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Replicated selection for insulin-like growth factor-1 and body weight in mice

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Summary. Five generations of divergent selection for plasma concentration of insulin-like growth factor-1 (IGF-1) and for 12-week body weight were carried out in mice, including randomly selected control lines for each trait. All lines were replicated once (12 lines in total). Each replicate line consisted of eight male and eight female parents per generation. Litter size was standardized to eight pups at birth. Mass selection was applied in the selected lines and within-family random selection in the control lines. Blood was taken from the orbital sinus of individual mice at 12 weeks of age for IGF-1 assay. Realized heritabilities were 0.10 ± 0.01 for IGF-1 and 0.41 ± 0.02 for 12-week weight. The realized genetic correlation between IGF-1 and 12-week weight was 0.58 ± 0.01, with a phenotypic correlation of 0.38. Although the genetic correlation between IGF-1 and body weight in mice is moderately positive, 12-week weight responded 3.5 times as fast to weight selection as to selection for IGF-1.

Key words: IGF-1 – Body weight – Realized heritability – Genetic correlation – Mice

Introduction

Information on the physiology, biochemistry, and mode of action of insulin-like growth factors (IGFs) has been reviewed recently (Gluckman et al. 1987; Daughaday and Rotwein 1989). IGFs form a link between growth hormone and metabolic processes of anabolism and growth (Clemmons and Van Wyk 1981), and they also produce a mitogenic stimulus leading to cellular proliferation (Zapf et al. 1984). There is evidence that IGFs stimulate protein synthesis in vitro (Canalis 1980; Monier et al. 1983) and display growth-promoting activity in vitro (Schmid et al. 1984) and in vivo (Schoenle et al. 1982). There are a number of reports of a positive phenotypic relationship between plasma insulin-like growth factor-1 (IGF-1) levels and growth rate in various domestic animal species (Breier et al. 1986, 1988a, b). There is also some indirect evidence for a positive genetic relationship between IGF-1 concentrations and body weight in distinct strains of poodles (Eigenmann et al. 1984) and pigs (Lund-Larsen and Bakke 1975).

There is only limited evidence on the amount of genetic variation that exists for plasma concentration of IGF-1 or on the genetic relationships between IGF-1 and other traits such as growth, reproduction, or lactation. However, a divergent selection experiment in mice for IGF-1 at 6 weeks of age resulted in a low realized heritability of 0.15 ± 0.12 and a positive correlated response in 6-week body weight (Blair et al. 1989).

The selection experiment with mice reported here was undertaken to determine the amount of genetic variation in plasma IGF-1 levels at a mature post pubertal age. In addition, the genetic relationship between plasma IGF-1 and body weight was investigated by direct divergent selection for IGF-1 levels and for body weight at 12 weeks of age.

Materials and methods

The foundation population for this study was the heterogeneous Q strain of mice, which was obtained from the Institute of Animal Genetics in Edinburgh in 1972 (Falconer 1973). Previous to this study, this strain of mice had been selected for five generations for high and low rectal temperature in two temperature environments. On completion of that study, all lines were recombined in a balanced diallel crossing program, which was followed by three generations of random mating with 36 pairs of mice mated in each generation. In the next generation, 48 pairs

of mice were mated and produced progeny, and this constituted the base generation for the present study. From this foundation, stock 12 lines were constituted to initiate the present study.

Divergent (high and low) selection lines were established for 12-week body weight and for plasma concentration of IGF-1 measured at 12 weeks of age. Each had an unselected control. Each of the six lines was replicated. To spread the technical work, the two replicates were mated 1 week apart.

Each line was maintained with eight single-pair matings in each generation. In the selection lines, mass selection was practiced and the eight highest or lowest mice of each sex for a given selection criterion were chosen. To reduce inbreeding, the restriction was made that no more than two males and two females be chosen from one litter, thereby ensuring that the next generation represented at least four litters. On average the selected mice represented five to six litters each generation. Mating in the selection lines was then at random, except for avoiding full- and half-sib matings where possible. In the control lines one male and one female were selected at random from each litter (i.e., within-litter selection). The variance in family size was therefore zero, thus doubling the effective population size. A cyclical mating plan (Falconer 1973) was then followed to minimize inbreeding. In all lines, selection was usually in first-parity litters only and selected mice were used for just one mating.

Mice were mated between 15 and 18 weeks of age. Males were left with their female mate during both gestation and lactation, and mating could continue for up to about 6 weeks. At birth, the number of young born (alive plus dead), sex ratio, and litter birth weights were recorded. Litter size was randomly standardized at birth to eight mice, as close as possible to four males and four females. Litters of fewer than eight mice were made up to eight from litters born on the same day, and the fostered mice were discarded at weaning at 3 weeks of age. Mice were weighed at weaning and placed in plastic boxes separately by sexes, with four to six mice in each box. All mice were weighed at 6, 9, and 12 weeks of age. Mice from all lines were housed in a single room with a constant light to dark ratio of 12 h:12 h. A complete pelleted feed and water were available ad libitum and room temperature varied from 21 to 23 °C.

