Chapter 7. Hormonal control of feed intake in swine

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Abstract

Voluntary feed intake is controlled by a plethora of factors including, but not limited to, day length, social interactions, environmental conditions, oronasal sensory cues (i.e. taste, smell, texture), gastrointestinal fill, health status, metabolic status, dietary composition, drug interactions, exercise (physical activity), mental status (i.e. depression) and gender. However, most, if not all, of these factors can mediate the hormonal milieu within the body that can ultimately control feeding behaviour. Therefore, the focus of this chapter will be on hormonal control of voluntary feed intake in swine. For detailed information pertaining to other factors that affect voluntary feed intake in swine such as perinatal flavour programming, oronasal chemosensory cues, metabolism, antinutritional factors, social interactions, environmental conditions and pathogen exposure, the reader is referred to the accompanying chapters within this book. With regard to hormonal regulation, voluntary feed intake is controlled by intricate and diverse afferent and efferent communication pathways that transmit hormonal and neural messages throughout the body that ultimately reflect the status of the body's energy balance to the hypothalamus. Collectively, these signals are responsible for coordinating a delicate balance between energy utilisation and energy intake in order to maintain energy homeostasis. Some of these biological messages such as glucose and cholecystokinin tend to be more reflective of short-term energy balances associated with food consumption, whereas others, such as insulin and leptin tend to be more reflective of long-term energy stores within the body. While numerous hormones have been shown to be involved in feed intake, this chapter will focus on hormones associated with the control of feed intake specifically in swine with supporting information generated in other species. Specifically, information will be provided on the relationship between feed intake and the somatotrophic axis, the appetite stimulating affects of ghrelin, orexin, neuropeptide Y (NPY) and agouti-related protein (AGRP), and the appetite suppressive effects of leptin and urocortin. Additionally, information will be presented related to the potential effects of glucocorticoids on appetite stimulation in swine.

Keywords: appetite, somatotrophic axis, neuropeptides, glucocorticoids

Introduction

Under normal circumstances, the regulation of feed intake is a complex, albeit finely orchestrated, biological process that involves multiple biochemical pathways, physiological processes and physical constraints within the body. Even minor disruptions to this finely tuned process can manifest themselves as phenotypic characteristics such as those associated with obesity and anorexia in humans. Even in an ideal nutritional environment, complications associated with adequate food consumption and appropriate nutrient intake becomes a complicated process regulated by psychological, sociological, physical, environmental and physiological inputs. In
livestock production, however, feed intake is largely controlled through management practices that strive to optimise the economic balance between food intake and overall animal health and productivity. For the most part, maintaining this balance in mature animals is less complex than that associated with young, growing animals as mature animals are typically retained in livestock production settings for reproductive and lactation purposes. Therefore, the nutritional requirements of these mature animals are associated with the maintenance energy required for a specific biological process and are typically easy to accomplish through proper nutritional management in the absence of extenuating circumstances that lead to undernourishment such as fluctuations in environmental conditions, social interactions, hormonal imbalances and disease challenges. Conversely, in the young, growing animal, nutritional requirements are changing rapidly as the animal grows and as they transition through the various stages of their production cycle. This is especially relevant in young pigs during the weaning process when they must transition from a liquid milk diet to a diet consisting of solid food and water at a time of rapid growth and during a time when their immune system has not fully developed. Complicating the situation even more for the young pig is the limited energy reserves to draw upon during this critical time.

In the absence of swine management intervention strategies, pigs gradually undergo the weaning process by consuming a solid diet while they are still suckling from the sow. However, in the majority of modern, intensive swine production systems, young pigs are weaned from the sow and moved to a nursery facility where they must be transitioned to a solid diet rapidly in order to survive and thrive in their new environment. During this transition, weaned pigs routinely experience a 1 to 3 day period of inappetence or voluntary feed deprivation and weight loss resulting in a period of growth stasis that can be detrimental to their health, productivity and overall well-being. While the precise mechanisms associated with this period of inappetence have not been fully elucidated, it is routinely attributed to several factors including maternal separation, transportation stress, stress associated with new environmental and social surroundings, possible exposure to new pathogens and the associated immunological challenges, and the transition from a liquid to solid feed diet (Forbes, 1995; Riley, 1989). The ability to successfully transition from a liquid milk to a solid food diet at weaning can be influenced by several factors including prior access to solid food while the pig is still suckling (Funderburke and Seerley, 1990), the establishment of social hierarchy within a group of weaned pigs, the availability of adequate feeder space, and the size of the pig at weaning as lighter weight pigs eat less and tend to have a lower daily weight gain in comparison to larger pigs (Georgsson and Svendsen, 2002).

Unravelling the controlling mechanisms underneath this common phenomenon becomes even more challenging given the individual piglet variation in behavior that exists and the differential responses to the weaning experience that are ultimately linked to post-weaning feed intake and growth rate (Giroux et al., 2000). Fortunately, the majority of pigs adjust fairly rapidly to the various stressors imposed upon them at weaning including the transition to solid feed. However, even a successful transition at weaning does not typically occur without an associated biological and economic cost associated with weight loss, the potential for increased susceptibility to pathogens due to an energy deficit, and expenditure of an already scarce energy reserve in order to maintain homeostasis while contending with numerous stress-related events. Therefore, one of the utmost challenges, and potentially one of the most lucrative opportunities, in swine production is the
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ability to prevent or decrease the amount of time that young pigs spend in this weaning-induce
period of inappetence, and the associated detrimental effects on health and productivity brought
about by inadequate nutrition, by being able to stimulate feed intake in the newly weaned pig.
However, to be able to capitalise on this opportunity by devising intervention strategies that
enhance post-weaning feed intake and growth performance, a better understanding of the impact
of weaning on the hormones that regulate growth and feed intake during the post-weaning period
would be beneficial, if not obligatory. To this end, the intent of this chapter is to provide the reader
with a broad overview of published literature pertaining to the association between feed intake
and regulation of the somatotrophic axis in swine, and the use of exogenous hormonal treatments
as a means to regulate feed intake in swine.

Feed intake and the somatotrophic axis

Brief overview of growth hormone regulation

The synthesis and secretion of growth hormone (GH) from somatotrophs within the anterior
pituitary gland is regulated by a complex interaction among hormonal signals and intracellular
signal transduction pathways. Classically, the primary stimulator of GH synthesis and secretion
is GH-releasing hormone (GHRH) and the primary inhibitor of GHRH-induced GH secretion
is somatostatin or somatotropin-release inhibiting factor (SRIF) (Plotsky and Vale, 1985) which
inhibits GHRH-induced GH secretion; however, it does not inhibit the synthesis of GH (Harvey,
1995). Both GHRH and SRIF are neurohormones synthesised in hypothalamic neurons that
enter the anterior pituitary via the hypothalamo-hypophyseal portal system. While GHRH is
synthesised in the arcuate and ventromedial nuclei of the hypothalamus, SRIF is predominantly
synthesised in the periventricular nuclei. Both of these neuropeptides are transported via axons
to nerve ending in the external layer of the median eminence where they are released into the
hypothalamo-hypophyseal portal system. The pulsatile pattern of GH secretion observed \textit{in vivo}
may be explained primarily by the pattern of GHRH and SRIF release from the hypothalamus
into the hypophysial portal system (Muller, 1987). Plotsky and Vale (1985) demonstrated that
these two neurohormones are released in episodic fashions which are 180° out of phase with each
other. A rapid release of GH is stimulated by a hypothalamic pulse of GHRH which results in a
subsequent hypothalamic pulse of SRIF that will terminate further GH release from somatotrophs
(Berelowitz \textit{et al.}, 1981; Molitch and Hlivyak, 1980).

