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Multiple effects of an additional growth hormone gene in adult sheep¹

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ABSTRACT: Molecular genetics provides an increasing capacity to modulate the function of individual genes, but the practical implications of these technologies are still poorly understood. This study examined adult Merino or Merino-cross sheep that had an additional copy of the ovine GH gene with a modified metallothioneine promoter, which resulted in a doubling of the plasma concentration of GH. Previous work showed that up to the age of 18 mo, GH sheep grew faster and had less s.c. fat, with only minor effects on fleece production. The present paper describes characteristics of reproduction, wool production, and animal health of these sheep during the following 2 yr of adult life. Ewes with the GH gene had a greater ovulation rate (1.78 vs. 1.35; $P < 0.05$), but bore fewer lambs, apparently

due to greater fetal loss after mating. Grease fleece weight was increased ($P < 0.05$) due mainly to a greater content of suint (9.1 vs. $7.7 \pm 0.4\%$, $P < 0.01$), which was associated with a deeper color of the raw wool. Effects on clean fleece weight and fiber diameter were not consistent between years. The GH sheep had swollen metatarsal and metacarpal joints, which was associated with a need for more frequent hoof-trimming, and more GH than control sheep died during the experiment ($P < 0.001$). All of these changes are consistent with previously reported effects of increased plasma GH. Results of this study show that increased activity of a single gene (GH) affected several production characteristics and predisposed the animals to a number of distinct health problems, some of which developed after the normal age of genetic selection.

Key Words: Growth Hormone, Health, Pleiotropy, Sheep, Somatotropin, Transgene

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Introduction

Growth hormone affects the partitioning of nutrients among tissues in sheep and cattle, increasing bone growth and milk production, and decreasing fatness. Plasma concentrations of GH are increased in cows genetically selected for high milk production (Bonczek et al., 1988) and in sheep selected for low levels of fatness (Francis et al., 1995), indicating that GH is genetically correlated with these traits. Many of the effects of GH are mediated by accompanying increases in the concentration of IGF-1 (Scaramuzzi et al., 1999).

The role of GH in sheep has been investigated by hormone injections, but longer-term studies have been facilitated by the production of sheep carrying an additional copy of the ovine GH gene with a downregulated

metallothioneine promoter (Ward and Brown, 1998). These sheep have plasma concentrations of GH that are approximately twice the normal range (Adams et al., 2002). Sheep carrying the GH transgene grew more rapidly and had decreased s.c. fat up to the age of 18 mo (Adams et al., 2002). Fecal nematode egg counts (FEC) were increased in the GH sheep, and a greater proportion of male animals had retained testes.

A variety of other functions in mammals are affected by GH, including female reproduction and milk production (Hull and Harvey, 2001), water and sodium metabolism (Johannsson et al., 2002), increased soft tissue growth in the extremities (Findling and Tyrrell, 1991), and impaired cardiac function (Bollano et al., 2000). The significance of these effects for animal production is not clear, although selection of cows for increased milk production, which increases plasma GH (Bonczek et al., 1988), is associated with increased foot problems and impaired fertility (Lyons et al., 1991). The present article defines the effect of increased GH in sheep on animal health, reproduction, and wool production in mature GH transgenic sheep.

Materials and Methods

Experimental Animals and Husbandry

Production of the transgenic experimental animals was described by Adams et al. (2002). In brief, 69 Me-

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rino, 49 Poll Dorset, and 49 Border Leicester ewes were inseminated with semen from three fourth-generation Merino rams derived from a single founder animal. These rams were heterozygous for a transgene of an ovine GH construct with a modified metallothionein promoter (Ward and Brown, 1998), which approximately doubled plasma concentrations of GH. The presence of the transgene in the progeny was established by Southern blot analysis (Adams et al., 2002). Sheep that did not carry the transgene were designated as controls. The additional gene was not expressed in progeny from one of the three rams, so that although they carried the inserted DNA, GH secretion was not affected, and they performed identically to the controls. Sheep with an active transgene (GH sheep) had higher plasma GH, grew faster, and were leaner than controls (Adams et al., 2002).

The performance of the Merino and Poll Dorset progeny up to the age of 18 mo, reached in January 2001, has been reported previously (Adams et al., 2002). The present article describes characteristics of the sheep over the following 2 yr, until March 2003. An additional 13 progeny of the Border Leicester ewes (11 controls and two transgenics) that were omitted from the previous paper are included in the present report.

