REGULAR REVIEW

Ontogeny of human pancreatic exocrine function

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At birth pancreatic exocrine function is far from mature and, like many other organ systems of the newborn, undergoes rapid development during early life. Knowledge of the functional capacity of the human pancreas during the perinatal period has important implications for the feeding of neonates, especially those born preterm or who are retarded in growth, and for making recommendations about the timing of introduction and the composition of weaning foods. Much of our knowledge has been derived from animals, but there are dangers in applying information gained therefrom to humans. In this review we summarise what is known about the ontogeny of the human pancreas, and refer to animal experiments only when no information is available about humans.

Embryology and morphological development

The human gut develops from an infolding of the endodermal layer of the embryo which remains in continuity with the dorsal part of the yolk sac. By four weeks after conception the intestine is tubular and two pancreatic buds have appeared as outgrowths of the lower end of the foregut. The dorsal bud, which forms most of the body of the pancreas, appears first. The smaller ventral bud, which becomes the uncinat process and part of the head of the pancreas, develops adjacent to the insertion of the common bile duct. The ventral bud and common bile duct rotate behind the duodenum and fuse with the dorsal bud. The ducts of the two buds fuse by about six weeks after conception. The main pancreatic duct is derived from the ducts of the ventral bud and the distal portion of the dorsal bud, whereas the accessory pancreatic duct, which drains the upper portion of the head of the pancreas, is derived from the proximal portion of the dorsal duct (fig 1).^{1 2}

Histologically the branching tubules can be seen to end blindly, and differentiation of acinar cells does not begin until the tenth week. The ratio of acinar cells to connective tissue increases linearly with advancing age.³ Zymogen granules appear in the apical region of the acinar cells at 14-17 weeks' gestation and are numerous by the fifth month after conception.⁴ Compared with acinar cells, duct cells are smaller and have poorly developed endoplasmic reticula, Golgi complexes, no zymogen granules, and few mitochondria.⁵ The ductal cells lining the acini are termed centroacinar cells. At 8-12

Figure 1 Diagram showing development of the pancreas. The dorsal and ventral buds are shown shortly before rotation and fusion at five weeks after conception.

weeks' gestation other primitive duct cells differentiate to form endocrine cells, which are initially located within the epithelium but later accumulate in pancreatic islets.⁶ Morphological cytodifferentiation is essentially completed before the third trimester of gestation (table).

Functional development

Enzyme activity is detectable in human fetal pancreatic tissue from before 20 weeks' gestation⁷ and pancreatic secretion begins around

Stages in the morphological development of the human pancreas

Weeks after conception	Morphological development
2-3	Infolding of endodermal layer of embryo to form gut in continuity with yolk sac
4	Intestine tubular. Two pancreatic buds present
5-6	Ventral bud rotates behind duodenum and fuses with dorsal bud
7	Gross morphology complete
10-14	Differentiation of pancreatic acinar cells, ductal, and endocrine cells
12-15	Zymogen granules appear

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Figure 2 Time of first appearance, rate of development, and age at which childhood levels of pancreatic enzymes are achieved. Numbers in parentheses refer to references in text. The percentage of childhood enzyme levels at birth is shown.

the fifth month.⁸ Each enzyme appears and develops in an individual manner (fig 2).

PROTEASES

Proteolytic activity is present in the pancreatic tissue of the fetus from 500 g in weight (around 22 weeks' gestation),⁹ but enterokinase, the enzyme responsible for the conversion of trypsinogen to the active enzyme trypsin (which in turn activates chymotrypsin, elastase, and carboxypeptidase) has not been detected in the small intestinal mucosa of fetuses before 26 weeks' gestation, and at birth its activity is still only 17% of that found in 1–4 year old children.¹⁰ Chymotrypsin, however, is detectable in the stools of preterm infants from 23 weeks' gestation¹¹ and protein digestion in the preterm neonate is adequate.¹² This may be aided by the early appearance of pepsin in the stomach (16 weeks)⁷ and mucosal peptidases of the small intestine (from eight weeks), some of which reach adult levels by 16 weeks' gestation.¹³