Biological action of growth hormone

Postnatal growth in the weaned pig is strongly influenced by production, secretion, and activity
of somatotrophic hormones (Carroll \textit{et al.}, 2000) and insulin-like growth factors. Growth
hormone is considered to be a major endocrine factor in regulating postnatal muscle growth
with direct influences on muscle metabolism (Novakofski and McCusker, 1993) and is considered
to be the key homeorhetic controller of partitioning nutrients for growth (Harrell \textit{et al.}, 1999).
Growth hormone, also known as somatotropin, regulates numerous biological activities within
the body including activation of hyperplasia, enhancement of amino acid uptake and nitrogen
retention, increasing mRNA for protein synthesis, decreasing lipogenesis while increasing fatty
acid oxidation and fatty acid release, increasing plasma glucose, triggering insulin secretion,
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and enhancing bone mineralisation. With regard to the development of skeletal muscle, GH elicits direct actions through amino acid uptake and nitrogen retention, increased mRNA for protein synthesis, and glucose sparing, and elicits indirect actions through insulin-like growth factor-1 (IGF-1) and/or cell proliferation. Growth hormone stimulates IGF-1 release from the liver as well as from target tissues such as muscle and bone. Insulin-like growth factor-1 exhibits both paracrine and endocrine actions with the major target tissues being muscle, cartilage, bone, liver, kidney, nerves, skin, and lungs. It promotes the growth of muscle and bone, and tissue regeneration of the other more biologically active target organs in part through regulation of cell growth by moving cells from a resting phase (G0) to an active phase of the cell cycle and by increasing a cell’s ability to complete DNA synthesis.

Growth hormone received considerable attention over the years in growth physiology research as a primary mediator of animal growth. Several studies have demonstrated that exogenous GH enhances growth rate, feed efficiency, bone mineralisation and lean tissue deposition while reducing carcass fatness in livestock (McLaughlin et al., 1991; Preston et al., 1995). However, the biological action of growth hormone within the body cannot be simply assigned to the endocrine, neuroendocrine or immune system due to its broad and diverse biological actions. Even the digestive and reproductive systems do not escape functional dependency from GH. It has been suggested however, that the biological actions of GH could be broadly classified as either somatogenic or metabolic (Underwood, 1995). The somatogenic roles include any GH effects which result in cell proliferation which is mediated either directly or indirectly by the somatomedins. The metabolic role of GH includes direct actions on a variety of tissues in addition to the metabolism of protein, carbohydrates, lipids and minerals.

With regard to carcass composition, GH exhibits both anabolic and catabolic actions. Its anabolic action results from an increase in muscle and intestinal protein synthesis (Eisemann et al., 1989) without affecting protein degradation (Hart and Johnsson, 1986) which in turn results in a net increase in protein accretion in the muscle and liver. The increase in whole body protein synthesis is associated with the ability of GH to increase nitrogen retention that results from a decrease in urinary nitrogen excretion (Eisemann et al., 1986). In cattle, exogenous GH increases nitrogen retention by 20 to 30% (Crooker et al., 1990; Eisemann et al., 1989). This anabolic action of GH on muscle tissue is coupled with the catabolic action of GH on adipose tissue (Eisemann et al., 1989; Moseley et al., 1992; Phillips, 1986; Schwarz et al., 1993).

The lipolytic action of GH becomes especially important during times of feed restriction. In fasting cattle, GH response to a stimulus such as intravenous injection of arginine is increased as compared to fed cattle (McAtee and Trenkle, 1971). This increase in GH during periods of fasting results in an increase of free fatty acids and glycerol from the hydrolysis of triglycerides. Harvey (1995) suggested that the lipolytic action of GH may be the result of one or more of the following actions: (1) the action of GH may be indirect by altering the secretion of endogenous hormones that mediate lipolysis. For example, GH may increase the secretion of lipolytic hormones such as epinephrine, norepinephrine and glucagon, or perhaps GH inhibits the secretion of anti-lipolytic hormones (e.g. insulin); (2) GH could possibly effect the sensitivity of adipose tissue to these lipolytic or anti-lipolytic hormones; or (3) GH may interact with its receptor on adipose tissue to directly increase lipolysis. The overall net result of the anabolic and catabolic actions is an
increase in lean tissue accretion and a subsequent decrease in lipid deposition which produces a desirable carcass.

In addition to the somatogenic and metabolic actions in the body, GH is now being recognised as an important mediator of the immune system. Interestingly, it has been demonstrated that GH is not only synthesised by somatotrophs in the anterior pituitary gland, but is also produced by cells of the immune system. Several research groups have demonstrated that there are similarities, as well as differences, that exist in the regulation of anterior pituitary synthesis and secretion of GH as compared to leukocyte synthesis and secretion of GH (Hattori et al., 1990; Kato et al., 1989; Weigent et al., 1988). Additionally, it has been reported that immune system peptides are capable of mediating the synthesis and secretion of anterior pituitary GH (Weigent and Blalock, 1990). This apparent bi-directional communication between the immune system and the endocrine system is further supported by evidence that demonstrated that GH is capable of altering the function and activity of all the major immune system cell types including T-cells, B-cells, natural killer cells (NK) and macrophages (Kelley, 1989). Establishing this bi-directional communication between the neuroendocrine, endocrine and immune systems has lead to the use of the term 'neuroimmunoendocrine system' by endocrinologists and physiologists.

A discussion pertaining to the biological action of GH would be incomplete without at least a brief introduction of The Dual Effector Theory (Green et al., 1985). The basis for this theory originates from the observation that IGF-1 stimulates in vitro amino acid uptake into the muscle but does not necessarily promote in vivo growth. Thus, GH is thought to control circulating as well as local tissue production of IGF-1. The theory proposes that GH not only controls IGF-1 production, but also controls differentiation of cells as mentioned above so that they can respond to the mitogenic effect of IGF-1. The Dual Effector Theory really comes into play during periods when there is uncoupling of the GH/IGF-1 axis. Having high concentrations of GH and low concentrations of IGF-1, such as during nutritional restriction brought about by the inappetence associated with weaning or activation of the acute phase immune response, suggests that GH plays a different role under these circumstances. However, it is important to note that changes in circulating concentrations of GH have been reported to be species specific (Daniel et al., 2002). In humans, sheep, and pigs, GH concentrations increase following activation of the innate immune system, while in rats, cattle, and birds, GH concentrations decrease.

Uncoupling of the GH/IGF-1 axis during inappetence in the weaned pig

The purpose of this section is to highlight changes associated with the uncoupling of the GH/IGF-1 axis during periods of inappetence or voluntary feed deprivation associated with weaning and immune system activation in the young pig as these events provide a valuable insight into the endocrine status of the pigs during these periods of nutritional restriction. While it has been questioned whether the GH/IGF-1 axis is physiologically active in young pigs (Hellstern et al., 1996), studies have demonstrated that the somatotrophic axis in neonatal pigs is not only functional (Wester et al., 1998) but undergoes significant maturational changes (Carroll et al., 1999). It has also been reported that in the neonatal pig, pituitary GH release influences IGF-1 secretion and stimulates growth (Matteri et al., 1994). Developmentally, GH concentrations are elevated initially following birth and subsequently decline during the pre-weaning period (Matteri et al., 1994).
Insulin-like growth factors share a similar structure with insulin and are associated with increases in DNA, RNA and protein synthesis. Insulin-like growth factor-1, considered to be the primary somatomedin, is produced in the liver, muscle and other tissues, and is responsible for several biological actions including bone and muscle growth. The primary target tissues for IGF-1 include muscle, cartilage, bone, liver, kidney, nerves, skin, and lungs. Insulin-like growth factor-1 has a potent affect on muscle growth and metabolism by suppressing protein degradation (Novakofski and McCusker, 1993). Unlike GH, IGF-1 concentrations are low during the prenatal period but increase during the perinatal period (Lee et al., 1991). Concentrations of serum IGF-1 in newborn piglets increases steadily after birth, and by 3 weeks of age, serum IGF-1 concentrations exceed those found in the maternal serum (Lee et al., 1991). Serum IGF-2 levels also increase following birth, but the magnitude is not the same as IGF-1. Insulin-like growth factor-2, comprised of 67 amino acids, is secreted from the liver in addition to various other tissues. The primary role of IGF-2 is not as well defined as is the role of IGF-1, but IGF-2 is more important for prenatal growth and development compared to postnatal development. The postnatal increase in both IGF-1 and IGF-2 suggests maturation of the somatotrophic axis (Lee et al., 1991).

