The Profile of Hepatic Gene Expression of Glucose Metabolism in Mice on High Fat Diet

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ABSTRACT

Obesity is a growing problem worldwide, and recent data indicated that 20% of the populations would be obese. Obesity arises as a multifactorial disease caused by inherited traits that interact with lifestyle factors such as diet and physical activity. The liver plays an essential role in the glucose regulation and metabolism of glucose, lipid and protein metabolism. The process of glucose metabolism is controlled by a range of molecular mechanisms and genes which affect the metabolism of the liver during intake of high fat diet (HFD). The objective of this research is to investigate the profile of hepatic gene expression of glucose metabolism in mice treated with leptin (5 mg/kg BW ip injection). Ten wild type CD1 mice fed on HFD was used for this study, where groups are control (vehicle - leptin) and test group (vehicle + leptin). Body weight (BW) was measured, and blood chemistry, insulin and leptin were measured at the end of the experiments. Total RNA was isolated from the liver tissue, and RT-PCR profiler array technology was used to evaluate the mRNA expression of 84 essential genes of hepatic glucose metabolism. The data of the BW and blood chemistry are not significantly different between the two groups. Leptin treatment enhanced the metabolic pathways and the candidate genes of the different metabolic pathways; glycolysis, glycogenolysis such as G6Pase, and genes which affect the metabolism of the liver during intake of HFD to induce obesity. The study aims is to investigate the hepatic gene expression of glucose metabolism in mice on HFD treated with leptin and the effect of leptin on glucose metabolism in mice on HFD treated with leptin.

RESULTS

Table 1: The age, body weight, and biochemical parameters of CD1 mice treated with Vehicles- saline and Vehicle+leptin

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 (Vehicle)</th>
<th>Group 2 (V+lep)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (weeks)</td>
<td>10.0</td>
<td>10.0</td>
<td>0.542</td>
</tr>
<tr>
<td>Body weight (mg)</td>
<td>33.43 ± 1.21</td>
<td>34.31 ± 2.22</td>
<td>0.754</td>
</tr>
<tr>
<td>Insulin (ng/ml)</td>
<td>3.16 ± 1.31</td>
<td>3.93 ± 3.79</td>
<td>0.437</td>
</tr>
<tr>
<td>Leptin (ng/ml)</td>
<td>1.32 ± 0.12</td>
<td>20.28 ± 2.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>157.44 ± 6.07</td>
<td>154.67 ± 4.83</td>
<td>0.925</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>194.5 ± 8.31</td>
<td>182.9 ± 5.48</td>
<td>0.266</td>
</tr>
<tr>
<td>Total Cholesterol (mg/dl)</td>
<td>192.9 ± 20.51</td>
<td>154.5 ± 3.48</td>
<td>0.076</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>24.33 ± 4.31</td>
<td>21.42 ± 2.77</td>
<td>0.586</td>
</tr>
</tbody>
</table>

CONCLUSION

The data of the BW and blood chemistry are not significantly different between the two groups. Treatment affects the regulation of multiple genes that are involved in multiple metabolic pathways. In glycogen synthesis pathway leptin up-regulates Gys1and Gys2 genes which enhances the process. However, it enhanced the expression of Pygm and Pnmd genes which are involved in glycolysis degradation. In the process of glycolysis, it does up-regulate the expression of Enos2 and Erno genes, and down-regulated the expression of Aldob gene, both effects enhanced the metabolism. In the TCA cycle the expression of Mdh2b and Aldob genes has increased, but the expression of Mbllhas decreased by the action of leptin. Pfp2 and G6pc3 which are involved in the process of gluconeogenesis their gene expression has increased, but Ppl1 and Pkl1 decreased.

REFERENCES


INTRODUCTION

• Obesity arises as a multifactorial disease caused by inherited traits that interact with lifestyle factors such as diet and physical activity.
• Obesity in Qatar is alarming and it is the leading country in GCC countries with obesity prevalence reached up to 41.4% (39.5% males, 43.2% females) (WHO, 2017).
• In experimental animal models, diet-induced obesity (DIO) in mice is similar to human obesity caused by lifestyle factors. In the liver, hepatic glucose production is upregulated with insulin resistance conditions and contributes to the hyperglycemic effects and several critical molecules involved in this phenotype(Kim and Ahn 2004).
• The metabolism is controlled by a range of molecular mechanisms and genes which affect the metabolism of the liver during intake of high fat diet (HFD) to induce DIO.
• Despite the extensive efforts done in previous studies, the genes identified thus far do not account for all of the variability in glucose homeostasis during HFD and DIO. Further insight may be obtained by conducting gene microarray studies during an early time of diet-induced obesity (DIO) and treatment by leptin as an anti-obesity hormone.
• The study aims to investigate the hepatic gene expression of glucose metabolism in mice on HFD and the effect of leptin treatment on anti-obesity tool to counteract such early changes in the metabolism of glucose.

METHODOLOGY

• lab mice fed on HFD is used for this study, where groups are assigned based on the leptin treatment with and without treatment.
• Food intake and body weight of the mice is measured at 1, 3, 6, 12 and 24 hr. post leptin injections. At the end of the treatment, liver tissues was collected quickly and snap frozen in liquid nitrogen.
• Total RNA was extracted from the liver tissues by the miRNeasy (Qiagen), and Qubit checked its quantity and quality by using by EPOCH2 microplate reader spectrophotometer to measure the absorbance at 260 and 280 nm.
• cDNA was generated from total RNA using High Capacity RNA-to-DNA Kit. The procedure was performed according to the manufacturer instructions and the final sample was stored at -20°C until use.
• The expression level of genes involved in glucose metabolism from the liver, were analyzed by the RT-PCR profiler array using cyber green technology. Pathway analysis and gene ontology was use for analysis.

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