Measurement of IGF-1

Before starting the selection experiment, a number of preliminary trials was undertaken to assess different sources of variation affecting IGF-1 plasma levels. Starvation of ten mice averaging 64 days of age reduced IGF-1 plasma levels by 18, 27, and 58% after 12, 24, and 48 h of starvation, respectively. In another preliminary trial, mice were bled at 60, 70, and 80 days of age to avoid known effects of puberty on IGF-1 plasma levels (Handelsman et al. 1987) and to determine an appropriate sampling age. There was a reduction in plasma IGF-1 levels with age and no significant difference between males and females at any of these ages (Table 1). The phenotypic correlation for IGF-1 measured in the same mice at 60 and 80 days of age was 0.65.

It was decided that for the selection experiment, mice would be bled at 12 weeks (84 days) of age after being lightly anesthetized with ether. Blood was collected in heparinized capillary tubes from the orbital sinus of individual mice from the high, low, and control IGF-1 lines for IGF-1 assay. All mice alive at 12 weeks of age in the IGF-1 selection and control lines were sampled, which meant that some 300 plasma samples were assayed for IGF-1 each generation (about every 5 months). This major undertaking precluded regular monitoring of IGF-1 in the body-weight selection lines. All 12 lines were assayed for IGF-1 after four generations of selection (635 mice sampled). Blood sampling was carried out between 13.00 and 15.00 h. Plasma was prepared from heparinized blood and stored at −20 °C pending analysis. IGF-1 concentrations were measured by radio immunoassay following acid-ethanol extraction (Gluckman and Butler 1983), as used by Blair et al. (1989). Intra- and interassay coefficients of variation were 5.0 and 9.8%, respectively.

Neither 12-week body weight nor 12-week IGF-1 plasma levels were adjusted for any non genetic effects prior to selection, since mice were recorded at a constant age, selection was carried out within each sex, and litter size had been standardized at birth. Food intake per rearing box (4–6 mice) was measured between 9 and 12 weeks of age to monitor for any decreased food intake which might affect the IGF-1 assay. No mice were rejected from selection for this criterion.

Analysis of selection responses

Direct and correlated responses to selection were first investigated separately for each sex. Because sexes did not show differential responses, results were pooled across sexes. Direct and correlated responses to selection were estimated from regression through the origin of the divergence of high and low lines on generation number for five generations of selection. Standard errors were calculated from the variance between replicates. Selection for both IGF-1 and 12-week weight took place in generation 5, but IGF-1 was not measured in generation 6 or later generations. From generation 6 onwards, all lines have been maintained using random selection, with recording of live weights. Asymmetry of response was investigated from deviation of the high or low lines from the contemporaneous control line, and standard errors were calculated from the variance between replicates.

Selection differentials were the mean differences in 12-week body weight or IGF-1 plasma concentrations between the selected individuals and the mean of their sex in each line each generation. Parents without offspring surviving to 12 weeks of age were excluded. Realized heritabilities were calculated as the regression through the origin of direct response on cumulative selection differentials for five generations of selection. Standard errors were calculated from the variance between replicates.

The realized genetic correlation (Falconer 1981) between IGF-1 (I) plasma concentration and 12-week weight (W) was estimated from the data recorded in generation 4 as:

$$r_G = (C_I \cdot C_W / R_W \cdot R_I)^{1/2},$$

where R and C are the direct and correlated responses estimated from the divergence between the high and low lines following selection for both I and W.

Symmetry of correlated responses was investigated by estimating genetic correlations from the correlated response of IGF-1 when selecting for 12-week weight and vice versa (Falconer 1954), as

$$r_G = (C_y \cdot h_x \cdot s_x)/(R_x \cdot h_y \cdot s_y),$$

where R_x and C_y are the direct and correlated responses for X and Y, respectively, h_x and h_y are the square roots of the realized heritability estimates, and s_x and s_y are the phenotypic standard deviations. Standard errors were calculated from the variance between replicates.

Results

Means and standard deviations for IGF-1 concentration and 12-week weight for control line mice are shown in Table 2. There was no significant difference between males and females for IGF-1 concentration, as also

