

# Nutritional regulation of the genes encoding the acid-labile subunit and other components of the circulating insulin-like growth factor system in the sheep<sup>1,2</sup>

R. P. Rhoads<sup>3</sup>, P. L. Greenwood<sup>4</sup>, A. W. Bell<sup>3</sup>, and Y. R. Boisclair<sup>3,5</sup>

Department of Animal Science, Cornell University, Ithaca, NY 14853-4801

**ABSTRACT:** In sheep, perinatal maturation of the endocrine arm of the insulin-like growth factor (IGF) system is characterized by two developmental events. First, concentrations of circulating IGF-I increase rapidly after birth and become responsive to changes in nutrition and growth hormone (GH). Second, the liver initiates synthesis of a serum protein called the *acid-labile subunit* (ALS). The acid-labile subunit promotes the endocrine actions of IGF-I and -II by recruiting them to long-lived complexes of 150 kDa. In this study, we examined the effect of nutrition on hepatic expression of the ALS gene around the time of birth and later in life. Expression of genes encoding other components of the circulating IGF system was also measured. At d 130 of fetal life, fetuses suffering from chronic undernutrition caused by placental insufficiency had lower expression of the ALS and IGF-I genes than well-nourished fetuses, but they did not have any changes in

the expression of the IGF-binding protein (IGFBP)-2 or IGFBP-3 genes. In early postnatal life, hepatic gene expression was analyzed between d 12 and 38 in lambs fed a milk replacer at levels sustaining weight gains of 150 or 337 g/d. The lower plane of nutrition decreased the expression of the ALS, IGF-I, and GH receptor genes and increased the expression of the IGFBP-2 gene; expression of the IGFBP-3 gene was not affected by nutrition at this stage of life. Finally, hepatic gene expression was measured in 3-mo-old lambs offered ad libitum levels of a balanced diet or of a diet limiting for both energy and protein. Although the rate of growth of the lambs fed the limiting diet was reduced by 38%, the only effect detected in hepatic gene expression was a ninefold increase in the abundance of IGFBP-2 mRNA. Overall, these results indicate that undernutrition during late fetal and early postnatal life delays hepatic expression of the ALS gene and final maturation of the endocrine IGF system.

Key Words: Fetus, Insulin-like Growth Factor, Liver, Postnatal Development, Somatotropin

©2000 American Society of Animal Science. All rights reserved.

J. Anim. Sci. 2000. 78:2681–2689

## Introduction

The insulin-like growth factor (IGF) system regulates growth and development in domestic animals (Bell et al., 1998). Early in development, the ligands of this growth factor system, IGF-I and -II, function primarily in autocrine and paracrine fashion; by late prenatal

life, however, the endocrine arm of the IGF system is activated (Daughaday and Rotwein, 1989; Stewart and Rotwein, 1996). Consistent with this view, the concentration of plasma IGF-I increases around the time of birth (Gluckman and Butler, 1983; Daughaday and Rotwein, 1989) and becomes responsive to changes in nutrition and growth hormone (GH) (Hua et al., 1993; Weller et al., 1994; McGuire et al., 1995).

A second event underlying the maturation of the IGF system is the onset of synthesis of the acid-labile subunit (**ALS**) after birth. Until then, plasma IGF are bound to members of a family of insulin-like binding proteins (**IGFBP**) and circulate at an apparent molecular weight of ~ 50 kDa (Baxter, 1994; Ooi and Boisclair, 1999). The acid-labile subunit is found almost exclusively in plasma and has the unique ability of associating with binary complexes containing IGF, IGFBP-3, or IGFBP-5, to form ternary complexes of 150 kDa (Baxter, 1994; Twigg and Baxter, 1998; Ooi and Boisclair, 1999). Circulation of IGF in 150-kDa complexes dramatically prolongs their half-lives (Hodgkinson et al., 1987; Baxter, 1994).

<sup>1</sup>This work was supported by the Cornell Univ. Agric. Exp. Sta.

<sup>2</sup>We thank J. Pell (Babraham Institute, Cambridge, UK) for providing DNA probes for the growth hormone receptor and insulin-like growth factor binding protein (IGFBP)-3 genes, E. Wong (Virginia Polytechnic Institute and State University, Blacksburg, VA) for providing the IGF-I probe, and D. Bauman (Cornell University, Ithaca, NY) for providing the IGFBP-2 probe.

<sup>3</sup>Present address: Department of Animal Science, Cornell University, Ithaca, NY 14853-4801.

<sup>4</sup>Present address: NSW Agriculture Beef Industry Centre, University of New England, Armidale, NSW 2351, Australia.

<sup>5</sup>Correspondence: phone: 607-254-4704; fax: 607-255-9829; E-mail: yrb1@cornell.edu.

Received October 29, 1999.

Accepted May 9, 2000.