Westernized Diet-induced Insulin Resistance in Mice is Associated with Focal Duodenal Hyperplasia

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Introduction

- A Westernized Diet high fat and sucrose induce an insulin resistant state and is associated with obesity and type 2 diabetes (T2D).
- Duodenal exclusion surgery in obese T2D patients implicates the duodenum as a key GI region involved in propagating systemic insulin resistance.

Objective

- To identify adaptive changes of pathophysiologic relevance, detailed analyses of the GI tract were undertaken following exposure of mice to Westernized Diet.

Methods

- C57BI/6J mice (male, 6 weeks of age) were exposed to either a lean (Altromin chow) or Westernized Diet (WD; 60% fat/20% sugar; D14623 DIET) for 7 or 13 weeks.
- Systemic metabolic measures were conducted over time including plasma glucose, insulin, body weight and fat content.
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- Histological analysis was conducted along the length of the gastrointestinal tract (duodenum, jejunum, ileum, colon) with mucosal surface staining.
- Transcriptomic analysis of gut and liver tissue samples was also conducted.

Results

Metabolic Measures

- Compared to mice fed a lean diet, mice fed a Westernized Diet had significantly higher plasma glucose, insulin and total cholesterol levels (Table 1).
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Table 1. Metabolic Changes in Mice Fed a Lean vs. Westernized Diet (WD)

<table>
<thead>
<tr>
<th>Measure, mean (SEM)</th>
<th>Lean 13 weeks</th>
<th>WD 13 weeks</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, g</td>
<td>20.6 (0.2)</td>
<td>27.8 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting blood glucose, mg/dl</td>
<td>7.0 (0.5)</td>
<td>6.8 (0.5)</td>
<td>0.19 (0.05)</td>
</tr>
<tr>
<td>Fasting plasma insulin, mg/dl</td>
<td>512 (50)</td>
<td>513 (50)</td>
<td>0.19 (0.05)</td>
</tr>
<tr>
<td>Total cholesterol** (mg/dl)</td>
<td>14.6 (0.5)</td>
<td>4.6 (0.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>2.0 (1.0)</td>
<td>5.9 (0.5)</td>
<td>0.01 (0.1)</td>
</tr>
</tbody>
</table>

- The hyperplastic duodenum seen in Westernized-Diet fed mice was also characterized by increased contractile area staining of enteroendocrine (EE) cells (Figure 1). Increased staining was also observed in the jejunum but not in ileum or colon.

Liver and Duodenal Tissue Findings

- Compared to lean fed controls, mean duodenal weight and liver weight was significantly increased at 13 weeks in mice fed a Westernized Diet.
- Unlike other intestinal segments, focal hyperplasia was observed in the duodenum with increased weight and surface area (~40%) (Table 2).
- Duodenal mucosal volume was also significantly increased at 13 weeks (Table 2); however, submucosal + muscular volume was unchanged (data not shown).

Table 2. Increased Duodenal Weight, Volume and Surface Area Observed in Mice Fed a Lean vs. Westernized Diet (WD)

<table>
<thead>
<tr>
<th>Measure, mean (SEM)</th>
<th>Lean 13 weeks</th>
<th>WD 13 weeks</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver weight** (g)</td>
<td>0.95 (0.52)</td>
<td>1.4 (0.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duodenal weight**, mg</td>
<td>152 (4)</td>
<td>172 (3.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duodenal mucosal volume** (cm^3)</td>
<td>150 (4)</td>
<td>190 (3.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duodenal surface area** (cm^2)</td>
<td>64.6 (0.4)</td>
<td>61.4 (0.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Compared to mice fed a lean diet, mice fed a Westernized Diet had a greater number of differentially expressed genes (compared to Lean Diet) at 13 weeks vs 7 weeks (Figure 2).
- A pathway perturbation analysis was conducted based on the number of differentially expressed genes in a given pathway, divided by the total number of genes in the pathway. In this analysis, certain metabolic pathways were differentially altered across gut regions with duodenum signature differentiated from other gut regions and the liver.

Transcriptomic Data

- In a principal component analysis of the 580 most variable genes, distinct differences were observed between mice on lean versus Westernized Diet (Figure 3).
- In liver and small intestine tissue (duodenum, jejunum, ileum), a distinct division was observed between samples from mice fed a Westernized vs Lean Diet.
- Overall, mice fed a Westernized Diet had a greater number of differentially expressed genes (compared to Lean Diet) at 13 weeks vs 7 weeks (Figure 3).
- A pathway perturbation analysis was conducted based on the number of differentially expressed genes in a given pathway, divided by the total number of genes in the pathway. In this analysis, certain metabolic pathways were differentially altered across gut regions with duodenum signature differentiated from other gut regions and the liver.

Figure 1. Number of Chromogranin-A Cells per Region of the Gut

Figure 2. Principal Component Analysis (PCA)

Figure 3. Duodenal Transcriptomic Analysis: Shared Regulated Genes

Figure 4. Gut Hormone Transcript Data

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Gut Hormone Transcript Data

- Significant perturbations in expression of gut hormones were seen across segments of the gut (generally increased) in mice fed a Westernized Diet (Figure 4).
- Expression changes appeared to manifest regionality with some specific hormones being perturbed more so in duodenum and proximal gut.

Conclusion

- Exposure to WD induces adaptive responses in duodenal mucosa, EE cell population, and the transcriptome.
- These findings suggest that the duodenum adapts when exposed to Westernized diet offering a pathophysiological linkage to the development of systemic insulin resistance. Conversely, this may also offer explanation for the apparent insulin-sensitizing effect observed with duodenal exclusion surgery.

References


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