Nutritional status has a strong influence on the production and secretion of a variety of growth-related hormones, including GH (Atinmo et al., 1978; Farmer et al., 1992; Straus, 1994), IGF-1 (Booth et al., 1994; Straus, 1994; Weller et al., 1994), IGF-2 (Buonomo et al., 1988), thyroid hormones (Booth et al., 1994; Dauncey and Morovat, 1993), and glucocorticoids (Farmer et al., 1992). Unfortunately, there have only been a relatively small number of studies that have evaluated metabolic and endocrine responses of the pig during weaning and during a dietary transition. In an early study by Carroll et al. (1998) the authors provided insight into the developmental and dietary related changes that occur in endocrine profiles in pigs that were weaned from their sows and placed on a commercial pre-starter ration at either 2 or 3 weeks of age. Twelve days after weaning, the pigs were transitioned from the commercial pre-starter ration to a starter ration. Specifically, these authors reported that weaning significantly reduced body weight regardless of age at weaning and regardless of gender. While average daily gain (ADG) was reduced in both groups of pigs following weaning, those weaned at 2 weeks of age experienced a greater decrease in ADG as compared to pigs weaned at 3 weeks of age. Interestingly, the authors also reported a decrease in ADG following the transition in diets at 12 days post-weaning, thus highlighting the importance of dietary consistency and the effects of abrupt changes in the ration. With regard to serum concentrations of GH, these authors reported significant developmental decreases that occurred from birth to weaning, followed by a significant increase post-weaning in both weaning groups. The authors also noted numerical increases in GH following the dietary transition. Serum concentrations of IGF-1 and IGF-2 both increased during the pre-weaning period, but fell dramatically after weaning. A significant decrease in IGF-1 was noted in the 2 week weaning group, but not the 3 week weaning group, following the dietary transition at 12 days post-weaning. As with IGF-1, serum concentrations of IGF-2 following the dietary transition revealed a weaning-age interaction. Collectively, the results from this previous study clearly demonstrate that weaning and even abrupt changes in the young pig’s diet post-weaning can have significant effects on the somatotrophic axis in the pig, and that the lack of feed consumption is directly related to the uncoupling of the GH/IGF-1 axis.
The results from the early study by Carroll et al. (1998) stimulated subsequent research by Matteri et al. (2000) that was aimed at distinguishing the differential effects between pig development and nutritional restriction associated with weaning as they relate to the changes in the somatotrophic axis. Additionally, these authors evaluated the potential use of spray-dried plasma as a means to stimulate feed intake and reduce the duration of voluntary feed deprivation associated with weaning. In this study, the authors weaned twenty-four pigs at exactly 14 days of age and divided them into three experimental groups: (1) pigs that were cross-fostered to another sow (not nursing any other pigs) at the same stage of lactation as the sows of the weaned pigs; (2) pigs weaned onto a commercial pre-starter ration containing no spray-dried plasma; and (3) pigs weaned onto a commercial starter ration containing 7% spray-dried plasma. For groups 2 and 3, diets were formulated to contain equal digestible essential amino acids and metabolisable energy. The results from this study revealed that during the first 3 days of the study, sow-nursed pigs gained significantly more weight than either group of pigs that were placed on the commercial pre-starter ration. However, during the last day of the study, day 4 post-weaning, weight gains in the pigs cross-fostered and nursing a sow, and those supplemented with 7% spray-dried plasma were equivalently elevated compared to the weaned pigs not supplemented with spray-dried plasma. These results are similar to previous studies that have reported increases in feed intake in weaned pigs supplemented with spray-dried plasma (Coffey and Cromwell, 1995; De Rodas et al., 1995; Touchette et al., 1998). However, this increase in growth for pigs supplemented with spray-dried plasma was not associated with increases in measures of somatotrophic function as the authors reported significant decreases in serum concentrations of IGF-1 and IGF-2 at 4 days post-weaning in both groups fed the commercial pre-starter ration. These results are similar to those previously reported by Carroll et al. (1998) for pigs weaned at either 2 or 3 weeks of age. Interestingly, Matteri et al. (2000) reported no differences in levels of muscle IGF-1, IGF-2, and GH receptor mRNA expression among the three weaning groups, thus suggesting that gene expression in these target tissues is related more to the developmental stage of the pig rather than the nutritional status. Consistent with a developmental aspect associated with nutritionally-linked uncoupling of the GH/IGF-1 axis are studies that demonstrate that total feed deprivation in the newborn pig actually results in increases in both IGF-1 and GH. However, the aforementioned studies do in fact demonstrate that nutritional deprivation results in an uncoupling of the GH/IGF-1 axis in pigs by at least 14 days of age.

While the uncoupling of the GH/IGF-1 axis related to immune system activation has not been as extensively researched in swine as in sheep and cattle, there is sufficient data within the literature and previous studies from our laboratory (Carroll et al., unpublished data; Figure 1) that do indeed support the existence of bi-directional communication between the immune system and somatotrophic axis in swine. Initial linkages stem primarily from studies that revealed that exogenous GH treatment could alter various aspects of the activated immune system. For example, Parrott et al. (1995) demonstrated acute increases in circulating concentrations of GH in pigs during the first 20 minutes following an immunological challenge with endotoxin (lipopolysaccharide; LPS). Later, Hevener et al. (1997) reported that in finishing pigs, an acute increase in GH occurred 40 minutes after an intra-peritoneal challenge with LPS. However, the authors reported that this increase in GH concentration was short-lived and was followed by a subsequent uncoupling of the GH/IGF-1 axis that persisted for 96 hours after LPS exposure. The research by Hevener et al. (1997) suggested that the persistent uncoupling of the GH/IGF-1
axis could be attributed to factors beyond nutritional influences as feed consumption did not differ between control and LPS-challenge pigs, a postulation consistent with that proposed for cattle (Elsasser et al., 1988). A subsequent study by Wright et al. (2000) also supports this hypothesis as the authors reported that in pigs challenged with LPS, serum concentrations of IGF-1 remained low even after the pigs resumed normal feed consumption. In weanling pigs, we have demonstrated that during the first 30 minutes post-LPS challenge, serum concentrations of GH are dramatically reduced while serum concentrations of IGF-1 are increased. However, subsequent to this initial acute reduction in GH, GH concentrations begin to increase and spike at 3 hours post-LPS challenge while IGF-1 concentrations decline (J.A. Carroll, unpublished data). The results from these studies highlight the importance of intensive serial blood sampling when attempting to profile the dynamic aspect associated with the uncoupling of the GH/IGF-1 axis, especially uncoupling of the axis associated with acute stimulation of the immune system. Collectively, these data suggest not only a time-dependent but also age-dependent aspect associated with the uncoupling of the GH/IGF-1 axis in swine.

**Stimulators of appetite**

**Ghrelin**

Ghrelin, a ligand capable of stimulating GH secretion via binding to the GH secretagogue receptor, is also capable of in vivo stimulation of adrenocorticotropic-releasing hormone

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**Figure 1.** Serum concentrations of growth hormone (GH) and insulin-like growth factor 1 (IGF-1) in weaned pigs following an endotoxin challenge. At Time 0, pigs received an intravenous dose of lipopolysaccharide (LPS; 25 μg/kg body weight). Data from Carroll et al. (unpublished).
Hormonal control of feed intake in swine (ACTH), cortisol, aldosterone, prolactin and epinephrine (Arvat et al., 2001; Takaya et al., 2000). While primarily produced and secreted from epithelial cells lining the fundus of the stomach, ghrelin is also produced in other organs including the pituitary, hypothalamus, small intestine, placenta, kidney, heart, thyroid gland, immune cells such as T-cells and neutrophils, pancreas endocrine cells, and the ovary (Gaytan et al., 2003; Hattori et al., 2001; Korbonits et al., 2001; Mori et al., 2000; Volante et al., 2002a,b). Even though the known biological actions of ghrelin are rather extensive, including effects on insulin secretion, glucose and lipid metabolism, gastric secretion and motility, various effects on the cardiovascular system, inhibition of reproductive processes, and potentially beneficial alterations associated with the immune system, within domestic livestock, it has received considerable attention primarily as means to stimulate GH secretion and increase food intake.

