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Prospects for the stimulation of lactation and growth of ruminants by the administration of growth hormone and related molecules

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ABSTRACT

Genetic engineering of micro-organisms to produce mammalian protein hormones promises to make the hormonal treatment of ruminants for the stimulation of lactation, growth and wool growth commercially viable. Treatment of lactating dairy cows with growth hormone (GH) commonly elevates milk production by about 4 kg milk/d. In growing beef and sheep GH increases nitrogen retention, reduces carcass fat content and may increase growth rate. Wool growth increases following the cessation of GH treatment.

Many of the actions of growth hormone are likely mediated by a 'family' of hormones, notably insulin-like growth factors I and II and epidermal growth factor. The efficacy of these materials in promoting production has not been investigated.

Sustained-release implants have been developed which will deliver protein hormones over prolonged periods. However, the ability to promote production by direct manipulation of the animal genome may be the most economic approach. For example, injection of rat GH genes into fertilised mouse eggs resulted in mice that grew 2 to 4 times faster than normal.

Keywords Growth hormone; insulin-like growth factors; epidermal growth factor; lactation; growth; carcass composition; wool growth

INTRODUCTION

Recent developments in recombinant DNA technology (see Charlton and Cox, 1983) have permitted the production of mammalian polypeptides by genetically modified micro-organisms. Such 'genetic engineering' has the potential to produce large quantities of biologically active proteins which previously were available only in limited quantities by extraction from tissues or blood plasma.

Among the mammalian proteins of agricultural interest, growth hormone (GH) and its 'family' of dependent and semi-dependent hormones promises to provide the means for substantial improvement in the efficiency of animal production. Administration of GH (extracted from pituitary glands) to ruminants and pigs has been shown to stimulate lactation, wool growth and lean carcass growth. These increases in production were achieved usually without any increase in feed intake. Thus GH enhanced the gross efficiency of conversion of feed to product.

Relevant Aspects of Growth Hormone Physiology

GH (molecular weight ca. 22 000) is produced by the anterior pituitary gland, production and secretion being regulated by positive (GH-releasing factor; Guillemin *et al.*, 1982) and negative (somatostatin; Brazeau *et al.*, 1973) stimuli. The release of GH from the pituitary is episodic, several 'spikes' of plasma GH concentration occurring during a 24 h period (Davis *et al.*, 1977).

While GH may have direct effects on muscle protein synthesis (Kostyo and Rillema, 1971) there is strong evidence that the major effects of GH on growth are mediated by a number of smaller growth factors (molecular weight ca. 7 000) whose concentration in blood plasma show at least some dependency upon GH (see Clemmons and Van Wyk, 1981).

Some of these factors are:

    (i) Somatomedins (Sm) A and C.
    (ii) Insulin-like growth factors (IGF) I and II.
    (iii) Multiplication stimulating activity (MSA).
    (iv) Epidermal growth factor (EGF).

IGF-I, IGF-II and EGF are discrete polypeptides with defined structure and activity (Clemmons and Van Wyk, 1981). It is likely that Sm-C and IGF-I are very similar molecules and certainly they show identical immunoreactive properties (Clemmons and Van Wyk, 1981). SmA and IGF-II show similar properties of size and charge and it has been proposed that the plasma fraction SmA is a mixture of IGF-I and IGF-II peptides (Daughaday, 1982). MSA isolated from rat liver cells in culture is a mitogen for a number of cell types (Clemmons and Van Wyk, 1981) but shows some structural similarities to IGF-II (see Daughaday 1982).

Both IGF-I and II are lipogenic. IGF-II has several

times the activity of IGF-I in stimulating glucose oxidation in rat adipose tissue but is relatively less active in promoting sulphate uptake by cartilage explants (Zapf *et al.*, 1978).

IGF-I is a major factor controlling growth. In similarity to GH, IGF-I will stimulate growth in hypophysectomised rats (Schoenle *et al.*, 1982). In humans, plasma IGF-I concentrations decrease in hypopituitarism and increase in acromegaly. Treatment of hypopituitary children with GH increased growth rate and IGF-I levels in plasma (Daughaday, 1982). In sheep some association of plasma IGF-I concentration with growth rate, plane of nutrition and immunisation against somatostatin has been reported (Bass *et al.*, 1983). Treatment of lambs with diethylstilbestrol increased IGF-I (SmC) concentrations in plasma and significantly increased average daily gain (Wien *et al.*, 1983).

