Regulation of growth and development of the gastrointestinal tract and adipose tissue from birth to weaning in pigs: influence of birth weight

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ABSTRACT

Piglet birth weight is an important risk factor for preweaning mortality. Low birth weight pigs exhibit lower postnatal growth rates and feed efficiency, which may be explained by an inadequate digestion and/or nutrient use as a consequence of prenatal under-nutrition. It is now documented that factors like under-nutrition during prenatal development may influence the development of organs, tissues and the endocrine system and the long-term physiology of the individual. During the neonatal period, the rapid somatic growth is accompanied by tremendous anatomical, physiological and chemical composition changes. The present review focuses primarily on the gastrointestinal tract and adipose tissue during the suckling and around weaning periods in function to birth weight. Hormones levels in plasma as well as receptors expression in target tissues are also considered. The ability of the neonate to express its growth potential is related to milk intake and milk quality. The relationship between nutrition, endocrine parameters and growth is presented.

INTRODUCTION

Over the last decade, genetic selection has resulted in an increase in litter size. This has been associated with a reduction in the mean piglet birth weight (BW) and concomitantly with an increased within-litter variation in BW leading to a rise in the proportion of small piglets (less than 1.0 kg BW) in large litters (Le Dividich, 1999; Milligan et al., 2002; Quiniou et al., 2002). According to Quiniou et al. (2002) data, small piglets weighing less than 1.0 kg at birth, represent on average 13% of total born piglets, ranging from 7% in litters with 11 piglets or less to 23% in litters with 16 piglets or more. Two-thirds of runt piglets (i.e. very low birth weight (VLBW) piglets weighing less than 0.8 kg) die during suckling and mortality

is 34% for low birth weight piglets (LBW, 0.81 to 1.0 kg BW) born alive and less than 10% for piglets above 1.6 kg BW. Therefore, 8% of weaned piglets are LBW (6%) and VLBW (2%) piglets.

The etiology and underlying mechanisms of intrauterine growth retardation (IUGR) in livestock as well as in humans and rodents have been recently reviewed (McMillen and Robinson, 2005; Foxcroft et al., 2006; Murphy et al., 2006; Wu et al.,2006). In agreement with the "thrifty phenotype" hypothesis developed by Hales and Barker (1992), it has been shown in several species that there is a relationship between BW and subsequent pattern of growth and development of tissues and organs (McMillen and Robinson, 2005). In pigs, LBW alters body composition and meat quality (Rehfeldt and Kuhn, 2006). For instance, a lower tenderness of meat has been reported in pigs with a low BW (Gondret et al., 2006).

The aim of the present paper is to review the influence of birth weight on growth and development of the neonatal pig during the suckling period. The review focuses primarily on the development of the digestive tract and adipose tissue. The importance of hormones and growth factors in the regulation of these developmental processes is also considered.

GROWTH IN LOW BIRTH WEIGHT PIGLETS

Growth and development processes of an organism involve weight gain and changes in shape, chemical composition and physiological functions. In the pig as well as in other species, these processes have been reviewed widely (Reeds et al., 1993). Mature body sizes and weights, the relationships between birth weights and mature weights, and the postnatal growth rates differ markedly between species. At birth, the pig is characterized by a weight which represents a very small proportion of its mature weight compared with the majority of mammals; the mature weight/birth weight ratio is about 300 whereas it varies between 20 and 40 for many other mammals including human and rat. The pig has a very high growth rate. During the 2- to 4-week suckling period, piglets from modern genotypes grow at the rate of about 250-270 g/day (King et al., 1999). The precise rate is very variable and depends mainly on the availability of milk (Louveau et al., 2000). Weaning weight is positively correlated to BW but relative growth of small piglets is higher than that of heavier piglets. LBW piglets are, to some extent, able to catch up heavier piglet growth. Between birth and weaning, VLBW and LBW piglets exhibit respectively a 7-fold and 6-fold increase in body weight whereas "normal" BW (equivalent to the mean litter BW) and "heavy" (more than 1.9 kg) BW piglets exhibit respectively a 5-fold and 4-fold increase in body weight (Quiniou et al.,

