Responses to divergent selection for plasma concentrations of insulin-like growth factor-1 in mice

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Summary
A divergent selection experiment with mice, using plasma concentrations of insulin-like growth factor-1 (IGF-1) at 42 days of age as the selection criterion, was undertaken for 7 generations. Lines were not replicated. To obtain sufficient plasma for the IGF-1 assay, blood from four individuals was volumetrically bulked to obtain a litter mean IGF-1 concentration. This necessitated the use of between family selection. Although inbreeding accumulated in a linear fashion in each of the high, control and low lines, the rates were different for each line (3.6, 1.6 and 5.3 % per generation for the high, control and low lines, respectively). As a consequence, the effects of selection and inbreeding are confounded in this experiment. Divergence between the high and low lines in plasma concentrations of IGF-1 continued steadily until generation 5. In generations 6 and 7, there was a reduced degree of divergence and this contributed towards the low realized heritability value of 0.15 ± 0.12. Six-week liveweight showed a steady positive correlated response to selection for or against plasma concentrations of IGF-1 until generation 4 (high-low difference = 1.7 g = 12%). In generation 5, a substantial drop in 6-week liveweight in the low line relative to both the high and control lines occurred (high-low difference, 3.9; g, 25%). This difference was maintained until generation 7.

This experiment suggests that genetic variation exists at 6 weeks of age in plasma concentrations of IGF-1 in mice. Furthermore, genetic covariation between plasma IGF-1 concentrations and liveweight at 6 weeks of age is likely to be positive. Further experiments have been initiated to examine these theories.

1. Introduction

Intensive research during the 1980s has investigated the role of insulin-like growth factor-1 (IGF-1) in the somatotrophic axis (Hall & Sara, 1983; Froesch et al. 1985; Breier et al. 1986) and other physiological functions such as reproduction (Adashi et al. 1985) and lactation (Gluckman et al. 1987). The possible involvement of IGF-1 in several important production traits, including liveweight gain, reproductive efficiency and milk production, has led to interest in its potential as a selection criterion.

Blair et al. (1987) reported a number of non-genetic factors affecting plasma IGF-1 concentrations which, in order to maximize the rate of genetic gain, would need to be corrected for prior to ranking animals for selection. They also reported a moderate heritability estimate (0.40) for plasma concentrations of IGF-1 at about 6 weeks of age in mice, suggesting that genetic variation exists for this trait. Phenotypic correlations between plasma concentrations of IGF-1 and liveweight at 6 weeks of age were positive and generally high in the above trial.

In an effort to provide more information about the level of genetic variation in plasma concentrations of IGF-1, and the degree of genetic covariation with other traits, a mouse selection experiment was initiated in 1985. This paper reports on direct responses to selection for plasma concentrations of IGF-1 at 6 weeks of age and correlated responses in 6-week liveweight.

2. Materials and methods

Four inbred strains of mice maintained at the Massey University Small Animal Production Unit (SAPU)
Selection of breeding stock for the high (low) line was calculated as the difference between high and low line means (Fig. 1). Under these circumstances, it was not possible to separate changes due to selection from those due to inbreeding.

(ii) Direct response

The mean IGF-1 concentrations for each line within generation are presented in Table 1. There was considerable between-generation fluctuation in the IGF-1 concentrations and this could not be accounted for by assay drift. Of particular concern is that values for the control line did not appear to vary in a similar fashion to those of the high and low lines. Therefore, direct response to selection in IGF-1 concentrations was calculated as the difference between high and low line means (Fig. 1). Under these circumstances, it was not possible to determine whether response was symmetrical or asymmetrical. However, it is clear that response to selection continued until generation 5. The reduced response in generations 6 and 7 could reflect reduced levels of genetic variation in either or
Table 1. Adjusted* means (± s.e.) by line and generation for 6-week plasma IGF-1 concentrations and 6-week liveweights

<table>
<thead>
<tr>
<th>Generation</th>
<th>IGF-1 concentration (ng/ml)</th>
<th>Liveweight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High</td>
<td>Control</td>
</tr>
<tr>
<td>0</td>
<td>132 ± 4</td>
<td>125 ± 5</td>
</tr>
<tr>
<td>1</td>
<td>102 ± 5</td>
<td>na</td>
</tr>
<tr>
<td>2</td>
<td>105 ± 3</td>
<td>76 ± 5</td>
</tr>
<tr>
<td>3</td>
<td>137 ± 5</td>
<td>133 ± 7</td>
</tr>
<tr>
<td>4</td>
<td>88 ± 9</td>
<td>87 ± 10</td>
</tr>
<tr>
<td>5</td>
<td>146 ± 4</td>
<td>114 ± 5</td>
</tr>
<tr>
<td>6</td>
<td>102 ± 3</td>
<td>100 ± 4</td>
</tr>
<tr>
<td>7</td>
<td>85 ± 2</td>
<td>72 ± 3</td>
</tr>
</tbody>
</table>

* Adjusted for age at weighing/sampling and litter size; liveweights also adjusted for sex.

