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Nutritional programming of gastrointestinal tract development. Is the pig a good model for man?

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The consequences of early-life nutritional programming in man and other mammalian species have been studied chiefly at the metabolic level. Very few studies, if any, have been performed in the gastrointestinal tract (GIT) as the target organ, but extensive GIT studies are needed since the GIT plays a key role in nutrient supply and has an impact on functions of the entire organism. The possible deleterious effects of nutritional programming at the metabolic level were discovered following epidemiological studies in human subjects, and confirmed in animal models. Investigating the impact of programming on GIT structure and function would need appropriate animal models due to ethical restrictions in the use of human subjects. The aim of the present review is to discuss the use of pigs as an animal model as a compromise between ethically acceptable animal studies and the requirement of data which can be interpolated to the human situation. In nutritional programming studies, rodents are the most frequently used model for man, but GIT development and digestive function in rodents are considerably different from those in man. In that aspect, the pig GIT is much closer to the human than that of rodents. The swine species is closely comparable with man in many nutritional and digestive aspects, and thus provides ample opportunity to be used in investigations on the consequences of nutritional programming for the GIT. In particular, the 'sow–piglets' dyad could be a useful tool to simulate the 'human mother–infant' dyad in studies which examine short-, middle- and long-term effects and is suggested as the reference model.

Intra-uterine growth retardation: Animal models: Swine: Human nutrition

Introduction

Programming is defined as the 'induction, silencing or restriction of development of a permanent somatic structure or physiological system with long term effects for function'[1]. This may be caused by stimuli or disturbing factors (for example, nutritional insults) acting during a sensitive time period (for example, time of maximal tissue growth) that trigger a line of consecutive events affecting fetal growth quality[1,2]. Programming is based on the observation that environmental changes can reset the developmental pathways during critical periods of life, when the tissues still have some plasticity and are in a proliferating and differentiating phase[3]. Developmental plasticity is defined as the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development[4]. This concept was introduced following epidemiological long-term studies in humans fed different diets in early life[5] and in infants suffering from intra-uterine growth retardation (IUGR)[6] which can be defined as impaired embryonic or fetal development. Developmental changes due to nutritional programming can become permanent (but may be reversible) and can predispose the individual to lifelong health problems such as the metabolic syndrome or related diseases (such as glucose intolerance, alteration of endocrine functions, insulin resistance, CVD, hypertension, diabetes and obesity)[7–19].

To date, reported consequences of nutritional programming are mostly studied at the metabolic level. Indeed, very few studies have addressed the gastrointestinal (GI) tract (GIT) as a target organ. Thus, first, we indicate that studies

Abbreviations: AGA, appropriate for gestational age; BW, body weight; CCK, cholecystokinin; GI, gastrointestinal; GIT, gastrointestinal tract; IGF, insulin-like growth factor; IUGR, intra-uterine growth retardation; LGA, large for gestational age; SGA, small for gestational age.

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involving the GIT are needed since the GIT plays a key role in nutrient supply and has an impact on functions of the entire organism. For this, whole-animal studies are necessary, but study is hampered by the lack of reliable animal models. Second, we compare animal models to study nutritional programming and development of the GIT with particular attention to the swine species as an optimal model for man. Finally, we provide arguments for the use of the 'sow–piglet' dyad as a model of the human 'mother–infant' dyad. Our intention is to provide the reader with a critical overview of ideas rather than an exhaustive review of the literature.

Effects of nutritional programming on the gastrointestinal tract

Why is the gastrointestinal tract important?

In animal and human nutrition, the GIT is responsible for the first physiological step of bringing nutrients to the body's cells and plays a crucial role in the regulation of the development of young mammals. Within this step the diet is digested and absorbed, and the intestinal mucosa is responsible for protection from injuries derived from microbiota or undesirable substances. In mammals, the fetus receives nutrients from the maternal blood via the placenta. However, starting at about mid-gestation the fetus also receives enteral nutrition by swallowing amniotic fluid (up to 20 % of body weight (BW) per d during late gestation). Although the nutrient content is relatively low (about 1 % protein), nutrients in swallowed amniotic fluid are estimated to contribute 10–20 % of fetal energy demands[20]. The prenatal expression of nutrient transporters in the alimentary tract during the third trimester of pregnancy allows the fetus to absorb carbohydrates, amino acids and proteins from swallowed amniotic fluid[21,22]. Thus, before and mainly after birth, the GIT must be sufficiently developed, providing optimal integrity. This development continues during the postnatal period.

The GIT is formed relatively early compared with other organs, and its embryonic, fetal and postnatal development is a complex combination of growth (increase in the mass of tissues and/or in the number and size of cells) and of maturation (changes in the structure and function of cells and tissues). To illustrate this complexity, there is a close relationship between the degree of maturation and absorptive functions of the intestine. In the neonatal intestine, nutrient transport occurs along the whole crypt–villus axis, whereas in the adult intestine the absorption of nutrients is shifted to the upper part of the villi[23]. These differences are associated with distinct populations of enterocytes lining the intestinal mucosa during perinatal development. Although GI tissues constitute only 2–6 % of BW in late gestation and at birth[24,25], they represent a disproportionate fraction (about 10–35 %) of the whole-body O_2 consumption and protein turnover[25] because of their inherently high rates of metabolism. The large surface area of the intestine is an interface between the internal and external environments, and, in adults, the number of immune cells associated with the GIT is estimated to exceed the residual number of body cells combined[26]. The first line of defence is the mucosa, which must prevent bacterial and viral invasion, and yet absorb nutrients[27]. Moreover, the GIT plays an important role in feedback regulation of its own functions as well as in neuro-hormonal regulation of the associated organs downstream to the GIT. It represents the largest endocrine organ in the body[28] and has its own nervous system (enteric nervous system). Most of the GI regulations depend on a complex regulatory system more and more recognised as a unique system with different components including hormonal, nervous and immune substances[29].

After birth the placental supply of nutrients is lost and the neonatal GIT is stimulated chiefly by enteral nutritive and non-nutritive (biologically active) substances from colostrum and milk. In rats fed parenterally, BW gain is comparable with that of normally fed animals. However, the mucosal mass of the stomach, small bowel and colon is only 30–40 % of that in control animals[30]. In piglets fed a constant overall nutrient supply, the rate of protein synthesis and cell proliferation plummeted and apoptosis soared when nutrient intake was strictly intravenous as opposed to delivery by combined enteral and intravenous routes[25,31]. After birth, nutrition is a critical determinant in the functional growth and maturation of the GIT while, on the other hand, fasting causes a marked intestinal atrophy in piglets and humans[32]. The importance of enteral nutrition was also noted, for example, in adult rats starved for 6 d in which the small intestine lost 53 % of its weight (a decrease of total intestinal cell population and RNA, protein and water content of the individual cells) as opposed to only 32 % for the whole body[33]. In addition to the provision of energy substrates and precursors for the synthesis of constitutive and secreted functional proteins, glycoproteins, nucleotides and membrane lipids, nutrients indirectly stimulate the production of endocrine as well as paracrine regulators and a variety of metabolites that modulate GI development. Although most of the amino acids derived from ingested protein are absorbed in the small intestine, protein intake may affect the colon as well, albeit in an indirect fashion, via interactions with intestinal microbiota. As a matter of fact, in adult human subjects fed a 'standard' normal-protein diet (70–100 g/d), 12 g nitrogenous compounds per d (proteins or peptides from ingested food, pancreatic enzymes, mucins, exfoliated cells) reached the colonic lumen[34]. Due to enzyme immaturity of the neonatal small intestine the fraction of ingested proteins reaching the colon, and the subsequent availability as substrate to be metabolised by colonic microbiota, may be even higher in infancy[34]. Increasing protein intake enhanced the faecal concentration of bacterial metabolites arising from putrefaction (ammonia, phenol compounds or polyamines) which are thought to have deleterious effects, except for polyamines which have been shown to be beneficial for epithelial cell proliferation[35].