2002; Gondret et al., 2006). Compared with high BW piglets, low BW piglets exhibit a lower growth rate (15-30%) in the first month of postnatal life (Wolter et al., 2002; Poore & Fowden, 2004; Gondret et al., 2005, 2006). It is likely related to a lower milk intake. During the suckling period, the higher BW piglets tend to select the anterior teats (Hartsock et al., 1997) that are easier for milk extraction. In addition, the positive relationship between piglets body weight and milk consumption indicates that heavier piglets are able to extract more milk from mammary glands of the lactating sows (King et al., 1997). Interestingly, this difference in growth rate persists until the market weight. This is illustrated by the observation that 10-15 more days are needed for LBW pigs to reach the market weight (100-110 kg; Powell and Aberle, 1980; Gondret et al., 2005, 2006). It has been reported that the effect of BW on postnatal growth pattern is sex-specific with females being more responsive to low birth weight than males (Poore & Fowden, 2004). With regards to morphology, IUGR is associated with lower abdominal circumference and crown-rump length at birth (Poore & Fowden, 2004; Mostyn et al., 2005). Significant differences have been also reported in the body composition of the piglet between birth and 28 days of age. Even though linear correlation between body weights and various organ weights have been reported, the extent of weight variation differs between the various organs examined (Bauer et al., 1998 and 2000). The lowest variation of organ weights has been observed in the brain (Table 1). The strongest growth restriction has been found in the liver, the thymus, the muscle mass and the pancreas. By chemical analysis of the whole body at birth, it has been reported that LBW piglets have less fat and protein and more water than their littermates (Rehfeldt and Khun, 2006). The impact of IUGR occurring naturally or induced experimentally on skeletal muscle has been recently reviewed in pigs (Rehfeldt and Kuhn, 2006).

DEVELOPMENT OF ADIPOSE TISSUE IN LOW BIRTH WEIGHT PIGLETS

The rapid increase in body weight is associated with marked changes in organ growth and body composition in the neonatal period. Pigs like sheep and rats, are characterized by a small amount of total body fat at birth (less than 2%) compared with guinea-pig and human neonates (∼10%). They have a remarkable capacity to deposit large amounts of fat soon after birth. Body fat is derived primarily from dietary fat. Depending on the colostrum fat content, carcass fat content increases by 25 to 100% during the first day life (Le Dividich et al., 1997) and continues to increase to reach 11% by 3 weeks. During the 3-week suckling period, 54% of milk fat intake is retained in the body (Noblet & Etienne, 1987) with fat accretion

occurring at a mean rate of 30-35 g. day^{-1}, depending mainly on the amount of ingested milk (Marion and Le Dividich, 1999) and on the milk fat content (Jones et al., 1999).

At the cellular level, growth of adipose tissue results from both proliferation and differentiation of adipocyte precursor cells, and subsequent enlargement of the mature fat cells. It is under the control of hormones and growth factors (Grégoire et al., 1998; Louveau & Gondret, 2004). Marked changes occur in morphology, cell size and chemical composition of adipose tissue during the neonatal period. In the fetus, fat cell cluster differentiation begins between 45 and 60 days of gestation in subcutaneous tissue (Hausman and Kauffman, 1986). At birth, the percentage of multilocular adipocytes is very high, but by day 3 postpartum, many unilocular adipocytes (one major central lipid droplet) are observed (Mersmann et al., 1975; Hauser et al., 1997). In subcutaneous adipose tissue, a marked increase in adipocyte size is observed with diameters increasing from 19-24 µm at 3 days of age to 36 µm at 23 days of age (Mersmann et al., 1973; 1975). A similar increase has been reported in leaf fat (Hauser et al., 1997). The total lipid content increases also in both subcutaneous and leaf fat between 7 and 30 days of age (Hauser et al., 1997). Post-natally, adipose tissue appears as a number of individual depots, some in the abdominal cavity (e.g. perirenal), some under the skin (subcutaneous depots, the more abundant in pigs) and some within the musculature (inter- and intra-muscular depots). Adipocytes from different depots, while having many features in common, are not identical varying in size and in some of their secretory properties (Gardan et al., 2006). Unlike other tissues, adipose tissue mass has considerable capacity to expand.

