ABSTRACT

Bile acids are significant physiological factors for digestion, solubilization, absorption, tissue metabolites and xenobiotics. In addition, bile acids are responsible of signal transduction as well as a metabolic regulation that activate several receptors such as farnesoid X receptor (FXR) and the membrane G-protein receptor 5 (TGR5). Activation of TGR5 by bile acids is associated with prevention of obesity as well as ameliorating the resistance to insulin via increasing energy expenditure. The objective of this study is to investigate TGR5 gene expression level in different fat depots including visceral or epididymal adipose tissue (eWAT), brown adipose tissue and inguinal adipose tissue (iWAT) and to study the response of TGR5 gene expression to the anti-obesity treatment (SFN). Three groups of male CD1 mice were used in this study; lean group fed with CD, Obese mice on HF diet and Obese mice treated with anti-obesity treatment. Body weight (BW) and phenotype data were evaluated by weekly including blood samples for analysis of insulin, glucose, leptin, triglycerides and HDL. Total RNA was extracted from different fat depots and RT-PCR profiler array technology was used to in order to assess the mRNA expression of TGR5 and leptin. There was significant downregulation of TGR5 gene expression level in obese (DIO) mice and remarkable upregulation of TGR5 gene-expression after successful weight loss in DIO mice treated with SFN in time dependent manner at 1 and 4 weeks of treatment. In conclusion, obesity is associated with decrease in expression of TGR5 in different fat depots and treatment with anti-obesity drug (Sulforaphane) causes stepwise upregulation of TGR5 gene expression in epididymal and brown adipose tissue and parallel decrease in body weight. Increase of expression of TGR5 in DIO mice in eWAT is accompanied by improvement in glucose homeostasis and insulin action.

RESULTS

Body weight changes and biochemical parameters:

Table 1: Body weight and biochemical data of the three groups of studied CD1 male mice (Lean-Vehicle, Obese-Vehicle, and Obese-SFN treated).

<table>
<thead>
<tr>
<th>Group</th>
<th>Body Weight (g)</th>
<th>Glucose (mg/dl)</th>
<th>Insulin (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lean-Vehicle</td>
<td>34.92 ± 0.75</td>
<td>7.42 ± 0.45</td>
<td>0.52 ± 0.03</td>
</tr>
<tr>
<td>Obese-Vehicle</td>
<td>43.52 ± 0.96</td>
<td>10.35 ± 0.89</td>
<td>1.34 ± 0.12</td>
</tr>
<tr>
<td>Obese-SFN</td>
<td>33.91 ± 0.87</td>
<td>7.95 ± 0.57</td>
<td>0.76 ± 0.04</td>
</tr>
</tbody>
</table>

**FIGURES:**

- **Figure 1:** Body weight changes of lean, DIO-vehicle, and DIO- treated CD male mice during days of treatment.
- **Figure 2:** Relative Fold changes in gene expression (over control group) of TGR5 gene expression in iWAT of obese (DIO) mice vs lean mice. The expression of bile acid receptor TGR5 is accompanied by improvement in glucose homeostasis and insulin action.

CONCLUSION

This study has demonstrated that obesity-induced by HF diet in DIO mice is associated with a decrease in expression of TGR5 in epididymal white adipose tissue (eWAT), brown fat and beige fat (iWAT). Treatment with anti-obesity drug using sulforaphane causes stepwise upregulation of TGR5 gene expression in epididymal white adipose tissue with parallel stepwise decrease in body weight of DIO mice with marked decrease in leptin expression in adipose tissue. Moreover, the increase of expression of TGR5 in DIO mice in eWAT is accompanied by improvement in glucose homeostasis and insulin action.

REFERENCES


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METHODOLOGY

CD1 male mice (n=20) were fed with a high fat diet (60%) for 12 weeks to generate diet-induced obese (DIO) mice with body weights between 45-50 g. Another group used as lean and fed with standard chow diet for 12 weeks. Thereafter, lean mice received vehicle and DIO mice received either SFN (5mg/kg BW) (n=10) or vehicle (n=10) daily by intraperitoneal injections for four weeks. Three groups of male CD1 mice were employed in this study; lean group, DIO group, and DIO treated the group with anti-obesity treatment (SFN). Body weight (BW) was evaluated daily during the study. Glucose tolerance test (1g/kg BW, IP) was evaluated in the third week of treatment. At the end of 4 weeks of the injection, samples of blood and adipose tissues of different depots were collected. The expression levels of TGR5 and leptin genes were analyzed by qRT-PCR. Blood was also used for glucose, triglycerides, leptin, and insulin measurements.

ACKNOWLEDGEMENTS

Special thanks go to Qatar Foundation for their fund (Research grant: NAHR 9-316-07), and thanks to the laboratory animal research center (LARC) for providing the mice.

I thank to Dr. Nasser Kifah for his supervision, help, and continuous support. Thanks to those who are behind the success of this research: Dr. Alshahat Alghazal, Miss. Dina, Miss. Amira Sabeel, Miss. Amira Albus, Miss. Diwa, and Miss. Aisha Alalawi.

Lastly, we would like to thank the biomedical research center (BRC), and the biomedical department labs in the science building for allowing us to access their labs to work on our researches.