Effects of nutritional programming on the gastrointestinal tract

In nutrition studies, data concerning nutritional programming were obtained in the context of placental adaptation[36,37], intra-uterine environment[38] including

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fetal nutrition and/or that of the pregnant mother[39–43] as well as early postnatal nutrition of offspring[44–48]. Moreover, in mammals, the mid- and long-term effects of nutritional programming were examined at several biological levels: system functions (respiration and circulation), organs (spleen, liver and kidney), tissues (muscle and adipose tissues), as well as at cellular and molecular levels[9,10,49,50]. To date, very few studies have been undertaken to explore effects on the GIT (except for the endocrine pancreas and some aspects concerning only the GIT in IUGR; see the section 'Small for gestational age' and Lebenthal & Young[51] for pig and rat species, respectively). Newborns from mothers fed a restricted-protein diet showed an alteration of the pancreas, more particularly in the proliferation of endocrine β-cells as well as in the size and vascularisation of the islets. As a result, the circulating insulin concentration and the stimulation of its secretion by arginine and leucine were decreased in the offspring[52,53]. In addition, small-intestinal hyperplasia, and the resultant increase of total activity of disaccharidases such as sucrase and isomaltase in the entire small intestine were noted, thereby leading to postprandial hyperglycaemia in diabetes mellitus[54].

Concerning normal development of the GIT, studies of the ontogeny of intestinal enzymes (for example, trehalase, see Gartner *et al.*[55]) and hormones in rodents suggest that epigenetic mechanisms of gene regulation in the intestine could be responsible for the continuity of maturation during postnatal growth. Direct evidence of the implication of epigenetic mechanisms in GIT pathology are provided by several examples in which an epigenetic deregulation is the cause of carcinogenesis[50]. Finally, recent data show that oral bacterial infection of pregnant mouse dams results in a methylation modification of the insulin-like growth factor (IGF)-2 gene in the placenta which could have consequences on the future development of offspring[56].

In summary, during the perinatal period, digestive functions supply nutrients to meet the requirement of different tissues, but nutrients also can generate signals for numerous immuno-neuro-hormonal regulatory cycles. The GIT must be sufficiently developed to (1) exert digestive functions for diet components and nutrient absorption, (2) provide efficient physiological 'selective' function (or 'intestinal barrier') as well as defence functions, and (3) respond to stimuli to orchestrate regulation during digestion, absorption and metabolism. Moreover, the developmental trajectory varies between different organs and tissues and the most nutritionally important organ during early development is probably the GIT[57]. Health, growth and wellbeing of the newborn animal and infant depend on the GIT. Taken together, because of the scarcity of data concerning nutritional programming effects on the GIT and due to their potentially important consequences, more research is needed in animal models due to the ethical constraints involved in using human subjects.

Animal models to study nutritional programming and development of the gastrointestinal tract

It is extremely difficult to perform studies in human subjects due to the multitude of ethical issues and the limitations of invasive procedures. Moreover, although the recent interest in the developmental origin of adult diseases was initiated by studies in human epidemiology, the epidemiological approach has several important limitations. Environmental conditions that affect study populations in human epidemiological studies are constantly changing. As an example, one of the most fascinating and instructive events that has led to a wealth of human epidemiological information is the Dutch Hunger Winter[58]. However, these observational data are difficult to evaluate in regard to the early life plane of nutrition for each individual because of a number of potential maternal confounders (exposure to cold, mental stress, strenuous activity, etc)[15]. Carefully performed epidemiological studies[59,60] raise a number of scientific hypotheses related to the underlying mechanisms that can be investigated in animals. Experiments in animal models are relevant and essential since they are complementary with human epidemiological studies. In animal experiments it is possible (1) to evaluate health and nutrition in the population of females (and/or offspring) to be studied before and during pregnancy as well as during lactation, (2) to control food intake and environmental factors in the different groups of interest, (3) to repeat experimentation, (4) to perform invasive techniques, thereby providing multiple measurements and mechanistic data within the same animal at several stages from fetal to postnatal development[15].

The most frequently used animal models

Many animal models have served to study the effects of factors acting during fetal or neonatal periods and leading to a predisposition to the development of chronic diseases in adults. As reported, *in vivo* and *in vitro* experiments have been conducted in rats, mice, guinea-pigs, sheep and non-human primates[8,10,45,51,61–63]. Studies in rodents largely dominate the literature to date. These protocols using dietary, pharmacological, genetic and surgical models have been explored in healthy animals[8]. The studies aimed to investigate mostly the effects of undernutrition and sometimes that of overnutrition[62], maternal stress and exposure to pharmacological substances[61]. Nathanielsz[15] has presented ten fundamental principles of developmental programming in the context of physiological systems involved, and the studies in animal models that were performed to evaluate exposures, mechanisms and outcomes. In the same review, this author describes the most suitable animal models to study different functions, among a number of models that have been developed. As an example, the most widely used model of brain injury (Rice-Vannuci) is the newborn rat aged 7 d because this model has the brain maturity equivalent to that of an early third trimester human fetus. In a similar way, the non-human primate is well suited for studying the pathogenesis of perinatal infections because monkeys and man have similar immunological responses to infection. Curiously, in the field of nutritional programming, relatively few studies have used the pig as a model for man.

Most of what is known about nutrition and GIT development is mainly based on studies in ten species of mammals (rats, man, guinea-pigs, rabbits, pigs, sheep, mice, dogs, cows, cats) and two other non-mammalian vertebrates

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(chickens and frogs)[27]. In the case of the GIT, we must focus on the animal model that is most similar to man in regard to GIT function. Although the use of a comparative approach has provided valuable insights into the role of nutrition in mediating intestinal development, extrapolation of results to human fetuses and infants is limited by differences in adult diets, pattern of development and GIT characteristics as well as ethical problems.

Development of the GIT *in utero* is characterised by extensive structural and functional changes in the intestinal epithelium[64,65]. However, there are marked differences in the stages of intestinal maturation in various mammalian species at birth. Variations in the timing and extent of intestinal maturation reflect the duration of the gestational period. Altricial species such as the mouse and rat, which are born after a short gestation, depend closely on their dams for nutrition, thermoregulation, locomotion, and evacuation of the bowels. They do not achieve independence until after weaning. In these species, adult diets are poorly tolerated until relatively late in postnatal life, and adult-type GIT functions develop rapidly after weaning. In contrast, intestinal development in precocial species that have a long gestation period such as the guinea-pig, pig and sheep occurs early *in utero* and major developmental events in the gut take place both before and after birth. As shown in Fig. 1, the porcine digestive enzymes resemble more closely human development in fetal and neonatal periods since, from a 'gut point of view', pigs like man and other primates have a precocious mode of development[66,67]. While non-human primates may seem to provide an obvious choice, a number of serious difficulties limit their use as models for man[68]. The primates reproduce slowly (one baby per year), are expensive and are difficult to manage in the laboratory. Only a few species (20 %) are laboratory bred, and there is considerable variation among species. Last, but not least, society disapproves of using primates as laboratory animals.

Thus, the few data that are available from studies in non-human primates might be useful but these models are hardly accessible. Rodent models are of little help due to large differences in GIT maturation around birth and weaning between rodents and man.