The sheep were grazed together as a group in a paddock with many shelter trees at the CSIRO Bakers Hill research station in Western Australia, and inspected regularly. Seasonal rainfall in this area leads to dependence on annual pastures for animal feed, with green and growing pasture only during winter and spring. The pastures senesced in early summer, and the sheep grazed dry dead pasture until the following winter. Sheep were given supplements of 150 g of lupin seed per animal per day during late summer and autumn to ameliorate the loss of live weight. Because the GH sheep were susceptible to intestinal helminths (Adams et al., 2002), all sheep were treated with an intraruminal controlled-release capsule containing the anthelmintic ivermectin (Ivomec Maximizer; Merial Australia, Parramatta, Australia) over the period when the pasture was green. Random samples indicated that FEC was low throughout the experiment.

The sheep were shorn in October 2001, 10 mo after the second shearing described by Adams et al. (2002). At this shearing, the sheep were 27 mo old, and there were 26 GH sheep, 35 controls, and 63 sheep that had descended from the ram with the silenced gene. Wool data from sheep with a silenced gene were incorporated with control data after preliminary statistical analysis indicated that they did not differ from sheep without the transgene. In December 2001, these 63 sheep were culled, and therefore were not present at the second shearing in October 2002.

By the second shearing at 39 mo of age, five GH sheep had died, and one was culled after it was recognized as a hermaphrodite, leaving 20 GH sheep and 35 controls. In addition, 16 female progeny aged 20 mo, born from the insemination in February 2001 (see below), were

shorn at this time. These were characterized as seven GH transgenics and nine controls, based on the presence of a transgene detected by Southern analysis of their DNA and confirmed by measurement of plasma concentrations of GH, as described previously (Adams et al., 2002). Wool data from these ewes are reported herein. The 14 male progeny from this mating were characterized as three controls and 11 transgenics. These animals were not castrated, and their data are not included herein because the effects of sex and transgene were confounded due to the low number of control rams.

Husbandry procedures were modified as much as possible to decrease physical stress on the animals. The CSIRO Floreat Park Animal Ethics Committee monitored the welfare of the animals involved in this study, and the genetically manipulated animals were managed and contained as required by the Australian Genetic Manipulation Advisory Committee and the Office of the Gene Technology Regulator, supervised by the CSIRO Floreat Park Institutional Biosafety Committee.

Reproduction

In February 2001, the ewes (12 GH and 42 controls) were artificially inseminated as described by Kadokawa et al. (2003a) with semen from rams heterozygous for the GH transgene. These rams were different from those used to commence the study (Adams et al. 2002), although all descended from the original founder animal. Female offspring resulting from this mating (seven GH and nine controls) were run with the main flock after weaning, as indicated previously.

In January 2002, the ewes (nine GH and 17 controls) were joined to two unrelated Merino rams fitted with harnesses and crayons to record mating events (Radford et al., 1960). Crayons were changed and marks recorded biweekly for 8 wk. The ovulation rate was recorded by laparoscopy 4 wk after the rams were introduced. Pregnancy was examined by ultrasound 85 d after the rams were introduced. The ewes were inspected daily around the expected time of parturition, and lamb births were recorded. Lambs resulting from this mating were not used in the study.

In March 2003, 16 ewes, aged 45 mo (seven GH and nine controls), and 12 ewes, aged 20 mo (six GH and six controls), were killed with an overdose of sodium pentobarbitone. Seven days before slaughter, ewes were fitted with a flugestone intravaginal sponge (Ovokron; Novartis Animal Health, Pendle Hill, Australia) to synchronize their estrous cycles. The reproductive tracts were recovered and weighed, and the number of corpora lutea was counted.

Measurements on Wool

Grease fleece weight (**GFW**) was recorded at each shearing, and the wool yield was used to calculate the

clean fleece weight (CFW). Wool characteristics including yield, fiber diameter (FD), CV of fiber diameter (CVfd), and staple strength (SS) were measured by a commercial laboratory (Australian Fibre Testers, York, Australia). Individual midside staples from the October 2002 shearing were washed in petroleum ether and the variation in FD both along and between wool fibers was measured with an OFDA2000 (BSC Electronics, Myaree, WA, Australia). Wax and suint content of greasy wool staples from these samples was measured as described by Hemsley and Marshall (1984). Wool color was measured on greasy and clean samples using a Minolta model CR310 Chromameter (Konica Minolta Sensing, Inc., Osaka, Japan), as described by Patterson and Whitely (1984).

Statistical Analyses

The data were analyzed statistically with the package Systat 10 (SPSS Inc., Chicago, IL), using a general linear model, and mean and SEM values are presented. The main factors (breed, sex and GH transgenesis in both years, and age in the 2002 shearing) and their interactions were examined. The final model presented does not include any factor or interaction that did not significantly ($P < 0.05$) improve the fit of the models. Categorical data, including the proportion of sheep that died and the ovulation rate, were analyzed by Fisher's Exact test using the same software.