In a previous study, Salfen et al. (2003) characterised the pattern of ghrelin secretion during a 72 hour feed deprivation followed by a subsequent re-feeding period in a group of weaned pigs. In their initial experiment, the authors reported that circulating concentrations of ghrelin were significantly decreased by 12 hours after total feed removal, but following this initial decrease, ghrelin concentrations significantly increased from 12 to 36 hours (Figure 2). The results from this study are consistent with those that have reported that ghrelin increases in the peripheral circulation during fasting (Tschop et al., 2000) in rodents, and after an overnight fast in anorectic humans (Cuntz et al., 2001). In a subsequent experiment reported within the same manuscript, the authors reported that following the 36 to 48 hour increase, ghrelin concentrations once again declined by 72 hours following feed deprivation. The authors speculated that ghrelin secretion

![Figure 2. Recreated from Salfen et al., 2003. Effect of ad libitum feeding (CON) or feed deprivation (FD) followed by re-feeding on serum concentrations of ghrelin expressed as a percent of the 0 hour concentration in weaned pigs. Values are the mean ±S.E.M. of n=4 pigs per group. Pigs in the FD treatment were given access to ad libitum feed after the 24 hour sample collection. * Denotes difference between FD and CON treatments (P=0.08). ** Denotes a difference in FD pigs from the 12 hour time point to the 24 hour time point (P<0.01).](image-url)
increased from 12 to 36 hours post-feed deprivation in order to initiate feeding activity even in the absence of food, but due to the absence of food and the abatement of hunger, ghrelin concentrations again fell to concentrations lower than basal levels.

While similar responses to the increases observed by Salfen et al. (2003) in serum concentrations of ghrelin in response to feed deprivation in pigs have subsequently been reported by other groups (Govoni et al., 2005; Inoue et al., 2005), a recent study by Scrimgeour et al. (2008) suggests that circulating concentrations of ghrelin may be more reflective of chronic changes in energy balance as opposed to actual feeding activity. In the study by Scrimgeour et al. (2008), circulating concentrations of ghrelin were profiled under three different feeding protocols that included ad libitum feeding, twice daily feeding and once daily feeding. During all three of the feeding protocols of the experiment, the authors reported no significant changes in circulating concentrations of ghrelin related to feed consumption. The authors did however report that ghrelin concentrations increased over the 12 hour blood sampling period when pigs were fed either once or twice daily rather than ad libitum and that this increase in circulating concentrations of ghrelin overlapped with increases in GH and non-esterified fatty acids. Additionally, the authors reported that these increases in ghrelin concentrations were not coupled with changes in either glucose or insulin concentrations, thus supporting their conclusion that circulating concentrations of ghrelin may be more reflective of energy balance rather than feeding behaviour. Interestingly, previous studies have reported that exogenous ghrelin treatment acutely increases plasma glucose and lowers insulin (Broglio et al., 2004), and alternatively, exogenous insulin as well as leptin has been reported to increase expression of ghrelin mRNA (Toshinai et al., 2001).

Subsequent to their initial observations that ghrelin concentrations were reduced in feed deprived pigs, and prior reports demonstrating that ghrelin was an important variable in the initiation of feeding behavior and appetite in rats (Nakazato et al., 2001; Shintani et al., 2001; Wren et al., 2001b), mice (Asakawa et al., 2001b), and humans (Cummings et al., 2001; Wren et al., 2001a), Salfen et al. (2004) evaluated the potential use of exogenous ghrelin as a means to stimulate feed intake in 18 day old pigs that were newly weaned. In this study, the authors evaluated the relative gain, feed intake, general behaviour and endocrine profiles of newly weaned pigs for 8 days subsequent to injections with either human ghrelin (2 μg/kg body weight) or with saline three times daily via an indwelling jugular catheter for 5 days. The authors reported that while there was a temporary decrease in body weights in both the saline and ghrelin injected pigs in response to weaning, the ghrelin injected pigs regained the lost body weight more rapidly than saline injected pigs. Interestingly, the authors did not report a significant difference in feed intake between the two treatment groups, a result similar to that previously reported in mice (Tschoop et al., 2000). Therefore, the authors speculated that the increases in weight gain observed for ghrelin injected pigs may not only reflect an increase in energy intake, but also potential alterations in energy utilisation and partitioning. Interestingly, in human trials in which patients were continuously infused with ghrelin intravenously, voluntary energy intake was increased by 28% compared with saline infusion (Wren et al., 2001a). In the study by Salfen et al. (2004), the authors reported that ghrelin was sufficiently metabolised from one injection to the next so there was no systemic accumulation of ghrelin throughout the experimental time period, therefore perhaps providing an explanation for the discrepancy in appetite between the human and pig trials. In addition to an increase in weight gain, Salfen et al. (2004) reported a significant increase in GH following the
initial ghrelin injection which was followed by a period of lower serum concentrations of GH at 2 hour after injection (Figure 3). Interestingly, while serum concentrations of insulin increased within 15 minutes following the initial injection of human ghrelin, serum concentrations of glucose were not affected.

While the orexigenic action of ghrelin is a significant stimulus to motivate re-nourishment of the animal, the fact that ghrelin is also a potent GH secretagogue may be central with regard to appropriate metabolic partitioning of nutrients. Previous studies have suggested that the appetite stimulatory function(s) of ghrelin and its GH secretagogue effects are independent of each other (Nakazato et al., 2001; Tschop et al., 2000) and may be mediated by separate subtypes of the ghrelin receptor. Finally, another function of ghrelin worth noting is its potential to initiate anxiogenic activities, an event that has been loosely defined as ‘food hunting behaviors’. Previous work has demonstrated that administration of exogenous ghrelin increases general activity in mice, and that experimentally imposed starvation stress and tail-pinched stress increased ghrelin gene expression in the stomach (Asakawa et al., 2001a).

In summary, exogenous ghrelin has a variety of endocrine effects and shows potential in increasing weight gain in pigs that could prove to be beneficial with regard to the overall health and productivity of the weaned pig. Given the reported associations between ghrelin and the stress axis, one might expect greater responses in older pigs that do not have confounding stressors impinging on them like recently weaned pigs as the stress associated with weaning may in part override the potential effectiveness of ghrelin in increasing appetite. However, the appropriate dosage, route of administration and duration of exposure necessary to elicit beneficial physiological responses in the pig remain undetermined.

Figure 3. Recreated from Salfen et al., 2004. Serum concentrations of growth hormone (GH) before and after administration of ghrelin (GR; 2 μg/kg body weight) or saline (CON). Pigs were weaned on day 0 of study and either injected with human ghrelin or saline at 0 min. * indicates that GR treatment means are higher than CON means (P<0.05). † indicates that CON treatment means are higher than GR means (P<0.05).
In 1998, Sakurai et al. (1998) described a family of hypothalamic neuropeptides, known as orexin-A and orexin-B, and their associated G protein-coupled receptors that were associated with regulation of feeding behaviour in the rat. This initial study revealed that intracerebroventricular (ICV) administration of orexin-A or orexin-B stimulated feed intake in rats and that the associated mRNA for the precursor of both of these neuropeptides, prepro-orexin, increased during food restriction. Subsequently, in a relatively short time, there have been a plethora of studies published on the topic of orexin and feed intake. In fact, in a recent review (Kirchgessner, 2002) on the subject of orexins and the brain-gut axis, the author noted that over 280 manuscripts had been published on the topic in the first four years after Sakurai and colleagues described the orexins and their receptors. Therefore, the intent of this section will be to only highlight the research that has been conducted with orexin and appetite stimulation in the pig. The reader is referred to the review by Kirchgessner (2002) for a more in depth discussion of the orexins and the orexin receptors as they relate to feeding behaviour, metabolic signalling, gut motility, as well as other important biological processes.