Swine as a model of the human species

Pond & Mersmann[69] pointed out that the pig is similar to man in dental characteristics, renal morphology and physiology, eye structure and visual acuity, skin morphology and physiology, cardiovascular anatomy and physiology, and digestive anatomy and physiology. Previous studies have shown that body composition (expressed in percent, on a fat-free basis) is very similar in pigs and man at three stages (birth, 3 months, 3 years for pigs and 33 years for man)[70]. Swine are recognised as a valuable model for man in a number of biomedical studies as well as in cardiovascular, pulmonary, GIT/nutrition, renal, immunological, metabolic, embryological/fetal, neonatal and integumentary domains[71–73]. The use of pigs in surgical research increased dramatically since the 1970s due to decreasing availability of dogs[74]. In many anatomical and physiological aspects it is even closer to man than a dog. Nowadays, the pig is routinely used as the model animal to practice endoscopy and laparoscopy techniques in human

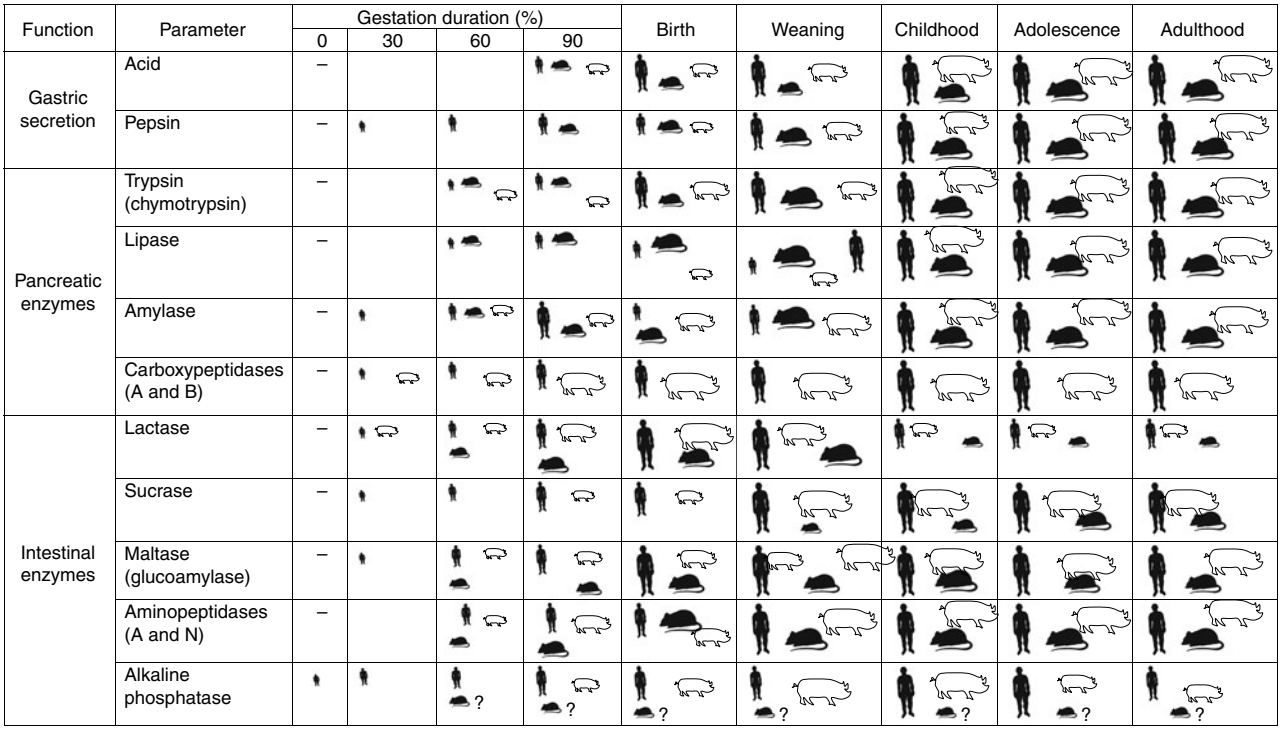

Fig. 1. Ontogeny of gastric acid production and gastric, pancreatic and intestinal enzyme activities. Comparisons are between man, the pig and the rat. For each species, the larger the body, the more mature is the enzyme activity. Synthetic schema are from previous studies[90,92,104,184–191].

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GI and gynaecology surgery. For example, effects of surgical techniques in the GIT on intestinal motility were studied in a pig model and could explain the difference in recovery in patients[75]. Besides the large size of adult pigs, anatomical similarities to the human GIT and pancreas and similar dietary requirements make this species amenable for studying human-sized equipment and developing new techniques in pancreatic surgery. The porcine pancreas is similar in colour, texture and density and has a true capsule similar to its human counterpart. Handling of the porcine pancreas resembles the human in most aspects, making it an ideal model for surgical experimentation[76]. The topography of the portal vein, mesenteric vessels and duodenum is similar to that in man. Examples of functional resemblances are similar distribution of cholecystokinin (CCK) receptors and neuro-hormonal mechanisms controlling pancreatic juice secretion. The pancreatic juice drainage system is not much different, since in many pigs both main and accessory pancreatic ducts exist, though the accessory duct drains most of the porcine juice[77].

Pigs are omnivorous mammals and have a remarkable similarity to man in GIT anatomy, physiology, biochemistry (and even pathology)[78–80]. Thus, this species is often used in paediatric and biomedical research[81,82] and more generally in the field of nutrition and associated domains (digestion, absorption, metabolism, immunology) (Table 1). As an example, similar systems have been used to evaluate infant formulas and milk substitutes and to assess diets for the rehabilitation of infants from protein–energy malnutrition[73]. As in man, subcutaneous fat in pigs is the largest fat depot of the body; it is anatomically similar in both species[83].

Knowledge about the progression of GIT structure and function during body development is important to validate animal models and to indicate limitations in extending results from animals to man. Thus, the chosen model must have an organ maturity similar to that of man during most of the different stages of development. This comparison has to take into account the GIT developmental time line as well as endocrine, metabolic and circulatory conditions.

Comparative gastrointestinal tract ontogeny. With respect to this term, we recognise that this theoretically could cover all events involved in the formation of a mature GIT. Here we focus on fetal and postnatal stages during which the GIT acquires its structural and functional characteristics. During the prenatal stage, for a species comparison the reference point is usually the duration of pregnancy with the different stages expressed as percentage of pregnancy duration. After birth, comparison of GIT maturation is less straightforward and we describe GIT function development at several stages according to Table 2. Thus, in most papers concerning postnatal development of the pig pancreas, gastric and small-intestinal function as well as absorption, it is generally said that the weaning time point, rather than chronological age, is a key factor in maturation. In pig production systems, the change in diet composition during weaning is abrupt and forced earlier than it would occur under natural conditions. In contrast, in man, natural weaning comprises a gradual reduction of breast milk feeding and an increased contribution of solid food slowly from 6 months up to 2–3 years of age. Surprisingly, there are no data available on GIT maturation in pigs weaned physiologically (i.e. starting at 1·5 months of age and lasting

Table 1. Utilisation of swine species as a model for man

Studied function	Studied parameters	Stage, age or type of pigs	References
Digestion and absorption	Intestinal enzymes	1–6 weeks*	192
	Gastrointestinal motility	12–28 d	120
	Protein digestion	3 weeks	89
	Gut growth and maturity, gut functions, blood flow	Neonate	85
	Digestion and absorption, digestive enzymes	Milk-fed (neonate) and solid food (adolescent)*	69, 171, 192–195
	Metabolism	Adolescent	195
Nutrition and development	Fasting and malnutrition	Adolescent	32
	Nutrition (including digestive tract)	From fetus to adult	73, 196, 197
	Lipid nutrition	Neonate	198, 199
	Adipose tissue development	Fetus	200
	Enteral and parenteral nutrition, body composition	Fetus, neonate	201–203
	Liver function and metabolism. Postnatal intestinal, splanchnic and whole-body nutrient metabolism	Neonate	85
Immunology	Immunology	From fetus to adolescent	121
Diseases	Diseases (periodontal, genetic, etc)	From birth to adult	204
	Diabetes	Around birth	68, 200, 205
Paediatric and biomedical research	Paediatric research and gastroenterology	Perinatal stage	206, 207
	Biomedical research on the digestive system (intestinal metabolism, etc)	From birth to adolescent	81
	Biomedicine, surgery and transplantation	Adult	
		From birth to adult*	78, 172, 185, 208–211
	Cardiac surgery	Adolescent	210

* Miniature pig.

