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Review

Endocrine regulation of gut maturation in early life in pigs

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ABSTRACT

After birth, the newborn must adapt to the acute challenges of circulatory changes, active respiration, thermoregulation, microbial colonization, and enteral nutrition. Whereas these processes normally occur without clinical complications in neonates born at term, birth at a preterm state of gestation is associated with high morbidity and mortality. In commercial pig production, perinatal mortality is higher than in any other mammalian species. Asphyxia, hypothermia, hypoglycemia, sepsis, and gut dysmotility, represent some of the most common findings. The intestine is a particularly sensitive organ after birth, as it must adapt acutely to enteral nutrition and microbial colonization. Likewise, during the weaning phase, the intestine must adapt to new diet types. Both critical phases are associated with high morbidity. This review focuses on the endocrine changes occurring around birth and weaning. There are a number of endocrine adaptations in late gestation and early postnatal life that are under influence of development stage and environmental factors such as diet. The review discusses general endocrine changes in perinatal life but specifically focuses on the role of glucagon-like peptide-2. This gut-derived hormone plays a key role in development and function of the intestine in early life.

1. Introduction

The porcine gestational length is relatively short (115–118 d), and the number of offspring is relatively large compared with humans, cows, and horses. On the other hand, porcine gestational length is relatively long compared with more altricial species such as rodents and carnivores. However, the intermediate nature of porcine gestational length cannot be taken directly as an indicator of degree of maturity at birth. Newborn pigs are able to stand and walk and have a well-developed neuromuscular system at the time of birth, compared with, for example, human infants. In contrast, human infants may have a more developed gastrointestinal system and are more immunologically protected, partly due to transplacental transfer of maternal immunoglobulins. From this notion, cross-species comparisons need to be organ-specific and must be done with some caution as there will be both similarities and discrepancies in any such comparison.

Specifically for the intestine, surprisingly, little is known about what regulates adaptation prenatally and postnatally. Numerous hormones are known to influence intestinal adaptation, of which glucocorticoids are key regulators [1,2]. Intestinal maturation in rats primarily takes place postnatally, whereas farm animals such as the porcine are more mature at birth [3]. The maturity at birth is associated with a gradual increase in fetal plasma corticosteroids, followed by a peak on the day of parturition [4]. Corticosteroids play a pivotal role in maturation of the gut, lungs, and brain and are commonly used to treat pregnant women with anticipated preterm delivery to accelerate fetal organ maturation.

After birth, the endocrine system continues to develop. Ingestion of the first milk, that is, colostrum, provides many hormones and regulatory peptides that support the neonate in the early days. Although the intestine absorbs intact proteins and peptides via endocytosis during the first

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1 to 2 postpartum days, it is not clear whether plasma hormone levels in the newborn pig, are the result of absorbed colostrum components or own endogenous production [5]. One study demonstrated an increase in plasma levels of anabolic hormones with increasing intake of colostrum [6], but whether this association reflects increased absorption of non-nutritive factors or increased endogenous responsiveness to nutritive factors in colostrum remains largely undetermined. Approximately 40 gut-derived peptides have been identified so far [7], providing effects on both the gut and other organs. Some of the important actions of regulatory peptides that relate to the gastrointestinal tract, include regulation of gastric emptying (motilin, gastrin, cholecystokinin [CCK]), regulation of digestion and transit time (CCK, secretin, gastric inhibitory polypeptide [GIP], motilin, GLP-1, and neurotensin), and intestinotrophic effect (GLP-2). The list is much longer but suffice it to say that these and other factors are released in response to ingestion of a meal and provide a coordinated regulation of the digestive process that follows. The fat-responsive hormone motilin is secreted from enteroendocrine M-cells in the duodenum and jejunum [8]. As the name indicates, this hormone has its main effect on gut motility and plays a key role in the initiation of the intestinal migrating motor complex. Other regulatory peptides, CCK, secretin, and gastrin, are simultaneously secreted from the same anatomical location (distal stomach, duodenum, and jejunum) and have supplemental effects on motilin [9]. Gastrin is released in response to luminal nutrients and stimulates gastric acid secretion as well as having trophic effects on the gastrointestinal mucosa. The primary actions of CCK and secretin are to stimulate enzyme and bicarbonate secretion from the pancreas, whereas their secondary actions are to inhibit gastric emptying (CCK) and stimulate biliary bicarbonate secretion (secretin). GIP and GLP-1 both inhibit gastric secretion and emptying although they are secreted from different anatomical sites in the gut, that is, GIP is released from enteroendocrine cells in the duodenum and jejunum, whereas GLP-1 and its sister-compound GLP-2 are primarily secreted from more distal parts of the small intestine. These peptides are both derived from the proglucagon gene and are discussed in more detail in the following sections.