Wool measurements were analyzed separately in each year because the sheep studied in each year were substantially different. There were low numbers of Poll Dorset and Border Leicester sheep in some cells, so the breed comparison was carried out as Merino vs. non-Merino breeds. The main factors (breed, sex, and GH transgenesis in both years, and age in the 2002 shearing) were examined initially with ANOVA. No significant interactions were detected, so the results presented are from the simplest general linear model that contained the factors that were statistically significant ($P < 0.05$). Sex was a significant factor for fleece weight, age for FD and CVfd, and age and breed were significant factors for wool color.

Results

Animal Health

The metacarpal and metatarsal joints of all of the GH sheep became swollen (Figure 1), a problem that increased in severity as the sheep aged. As a result of joint softening, the toes became splayed and the phalangeal bones in the toes became displaced, allowing the toes to rotate so that the hooves did not come in normal contact with the ground. As a result of the decreased wear on the hooves, excessive horn growth needed to be trimmed more frequently in the GH sheep; no trimming was required before the age of 15 mo, but after that, the 30 GH sheep required nearly twice the number of

trimmings that the 76 control sheep required before the second shearing 24 mo later (2.9 vs. 1.5 times \pm 0.1; $P < 0.001$).

From the total of 35 sheep without a transgene and 26 GH adults present at shearing in October 2001, no controls and nine GH sheep ($P < 0.001$) died before March 2003 when the study was terminated. These deaths came from a variety of causes: five died at times of normal husbandry procedures, including three that died during droving or shearing from what was diagnosed clinically and upon postmortem examination to be cardiac arrest, and two that died in the 2 wk before parturition was due. One sheep was euthanatized because it developed skin cancer and another because it had severe lameness in the hip joint. An additional two sheep were found dead in the paddock of unknown causes.

A further GH sheep was culled in December 2001 because it was recognized to be a hermaphrodite, having inguinal testes and female external genitalia.

Reproduction

When the ewes were mated naturally with rams in 2002, 11 of the 17 controls and four of the nine GH ewes were marked by the rams in the first period, 10 control and five GH ewes were marked in the second period, and one control and one GH ewe were marked in the third period. Return to service rates calculated over the four service periods were 24% for controls and 30% for GH ewes. At laparoscopy, all the ewes had corpora lutea in their ovaries, and the ovulation rate was lower in the controls than in the GH ewes (1.35 vs. 1.78; $P < 0.05$). Ewes lambed in the paddock, and as indicated above, two of the nine GH ewes died in the last 2 wk of pregnancy compared with zero controls. Both groups had similar embryonic loss during the time between mating and ultrasound at d 60, but calculated fetal losses after d 60 were somewhat greater in the GH ewes (Table 1).

At slaughter in March 2003, the paired ovaries from the GH sheep were heavier than controls (3.8 vs. 2.2 ± 0.4 g; $P = 0.01$). Half the ewes (6/14 controls and 7/13 GH ewes) were anovulatory at the time of slaughter. Among sheep that did have a corpus luteum, three of eight controls and four of six GH ewes had twins, and the other animals had singles. There was no significant effect of the age of ewe on these data. The weight of the uterus in GH ewes was similar to that of controls (35.3 vs. 34.9 ± 2.3 g,) and the weight of the cervix also was similar to the controls (8.1 vs. 7.7 ± 0.5 g).

Live Weight and Wool Characteristics

All the sheep became heavier over time, but the GH sheep were consistently 15% heavier than controls throughout the study. At the beginning of the study in February 2001, the GH sheep weighed 62.5 ± 1.3 kg compared with 54.4 ± 1.2 kg for the controls ($P < 0.001$),



Figure 1. Foreleg from a control (left) and a GH (Merino-cross sheep that had an additional copy of the ovine GH gene with a modified metallothionine promoter) sheep (right), showing swelling of the terminal joints and distortion of the hoof of the GH ewe.

and at the end of the experiment in February 2003, the respective weights were 82.2 vs. 71.4 ± 1.6 kg ($P < 0.01$).

In both years, GH sheep had a heavier grease fleece ($P < 0.05$; Table 2) mainly because of lower yield (i.e., a greater proportion of wax, suint, or dust). Measurements on the October 2002 wools showed the difference was due predominantly to a greater content of suint (Table 3). This difference was accompanied by a deeper color in the fleece from the GH sheep (measured as tristimulus values X, Y, and Z; Table 3); however, the scoured color was not affected by GH status (data not presented).