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Table 2. Approximate age and body weight (BW) values in human, pig, rat and mouse species at corresponding stages of development (data obtained from global bibliography and own observations)

Species	Age and BW	Pregnancy duration (d)	Newborn	Weaned	Infant or child	Adolescent	Adult	Senescent
Man	Age	267	0 d	4–6 months	0·5–12 years	13–18 years	> 20 years	> 65 years
	BW (kg)		2·5–4·5	5–9	6–50	40–65	65–80	–
Pig	Age	124	0 d	21–35 d	2 d–10 weeks	4–7 months	1–2 years	> 12 years
	BW (kg)		1·0–1·8	6–10	1·2–30	50–100	> 140	–
Rat	Age	22	0 d	21–28 d	2 d–40 d	1·25–2·0 months	About 3 months	> 2·5 y
	BW (g)		5·1–6·4	30–40	10–70	80–140	> 160 (females), > 180 (males)	–
Mouse	Age	19–21	0 d	21 d	2–21 d	3–6 weeks	≅ 2·0 months	> 1·0–1·5 y
	BW (g)		1–2	6–12	3–20	20–25	18–30 (females), 22–40 (males)	–

for about a 2-month period). Thus, around weaning, GIT development must be compared with caution between human and swine species.

Global aspects of nutrition. Both man and pigs are dependent on dietary quality (for example, amino acids, digestible carbohydrates), since symbiotic micro-organisms within the gut play a relatively small role (as compared with, for example, ruminants and horses) in modifying the nutrients that are ingested (even if there is a difference between pig and human gut size and fermentation intensity). The digesta transit time and digestive efficiencies are comparable. However, the porcine lower small intestine has a much higher microbial density and thus pigs can degrade certain indigestible carbohydrates to a higher degree than man[83]. Post-absorptive metabolism is also similar in many aspects[69]. The wide differences in length of gestation and the number of offspring introduce a potentially significant divergence in nutrient needs for reproduction. Nevertheless, when minimum nutrient requirements of swine and established recommended daily allowances of humans are expressed per kg dietary DM (assuming an intake of 500–800 g DM per d by teenagers and adults), these values are similar[73]. Thus, it is apparent that the omnivorous pig is one of the best models to study nutrition issues in the omnivorous human[73,84]. Total parenteral nutrition (TPN) is necessary in health-compromised human infants during the peripartum phase, and neonatal and preterm piglet models have been applied to study specific effects of TPN on intestinal growth, blood flow, digestion, absorptive function, epithelial integrity, and gut barrier function[85]. TPN-associated liver injury in piglets resembles that seen in the human neonate[85]. Moreover, nutritional needs are very well known in the pig[86] and it is possible to precisely control intake.

At birth there are many differences between the species in respect to enterocyte morphology and macromolecule absorption[87] as well as activities of pancreatic trypsin and small-intestinal dipeptidase isoforms, reflecting a greater degree of development in man compared with in pigs. This may be artificially produced by a relatively low bioactive substance intake in farm piglets since the offspring from pregnant and lactating sows fed a diet rich in PUFA (*n*-3 fatty acids), plant polyphenols, other antioxidants, taurine and L-carnitine showed a more advanced development of stomach and gut epithelium as compared with untreated controls (Zabielski *et al.*[88]; B Bałasińska, M Grabowska, J Wilczak, G Kulasek and R Zabielski, unpublished results). However, if a comparison is made between the two species at the more physiologically comparable stage of peak lactation in the mother (about 3 weeks in the piglet and 3 months in the infant), the major enzymes involved in the digestion of milk protein and the other milk components have similar activities in piglets and human infants (Fig. 1). There is another difference between the two species: at peak lactation in the mother, the gut capacity of the piglet is about double that of the human infant although the BW is similar. This difference needs to be considered when using the piglet as a model for digestion and absorption studies[89]. Overall, the digestive function of the newborn piglet and human infant bear many similarities in terms of enzyme activity and digestive capacity[90].

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Recently, Dziaman *et al.*[91] evaluated the oxidative status in healthy full-term children and piglets by urinary excretion of 8-oxoGua (8-oxoguanine) and 8-oxodG (8-oxo-2′-deoxyguanosine), and concentrations of vitamins A, C and E. Accordingly, healthy full-term newborns show signs of oxidative stress, and urinary excretion of 8-oxoGua and 8-oxodG was found to be a marker of oxidative stress in newborns of both species. Antioxidant vitamins, especially vitamin C, were found to play an important role in protecting newborns against stress. The neonatal blood vitamin C content depended on corresponding maternal levels and the values in cord blood were about two times higher than in the maternal blood. Taking into account differences in kinetics between the species, it was concluded that the pig is an excellent model to study oxidative stress in newborn children.

Fetal development. In both man and pigs, prenatal development in GIT function occurs mostly during the third trimester[92,93].

Fetal development: intestinal morphometry. The processes that accompany the morphogenesis and cytodifferentiation of the intestinal mucosa are temporally and topologically highly organised when temporal changes superimpose on the spatial diversity of gene expression found along the crypt–villus and duodenal–colonic axes[66,94]. Early crypt development is typical for man and species with a long gestation period, but not for rodents where the formation of crypts is observed only after birth. Rapid reduction of villus height and increase of crypt depth was observed during suckling and weaning periods in species with longer gestation (lambs, piglets, guinea-pigs, man). The developmental changes of surface area are influenced by rapid growth of the intestinal mucosa that is predetermined in altricial species by decreased cell turnover[66].

Fetal development: digestive enzymes. In pigs the most distinct maturational changes occur for stomach acidity and chymosin concentrations, pancreatic amylase and trypsin, as well as intestinal lactase and aminopeptidase N activities (Fig. 1) as well as for intestinal absorption of glucose and protein molecules. Reviews on the ontogeny of GI functions in man show that rapid maturational changes also take place for many gut functions in human fetuses in late gestation although the exact age-related development varies widely among different functions[92,93]. When expressed as percent of the maximum value during development, sucrase (after birth) and lactase activities have a similar pattern[90]. Sucrase and maltase have often been used as marker proteins for the development of mature brush-border function in mammals[95,96], and, interestingly, these two enzymes have a similar development in pig and human species (Fig. 1).

Fetal development: active transporters. Apical transporters for amino acids and sugars can be detected at around 40 % of gestation in pigs, even earlier in man (25 % of gestation) and much later for altricial rats and mice (80 %)[97]. In man, active electrogenic transport of glucose is already present in the human fetal small intestine, and the duodenum-to-ileum gradient of glucose absorption is established between 17 and 30 weeks of gestation. A detailed analysis of glucose uptake across the apical membrane of fetal enterocytes demonstrated two Na^+-dependent pathways differing in their affinities, whereas a single system has been found in adulthood[66]. Similarly, two Na^+-dependent glucose transport systems have been found in porcine proximal small intestine at a comparable gestational age, which was followed by a shift to a single high-affinity transport system at birth[98]. In the neonatal intestine, nutrient transport occurs along the whole crypt–villus axis whereas in the adult intestine absorption of nutrients is shifted to the upper part of the villi[66].

