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A comprehensive review on *in vitro* digestion of infant formula

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ABSTRACT

Although mothers' milk is the best food for babies, infant formula has become an alternative when breastfeeding is not possible or inadequate for babies. To design a proper formula for babies, understanding digestibility of macronutrients and their bio-accessibility in the gastrointestinal tract is essential. *In vivo* gastrointestinal studies on human infants are restricted by ethical constraint, cost issues, and intensive resource. However, in vitro models offer many advantages with low cost, easy sampling accessibility and no ethical issues. This article aims at reviewing the main aspects of the infant physiological gastrointestinal tract and providing an insight on recent in vitro research on infant formula.

Contents

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1. Introduction

Infants are the people under the age of 12 months and infant formula is a product presented as mothers' milk substitute, which satisfies the nutritional requirements of infants up to four to six months of age (Australia Government, Commonwealth Law, 2000). Mothers' milk is the best food for adequate growth and development of infants as it contains a balance of essential nutrients and specific bioactive components such as growth factors, immune factors and enzymes that are explicitly available only in mothers' milk (Alles, Scholtens, & Bindels, 2004). Infant formula forms a substitute only when breast milk is inadequate or ceases for some reason. At present, due to the advances in food technology and engineering, the main targets of current infant formula have been supposedly met from the point of view of safety for infants and the composition in macro-nutrients (protein, fat, and carbohydrates) and micro-nutrients (vitamins and minerals) comparable to mothers' milk (Hernell, 2011). However, there can be differences in outcomes in growth and development patterns between breast-fed infants and formula-fed infants in both the short and long term. For instance, formula-fed infants gain weight faster and have more body fat from 3 months of age; have different gut microbiota; and also have higher concentration of serum amino acids, insulin, blood urea nitrogen compared to breast-fed infants. These factors are related to higher risk of obesity, diabetes, and cardiovascular disease (Lönnerdal, 2014). Ideally, both breast-fed and formula-fed infants should show similar growth and development patterns (Lönnerdal, 2014). To achieve this goal, modifications of nutrients in infant formula with clinical trials are being carried out (Lönnerdal, 2014). Alongside this, there is a need to study the digestibility of various ingredients supplemented in infant formula to better understand the degradation mechanism of these components as well as the bio-accessibility of the digested nutrients in the gastrointestinal tract. Application of in vitro models to simulate digestion through the gastrointestinal tract has become widely more popular than obtaining data from in vivo experiments due to no ethical restrictions, low cost, and less time requirements. The in vitro models help observe the digestibility, structural changes, and the release of nutrients under simulated gastrointestinal digestion (Hur, Lim, Decker, & McClements, 2011).

2. Digestion in infants with comparison to adults

Mothers' milk and infant formula, the main food for infants, are a rich source of proteins, fats and carbohydrates. The digestion of these ingredients provides the essential nutrients for the growth and development of babies. The knowledge of infant gastrointestinal function plays an important role in infant feeding application and has advanced rapidly over the past few decades (Friedt & Welsch, 2013; Lebenthal, Lee, & Heitlinger, 1983).

Digestion process in infants aged between 0–6 months who exclusively consume liquid milk does not happen at the oral phase due to the very short transit time through the mouth, pharynx and oesophagus (10–15 s) (Arvedson & Brodsky, 2002). Therefore, infant digestion of macronutrients mainly occurs in the gastric and intestinal phases. Although it is clear that the gastrointestinal system is quite mature in full-term newborns (newborns are human infants in the first 28 days of life; WHO), the availability of some digestive enzymes, their concentration, and gastric pH are different between infants and adults (Bourlieu et al., 2014). The digestive enzymes are salivary amylase secreted by the salivary gland, pepsin and gastric lipase secreted by human gastric mucosa, pancreatic enzymes, and brush border mucosal enzymes (Hamosh, 1996; Moreau, Laugier, Gargouri, Ferrato, & Verger, 1988). The pancreatic enzymes contain proteases (trypsin, chymotrypsins, etalastase, carboxypeptidases) and lipases (colipase-dependent lipase, carboxyester lipase, pancreatic lipase related proteins, bile salt dependent lipase). Brush border mucosal enzymes contain lactase, glucoamylase, sucrase and isomaltase which hydrolyse carbohydrates (Hamosh, 1996). Table 1 summarises and compares the activities of the digestive enzymes found in the gastrointestinal tract of both adults and infants.

Infant gastric pH is less acidic compared to that of adults. It has been reported that gastric pH in pre-term infants varied from 3.2 to 3.5 before feeding and raised to 6.0–6.5 immediately after having a meal (Bourlieu et al., 2014). In an earlier study Nagita et al. (1996) observed a gastric pH of 3.0–4.0 in newborns (under 28 days old) and 1.5–3.0 in infants (under 12 months old) during fasting. Fig. 1 shows that the pH in the infant's stomach increases from 3.5 to 6.4 before and after 30 min of feeding with mothers' milk and then decreases to above pH 3 after 180 min of gastric digestion (Roman et al., 2007; Mason, 1962). Cavell (1983) also observed a decrease in pH of infant gastric content 6.0 (after 30 min of feeding) and further decreased to pH 5.2 (after 2 h of feeding). The corresponding pH figures in the adult stomach is 1.5–1.8 (Mitchell, McClure, & Tubman, 2001; Shani-Levi, Levi-Tal, & Lesmes, 2013). Thus based on the above study it is clear that after 2 h of feeding, gastric pH in the infant stomach remains between 4–5, while the pH for adults is lower than 2 which has also been reported by Li-Chan and Nakai (1989). Table 2 summarises the pH change after 1 h of feeding for infants of different ages. In

Table 1
Gastrointestinal enzymes in infants and their activity compared to adults.
Adapted from Lebenthal et al. (1983), Hamosh (1996), and Lindquist and Hernell (2010).

Enzymes	Contribution to infant digestion	Activity (% of adult)
Protein digestion		
Pepsin	Low	<10
Trypsin	Adequate	10–60
Chymotrypsin	Adequate	10–60
Elastases	Low	NA
Carboxypeptidases (A and B)	Adequate	NA
Lipid digestion		NA
Gastric lipase		100
Pancreatic triglyceride lipase	Low	5–10
Bile salt dependant lipase	Moderate	NA
Pancreatic lipase-related to protein 2	Important	NA
Carbohydrate digestion		NA
Salivary α-amylase	Moderate	10
Pancreatic α-amylase	Absent in infants <6 months	0
Glucoamylase	High	50–100
Lactase	High	>100
Sucrase-isomaltase	High	100

NA: not available.