During the past two decades, various clinical and experimental observations have indicated that BW influences the subsequent development of adipose tissue (Symonds et al., 2004; McMillen and Robinson, 2005). In contrast to other tissues, the effect of poor fetal growth on adipose tissue is poorly documented in the neonatal pig. This paucity of data might be explained by the fact that piglets have a very low fat content at birth compared to human or guinea pigs. In a recent experiment, we have shown that the weight of the perirenal fat depot was reduced in 7-day-old piglets (-30%) and in 28-day-old piglets (-15%) exhibiting a low birth weight (Louveau et al., unpublished data). No difference in fat weights was detected between males and females. This decrease in weight of adipose tissue in LBW piglets may involve reduced rates of adipocyte proliferation or high rate of proliferation with a delay in adipocyte differentiation. It may also result from an alteration of the IGF system as shown in liver and skeletal muscle of growth retarded fetuses and neonates in pigs (Kampman et al. 1993, 1994; Tilley et al., 2006). In the neonatal sheep, a

relationship between adipose tissue growth and IGF receptor mRNA has been shown (Symonds et al., 2004).

The impact of low BW on subsequent adipose tissue development is more documented in pigs (Powell and Aberle, 1981; Poore and Fowden, 2004; Gondret et al., 2005; 2006). These studies indicate that low BW piglets compared with normal or high BW piglets exhibit an increase in fat deposition when the nutrient supply is adequate during the postnatal period. At market weight, mean backfat thickness and perirenal fat weight have been reported to be higher in pigs with low BW than in pigs with high BW (Powell and Aberle, 1981; Gondret et al., 2006). These observations are associated with differences in adipose tissue cellularity (Powell and Aberle, 1981). Average diameters of adipocytes in the perirenal and subcutaneous adipose tissue have been reported to be smaller in pigs with low BW than in pigs with high BW.

DEVELOPMENT OF THE GASTROINTESTINAL TRACT IN LOW BIRTH WEIGHT PIGLETS

The effects of IUGR on various digestive organs have been investigated by several research groups in neonates (Table 2). Development of digestive organs, except that of pancreas, of the IUGR fetus during pregnancy is symmetrically restricted (Xu et al., 1994; Wang et al., 2005). Indeed, at birth the relative weight of pancreas is reduced but in a smaller proportion to overall body weight whereas stomach, small intestine and colon relative weight are not affected by IUGR. IUGR is associated with a reduction in wall thickness of the stomach, small intestine and colon and with a proportionally longer intestine. However, the intestinal surface area for absorption is highly lowered since the average number of villi per unit area and the height of villi are 15-20% lower in IUGR piglets than in normal BW piglets (Xu et al., 1994). Impairment of intestinal function is also observed in IUGR piglets at birth. As lactase and aminopeptidase N peak at birth or just after birth in normal BW piglets (Sangild et al., 2002), the lower lactase and aminopeptidase N activities reported in IUGR piglets (Table 3) indicate a retardation in maturation of the small intestinal function and lowered digestive capacities, as reported in preterms (Shulman et al., 2005). Although still observed at 28 days of age, differences in intestinal shape and enzymatic functions between IUGR and normal BW piglets lessen when age increases (Tables 2 & 3). However, differences in maturational rate persist when epithelial barrier properties are considered. Recent experiments performed in our laboratory indicates that in normal BW piglets, permeability to macromolecules determined in Ussing chambers, decreased in the jejunum and

increased in the ileum during the suckling period. In contrast, no change with age was observed in LBW piglets (Boudry et al, unpublished data). In conclusion, while immaturity signs of the gut are obvious in IUGR neonates, some of them persist up to the end of the suckling period. The immaturity of the small intestine physiology enhances risks of developing intestinal diseases and may reduce digestive capacities.