Fetal development: regulation. A co-localisation of all the major islet hormones within individual endocrine cells in both the porcine and human fetal pancreas has been shown. Furthermore, co-localisation of islet cell hormones has been demonstrated within individual granules. In the adult pancreas, however, no such co-localisation is discernible. The adult distribution and cellular composition of the endocrine pancreas in higher mammals is not attained until several months after birth[99,100]. Generally, GIT endocrine cell development has been studied in pigs from fetal to adult stages and results suggest that the evolution of gut regulatory peptide production is similar in pigs and man[101,102].

Postnatal development. GIT growth and maturation before birth prepare neonates for the abrupt transition from acquiring the majority of nutrients via the placenta and umbilical vein, mostly bypassing the intestine, to complete dependence on the intestine for processing and absorbing nutrients from milk. Just after birth, colostrum ingestion enhances disease resistance, GIT growth and maturation[103,104]. The GIT growth response to oral feeding is necessary for efficient digestion and absorption of nutrients to accommodate the nutrient demands of the developing neonate.

Postnatal development: colostrum and milk composition. Colostrum and milk contain a number of regulators (hormones and growth factors) that are crucial for early postnatal development of the GIT, the nervous system, and the entire neonatal organism (Table 3). These substances are present in milk at concentrations usually much higher than those found in maternal blood or in the blood and tissues of their offspring. Weström *et al.*[105] have reported that the concentration of insulin in sows' colostrum is over 100 times greater than in maternal plasma and it drops gradually during the lactation. Blum & Hammon[106] have demonstrated similar patterns in regard to insulin, prolactin and IGF-1 in bovine colostrum and milk. High concentrations of insulin and IGF-1 in colostrum and milk coincide with intensive growth of the intestinal mucosa and pancreas tissue just after birth[107]. In contrast, rat colostrum contains lower concentration of regulators as compared with early lactation milk[108]. Colostrum, milk hormones and growth factors seem to be particularly important in neonates to support their neuroendocrine function and regulate the

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Table 3. Immunoglobulin, hormone and growth factor concentrations in human and sows' colostrum and milk*

	Man		Pig		
	Colostrum	Milk	Colostrum	Milk	References
Insulin (μIU/ml)	15–85	12–70	130–830	22–100	212–214
Leptin (ng/ml)	2	2	40–72	30–40	215–217
Acylated ghrelin (pg/ml)	64	77	750	1100	216–218
IGF-1 (ng/ml)	17–30	6–10	70–136	10–27	111, 213, 219
EGF (ng/ml)	40–400	30–60	1500	150–250	109, 111, 220
IgA (mg/ml)	12	0·9	10–20	6	221–222; C Rehfeldt, W Otten and CC Metges, unpublished results
IgM (mg/ml)	0·6	0·2	10	1·7	221–222
IgG (mg/ml)	0·1	0·1	30–95	3·3	221–222; C Rehfeldt, W Otten and CC Metges, unpublished results

IGF, insulin-like growth factor; EGF, epidermal growth factor.
* No data are available on glucagon-like peptide in colostrum and milk in any of the mammalian species.

development of GIT structure and function until the neonate's own endocrine system achieves maturity. The degradation of hormones and growth factors by digestive juices occurs to a much lower degree in neonate and suckling than in weaned or adult animals[109–111]. Differences in colostrum and milk composition between species and responses to milk-borne bioactive components may be expected due to ontogenic development of tissues and organs[112]. In whey samples of human, cow and sow colostrum the insulin concentrations were high and changed similarly on the day before and at parturition. On the day after delivery insulin concentration remained high in human and sow colostrum but in cows it decreased to one-twelth compared with the level at parturition[113]. In conclusion, the data presented demonstrate a similar developmental pattern for GIT growth factor concentration in human and sow colostrum and milk which may suggest similar controlling pathways during early postnatal development.

Postnatal development: gut closure and macromolecule absorption. Gut closure is the process whereby macromolecules cease to be absorbed. It occurs in pigs after birth whereas in man there is some evidence that it occurs in early to mid-gestation if it occurs at all[90,114,115]. This process depends on factors such as epithelial maturation or increased intraluminal proteolysis. After birth, cessation of macromolecule transfer across the intestine progresses rapidly to completion at approximately 24–72 h in newborn piglets but is delayed until several weeks after birth in rats and mice[116]. From a physiological point of view, the transport of macromolecules such as growth factors and IgG is crucial for ungulates such as piglets that are born nearly without γ-globulins but are capable of transferring intact immunoglobulins from ingested colostrum to the circulation during the first postnatal days[117]. In human infants IgG is mainly transferred by the placenta during late gestation; nevertheless, those which are born more or less hypoglobulinaemic also receive IgG passively from the maternal milk through proximal intestine absorption, but in lesser quantity than in swine species[66] (Table 3). The effective transport of ingested functional proteins is facilitated by decreased proteolytic degradation due to the presence of colostral protease inhibitors. In contrast to ungulates, rat and rabbit milk has a relatively low protease inhibitor capacity[66].

The intestine of altricial species contains fetal-type enterocytes equipped with apical tubular systems and endocytotic complexes until weaning when the immature vacuolated enterocytes are replaced by mature non-vacuolated cells[118]. In ungulates, massive non-selective endocytosis and transport of all intraluminal macromolecules take place during the first 2 postnatal days, and immunoglobulins compete with other proteins. In newborn pigs, guinea-pigs and hamsters, the transport capacity decreases rapidly within the first postnatal days, whereas the transfer is terminated around 21 d after birth in rats and rabbits[66].

Postnatal development: organ development, motility and digestive enzymes. Piglets are slightly less mature at birth than human neonates in several aspects including the digestive system and body composition (piglets have a lower body fat content)[85,119]. However, during the neonatal period, protein deposition is very rapid and owing to similarities of postnatal nutrition and intestinal development to man, the piglet can be viewed as an accelerated model of postnatal growth and development[67]. The pig stomach increases in weight by 28 % during the first 24 h and it continues to grow but less intensively in the following 9 d. By day 10, its weight is 3·5-fold higher than at birth. It has been reported also that during the first 24 h the stomach grows more rapidly than the body as a whole[115]. In piglets aged 12–27 d, the antral and duodenal electrical control activity frequencies are similar to values reported in human adults and the migrating myoelectric complex is slightly shorter. Globally, the neonatal piglet model is reproducible and has similarities to the human infant's GI physiology[120]. The human, pig and rodent GIT enzymic development is reported in Fig. 1, showing that the pig is nearer to man than rodent species. Lingual lipase is quantitatively the most important lipase for digestion of fat in suckling infants and piglets[115].

Postnatal development: absorption. With a few exceptions, the total intestinal transport capacity increases with age due to the increase of intestinal mass, but the transport rate for most carbohydrates and amino acids studied so far decreases relative to the increase in intestinal weight. In pigs this decline may reach 50 % of the initial values. Fructose absorption follows quite a different developmental pattern,

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since it increases in the small intestine during weaning in rats and rabbits, but a smaller increase has been found in pigs[66]. Because juvenile pigs are able to modulate brush-border hydrolases and transporters in response to changes in diet composition, the capacities for adaptive modulation must be acquired at, or shortly after, weaning. There is no information on when human infants acquire the capacities for adaptive modulation of intestinal functions[27].

Postnatal development: immune system. Standard pigs and miniature pigs may be a cost-effective experimental compromise compared with studies in rodents and non-human primates and a valuable addition to observations on the developing immune system in man[121]. Development of the mucosal immune system occurs with age, but is strongly influenced by environmental factors including microbial colonisation and exposure to specific antigens. Thus, relatively little development of the mucosal immune system occurs in neonatal piglets in the absence of a commensurate microbiota. Similarly, epidemiological evidence in human infants has also suggested that exposure to microbiota and potential pathogens is associated with decreased risk of allergic diseases[122]. In this context Jaworek *et al.*[123] provided evidence that pretreatment of rat neonates with low doses of the lipopolysaccharide (endotoxin) component of the cellular wall of Gram-negative bacteria reduced gene expression of CCK_1 receptor and showed impaired exocrine pancreatic function at adult age. Exposure of suckling rats to bacterial endotoxin attenuated acute pancreatitis induced in these animals at adult age and this effect was attributed to the increased concentration of the antioxidative enzyme superoxide dismutase in the pancreatic tissue as well as modulation of the production of a number of pro- and anti-inflammatory cytokines. This work provides impetus for further studies aiming to counteract the problems related to immune system malfunction.