As early as 1999, Dyer et al. (1999) described the first study to successfully stimulate feed intake in weanling pigs via an intramuscular injection of synthetic porcine orexin. The study was conducted in three replicates with 8 to 10 weanling pigs per replicate. The authors reported that the pigs used had been weaned at approximately 16 days of age, and for a period of one week prior the application of treatments. To account for possible biases associated with individual feed intake in the weaned pigs, the authors monitored feed intake during a 24 hour period prior to treatment and reported that there were no differences between treatment groups. Subsequently, the pigs were injected with either synthetic porcine orexin at a dose of 3 mg/kg or sterile water. Following the treatments, the authors recorded feed intake every 2 hour for a 24 hour period. Based upon the feed intake data, the authors reported that the orexin treated pigs consumed three times as much feed as the control pigs at 12 hours after treatment, and suggested that orexin treatment resulted in an extra meal or feeding bout during this time frame. While the authors did not report any significant differences in feed intake at other time periods examined, they suggested that at a regular mealtime, the orexin-B treated pigs ingested more feed over an extended feeding period. The authors noted that this speculation was supported by the fact that cumulative feed intake was significantly greater in orexin treated pigs as compared to the control pigs from 12 to 24 hours after treatment. Overall, the authors reported that cumulative feed intake for the orexin treated pigs was approximately 18% greater than that observed in the control pigs. The authors speculated that the lag in the appetite response and feed consumption noted in their study, as compared to the initial study in rodents by Sakurai and colleagues, could be explained by the differences associated with intramuscular versus intracerebro-ventricular administered orexin. A subsequent study from our laboratory (Kojima et al., 2007), demonstrated that weaning did not result in altered expression of orexin mRNA in hypothalamic tissue, however, orexin mRNA expression was highly correlated to the size of the pig at weaning. Interestingly, despite the positive results reported by Dyer et al. (1999) in pigs, and supporting evidence in rodents (Muroya et al., 2004; Sakurai et al., 1998) and sheep (Sartin et al., 2001), there have been no further published studies evaluating the use of exogenous orexin as a means to enhance feed intake in the weaned pig.
7. Hormonal control of feed intake in swine

Neuropeptide Y

Neuropeptide Y (NPY), originally isolated in the porcine brain (Tatemoto, 1982), is a hypothalamic peptide found in the brain and autonomic nervous system that has been associated with a number of physiological activities within the brain including memory, learning, epilepsy and appetite stimulation (Billington et al., 1991; Colmers and El, 2003). It has also been associated with other physiological activities such as circadian rhythms, reproductive function, anxiety, energy expenditure and fat deposition, and vascular resistance. In rodents, sheep and pigs, NPY has even been implicated in the regulation of lutenising hormone and GH secretion (Barb et al., 2006; Jain et al., 1999; McShane et al., 1992). Interestingly, in rodents, NPY has been reported to be an inhibitor of GH secretion (Rettori et al., 1990) whereas in sheep, cattle and pigs, ICV injections of NPY stimulated GH secretion (Barb et al., 2006; McMahon et al., 1999; Thomas et al., 1999).

With regard to appetite stimulation, NPY is a potent neuropeptide that has been previously reported to increase feeding behaviour in a number of domestic livestock including poultry (Kuenzel et al., 1987), sheep (Miner et al., 1989) and pigs (Parrott et al., 1986). Supporting a role for NPY in appetite stimulation are data that demonstrate that injections of antibodies or antisense RNAs against NPY reduces feeding behaviour, and the fact that NPY was reported to be a more potent stimulator of feed intake than orexin in rodents (Edwards et al., 1999). Subsequent studies also revealed that NPY gene expression in the hypothalamus is up-regulated in following food deprivation in rodents and sheep (Brady et al., 1990; McShane et al., 1993).

In pigs, Parrott et al. (1986) demonstrated that even in a satiated state, lateral cerebral ventricular injections of NPY significantly stimulated operant feeding behaviour during a 30 minute post-treatment period in a dose-dependent manner. In a recent study by Barb et al. (2006), the authors evaluated the potential interactions between ICV injections of porcine NPY and recombinant human leptin as related to feed intake in growing pigs. After a 4 hour period associated with blood collection following treatments, feeders were placed in the pens and the pigs were allowed ad libitum access to feed. Feed intake was subsequently monitored at 4, 20 and 44 hours after the feed was placed into the pens. At the 4 hour time point, the authors reported that cumulative feed intake was significantly reduced in those pigs injected with either leptin or the combined treatment of leptin plus NPY. Feed intake did not differ between NPY and saline injected pigs at this same time point. However, at the 20 hour time point, the authors reported that cumulative feed intake was greater in the NPY and leptin plus NPY treatment groups as compared to the saline and leptin treatment groups, and that there was no difference in cumulative feed intake between these two group. By 44 hours, cumulative feed intake for the NPY treated pig remained higher than any of the other treatment groups, but feed intake for the leptin plus NPY treatment group had returned to control levels. Leptin suppressed cumulative feed intake at all time points monitored relative to the control and NPY treatment groups. While the study by Parrott et al. (1986) was the first to demonstrate that NPY was capable of increasing feeding behaviour in pigs, the more recent study by Barb et al. (2006) was the first to demonstrate an increase in cumulative feed intake as a result of NPY administration.

Adding to the evidence that NPY is intimately involved in feed intake in swine is a recent study from our laboratory (Kojima et al., 2007) that demonstrated positive relationships between pre-
weaning body weight and post-weaning hypothalamic gene expression in young pigs. Although sufficient evidence exists demonstrating that NPY is clearly involved in control of food intake, there is apparently enough redundancy in the control mechanisms associated with appetite regulation that the presence of NPY is apparently not obligatory. For example, in studies with knockout mice targeting the disruption of the NPY gene, the mice maintained normal body weights and continued to be responsive to the effects of leptin. Additionally, mating of the NPY knockout mice to leptin deficient ob/ob mice resulted in offspring that were less obese than the ob/ob mice (Palmiter et al., 1998). Results from these studies lead to the speculation that the effects of leptin on body weight is mediated, at least in part, by its effect on NPY. Collectively, these studies point to an obvious redundancy in the regulation of appetite. However, given the importance of nutrient intake to survival of the individual and the continued propagation of the species, is should not be surprising that something as essential as the regulation of food consumption would have evolved in a manner that includes overlapping mediators of feeding behaviour and energy expenditure.

**Agouti-related protein (AGRP)**

Agouti-related protein is an orexigenic neuropeptide that is produced exclusively in the neurons of the arcuate nucleus and has been shown to be co-localised with another potent stimulator of appetite, NPY, in rats and sheep (Adam et al., 2002; Hahn et al., 1998; Henry, 2003). The biological action of AGRP is mediated through its antagonistic actions on the melanocortin-4 receptor by which it blocks the appetite-suppressive effects of alpha-melanocyte stimulating hormone [alpha-MSH; (Rossi et al., 1998)]. Early investigations suggested that AGRP was associated with the regulation of energy balance and body adiposity within the body as transgenic mice overexpressing AGRP became obese (Graham et al., 1997). Subsequently, it was reported that the neurons that produce AGRP do indeed recognise and respond to several peripheral indicators of energy balance including insulin and leptin (Mizuno and Mobbs, 1999). In the obese line of mice, ob/ob mice, leptin deficiency has been reported to be associated with increased expression of AGRP within the arcuate nucleus (Shutter et al., 1997) and in a later study Tritos et al. (1998) demonstrated that in brown adipose tissue-deficient mice, expression of mRNA encoding ACRP in the arcuate nucleus is decreased. Additionally, a study by Rossi et al. (1998) reported that ICV injection of the C-terminal fragment of AGRP increased feed intake in mice over a 24-hour period. Likewise, transferring an expression plasmid of AGRP gene into leg muscle of mice by electroporation resulted in increased body weight gain and daily food intake (Xiang et al., 2004). In addition to potential mediation of AGRP via peripheral indicators of energy balance, recent work has reported that AGRP containing neurons respond to acute and chronic inflammatory cytokines (Scarlett et al., 2008), perhaps suggesting a role for AGRP in disease induced inappetence.