2. Proglucagon and its peptide derivatives

The proglucagon gene is expressed in pancreatic α-cells, and enteroendocrine L-cells are primarily localized in the distal small intestine. Whereas posttranslational processing in the pancreas results in several fragments including glucagon, posttranslational processing in the intestine results in a different set of peptide fragments. These include GLP-1, GLP-2, intervening peptide-2, glicentin, glicentin-related pancreatic polypeptide, and oxyntomodulin. Although it follows that GLP-1 and GLP-2 are derived in an equimolar ratio, it is unclear whether the coordinated nature of their release from enteric L-cells has an important physiological rationale. This should be addressed in future studies with co-infusion of GLP-1 and GLP-2. The best-known effects of GLP-1 include delayed gastric emptying, trophic effects on pancreatic β-cell mass, and higher insulin-sensitivity in peripheral tissues [10]. In contrast, GLP-2 effects have mainly been demonstrated on the intestinal mucosa, although some effects on bone [11] and neuronal tissue [12,13] have also been shown. Although the effects of these 2 peptides may seem distinct, recent data indicate that GLP-1 can also exert some intestinotrophic effects [14] although this peptide was largely thought to stimulate pancreas function and control glucose homeostasis.

Presence of luminal nutrients, in particular, fat and carbohydrate and to a lesser extent protein, in the distal small intestine, stimulates enteroendocrine L-cells in the gut epithelial layer to release GLP-1 and GLP-2 [15]. Enteroendocrine cells in the gut express G-protein–coupled receptors that are activated by luminal nutrients, as reviewed in detail by Raybould [16]. Although this mechanism is partly thought of as an ileal break to signal satiety, L-cells are also under influence of compounds not directly related to satiation. In this context, the stimulatory effect of luminal bile acids on GLP-2 secretion, has received some attention (discussed later) [17].

3. GLP-2 effects during perinatal gut development

The intestine grows rapidly during the last 3 wk of gestation, which coincides with a gradual increase in fetal plasma GLP-2 [18]. During the first 24 h after birth, there is a very large increase in gut weight, which also coincides with a transient increase in plasma GLP-2 [18]. It is likely that this rapid increase in gut weight in pigs in the immediate postnatal period is driven by ingestion of milk and GLP-2 release. It has further been shown that postnatal GLP-2 release and gut growth is lower during total parenteral nutrition where nutrients are supplied intravenously and therefore bypass the gut mucosal surface where GLP-2 secreting cells are located [19]. Although some hormone levels peak as a result of the birth process per se, the aforementioned study indicates that the postnatal peak in GLP-2 is mainly driven by ingestion of enteral food. As a further substantiation of this point, it has been shown that fetal secretion of GLP-2 and gut growth during late gestation is responsive to enteral nutrition [20]. In their study, fetuses were surgically equipped with esophageal catheters allowing in utero enteral nutrition from an ex utero source. Enteral nutrition of fetuses resulted in elevated plasma GLP-2 levels and had a trophic effect on the intestine [20]. However, despite the nutrient responsiveness and its association with GLP-2, the fetal intestine is largely unresponsive to supraphysiological treatments with exogenous GLP-2 [21]. This is in contrast to studies with both premature and mature neonatal pigs that show positive effects on gut growth in response to pharmacologic doses of GLP-2 [22–25]. Expression levels of the GLP-2 receptor are not lower in fetal pigs compared with neonatal pigs [18], but given their continuous intravenous nutrition via the umbilical cord, they may be more prone to respond to continuous release of endogenous GLP-2 rather than the more pulsatile GLP-2 release that occurs after ingestion of a meal after birth. Collectively, these observations suggest that GLP-2 induces intestinal growth from the last 3 wk of