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The mechanism of action of growth hormone on milk production of ruminants

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ABSTRACT

There is strong evidence that growth hormone (GH) does not enhance lactation through a direct effect on the udder but rather that the effect is mediated by insulin-like growth factors (IGF) -I and/or IGF-II produced by the liver.

While plasma IGF-I concentrations rose following GH injection of dairy cows and goats, intravenous infusion of goats with IGF-I did not increase milk yield. However, GH treatment increased the relative binding of IGF-I to a high molecular weight binding protein in plasma. Plasma binding proteins may crucially affect the transport of IGF's from plasma to tissues.

Plasma IGF-II concentrations doubled during GH treatment of lactating goats. In view of the increased presence of IGF-II receptors in mammary tissue during lactation it is possible that plasma IGF-II is involved in mediation of the GH effect on lactation.

The increased partition of nutrients for milk synthesis achieved during GH treatment is facilitated by increased blood flow to the udder. There is little change in the plasma concentration of substrates for milk synthesis. It is likely that the increased blood flow occurs as a metabolic consequence of increased milk synthesis.

Keywords Growth hormone; insulin-like growth factor; lactation.

INTRODUCTION

The appearance of recombinant (genetically-engineered) bovine growth hormone (GH) in the early 1980's signalled the onset of commercial interest in the development of bovine GH as a lactation stimulant for dairy cattle. One of the first consequences of this commercial activity was that growth hormone became more widely known as *bovine somatotropin* (BST), particularly outside of the scientific literature.

Daily injection of cows with 15 to 25 mg recombinant GH results in an increased milk yield of 15 to 25%. Several studies have been completed showing this response over 1 or more lactations (Bauman *et al.*, 1985; McGuffey *et al.*, 1987; Annexstad *et al.*, 1987). Of major practical importance is the 10 to 15% improvement which GH brings to food conversion efficiency (Bauman *et al.*, 1985) which is an effect associated with the increased partitioning of feed into milk.

While much is known of the effects of GH on lactation the mechanism of action of GH has not been established (Gluckman *et al.*, 1987). The following paper briefly describes the physiological and endocrine consequences of GH injection of lactating ruminants and the possible role of other hormones or growth factors in mediating the milk yield response.

THE MILK PRODUCTION RESPONSE

The milk production response of cows to GH injection is apparent within 24h and increases to near maximum over the next 10d (Machlin, 1976; Peel *et al.*, 1981). The rapidity of the rise or fall in milk yield in response to the onset or cessation of GH injections indicates that the effect of GH is produced via an increase in the secretion rate of mammary epithelial cells rather than any change in mammary cell numbers.

A consequence of the increased cell secretion rates is that the filling-rate of the udder is increased. Most trials evaluating the efficacy of GH have used Holstein cows where udder capacity amounts to about 16h worth of secretion (S.R. Davis, A.F. Kertz and N.E. Smith, unpublished). Thus the production of Holstein cows milked at 12h intervals can only be increased by up to a maximum of about 33% before udder capacity limits further response. It is likely that the functional capacity of the udder is responsible, at least in part, for the curvilinear nature of the dose-response relationship between GH and milk yield (Eppard *et al.*, 1985b).

Milk composition is largely unaffected by GH treatment although a change may occur in the fatty acid composition of milk fat to contain a greater proportion of long chain fatty acids; particularly in cows which are in negative energy balance before or

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because of GH injection (Bitman *et al.*, 1984; Eppard *et al.*, 1985a). In view of the role of α -lactalbumin in lactose synthesis specific increase in α -lactalbumin synthesis may be crucial to the milk yield response to GH injection.

CARDIOVASCULAR RESPONSES AND MAMMARY NUTRIENT SUPPLY

Increased milk output increases the substrate requirements of the udder for milk synthesis. An increased supply of substrates is facilitated largely by a change in mammary blood flow rather than any increase in substrate concentrations in blood, although small changes in the latter have been reported (McDowell *et al.*, 1987a,b). Substantial increases in mammary blood flow have been observed in goats and cows in response to GH treatment (Mephram *et al.*, 1984, Davis *et al.*, 1988b).

Cardiac output increased from 46.2 to 50.8 ℓ min in Jersey cows treated with GH (Davis *et al.*, 1988b). Of this increase, 48% could be accounted for by an increase in blood flow to the udder. The remainder of the increase was likely required to maintain increased flow through other GH-sensitive tissues such as muscle. GH injection of cattle increased blood flow through the hind limb by 20% (McDowell *et al.*, 1987a).

The proportion of cardiac output perfusing the udder also increased with GH treatment from 14.4% (6.7 ℓ /min) to 18.7% (9.5 ℓ /min; Davis *et al.*, 1988b). In view of the avidity which mammary tissue has for nutrients in blood it is likely that his change in the distribution of cardiac output has a major influence on increasing the partition of nutrients for milk synthesis; a phenomenon which was observed in calorimetric studies with GH-treated cows (Tyrell *et al.*, 1982).

It is unlikely that the GH-induced increase in mammary blood flow *drives* the increase in milk production observed with GH. Rather, the increased blood flow is a compliant response of the udder to increased metabolism resulting in increased production of a local (mammary) vasodilator. Certainly GH injection induces an increase in mammary oxidative metabolism as shown by an increase of 37% in mammary oxygen consumption of cows after 4d of GH injection (Davis *et al.*, 1988a). The increase in cardiac output is essential to maintain blood pressure following reduction of peripheral resistance in GH-sensitive tissues.