Postnatal development: regulation. In man and swine, the small intestine is relatively mature at birth. Correspondingly, intestinal maturation appears most glucocorticoid-sensitive in the late fetal and early neonatal period, in association with a peak of circulating levels of glucocorticoids at this time[93]. Pancreatic secretion in human neonates is low, but the pancreas responds to nutritional stimulation from the first days of life, and can adapt its response to changes in milk formula composition[124]. In pigs, as in man, functional parameters of pancreatic juice (normalised to BW), such as volume, protein concentration, trypsin concentration, and response to feeding and secretagogues, are all low before weaning and increase thereafter[125]. The ability of secretin to increase fluid secretion is present at the time of birth, but CCK did not increase the concentration (units/mg proteins or units/ml) of amylase, trypsin, chymotrypsin, carboxypeptidase or lipase in duodenal aspirates at 1 d or 1 month, but did so in children aged 2 years or older[125]. In suckling pigs with catheterised pancreas, the secretion of pancreatic juice and enzyme output in response to exogenous secretin + CCK was small, but significantly increased after weaning[126]. No such data are available in humans. The response to stimulation in adolescents and adults seems to depend on the neonatal background. As mentioned above, pretreatment of rat neonates with low doses of lipopolysaccharide has an impact on neuro-hormonal mechanisms controlling the exocrine pancreas in adulthood, resulting in reduced enzyme responses toward hormonal stimulation[123].

In summary, numerous species have been used as a model for man in research of nutrition and developmental programming. Rodent species are the most frequently used, even if they seem not the most suitable model concerning the GIT. In contrast, gut physiology and GIT development (growth and maturation) in pigs are closer and often similar to that of man in many features during fetal and postnatal development. Some differences are noticed (gut closure, materno-fetal transfer of immunity) but these differences do not seem to compromise the pig as a model.

The sow–piglet dyad as a model for understanding nutritional programming in the human mother–infant dyad

In view of the incidence of obesity worldwide there is increasing interest in the extent to which body composition, both in the short and long term, differs in infant and children born with a very low or a very high BW. This is because a growing number of studies have linked low BW and fetal growth restriction to an increased risk for chronic diseases in adulthood that often are obesity-related. In addition, there is also evidence to suggest that heavy infants may be at increased risk for obesity and associated diseases in later life[127]. In human infants, low BW or small for gestational age (SGA) is defined as a BW $< 2{\cdot}5$ kg at full term (or $<$ 10th percentile of Lubchenco charts)[128]; it concerns neonates who have experienced IUGR and does not include preterm neonates who also present a low BW[60]. Large BW or large-for-gestational-age (LGA) is defined as a BW $> 3{\cdot}5$ kg (or $>$ 90th percentile). Both populations are compared with infants born with normal BW status, appropriate for gestational age (AGA).

Similarly, in pigs the newborn population can be divided into three groups, and the same classification of birth weight of human infants can be applied to pig species. Based on data of 12 041 piglets from 965 litters (generated from 168 Large White × Landrace crossbred sows) Quiniou *et al.*[129] showed that the piglet population at birth follows a normal distribution and can be classified as SGA or IUGR (0·6 to 1·0 kg or $<$ 11th percentile), LGA ($>1{\cdot}5$ kg or $>$ 85th percentile) and AGA ($>1{\cdot}0$ kg and $<1{\cdot}5$ kg) (Fig. 2). This classification is precise for a large population of newborn piglets as is the case for human neonates. However, this percentile classification cannot be applied to a single litter because birth weights do not follow a normal distribution. This means that a classification of SGA or LGA piglets must be based on the absolute value of birth BW for the considered breed.

Small for gestational age or intra-uterine growth retardation

Over the last 50 years several studies have reported the occurrence and phenotype of the low-BW or runt piglet using terms including IUGR and SGA[130,131] or it can be

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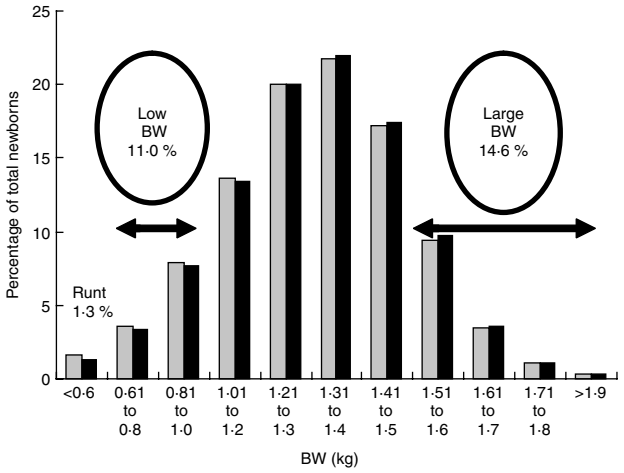

Fig. 2. Distribution of piglets according to birth weight (BW; kg). The figure is based on data obtained from a population of 12 041 piglets from 965 litters[129]. (■), Total born piglets; (□), live-born piglets.

defined by using the several criteria suggested[132–134]. The utilisation of the low-BW piglet as a model for IUGR is not a recent idea[135], but then was suggested by other authors[135–138].

Naturally occurring and environmentally induced IUGR is well documented for livestock, including cattle, goats, horses, pigs and sheep. Despite improvement of management techniques and research on nutrient requirements, IUGR remains a significant problem in livestock production because of our incomplete knowledge concerning the impact of nutrition on the mechanisms regulating fetal growth. In an elegant review, Wu *et al.*[139] have examined these phenomena (causes and consequences) and the mechanisms involved (including fetal programming) and presented several potential solutions to prevent IUGR. In human medicine, runt piglets have been used in studies of very low BW and its consequences[140].

In our opinion, the most promising model for the 'human mother–infant' dyad is the 'sow–piglet' dyad. This model allows studying the effects of nutritional programming on the development of GIT functions (Table 4). In the following we present data on how IUGR affects development and health mainly in piglets and, wherever data are available, comparison is made with man.

Weight and length of organs. IUGR piglets need more time to reach a similar BW than AGA piglets. For instance, 23 extra days are necessary for Yorkshire or Yorkshire crossbred IUGR pigs to reach 107 kg of BW[141,142]. IUGR in piglets does not have a uniform effect on all internal organs. In newborns, the relative weights of internal organs (salivary glands, stomach, small intestine, colon, liver, spleen, kidneys and heart) are lower in IUGR compared with normal piglets[138,143]. This suggests that mass accretion of different organs of the IUGR fetus during pregnancy was symmetrically restricted[136–138,143]. The length of the small intestine relative to BW in IUGR pigs is 23–55 % greater than that in normally grown animals and the small-intestinal weight:small-intestinal length ratio is only 61–76 % of that of normal pigs. This suggests that the effect on intestinal weight is greater than that on intestinal length[138,143].

