Biotechnology in the potential practical application of somatotrophic hormones for improving animal performance

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Summary. The use of biotechnology now allows adequate supplies of previously scarce substances. This has enabled evaluation of some of these substances as enhancers of animal performance. Growth hormone (GH) shows promise as a stimulator of lactation in a number of species, but its effects on the stimulation of growth are somewhat equivocal. Somatocrinin, by virtue of its GH-releasing activity, may also be potentially useful, though to date the effects of somatocrinin administration have been less promising than those for GH directly. Somatomedin (IGF-1), as the active mediator of GH, might be expected to be useful in growth promotion but, as yet, it has not been convincingly demonstrated to stimulate growth in normal animals. All these hormones have the major drawback that, until a suitable slow-release/delivery mechanism is available, they need to be administered very frequently. An alternative approach, immuno-neutralization of the growth inhibiting effects of somatostatin, has been demonstrated to enhance growth; although at present still requiring multiple treatments such a technique potentially has many advantages.

Introduction.

Recent developments in our understanding of neuro-endocrine and hormonal factors involved in growth, together with rapid advances in biotechnology, have produced an environment for potentially exciting changes in our ability to regulate animal performance. For example, recombinant DNA technology has made possible the large scale production of metabolic hormones that were previously available only in small quantities. Such use of biotechnology is, however, just one of the steps that need to be taken if the somatotrophic hormones are to be used as a means of improving animal performance. One of the first requirements is to show that the hormones can actually have a beneficial effect; for the most part, such data are not still available.

The principal somatotrophic hormones are: somatotropin (growth hormone, GH), somatomedin-C (insulin-like growth factor 1, IGF-1), somatocrinin (GH releasing factor, GRF) and somatostatin (GH release inhibiting factor, SRIF). The major potential applications for the somatotrophic hormones are in growth and lactation, however the hormonal control of these phenomena relies upon a com-

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plex interaction between many different hormones (Spencer, 1985). Thus, although these hormones are the central factors involved in growth and lactation, simple application of a single hormone may not be sufficient to enhance productivity.

The following discussion will review the available data to support a practical application for each of these hormones in the stimulation of growth and lactation and assess the potential of each at present.

Lactation

Growth hormone

It appears that GH plays two distinct, yet contradictory roles. It has a positive effect in stimulating growth (most, if not all, of which is believed to be mediated by IGF-1) and a potent catabolic effect as demonstrated by its ability to breakdown fats (Jagannadha and Ramachandran, 1977).

It is well known that administration of exogenous growth hormone during established lactation increases milk yield. Consistent positive effects, with increases of between 10 and 40% in milk yield, have been observed with GH administration to cows during mid- or late-lactation, but the effect on milk production in early lactation is equivocal (Bines and Hart, 1982; Brumby and Hancock, 1955). This galactopoietic effect has been demonstrated in not only in cattle (e.g. Peel et al., 1983), but also in sheep (Jordan and Schaffhausen, 1954), goats (Mepham et al., 1984) and pigs (Harkins et al., 1985).

The precise mechanisms by which GH stimulates milk production are unknown. The catabolic effects of GH are likely to be important in providing at least part of the energy required and it appears that the improvement in milk yield is due to increased utilization of body tissues for milk production (Peel et al., 1982). It also seems possible, however, that increased IGF-1 production following GH treatment in lactation (Peel et al., 1985) may have effects on the mammary gland (Baumrucker, 1986).

There is neither an apparent increase in digestibility (Peel et al., 1982; Tyrrell et al., 1982) nor a change in partial efficiency of milk synthesis (Tyrrell et al., 1982) when lactating cattle are treated with GH, but the increase in milk yield is associated with a marked increase in voluntary food intake within a few weeks of the start of treatment (Bauman et al., 1985). Depending upon the feeding regime and production response, it has been estimated that this increase in intake may result in up to a 110% increase in concentrate requirements (Kalter et al., 1985), however it may still remain a viable approach to increasing overall milk production efficiency.

Perhaps the major unresolved variables are: whether there is any detrimental effect of such alteration of maternal metabolism on the viability and subsequent performance of the calf; whether or not there is a prolonged increase in food intake during the re-feeding period; and what is the effect of such treatment upon subsequent lactational performance. In addition to this there is also the
major practical disadvantage that currently there is no effective long-term, or slow-release mechanism for such peptides which seems suitable for practical use.

**Somatocrinin**

With the isolation and characterization of GRF, attention has recently been paid to the use of GRF to stimulate endogenous GH release in dairy cattle. In short-term experiments, human pancreatic GRF administered to mid-to late-lactation cows stimulated an 11% increase in milk yield (Enright et al., 1986). Although the results look promising, there are some reservations. On the practical side, the same problems of administration are present with GRF as with GH. On the physiological side, it has been shown that long-term administration of GRF depletes pituitary GH stores (Wehrenberg et al., 1984; von Werder et al., 1984). Furthermore, there may be receptor down-regulation as occurs with repeated LHRH administration. Thus the long-term use of GRF during lactation may be precluded.

