THE EFFECT OF THE TRANSGENE FOR PORCINE GROWTH HORMONE ON GENETIC AND PHENOTYPIC PARAMETERS FOR GROWTH AND REPRODUCTION IN MICE.

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INTRODUCTION

Transfer of extra copies of the gene for growth hormone into the genome of mice and pigs has been shown to increase growth performance (Owens et al. 1989; Vize et al. 1988). An important step in the integration of transgenes into a breeding programme is the determination of their effect on phenotypic and genetic parameters. Transgenic mice provide a useful model for these investigations. This study was designed to evaluate the effect of a porcine growth hormone (pGH) transgene on some genetic and phenotypic parameters for growth and reproduction traits in mice. Preliminary results are presented.

MATERIALS AND METHODS

MICE

The transgenic mice were eighth generation descendents of an individual founder mouse. The gene construct used in the production of the founder mouse contained a porcine growth hormone fusion gene under the transcriptional control of the human metallothionein-IIa promotor (for details see Vize et al. 1988). There was no exogenous control of the expression of the transgene. The line was maintained by mating hemizygous transgenic males to non-transgenic females from a random bred control line.

EXPERIMENTAL DESIGN

Sixty hemizygous transgenic male mice were each mated to five non-transgenic Balb/C females in order to produce a population of male mice (n=336). The level of pGH secretion in these male mice was determined by a radioimmunoassay of plasma for pGH in which mouse pituitary GH has extremely poor crossreactivity. Previous studies with mice possessing this transgene had shown the level of pGH to be around 5.2 ng/ml in non-transgenic mice (Seamark, pers comm) and between 80 and 9,000 ng/ml in transgenic mice (Owens et al. 1989) with this assay. For the purposes of this experiment, mice with a pGH level of greater than 100ng/ml were designated transgenic (T) and those with a pGH level of less than 20ng/ml were designated non-transgenic (N).

The experimental design of Hill and Thompson (1977) uses the selection of high and low ranking parents to increase the precision of a heritability estimate obtained by the parent-offspring regression method. In this study, the fifteen highest and lowest ranking males, based on body weight at nine weeks of age, were selected in each population i.e. transgenic and non-transgenic. The thirty selected males in each population were each mated to five non-transgenic Balb/C females. Levels of insulin-like growth factor-1 (IGF-1) in the selected males were measured on acid-ethanol extracts of plasma by human IGF-1 immunoassay. The sires were removed seventeen days after mating and the dams were caged individually. The progeny were weaned 21 days after birth. The male progeny were individually identified and kept until they reached nine weeks of age.

The mating of a hemizygous transgenic mouse to a non-transgenic mouse will produce progeny of which on average half are transgenic and half are non-transgenic. At the time of publication the progeny of the transgenic sires had not been identified as transgenic or non-transgenic by pGH radioimmunoassay. Therefore the progeny of the transgenic sires are a mixed population of transgenic and non-transgenic mice.

RESULTS

Means and standard deviations for growth and reproduction traits for the two groups of sires are presented in Table1.

TABLE 1 PHENOTYPIC PARAMETERS FOR GROWTH AND REPRODUCTON

	SIRE TRAITS			PROGENY TRAITS			
	9ww (g)	pGH ng/ml	IGF1 ng/ml	CR %	AWB (g)	AWW (g)	SUR %
T	38.6[a]	586.3[a]	285.1[a]	68.0	1.58	8.83	87.7
N	29.7[b]	16.2[b]	186.7[b]	82.0	1.53	8.41	87.8

a,b different superscripts indicate significant difference ($P<0.001$)

The group means for 9ww (9 week weight), pGH and IGF1 of the sires, conception rate measured as percentage of dams mated that littered (CR) and the pre-weaning survival (SUR) of the progeny were compared using an analysis of variance. There was no significant difference between the groups for SUR or CR. The group means for average weight at birth (AWB) and average weight at weaning (AWW) of the progeny were compared using an analysis of variance taking numbers born alive and numbers weaned as covariates respectively. No significant differences were found.

In Table 2 phenotypic correlations between 9ww, pGH and IGF1 levels are given for the transgenic (above the diagonal) and non-transgenic sires (below the diagonal).

TABLE 2 PHENOTYPIC CORRELATIONS FOR 9ww, GH, IGF1 and CONCEPTION RATE.

	9WW	pGH	IGF1	CR
9WW		0.21	-0.18	-0.18
pGH	-0.25		-0.08	0.17
IGF1	0.40 *	-0.14		0.12
CR	0.11	0.05	0.24	

* P<0.05

Table 3 presents the mean weight of the male progeny of the transgenic (T) and non-transgenic sires (N) at birth (Bw), 3(3ww), 6 (6ww) and 9 (9ww) weeks of age

TABLE 3 GROWTH OF MALE PROGENY OF TRANSGENIC AND NON-TRANSGENIC SIRES (g)

	Bw	3ww	6 ww	9 ww
T	1.58 (0.19)+	9.37(1.94)	23.96 (4.13)	30.42 (6.42)
N	1.53 (0.27)	8.76(1.73)	21.90 (2.82)	26.90(2.60)

+ standard deviation

Birth weight is a mean calculated from the total litter weight at birth divided by the number born alive.

The heritability for 9ww were 0.28 $\pm$ 0.07 for the transgenic population and and 0.27$\pm$0.08 non-transgenic population..

DISCUSSION

The stimulation of growth through the expression of a synthetic growth hormone gene introduced into the genome is well established (Owens et al. 1989, Palmiter et al. 1982). In this study expression of the pGH transgene in mice was associated with a 35 fold increase in circulating GH, a 1.5 fold increase in plasma IGF1 and a 1.3 fold increase in body weight at nine weeks of age. The concommitant elevation of GH and IGF1 levels in transgenic mice observed here is consistent with other studies in both mice and pigs possessing growth hormone transgenes (Mathews et al. 1988a, Mathews et al. 1988b, Miller et al. 1988, Owens et al, 1989). These results support the somatomedin hypothesis that IGF1 mediates the somatotrophic effects of GH. The absence of a positive phenotypic correlation between IGF1 and 9wwin the population of transgenic mice is

consistent with the relationship between IGF1 and growth rate being curvilinear. Miller et al. 1988 also found no correlation between IGF1 and growth rate or GH levels in growth hormone transgenic pigs.

The negative effect of the transgene on conception rate approached significance (P=0.07). Male fertility may be adversely affected by high levels of GH. Barria and Bradford (1981) reported reduced male fertility in a line of mice selected for rapid gain

The heritability estimates for nine week weight reported here indicate that the presence of the transgene in the "mixed" population did not alter the heritability of growth rate. In a population consisting soley of transgenic animals, the chronic expression of GH may remove some of the genetic variation for growth, and thus reduce the heritability of this trait. Pidduck and Falconer, (1978) demonstrated this by introducing the gene for hypopituitary dwarfism into strains of mice differing genetically in growth rate through previous selection. Their results indicate that GH is responsible for some, but not all, of the genetic variation in growth.

This study has demonstrated that the presence of a transgene will alter the phenotypic correlations between some traits. We may expect that the transgene will alter the genetic and phenotypic parameters for other traits, particularly those directly influenced by GH such as carcass composition and efficiency.

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