Colostrum elicits also remarkable growth of the gastrointestinal tract, and especially of the small intestine (SI). Feeding the piglet ad libitum with colostrum during the first 36 hours postnatally induces an 80% increase in small intestinal weight (Schober et al., 1990; Le Dividich et al., 1997). This rapid growth of SI is largely attributed to endocytosis of ingested immunoglobulins (Ig), mucosa hyperplasia and protein synthesis (Burrin et al., 1992; Kelly, 1994; Xu et al., 1996)(Kelly, 1994; Xu, 1996). Therefore, the lower colostrum and milk intake may participate to the digestive tract immaturity of IUGR piglets. Besides nutrients, colostrum and, but to a lesser extent, milk contain a variety of bioactive components (Grosvernor et al., 1992; Zabielski, 1998)(Zabielski, 1998). Among them, IGF-I and insulin are potentially active since the apical membranes of SI contains functional receptors to these factors, suggesting that the developing intestine is a target organ for milk-born growth factors (Schober et al., 1990; Kelly et al., 1994; Morgan et al, 1996). Feeding neonates with milk protein-based formula deprived of immunogloblins and growth factors, reduces cell turnover and delays cell maturation, as indicated with the lower mitotic index and the higher number and size of vacuolated enterocytes compared to colostrum- and milk-fed 7 d–old piglets (Le Huërou-Luron et al. unpublished data). Long-term effects of fetal and postnatal under-nutrition have not been studied in pigs and await for investigation.

REGULATION OF PORCINE NEONATAL GROWTH AND DEVELOPMENT BY HORMONES AND GROWTH FACTORS

Somatotropic axis

Growth hormone (GH) and the insulin like growth factor I (IGF-I) are two of the main regulators of postnatal growth: GH and IGF-I deficiencies are associated with prenatal and postnatal growth failure (Baker et al., 1993; Ranke, 1987). GH acts mainly through IGF-I that induces mitogenesis in target tissues (Louveau and Gondret, 2004). In the newborn pig, plasma GH concentrations are very high at birth and decrease sharply during the next 2-3 days (Scanes et al., 1987; Carroll et al., 1998). Although the significance of these high

levels of plasma GH is not completely understood, GH could contribute to the maintenance of protein accretion in the newborn pig, even in negative energy balance (Herpin et al., 1992). Plasma IGF-I concentrations increase significantly during the first 3 weeks after birth (Lee et al., 1991, 1993; Louveau et al., 1996).

There are discrepancies in the literature on the effect of IUGR on IGF-I plasma concentration : in few studies, low BW piglets have lower IGF-I plasma concentration at birth and in the first days of life (Davis et al., 1997; Schoknecht et al., 1997b), but that is not always the case (**Table 4**). However, in most mammalian studies (including pigs and human) a positive correlation between BW and plasma IGF-I has been established (Herpin et al., 1992; Thieriot-Prevost et al., 1988). Moreover 14 days-LBW piglets have lower hepatic IGF-I concentration than normal BW piglets fed *ad libitum* but similar to their pair fed normal BW littermate (Dauncey *et al.* 1994). That suggests that low IGF-I hepatic concentrations of LBW piglets are probably due to their low *ad libitum* food intake.

GH receptors increase over the first 10 days of life in liver and IGF-I receptors decrease in skeletal muscle and liver (Breier et al., 1989; Lee et al., 1993; Louveau et al., 1996; Schnoebelen-Combes et al., 1996). The somatotropic axis appears to be functional and responsive to GH administration in neonatal pigs, although the responsiveness is reduced compared to older pigs (Harrell et al., 1999). The administration of GH at a dose that is commonly used in older pigs has little or no effect on growth rate or plasma IGF-I or IGFBP-3 (Dunshea et al., 2001; Harrell et al., 1999). However, the lack of growth rate response is not surprising due to the already high rate of protein synthesis. Similarly, GH delivered with an osmotic minipump into abdominal cavity of newborn piglets failed to improve absorptive capacity of small intestine (Fholenhag et al., 1999). However, in the newborn piglets, IGF-I infusion with minipumps results in a 10% increase in weight gain, due to an increased rate of protein and fat accretion (Schoknecht et al., 1997a). IGF-I infusion has a more marked effect on IUGR piglets, which have a higher protein and fat accretion than control animals. In these animals, IGF-I infusion is able to restore body weight and composition to normal (Schoknecht et al., 1997c).