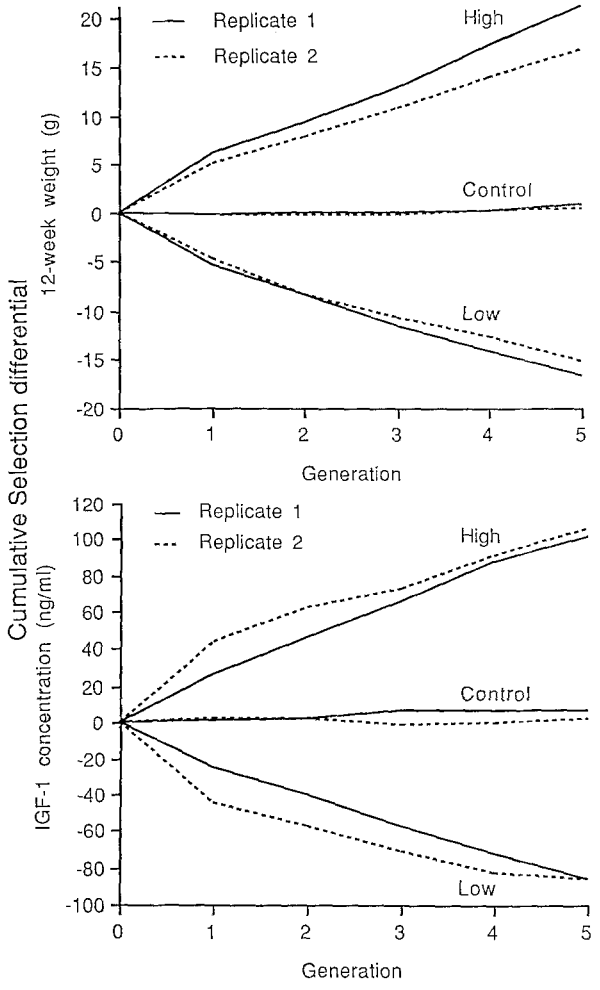

Fig. 1. Cumulative selection differentials plotted against generation number for 12-week weight and IGF-1 concentration

found in the preliminary trial (Table 1). The coefficient of variation of IGF-1 concentration was about double that for 12-week weight (20% versus 10%, respectively.

Selection differentials

Cumulative selection differentials over five generations for both IGF-1 and 12-week weight plotted by generation are shown in Fig. 1. The selection differentials were symmetric in the high and low lines and were similar in the two replicates (Table 3). The cumulative selection differentials (high-low lines) per generation averaged over the two replicates were 41.7 ng/ml for IGF-1 and 7.32 g for 12-week weight and, in standard deviation units (using the standard deviations from the control lines given in Table 2), were 2.64 and 2.61, respectively. The higher selection differentials applied in generation 1 were due to the method used to establish the selection lines. After splitting the base population in half to constitute the weight and IGF-1 lines, the most extreme animals from 24 litters (80–90 mice of each sex) were selected to establish the high and low lines, thus applying a greater selection intensity than was possible within each line in subsequent generations (eight pairs mated).

Table 1. Preliminary trial to investigate the effect of age of measurement on IGF-1 plasma concentration

Age (days)	Sex[a]	IGF-1 (ng/ml)		Body weight (g)	
		Mean	SD[b]	Mean	SD
60	Female	134.0	23.0	23.4	1.9
	Male	138.7	17.8	26.1	2.7
70	Female	114.7	21.0	23.8	2.4
	Male	122.4	11.0	26.9	3.2
80	Female	122.4	21.2	25.0	2.3
	Male	122.8	8.8	27.4	3.2

[a] Ten female and nine mice
[b] Standard deviation

Table 2. Means and standard deviations (SD)[a] for IGF-1 concentration (ng/ml) and 12-week weight (g) in the control lines (generations 1 to 5)

Trait	Item	Replicate 1		Replicate 2	
		Males	Females	Males	Females
IGF-1	Number	143	146	144	125
	Mean	80.3	80.6	71.3	74.5
	SD	16.4	15.8	13.8	17.2
12-week wt.	Number	137	151	131	123
	Mean	29.1	24.6	28.8	24.7
	SD	2.9	2.7	3.1	2.5

[a] Pooled within generations

Direct response

Response to selection for IGF-1 revealed considerable fluctuation by generation and a decline in average IGF-1 concentration over generations, which was consistent in all three lines (high, low, and control) and both replicates (Fig. 2). The control line declined at a rate of -8.5 ± 2.5 ng/ml per generation in replicate 1 and -10.2 ± 4.3 ng/ml per generation in replicate 2.

Response to selection for IGF-1 is illustrated by the deviation of the high or low line performance from that of the control line (Fig. 3). While Fig. 3 suggests there is greater response for low levels of IGF-1 than high levels, this asymmetry is not significant (Table 4). The response measured as the divergence between the high and low lines averaged over the two replicates was 4.22 ng/ml per generation (Table 4). There was considerable variation between the replicates from generation to generation (Fig. 3), but the divergence between the high and low lines was not significantly different in the two replicates (Table 4).