Trypsin activity increases gradually during fetal life to reach almost 90% of childhood levels by term.¹⁴ Its activity continues to increase during the first three weeks after birth, but thereafter does not vary much with age.¹⁵ In contrast, at birth chymotrypsin and carboxypeptidase B activities are less than 60 and 25% of childhood levels respectively.¹⁴

AMYLASE

α -Amylase activity has been detected in the pancreas of 50% of fetuses aborted at 22 weeks' gestation, but it remains negligible throughout fetal life and is still undetectable in the pancreas of 50% of full term abortuses.⁷ It has been suggested that in these earlier studies salivary rather than pancreatic

amylase was measured; more recent investigations have not detected pancreatic amylase until 1 month of age.^{14 16} Other sources of amylase activity in the newborn infant include salivary amylase, detectable from about 20 weeks' gestation.¹⁷ Its activity is still low at birth, but increases rapidly, reaching adult levels by the third month after birth.¹⁸ Amylase is also present in various amounts in human milk and may aid the digestion of starch in weaning foods.¹⁹

LIPASES

Several pancreatic enzymes play a part in fat digestion: pancreatic lipase, phospholipase A₂, cholesteryl esterase, and the coenzyme co-lipase. Most studies of the development of pancreatic function have focused on lipase activity. This appears at 32 weeks' gestation⁷ but is still low at birth (less than 10% of childhood levels).¹⁴ Activity increases rapidly from 10 weeks after birth.¹⁵ The relative deficiency of pancreatic lipase at birth, plus the low concentrations of bile salts in the neonatal duodenum,²⁰ suggest that pancreatic lipase is less important in the digestion of fat in newborn infants than in older children and adults. Lingual and gastric lipases are detectable from at least 26 weeks' gestation²¹ and by birth they can hydrolyse 60–70% of ingested fat in the absence of pancreatic lipase.²² Thereafter, lingual lipase activity decreases with increasing age.^{21 23} Lipase and esterase activity are also present in breast milk and the presence of these enzymes accounts, at least in part, for the greater fat absorption in neonates who receive human milk over those receiving formula milk.²⁴

FLUID AND ELECTROLYTES

The development of fluid and electrolyte secretion in humans has rarely been investigated. Lebenthal and Lee noted a minimal pancreatic secretory response to intravenous secretin in preterm and term infants under 1 month of age, which was more substantial at 2 years of age.¹⁴ Culture of a pancreatic rudiment from a 13–15 day old fetal rat resulted in the development of a large fluid filled cyst of mainly duct origin.⁶ Similarly culture of the epithelial component of a 12 day old rat pancreatic rudiment in the presence of cyclic AMP resulted in the appearance of fluid filled cysts,²⁵ suggesting that fluid and electrolyte secretion occurs well before birth in the pancreas of the developing rat (gestation period 21 days).

Effect of nutritional status on the development of the pancreas

The structural and functional development of the pancreas is influenced by the nutritional status of the subject. Prenatal malnutrition leads to intrauterine growth retardation. In animal studies, placental insufficiency led to decreased pancreatic weight and reduced amylase and lipase, but normal protease con-

tent in newborn rat pups.²⁶ Similarly, preprandial, unstimulated activities of lipase in the duodenal fluid of human infants born small for gestational age were reduced compared with appropriately grown controls.²⁷ Stool chymotrypsin is also reduced in intrauterine growth retarded infants,¹¹ but trypsin activity remains within the normal range.²⁷

Similar results were obtained from duodenal intubation studies of human infants with malnutrition.²⁸⁻³³ When malnutrition is mild or of limited duration the secretion of bicarbonate and proteases is preserved and enzyme activities return to normal following nutritional rehabilitation.³¹⁻³³ In chronic or recurrent malnutrition the protease enzymes are depleted³¹ and refeeding does not result in the recovery of function.²⁸⁻³² There is evidence that 'healthy' children in some West African communities have decreased pancreatic enzyme secretion compared with healthy European children, suggesting that chronic suboptimal nutrition has a long term adverse effect on pancreatic development.³¹⁻³² In developed countries malnutrition secondary to malabsorption may have a reversible deleterious effect on pancreatic exocrine function.³⁴

These functional effects of malnutrition are reflected in structural changes of the pancreas. The lesions include acinar cell atrophy, with decreased numbers of zymogen granules and variable degrees of fibrosis.³⁵ Electron microscopy of the pancreatic cells shows abnormalities of the rough endoplasmic reticulum, decreased numbers of mitochondria and the presence of cystic vesicles and lysosomes.³⁶ Structural recovery occurs over several weeks but fibrosis and atrophy may persist in children with chronic malnutrition.