In addition, IGF-I present in sow colostrum and milk stimulate gastrointestinal tissue growth and functional maturation in newborn piglets. IGF-I adjunction to milk formulas increases intestinal weight and villosity height (Burrin et al., 1996), brush border enzyme activities (Houle et al., 1995; Houle et al., 1997), and the rates of net Na^+ and Na^+ dependant nutrient absorption (Alexander and Carey, 1999). Besides, hormonal regulation of intestinal development seems to be affected by IUGR. Indeed, in association with an

altered intestinal morphology, IUGR piglets have a lower mucosal IGF-I expression than controls, whereas they tend to express less GH and insulin receptors than controls (Wang et al., 2005).

Insulin

In addition to its well known acute metabolic actions, insulin plays a role in the control of normal body growth. First, it is a potent mitogen for many cell types *in vitro*, but its role as growth factor has also been demonstrated *in vivo*. Child with diabetes exhibits a poor growth contrasting with the overgrowth of the hyperinsulinemic infant of a diabetic mother (for review, see (Hill and Milner, 1985b)). Diabetic pigs have a 50% lower body weight than the controls (Romsos et al., 1971c). Administration of insulin restores growth to a rate comparable with that of control pigs (Romsos et al., 1971a). Growth retardation in diabetic rats is associated with a rapid decline in the circulating levels of IGF-I (Maes et al., 1983) that is not restored by GH administration but by insulin only (Phillips and Young, 1976), suggesting a modulation of IGF-I release by insulin (for review, (Hill and Milner, 1985a)). While insulin seems to be essential for growth, daily administration of insulin to young healthy growing pigs does not affect the growth rate, feed efficiency, or muscle and adipose tissue mass, suggesting that in swine, insulin is not a rate-limiting factor of animal growth (Steele and Etherton, 1983). Similarly, low fetal growth does not seem to be due to poor insulinemia since low BW and normal BW piglets have identical fasting insulinemia (**Table 5**). However, if IUGR does not affect insulinemia in piglets at birth, it enhances the risk of developing insulin resistance (Poore and Fowden 2004) as it does in human (Ong and Dunger, 2004). Adult pigs of low BW have a poor glucose tolerance (Poore and Fowden, 2002) that is likely to be due to reduced insulin sensitivity (Poore and Fowden, 2004).

In skeletal muscle, postnatal growth is driven by hypertrophy of the existing fibers that requires both an increase in myonuclear content and the accretion of muscle proteins. Insulin clearly stimulates protein synthesis in growing animals. In the fasted neonatal pig, raising insulin concentrations to levels typical of the fed state increases the rate of skeletal muscle protein synthesis to within the range normally present in the fed state, even when amino acids and glucose are maintained at fasting levels. However, the stimulation of muscle protein synthesis by insulin is lower in 26- than in 7- day-old pigs (Wray-Cahen et al., 1998). In adult animals, this response to insulin is very little or inexistent (McNulty et al., 1993). Besides, in the pig the abundance of insulin receptor protein in muscle during the

early suckling period is 2-fold higher than at weaning (Suryawan et al., 2001). This decline likely contributes to the overall decline in the responsiveness of muscle protein synthesis to feeding that occurs over the course of development.

In adipose tissue of many mammalian species, including pigs, insulin stimulates the anabolic lipid metabolism pathways (Mills, 1999; Romsos et al., 1971b). It also plays a major role in the regulation of maturation of preadiocytes into adipocytes, since *in vitro*, insulin is required for all adipocyte cell type differentiation (Mersmann and Smith, 2005).

