Growth after Hypophyseal Stalk Transection and Hypophysectomy in Beef Calves

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Summary

Growth hormone (GH) is a metabolic hormone that plays an important role in long-bone growth and muscle accretion in mammals. The anterior pituitary gland at the base of the brain is the primary site of GH production and release into the general circulation. Neurons in the arcuate nucleus of the hypothalamus in the lower part of the brain secrete GH-releasing hormone ([GHRH] or factor [GRF]) and GH-release-inhibiting hormone ([GHRIH] or somatostatin [SRIH]) that acutely modulate GH secretion by the pituitary gland. The pituitary gland is connected to the median eminence of the hypothalamus by a stalk (hypophyseal stalk). Complete surgical removal of the pituitary gland (hypophysectomy) arrests growth and greatly impairs metabolism in laboratory and farm animal species. Daily subcutaneous injection of bovine GH (bGH) in immature hypophysectomized rats significantly increased body growth and epiphyseal plate width of the long-bone (tibia) compared with diluent-treated hypophysectomized controls. Growth rate was less, however, in the bGH-treated animals compared with intact controls. In beef calves, hypophysectomy completely arrested body weight gain and long-bone growth. GH is secreted in an episodic pattern in young growing intact calves. Episodic GH secretion was abolished immediately following hypophyseal stalk transection, and basal GH blood concentration was less than in sham-operated controls. Regardless, growth continued in these stalk-transected calves during a 1,008-day period, but at a lower growth rate than seen in the sham-operated controls. At autopsy, pituitary gland weight was greatly decreased in hypophyseal stalk-transected compared with sham-operated calves. Thus, in spite of obliterated episodic GH release and decreased basal secretion of GH, the isolated pituitary gland of hypophyseal stalk transected calves continues to secrete sufficient amounts of GH for significant growth and development throughout a long period.

Introduction

Hypothalamic regulation of GH secretion is mediated by a stimulatory factor, GH-releasing hormone (GHRH or factor [GRF]), and GH-release-inhibitory hormone (GHRIH), or designated somatotropin-release-inhibiting hormone (SRIH), somatostatin. Endogenous GHRH and SRIH secretion from arcuate nuclei in the hypothalamus modulate a pattern of episodic release of GH by the pituitary gland throughout the 24-hour day in mammals. In rats and humans the greatest amplitude and frequency of GH release occur during the dark period of the day, but GH secretion is less defined with photoperiod in ruminants. In normal young animals, greater GH secretion causes optimal rapid growth; GH secretion decreases with age that is accompanied by slower growth rates or stasis, and less immune resistance. This report focuses on growth in calves in which the pituitary source of GH has been eliminated and in animals in which central nervous system control of GH release has been interrupted. Additionally, the effects of pituitary gland removal and GH replacement in rats are presented.

Materials and Methods

Animals

Thirty Aberdeen Angus and crossbred (Aberdeen Angus x Hereford) calves born at the Animal Reproduction Farm, Iowa State University, were subjected to hypophysectomy (HYPOX, n=5), hypophyseal stalk transection (HST, n=10), or sham operation control (SOC, n=15) by our previously described surgical procedures. Calves were fitted with a jugular cannula for hormone and diluent injections, and repeat blood sampling for radioimmunoassay of hormones. Body weight was determined at birth and at 21-day intervals.

Thirty-three Sprague-Dawley female rats, weaned at 21 days of age, were subjected to hypophysectomy (HYPOX, n=15) or remained as unoperated intact controls (Intact, n=18), and were shipped to arrive at Iowa

State University on day 23. On day 24 the hypophysectomized rats were assigned randomly to receive daily subcutaneous injection of phosphate buffer saline (PBS .2 ml; n=7) or bovine GH (75 mg bGH [USDA-bGH-B-1] in .2 ml PBS; n=8). The intact controls received .2 ml PBS subcutaneously daily to day 61. Body weight was determined each day. On day 61, rats were sacrificed, and the tibia bone was removed and cut sagittally to measure epiphyseal plate width (average of 10 measurements per animal) with an ocular micrometer in a Zeiss Stereomicroscope III.

Statistical Analysis

The experimental units were the individual calves or rats randomly assigned to treatments. Body weight and hormone data were analyzed by split-plot design using both the general linear model and student's *t*-test for comparison between treatment groups.

Results and Discussion

In beef calves, growth during a prolonged period after hypophysectomy was limited severely ($p < .01$) compared with sham-operated controls (Table 1). Overall growth rate was .075 kg/day in these hypophysectomized calves. Blood concentration of GH was at the limits of radioimmunoassay sensitivity. Growth continued but at a lesser rate ($p < .05$) in hypophyseal stalk transected calves compared with sham-operated controls (Table 1). Growth rate of sham-operated controls was .505 kg/day. Overall growth rate for calves stalk-transected at day 273 (.323 kg/day) was greater than those stalk-transected at day 147 (.306 kg/day). Sequential bleeding at 20-minute intervals for 480 minutes revealed a complete lack of episodic GH secretion in hypophyseal stalk-transected calves compared with sham-operated controls. Furthermore, basal blood concentration of GH was less ($p < .05$) in stalk-transected compared with sham-operated calves.

In immature rats hypophysectomized at 21 days of age and given daily vehicle (PBS) injection, growth was arrested during a 36-day period ($p < .01$) compared with intact controls (Figure 1). Daily injection of 75 mg/bGH in hypophysectomized rats significantly increased body weight ($p < .05$) compared with PBS-treated hypophysectomized animals (Figure 1). Weight gain in bGH-treated hypophysectomized rats, however, was less ($p < .05$) than seen in PBS-treated intact controls at sacrifice on day 61. Epiphyseal cartilage plate width of the tibia was significantly less ($p < .05$) in hypophysectomized rats given PBS and bGH than PBS-treated intact controls (Figure 2). Epiphyseal plate width was greater ($p < .01$) in PBS-treated intact rats compared with hypophysectomized rats given bGH or PBS. Regulation of growth in mammals is a complex interaction between GH, the insulin-like growth factors (IGFs), their receptors and binding proteins. The classic somatomedian hypothesis proposed that pituitary-derived GH in the circulating blood stimulates production of intermediary molecules (somatomedian, or IGFs) that mediate the effects of GH. Recent studies in rats have shown that GH and IGRF-I have independent and differential activities, and when given together they can have additive or synergistic actions. Although IGF-I is growth promoting in animals compared with GH, it appears to have only partial agonist activity on whole body growth in GH-deficient rodents.

Implications

Episodic and basal secretion of growth hormone by the pituitary gland in calves and rats is necessary for optimal growth and development. Pituitary gland removal (hypophysectomy) arrests growth in these species. Replacement with daily treatment of bGH in hypophysectomized rats markedly increased growth, but at a lesser rate than in diluent treated intact controls. In calves, surgical interruption of the connecting link between the hypothalamus in the lower part of the brain to the pituitary gland obliterates episodic growth hormone secretion, but growth continues at a rate less than seen in sham-operated controls.

Table 1. Growth after hypophyseal stalk transection (HST), hypophysectomy (HYPOX) or sham operation (SOC) of beef calves.

Surgery		Number of	Body weight, kg											
			Day											
Type	Day	calves	Birth	105	147	273	378	483	588	693	798	882	987	
SOC	147	15	35	123	156	247	308	397	441	465	502	542	580	
HST	273	5	35	123	156	240	304	355	386	424	437	424	471*	
HST	147	5	35	123	169	209	268	308	335	374	403	406	426*	
HYPOX	147	5	35	123	153	141	149	157	165	173	181	187	195*	

*p < .05 compared with SOC.
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Figure 1. Effect on body weight of daily subcutaneous injection of 75 mg bGH in .2 ml PBS or PBS alone in immature hypophysectomized rats compared with PBS-treated intact controls. Values are mean ± standard error.

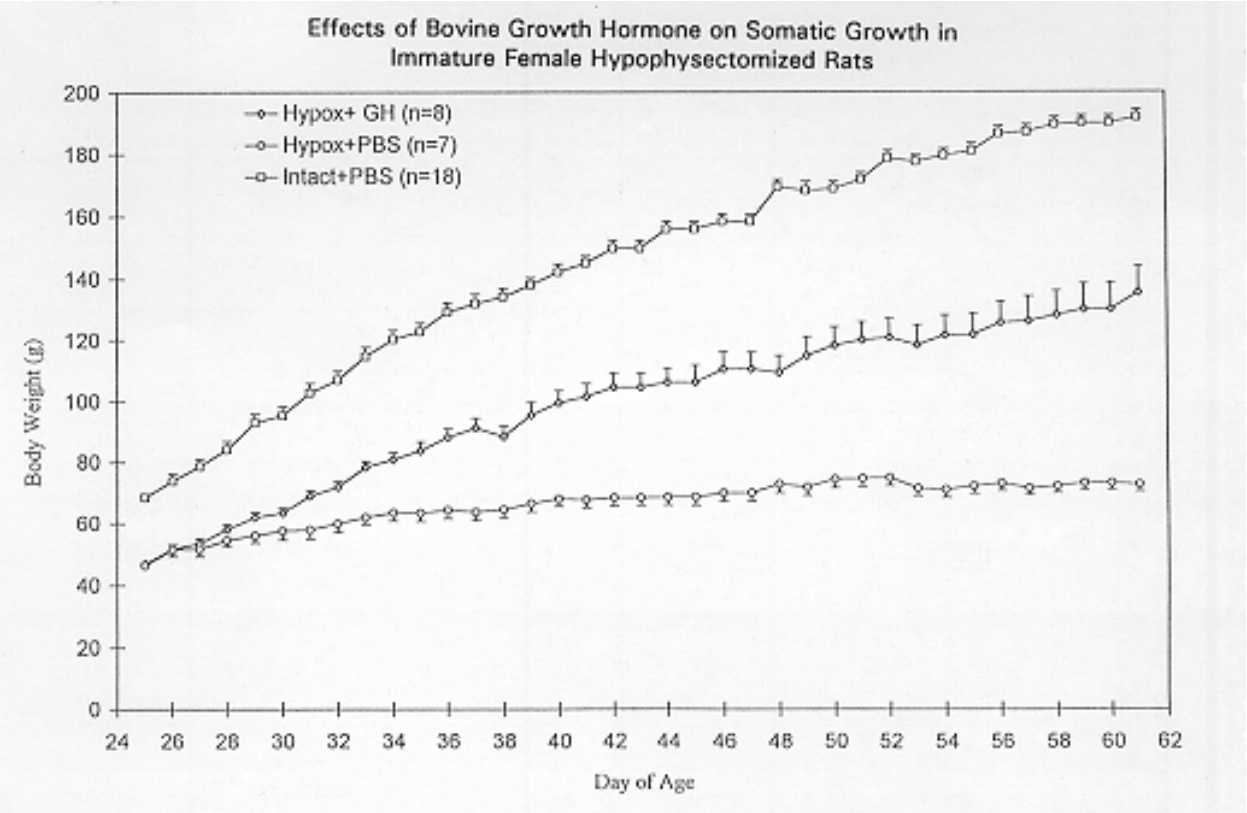

Figure 2. Epiphyseal cartilage plate width in immature hypophysectomized rats given bGH or PBS compared with PBS-treated intact controls. Values are mean ± standard error.