It has been suggested that the overall biological action of AGRP may be mediated by both its ability to alleviate the appetite-suppressive effects of alpha-MSH and by allowing the endorphins to stimulate appetite. However, other studies have suggested a link between AGRP and other appetite regulators as well. In a study by Dhillo et al. (2002) the authors reported that in rats, administering AGRP to hypothalamic explants significantly increased the release of immunoreactive NPY and significantly decreased the release of the cocaine- and amphetamine-
regulated transcript (CART). The authors' interpretation of their data was that the orexigenic neuropeptides in the arcuate nucleus stimulate the release of each other, perhaps to reinforce orexigenic behaviour via a positive-feedback loop.

In sheep, food deprivation for a period of 4 days resulted in increased hypothalamic expression of the genes encoding for NPY and AGRP (Adam et al., 2002; Henry, 2003). Additionally, ICV injections of 2.0 nmol/kg body weight significantly increased food intake at 4, 6 and 12 hours post-injection in sheep that were being fed ad libitum prior to injection (Wagner et al., 2004). In this particular study, the authors reported that co-injection of AGRP with NPY did not increase food intake beyond that achieved with AGRP or NPY alone. In addition to potential mediation of AGRP via peripheral indicators of energy balance, AGRP containing neurons have been reported to respond to acute and chronic inflammatory cytokines (Scarlett et al., 2008), perhaps suggesting a role for AGRP in disease-induced inappetence. Supporting evidence for this hypothesis was recently provided by Sartin et al. (2008) who reported that ICV injections of 0.5 nmol/kg body weight one hour prior to endotoxin administration prevented the reduction in endotoxin-induced food intake presumably through the blockage of melanocortin-4 receptors.

While several studies have demonstrated AGRP as a potent stimulator of feed intake, relatively little is known regarding AGRP and its association with feed intake, weight gain and/or disease-induced inappetence in swine. In fact, there is only one reported study related to the effects of weaning and body weight on AGRP in swine, and that is a previous study from our laboratory that evaluated hypothalamic genes encoding several of the appetite regulating hormones including AGRP (Kojima et al., 2007). In this particular study, we reported that the expression of AGRP was strongly correlated with POMC expression and moderately correlated to the long form leptin receptor in weaned pigs four days after weaning. However, we did not observe an affect of weaning on AGRP mRNA expression in the hypothalamus. Interestingly though, expression of mRNA coding for AGRP was greater in the heavier weight pigs as compared to the lighter weight pigs. To our knowledge, the positive correlations observed between body weight and expression of hypothalamic NPY, orexin, type 2 orexin receptor and agouti-related protein reported in this study represent the first known associations of body weight and neuroendocrine regulators of feed intake in weanling pigs. The authors acknowledge that a lack of a difference at a single time point following weaning in the pig does not necessarily eliminate a potential role for AGRP during this aspect of the production cycle and that further studies regarding a potential role for AGRP in the voluntary inappetence during weaning are warranted.

**Appetite suppressors**

**Leptin**

While leptin is primarily produced by adipocytes in white adipose tissue, it has been found in other tissues including brown adipose, placenta, ovaries, skeletal muscle, mammary cells, bone marrow, the pituitary gland and the liver (Margetic et al., 2002). Leptin elicits its biological effect by binding to a receptor that has been classified as a member of the class 1 cytokine receptors and transmits its cellular signal via janus-activated kinases (JAK)/signal transducers and activators of transcription (STAT) and mitogen-activated protein kinase (MAPK) pathways (Houseknecht
In fact, leptin itself has been classified as a cytokine due to the structural homology of the leptin receptor with a member of the interleukin-6 family of receptors, specifically gp130, and common down-stream signaling pathways (Tartaglia et al., 1995). Collectively, leptin has been shown to bind to at least six isoforms of the leptin receptor family that have been previously identified including a long form of the receptor, denoted as OB-rb, and four short forms of the receptor, denoted OB-ra, OB-rc, OB-rd and OB-rf (Tartaglia, 1997). Previous research characterising these isoforms revealed that the extracellular and transmembrane domains are identical between the short and long isoforms and that the differences between these isoforms arise from changes in the length of the cytoplasmic domain (Lee et al., 1996). The sixth isoform of the leptin receptor, denoted OB-re, is a soluble receptor that circulates in plasma and is comprised of an extracellular loop with no intracellular motifs or transmembrane residues (Tartaglia, 1997). The long form of the leptin receptor, OB-rb, is the only receptor isoform that can signal intracellularly via the Jak-Stat and MAPK signal transduction pathways (Malendowicz et al., 2006) and has been reported to be abundant in the hypothalamus, especially in the ventromedial nucleus (Tartaglia et al., 1995), often referred to as the ‘appetite center’ of the brain. With regard to leptin’s influence on appetite regulation, it has been suggested that it elicits its biological actions by inhibiting the activity of NPY and AGRP neurons and by increasing the activity of alpha-MSH neurons (Elias et al., 1999). The remaining isoforms of the leptin receptor are abundant throughout the body and have been isolated in almost every tissue tested for their presence (Houseknecht and Portocarrero, 1998). In addition to its role in regulating food intake and energy balance, leptin has also been implicated in numerous other physiological processes including mediation of GH secretion, the onset of puberty regulation of the reproductive axis, and regulation of immunological processes such as hematopoiesis, inflammation and overall immunocompetency (Barb et al., 2001).

While the phenotypic manifestations associated with a leptin deficiency have been observed in laboratory mice as early as 1950 (Ingalls et al., 1950) it was not until 1994 that Zhang et al. (1994) identified leptin as the gene product that was deficient in obese mice. In the ob/ob mice, functional leptin is not produced, resulting in an uninhibited intake of food and subsequent obesity. Similar phenotypic manifestations have also been reported in mice and rats that lack a functional leptin receptor (Chen et al., 1996; Phillips et al., 1996). In vivo studies revealed that treatment with exogenous leptin resulted in reduced feed intake and body weight in obese mice (Campfield et al., 1995; Pelleymounter et al., 1995). Since its discovery, leptin has received much attention in the scientific community, and due to the potential economic impact, there have been numerous studies evaluating the biological activities of leptin as they relate to appetite regulation, weight gain, body composition and reproductive performance in domestic livestock.

In swine, early studies demonstrated that leptin gene expression and plasma concentrations of leptin are higher in pigs with greater adipose mass and pigs selected for greater fat deposition (Bidwell et al., 1997; Yen et al., 1997) Further investigation into the relationships among weight loss and food intake restriction with leptin gene expression in pigs at various body weights revealed that the abundance of leptin mRNA in pigs correlates with fat mass and percentage of body fat under conditions of unrestricted food intake (Spurlock et al., 1998a). However, the authors reported that while total food deprivation reduced the expression of leptin mRNA, feed restriction alone, even at levels associated with weight loss, did not change the abundance of
7. Hormonal control of feed intake in swine

leptin mRNA compared to control pigs. Specifically, the authors reported that under conditions of ad libitum consumption, leptin mRNA expression in castrated male pigs increased with body weight from 55 to 163 kg and that leptin mRNA expression was highly correlated to fat mass and percentage of fat. However, in 159 kg pigs that were fed ad libitum, maintenance or 23% of maintenance for a period of 28 days, the relative abundance of leptin mRNA did not differ despite considerable weight differences among treatment groups. However, the authors did report that in pigs weighing 60 and 136 kg, the abundance of leptin mRNA in pigs experiencing total food deprivation for a period of 3 days was reduced by more than 30% as compared to pigs fed ad libitum. Based upon studies relating leptin concentrations to weight loss in humans, and their data pertaining to relative abundance of leptin mRNA in pigs, the authors speculated that weight loss and food intake restrictions do not necessarily invoke parallel reductions in blood leptin or obese mRNA.

Evidence soon appeared demonstrating that exogenous leptin treatment was capable of stimulating GH secretion and reducing feed intake in swine (Barb et al., 1998). In this study, the authors reported that ICV injection of recombinant porcine leptin significantly increase GH concentrations within 15 minutes. Interestingly, the authors reported that the GH response to 10 µg of leptin was greater than that elicited by either 50 or 100 µg. With regard to feed intake, the authors reported no differences among treatment groups at 4 hours post-injection, however, by 20 hours post-injection, feed intake had been reduced by 53%, 76% and 90% by ICV treatment with 10, 50 and 100 µg of recombinant porcine leptin, respectively. In addition to their in vivo data, the authors provided the first in vitro evidence that demonstrated a direct effect of leptin on pituitary secretion of GH, albeit, the authors did indicate that this increase only occurred at what may be considered supraphysiological concentrations.

