Maternal Obesity in the Ewe Alters Pituitary Function, Programming Increased Adiposity and Reduced Skeletal Muscle Mass in Adult Male Offspring

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Introduction

The growth hormone (GH)/insulin-like growth factor-1 (IGF-1) axis profoundly influences body composition. GH increases liver synthesis of IGF-1 upon binding to GH receptors (GHR), which in turn stimulates skeletal muscle growth. Therefore, a decrease in the IGF-1 level would result in reduced skeletal muscle mass and increased fat deposition in animals. We have developed and characterized an ovine model of maternal obesity. From 60 days before conception, through parturition, control (C) ewes are fed 100 percent of National Research Council (NRC) recommendations, while obese (OB) ewes are fed 150 percent of NRC. We have previously reported that maternal obesity throughout gestation in the ewe results in decreased GH production by the pituitary, with a resultant decrease in blood levels of IGF-1 and increased adiposity in adult male offspring. These results indicated that reduced circulating IGF-1 is the cause for the increased adiposity and the decrease in lean mass-to-fat ratio seen in OB offspring compared with C offspring. Recent reports in rodents indicate that leptin, a hormone secreted by fat cells, stimulates pituitary secretion of GH through its binding to a receptor (OB-Rb) on GH-secreting cells. Additionally, peroxisome proliferator-activated receptor gamma (PPAR-γ) and the GH secretagogue receptor (GHSR) have also been shown to play important roles in inhibition and stimulation of pituitary GH secretion, respectively.

Objectives

While we have previously reported the negative effects of maternal obesity on reducing pituitary secretion of GH, the goal of this study was to determine which of these factors—leptin, PPAR-γ, or GHSR—mediated this effect.

Materials and Methods

Male singleton offspring born to obese (OB;150 percent of NRC recommendations, n=6) and control (C;100 percent of NRC, n=6) ewes were maintained together and fed to 100 percent NRC from weaning through adulthood (2–3 years of age) and then subjected to a 12-week ad libitum feeding challenge before necropsy. Pituitary and liver tissue were collected and snap frozen at -80°C, and pituitary tissue was fixed and paraffin was embedded to evaluate colocalization of pituitary GH and OB-Rb using fluorescence microscopy. Pituitary expression of PPAR-γ and GHSR,
as well as liver expression of GH receptor (GHR) and IGF-1, were determined.

**Results and Discussion**

OB-Rb receptors were localized to GH-secreting pituitary cells, but they were markedly reduced in number in OB offspring. Further, pituitary protein expression of PPAR-γ was higher (*P*<0.05) in OB offspring than C offspring (Fig. 1), while protein expression of GHSR remained similar between groups. Liver expression of IGF-1 was lower (*P*<0.05) in OB vs. C offspring (Fig. 2), while liver expression of GHR remained similar between groups. These data suggest that the reduced number of leptin receptor sites on GH secreting cells, and their increased exposure to PPAR-γ, resulted in decreased GH secretion with a subsequent decrease in liver secretion of IGF-1. In conclusion, maternal obesity during gestation results in increased adiposity in their offspring by programming decreased pituitary GH secretion, and it results in reduced carcass quality.

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