Preservation of Pancreatic beta cell mass in high fat-fed STZ treated mice by the Dipeptidyl peptidase-4 inhibitors Saxagliptin and Sitagliptin.

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ABSTRACT

Background and aims: Saxagliptin is a potent, selective DPP-4 inhibitor, specifically designed for extended inhibition of the DPP-4 enzyme. DPP-4 inhibition leads to elevated glucagon-like peptide-1 (GLP-1) levels, which are known to promote beta cell mass expansion.

Methods and materials: Groups of male C57BL6J mice (n=12 per group) were placed on high fat diet (60%, D12492, Research Diets) four weeks prior to 50mg/kg streptozotocin (STZ, ip, daily for 3 days). Mice were treated orally with vehicle (water), sitagliptin (10mg/kg/day, po) or saxagliptin (10mg/kg/day, po) and subjected to procedures as outlined below. An oral glucose tolerance test (OGTT) was undertaken following an overnight fast using a glucose dose of 2g/kg.

RESULTS

Compounds exposure.
Free plasma concentration of saxagliptin and sitagliptin measured 24 hours prior to the final dose were 10.1 and 40.2 mM, respectively.

Glycaemic control.

Small improvements were seen in glycaemic control in the groups treated with saxagliptin when given after STZ and with sitagliptin given prior to STZ. We did not observe improvements in systemic fasting insulin concentration following treatment. However, small improvements were seen in glycaemic control in the groups treated with saxagliptin when given after STZ and with sitagliptin given prior to STZ.

SUMMARY/CONCLUSIONS

Overall both saxagliptin and sitagliptin showed similar improvements in glycaemic control and beta cell mass preservation in the high fat-fed, STZ model, and demonstrated beta cell sparing effects. We therefore demonstrated that saxagliptin along with improving glycaemic control had a positive impact on beta cell preservation in a rodent model of type 2 diabetes.

This study was supported by Bristol-Myers Squibb and AstraZeneca.

INTRODUCTION

In light of data suggesting that GLP-1 may have a role in islet neogenesis, differentiation, and the concomitant regulation of β-cell mass and preservation1,2, the effect of saxagliptin and sitagliptin was assessed in the present study by initiating dosing both before and immediately after induction of diabetes in the high fat fed low dose streptozotocin mouse model of Type 2 diabetes.

OBJECTIVES

1. The present study assessed the efficacy of saxagliptin and sitagliptin in controlling the hyperglycaemia and β-cell mass effects induced by the administration of low doses of the β-cell toxin, streptozotocin (STZ), to mice with moderate insulin resistance due to exposure to a diet high in fat.

2. In vivo
Groups of male C57BL6J mice (n=12 per group) were placed on high fat diet (60%, D12492, Research Diets) four weeks prior to 50mg/kg streptozotocin (STZ, ip, daily for 3 days). Mice were treated orally with vehicle (water), sitagliptin (10mg/kg/day, po) or saxagliptin (10mg/kg/day, po) and subjected to procedures as outlined above. An oral glucose tolerance test (OGTT) was undertaken following an overnight fast using a glucose dose of 2g/kg.

Figure 1. Experimental protocol

Figure 2. Method for islet evaluation.

Table 1. Glycemic control and β-cell mass following compound treatment.

<table>
<thead>
<tr>
<th>Compound / vehicle treatment</th>
<th>Baseline</th>
<th>STZ</th>
<th>Day 31 or 32</th>
</tr>
</thead>
<tbody>
<tr>
<td>STZ</td>
<td>0.4</td>
<td>0.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Saxagliptin (Saxa)</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
</tr>
<tr>
<td>Sitagliptin (Sita)</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Figure 3. Effect of saxagliptin and sitagliptin upon glucose tolerance on day 31 or 32.

Figure 4. Effect of saxagliptin and sitagliptin on long term glycaemic control.

Figure 5. Representative islet images for each treatment.

Figure 6. The impact of Sitagliptin and Saxagliptin treatment on pancreatic islet morphology and beta cell mass at day 46.

Beta cell mass

Both treatments were able to induce small and statistically significant improvements in beta cell endpoints, though interestingly only saxagliptin demonstrated benefits, compared to vehicle, when administered both before and after the initiation of hyperglycaemia.