Our laboratory has previously reported that in weaned pigs that were acclimated to solid food for a period of 10 days, subsequent feed deprivation resulted in a significant reduction in serum concentrations of leptin by 12 hours after feed removal and a decrease in leptin mRNA expression at 72 hours after feed removal when fat samples were collected (Salfen et al., 2003; Figure 4). A reduction in leptin mRNA expression in adipose tissue is consistent with prior studies conducted in older pigs by Spurlock et al. (1998) and Barb et al. (2001). An interesting aspect in our study relates to the rapid recovery of serum concentrations of leptin following the re-feeding protocol after the 72 hour feed deprivation period. One might expect that in young pigs with relatively low lipid stores, the recovery of serum leptin from a 72 hour feed deprivation may take a substantial amount of time. However, our data revealed that serum concentrations of leptin had returned to control levels within 12 hours of re-feeding. The rather rapid and dramatic reduction in serum concentrations of leptin in our study may reflect differences in percent body fat and/or differences in metabolism between adult and young animals. While serum concentrations of leptin recovered rather rapidly, we did not observe a similar recovery in the expression of leptin mRNA in fat tissue. In fact, the abundance of leptin mRNA in fat tissue was not increased following the 24 re-feeding period. However, this observation is not without precedent as there is evidence that insulin may be the acute regulator of leptin in pigs (Spurlock et al., 1998b) and the regulation of leptin secretion has been suggested to be mediated via neural inputs into adipose tissue (Youngstrom and Bartness, 1995). Indeed, our results actually support the speculation of
Figure 4. Recreated from Salfen et al., 2003. Effect of feed deprivation for 72 hours (FD72) and FD72 followed by re-feeding until 96 hours (FD72/RF24) on serum concentrations of leptin compared to ad libitum feeding for 72 hours (CON72) or 96 hours (CON96). Values are the mean ±S.E.M. of n=8 pigs per group.

* Denotes difference from the 0 hour concentration within the same treatment (P<0.05).

Denotes change in hormone concentrations of the FD72/RF24 treatment compared to the 72 hour time point (P<0.05).

Spurlock et al. (1998b) that weight loss and food intake restrictions do not necessarily invoke parallel reductions in blood leptin or obese mRNA.

For a more detailed review of leptin and its biological role in the pig associated with appetite regulation, reproduction, mediation of GH secretion, the onset of puberty and associations with the immune system, the reader is referred to the review by Barb et al. (2001).

**Urocortin**

Urocortin is a 41 amino acid neuropeptide that is structurally related to CRH that belongs to the CRH family that includes CRH, urotensin I, sauvagine, urocortin II and urocortin III. While it binds to both the CRH type 1 and the CRH type 2 receptors, it binds to the CRH type 2 receptor with higher affinity (Spina et al., 1996). Given the structural similarity to CRH and the affinity for the CRH receptors, urocortin was thought to have overlapping biological activities with CRH including suppressive effects on appetite (Parkes et al., 1997; Spina et al., 1996). Urocortin has been localised in regions of the brain associated with the control of fluid and electrolyte metabolism, including the supraoptic and paraventricular nuclei and the organum vasculosum of the lamina terminalis (Kozicz et al., 1998; Vaughan et al., 1995). A unique characteristic associated with urocortin activity is that while it elicits more of an appetite suppressive effect than CRH, it does not elicit the anxiogenic activities to the extent of CRH (Spina et al., 1996).

One of the first *in vivo* evaluations of urocortin as a potential mediator of food intake was published by Spina et al. (1996) in which the authors demonstrated that in food deprived rats,
ICV injections of urocortin significantly suppressed food intake in a dose-dependent manner. The authors further elucidated the appetite suppressive effects of urocortin in fed animals, demonstrating that significant decreases in food and water intake were observed with doses as low as 100 ng. At the higher doses of urocortin, food and water intake were decreased for up to 12 hours. The overall effect on food consumption was attributed to both a decrease in the meal size and frequency of meals with significant effects at 10 ng for meal size and 1000 ng for meal bouts. The authors reported that at the 1000 ng dose, meal bouts were virtually abolished for 6 hours. The authors also reported that water intake paralleled that of food intake regardless of treatment. A reduction in food intake associated with ICy injections of urocortin was subsequently reported in sheep by Weisinger et al. (2000). However, these authors reported that urocortin administration did not elicit a decrease in water intake as seen in the previous rodent study.

Unfortunately, relatively little is known with regard to the appetite suppressive effects of urocortin in swine. In 2000, the only reported study associated with the effects of urocortin on appetite regulation in swine was published by Whitley et al. (2000). In this study, the authors conducted three experiments to evaluate the effects of intracerebroventricular injection of urocortin and intravenous injections of urocortin at various dosages on feed intake and serum concentrations of GH, LH and cortisol in ovariectomised gilts. In their first experiment, the authors evaluated the effects of an ICy injection of urocortin in gilts that were restrained. Their second experiment was the same as the first with the exception that the gilts were not restrained, and the third experiment evaluated intravenous injections of urocortin. In all three experiments, the gilts were fasted for a 20-hour period, and then allowed ad libitum access to feed at either one hour (experiment 1) or 30 minutes (experiments 2 and 3) following administration of the urocortin. The authors reported that treatment with 50 micrograms/pig decreased food consumption as compared to saline treated animals when urocortin was administered as centrally, but not when administered as a peripheral injection. With regard to serum concentrations of GH, the authors reported that urocortin treatment increased GH concentrations regardless of the route of administration. Conversely, serum concentrations of LH were decreased by urocortin administration, but only in those animals receiving the treatment via ICV injection. The effects of urocortin treatment on serum concentrations of cortisol were less consistent as the responses varied depending on the dose of urocortin and the experimental design. Given the lack of a cortisol response in experiment 1, it's tempting to speculate that any potential effects of urocortin on the hypothalamic-pituitary-adrenal axis may have been masked due to the gilts being restrained. Collectively, the data from this study provided clear evidence that urocortin administration elicited a significant suppressive effect on appetite, and significantly altered hormones associated with growth performance and reproductive capability.

A potential role for glucocorticoids on neonatal pig growth and feed intake

A rather unconventional approach to stimulating feed intake and growth in neonatal swine has been explored in our laboratory through the administration of the synthetic glucocorticoid, dexamethasone (Carroll, 2001; Gaines et al., 2002, 2004; Seaman-Bridges et al., 2003). These studies evolved from our prior research that demonstrated that bypassing the glucocorticoid surge associated with the natural birth process, via caesarean section, reduces piglet growth (Figure 5) and alters the somatotrophic axis (Carroll et al., 2000). In swine, there is an increase
in maternal circulating cortisol, as well as a final fetal cortisol surge during labor (Randall, 1983). Fetal serum cortisol levels increase during the last two weeks of gestation, and levels in swine rise dramatically during the last 8 hours prior to parturition (Randall, 1983). This surge of cortisol is necessary for the initiation of the birth process (Kattesh et al., 1990) and to signal the maturation of fetal tissue in preparation for life outside of the uterine environment (Seckl et al., 1999). Indeed, the prepartum surge in glucocorticoids has been shown to be an important mediator of intestinal maturation and function. Sangild et al. (1991, 1994, 1995) have demonstrated through a series of glucocorticoid exclusion and glucocorticoid replacement studies that the prepartum surge in cortisol plays a critical role in the development of digestive capability in the pig. Additionally, they suggested that the glucocorticoid role in intestinal maturation and function is most likely limited to the immediate perinatal period (Sangild et al., 1991). Glucocorticoids have also been implicated as having an important role in the fetal development of somatotrophs (Nogami et al., 1997; Nogami and Tachibana, 1993) and various stimulatory effects on components of the somatotrophic axis (Miell et al., 1993; Miell et al., 1994; Miller and Mayo, 1997; Tamura et al., 2000; Wehrenberg et al., 1990). Consistent with the hypothesis that glucocorticoids mediate postnatal growth is a study by Li et al. (1996) which suggested that the prepartum cortisol surge associated with parturition in sheep was the maturational signal necessary for the switch from fetal to postnatal modes of somatotrophic function. Therefore, it is during this perinatal period that we hypothesised that a ‘window of opportunity’ may exist to permanently alter or preset physiological parameters to enhance growth and performance through exogenous glucocorticoid therapy.