Renal function is also modified by GH injection and, in sheep, urinary volume is reduced, an effect which is presumable an accommodation to the increased water output in milk (Fleet *et al.*, 1986).

ENDOCRINE RESPONSES TO GH INJECTION

There is strong evidence that GH does not act directly on mammary tissue. Firstly, no direct effect of GH on milk synthesis is apparent with mammary explants *in vitro* (Gertler *et al.*, 1983). Secondly, unilateral, close-arterial infusion of GH into the udder of lactating ewes does not induce a differential response in milk production between each udder-half (McDowell *et al.*, 1987c). Finally, efforts to measure specific binding of bovine GH to mammary membranes from lactating ewes or cows have not been successful (Akers, 1985).

It is likely that one or both of the GH-responsive peptides insulin-like growth factor (IGF)-I and IGF-II mediate the lactation-stimulating effect of GH. Certainly the growth-promoting effects of GH in rats can be mimicked by infusion of IGF-I (Schoenle *et al.*, 1982). Plasma concentrations of IGF-I increase in lactating cows in response to GH injection (Davis *et al.*, 1987) and effects of IGF-I on lactose synthesis by bovine mammary tissue *in vitro* have been reported (Baumrucker, 1986). Further, the presence of IGF-I and IGF-II receptors in bovine mammary cell membranes has been demonstrated (Dehoff *et al.*, 1986). However, intravenous infusion of 3 goats with IGF-I, sufficient to approximately double plasma IGF-I concentration has failed to elicit an increase in milk yield (S.R. Davis, P.D. Gluckman and B.D. Burleigh, unpublished).

While plasma IGF-II concentrations did not increase convincingly following GH injection of cows (Davis *et al.*, 1987), further work with lactating goats treated with GH has shown close to a doubling of plasma IGF-II content following 3d of treatment (15 mg/day) (S.R. Davis, P.D. Gluckman and B.H. Breier, unpublished). This effect was associated with a 19% increase in milk production.

Plasma IGF is produced largely by the liver (D'Ercole *et al.*, 1984) and circulates in plasma bound to larger molecular weight carrier proteins, the major species of which are of 50 k and 150 k daltons (Hodgkinson *et al.*, 1987). These binding proteins limit the accessibility of IGF to the tissues as shown by the relatively long half-life of plasma IGF-I in sheep (50k-46min; 150k-760min)(Hodgkinson *et al.*, 1987) compared with, for example, GH (9.2 min)(Trenkle, 1976). The half-lives of IGF-II bound species are respectively shorter than those of bound IGF-I but differ by a similar order of magnitude to that found with the IGF-I species (S.C. Hodgkinson, S.R. Davis and L.G. Moore, unpublished).

While plasma concentration of IGF-I increases in response to GH injection the distribution of IGF-I between 50k and 150k bound species changes in favour of 150k (Table 1). The effect of this must be to increase the overall half-life of IGF-I in plasma.

TABLE 1 Mean (\pm standard error) and ratio of IGF-I content of 50 k and 150 k binding protein fractions of plasma from *normal* goats and goats treated with 15 mg/d GH.

Treatment	Number of goats	Plasma IGF-I (ng/ml)		Ratio 150k:50k
		50k	150k	
Control	3	173 \pm 6	194 \pm 16	1.12
GH-injected	3	334 \pm 36	621 \pm 25	1.86

The physiological consequences of change in the relative distribution of 50k and 150k-bound IGF-I in plasma are unknown.

If IGF's are responsible for mediating the effect of GH on lactation the question remains as to how the *signal* is received at the mammary gland. It is unlikely that the mammary gland itself produces IGF, at least during established lactation, as milk concentrations of IGF are several-fold lower than those found in plasma (Prosser *et al.*, 1986). The transfer of plasma IGF-I to milk has been demonstrated (Prosser *et al.*, 1987) and the presence of IGF binding proteins demonstrated in milk and colostrum (S.C. Hodkinson, J.Napier and S.R. Davis, unpublished). The mechanism of the transfer of IGF to the secretory cells and the manner in which the concentration of IGF at the cell surface is controlled is critical information in understanding the endocrine regulation of established lactation. How the interaction of IGF's with cell surface receptors leads to increased milk output is a question whose answer will define the rate-limiting pathways in milk biosynthesis.

CONCLUSIONS

The commercial development of GH as a lactation stimulant has led to a far greater understanding of the process of lactation and its endocrine regulation. While treatment of cows with exogenous GH is currently the focus of commercial activity there are several other avenues through which the GH endocrine axis might be manipulated. These might involve administration of exogenous hormones such as IGF or GH-releasing factor or the use of immunological techniques. In the latter context the use of *vaccinations* rather than *hormones* would appear to be more acceptable (or less emotive) to the public as pointed out by Flint (1987). Time will reveal whether application of this knowledge in the form of lactation-stimulating injections will be permitted and also whether this information will be used to develop techniques which can improve the efficiency of animal production through increasing the rate of genetic gain or reducing the financial cost of genetic selection.

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