The FXR agonist obeticholic acid normalizes lipid droplet and triglyceride handling in visceral adipose tissue preadipocytes from a non-genomic rabbit model of metabolic syndrome


Introduction: Adipose tissue (AT) dysfunction is characterized by ectopic fat deposition in the abdominal viscera and liver, inflammatory and adipokine dysregulation, and insulin resistance and may be a more important mediator than total fat mass of type 2 diabetes, hypertension and dyslipidemia development, at these features clustering in the metabolic syndrome (MeS). We recently demonstrated that the selective FXR agonist obeticholic acid (OCA) ameliorates the metabolic profile and reduces visceral AT (VAT) in a high-fat diet (HFD)-induced rabbit model of MeS [1].

Aim: We studied the effects of in vivo OCA dosing on the adipogenic capacity of isolated VAT preadipocytes (rPAD) from MeS rabbits, compared to control diet (CON).

Methods: VAT and liver were studied by immunohistochemistry, western blot, and RT-PCR. Isolated rPAD were exposed to adipocyte differentiating mixture (DIM) [0.5 Mm 3-isobutyl-1-methylxanthine, 5µg/ml insulin, 1µM dexamethasone] for 10 days to evaluate adipogenic potential.

Analysis of adipocyte size, hypoxia and GLUT4 membrane translocation in VAT from experimental rabbits

Histomorphometric analysis

Immunohistochemical staining

Western Blot analysis

Adipocyte size, hypoxia, expression of perilipin and cytosolic GLUT4 were significantly increased in HFD VAT and normalized by OCA.

Data are expressed as percentage of variation with HFD, *p<0.05; **p<0.01; ***p<0.001 vs. HFD.

Effect of OCA treatment on mRNA expression of VAT-specific genes

CON

HFD

HFD+OCA

Oil Red O staining

Immunohistochemistry for TNFα

OCA ameliorates liver stenosis and inflammation

OCA ameliorates spontaneous adipogenic differentiation in untreated rPAD

CON

HFD

HFD+OCA

OCA ameliorates DIM-induced adipogenic differentiation in rPAD

CON

HFD

HFD+OCA

Quantitative real time RT-PCR of adipocyte-specific genes in rPAD

<table>
<thead>
<tr>
<th>Genes</th>
<th>HFD</th>
<th>HFD+OCA</th>
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<tbody>
<tr>
<td>DKK1</td>
<td>6.4±2**</td>
<td>13±1.3**</td>
</tr>
<tr>
<td>c/EBPa</td>
<td>1.2±1.3</td>
<td>1.2±1.3</td>
</tr>
<tr>
<td>PPARγ</td>
<td>2.2±1.2</td>
<td>1.6±1.2</td>
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<tr>
<td>FABP4</td>
<td>5.4±1.3</td>
<td>10.0±3.4</td>
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<tr>
<td>adiponectin</td>
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<td>1.8±1.2</td>
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<tr>
<td>leptin</td>
<td>8.7±2.6*</td>
<td>1.8±0.4</td>
</tr>
<tr>
<td>CCND1</td>
<td>6.0±1.3</td>
<td>2.1±1.0</td>
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<tr>
<td>CCND3</td>
<td>2.1±0.4</td>
<td>1.9±1.2***</td>
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</tbody>
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*p<0.01, **p<0.05, ***p<0.001 vs. HFD; p<0.01 vs. all other groups.

Conclusions: Overall, OCA dosing in a MeS rabbit model ameliorates liver and VAT functions. This could reflect the ability of OCA to restore insulin sensitivity in AT unable to finalize its storage function, counteracting MeS-induced metabolic alterations and pathological AT deposition.