EGF is a polypeptide isolated originally from extracts of mouse submaxillary gland. It has a variety of biological effects, notably on epidermal tissues. Infusion of EGF into foetal sheep in late gestation resulted in hypertrophy of skin and wool follicles and a reduction in the ratio of secondary to primary follicles (Thorburn *et al.*, 1981).

EGF shows potential as a defleecing agent in sheep. Six days after infusion of EGF into adult sheep (2.8 mg over 24 h), wool was readily plucked by hand. Thirty days after infusion, staples broke readily 5 to 6 mm above skin level, leaving a dense wool covering (Thorburn *et al.*, 1981).

EGF stimulates DNA synthesis in mouse mammary epithelial cells *in vitro* (Taketani and Oka, 1983). In view of the close relationship between mammary epithelial cell numbers, udder size and milk production (Davis *et al.*, 1980; Davis *et al.*, 1983c) identification of such mammary mitogens may enable the enhancement of mammary development during pregnancy and thus subsequent milk production.

EFFECTS OF GROWTH HORMONE ON GROWTH AND CARCASS COMPOSITION

Injections of growth hormone have increased nitrogen retention, live-weight gain and feed conversion efficiency of pigs (Machlin 1976) steers (Moseley *et al.*, 1982), heifers (Brumby, 1959), lambs (Davis *et al.*, 1969; Wagner and Veenhuizen, 1978; Muir *et al.*, 1983; Wien *et al.*, 1983) and bulls (zNidar, 1976). Some reports illustrating these effects are summarised below.

In a New Zealand study (Brumby, 1959) GH was injected (11 mg/100 kg body weight) into heifer calves (ca. 100 kg live weight) daily for 12 weeks. During the injection period the GH group only gained in live weight by 7 kg more than the control group. However, the magnitude of the growth response may have been reduced by thyroid-stimulating hormone contamination of the GH preparation.

Treatment of steers (195 kg) with GH by continuous intravenous infusion or by pulse injections of GH for 10 days resulted in a 15 to 20% increase in nitrogen retention during the final 3 days of treatment (Moseley *et al.*, 1982).

Injection of GH into growing lambs has not always increased live-weight gain. Muir *et al.* (1983) injected wether lambs (28 kg) for 8 weeks with GH (7 mg/d). There was no response of live-weight gain but feed conversion efficiency was increased by 7.4% and carcass fat was reduced by 8.9%. However, Wagner and Veenhuizen (1978) obtained a 20% increase in growth rate from GH treatment (15 mg/d) of wether lambs. Protein gain was increased and fat gain reduced over the 15-week treatment period.

Injection of pigs (45 kg) with porcine GH (0.13 mg/kg live weight/d) increased average daily gain from 0.74 to 0.86 kg and reduced feed conversion ratio from 3.33 to 2.89 and ham fat content from 21.0 to 13.6% (Machlin, 1976).

It is likely that the ability of GH to evoke a growth response is dependent upon its ability to induce IGF-I production. Growth has been restored in hypophysectomised rats by injections of GH or IGF-I (Schoenle *et al.*, 1982). In lambs diethylstilbestrol injection significantly increased plasma SmC (IGF-I) concentrations in association with increased live-weight gain and feed conversion efficiency (Wien *et al.*, 1983). Ovine GH injections increased feed conversion efficiency but not live-weight gain and these effects were associated with a non significant increase in plasma SmC concentrations (Wien *et al.*, 1983).

In deer IGF-I concentrations in plasma increase in spring time in association with antler growth and resumption of live-weight gain (Suttie *et al.*, 1983).

When recombinant DNA technology increases the availability of somatomedins and other growth factors, the direct effects of these materials on growth and carcass composition may be examined.

EFFECTS OF GROWTH HORMONE ON WOOL GROWTH

The effect of GH on wool growth has been investigated mainly in adult sheep (Downes and Wallace, 1965; Wheatley *et al.*, 1966). In these studies GH increased wool growth but the main effect was in the period following injections.

Injection of bovine GH at 15-day intervals into growing lambs from 2 to 100 days of age increased fleece weight considerably (Reklewska, 1974). Growth rates of treated and control groups were similar but the feed intake of the treated group was markedly higher.

In recent experiments in Australia the administration of purified ovine GH (10 mg/d) to sheep for 30 days resulted in a significant decline in wool growth accompanied by increased nitrogen retention (Wynn

et al., 1979). Wool growth increased after the injection period. These effects of GH on wool growth may be mediated through GH modifying the availability of sulphur amino acids (Wynn et al., 1980).