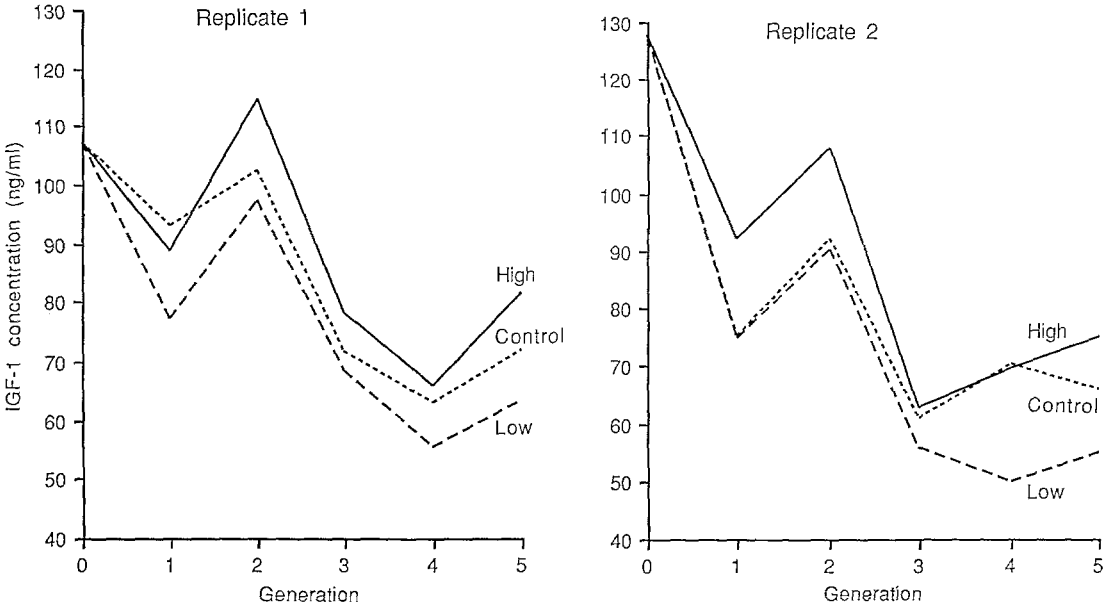

Fig. 2. Direct response for IGF-1 concentration

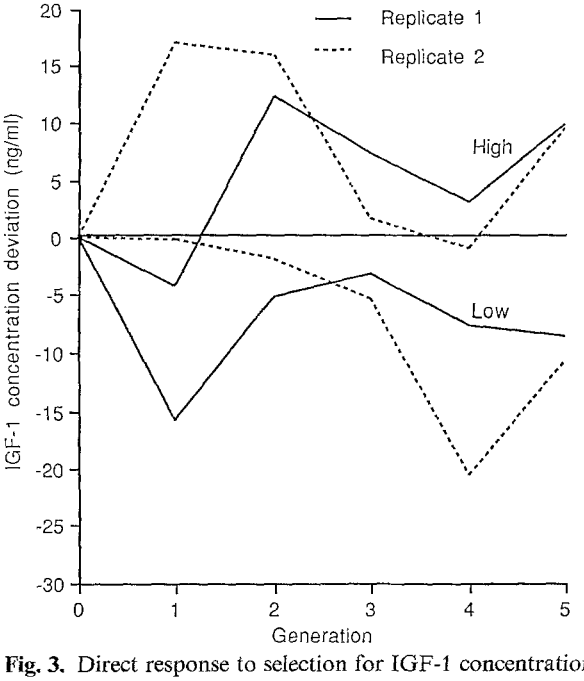

Fig. 3. Direct response to selection for IGF-1 concentration as a deviation from control

Table 3. Regression coefficients (±SE) of cumulative selection differentials (high–low lines) on generation number

Replicate	IGF-1 concentration (ng/ml)	12-week weight (g)
1	39.5±1.1	7.88±0.27
2	43.9±3.8	6.77±0.28
Average	41.7±2.4	7.32±0.28
Average[a]	2.64	2.61

[a] In phenotypic standard deviation units

Response to selection for both high and low 12-week weight was linear and very regular in both replicates over five generations of selection (Fig. 4), with no significant trend in the control lines. Response to selection was symmetric in replicate 1, but in replicate 2 there was greater response for low than for high 12-week weight (Fig. 5 and Table 5). The divergence between the high and low lines averaged over replicates was 3.03 g per generation, with no significant difference between the replicates (Table 5).

Table 4. Regression coefficients (±SE)[a] of direct and correlated responses on generation number in the IGF-1 selection lines

Estimate	IGF-1 concentration (ng/ml)			12-week weight (g)		
	Repl. 1	Repl. 2	Average	Repl. 1	Repl. 2	Average
High-Control	1.89±0.69	1.77±1.30	1.83±0.06	0.20±0.08	0.31±0.05	0.26±0.06
Low-Control	−1.95±0.86	−2.83±0.68	−2.39±0.44	−1.03±0.14	−0.19±0.15	−0.61±0.42
High–Low	3.85±0.82	4.60±1.02	4.22±0.38	1.23±0.17	0.50±0.18	0.87±0.37

[a] The standard error for each replicate is that of respective regression coefficient. The standard error of the average is the empirical standard error based on the variance between replicates of the regression coefficients