Weaning

Changes in the pattern and extent of pancreatic enzyme secretion occur at weaning with the introduction of a non-milk diet. In weanling rats diets rich in carbohydrates resulted in increased amylase activity,³⁷⁻³⁸ whereas a high fat diet promoted increased lipase,³⁷ and a high casein diet increased trypsinogen activity.³⁷ In human preterm infants, milk enriched with starch stimulated the appearance of amylase in duodenal aspirates, and milk enriched with protein resulted in increased secretion of trypsin and lipase.³⁹ A fat enriched milk had no effect on the enzyme content of duodenal fluid.³⁹ Serial measurements of serum lipase in term and preterm infants, however, showed that by 6 to 12 months of age concentrations were higher in the preterm group, suggesting that the development of lipase activity may be accelerated by feeding.¹⁵ Although dietary factors may modify the pancreatic exocrine response at weaning, they do not appear to be the primary signal for the postnatal increase in pancreatic enzymes. A persistent increase in amylase activity was noted in rats undergoing prolonged nursing even though they were

obviously not ingesting dietary starch.⁴⁰ It is more likely that dietary factors modulate an inherent genetic programme of postnatal pancreatic development.⁴¹

Endogenous factors and the development of pancreatic function

Studies of animals show that humoral and neuroendocrine factors modify the growth and enzyme activity of the developing pancreas.⁴² No information is available about the effect of these factors on the human pancreas.

Corticosterone and thyroxine appear to have important and synergistic roles in modifying the secretion of pancreatic enzymes, especially around the time of weaning when serum concentrations of the hormones and the numbers of pancreatic receptor sites are at their highest. These effects are also influenced by hypothalamic function.

Several gastrointestinal hormones are thought to modify postnatal pancreatic development. Cholecystokinin has been studied most extensively, and although reports of its effect on prenatal pancreatic growth conflict, they do not suggest that circulating cholecystokinin enhances enzyme activity in the fetal pancreas at term.⁴³ Although immunohistochemical techniques have revealed cholecystokinin containing cells in mucosa from the human fetal small intestine, owing to the lack of a reliable assay for cholecystokinin circulating concentrations in human neonates have not been measured.⁴⁴ Intravenous infusion of cholecystokinin in human infants does not result in significant pancreatic exocrine secretion before the age of 2 years, however.¹⁴ This may be due to decreased concentrations of high affinity binding sites for cholecystokinin in the pancreas of newborn infants, or to low concentrations of intracellular mediators of secretion. Animal studies suggest that a combination of these factors is responsible.⁴⁵⁻⁴⁷

Conclusions

The human pancreas appears anatomically and histologically mature by full term but enzyme secretion is still immature, and readily influenced by several exogenous and endogenous factors. With its high rate of protein synthesis and turnover, the pancreas is particularly vulnerable to undernutrition and other adverse effects on cell replication and secretion. These factors may modify the development of pancreatic function, both before and after birth, but how they interact with the genetic control of events in pancreatic ontogeny remains to be elucidated. It is likely that early life, during the transition from intrauterine nutrition to milk and then solid feeding, is a critical period in the development of the digestive system, and that the amount and composition of the diet may be factors which influence pancreatic function not only during the short term, but also in the long term.⁴⁸

In infancy non-pancreatic sources of digestive enzymes (lingual and gastric lipase,

salivary amylase, and breast milk enzymes) are important, particularly if pancreatic enzyme activity is depressed by malnutrition. In these circumstances prolonged breast feeding into the second year of life not only provides energy and other nutrients, but also significant additional enzyme activity to aid the digestion of weaning foods.⁴⁹

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