EFFECTS OF GROWTH HORMONE ON LACTATION

It was first demonstrated by Stricker and Grueter (1928) that crude extracts of ox pituitary gland could increase milk production in cows. Cotes et al. (1949) showed that the galactopoietic (lactation stimulating) activity of anterior pituitary preparations was mainly due to GH content. Relatively impure preparations of GH became available and its galactopoietic activity tested (Table 1). The most convincing demonstration of the galactopoietic activity of GH was that bovine GH derived from genetically modified bacteria was capable of stimulating lactation with similar efficacy to material extracted from the pituitary (Bauman et al., 1982a, Table 1).

stimulating hormone. The enhancing effects of thyroxine and growth hormone may be additive (Young, 1947; Meites, 1961) so that the responses obtained by Brumby and Hancock (1955) may be unusually high.

More recently, pituitary-extracted growth hormone was administered to pasture-fed cows at peak lactation. Peak response in production was 2.5 ℓ milk following 4 days of GH injection (S. R. Davis; I. C. Hart; P. D. Gluckman; unpublished).

Hutton (1957) showed that there was a significant linear relationship between the log-dose of GH injected and the milk production response to a single GH injection. Eppard et al. (1983) have shown that the milk yield response in the last 5 days of a 10-day GH injection period increased in a curvilinear manner with the daily dose of GH. Maximum response (an increase in yield from 26.7 kg/d to 35.0 kg/d) was achieved in these Holstein cows by a daily dose of 77 mg GH. The percentage increases in milk, fat and protein yield were 32, 46 and 27% respectively.

TABLE 1 The effect of growth hormone on milk production of cows: a comparison of results.

Reference	Control milk yield kg	Increase in milk yield kg	GH dose mg/d
Brumby and Hancock (1955)[1]	11.0	7.0 (64)[2]	50
Brumby and Hancock (1955)[1]	7.0	3.0 (43)	50
Machlin (1976)	14.0	5.0 (35)	40
Bines et al. (1980)	18.0	2.3 (13)	30
Davis, Hart and Gluckman (1983, unpublished)[1]	14.5	2.5 (17)	40
Peel et al. (1983)	28.0	4.3 (14)	44
Peel et al. (1983)	12.0	3.9 (31)	44
Bauman, et al. (1982a)	32.0	4.1 (13)	25

[1] New Zealand experiments.
[2] Percentage increase in parenthesis.

The milk production response of dairy cows to GH is summarised in Table 1. The average daily increase in milk yield produced in the 8 reported trials was 4.0 kg. In general, the lower the milk yield at the time of treatment the greater was the percentage increase in production. The data of Peel et al. (1983) where Holstein cows were treated with the same dose of GH in early and late lactation illustrate this. In both treatment periods the absolute enhancement of milk production was similar (4.3 early v 3.9 late) but the percentage increase was markedly different (14% early v 31% late).

The pattern of GH administration (single injection: 'pulsed injection'; continuous infusion) does not influence the milk production response (Fronk et al., 1983).

In New Zealand experiments (Brumby and Hancock, 1955) identical twin cows were treated with a preparation of GH contaminated with thyroid

The only experiments where long-term treatments of dairy cows with GH have been reported are those of Brumby and Hancock (1955) and Machlin (1976). The lactation response to GH treatment was sustained over a 12-week and 10-week period repectively (see Table 1). In the New Zealand experiment there was a small (10 kg) live-weight loss of treated cows relative to control cows at the end of the treatment period (Brumby and Hancock, 1955).

Bovine growth hormone has also been shown to be galactopoietic in sheep (Jordan and Shaffhausen, 1954) and goats (Hart et al., 1980).

EFFECTS OF GROWTH HORMONE ON THE GROSS EFFICENCY OF FEED CONVERSION INTO MILK

An improvement in the gross efficiency of feed conversion to milk has been shown in several studies of

GH-treated dairy cows (Brumby and Hancock, 1955; Hutton, 1957; Machlin, 1976; Bines *et al.*, 1980; Peel *et al.*, 1981; Fronk *et al.*, 1983). The extent of this effect is illustrated in Table 2 by the data of Peel *et al.*, (1983), demonstrating the substantial improvement in gross feed conversion efficiency, particularly in late lactation.

production was accompanied by an increase in milk fat percentage and a decrease in milk protein content. In contrast, if energy and protein intakes were adequate then administration of GH caused an increase in milk yield with no change in composition.

The increased milkfat content of milk from some GH treated cows almost certainly reflects increased

TABLE 2 Effects of growth hormone (44 mg/d) on milk production and gross feed conversion efficiency of Holstein cows in early and late lactation. Data are summarised from Peel *et al.* (1983).