In our initial study (Carroll, 2001) evaluating the use of dexamethasone as a potential mediator of postnatal growth, we injected forty crossbred pigs intramuscularly with either sterile saline or dexamethasone (1 mg/kg body weight) within 1 hour of birth. All pigs remained with their respective dams until 18 days of age and we recorded body weights weekly and on day 18. On
day 17, all pigs were non-surgically fitted with an indwelling jugular catheter and placed back with the sows. On the following day, all pigs were placed in individual pens for serial blood collection to evaluate the somatotrophic axis. Body weights after the 18-day trial were 10.1% greater in pigs that were injected with dexamethasone within 1 hour of birth as compared to those injected with saline and had a corresponding increase in average daily gain of 12.2% (Figure 6). Dexamethasone treatment within 1 hour of birth also altered the basal profiles of somatotrophic hormones at 18 days of age. Serum concentrations of GH were significantly reduced in all pigs that had received the dexamethasone injection as compared to the saline injected pigs, however, the magnitude of reduction was greater in the males as compared to the females. Conversely, serum concentrations of IGF-1 were increased by dexamethasone injection. In the male pigs, dexamethasone increased serum concentration of IGF-1 by 47% as compared to saline injected male pigs, whereas in the females, dexamethasone increased serum concentration of IGF-1 by 34% as compared to saline injected female pigs (Figure 7). As with serum concentrations of GH, serum concentrations of IGF-2 were reduced in the dexamethasone treated pigs.

Interestingly, Weiler et al. (1997) had previously reported that chronic administration of dexamethasone for a period of 15 days to one-week old pigs actually reduced piglet growth and increased protein catabolism. The dichotomy that exists in our previous data and that reported

![Graph](7.5 7.0 6.5 6.0 5.5 0 4.5 4.0 3.5 0 2.5)

*Figure 6. Recreated from Carroll (2007). Effect of dexamethasone treatment (Dex; 7 mg/kg body weight) on body weight from birth (Day 0) until 78 days of age. Body weights were not significantly different until day 18 at which time body weights were 10.1% greater for the dexamethasone treated (Dex) pigs as compared to the control (Cont) pigs (7.06±0.16 and 6.41±0.2 kg, respectively). Standard error bars represent the pooled SEM for the Dex (0.123 kg) and Cont groups (0.157 kg).

*Significant at P=0.015.
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Figure 7. Recreated from Carroll (2007). Effect of birth treatment and sex on serum concentrations of insulin-like growth factor 1 (IGF-1). At 18 days of age, serum IGF-1 was higher in dexamethasone (Dex; 1 mg/kg body weight) treated boars and gilts as compared to saline (Control) treated boars and gilts (a versus b, P=0.004; c versus d, P=0.01). Overall, serum concentration of IGF-1 was lower in gilts as compared to boars (P<0.013). Bars represent the mean +SE.

by Weiler et al. (1997) may be attributed to the duration of glucocorticoid exposure as well as the developmental stage of the piglet. In the rat fetus, limited glucocorticoid exposure has been suggested to be an important mediator of somatotroph recruitment and development (Nogami et al., 1997; Nogami and Tachibana, 1993). Previous studies have also reported that glucocorticoids alter various components of the somatotrophic axis including increased secretion of GH and IGF-1, and enhanced pituitary responsiveness to GH releasing hormone (Miellet et al., 1994; Miller and Mayo, 1997; Tamura et al., 2000; Wehrenberg et al., 1990). In our study, the dexamethasone-induced increase in pig growth was accompanied by a substantially higher concentration of circulating IGF-1, considered by many as the primary regulator of postnatal somatic growth in the pig and other domestic species. A positive relationship between circulating concentrations of IGF-1 and postnatal growth in the pig have been reported by several research groups (Breier and Gluckman, 1991; Schoknecht et al., 1997; Walton et al., 1995). Our data also supports a positive relationship between circulating concentrations of IGF-1 and postnatal growth in the young pig.

While we initially interpreted these data to indicate that dexamethasone treatment may have resulted in a 're-programming' of the somatotrophic axis, perhaps from an acute or short-term stress induced increase in GHRH from the hypothalamus, we could not dismiss the concept that the acute glucocorticoid treatment at birth stimulated appetite and increased milk consumption during the early postpartum period. Glucocorticoids have been reported to promote feed intake by directly stimulating neuropeptide Y (NPY) and inhibiting corticotrophin-releasing hormone (Cavagnini et al., 2000). Glucocorticoids have also been shown to reverse the suppressive

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effects of leptin on appetite via NPY-independent pathways (Solano and Jacobson, 1999). Thus, an alternative explanation for the differences observed in the somatotrophic axis for the dexamethasone treated pigs is that these differences merely reflected the enhanced growth rate associated with greater food intake during the perinatal. This would suggest that the observed elevation in IGF-1 in the dexamethasone treated pigs may be more reflective of increased growth rather than the causal agent. If this is indeed the case in the present study, then one could speculate that circulating IGFs do not predict the future growth potential of the growing pig, and that circulating IGFs have already acted on target tissues and are in the circulation for clearance. This idea is somewhat in conformity with that proposed by Owens et al. (1994) who suggested that circulating IGF-1 serves a role as a reporter of growth performance, rather than a mediator of growth performance. Given that appetite and milk consumption were not monitored in our prior study, we can neither accept nor dismiss this possibility.

In our subsequent studies evaluating the use of synthetic glucocorticoids to enhance neonatal growth in pigs, we observed similar responses to that of our original study. Specifically, in the study by Gaines et al. (2002) that evaluated pre- and post-weaning performance of pigs injected with dexamethasone in three separate experiments at either 1 or 24 hours after birth, we observed an 8-10% increase in body weight of male pigs at weaning that had been injected with dexamethasone at both 1 and 24 hours after birth. However, we did not observe any significant difference in weaning weight for female pigs regardless of treatment. In the final experiment of this study, we observed that at the end of an 83 day period, male pigs injected with dexamethasone were on average 5.45 kg heavier than control males, but again no difference was observed among females regardless of treatment. In the following study by Seaman-Bridges et al. (2003), we again observed increased weaning weights and market weights in pigs that had been injected with dexamethasone within 1 hour of birth, without any negative effects on carcass or meat quality. Collectively, these studies provided convincing evidence that demonstrate that dexamethasone given within 24 hours of birth significantly improved both pre- and postweaning performance of pigs. Given previous research that potentially linked glucocorticoids to appetite stimulation, we conducted a final study to determine if providing supplemental milk to dexamethasone treated pigs while they were still nursing the sow would provide an even greater growth response during the pre-weaning period (Gaines et al., 2004). Data from this study did not reveal an increase in weaning weights associated with dexamethasone treatment. However, results from this study did indicate that the management practices on some commercial farms may eliminate any positive effect associated with glucocorticoid treatment and highlights the importance of other factors that may influence the appetite and growth in neonatal pigs. Unquestionably, the collective results from these four studies warrant further investigation into the possible appetite stimulating effects of glucocorticoid therapy in the neonatal pig, and may provide further insight into the underlying mechanisms associated with appetite regulation.

Conclusion

The ability to effectively control feed intake during critical periods of development within livestock production systems will undoubtedly come to pass as scientists continue to elucidate the complex and multifaceted pathways that regulate feed intake, and develop novel approaches to manipulate these systems in a beneficial manner. The economic importance associated with
achieving optimal feed intake associated with growth, health and reproduction will continue to drive research directed at understanding and conquering this complex system.

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References

7. Hormonal control of feed intake in swine


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