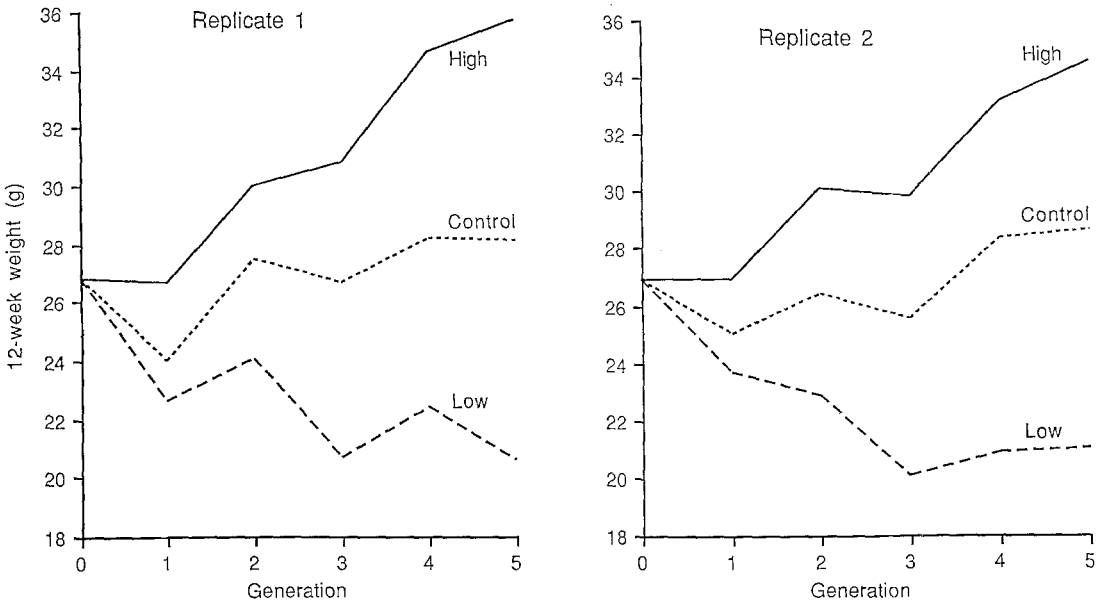

Fig. 4. Direct response to selection for 12-week weight

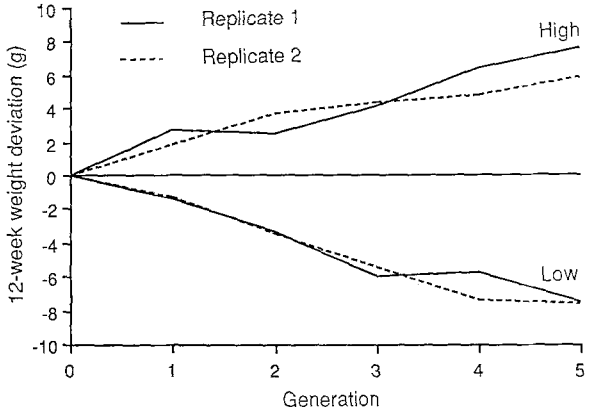

Fig. 5. Direct response to selection for 12-week weight as a deviation from control

Correlated response in 12-week weight

Correlated response in 12-week weight following selection for IGF-1 was not consistent in the two replicates (Fig. 6 and Table 4). While there was a negative trend for IGF-1 in the control lines, the trend for 12-week weight was positive (0.73 and 0.72 g per generation in replicates 1 and 2, respectively). The divergence between high and low lines in replicate 1 was 1.23 g per generation, with greater response for low than for high 12-week weight. In replicate 2 the divergence was 0.50 g per generation, with greater response for high than for low 12-week weight.

Both direct and correlated responses for 12-week weight averaged over replicates are presented in Fig. 7. Divergent response was 3.5 times greater with direct selection for 12-week weight (3.03 g per generation) than through correlated response to selection for IGF-1 (0.87 g per generation). The selection response achieved by five generations of selection has been maintained through to generation 9, despite relaxation of selection from generation 6 onwards.

Table 5. Regression coefficients (±SE)[a] of direct responses on generation number in the 12-week weight selection lines

Estimate	12-week weight (g)		
	Repl. 1	Repl. 2	Average
High-Control	1.52±0.09	1.29±0.09	1.40±0.12
Low-Control	−1.58±0.09	−1.67±0.07	−1.63±0.05
High−Low	3.10±0.08	2.96±0.12	3.03±0.07

[a] See footnote to Table 4

Table 6. Realized heritability estimates (±SE)[a] from the regression of divergence between high and low lines on cumulative selection differential

Replicate	IGF-1 concentration	12-week weight
1	0.10±0.02	0.39±0.01
2	0.11±0.02	0.44±0.01
Average	0.10±0.01	0.41±0.02

[a] See footnote to Table 4

Realized heritabilities and genetic and phenotypic correlations

Realized heritabilities for both IGF-1 and 12-week weight did not differ significantly in the two replicates. Averaged over replicates, they were 0.10±0.01 and 0.41±0.02, respectively (Table 6).