	Early lactation			Late lactation		
	Control	Treated	Sig	Control	Treated	Sig
Milk yield, kg	28.0	32.3	*	12.0	15.9	**
Feed efficiency, kg milk/kg feed	1.25	1.47	**	0.84	1.32	**
Feed intake, kg DM	22.9	22.3	ns	15.9	13.3	ns

The increase in gross efficiency of feed conversion of GH-treated dairy cows is not due to any change in the partial efficiency of utilisation of metabolisable energy for milk synthesis (Tyrrell *et al.*, 1982). It is most likely that the effect is realised by preferential partitioning of nutrients to the mammary gland at the expense of other body tissues. This hypothesis is supported by the observation that mammary blood flow increases as a proportion of cardiac output in GH-treated dairy cows hence diverting nutrients preferentially to the udder (Davis *et al.*, 1983b).

The effect on nutrient partitioning can be achieved in animals in negative energy balance (Bauman *et al.*, 1982b). Thus prolonged GH treatment of underfed cows may result in excessive tissue mobilisation. Certainly irreversible loss rates of free fatty acids in blood plasma are substantially increased in GH-treated cows, and the irreversible loss correlated with tissue fat losses measured by indirect calorimetry (Bauman *et al.*, 1982b).

However, the enhancement of lactation by GH treatment cannot be improved by increasing the abomasal supply of glucose and protein, at least in relatively well-fed animals (Peel *et al.*, 1982).

In one study (Bines *et al.*, 1980), the extra nitrogen excreted as milk protein was more than accounted for by a reduction in urinary nitrogen excretion. However, Peel *et al.* (1981) reported that GH treatment did not reduce urinary nitrogen loss and suggested that the increased milk nitrogen output was derived from tissue reserves.

EFFECTS OF GROWTH HORMONE TREATMENT ON MILK COMPOSITION

In many experiments an increase in milkfat content was reported as well as an increase in milk yield. Bauman *et al.*, (1982b) related the response of milk composition to nutrient intake. If cows were in negative energy and nitrogen balance the increase in milk

mammary fatty acid utilisation provided by the mobilisation of body stores. As such there may be changes in the processing characteristics of milk produced from GH-treated animals.

In New Zealand experiments (Brumby and Hancock, 1955) milkfat content was apparently unaffected by GH treatment.

TREATMENT STRATEGIES FOR ENHANCEMENT OF LACTATION AND GROWTH

To be a commercially viable treatment the stimulation of lactation and growth by GH or other hormones must be achieved by the use of a sustained delivery system which obviates the need for daily injections. A GH implant for lambs has been developed (Davis *et al.*, 1983a) which maintained elevated GH concentrations in blood plasma over 1 week. Undoubtedly implants active over a longer term will become available.

Alternatively it may be that relatively short-term treatments could provide long-term production responses. In one experiment (Chung, 1955), but not another (Brumby, 1956), there was an indication that GH treatment of cows in late pregnancy promoted subsequent milk production. Such an effect may be mediated through promotion of mammary development. Certainly the enhanced rate of udder growth in pregnancy found in twinning sheep (Davis *et al.*, 1980) and Jersey cattle of high genetic merit (S. R. Davis; G. A. Hughson; A. M. Bryant; unpublished data) is associated with increased milk production.

Further, it has been suggested that impairment of mammary development around puberty through excess feeding is associated with reduced concentrations of GH in blood (Sejrsen *et al.*, 1983). Strategic treatment with GH at this time may alleviate this impairment or even enhance normal development.

Elevation of plasma GH concentration may be

achieved by administration of GH (Moseley *et al.*, 1982; Fronk *et al.*, 1983), GH-releasing factor (Baile *et al.*, 1983; Plouzek *et al.*, 1983) or, for example, intra-venous infusion of arginine (Chew *et al.*, 1983). However, as the effects of GH are likely to be mediated by growth factors such as the somatomedins, the identification of these factors and their activity may lead to improved methods of stimulating production.

Ultimately the most economic treatment will be direct manipulation of the animal genome to promote desirable traits such as increased GH secretion. Such manipulations have already been carried out and incorportion of rat GH genes into fertilised mouse eggs successfully achieved. Expression of these genes caused several hundred-fold increases in plasma GH concentration and the mice grew 2 to 4 times faster than normal mice (Palmiter *et al.*, 1982).

CONCLUSIONS

Growth hormone is likely to be one of the first agriculturally useful products of recombinant DNA technology. Whether or not the economics of GH production will enable it to be used commercially in New Zealand to stimulate lactation and growth is unknown. However, it must be recognised that recombinant DNA technology provides the potential for substantial improvements in ruminant animal production.

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