preserve functional beta cells.

Effect of MSDC-0602 and GLP1 on Pancreatic Islets in ZDSD/PCO Rats

Effect of Glucose and Insulin

Glucose

Insulin (change at 30 min)

Effect on Glucose and Insulin

Oral Glucose Tolerance

Glucose

Insulin (change at 30 min)

Effects on Pancreatic Islets

Insulin Positive Islet Cells

Insulin Positive Islet Cells

Bcl2 staining in an islet and ductal epithelium of 0602-exendin group. Ki67 stain is shown.

PDX-1 staining in an islet of 0602-exendin group.