Insulin plays also an important role in the development of the intestine. It is naturally present in milk and even more in colostrum. In sow colostrum, insulin concentration is many times higher than in blood plasma: 411 µU/mL vs 5 µU/ml (and this concentration declines after 72 h lactation) (Westrom et al., 1987). There is tangible evidence suggesting that insulin, like other milk growth factors can act locally on the gastrointestinal tract or can be absorbed and act on peripheral targets (for review, see (Xu et al., 2000; Zabielski et al., 2005)). Oral insulin (85 mU/mL) enhances growth of the intestine (increase in the weight of small intestine and of mucosal) and increases the activity of brush border lactase and maltase in pig neonates fed with milk formulas (Shulman, 1990; Shulman et al., 1992). Interestingly, oral insulin also enhances the expression of its own receptor in small intestine, which could explain the effect of dietary insulin on receptor-mediated postnatal development of the small intestine (Huo et al., 2006).

Leptin

Leptin is the protein product of the obese gene and is involved in the regulation of food intake, body weight and whole body energy balance (Barb et al., 2001). Studies on the effects of exogenous leptin on growing pigs are scarce and use different doses (4-500 µg/kg BW) and way of leptin administration (intramuscular, intracerebro-ventricular, and intravenous, single or chronic injection). Thereby it is difficult to draw a clear cut painting on the effects of exogenous leptin. Single injection of high dose leptin (intra-cerebro-ventricular or in the carotid artery) increases GH secretion and decreases food intake (Barb et al., 1998). It also induces hypoglycaemia, hypoinsulinemia and an increased concentration of NEFA (Ramsay et al., 2004). Chronically administered leptin (50µg/d/kg BW) reduces food intake resulting in decreased growth rates in 27kg-pigs. It also seems to regulate IGF-I liver production in a dose-dependant manner (Ajuwon et al., 2003). In the neonatal pig, intravenous administration of much lower dose of leptin (4µg/kg BW/d)

increased growth rate and promoted skeletal growth in favour of adipose tissue accretion without any effect on insulinemia, glycaemia or NEFA concentrations (Litten et al., 2005).

Very few are known on the effects of IUGR on leptinemia in the pig. A negative correlation between BW and leptin mRNA abundance in adipose tissue has been established in 59 days old gilts (Eckert et al., 2000). This is in agreement with studies in human, where adults with LBW have higher leptin concentration than individuals at the same BMI but with a higher BW (Phillips et al., 1999). Leptin concentrations are low in IUGR infants at birth, and increase to become higher in these infants at 1 year of age than their normal birth weight counterparts (Jaquet et al., 1999). Thus, programming of relative leptin concentrations by early diet may be one mechanism that links early nutrition with later obesity (Singhal et al., 2002). This is comforted by studies in rodents where rats from undernourished mothers and fed a high fat diet exhibit in adulthood higher leptin, insulin and glucose concentrations and fat pad mass than the control rats (Vickers et al., 2001), but these metabolic consequences of maternal undernutrition were reversed by a period of neonatal leptin treatment in females rats (Vickers et al., 2005). However, there are many differences between rodent and human adipoinsular axis regulation and studies in other species are required to conclude on the physiologic role of leptin in the metabolic imprinting.

Like insulin and IGF-I, leptin is also present in sow colostrum and milk (Estienne et al., 2000). Leptin supplementation in milk formulas increases intestinal crypt depth in the upper jejunum, reduces intestinal villi length and the number of vacuolated enterocytes and increases the mitotic index. These results suggest that leptin given into gastrointestinal tract lumen speeds up the maturation of the small intestine mucosa (Wolinski et al., 2003).

Epidermal growth factor

Sow colostrum and milk contain high concentration of epidermal growth factor (EGF) that is involved in the development of intestinal mucosa in newborn pigs. EGF receptor have been identified on the epithelial cells of the GI tract, from the oesophagus to the ileum in 1- to 28- day-old pigs (Jaeger and Lamar, 1992). It has been shown in several studies that exogenous EGF influences GI epithelial maturation and function. It increases lactase and sucrase specific activities and protein synthesis rate in jejunal explants and limits gastric acid secretion. In addition, exogenous EGF may aid in the recovery of traumatized gastric and intestinal tissues (for review, see (Xu et al., 2000)).