**IGF-1**

It has been postulated that IGF-1 may modulate some of the galactopoietic effects of GH at the level of the mammary gland, but so far direct data are lacking. The recent production of IGF-1 from bacterial sources now offers the opportunity for such studies. The finding of IGF-1 receptors in mammary tissue, the changes in these receptors during pregnancy and lactation (Campbell and Baumrucker, 1986) and the stimulation of milk production by IGF-1 in vitro (Baumrucker, 1986) lend support to the possible use of IGF-1 as a stimulator of milk yield.

**Somatostatin**

Somatostatin, by inhibiting GH release, would be expected to reduce milk yield; removal of the SRIF, on the other hand, elevates GH levels (Ferland et al., 1976) and might be expected to increase milk yields. There is only one published report on the effects of immuno-neutralization of SRIF on milk yield. In a preliminary study with goats it was found that immuno-neutralization of somatostatin during pregnancy resulted in increased milk production up until the time of peak lactation, thereafter there was no difference between treated and control animals (Spencer, Garssen and Welling, 1985). This preliminary observations needs to be confirmed, but such immuno-neutralization, or use of an antagonist to SRIF (Spencer and Hallett, 1985) could provide an alternative approach to the use of GH.

**Growth**

**Growth hormone**

The relative roles of various hormones in regulating growth have recently been reviewed (Spencer, 1985). Although GH is a central factor in regulating growth, there is little correlation between circulating GH levels and growth rate in
normal animals. The reason for this seems to be due to the complex interactions between GH and other hormones that is required for growth (Spencer, 1985). Thus, although GH is essential for growth, and restores growth in hypopituitary or hypophysectomized animals, its effects on stimulating growth rates in normal farm animal species is far from consistent; even consecutive studies from the same laboratory produce conflicting results (Wolfram, Ivy and Baldwin, 1985). Some of the problems associated with this variability in response (e.g. use of heterologous GH, purity, dose) have recently been discussed by Chung, Etherton and Wiggins (1985).

Some of the studies attempting to stimulate growth using GH are shown in Table 1. Machlin (1972) and Chung, Etherton and Wiggins (1985) have reported stimulation of growth in swine using porcine GH. In sheep, Wagner and Veenhuizen (1978) found stimulation of growth with GH administration, while Wheatley et al. (1966) and Muir et al. (1983) were unable to get a positive effect. In poultry, Leung et al. (1986) have reported a slight positive effect during the first week of treatment, but no significant effect during the later stages. On the positive side, an almost universal finding in these studies is an improvement in food conversion efficiency and a decrease in the amount of carcass fat, even when there is no effect on growth rate.

To summarize, the effects of GH administration are, as yet, not reliable enough to consider its use in practice; probably because administration of exogenous hormones ignores (and upsets) the sensitive interrelationship between various hormones and ignores the possible effect of elevation of plasma levels on receptor populations.

Thus, although biotechnology has brought the ability to make pure preparations of growth hormones in large quantities, it has not yet produced the wherewithal to provide a long-term, or slow-release, mechanism for administration.

Somatocrinin

The isolation and chemical characterization of GRF has now enabled evaluation of this substance as a growth promotor. The studies undertaken so far have not suggested that this is a useful way of stimulating growth rate. Immunoneutralization of GRF is a potent inhibitor of growth (Wehrenberg, Bloch and Phillips,
1984), but in chickens (Baile, Della-Fera and Buonomo, 1985; Leung et al., 1986) and in swine (Etherton et al., 1985) administration of exogenous GRF has no significant effect on growth. Possibly this may be due to inappropriate dosage or route of administration, but the effect of continued GRF in exhausting releasable GH from the pituitary may also be a factor (Wehrenber et al., 1984; Baile, Della-Fera and Buonomo, 1985).

**IGF-1**

As with GRF, the availability of large quantities of IGF-1 is only now allowing studies on the effects of IGF-1 in normal animals. IGF-1 has been shown to partially restore growth in hypophysectomized (Schoenle et al., 1982) and hypopituitary (van Buul-Offers and Van den Brande, 1979) animals, but published data on the effects in normal animals are lacking; unpublished data, however, suggest that exogenous IGF-1 has no effect on total body growth. As with GH and GRF, there is no suitable vehicle available for long-term administration, thus whatever the effects of IGF-1 on growth in farm animal species, its use is at present restricted.

**Somatostatin**

As an alternative to increasing the levels of growth stimulating hormones it may prove equally, or even more, effective to remove endogenous growth inhibitors. Perhaps the major inhibitor of total somatic growth is SRIF. As well as inhibiting the release of GH, it also inhibits the release of insulin, thyroid hormones and many gastro-intestinal hormones, thereby affecting both the ability of the animal to absorb nutrients and its subsequent ability to direct these nutrients into tissue growth.