Table 1. Number of ewes with single or twin ovulations, twin pregnancies, and twin births in 17 control ewes and nine GH ewes after natural mating in 2002^a

Item	Control		GH	
	Single	Twin	Single	Twin
Corpora lutea by laparoscopy	11	6	2	7
Pregnant at ultrasound around d 60	13	4	3	5 ^b
Ewes bearing single or twin lambs	13	4	5	1 ^c

^aGH = Merino-cross sheep that had an additional copy of the ovine GH gene with a modified metallothionine promoter.

^bOne GH ewe was not pregnant.

^cTwo GH ewes died in the last 2 wk of pregnancy.

The only other finding consistent across both years was an increase in variation in FD along the fiber (Table 2). Increases in CFW, FD, and SS were observed in one of the two years.

Discussion

This study enabled us to define the effect of enhanced GH secretion in adult sheep under normal husbandry conditions. The GH sheep were not exactly analogous to sheep in which GH has been increased through genetic selection: for example, GH secretion was continuous rather than pulsatile, and it is possible that inserting the gene interrupted the function of other genes. Nevertheless, the discussion below indicates that most of the effects observed can be mimicked by treatment with GH, or by elevated GH in humans. Therefore, it is reasonable to conclude that the biological changes reported resulted from exposure to an approximate doubling of plasma GH concentrations (Briegel and Adams, 2002) over a prolonged period.

It is likely that the increased death rate in the GH sheep can be attributed to the increased plasma concentration of GH. Increased GH has been associated with decreased longevity in mice (Brown-Borg et al., 1996). In humans, excessive GH causes a syndrome called

Table 2. Mean values and standard errors for wool production in control sheep and sheep carrying an additional GH gene^a

Item	2001 shearing			2002 shearing		
	Control	GH	SEM	Control	GH	SEM
No. of sheep	98	26		44	27	
Wool characteristic ^b						
GFW, kg	3.4	3.7*	0.1	3.9	4.6*	0.2
Yield, %	72.2	65.4***	0.8	68.5	66.7	1.0
CFW, kg	2.45	2.41	0.07	2.7	3.2**	0.1
FD, μm	23.8	24.7**	0.2	22.1	22.8	0.2
SS, Newtons/kilotex	19.7	34.3***	1.3	21.4	22.5	1.5
CVfd, %	20.7	20.5	0.3	23.2	24.4	0.5
CValong, %	7.9	8.8*	0.2	9.9	11.7**	0.6
CVacross, %	19.5	20.1	0.2	19.8	19.9	0.5

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; for comparisons within year.

^aGH = Merino-cross sheep that had an additional copy of the ovine GH gene with a modified metallothionein promoter.

^bGFW = grease fleece weight; CFW = clean fleece weight; FD = fiber diameter; SS = staple strength; CVfd = CV in fiber diameter; CValong = CV in fiber diameter along the staple; and CVacross = CV in fiber diameter across the staple.

acromegaly (Findling and Tyrell, 1991), accompanied by an increased death rate from cardiovascular disease and cancer (Orme et al., 1998). In affected people, the heart may function normally at rest, but it fails to meet increased demand during exercise (Spinelli et al., 2003), leading to cardiac failure. A similar phenomenon of sudden death in otherwise healthy sheep was responsible for up to half the unexpected deaths in the GH sheep.

Swelling of the metacarpal joints and surrounding tissue also is common in human acromegaly (Findling and Tyrell, 1991). The condition in the GH sheep required constant attention to prevent problems with lameness. Foot problems and lameness also are an issue in dairy cows (Rauw et al., 1998), where they are associated genetically with high milk productivity (Lyons et al., 1991). Interestingly, a preliminary study indicated that milk production in GH sheep was approximately double that of controls (R. Bencini and J. R. Briegel, unpublished data).

Table 3. Characteristics associated with differences in yield of wool from 44 control and 27 GH sheep after shearing in 2002^a

Item	Control	GH	SEM	P-value
Yield component, %				
Suint	7.7	9.1	0.4	0.005
Wax	15.5	16.9	0.6	0.09
Dust	5.4	5.6	0.5	0.90
Tristimulus color of raw wool ^b				
X	46.1	43.2	0.8	0.01
Y	46.1	43.0	0.9	0.01
Z	37.9	34.5	0.9	0.01
Y-Z	8.5	8.5	0.3	0.90

^aGH = Merino-cross sheep that had an additional copy of the ovine GH gene with a modified metallothionein promoter.