CONCLUSION

Changes in nutritional status during the neonatal period are associated with several changes in the GH-IGF-I axis. Both moderate and severe feed restriction (Dauncey et al., 1994; Louveau and Le Dividich, 2002) in the suckling period decrease plasma IGF-I and IGFBP-3 levels. Regulation of receptors may represent an important mechanism of control within the GH-IGF-I axis. Regulation of IGF-I and GH receptors is tissue-specific and dependent on the type of under nutrition during the suckling period (Louveau and Le Dividich, 2002). Development of the gastrointestinal tract is also under nutritional control, and low milk intake delays its maturation. Therefore, improving feed intake in the early life would speed up tissue and organs maturation.

Further research in the hormonal control of adipose tissue and gastrointestinal warrants a better understanding of the underlying mechanisms of long-term effects of fetal restriction. Such investigations will find applications in human nutrition, the piglet being used as an animal model in studies of IUGR.

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Table 1. Differences in body and organ weights between IUGR and normal birth weight piglets (expressed as a percentage of normal birth weight piglets).

Age	**Birth**			**7 days of age**		**28 days of age**
Reference	Widdowson, 1971[1]	Bauer et al., 2000[2]	Rehfeldt & Kuhn, 2006[2]	Mostyn et al., 2005[2]	Le Huërou-Luron et al., 2006[2] unpublished data	Le Huërou-Luron et al., 2006[2] unpublished data
Number of animals per group	7	38	12-20	5	9	10
Body weight	- 61%	- 46%	- 32%	- 27%	- 21%	- 21%
Organ weights						
Brain	- 24%	- 11%				
Lung				- 23%		
Kidney	- 60%	- 46%				
Liver	- 73%	- 50%			-19%	-18%
Muscle						
Semitendinous			- 36%			
Psoas major			- 36%			
Quadriceps	- 69%					
Perirenal adipose tissue					- 39%	-18%

For IUGR piglets, birth weights were [1]0.63 ± 011 kg and [2]0.8-1.0 kg. For normal piglets, birth weights were 1.4-1.6 kg in all studies.

Table 2. Birth weight and relative weight and length of digestive organs of IUGR and normal birth weight piglets, and the percentage ratio of IUGR to normal piglets (expressed as a percentage).

Reference	Xu et al., 1994			Wang et al., 2005			Le Huërou-Luron et al., unpublished data			Le Huërou-Luron et al., unpublished data					
Age	Birth			Birth			Birth			7 days			28 days		
	IUGR	Normal	*%*	IUGR	Normal	*%*	IUGR	Normal	*%*	IUGR	Normal	*%*	IUGR	Normal	*%*
Number of animals	5	5		5	5										
Birth weight, kg	0.6	1.3	*44*	0.6	1.0	*59*	0.6	1.4	*42*	0.92	1.43	*64*	1.00	1.38	*72*
Stomach, g/kg BW	4.8	4.3	*112*	5.3	4.9	*108*	5.6	5.0	*112*	6.1	5.8	*105*	6.0	5.5	*109*
Pancreas, g/kg BW	1.0	1.2	*83*	1.3	1.2	*101*	0.73	1.0	*73*	1.6	1.6	*100*	1.4	1.6	*87.5*
SI weight, g/kg BW [1]	25	27	*93*	24	25	*96*	23	26	*86*	39	37	*105*	35	32	*109*
SI lenght, cm/kg BW	399	258	*155*	289	239	*121*	410	230	*178*	248	218	*114*	134	114	*118*
SI density, g/cm [2]	0.06	0.11	*55*	0.08	0.11	*73*	0.06	0.12	*50*	0.13	0.13	*100*	0.18	0.19	*95*
Colon weight, g/kg BW	5.6	5.2	*108*	6.5	7.4	*88*	-	-		-	-		-	-	
Colon length, cm/kg BW	-	-		85	68	*125*	-	-		49	41	*120*	25	22	*114*
Colon density, g/cm	-	-		0.08	0.11	*73*	-	-		-	-		-	-	

[1] SI, small intestine; [2] data obtained in the proximal jejunum for Le Huërou-Luron and Boudry, and our unpublished data

Table 3.Structural and functional characteristics of the small intestine in IUGR and normal birth weight piglets.

