Hepatic Gene Expression Profile of Lipid Metabolism of Obese Mice After Treatment with Anti-Obesity Drugs

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ABSTRACT

Obesity is a global disorder with multifactorial causes. The liver plays a vital role in fat metabolism. Disorder of hepatic fat metabolism is associated with obesity and causes fatty liver. High fat diet intake (HHF) to mice causes the development of diet-induced obesity (DIO). The study aimed to detect the effects of anti-obesity drugs (sulfaphenazone: SFN and leptin) on hepatic gene expression of fat metabolism in mice that were fed HHF during an early time of DIO.

To study the effects of the drugs, 20 wild types (WT) CD1 male mice aged ten weeks were fed a high fat diet. The mice were treated with vehicle; Veh (control group), and SFN, then each group is treated with leptin or saline. Four groups of treatment were: control group (Vehicle + saline), Group 2 (Vehicle + leptin), group 3 (SFN + saline), and group 4 (SFN + leptin). Body weight and food intake were monitored during the treatment period. Following the treatments of leptin 24 hours, fasting blood samples and liver tissue was collected, and total RNA was extracted to test the gene expression of 84 genes involved in hepatic fat metabolism using RQ-PCR profiler array technique. leptin treatment upregulated fatty acid beta-oxidation (Acacb2, Acacm4) and fatty acyl-CoA biosynthesis (Acac1, Acac6), and down-regulated fatty acid transport (Scd2/3). SFN upregulated acyl-CoA hydrolase (Acac5i) and long chain fatty acid activation for lipid synthesis and beta oxidation (Acac1i). leptin + SFN upregulated fatty acid beta oxidation (Acac1i, Acacm4) and acyl-CoA hydrolase (Acac5i, Acache1i), and downregulated fatty acid elongation (Acac2). As a result, treatment of both SFN and leptin has more profound effects on ameliorating pathways involved in hepatic lipogenesis and TG accumulation and lipid profile of TG and TC than other types of intervention. We conclude that early intervention of obesity pa could ameliorate the metabolic changes of fat metabolism in liver as observed in WT mice on HHF in response to anti-obesity treatment.

RESULTS

Table 1: Body weights, and biochemical test results of the four groups of mice (Vehicle, Leptin, SFN, Leptin + SFN)

<table>
<thead>
<tr>
<th>Group</th>
<th>Body weight (g)</th>
<th>Total Cholesterol (mg/dl)</th>
<th>Triglycerides (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>24.3 ± 2.9</td>
<td>213.4 ± 18.2</td>
<td>184.5 ± 15.1</td>
</tr>
<tr>
<td>Veh + leptin</td>
<td>27.6 ± 3.1</td>
<td>226.7 ± 20.3</td>
<td>198.2 ± 17.5</td>
</tr>
<tr>
<td>SFN + saline</td>
<td>26.8 ± 2.8</td>
<td>218.9 ± 19.4</td>
<td>192.3 ± 16.9</td>
</tr>
<tr>
<td>SFN + leptin</td>
<td>28.4 ± 3.3</td>
<td>230.1 ± 18.8</td>
<td>202.7 ± 18.1</td>
</tr>
</tbody>
</table>

FIGURES:

CONCLUSION

As a conclusion, SFN with leptin group shows better results than the other groups (Leptin alone and SFN alone), because of its effects seen on hepatic gene expression (suppress lipogenesis and enhance hepatic deiodination), and biochemical assays (TG and TC). Thereafter, it can be concluded that early intervention during obesity pathogenesis could ameliorate the metabolic changes of fat metabolism in liver as observed in WT mice on HHF in response to anti-obesity treatment.

REFERENCES


ACKNOWLEGEMENTS

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METHODOLOGY

The study protocol is shown in chart 1. After two weeks on HHF, mice were acclimated for four days with daily ip saline injections. Following acclimation, mice were divided into two groups and received either ip vehicle (a cocktail of 30% Dimethyl sulfoxide (DMSO), 40% polyethylene glycol (PEG), and 30% phosphate buffered saline (PBS), n=10 mice) or SFN (5 mg/kg, n=10 mice) for six consecutive days. On the 7th day, 30 mins after vehicle/SFN injections, mice in either group received either saline or leptin (5 mg/kg BW). At the termination of the experiment, fasting mice were decapitated post 24 hours of leptin treatment liver was collected and stored at a temperature of ~8 °C for further studies including gene expression for functional genomics.

RNA was extracted based on the procedure provided by the manufacturer with the kit [The RNeasy MiniElute cleanup kit By QIAGEN]. RT-PCR is used for the gene expression profiling to analyze candidate gene panels and their metabolic pathways by using real time PCR. IPIA software was used for pathway analysis.