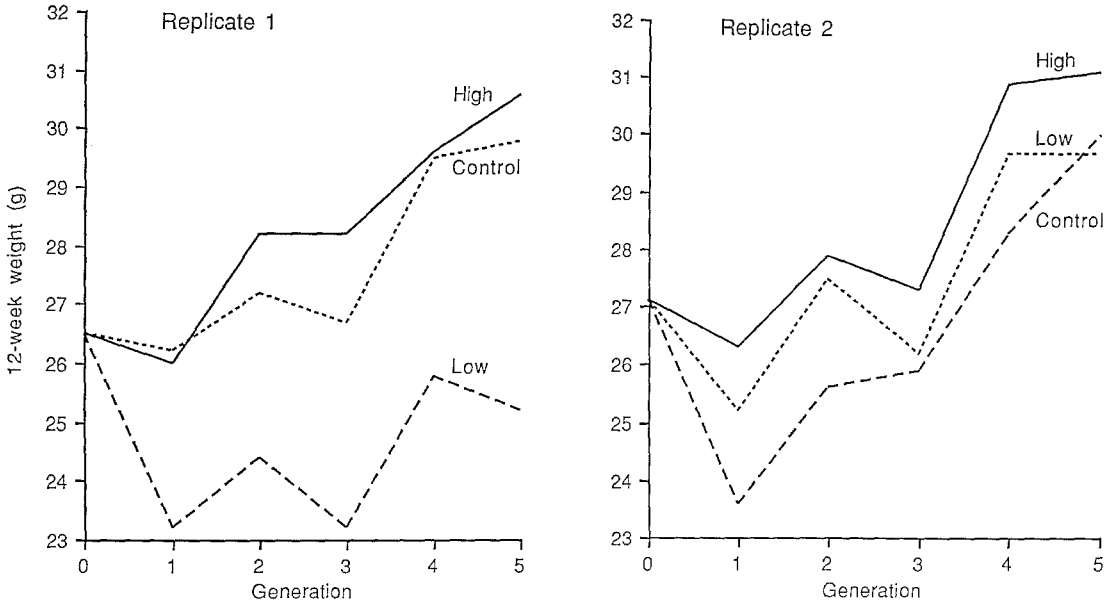

Fig. 6. Correlated response in 12-week weight to selection for IGF-1 concentration

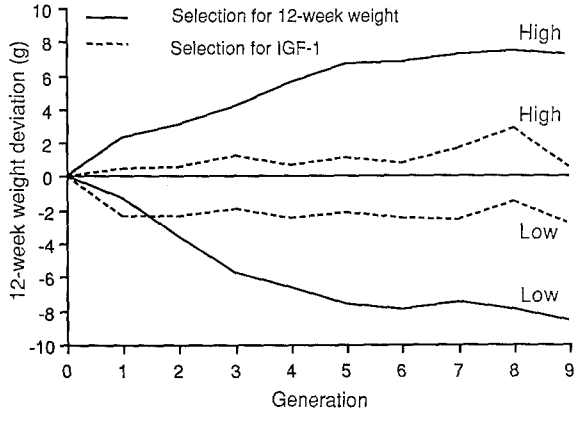

Fig. 7. Direct and correlated responses in 12-week weight as a deviation from control (replicates averaged)

The realized genetic correlation from direct and correlated responses (high-low) for both IGF-1 and 12-week weight measured in generation 4 (Table 7) was 0.58 ± 0.01. The small standard error on this estimate was due to very similar estimates in the two replicates (0.59 and 0.57 in replicates 1 and 2, respectively). The correlated responses were symmetrical, with genetic correlation estimates of 0.66 ± 0.34 and 0.50 ± 0.22 from selection for IGF-1 and 12-week weight, respectively. The phenotypic correlation between IGF-1 and 12-week weight from the 635 mice recorded in generation 4 was 0.38.

Since many previous studies with mice have selected for 6-week weight rather than 12-week weight, the correlated response for 6-week weight in generation 4 is also given in Table 7. After selection for 12-week weight, the divergence between the high and low lines was 8.6 g at 6

Table 7. Direct and correlated responses to selection for IGF-1 and 12-week weight and the correlation response in 6-week weight measured at generation 4

Selection trait	Selection line	No. of mice	IGF-1 (ng/ml)	12-week (g)	6-week wt (g)
IGF-1	High (H)	110	67.0	30.3	25.2
	Control	107	66.8	29.7	23.7
	Low (L)	104	52.7	26.9	22.4
	Divergence (H−L)		14.3	3.4	2.8
12-week wt	High (H)	116	68.0	33.9	26.7
	Control	98	69.5	28.2	23.2
	Low (L)	100	50.8	21.6	18.1
	Divergence (H−L)		17.2	12.3	8.6
	S.E.D.[a]		10.1	1.1	0.9

[a] Standard error of the difference from variation between replicates from a statistical analysis fitting sex, selection line, and selection trait as fixed effects and nesting replicates (random effect) within line and trait

Fig. 8. Inbreeding levels (%) in the different lines at generation 5

Selection trait	Selection line	Replicate 1	Replicate 2	Average of replicates
IGF-1	High	5.5	3.3	4.4
	Control	2.1	2.6	2.4
	Low	5.2	4.7	5.0
12-week wt	High	5.6	4.2	4.9
	Control	2.0	3.3	2.7
	Low	4.6	5.9	5.3

weeks and 12.3 g at 12 weeks. Selection for IGF-1 resulted in a divergence of 2.8 g at 6 weeks and 3.4 g at 12 weeks.

