The collapse of the BDNF/POMC system in the hypothalamus is responsible for the extreme obesity with hyperphagia observed in female heterozygous MeCP2 null mice

OBJECTIVES

The objective was to elucidate the mechanism underlying the extreme obesity observed in female heterozygous MeCP2 null mice, generated a mouse model of Rett syndrome. Rett syndrome is an epigenetic X-linked neurodevelopmental disorder that affects girls due primarily to mutations in the gene encoding methyl-CpG binding protein 2 (MeCP2). Clinically, Zappella variant Rett syndrome patients have autism spectrum disorder and obesity from childhood.

Hypothesis of the mechanism of obesity in the MeCP2-/- mice

1. Food intake suppression
2. Energy expenditure
3. Fat preference

RESULTS

We examined the molecular biology and physiology of female heterozygous MeCP2 null mice (MeCP2 tm1.1 Bird/J, MeCP2-/- mice) fed a normal-chow diet (NC) or a high-fat diet (HFD) for 12-weeks since 4-weeks of age using analytical tools. C57/B6 mice were used as controls.

Table 1. Metabolic parameters in 16-week-old mice

<table>
<thead>
<tr>
<th>Parameter</th>
<th>WT+NC</th>
<th>MeCP2-/-+NC</th>
<th>WT+HFD</th>
<th>MeCP2-/-+HFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>pGAL</td>
<td>0.12±0.02</td>
<td>0.46±0.13</td>
<td>0.64±0.2</td>
<td>1.74±0.33</td>
</tr>
<tr>
<td>sGAL</td>
<td>0.16±0.03</td>
<td>0.38±0.11</td>
<td>0.50±0.18</td>
<td>1.41±0.22</td>
</tr>
<tr>
<td>iGAL</td>
<td>0.05±0.01</td>
<td>0.19±0.04</td>
<td>0.31±0.12</td>
<td>0.64±0.15</td>
</tr>
<tr>
<td>BAT</td>
<td>0.06±0.00</td>
<td>0.061±0.00</td>
<td>0.109±0.01</td>
<td>0.089±0.01</td>
</tr>
<tr>
<td>Liver</td>
<td>0.68±0.05</td>
<td>0.81±0.04</td>
<td>1.01±0.13</td>
<td>1.53±0.28</td>
</tr>
<tr>
<td>TCHO</td>
<td>57.7±3.9</td>
<td>59.9±5.1</td>
<td>89.3±11.1</td>
<td>144.3±16.4</td>
</tr>
<tr>
<td>Glucose</td>
<td>79.6±6</td>
<td>121±20</td>
<td>183±19</td>
<td>185±21</td>
</tr>
<tr>
<td>Insulin (μIU/ml)</td>
<td>8.4±0.8</td>
<td>12.1±1.0</td>
<td>15.4±2.6</td>
<td>23.2±4.6</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>1.6±0.2</td>
<td>3.8±0.9</td>
<td>7.8±2.0</td>
<td>10.2±2.1</td>
</tr>
<tr>
<td>Leptin</td>
<td>1.9±0.5</td>
<td>6.7±1.7</td>
<td>16.1±5.8</td>
<td>18.6±9.4</td>
</tr>
</tbody>
</table>

Conclusions

1. Our experiments showed that the MeCP2-/- mice fed a HFD expressed extreme obesity with hyperphagia.
2. Oxygen consumption and locomotor activity were not different between the MeCP2-/- mice fed with a HFD and the controls fed with a HFD. A dietary preference test revealed that the MeCP2-/- mice fed a HFD greatly preferred to HFD.
3. A decrease of POMC expression in the hypothalamus and decreased expressions of BDNF in the hypothalamus and the VTA could account for central leptin resistance, which might lead to obesity on the MeCP2-/- mice fed with a HFD.
4. We think that epigenetic pathogenesis rather than disturbances in the leptin receptor /Stat3 signaling could be one of the mechanisms underlying the hyperphagia with leptin resistance observed in the MeCP2-/- mice fed with a HFD.

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REFERENCES


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