The use of a somatostatin antagonist has been found to stimulate growth in rats (Spencer and Hallett, 1985), but this kind of treatment also suffers from the drawbacks of GH, IGF-1 and GRF in that it requires daily injections. A possible practical alternative is the use of immuno-neutralization. To date, passive immunization of SRIF (administration of antibodies into the animal) has not been found

### TABLE 2

<table>
<thead>
<tr>
<th>First author</th>
<th>Date</th>
<th>Species</th>
<th>Growth</th>
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<tr>
<td>Spencer et al.</td>
<td>1981</td>
<td>sheep</td>
<td>176 %</td>
</tr>
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<td>Spencer et al.</td>
<td>1983</td>
<td>sheep</td>
<td>125 %</td>
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<tr>
<td>Bass et al.</td>
<td>1983</td>
<td>sheep</td>
<td>110 %</td>
</tr>
<tr>
<td>Spencer et al.</td>
<td>1984</td>
<td>pig</td>
<td>118 %</td>
</tr>
<tr>
<td>Spencer et al.</td>
<td>1985</td>
<td>sheep</td>
<td>109 %</td>
</tr>
<tr>
<td>Laarveld et al.</td>
<td>1986</td>
<td>sheep</td>
<td>117 %</td>
</tr>
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<td>Closet et al.</td>
<td>1986</td>
<td>cattle</td>
<td>111 %</td>
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<td>Lawrence et al.</td>
<td>1986</td>
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</tr>
<tr>
<td>Spencer et al.</td>
<td>1986</td>
<td>chicken</td>
<td>115 %</td>
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to have any growth stimulating effect (Spencer et al., 1986), but active immunization appears to be a powerful, safe, effective tool to enhance growth (for a review see Spencer, 1986).

In a preliminary study using twin St Kilda lambs, active immunization against SRIF resulted in the treated lambs growing at 176 % of the rate of the control lambs (Spencer and Williamson, 1981). Subsequent studies have been unable to reproduce this figure, but an improvement of 15-20 % in growth rate is more usual (Table 2). The somatostatin-14 molecule is the same in all farm animal species, and it has now been shown that active immunization against SRIF can stimulate growth in commercially important breeds of sheep (Spencer, Hallett, and Fadlalla, 1985; Laarveld et al., 1986), cattle (Closset et al., 1986; Lawrence et al., 1986), pigs (Spencer, 1984; Laarveld, personal communication) and chickens (Spencer et al., 1986).

As well as stimulating growth rate and leading to a 20 % reduction in rearing time (Spencer, 1984), active immunization against SRIF also has a beneficial effect on food conversion efficiency. In addition to the saving on food by virtue of more rapid growth, the animals actually utilise their food more efficiently during the growing period (Spencer, Garssen and Bergström, 1983), at least partly as a result of changes in gut motility (Fadlalla, Spencer and Lister, 1985; Faichney and Barry, 1985). The treatment does not have any marked effect on carcass composition (Spencer, Garssen and Bergstrom, 1983) but there are indications that, when killed at equal weights, treated animals may be leaner, perhaps by virtue of being youger (unpublished observations).

There are numerous advantages to the use of immuno-neutralization against SRIF as a means of growth promotion: since SRIF regulates the release of many interrelated hormones, the treatment does not affect a single hormone, but a whole endocrine system; it is also essentially free from residues since the antibodies remove all administered materials; and, being fairly long-term in its effects, it does not require continuous treatment. The disadvantage is that the results are variable due to differences in immune response between animals. A better understanding of the workings of the immune system should help alleviate this problem.


Résumé. Possibilités offertes par la biotechnologie dans l’amélioration des performances animales par les hormones somatotropes.

La biotechnologie permet aujourd’hui d’obtenir en quantité convenable des substances autrefois très rares. Ceci a rendu possible l’appréciation de l’aptitude de ces substances à augmenter les performances des animaux d’élevage. L’hormone somatotrope (GH) stimule la lactation dans plusieurs espèces, mais ses effets sur la croissance sont ambigüs. La somatocrinine, par le biais de son action sur l’excrétion de la GH, peut également être utile, quoique ses effets soient moins prometteurs que ceux de la GH. La somatomédine (IGF-1), médiateur de la GH, devrait stimuler la croissance, mais chez l’animal normal son action ne s’est pas montrée convaincante. Toutes ces hormones présentent le même inconvénient : tant qu’un procédé ne permettra pas leur libération progressive dans l’organisme, leur administration devra être répétée à intervalles rapprochés. Une autre éventualité serait la neutralisation, par des anticorps, de la somatostatine, substance inhibitrice de la croissance. Bien qu’elle nécessite également des interventions multiples, cette technique présente de nombreux avantages.
Références


BAUMRUCKER C. R., 1986. Insulin-like growth factor-1 (IGF-1) and insulin stimulates lactating bovine mammary tissue DNA synthesis and milk production in vitro. J. Dairy Sci., 69, Suppl. 1, p. 120.