Stomach. The thickness of the stomach wall and *muscularis externa* is less in IUGR piglets compared with controls, and the depth of gastric glands is decreased, but the percentage of gastric mucosa occupied by parietal cells is the same[138]. The gastric pits in IUGR piglets are deeper than those of normal piglets, and hyperplasia

Table 4. Studies examining the effects of intra-uterine growth retardation (IUGR) on several parameters

Species and studied parameters	Stage or age	Remarks	References
Piglets			
Body weight, organ size, organ function	Newborn		155, 183
Organ weight (including pancreas), body-glucose turnover	4–28 d Neonate		136, 137
Growth	Fetus		131
GIT development			143
GIT and pancreas development			138
Endocrine and exocrine pancreas	6–8 weeks	Growth retarded after birth	223
Organs (including digestive organs) and muscle weight, protein and DNA composition		Runt, SGA and and normal-birth-weight neonates	146
Cholesterol concentration	Fetus	Light and heavy fetuses	224
Postnatal growth, body fat depth, plasma leptin and other hormone concentrations, insulin sensitivity	Juvenile and adult	Two birth-weight classes	149, 150
Growth and carcass composition	Adult	Four birth-weight classes	142
Skeletal muscle and adipose cellularity	Adult	Runt and normal birth weight	225
Growth and skeletal muscle	Adult	Runt	141
Protein synthesis	Newborn		221, 222, 226
Infants			
Intestinal length	Fetus		227
Postnatal visceral and cerebral blood flow velocity	1, 3 and 7 d	IUGR, SGA, normal birth weight	228
Aetiology, morphology and body composition	Birth and first months	SGA and IUGR	229
Kidneys, liver and spleen volumes	Infant	AGA and SGA	230

GIT, gastrointestinal tract; SGA, small for gestational age; AGA, appropriate for gestational age.

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is clearly evident around the gastric pits in IUGR piglets, indicating deceased wall protection[143].

Pancreas. IUGR appears to have a severe effect on the pancreas, which was smaller in size relative to BW. This seems to be due to reduced cell numbers, as indicated by the lower DNA content, and decreased acinar cell size, as confirmed by histological examination. The lower protein:DNA ratio could reflect smaller cell size, fewer zymogen granules stored within the cytoplasm or less protein synthesis by the rough endoplasmic reticulum. Adding the lower lipase activity, all these data indicate an impairment of pancreatic exocrine cell function associated with IUGR[138]. This is in agreement with reports in infants with IUGR where trypsin and mainly lipase activities decrease in duodenal juice[144]. Faecal chymotrypsin concentration is lower[145], suggesting that activities of these last enzymes can be a limiting factor for optimal digestion.

Small intestine. IUGR is associated with a proportionately greater length but thinner small-intestinal wall. The small-intestinal surface in IUGR piglets is reduced compared with in normal pigs mainly due to a lower average number of villi per unit of area and a lower height of the villi[138,143,146]. In contrast, intestinal crypts are deeper in IUGR piglets (P Guilloteau, M Mickiewicz, CC Metges and R Zabielski, unpublished results). Consequently, the loss of intestinal absorptive area is associated with the precocious occurrence of maltase and sucrase activity in the mucosa, although the specific lactase activity per unit tissue mass is not affected[137]. The size of the villi seems not to be a reliable marker of gut maturation, since the level of food intake affects villus size but without major effects on maturation[147].

Metabolism. Both the rate of glucose utilisation and the total body-glucose pool size are reduced in IUGR piglets, but they seem to be appropriate for their reduced BW[137]. In a number of studies in SGA pigs, Poore & Fowden[148–150] have demonstrated the negative effects of low birth weight on glucose metabolism and body composition in juvenile and young adult pigs. Our own studies demonstrated that glucose tolerance was impaired in adolescent pig offspring born to sows fed an inadequate level of dietary protein during gestation[151]. In a Finish survey, SGA infants who had a BW in the highest quartile at 3 and 6 months of age had a 1·5-fold risk of type 1 diabetes later in childhood[152].

Body composition. Body composition in normal piglets has been studied[153] and can be used as a reference. At a similar adult BW, IUGR and control piglets show similar length of three bones (femur, tibia and fibula)[141]. The growth potential of some of the skeletal muscles of the IUGR pigs appears to be limited by the apparent decreased number of muscle fibres and by the physiological limits on fibre hypertrophy. Long term, the muscles of the IUGR piglets seem more mature than in controls. This observation is confirmed by a greater quantity of intramuscular fat. Thus, *in utero* development associated with the generation of IUGR pigs results in postnatal effects on growth and composition of some porcine muscles[141,154,155].

Regulation. Elevated plasma gastrin and somatostatin levels in infants with GIT diseases when compared with normal infants[156] could explain, in part, some observations in GIT modifications. The expression levels of growth hormone receptors and insulin receptors tend to decrease and that of IGF-1 in IUGR piglets is lower than that in normal pigs. This might be related to lower insulin and growth hormone levels in plasma[143]. Notwithstanding the reported association of IUGR with later developmental disorders and increased health risks, birth weight is just one parameter to measure intra-uterine development. This has to be considered in view of the fact that effects of nutritional programming have been described without association to IUGR[157].

Large for gestational age

Fewer scientific reports are available on the effects of LGA in human neonates and piglets than for SGA or IUGR. However, a growing body of evidence from epidemiological studies in human subjects suggests that a high BW at birth (mainly offspring of obese women[158]) has health consequences during later life. As an example, heavy BW during infancy has been implicated as a risk factor for type 1 diabetes[159,160]. Mothers of LGA babies have a higher level of glycated Hb (HbA1c) of dense erythrocytes and a higher maternal BMI, which are independent factors that affect fetal oversize. LGA infants may be a consequence of maternal hyperglycaemia in late pregnancy which is not detected by the routine screening test for gestational diabetes mellitus[157].

A study of Japanese newborns found the morbidity rate of newborns excluding idiopathic hyperbilirubinaemia to be 10 %, which increased with gestational age and was accompanied by an increment of birth trauma. The main causes of hospitalisation of LGA neonates are associated with difficulty at delivery due to their heavy weight. In addition, neonates of BW over 3·75 kg have a higher morbidity rate[161].

In a population of 190 children (age 9 years) of known height, weight and size at birth, the highest urinary excretion of glucocorticoid metabolites was found in children who were either light (SGA) or heavy (LGA) at birth. These findings suggest that the intra-uterine environment, as measured by fetal size at birth, has long-lasting effects on the function of the hypothalamo–pituitary–adrenal axis[162]. Body composition was examined in infants and young children, aged 2–47 months[127]. The LGA infants remained larger in size through early childhood but the discrepancies in BW are primarily attributable to differences in lean body mass (muscularity), since fatness was less affected. Thus, based on the fatness indicators used at any given BW for these infants and children, percentage of body fat appears to be relatively lower for children who were LGA at birth[127].

In regard to long-term effects, an epidemiological study in adults (18 years) observed a positive association between birth length and adult BW that was stronger than between birth BW and adult BW. These associations appear the strongest among individuals born at gestational age 39 to 41 weeks. Length and BW at birth each contribute

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independently to adult stature and BW. The increase in adult BW per relative BW category was greatest for infants who are born heavy and long at birth[163]. Moreover, early postnatal growth is strongly influenced by BMI at birth[164], but large BW newborns become fat adolescents only when their mother or father is also overweight or fat (i.e. has either a high BMI or large skinfold thickness), suggesting that fatness during adolescence is related to parental fatness but not to prenatal fatness[165]. High birth BW of women could increase the incidence of breast cancer after delivery; thus, there is evidence of greater risk with greater BW or BW $\geq$ 3–3·5 kg *v.* BW $<$ 3·5–3·75 kg[166–168]. These results suggest that the effect of birth BW on breast cancer risk may be modulated by childhood events[167] and are compatible with the hypothesis that the hormonal level during pregnancy influences the risk of breast cancer in the years closely following delivery[166].