Inbreeding

Due to the selection and mating systems used in this study, no inbreeding occurred until generation 4 in the selection lines and until generation 5 in the control lines. The average inbreeding levels at generation 5 were similar in both the IGF-1 and 12-week weight selected lines (about 5%) and about half of this in the control lines (Table 8).

Discussion

The low realized heritability for IGF-1 in the present study (0.10 ± 0.01) is consistent with the estimate of 0.15 ± 0.12 reported by Blair et al. (1989) following seven generations of divergent selection for IGF-1 measured at 6 weeks of age in mice. The study of Blair et al. (1989) was not replicated, and family selection was used with litter means based on blood bulked from four mice from each litter. Despite both the different sampling ages and the methods of selection, the pattern of selection response for IGF-1 was remarkably similar in the two studies. In both studies there were large fluctuations between generations in IGF-1, the control line fluctuated in its position relative to the high or low lines from generation to generation, and there was a decline in average IGF-1 levels over generations. Blair et al. (1989) expressed concern both about the inconsistent performance of their control line from generation to generation and the different rates of accumulation of inbreeding in their three lines (high, low, and control). They concluded that it was not possible in their study to determine if response to selection for IGF-1 was symmetrical. The present study did not detect any significant degree of asymmetry for high or low selection for IGF-1 (Table 4), and this conclusion is not confounded with different inbreeding levels (Table 8). If asymmetrical selection responses are not important, then the response to selection calculated from the divergence between the high and low lines is the most precise measure of selection response. The estimates in the present study were 3.9 and 4.6 ng/ml per generation in replicates 1 and 2, respectively while Blair et al. (1989) reported a response of 4.9 ng/ml per generation.

We are not aware of any other selection studies in mice for 12-week weight to compare with our realized heritability estimate of 0.41 ± 0.02. There have been numerous selection studies for 6-week weight in mice (reviewed by McCarthy 1982). The best estimate of the realized heritability for 6-week weight in this Q strain of mice following divergent high and low selection is 0.37 ± 0.03, as reported by Falconer (1973) in his classical paper on replicated selection. Since the genetic correlation between 6- and 12-week weight in mice is not significantly different from unity (Kachman et al. 1988), it is not surprising that realized heritabilities at these two ages are similar.

The realized genetic correlation between IGF-1 and 12-week weight was positive and moderately high (0.58 ± 0.01), with no evidence of asymmetry. Blair et al. (1989) found a positive correlated response in 6-week weight following selection for IGF-1 measured at 6 weeks of age. They were not prepared to conclude that this was directly associated with selection for IGF-1 due to erratic changes in 6-week weight over generations, particularly in the line selected for low IGF-1. There was also some variability between replicates in the correlated response in 12-week weight in the present study (Table 4). Averaged over replicates, there was greater response in 12-week weight in the low than the high IGF-1 line, but this asymmetry was not significant. No significant asymmetrical response was found for 6-week weight, with correlated responses averaged over replicates of 0.37 ± 0.02 g per generation in the high IGF-1 line and -0.47 ± 0.10 g per generation in the low IGF-1 line. The correlated response for 6-week weight from the divergence between the high and low line was 0.61 g per generation, which was very similar to that found by Blair et al. (1989) of 0.69 g per generation.

While there is evidence for a positive genetic association between IGF-1 and body weight in mice, this does not mean that IGF-1 is necessarily a useful criterion for indirect selection. The merit of indirect selection relative to direct selection also depends on the intensities of selection that can be applied and on the heritabilities of the direct and indirect traits (Eq. 19.9, Falconer 1981). Selection intensities were almost identical for IGF-1 and 12-week weight (Table 3). Thus, the substantially higher heritability of either 6-week weight or 12-week weight than IGF-1 favors direct selection for body weight, which was clearly demonstrated in this study (Fig. 7).

The classical somatomedin hypothesis, which postulated that the effects of growth hormone are mediated by circulating IGFs of hepatic origin, has recently been modified in several important respects (D'Ercole et al. 1984). It is now appreciated that IGFs are produced at multiple sites. The concept of local action of growth hormone in some tissues to promote both cell differentiation and proliferation through local production of IGF-1 acting in an autocrine or paracrine manner has been established. The extent to which the differences in circulating IGF-1 in the high and low IGF-1 selection lines of our present study reflect the true biological differences in active IGF-1 between the two lines is unknown.

There is now increasing evidence that the IGF plasma binding proteins may play a functional role in controlling the biological activity of the bound IGF-1 (Ooi and Her-

ington 1988). As over 95% of circulating IGF-1 is bound, the binding proteins will have a profound effect on circulating and locally produced IGF-1 actions. The binding proteins themselves appear to be regulated by growth hormone and IGFs (Zapf et al. 1989; Clemmons et al. 1989). It is therefore possible that changes in plasma IGF-1 through genetic selection may be mediated by changes in binding proteins. Possible changes in binding proteins in the high and low IGF-1 lines of mice and their biological consequences await evaluation.

