Recent evidence suggests that endoplasmic reticulum (ER) stress can induce impairments in both insulin secretion and insulin action. The aim of the present study was to examine the effects of ER stress on glucose production in vivo. Fasted rats were anesthetized and catheters were placed in the carotid artery, jugular vein, and jejunal vein. A pancreatic clamp was performed in which somatostatin was infused to inhibit pancreatic insulin and glucagon secretion. These hormones were then replaced at basal levels. To examine the effects of ER stress on glucose production and insulin secretion, 4.8-hour fasted rats were used. Tunicamycin (TUN) induces ER stress through inhibition of protein glycosylation. Arterial insulin, glucagon, corticosterone, and free fatty acid concentrations were constant throughout experiments and were not different between groups. Glucose concentration and production increased significantly in TUN (7.25±0.1 vs. CON [0.2±0.3]). The increase in glucose production was due to an increase in glucose production, decrease in glucagon levels, and insulin levels were measured using standard techniques.

**Figure 1. ER Stress Response**

**Figure 2. Experimental Design**

**Figure 3. Plasma Insulin and Glucagon Levels Prior to and During Pancreatic Clamps**

**Figure 4. Plasma Corticosterone and Free Fatty Acid Levels Prior to and During Pancreatic Clamp**

**Figure 5. Plasma Glucose Levels Prior to and During Pancreatic Clamp**

**Figure 6. Glucose Production (Ra), Glucose Uptake (Rd), and Glucose Clearance**

**Figure 7. Glucose-6-Phosphatase Activity Following Pancreatic Clamps**

**Figure 8. Terminal Liver Glyceroneogenesis**

**Summary:**

Increased glucose production in response to Tunicamycin could result from:
1. Increased expression of genes/proteins involved in glycolysis, gluconeogenesis, and/or glucose release.
2. Activation of glycolysis, gluconeogenesis, and/or glucose release (via分析 of phosphophorylpyruvate carboxykinase (PEPCK, a rate-limiting enzyme in gluconeogenesis) and glucose-6-phosphatase (GPase), responsible for glucose release from hepatocyte) demonstrated that these two genes were not increased over the time course of the experiment.

**Table 1. Summary of Results**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glucose Production (mg/dl)</th>
<th>Glucagon Levels (pg/ml)</th>
<th>Insulin Levels (μU/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CON</td>
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<td>50</td>
<td>10</td>
</tr>
<tr>
<td>TUN</td>
<td>200</td>
<td>25</td>
<td>5</td>
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</table>

**References:**