Growth hormone technology develops new twist

Terry D. Etherton

Since the seminal studies of Evans' and colleagues[1] that presaged the discovery of growth hormone (GH), the elucidation of GH biology has led to a variety of applications. In animal agriculture, the most notable were made in the early 1980s[2,3]. Exogenous administration to dairy cows of recombinant bovine GH (bGH) over the last 80% of the lactation cycle increases both the level by 10–15% (approximately 4–6 kg/d), and efficiency of milk production[2]. Even greater increases can occur when the management and care of the animals are excellent. Similarly, by administration of porcine GH (pGH) to pigs, muscle growth can be increased by as much 50–60% while reducing adipose tissue accretion by 75%[3].

These discoveries sparked the commercial development of products for the dairy and swine industries that were based on the idea of elevating plasma GH levels by exogenous injection of sustained-release formulations of GH. Commercial use of bGH in the United States began in early 1994 and its general acceptance has been unusually rapid for an agricultural technology; approximately 3 million dairy cows (about one-third of the US dairy herd) are presently receiving bGH. Approval of a pGH-based product is pending by the US Food and Drug Administration (Rockville, MD).

The approach of administering a sustained-release formulation of GH by injection necessitates that the hormone be "delivered" frequently. The bovine somatotropin (bST) product, Posilac, is administered by injection every 2 weeks; although not yet approved, it is likely that the sustained-release formulation for growing pigs will be injected every 14 to 28 days. Because of this, efforts have been ongoing to develop alternative strategies to elevate GH that either increase the interval between administration or eliminate it.

In this issue, Draghia-Akli et al.[4] clearly show that we are progressing toward this goal by describing a novel way to elevate plasma GH levels sufficiently to stimulate mouse growth without the exogenous administration of GH. This was achieved by injecting a myogenic expression plasmid vector that drives high level human growth hormone-releasing hormone (hGHRH) expression from muscle. The plasmid vector was generated using a 228 bp fragment that encodes the 31 amino acid signal peptide and the entire mature hGHRH [(1–44)-OH form] peptide; this is the hypothalamic peptide that regulates stimulation of GH synthesis and secretion from the pituitary. Muscle-specific expression was established by using the avian skeletal muscle actin gene control elements.

Expression of GHRH mRNA in vivo was maintained for the the entire 21 days in which the experiment was conducted. As expected from previous studies of ectopic tumors that secrete the hGHRH[5], there was an increase in plasma GH and insulin-like growth factor-I (IGF-I) levels. More importantly, mouse growth was increased by approximately 16% 21 days after injection of the expression plasmid vector into muscle of C57/Bl6 mice, a level of growth enhancement that is comparable to what has been seen in pigs treated with exogenous pGH. These are exciting findings and suggest that this strategy may be an alternative for animal agriculture.

The expression of GHRH mRNA from muscle may be an alternative strategy for animal agriculture.

Before this technology can be applied to domestic animals, several questions remain to be addressed. A significant increase in plasma GH levels was only observed 7 and 10 days post-injection, thereafter there was no significant increase. This transient increase was likely the result of antibodies that were produced in the mice against the human GHRH peptide indicating the necessity of using species specific genes. It therefore will be important to verify in domestic animals, where the exogenous GHRH produced is identical to that of the target animal, that the sustained elevation in transcription correlates with an elevation in plasma levels of the hormone and importantly, that an improvement in lactation or growth in observed. It has also yet to be determined that elevated expression of GHRH in farm animals can be maintained for the appropriate time to result in a change in milk production or growth in an economically viable manner. In the case of growing pigs, it is likely that expression will need to be maintained for 60 days and for lactating dairy cows the period of time could be as long as 250 days. In addition, there is the issue of whether regulation of expression in vivo will be important.

One of the challenges for the development of new biotechnologies in animal agriculture that modify growth or lactation, besides safety and efficacy, is that it must be cost-effective to "deliver" the treatment to the animal. Thus, in contrast to the notion conveyed by Draghia-Akli et al. that the production cost of recombinant proteins is a possible limitation and that injectable expression vectors may be a viable alternative, the fact is that recombinant bGH can be manufactured and delivered via a sustained-release formulation at a cost that enables dairy farmers to buy the technology and realize an economic gain. Currently, dairy farmers can purchase Posilac, the sustained-release bGH formulation produced by Monsanto (St. Louis, MO), for $5.80 per dose. This product contains 0.5 g of recombinantly derived bGH and is injected once every two weeks. The scope of commercial plasmid production necessary to compete against recombinant pGH or bGH can perhaps best be appreciated in the context that greater than 12.5×10^6 g of bGH will be sold in the United States this year for the approximate 3 million cows on treatment!

The report by Draghia-Akli et al. is another exciting chapter in the "GH story." In the early 1980s it would have been inconceivable to many of us involved in developing a GH-based product for animal agriculture that such remarkable progress could be made in the ensuing years. Likewise, it not unreasonable to speculate that technologies developed using the approach described by Draghia-Akli et al. will be as routine 15 years from now as is the current practice of administering recombinant bGH to lactating dairy cows.

Terry D. Etherton is distinguished professor of animal nutrition, department of dairy and animal science, Penn State University, 324 W.L. Henning Building, University Park, PA 16802 (tetherton@das.cas.psu.edu).

1. Evans, H.M. and Simpson, M.E. 1931. *Am. J. Physiol.* **98:**511–546.
2. Bauman, D.E. and Vernon, R.G. 1993. *Annu. Rev. Nutrit.* **13:**437–461.
3. Etherton, T.D., Louveau, I., Sørensen, M.T., and Chaudhuri, S. 1993. *Am. J. Clin. Nutrition* **58**(Suppl.): 287S–295S.
4. Draghia-Akli, R., Li, X., and Schwartz, R.J. 1997. *Nature Biotechnology* **15:**1285–1289.
5. Cronin, M.J. et al. 1983. *Am. J. Physiol.* **244:** E346–E353.