Fig. 1. Differences between high and low line IGF-1 concentrations by generation and the regression fitted through the origin (b = 4.86).

both lines due to selection or inbreeding. Alternatively, the reduced response could be caused by the inefficiency of family selection. It is unlikely that the change in feed pellet composition after generation 4 contributed to the reduced response, since further divergence occurred in generation 5. The average rates of accumulation of selection differential per generation were 16.0 ng/ml in the high line and -15.7 ng/ml in the low line. There was no indication of a decline in the selection differentials in later generations. Since generations were discrete in this trial, cumulative selection differentials were obtained by adding successive selection differentials together. A realized heritability of 0.15 ± 0.12 based on response to family selection was generated by regressing the divergence between the high and low lines on the cumulative selection differential. However, this value would be significantly affected by the poor responses found in the last two generations. Since the reason for the decline in response is unknown, this realized heritability estimate must be treated with caution. Furthermore, the use of family selection contributed to a high standard error via random genetic drift.

(iii) Correlated response in 6-week liveweight

Mean adjusted 6-week liveweights for the various generations are presented in Table 1. Perusal of the generation means reveals a downward trend in liveweights until generation 4. From generation 5 onwards, liveweights steadily improved until the high and control lines returned to weights similar to those obtained at the outset of the experiment. The reason for these changes is unknown; the consistency of change does not suggest a nutritional effect (although a diet modification occurred after generation 4), and the steady increase in mean liveweight in generations 5–7 is the opposite of what would be expected due to inbreeding.

The divergence of the high and low lines from the control line in 6-week weight is shown in Fig. 2. The high-low difference was significant from generation 1 onwards, while the high-control and control-low differences were significant only on an irregular basis. The rate of divergence appeared relatively steady up to generation 4. However, a major difference between the high and control lines and the low line developed
Fig. 2. Deviation of the high and low lines from the control line for liveweight (g). (—, high line; ———, low line).

in generation 5 and persisted in the following 2 generations. Examination of the mean low-line weights in Table 1 shows that liveweights actually increased after generation 4, but at a lesser rate compared with the high and control lines. There was no major change in the levels of inbreeding in any of the lines at generation 5. Rather, inbreeding accumulated in a relatively linear fashion.

4. Discussion

It is clear from the results that any discussion of responses to selection in IGF-1 concentrations and liveweight must be undertaken with care, given the different rates of accumulation in inbreeding.

Fig. 1 clearly shows that response to selection for IGF-1 concentrations has occurred, but it is not possible to conclude whether change has been in one or both directions. Since there was a much reduced response in generations 5 and 6 the realized heritability value of 0.15 is of limited value in making comparisons with other information in the literature. Blair et al. (1987) reported a heritability of 0.40 for IGF-1 concentrations at 35 days of age in mice. This estimate was based on a small number of full-sib litters from one unselected generation. The other evidence for genetic variation in IGF-1 levels comes from two studies where selection has been for body-size or liveweight [Lund-Larsen & Bakke, 1975, (pigs); Eigenmann et al. 1984, (dogs)]. A further study by Buonomo et al. (1987) with pigs is of limited value in supporting the current argument since the 3 body-sizes investigated did not come from common genetic stock. A substantial body of evidence is accumulating to show that IGF-1 concentrations are often involved in major growth disturbances (particularly dwarfism), but these tend to involve major genes rather than the quantitative aspects being addressed here (Willeberg et al. 1975; Holder & Willis, 1977; Huybrechts et al. 1985; Merimee et al. 1987).

Although substantial changes have occurred in 6-week liveweight, it would be unwise to attribute all of the difference to a correlated response to selection for IGF-1 levels. The substantial change in generation 5 is of particular concern and would be consistent with the appearance of a major gene for dwarfism. However, in 4 randomly bred generations observed since selection was suspended, no evidence to support this theory has emerged.

There is no direct evidence in the literature regarding the possible existence of a genetic correlation between IGF-1 concentrations and liveweight. The studies of Lund-Larsen & Bakke (1975) and Eigenmann et al. (1984) provide some indirect support.

In conclusion, the use of family selection caused unequal rates of inbreeding accumulation in the three lines. As a consequence, it was not possible to separate the effects of selection and inbreeding. However, results were sufficiently favourable to suggest that further work is warranted to investigate the genetic nature of the IGF-1 concentration/liveweight relationship. To this end, a selection experiment involving Romney sheep has been established in which plasma levels of IGF-1 in individuals at about 5 months of age are being used as the selection criterion.

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References


