Possible role for PI3 kinase but not p70S6K in regulation of lipogenesis by insulin and growth hormone in sheep adipose tissue.

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The signalling system involved in the chronic, insulin-antagonistic effect of growth hormone (GH) on lipogenesis in adipose tissue is not known. Indeed the system responsible for the insulin induction of lipogenesis itself has not been elucidated. The interaction of insulin with its receptor is thought to trigger signalling through a branching signal transduction system. One component of this system is phosphatidylinositol 3-kinase (PI3-kinase) [1] which is inhibited by wortmannin [2]. Use of wortmannin has implicated PI3-kinase in the activation of glucose transport and inhibition of lipolysis by insulin [3] and, very recently, activation of lipogenesis [4]. PI3-kinase is also involved in the activation of p70 S6 kinase (p70S6K) [3]; activation of this latter enzyme is mimicked by wortmannin (100 nM) (Sigma and Affinity Research Products Ltd.) when included was added at the start of 5 h following which the rate of lipogenesis was measured [6]. Wortmannin (100 nM) (Sigma and Affinity Research Products Ltd.) when included was added after 3 h. 100 nM wortmannin was also included during the assay of lipogenesis. Rapamycin (50 nM) was added to other cultures and the rate of lipogenesis measured 24 h later. Results were analysed by ANOVA.

Table 1. Effects of wortmannin and rapamycin on the ability of growth hormone (GH) to inhibit and insulin (Ins) plus dexamethasone (Dex) to increase the rate of lipogenesis in sheep adipose tissue

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Wortmannin</th>
<th>Rapamycin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- 100nM</td>
<td>- 50nM</td>
</tr>
<tr>
<td>None</td>
<td>875 601</td>
<td>687 1151</td>
</tr>
<tr>
<td>GH</td>
<td>518 434</td>
<td>166 188</td>
</tr>
<tr>
<td>Ins, Dex</td>
<td>2607 1681</td>
<td>3317 2606</td>
</tr>
<tr>
<td>Ins, Dex, GH</td>
<td>2088 1365</td>
<td>1413 1067</td>
</tr>
</tbody>
</table>

As reported previously [6] addition of GH decreased (P < 0.05) the rate of lipogenesis over 5 h of culture and to a greater extent (P < 0.05) over a 24 h period (Table 1). Addition of wortmannin had a similar inhibitory effect to GH; effects of the two agents were not additive (Table 1). Insulin increased the rate of lipogenesis (P < 0.01) and this was partly blocked by 100 nM wortmannin (P < 0.05). GH tended to decrease this insulin-induced increase in lipogenesis (the inhibitory effect of GH develops more slowly in the presence of insulin [6]) and this inhibition was enhanced (P < 0.05) by wortmannin.

In contrast to wortmannin, rapamycin neither mimicked the effect of GH nor prevented the antagonistic effect of GH either in the presence or absence of insulin.

These observations are consistent with PI3-kinase being a target for the insulin antagonistic effect of GH as wortmannin mimicked the effect of GH and the effects were not additive in the absence of insulin. A partial inhibition of insulin-induced fatty acid synthesis by wortmannin (100 nM) is consistent with a previous report which showed that 1 µM wortmannin was required for complete inhibition [4]. That GH and wortmannin together were more effective than either alone in the presence of insulin is consistent with this.

In contrast to PI3-kinase, p70S6K does not appear to be involved in the effect of insulin or GH on lipogenesis.

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References: