



## REVIEW

## Open Access

# Developmental programming: the role of growth hormone

Anita M Oberbauer

**Abstract**

Developmental programming of the fetus has consequences for physiologic responses in the offspring as an adult and, more recently, is implicated in the expression of altered phenotypes of future generations. Some phenotypes, such as fertility, bone strength, and adiposity are highly relevant to food animal production and *in utero* factors that impinge on those traits are vital to understand. A key systemic regulatory hormone is growth hormone (GH), which has a developmental role in virtually all tissues and organs. This review catalogs the impact of GH on tissue programming and how perturbations early in development influence GH function.

**Keywords:** Epigenetic, Growth hormone, Programming, Transgeneration

**Introduction**

Broadly considered, development has two distinct yet interrelated facets: alterations in gene expression associated with the normal developmental profile of an organism and alterations associated with developmental plasticity permitting adaptation to environment perturbations. The fundamental role of normal fetal development is best exemplified by pattern formation in the embryo. “Programming” was a term coined in 1986 to reflect that events occurring *in utero* alter adult phenotypic and metabolic traits [1]. The influence of fetal and neonatal nutritional environments on metabolic programming was first conceptualized by Lucas [2] and the concept of developmental programming was later expanded to include other environmental perturbations [3,4]. The impact of environmental challenges experienced in the neonatal period emphasizes the need to understand both inherent development as well as the mechanistic processes by which developmental programming is achieved.

Recent data highlight that the metabolic environment experienced by the fetus influences phenotypic expression and disease susceptibility in later life [5,6]. Small for gestational age (SGA) offspring, often arising as a consequence of malnourished mothers, is correlated with adult hypertension, glucose intolerance, insulin resistance, type 2 diabetes, dyslipidemia, and diminished measures of bone

strength. Metabolic bone disease is also associated with prenatal nutrient deprivation [7]. Adult-onset disorders associated with SGA neonates represent programming occurring at the gene level by methylation, gene silencing, and other epigenetic modifications established during fetal development (reviewed in [8]). It is worth noting that the definition of epigenetics used in this review is “the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states” first proposed by Bird in 2007 to encompass the many aspects of epigenetic alterations [9].

Although not developmental programming, the most familiar illustration of developmental epigenetic imprinting is the insulin-like growth factor-2 (IGF-2) pathway. The methylation status differs between the paternally and maternally inherited *Igf-2* gene with the paternal copy as the sole source of IGF-2 during development and the maternally inherited copy silenced. It is hypothesized that the maternal and paternal expression are balanced to maximally promote fetal growth while preventing excessive depletion of the dam’s resources [10]. Another example of the role of epigenetic imprinting occurs in Prader-Willi Syndrome, a syndrome characterized by growth hormone (GH) insufficiency [11]. The genetic cause is the deletions of paternal chromosome 15; the maternal region is silenced by epigenetic factors. While IGF-2’s role is predominantly in prenatal development, the key postnatal hormone is GH. Growth hormone effects are either direct or mediated through the

Correspondence: [amoberbauer@ucdavis.edu](mailto:amoberbauer@ucdavis.edu)  
Department of Animal Science, University of California, One Shields Ave,  
Davis, CA 95616, USA

induction of IGF-1 [12] to regulate overall body growth through its effects on adipose, bone, and muscle, is growth hormone (GH) [13].

Importantly, developmental programming may have multigenerational consequences transmitted through epigenetic modifications of the genome. Transgenerational epigenetic programming was initially recognized as a result of malnourishment. The Dutch famine, sometimes referred to as the “Hunger winter”, is most often cited as the initial epidemiological human case study illustrating the impacts of nutritional stress upon both physical and behavioral traits in subsequent generations (reviewed in [14]). More recent evidence of transgenerational consequences has been associated with environmental perturbations including toxicants and hormonal manipulations [15-17]. Although many effects are termed “transgenerational,” Heard and Martienssen [18] recommend a more parsimonious use of the term and define much of what has been observed as “intergenerational” which will be employed in this review. Nevertheless, understanding the link between fetal and neonatal programming and subsequent phenotypic expression is important for human health and has value for sustainable food animal production systems. Nutritional, physical, and psychological stress experienced by livestock influences immediate productivity and health [19-21] and yet notably can also affect future generations’ production through developmental programming.

## Review

### Role of GH in normal development

The accepted role of GH and the GH-IGF axis in tissue development is predominantly postnatal with other hormones assuming importance *in utero* [5]. Yet GH is known to influence fetal development. For example, transgenic mice overexpressing GH, produce offspring with a 12% reduction in birth weight [22] and calves born to dams given exogenous bovine somatotropin (GH) have reduced birth weights [23,24]. These findings indicate that GH, or its downstream regulators, plays a significant role in normal fetal development. The intimate link between GH and generalized growth has led to the speculation that GH may also affect the expression of IGF-2 though the evidence does not support this supposition to any great extent [25].

Evidence that fetal perturbations program GH signaling is also emerging. A common model used to define the role of GH in developmental programming is the neonate that experienced impaired fetal growth, specifically SGA infants, who are characterized by compromised bone growth and reduced body mass. Infants having low birth weights trend to lower circulating GH as young adults [26] indicating persistent effects by early developmental experiences on GH secretion. Despite prenatal

growth impairment, approximately 90% of SGA births have accelerated growth in the first two postnatal years achieving heights in the normal range [27,28]; however the remaining 10% do not exhibit catch-up growth giving evidence of fetal programming of the GH-IGF endocrine axis as a consequence of early growth dysfunction [29]. Also associated with SGA is reduced bone mass and strength in adulthood [30] indicative of developmental programming of bone remodeling. GH, with its role in bone mineral density [31], may mediate the adult bone characteristics arising from *in utero* growth restriction. Furthermore, adult height is correlated with placental GH expression. Genetic variation within the sequence of the placental-form of GH is significantly associated with mature height confirming that altered expression of GH *in utero* governs longitudinal bone growth potential [32]. Immune function is depressed chronically in SGA rat pups, although the condition can be reversed by provision of exogenous GH during the pre-weaning growth stage [33] indicating GH is important in the ontogeny of immune competence.

Birth weight and neonatal growth is predictive of adult circulating GH levels suggesting that the intrauterine environment programs GH secretion [34] or tissue responsiveness to GH. Waldman and Chia postulate that idiopathic short stature reflects epigenetic changes to the GH receptor or to IGF-1 genes [35]. Research exploring the chromatin landscape suggests a tissue specificity in the accessibility of the IGF-1 promoter indicating epigenetic regulation of the GH-IGF-1 axis [36,37]. This view is supported by developmental profiling of IGF-1 mRNA expression in cattle; as female calves mature, IGF-1 gene expression in the pituitary is reduced, particularly the exon most responsive to GH, whereas IGF-1 expression in the uterus increased [38].

### Elevated GH models

#### *In utero exposure*

The role of GH in normal development was established decades ago through ablation studies and assessing the physiological consequences of the absence of GH. Additional models to characterize GH action elevate the hormone either through exogenous administration of GH, GH-transgene expression, or chemical compounds that induce GH. Elevated GH *in utero* reduces birth weights of calves [23], lambs [39], and rodents [22]. In sheep, fetal adipogenesis is enhanced when dams are exposed to GH indicating the direct effect of GH on adipose metabolism [39]. For rodent models, neonates are both lighter in weight and have reduced skeletal size at birth. In contrast, pregnant sows given hydroxyl beta methylbutyrate (HMB), a compound that enhances fetal GH and IGF-1, give birth to piglets with increased birth weights [40]. Furthermore, the piglet data indicate that

fetal exposure to elevated GH has persistent effects on growth parameters into adulthood; they had increased growth rate to slaughter, lean carcass content and indices of bone strength [40]. Similar to the rodents, piglets from HMB treated sows had shorter femurs although in a different study, provision of GH directly to pregnant sows did not affect bone length in the neonates [41]. Ewes treated with extended -release GH during gestation delivered lambs having heavier birth weights and a sustained postnatal growth advantage over lambs born of untreated ewes as well as a blunted response to stimulation of the GH axis [42,43]. Taken together, the evidence suggests that exposure to elevated GH *in utero* exerts long term consequences on the offspring possibly through alteration of maternal metabolic pathways and placental function.

#### **Postnatal exposure**

Elevated GH postnatally has significant effects on bone, muscle, and adipose. Human SGA infants given GH respond with increased bone growth velocity for the duration of GH treatment [8]. In rodents, provision of GH during the postnatal period can reverse the *in utero* growth inhibition and restore overall bone length [22]. GH exerts stimulatory effects on linear growth rates in rodents with transient elevation of GH increasing bone growth rate. At the cellular level, GH accelerates bone growth by hyperplasia with little impact on hypertrophy [44]. Provision of elevated GH in a GH-transgenic mouse model also increases the duration of bone elongation though the degree of responsiveness is sensitive to the chronological age of exposure with early neonatal tissue more responsive than slightly older ages.

Lambs given HMB during the first 3 postnatal weeks show elevated circulating levels of GH, IGF-1, and biochemical markers of bone turnover. However once the HMB treatment concludes, these indices all fall to control values indicating resistance to long term bone programming by HMB when provided postnatally [45]. The failure of persistent HMB treatment effects in lambs, in contrast to the direct GH effects seen in rodents and pigs, may reflect the precocial development of sheep when compared to that of rodents and pigs suggesting that the period responsive to GH programming may be *in utero* for lambs.

The enhanced gain accompanying elevated GH has a greater proportion of protein than normal tissue accrual in rodents. Rodent development is characterized by each unit of gain being composed of the same proportions of water, lipid, protein and ash across the entire growth phase, despite the speed of accrual [46]. In contrast, under conditions of elevated GH, protein comprises a larger proportion of gain [47]. This preferential repartitioning by GH of nutrients to muscle is also seen in pigs

transgenic for GH [48], broilers supplemented with HMB [49], fish given exogenous GH [50], and GH-transgenic fish [51]. Exogenous GH increases protein anabolism by enhancing protein synthesis [52,53].

Therapeutic GH treatment of SGA children offers growth advantages as noted above, yet the elevated GH also reduces insulin sensitivity potentially increasing the risk of diabetes. Recent studies of children born SGA and treated with GH would suggest this is not a valid concern as they have normal insulin post-GH treatment [8]. However, these children have not aged to a point wherein the long term consequences of GH treatment can be evaluated; thus, adult onset diabetes remains a concern. In a rodent model, elevating GH in adult mice increases circulating insulin with levels remaining elevated even after reduction of GH consistent with an insulin resistant state, though persistence of this condition was not determined [54].

The role of GH in adipogenesis is complex. *In utero* or postnatal exposure to elevated GH in a GH-transgenic mouse model increases adipose storage by increasing adipocyte hyperplasia, differentiation, and cellular lipid content [39,54,55]. Artificially elevating GH induces lipoprotein lipase which in turn stimulates adipogenesis; the elevated GH also increases circulating insulin which then can induce lipoprotein lipase further promoting adipose storage [56]. Postnatal exposure to GH acts on membrane lipids to program response to cellular perturbations. Elevated GH in rodents creates a more unsaturated lipid profile in cell membranes by activating membrane desaturase pathways [57]. This net flux through the lipid metabolism pathways generates eicosanoids important in the inflammation process [58].

The interplay with leptin adds more complexity to the influence of GH on adipose. Leptin, synthesized by adipose cells, regulates energy metabolism (reviewed in [59]) and influences fetal brain and bone development [60]. Leptin also defines energy storage adequacy during neonatal life and can program the neuronal regulation of adult food intake and satiety with leptin programming in early development altering adiposity at later ages [61,62]. Newborn rodents and piglets born SGA experience adipogenesis however neonatal provision of exogenous leptin can reverse the adipocyte proliferation induced by intrauterine growth restriction [61,63]. Leptin levels correlate with birth weight with SGA infants having low leptin levels while large for gestational age babies have high leptin concentrations [64]. Although the correlation is largely independent of the GH-IGF-1 axis (reviewed by [62]), GH levels influence maternal and fetal leptin levels. In sheep, fetal adipogenesis is enhanced when dams are exposed to GH and leptin levels are reduced in the dam and the fetus, demonstrating a direct effect of GH on adipose *in utero* [39] with potential of long term programming impacts.

Early dysregulation of GH promotes adipogenesis which in turn elevates leptin that influences adipose function at later ages. Elevated GH in a GH-transgenic mouse model increases plasma leptin [65] while mice transiently exposed to elevated GH during early postnatal development become obese having increased circulating leptin once the excess GH is withdrawn [54]. In these GH-transgenic mice, although each adipocyte expresses less leptin, the leptin in circulation is greater due to the increased overall adiposity. This suggests that prolonged elevation of GH disrupts normal physiological responses to elevated plasma leptin, creating leptin resistance and obesity; in the case of elevated GH, the most likely site of leptin signaling impairment is at the hypothalamic axis. Supporting this view of GH generating leptin resistance is that the elevated GH in the GH-transgenic mouse increases plasma leptin as well as the leptin receptor (NPY) gene and protein expression [65]. It is proposed that leptin resistance can be programmed during fetal and neonatal life with long term impacts on body energy stores potentiating adult onset metabolic disorders [63].

#### **Models of *in utero* programming**

Studies in multiple mammalian species demonstrate that aberrant programming of adult tissue response is associated with stress-induced glucocorticoid secretion during fetal and perinatal development. Maternal stress in humans is known to impact neurological circuitry of the offspring: infants have an increased risk of neuropsychiatric disease when the mother experienced psychological stress during the first trimester (reviewed in [66]). Similarly, prospective stress research with rodents and non-human primates have identified gestational periods of increased susceptibility to developmental disruption [66]. Importantly the maternal stress response is characterized by altered methylation patterns in the fetal DNA [67] thereby programming future gene expression patterns that may also be transmitted to the next generation. Similar changes in methylation patterns have been detected in response to maternal exposure to toxins and hormones [68] resulting in intergenerational epigenetic changes having significant impact on future physiological performance and significant implications on selection for production species.

Early research demonstrated that adult GH secretory patterns are influenced by perturbations during the perinatal period. For example, male rats normally express a high amplitude secretory pattern of GH whereas females have low amplitude pulses within a higher basal background. Transient manipulation of sex steroids in the neonatal period can modify the GH secretory pattern to that of the opposite sex [69]. Glucocorticoids are viewed as critical modulators of GH in a wide range of species including chickens, rodents, and humans with impacts

on the hypothalamus and pituitary regulation of GH release, somatotrope development, and peripheral tissue responsivity [70-74]. In turn, GH mediates gene regulation by increasing accessibility of the transcriptional machinery by chromatin remodeling of promoters through histone acetylation [36]. Taken together, stress has profound impacts on the development of the neonate that may transcend a single generation and GH plays a role in programming the consequences of the stress.

#### **Nutritional stress**

Mothers who are undernourished during pregnancy give birth to SGA infants and when adult those children exhibit adult-onset obesity, insulin resistance, hypertension, and metabolic dysfunction. Maternal nutritional deprivation stress also is implicated in intergenerational epigenetic programming to alter future generations' growth and metabolic phenotypes. This phenomenon is suggested to account for the rising cases of human obesity, diabetes, and coronary disease (reviewed in [66]).

Levels of placental GH found in maternal circulation are positively correlated with fetal birth weight and in times of maternal nutrient deprivation and SGA pregnancies, placental GH secretion is reduced [32]. A recent study of ewes undernourished during gestation reported that although maternal circulating GH and placental weight were not reduced [75], birth weights and crown rump lengths were [76]. Newbern and Freemark [77] review the evidence that supports a direct role of GH and placental GH in the programming of fetal growth and long-term metabolic function. Some evidence is based upon transgenic mice that overexpress placental GH and their high birth weight pups with enhanced growth capacity relative to their non-transgenic littermates [78].

As noted above, there are generalized consequences of SGA on bone characteristics but SGA due to nutritional deprivation also programs bone through the GH-IGF axis. The necessity of adequate fetal and neonatal nutrition for normal bone growth and adult bone integrity was underscored by Eastell and Lambert in their review [79]. In rats, post-weaning dietary protein restriction alters the GH secretory profile, blunting the peak GH pulses [80] which alters growth and metabolic responses. It is known that neonatal nutrition programs adult bone mass [81] and bone density is positively associated with peak GH and IGF-1 concentrations but elevated median GH concentrations, as seen with dietary restriction, is negatively associated with bone density [34]. Presumably the effects on bone are due to the role that GH plays in opening the chromatin surrounding the IGF-1 gene. Moreover, maternal malnutrition alters methylation of the GH responsive promoter 2 of the IGF-1 gene (reviewed in [12]) and intrauterine growth restriction is associated with sustained hypermethylation of the IGF-1 promoter in

rats [82] thereby amplifying the signaling impairment of GH in the neonate.

Another mechanism of nutritional programming on bone is by its effects on the formation of the embryonic skeletal anlage. Fetal and postnatal bone growth depends upon chondrocyte hypertrophy and hyperplasia. Fibroblast growth factors (FGF) and their cognate fibroblast growth factor receptors (FGFR) are key signaling molecules of chondrocyte function in developing bone. Activation of different FGFR family members both promote and inhibit chondrocyte proliferation [83]. The FGF21 ligand directly inhibits chondrocyte proliferation and antagonizes the proliferative effects of GH on growth plate chondrocytes [84] thereby impairing chondrogenesis and bone growth. FGF21 is increased during food restriction and attenuates the action of GH at the chondrocytic level and at the systemic level by impairing IGF-1 expression [84]. Antagonizing GH action by elevated FGF as result of food restriction has implications for many of the body systems because of GH's extensive broad range of target tissues.

In rats, restricting maternal dietary protein to induce intrauterine growth restriction enlarges abdominal adipose depots when animals are adult [85]. The enlarged adipose depots upregulate expression of genes associated with enhanced lipid metabolism and adipose accrual. Provision of exogenous GH postnatally can minimize those adult conditions [33,86]. Specifically, adult-onset obesity seen in pups born to undernourished rat dams can be prevented with preweaning GH treatment [87] (reviewed in [88]). This provides compelling evidence of early GH programming the adult physiological response.

Intrauterine growth restricted babies, piglets, and rodent pups have reduced leptin at birth and then propensity for obesity at adulthood [89]; provision of leptin reverses this tendency [61]. At birth infants considered SGA have greater methylation of the leptin promoter correlating with the reduced circulating leptin levels [90]. In contrast, using a mouse model, early nutritional programming of the fetus by low protein diets is correlated with hypomethylation of the leptin gene that is maintained throughout life [91]. In the latter study, the authors acknowledge their results differ from the pattern of leptin expression, and methylation, observed in other species in response to maternal malnutrition. Adipocyte hypertrophy results in hypomethylation of the leptin gene and increases leptin expression which increases adipose hyperplasia [89]. Clearly the specifics of the nutritional deprivation, timing, and species evaluated have significant impact on the manifestation of maternal malnutrition on adult susceptibility to metabolic disruption.

### **Physical stress**

Physical stressors, often modeled with induced hypoxia, have been used to assess the epigenetic consequences of

stress. Hypoxia-inducible factor 1 (HIF-1), induced under conditions of hypoxia to adapt to reduced oxygen supply, is also required for normal fetal tissue and skeletal development [92]. The transcription factor HIF-1 coordinates with additional factors to induce chromatin remodeling of target genes [93]. In addition to the role of HIF-1 in hypoxia adaptation, in rodents the GH axis modulates the hypoxic stress response [94]. In periods of intermittent hypoxia, GH is neuroprotective [95]. However, hypoxia elevates glucocorticoid expression from the fetal adrenal gland [96] and elevated glucocorticoids can lead to the programming of the fetal GH axis as detailed earlier in this article [73,74]. Furthermore, hypoxia inhibits GH release by enhancing the expression of somatostatin, the hypothalamic GH inhibitor [97]. Varvarigou et al [98] propose that severe hypoxia permanently damages the fetal hypothalamic-hypophyseal axis leading to greatly diminished GH secretory profiles. Despite the knowledge that fetal programming is a consequence of hypoxia, defining the long term and intergenerational effects of physical stressors are yet to be fully explored.

### **Conclusions**

Growth hormone has a pivotal role in pre and postnatal development although its effects on intergenerational programming are as yet under studied. Given the plasticity of postnatal development, defining fetal and neonatal programming and the effect upon later phenotypes is important to maximize the expression of desirable traits in food animals. This is particularly important on the impact of more permanent epigenetic alterations of gene expression that may have future consequences. Historically, classical genetic selection has permitted extremely favorable phenotypic advances. The implementation of quantitative trait loci selection schemes for livestock based upon genomic signatures will accelerate genetic improvement. Overlaid upon genetic selection one must be mindful of the epigenetic programming that environmental perturbations can exert on future trait expression and how that may factor into selection schemes for agricultural livestock production in a changing environment. Better defined knowledge of the mechanisms of programming will facilitate incorporation of epigenetic factors into selection.

### **Abbreviations**

GH: Growth hormone; HIF-1: Hypoxia-inducible factor 1; HMB: Hydroxyl beta methylbutyrate; IGF-1: Insulin-like growth factor 1; FGF: Fibroblast growth factors; FGFR: Fibroblast growth factor receptors; SGA: Small for gestational age.

### **Competing interests**

The author declares that she has no competing interests.

### **Authors' contributions**

AMO reviewed the literature and drafted and edited the manuscript.

Received: 18 September 2014 Accepted: 20 January 2015

Published online: 12 February 2015

## References

- Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet*. 1986;327:1077–81.
- Lucas A. Programming by early nutrition in man. *Childhood Environ Adult Dis*. 1991;1991:38–55.
- Myatt L. Placental adaptive responses and fetal programming. *J Physiol*. 2006;572:25–30.
- Langley-Evans SC. Developmental programming of health and disease. *Proc Nutr Soc*. 2006;65:97–105.
- Fowden AL, Forhead AJ. Endocrine regulation of feto-placental growth. *Horm Res Paediatr*. 2009;72:257–65.
- Gluckman PD, Hanson MA, Cooper C, Thornburg KL. Effect of in utero and early-life conditions on adult health and disease. *N Engl J Med*. 2008;359:61–73.
- Cooper C, Javaid M, Taylor P, Walker-Bone K, Dennison E, Arden N. The fetal origins of osteoporotic fracture. *Calcif Tissue Int*. 2002;70:391–4.
- Jung H, Rosilio M, Blum WF, Drop SL. Growth hormone treatment for short stature in children born small for gestational age. *Adv Ther*. 2008;25:951–78.
- Bird A. Perceptions of epigenetics. *Nature*. 2007;447:396–8.
- Bergman D, Halje M, Nordin M, Engström W. Insulin-like growth factor 2 in development and disease: a mini-review. *Gerontology*. 2012;59:240–9.
- Cassidy SB, Schwartz S, Miller JL, Driscoll DJ. Prader-will syndrome. *Genet Med*. 2011;14:10–26.
- Oberbauer A. The regulation of IGF-1 gene transcription and splicing during development and aging. *Front Endocrinol*. 2013;4:1–9. doi:10.3389/fendo.2013.00039.
- Bartke A, Sun LY, Longo V. Somatotrophic Signaling: Trade-Offs Between Growth, Reproductive Development, and Longevity. *Physiol Rev*. 2013;93:571–98.
- Schulz LC. The Dutch Hunger Winter and the developmental origins of health and disease. *Proc Natl Acad Sci*. 2010;107:16757–8.
- Goerlich VC, Nätt D, Elfving M, Macdonald B, Jensen P. Transgenerational effects of early experience on behavioral, hormonal and gene expression responses to acute stress in the precocial chicken. *Horm Behav*. 2012;61:711–8.
- Guerrero-Bosagna C, Skinner MK. Environmentally induced epigenetic transgenerational inheritance of male infertility. *Curr Opin Genet Dev*. 2014;26:79–88.
- Baker TR, Peterson RE, Heideman W. Using Zebrafish as a Model System for Studying the Transgenerational Effects of Dioxin. *Toxic Sci*. 2014; kfu006.
- Heard E, Martienssen RA. Transgenerational Epigenetic Inheritance: Myths and Mechanisms. *Cell*. 2014;157:95–109.
- Zulkifli I. Review of human-animal interactions and their impact on animal productivity and welfare. *J Anim Sci Biotechnol*. 2013;4:25.
- Reynolds L, Borowicz P, Caton J, Vonnahme K, Luther J, Hammer C, et al. Developmental programming: the concept, large animal models, and the key role of uteroplacental vascular development. *J Anim Sci*. 2010;88:E61–72.
- Reynolds LP, Caton JS. Role of the pre- and post-natal environment in developmental programming of health and productivity. *Mol Cell Endocrinol*. 2012;354:54–9.
- Oberbauer A, Cruickshank J, Thomas A, Stumbaugh A, Evans K, Murray J, et al. Effects of pre and antenatal elevated and chronic oMT1a-oGH transgene expression on adipose deposition and linear bone growth in mice. *Growth Dev Aging*. 2001;65:3–13.
- Oldenbroek J, Garssen G, Jonker L, Wilkinson J. Effects of treatment of dairy cows with recombinant bovine somatotropin over three or four lactations. *J Dairy Sci*. 1993;76:453–67.
- Gallo GF, Block E. Effects of recombinant bovine somatotropin on nutritional status of dairy cows during pregnancy and of their calves. *J Dairy Sci*. 1990;73:3266–75.
- Holly JM. The IGF-II enigma. *Growth Horm IGF Res*. 1998;8:183–4.
- Jensen RB, Vielwerth S, Frystyk J, Veldhuis J, Larsen T, Mølgaard C, et al. Fetal growth velocity, size in early life and adolescence, and prediction of bone mass: association to the GH-IGF axis. *J Bone Miner Res*. 2008;23:439–46.
- Karlberg J, Albertsson-Wikland K. Growth in full-term small-for-gestational-age infants: from birth to final height. *Pediatr Res*. 1995;38:733–9.
- Hokken-Koelega A, De Ridder M, Lemmen R, Den Hartog H, Keizer-Schrama SDM, Drop S. Children Born Small for Gestational Age: Do They Catch Up? *Pediatr Res*. 1995;38:267–71.
- Jensen RB, Chellakooty M, Vielwerth S, Vaag A, Larsen T, Greisen G, et al. Intrauterine growth retardation and consequences for endocrine and cardiovascular diseases in adult life: does insulin-like growth factor-I play a role? *Horm Res Paediatr*. 2003;60:136–48.
- Sayer AA, Cooper C. Fetal programming of body composition and musculoskeletal development. *Early Hum Dev*. 2005;81:735–44.
- Doga M, Bonadonna S, Gola M, Mazziotti G, Nuzzo M, Giustina A. GH deficiency in the adult and bone. *J Endocrinol Invest*. 2004;28:18–23.
- Timasheva Y, Putku M, Kivi R, Kožich V, Männik J, Laan M. Developmental programming of growth: Genetic variant in *GH2* gene encoding placental growth hormone contributes to adult height determination. *Placenta*. 2013;34:995–1001.
- Reynolds CM, Li M, Gray C, Vickers MH. Pre-weaning growth hormone treatment ameliorates bone marrow macrophage inflammation in adult male rat offspring following maternal undernutrition. *PLoS ONE*. 2013;8:e68262.
- Fall C, Hindmarsh P, Dennison E, Kellingray S, Barker D, Cooper C. Programming of Growth Hormone Secretion and Bone Mineral Density in Elderly Men: A Hypothesis 1. *J Clin Endocrinol Metab*. 1998;83:135–9.
- Waldman LA, Chia DJ. Towards identification of molecular mechanisms of short stature. *Int J Pediatr Endocrinol*. 2013;2013:19.
- Chia DJ, Rotwein P. Defining the epigenetic actions of growth hormone: acute chromatin changes accompany GH-activated gene transcription. *Mol Endocrinol*. 2010;24:2038–49.
- Chia DJ, Young JJ, Mertens AR, Rotwein P. Distinct alterations in chromatin organization of the two IGF-I promoters precede growth hormone-induced activation of IGF-I gene transcription. *Mol Endocrinol*. 2010;24:779–89.
- Oberbauer A, Belanger J, Rincon G, Cánovas A, Islas-Trejo A, Gularte-Mérida R, et al. Bovine and murine tissue expression of insulin like growth factor-I. *Gene*. 2014;535:101–5.
- Wallace JM, Matsuzaki M, Milne J, Aitken R. Late but not early gestational maternal growth hormone treatment increases fetal adiposity in overnourished adolescent sheep. *Biol Reprod*. 2006;75:231–9.
- Tatara MR, Śliwa E, Krupski W. Prenatal programming of skeletal development in the offspring: effects of maternal treatment with  $\beta$ -hydroxy- $\beta$ -methylbutyrate (HMB) on femur properties in pigs at slaughter age. *Bone*. 2007;40:1615–22.
- Rehfeldt C, Kuhn G, Nürnberg G, Kanitz E, Schneider F, Beyer M, et al. Effects of exogenous somatotropin during early gestation on maternal performance, fetal growth, and compositional traits in pigs. *J Anim Sci*. 2001;79:1789–99.
- Koch J, Wilmoth T, Wilson M. Periconceptual growth hormone treatment alters fetal growth and development in lambs. *J Anim Sci*. 2010;88:1619–25.
- Costine B, Inskeep E, Wilson M. Growth hormone at breeding modifies conceptus development and postnatal growth in sheep. *J Anim Sci*. 2005;83:810–5.
- Oberbauer A, Pomp D, Murray J. Dependence of increased linear bone growth on age at oMT1a-oGH transgene expression in mice. *Growth Dev Aging*. 1994;58:83–93.
- Tatara MR. Neonatal programming of skeletal development in sheep is mediated by somatotrophic axis function. *Exp Physiol*. 2008;93:763–72.
- Thonney ML, Oberbauer AM, Duhaime DJ, Jenkins TC, Firth NL. Empty body component gain of rats grown at different rates to a range of final weights. *J Nutr*. 1984;114:1777–86.
- Pomp D, Narcarrow CD, Ward KA, Murray JD. Growth, feed efficiency and body composition of transgenic mice expressing a sheep metallothionein 1a-sheep growth hormone fusion gene. *Livest Prod Sci*. 1992;31:335–50.
- Pursell VG, Hammer R, Bolt D, Palmiter R, Brinster R. Integration, expression and germ-line transmission of growth-related genes in pigs. *J Reprod Fertil Suppl*. 1989;41:77–87.
- Qiao X, Zhang H, Wu S, Yue H, Zuo J, Feng D, et al. Effect of  $\beta$ -hydroxy- $\beta$ -methylbutyrate calcium on growth, blood parameters, and carcass qualities of broiler chickens. *Poult Sci*. 2013;92:753–9.
- Gahr SA, Vallejo RL, Weber GM, Shepherd BS, Silverstein JT, Rexroad III CE. Effects of short-term growth hormone treatment on liver and muscle transcriptomes in rainbow trout (*Oncorhynchus mykiss*). *Physiol Genomics*. 2008;32:380–92.
- Johnston IA, Devlin RH. Muscle fibre size optimisation provides flexibility to energy budgeting in calorie-restricted Coho salmon transgenic for growth hormone. *J Exper Biol* 2014. jeb. 107664.
- Bush JA, Burrin DG, Suryawan A, O'Connor PM, Nguyen HV, Reeds PJ, et al. Somatotropin-induced protein anabolism in hindquarters and portal-drained viscera of growing pigs. *Am J Phy Endocrin Metab*. 2003;284:E302–12.

53. López-Oliva M, Agis-Torres A, Muñoz-Martínez E. Growth hormone administration produces a biphasic cellular muscle growth in weaning mice. *J Physiol Biochem*. 2001;57:255–63.
54. Oberbauer A, Stern J, Johnson P, Horwitz B, German J, Phinney S, et al. Body composition of inactivated growth hormone (oMt1a-oGH) transgenic mice: generation of an obese phenotype. *Growth Dev Aging*. 1997;61:169–79.
55. Oberbauer AM, Runstadler JA, Murray JD, Havel PJ. Obesity and Elevated Plasma Leptin Concentration in oMT1A-o Growth Hormone Transgenic Mice. *Obes Res*. 2001;9:51–8.
56. Oberbauer A, Stiglich C, Murray J, Keen C, Fong D, Smith L, et al. Dissociation of body growth and adipose deposition effects of growth hormone in oMt1a-oGH transgenic mice. *Growth Dev Aging*. 2003;68:33–45.
57. Murray J, Oberbauer A, Sharp K, German J. Expression of an ovine growth hormone transgene in mice increases arachidonic acid in cellular membranes. *Transgenic Res*. 1994;3:241–8.
58. Oberbauer A, German J, Murray J. Growth Hormone Enhances Arachidonic Acid Metabolites in a Growth Hormone Transgenic Mouse. *Lipids*. 2011;46:495–504.
59. Forhead AJ, Fowden AL. The hungry fetus? Role of leptin as a nutritional signal before birth. *J Physiol*. 2009;587:1145–52.
60. Hoggard N, Haggarty P, Thomas L, Lea R. Leptin expression in placental and fetal tissues: does leptin have a functional role? *Biochem Soc Trans*. 2001;29:57–62.
61. Vickers M, Gluckman P, Coveny A, Hofman P, Cutfield W, Gertler A, et al. Neonatal leptin treatment reverses developmental programming. *Endocrinology*. 2005;146:4211–6.
62. Alexe D-M, Syridou G, Petridou ET. Determinants of early life leptin levels and later life degenerative outcomes. *Clin Med Res*. 2006;4:326–35.
63. Attig L, Djiane J, Gertler A, Rampin O, Larcher T, Boukthir S, et al. Study of hypothalamic leptin receptor expression in low-birth-weight piglets and effects of leptin supplementation on neonatal growth and development. *Am J Phys Endocrin Metab*. 2008;295:E1117–25.
64. Lea R, Howe D, Hannah L, Bonneau O, Hunter L, Hoggard N. Placental leptin in normal, diabetic and fetal growth-retarded pregnancies. *Mol Hum Reprod*. 2000;6:763–9.
65. Thomas A, Murray J, Oberbauer A. Leptin modulates fertility under the influence of elevated growth hormone as modeled in oMt1a-oGH transgenic mice. *J Endocrinol*. 2004;182:421–32.
66. Dunn GA, Morgan CP, Bale TL. Sex-specificity in transgenerational epigenetic programming. *Horm Behav*. 2011;59:290–5.
67. Mueller BR, Bale TL. Sex-specific programming of offspring emotionality after stress early in pregnancy. *J Neurosci*. 2008;28:9055–65.
68. Anway MD, Cupp AS, Uzumcu M, Skinner MK. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science*. 2005;308:1466–9.
69. Jansson J-O, Ekberg S, Isaksson O, Mode A, Gustafsson J-Å. Imprinting of Growth Hormone Secretion, Body Growth, and Hepatic Steroid Metabolism by Neonatal Testosterone\*. *Endocrinology*. 1985;117:1881–9.
70. Giustina A, Wehrenberg WB. The role of glucocorticoids in the regulation of growth hormone secretion mechanisms and clinical significance. *Trends Endocrinol Metab*. 1992;3:306–11.
71. Mazziotti G, Giustina A. Glucocorticoids and the regulation of growth hormone secretion. *Nat Rev Endocrinol*. 2013;9:265–76.
72. Giustina A, Mazziotti G. Impaired growth hormone secretion associated with low glucocorticoid levels: an experimental model for the Giustina effect. *Endocrine*. 2014;1–3.
73. Nogami H, Hisano S. Functional maturation of growth hormone cells in the anterior pituitary gland of the fetus. *Growth Horm IGF Res*. 2008;18:379–88.
74. Dean CE, Mörpurgó B, Porter TE. Induction of somatotroph differentiation in vivo by corticosterone administration during chicken embryonic development. *Endocrine*. 1999;11:151–6.
75. Lemley C, Meyer A, Neville T, Hallford D, Camacho L, Maddock-Carlin K, et al. Dietary selenium and nutritional plane alter specific aspects of maternal endocrine status during pregnancy and lactation. *Domest Anim Endocrinol*. 2014;46:1–11.
76. Meyer A, Reed J, Neville T, Taylor J, Hammer C, Reynolds L, et al. Effects of plane of nutrition and selenium supply during gestation on ewe and neonatal offspring performance, body composition, and serum selenium. *J Anim Sci*. 2010;88:1786–800.
77. Newbern D, Freemark M. Placental hormones and the control of maternal metabolism and fetal growth. *Curr Opin Endocrinol Diabetes Obes*. 2011;18:409–16.
78. Barbour LA, Shao J, Qiao L, Pulawa LK, Jensen DR, Bartke A, et al. Human placental growth hormone causes severe insulin resistance in transgenic mice. *Am J Obstet Gynecol*. 2002;186:512–7.
79. Eastell R, Lambert H. Diet and healthy bones. *Calcif Tissue Int*. 2002;70:400–4.
80. Harel Z, Tannenbaum GS. Long-term alterations in growth hormone and insulin secretion after temporary dietary protein restriction in early life in the rat. *Pediatr Res*. 1995;38:747–53.
81. Cooper C, Walker Bone K, Arden N, Dennison E. Novel insights into the pathogenesis of osteoporosis: the role of intrauterine programming. *Rheumatology*. 2000;39:1312–5.
82. Fu Q, Yu X, Callaway CW, Lane RH, McKnight RA. Epigenetics: intrauterine growth retardation (IUGR) modifies the histone code along the rat hepatic IGF-1 gene. *FASEB J*. 2009;23:2438–49.
83. Smith LB, Belanger JM, Oberbauer AM: Fibroblast growth factor receptor 3 effects on proliferation and telomerase activity in sheep growth plate chondrocytes. *J Anim Sci Biotec*. 2012, 3:doi: 10.1186/2049-1891-1183-1139.
84. Wu S, Levenson A, Kharitonov A, De Luca F. Fibroblast growth factor 21 (FGF21) inhibits chondrocyte function and growth hormone action directly at the growth plate. *J Biol Chem*. 2012;287:26060–7.
85. Guan H, Arany E, van Beek JP, Chamson-Reig A, Thyssen S, Hill DJ, et al. Adipose tissue gene expression profiling reveals distinct molecular pathways that define visceral adiposity in offspring of maternal protein-restricted rats. *Am J Phys Endocrin Metab*. 2005;288:E663–73.
86. Gray C, Li M, Reynolds CM, Vickers MH. Pre-weaning growth hormone treatment reverses hypertension and endothelial dysfunction in adult male offspring of mothers undernourished during pregnancy. *PLoS ONE*. 2013;8:e53505.
87. Reynolds C, Li M, Gray C, Vickers M. Pre-weaning growth hormone treatment ameliorates adipose tissue insulin resistance and inflammation in adult male offspring following maternal undernutrition. *Endocrinology*. 2013;154:2676–86.
88. Vickers MH, Sloboda DM. Strategies for reversing the effects of metabolic disorders induced as a consequence of developmental programming. *Front Physiol*. 2012;3:342.
89. Sarr O, Yang K, Regnault TR: In utero programming of later adiposity: the role of fetal growth restriction. *J Preg*. 2012, 2012:doi:10.1155/2012/134758.
90. Llescur C, Armstrong DA, Paquette AG, Koestler DC, Padbury JF, Marsit CJ. Tissue-specific Leptin promoter DNA methylation is associated with maternal and infant perinatal factors. *Mol Cell Endocrinol*. 2013;381:160–7.
91. Jousse C, Parry L, Lambert-Langlais S, Maurin A-C, Averous J, Bruhat A, et al. Perinatal undernutrition affects the methylation and expression of the leptin gene in adults: implication for the understanding of metabolic syndrome. *FASEB J*. 2011;25:3271–8.
92. Shao Y, Zhao F-Q: Emerging evidence of the physiological role of hypoxia in mammary development and lactation. *J Anim Sci Biotec*. 2014, 5:doi:10.1186/2049-1891-1185-1189.
93. Melvin A, Mudie S, Rocha S. The chromatin remodeler ISWI regulates the cellular response to hypoxia: role of FIH. *Mol Biol Cell*. 2011;22:4171–81.
94. Nair D, Ramesh V, Li RC, Schally AV, Gozal D. Growth hormone releasing hormone (GHRH) signaling modulates intermittent hypoxia-induced oxidative stress and cognitive deficits in mouse. *J Neurochem*. 2013;127:531–40.
95. Li RC, Guo SZ, Raccurr M, Moudilou E, Morel G, Brittan KR, et al. Exogenous growth hormone attenuates cognitive deficits induced by intermittent hypoxia in rats. *Neuroscience*. 2011;196:237–50.
96. Braems G, Han V. Gestational age-dependent changes in the levels of mRNAs encoding cortisol biosynthetic enzymes and IGF-II in the adrenal gland of fetal sheep during prolonged hypoxemia. *J Endocrinol*. 1998;159:257–64.
97. Chen X-Q, Du J-Z. Increased somatostatin mRNA expression in periventricular nucleus of rat hypothalamus during hypoxia. *Regul Pept*. 2002;105:197–201.
98. Varvarigou A, Vagenakis A, Makri M, Beratis N. Growth hormone, insulin-like growth factor-I and prolactin in small for gestational age neonates. *Neonatology*. 1994;65:94–102.