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References

Blair HT, McCutcheon SW, Mackenzie DDS, Gluckman PD, Ormsby JE, Breier BH (1989) Responses to divergent selection for plasma concentrations of insulin-like growth factor-1 in mice. Genet Res 53:187–191

Breier BH, Bass JJ, Butler JH, Gluckman PD (1986) The somatotrophic axis in young steers: influence of nutritional status on pulsatile release of growth hormone and circulating concentrations of insulin-like growth factor-1. J Endocrinol 111:209–215

Breier BH, Gluckman PD, Bass JJ (1988a) Influence of nutritional status and oestrodial-17β on plasma growth hormone, insulin-like growth factors-I and -II, and the response to exogenous growth hormone in young steers. J Endocrinol 118:243–250

Breier BH, Gluckman PD, Bass JJ (1988b) Plasma concentrations of insulin-like growth factor-1 and insulin in the infant calf: ontogeny and influence of altered nutrition. J Endocrinol 119:43–50

Canalis E (1980) Effect of insulin-like growth factor-I on DNA and protein synthesis in cultured rat calvarie. J Clin Invest 66:709–719

Clemmons DR, Van Wyk JJ (1981) Somatomedin: physiological control and effects on cell proliferation. In: Basearga R (ed) Tissue growth factors. Handbook of experimental pharmacology. Springer, Berlin, pp 161–208

Clemmons DR, Thissen JP, Maes M, Ketelslegers JM, Underwood LE (1989) Insulin-like growth factor-1 infusion into hypophysectomized or protein-deprived rats induces specific IGF binding proteins in serum. Endocrinology 125:2969–2972

D'Ercole AJ, Stiles AD, Underwood LE (1984) Tissue concentrations of somatomedin C: further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action. Proc Natl Acad Sci USA 81:935–939

Daughaday WH, Rotwein P (1989) Insulin-like growth factors-I and -II. Peptide, messenger ribonucleic acid and gene structures, serum and tissue concentrations. Endocrinol Rev 10:68–91

Eigenmann JE, Patterson DF, Froesch ER (1984) Body size parallels insulin-like growth factor-I levels but not growth hormone secretary capacity. Acta Endocrinol 106:448–453

Falconer DS (1954) Validity of the theory of genetic correlation. J Hered 45:42–44

Falconer DS (1973) Replicated selection for body weight in mice. Genet Res 22:291–321

Falconer DS (1981) Introduction to quantitative genetics, 2nd edn. Longman, London New York, 340 pp

Gluckman PD, Butler JH (1983) Parturition-related changes in the insulin-like growth factors-1 and -2 in the perinatal lamb. J Endocrinol 99:223–232

Gluckman PD, Breier BH, Davis SR (1987) Physiology of the somatotropic axis with particular reference to the ruminant. J Dairy Sci 70:442–466

Handelsman DJ, Spaliviero JA, Scott DC, Baxter RC (1987) Hormonal regulation of the peripubertal surge of insulin-like growth factor-1 in the rat. Endocrinology 120:491–496

Kachman SD, Baker RL, Gianola D (1988) Phenotypic and genetic variability of estimated growth curve parameters in mice. Theor Appl Genet 76:148–156

Lund-Larsen TR, Bakke H (1975) Growth hormone and somatomedin activities in lines of pigs selected for rate of gain and thickness of backfat. Acta Agric Scand 25:231–234

McCarthy JC (1982) The laboratory mouse as a model for animal breeding: a review of selection for increased body weight and litter size. Proc 2nd World Congr Genet Appl Livest Prod 5:66–83

Monier S, Le Cam A, Le Marchand-Brustel Y (1983) Insulin and insulin-like growth factor-I. Effects on protein synthesis in isolated muscles from len and goldthioglucose-obese mice. Diabetes 32:392–397

Ooi GT, Herington AC (1988) The biological and structural characterization of specific serum binding proteins for insulin-like growth factors. J Endocrinol 118:7–18

Schmid C, Steiner I, Froesch ER (1984) Insulin-like growth factor-I supports differentiation of cultural osteoblast-like cells. FEBS Lett 173:48–52

Schoenle E, Zapf J, Humbel RE, Froesch ER (1982) Insulin-like growth factor-I stimulates growth in hypophysectomized rats. Nature 296:252–253

Zapf J, Schmid C, Froesch ER (1984) Biological and immunological properties of insulin-like growth factors (IGF) I and II. Clin Endocrinol Metab 13:3–30

Zapf J, Hauri C, Waldvogel M, Futo E, Hasler H, Binz K, Guler HP, Schmid C, Froesch ER (1989) Recombinant human insulin-like growth factor-1 induces its own specific carrier protein in hypophysectomized and diabetic rats. Proc Natl Acad Sci USA 86:3813–3817