^bX = red; Y = green (brightness); Z = blue; Y-Z = yellowness.

Two other health problems were observed in the GH sheep when they were younger: 1) higher nematode FEC; and 2) an increased proportion of males with retained testes (Adams et al., 2002). In the current study, control measures kept the FEC to very low levels. Polcott and Greeff (2004) reported a negative genetic correlation (-0.26) between fat depth and FEC, and results of the present study suggest that GH may contribute to this relationship.

This work highlights the importance of examining the effects of genetic selection in sheep beyond the normal time at which selection is made. At a younger age, the GH sheep had several advantages, including faster growth rate and less s.c. fat (Adams et al., 2002). The foot problems and increased death rate did not become apparent until later life. Therefore, it would be wise to continue monitoring health effects throughout the life of sheep genetically selected for rapid lean growth or for increased milk production.

Results of the present study indicate that the reproductive process in GH ewes may be affected at almost every stage. First, the GH ewes had increased ovulation rate and heavier ovaries, as noted in most animal species treated with GH (Hull and Harvey, 2001). Ewes treated with GH have more large, healthy ovarian follicles (Joyce et al., 2000), probably through the action of IGF-1, rather than a direct effect of the GH itself (Scaramuzzi et al., 1999). Plasma concentrations of IGF-1 and insulin in the GH ewes around the time of artificial insemination in 2001 were increased almost threefold compared with the controls (Kadokawa et al., 2003a), whereas follicle-stimulating hormone was decreased.

Second, the capacity to conceive was decreased in some circumstances. As reported by Kadokawa et al. (2003a), only 3 of the 12 GH ewes lambed after AI in 2001 compared with 27 of the 42 control ewes. The

hormone data and other details of the outcomes presented by Kadokawa et al. (2003a) indicated that the GH ewes failed to conceive. This was overcome in the next year by mating the GH ewes naturally to a relatively high proportion of rams, at which time they achieved similar conception rates to controls, as judged by returns to service and number of ewes pregnant at approximately 60 d.

Finally, survival of the fetus was impaired in those GH ewes that did conceive. After d 60 of pregnancy, the GH sheep lost four of five twin fetuses, compared with zero of four twin fetuses in the controls. The cause of fetal loss was unclear, but it may have been related to the relatively poor control of plasma glucose concentrations in the GH sheep (Kadokawa et al., 2003b).

Ewes selected genetically for leanness had a higher twinning rate (McEwan et al., 1992; McEwan et al., 2001), which normally results from more twin ovulations. This is counterintuitive because an increased ovulation rate is usually associated with increased fatness resulting from good nutrition (Gunn et al., 1969), but the outcome has been observed in several selection lines (McEwan et al., 2001). There are no reports of higher fetal loss in animals selected for growth or milk production.

Effects of GH on wool production and quality were relatively minor. The GH sheep consistently had a lower wool yield (Adams et al., 2002) due to an increased content of suint, a product of the accumulation of salts derived from sweating. Increased sweating is a recognized effect of increased plasma GH in humans (Sneppen et al., 2000), and the increased suint indicates that a similar phenomenon occurred in the GH sheep. Suint content also is associated with increased yellow wool color (Sumner et al., 2004), which probably caused the increased color in the greasy wool from GH sheep. It is possible that selection of sheep for bright colored wool might result in sheep with lower GH activity, but this has not been investigated.

Variation in diameter along the fiber was increased in both years, whereas variation between fibers was unaffected. The increased variation in diameter along the fiber indicates a more variable rate of wool growth rate in the GH sheep in response to nutrition. This explanation is supported by the decrease in responsiveness to nutritional variation observed in sheep with decreased plasma GH after immunization against GHRH (Adams et al., 1996). These authors found that sheep with decreased GH accumulated fat in spring, thereby reducing feed intake and wool growth. Interactions between fatness, feed availability, and feed intake also may explain the variable effects of GH on other wool characteristics including CFW, FD, and SS (Adams et al., 2002).

Implications

This study describes the complex effects that a single gene can have, even when it is well characterized. We

reported previously (Adams et al., 2002) that live weight gain, carcass leanness, and wool production were all enhanced by the growth hormone transgene in young growing sheep, particularly in the Merino breed. In contrast, the present study shows that these gains in productivity were counterbalanced by decreased fitness (decreased reproductive efficiency and increased disease problems) when the animal matured. Sheep with increased growth hormone had several different disease problems, which became more obvious as the animals aged. Trade-offs across age groups between productivity and fitness may need to be considered in situations where endogenous growth hormone activity is likely to be raised, for example in selective breeding for milk or rapid lean growth.

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