EFFECT OF GROWTH HORMONE TREATMENT ON INSULIN ACTION IN MUSCLE OF GROWTH HORMONE DEFICIENT RATS.


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INTRODUCTION
Excess of growth hormone, as in acromegaly, has been shown to be associated with insulin resistance (Hansen 1986), whereas growth hormone deficiency in rats, as after hypophysectomy, is associated with increased sensitivity to insulin (Davidson 1987). With the introduction of recombinant human growth hormone (rhGH) it is becoming common to treat growth hormone deficient patients with rhGH. Muscle tissue is the major site of glucose disposal and it is therefore of interest to study how the effect of insulin in skeletal muscle is affected after treatment with rhGH.

METHODS
48 growth hormone deficient rats (dw/dw) were obtained from Novo Nordisk, Denmark. (Weight 203 ± 2 g, age 25 ± 1 weeks (mean ± SE). The rats were divided into 2 groups. Twice daily, the groups received subcutaneous injections with either rhGH (0.5 mg/kg/day) (GH) or an equivalent amount of saline solution (CON).

After 10 days of treatment the rats were prepared for hindlimb perfusion as described by Ruderman et al. (1971). The rats were perfused without (0 nU/ml) (BAS) or with a submaximal (100 uU/ml) (SUB) or maximal (10000 uAJ/ml) concentration of insulin, respectively.

Glucose uptake was determined by measuring the arterial minus venous concentration difference multiplied by the perfusate flow (12.5 ml/min). To determine the muscle membrane glucose transport in individual muscle fiber types, 0.1 mCi/ml of 3-O-[14C]methyl-D-Glucose along with 1 mCi/ml of 3H]mannitol was added to the perfusate. At the end of the perfusion the superficial part of the gastrocnemius, consisting primarily of fast-twisch white fibers (GW), the soleus consisting primarily of slow-twisch red fibers (SOL) and the deep part of medial head of the gastrocnemius which contains mainly fast-twisch red fibers (RG) was excised and freeze clamped in liquid nitrogen and stored at -80 °C until further analysis.

RESULTS
The growth rate was increased significantly (p<0.05) from 0.1 ± 0.1 g/day in CON to 3.6 ± 0.1 g/day in GH and the wet weight of the soleus muscle was significantly (p<0.05) higher in the GH (72 ± 2 mg) than in CON (65 ± 2 mg). The percentage of water in the soleus muscle was not changed following growth hormone treatment. Plasma concentration of Insulin-like Growth Factor-1 (IGF-1) was determined in the control group to 364 ± 23 ng/ml and it was significantly (p<0.05) higher in the GH group (451 ± 32 ng/ml).

In the CON group the glucose uptake in the BAS was 3.3 ± 0.7 nmol/g/h. Glucose uptake was significantly higher in submaximal (11.7 ± 1.1 nmol/g/h) and maximal (21.5 ± 1.7 umol/g/h) insulin-stimulated conditions, respectively. There was no significant difference (p<0.05) in glucose uptake between the GH group and the CON group at any insulin concentration (Fig. 1). Glucose transport in individual muscle fiber types was significantly (p<0.05) higher in the two insulin-stimulated states compared to BAS, but there was no difference in glucose transport in the 3 types of muscle investigated, when CON was compared with the GH (Table 1).
FIGURE 1. Glucose uptake.

TABLE 1. Glucose transport rate in White Gastrocnemius (GW), Soleus (SOL) and Red Gastrocnemius (GR).

<table>
<thead>
<tr>
<th>Muscle</th>
<th>No Insulin</th>
<th>Submax Insulin</th>
<th>Max Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>GW</td>
<td>0.9±0.3</td>
<td>3.8±0.6*</td>
<td>13.5±1.3*</td>
</tr>
<tr>
<td>Control</td>
<td>1.7±0.3</td>
<td>4.9±0.9*</td>
<td>11.6±0.7*</td>
</tr>
<tr>
<td>GH treated</td>
<td>2.0±0.4</td>
<td>11.6±1.2*</td>
<td>27.8±3.6*</td>
</tr>
<tr>
<td>SOL</td>
<td>3.0±0.6</td>
<td>12.5±1.1*</td>
<td>23.4±2.1*</td>
</tr>
<tr>
<td>Control</td>
<td>1.3±0.4</td>
<td>12.6±0.8*</td>
<td>28.4±1.1*</td>
</tr>
<tr>
<td>RG</td>
<td>1.7±0.4</td>
<td>12.0±1.2*</td>
<td>26.2±0.9*</td>
</tr>
</tbody>
</table>

Value are means ± SE of 8 observations, given in u.mol/g/h. There was no significant difference between treated and control in any of the groups. *P<0.05 compared with the value in absence of insulin.

DISCUSSION

Treatment of growth hormone deficient rats with rhGH restored growth rates. In vivo, growth hormone excess is associated with insulin resistance (Ng 1990), but whether replacement of growth hormone in GH-deficiency has any effect on insulin sensitivity is not known. The present data clearly show that despite clear growth-promoting effects of rhGH-treatment no effect on insulin sensitivity of glucose uptake in perfused muscle could be demonstrated. It is concluded that treatment with rhGH of growth hormone deficient rats has no effect on basal and insulin-stimulated glucose uptake and transport in muscle in vitro.

REFERENCES


