Effect of rimonabant on body weight, glucose tolerance, body composition and lipolysis in fa/†fa Zucker rats: a comparison with pair-fed controls.


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INTRODUCTION

The CB1 receptor antagonist, rimonabant, reduces food intake and body weight in preclinical and clinical studies. The mechanisms through which these effects are manifest remain unclear since although CB1 receptors are widespread throughout the CNS, they are also located in the periphery: particularly in adipose tissue and pancreatic islets. Such tissues have been identified as potential targets mediating a "peripheral" metabolic effect of rimonabant in addition to a known "central" effect on food intake.

The present study investigated the effect of rimonabant on glucose tolerance, body composition, ex vivo lipolysis and Acrp30 (adiponectin) mRNA in obese, insulin resistant, fa/†fa Zucker rats. Pair-fed controls were included to address whether the effects of rimonabant on these parameters were attributable to drug-induced changes in food intake and body weight, or if additional mechanisms (e.g. drug-induced changes in plasma adiponectin) were responsible.

MATERIALS AND METHODS

Male fa/†fa Zucker rats (Charles River, France; 450-500g at the start of baseline) were individually housed and maintained on normal-phase lighting with free access to standard laboratory chow and water. After acclimatisation, the rats were administered orally with vehicle or rimonabant (3, 10 mg/kg q.d.) for 14 days. Pair-fed controls received vehicle and a daily food ration equal to that consumed by a drug treated counterpart over the previous 24h period. On Day 14, animals were fasted overnight. On day 15, 1 hour after dosing, an oral glucose load (2 g/kg D-glucose) was administered. Blood samples were taken immediately before the glucose load and 30, 60 and 120 minutes afterwards. Plasma glucose and insulin were subsequently determined. At termination a blood sample was taken to assess plasma Acrp30. In addition, basal and isoproterenol-stimulated lipolysis were assessed in ex vivo explants of epidymal adipose tissue and Acrp30 mRNA was also quantified. Finally, a full body composition analysis was carried out.

Results are mean ± SEM (calculated from residuals of the statistical model), n=10.

REFERENCE


ACKNOWLEDGEMENTS

Poster presented at the Neuroscience 2008, the 38th annual meeting of the Society for Neuroscience, November 15 - 19, Washington, DC.

RESULTS

• Rimonabant dose-dependently reduced body weight (Fig.1). This reduction in body weight was slightly less than that in pair-fed controls. The body composition of pair-fed controls differed to that of rimonabant-treated animals (Table 1). Hence, rimonabant (10 mg/kg po) reduced final carcass weight by 9.3% compared to vehicle of which 64.9% was attributable to fat whereas pair-fed controls lost 9.8% of body weight yet only 47% was attributable to fat.

• Both rimonabant and pair-feeding improved the profiles in an oral glucose tolerance test (Fig.2). This improvement appears to be through different mechanisms since the insulin response to the glucose load is markedly different in pair-fed controls compared to rimonabant-treated counterparts (Fig.2).

• Both rimonabant and pair-feeding elevated Acrp30 (adiponectin) message in epidymal fat (Fig.3). However, neither treatment had an effect on plasma levels of adiponectin at termination (Fig.3) nor altered lipolysis in ex vivo epidymal adipose tissue explants (Fig.4).

SUMMARY

• Chronic administration of rimonabant leads to fat loss and improvements in insulin sensitivity that are different to pair-fed controls in fa/†fa Zucker rats.

• The mechanism for these effects is unlikely to involve Acrp30 or the stimulation of lipolysis.

Fig 1. Body weight gain of rimonabant-treated fa/†fa Zucker rats and pair-fed controls

Fig 2. Effect of rimonabant on glucose tolerance in male fa/†fa Zucker rats and pair-fed controls

Fig 3. Terminal plasma Acrp30 levels and message expression in epidymal fat subsequent to rimonabant treatment or pair feeding

Fig 4 Ex vivo lipolysis (glycerol release) in epidymal fat explants in fa/†fa Zucker rats treated with rimonabant or pair-fed controls.

Table 1. Terminal body composition

<table>
<thead>
<tr>
<th>Group</th>
<th>Water (g)</th>
<th>Fat (g)</th>
<th>Protein (g)</th>
<th>Ash (g)</th>
<th>Carcass weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle po bid</td>
<td>194.1</td>
<td>23.1</td>
<td>67.7</td>
<td>1.3</td>
<td>211.1</td>
</tr>
<tr>
<td>Rimonabant 3mg/kg</td>
<td>192.5</td>
<td>23.4</td>
<td>65.3</td>
<td>1.3</td>
<td>190.9</td>
</tr>
<tr>
<td>Rimonabant 10mg/kg</td>
<td>192.0</td>
<td>31.2</td>
<td>61.1</td>
<td>1.3</td>
<td>190.0</td>
</tr>
<tr>
<td>Pair-fed to Group B</td>
<td>192.5</td>
<td>31.2</td>
<td>61.1</td>
<td>1.3</td>
<td>190.0</td>
</tr>
<tr>
<td>Pair-fed to Group C</td>
<td>173.6</td>
<td>12.2</td>
<td>62.3</td>
<td>0.9</td>
<td>186.4</td>
</tr>
</tbody>
</table>

Results are mean ± SEM. Differences between vehicle and rimonabant treated animals or pair-fed controls. Lipolysis was assessed at time 30 in rimonabant treated group and pair-fed counterparts.