Reference	Xu et al., 1994[1]			Le Huërou-Luron and Boudry, unpublished data		
	IUGR	Normal	*%*	IUGR	Normal	*%*
Birth weight, kg	0.59	1.33	*44*	0.6	1.4	*43*
Number of animals	5	5		5	8	
Protein content, mg/g mucosa	135	99	*136*	86	76	*113*
DNA, mg/ g mucosa	3.6	4.2	*86*	-	-	
RNA, mg/ g mucosa	5.0	5.0	*100*	-	-	
Lactase activity, U/mg protein	0.11	0.17	*65*	0.14	0.21	*67*
Villus height in proximal jejunum, µm	770	960	*80*	717	852	*84*
Crypt depth in proximal jejunum, µm	70	80	*88*	94	94	*100*

[1] estimated values from original data

Table 4. Plasma IGF-I concentrations in IUGR and normal birth weight piglets.

Reference	Model			IGF-I concentration		*Statistics*
	number of animals	Piglet age	Birth weights (kg)	IUGR	NW	
Mostyn et al., 2004	IUGR:11 NBW:11	4 days	IUGR: 1 NBW: 1.5	31 ng/mL	35 ng/mL	*NS*
		7 days		43 ng/mL	42 ng/mL	*NS*
		14 days		36 ng/mL	48 ng/mL	*NS*
Davis et al., 1997	IUGR:6 NBW:6	At birth	IUGR: 0.92 NBW: 1.38	8 ng/mL	15 ng/mL	*-41%, S*
Shoknecht et al., 1997	IUGR:10 NBW:10	3 days	IUGR: 1.54 NBW: 1.74	13 ng/mL	20 ng/mL	*-30%, S*
		10 days		58 ng/mL	60 ng/mL	*NS*
Dauncey et al., 1994	IUGR: 6 NBW: 6	14 days	IUGR: 0.72 NBW: 1.40	1.05 nmol/L	1.30 nmol/L	*NS*
Louveau et al., unpublished data	IUGR:10 NBW:10	7 days	IUGR: 0.99 NBW: 1.41	27. ng/mL	27 ng/mL	*NS*
		28 days		24 ng/mL	26 ng/mL	*NS*
Kimberly et al., 1994	IUGR:18 NBW:18	At birth	IUGR <0.9 NBW: litter mean	18 ng/mL	16 ng/mL	*NS*
		7 days		35 ng/mL	45 ng/mL	*NS*
Herpin et al., 1992	IUGR:6 NBW:18	At birth	IUGR:8 NBW:8	4 nmol/L	5.8 nmol/L	*S*

NBW: normal birth weight; NS, not significantly different (P<0.05); S, significantly different (P<0.05)

Table 5: Fasting plasma insulin concentrations in IUGR and normal birth weight piglets.

authors	model			Fasting insulin concentration		*Difference, statistics*
	number of animals	Piglets age	Birth weights (kg)	IUGR	NW	
Mostyn et al., 2004	IUGR:11 NBW:11	4 days	1.0 1.5	1.6 µmol/mL	1.4 µmol/mL	*NS*
Davis et al., 1997	IUGR:6 NBW:6	At birth	0.92 1.38	10 µU/mL	10 µU/mL	*NS*
Shoknecht et al., 1997	IUGR:10 NBW:10	3 days	1.54 1.74	98 pmol/L	94pmol/L	*NS*
Poore et al., 2004	IUGR:22 NBW:25	3 months	1.13 1.90	15.7 UI/mL	15.8 UI/mL	*NS*