Our objective in this part of the review is to suggest the 'LGA piglet–sow' dyad as a model of the human 'LGA mother–infant' dyad to study the effects of nutritional programming at short, medium and long term in the development of GIT functions. In the pig, no studies have been reported in regard to the GIT for LGA since IUGR is among the most important problems related to pig production. More generally, to our knowledge, there are almost no studies on nutritional programming of offspring from overweight sows on one hand and studies on long-term effects of being LGA are missing on the other hand. Only two studies came to our attention evaluating the effect of high birth weight on later health and performance. Gwatkin & Annau[169] have compared resistance of light and heavy birth BW pigs to rhinitis under natural conditions. More recently, Wolter *et al.*[170] have evaluated the effect of weaning weight as affected by birth BW and feeding a supplemental liquid milk replacer diet during lactation on pig performance from weaning to a common slaughter weight. Thus, to date the comparison between the two species is not possible. Thus, we suggest more experimentation in this field to obtain data in swine and to verify that the results are in agreement with the hypothesis coming from epidemiological studies dealing with LGA infants.

Other benefits and limitations of swine and the 'sow–piglet' dyad

Nutrient needs are well known for healthy humans and pigs[86,171]. As an example, distribution of a protein-enriched supplemental diet to IUGR infants permits catch-up growth which is believed to be beneficial for the nervous system but which could result in the appearance of nutritional diseases in the adult. Thus, after the characterisation of the abnormal type of BW (SGA and LGA), it would be useful to perform experiments with the objective of determining adequate nutrient needs for these populations.

Relative to man, pigs have a shorter gestation (114 d), and produce large litters with the result that piglets from the same litter can be divided among several experimental groups. Sows have two or more gestations per year with a relatively long duration of gestation and fetal and neonatal development closer to human than altricial species. As shown in Table 2, the generation cycle (pregnancy and offspring development to adult stage) is relatively short (1 year). Thus, the pig model allows exploration of nutritional programming at short, mid and long term as well as the mechanisms involved including the intergenerational effects.

The pig has the added benefit of a body size that allows surgical manipulation and a GIT that is relatively easy to handle. In considering ethical aspects, the utilisation of pig models presents fewer constraints as compared with using non-human primates. The pig species offers the advantage of having a GIT that is large enough to be fistulated/cannulated to permit studies *in vivo* over a long time in the same animal. It allows the collection of adequate samples (quantity and quality) of tissues, GIT contents, and blood at different fetal and postnatal developmental stages with several animals to compare treatments since conventional pigs are not expensive.

Modern swine breeds are generated by long-term genetic selection, with the objective to obtain maximal performance in terms of meat quantity and quality. The rapid growth and mature size of these animals could be limiting factors for the porcine model (90–120 kg and 330–450 kg at age 6 months and at adult stage, respectively)[80,172]. As an example, a Large White pig weighing 100–120 kg represents an adolescent rather than an adult model (Table 2). Utilisation of minipigs with an adult BW of 70–120 kg[82] could be a useful alternative, since compared with conventional pigs, minipigs are easier to handle but currently more expensive. As an example, this model has been used to study the effects of trypsin inhibitors on protein digestibility, to compare the protein flow of endogenous and microbial origin and to estimate ileal digestibility of amino acids for feed evaluation[173].

During pregnancy, maternal–fetal exchanges occur via the placenta, which is different in swine (epitheliochorial) in comparison with man (haemochorial, as in rodent species). The human placenta is more permeable than that of the swine. However, Père[174] has compared maternal–fetal exchanges and utilisation of nutrients by the fetus in several species (rat, guinea-pig, ruminant, swine and man) but could not suggest a suitable model for man. Nevertheless, in pregnant sows, maternal–fetal nutrient exchanges can be quantified through probes and catheters inserted into the umbilical vein and femoral artery (fetus) on one hand and/or in the uterine artery and vein (fetus + placenta) on the other hand. During the 2 weeks preceding birth, this procedure permits the estimation of the quantity and quality of the nutrients supplied to the fetus and their effective utilisation[175,176]. Such techniques can be applied to AGA, IUGR and LGA fetuses since they can be easily identified in the uterine horns during surgical intervention. To use all these techniques in one study is difficult and can be simplified by only using catheters (blood sample collections), since blood flow rates are available from other studies during several stages of pregnancy[177].

Scientists now have new tools such as genomic, proteomic and metabolomic techniques. This makes it possible to elucidate and analyse simultaneously several thousands of genes implicated in multifactorial metabolic

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ways concerning the biological effects of nutrients on cellular functions as well as their consequences for neuro-immuno-hormonal regulatory mechanisms, in individuals and their descendents[178,179]. Currently, in the literature it is easier to find examples in the rat species. A study of gene expression in aorta tissue from offspring of female rats fed a lipid-enriched diet resulted in alteration in the expression of more than 200 mRNA sequences; among these were genes that coded for collagen, elastin and NO synthetase[62,180].

In summary, at birth piglets can be classified according to BW in three main classes (AGA, SGA or IUGR and LGA) in a similar way as in human neonates representing three types of intra-uterine development. It seems clear that the pattern of growth retardation in the naturally occurring IUGR piglet is very similar to that which occurs naturally in the IUGR human neonate[136,137,171–183]. This is of some practical importance in view of the dearth of suitable animal models for the investigation of health problems associated with IUGR in infants[136,140]. In the literature, few data are reported concerning the effects of LGA. Some examples show that this phenomenon can be deleterious for the offspring, suggesting that it should be further investigated. Moreover, the particularities of swine provide many opportunities to research the effects of nutritional programming that are not present in the human species. Indeed, the 'sow–piglet' dyad could be a useful tool to simulate the 'human mother–infant' dyad in studies which examine short-, mid- and long-term effects.

Conclusion

The programming concept is based on results of epidemiological studies in human subjects. Many experiments in animals (mainly using rodents as the model) have been performed to verify this hypothesis. Most of them confirm the hypothesis but others do not. Rodents belong to altricial species, which are considered not suitable as a model for man in regard to the GIT. Since most of the experiments cannot be performed in human subjects, more adequate animal models are necessary and the pig seems to be most appropriate for these purposes.

The statistical distribution of birth BW is similar in both swine and human species. With respect to nutritional programming in man, both the IUGR as well as the LGA offspring carry a higher risk for health problems later in life (short-, mid- and long-term effects). In swine, these extreme birth BW can naturally occur because of its multiparous nature. Pigs and man have many similarities in the general structure of the GIT, the digestive functions of GIT segments, and in the control of development and functions of the digestive system. In swine, we have access to three classes of piglets (AGA, IUGR or SGA and LGA) often in the same litter, providing a chance to reduce genetic effects. Nevertheless, one has to keep in mind that birth weight is a rather crude parameter reflecting intra-uterine developmental conditions.

From a GIT point of view, the utilisation of the 'sow–piglet' dyad as a model of the human 'mother–infant' dyad seems appropriate when studying the effects of nutritional programming. Some data can be found in the literature concerning GIT development around birth in the IUGR piglet, but only very few data are available at other stages of life and data are missing for high-birth-weight piglets. First, it appears that GIT development must be characterised in SGA and LGA in comparison with normal birth BW. Second, it is necessary to study the implication of nutritional programming for the GIT (ingestion, digestion, absorption, selection, defence, regulation, etc) and to understand the mechanisms implicated. Since the GIT is of paramount importance to nutrient uptake and due to the lack of data on long-term effects of nutritional programming in the GIT, effects due to early-life nutrition must be explored in this organ system.

The results obtained from the suggested research, associated with the data currently available, will give us a better understanding of some of the biological mechanisms that explain, at least in part, the observational association between nutritional programming and resulting morbidities in adults such as hypertension, cardiovascular diseases, obesity and diabetes. Eventually, this knowledge will also lead to nutritional recommendations and therapies for prevention and treatment after validation in human subjects.

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