Nutritional and physiologic significance of human milk proteins[1–4]

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ABSTRACT

Human milk contains a wide variety of proteins that contribute to its unique qualities. Many of these proteins are digested and provide a well-balanced source of amino acids to rapidly growing infants. Some proteins, such as bile salt–stimulated lipase, amylase, β-casein, lactoferrin, haptocorrin, and α_1-antitrypsin, assist in the digestion and utilization of micronutrients and macronutrients from the milk. Several proteins with antimicrobial activity, such as immunoglobulins, κ-casein, lysozyme, lactoferrin, haptocorrin, α-lactalbumin, and lactoperoxidase, are relatively resistant against proteolysis in the gastrointestinal tract and may, in intact or partially digested form, contribute to the defense of breastfed infants against pathogenic bacteria and viruses. Prebiotic activity, such as the promotion of the growth of beneficial bacteria such as *Lactobacilli* and *Bifidobacteria*, may also be provided by human milk proteins. This type of activity can limit the growth of several pathogens by decreasing intestinal pH. Some proteins and peptides have immunomodulatory activities (eg, cytokines and lactoferrin), whereas others (eg, insulin-like growth factor, epidermal growth factor, and lactoferrin) are likely to be involved in the development of the intestinal mucosa and other organs of newborns. In combination, breast-milk proteins assist in providing adequate nutrition to breastfed infants while simultaneously aiding in the defense against infection and facilitating optimal development of important physiologic functions in newborns. *Am J Clin Nutr* 2003;77(suppl):1537S–43S.

KEY WORDS Human milk, breast milk, milk proteins, casein, whey proteins, lactoferrin, immunoglobulins, lactoperoxidase, haptocorrin, lysozyme, α-lactalbumin

INTRODUCTION

There is no doubt that the proteins in human milk provide an important source of amino acids to rapidly growing breastfed infants. However, many human milk proteins also play a role in facilitating the digestion and uptake of other nutrients in breast milk. Examples of such proteins are bile salt–stimulated lipase and amylase, which may aid lipid and starch digestion, and β-casein, lactoferrin, and haptocorrin, which may assist in the absorption of calcium, iron, and vitamin B-12, respectively. Human milk proteins also exert numerous physiologic activities, benefiting breastfed infants in a variety of ways. These activities include enhancement of immune function, defense against pathogenic bacteria, viruses and yeasts, and development of the gut and its functions.

NUTRITIONAL ASPECTS OF HUMAN MILK PROTEINS

The protein content of human milk decreases rapidly during the first month of lactation (1) and declines much more slowly after that. Most proteins are synthesized by the mammary gland, with a few possible exceptions, such as serum albumin (which appears from the maternal circulation). Milk proteins can be classified into 3 groups: mucins, caseins, and whey proteins. Mucins, also known as milk fat globule membrane proteins, surround the lipid globules in milk and contribute only a small percentage of the total protein content of human milk (2). Because the fat content of human milk does not vary during the course of lactation, the milk mucin concentration is most likely constant, although little information is available concerning this topic. The contents of casein and whey proteins, however, change profoundly early in lactation; the concentration of whey proteins is very high, whereas casein is virtually undetectable during the first days of lactation (3, 4). Subsequently, casein synthesis in the mammary gland and milk casein concentrations increase, whereas the concentration of total whey proteins decreases, partially because of an increased volume of milk being produced (**Figure 1**). As a consequence, there is no "fixed" ratio of whey to casein in human milk; it varies throughout lactation (**Figure 2**). The frequently cited ratio of 60:40 is an approximation of the ratio during the normal course of lactation, but it does vary from ≈80:20 in early lactation to 50:50 in late lactation. Because the amino acid compositions of caseins and whey proteins differ, the amino acid content of human milk also varies during lactation. This is rarely considered when estimating requirements.

The true protein content of human milk is often overestimated because of the high proportion of nonprotein nitrogen (NPN) in human milk (5). The fraction of NPN is low (< 5%) in the milk of most species, which allows a fairly accurate estimation of the true milk protein content by total nitrogen analysis. The true milk protein content is estimated by multiplying the nitrogen content of the milk by a dairy protein conversion factor of 6.38, which takes into account such a fraction of NPN. In human milk, however,

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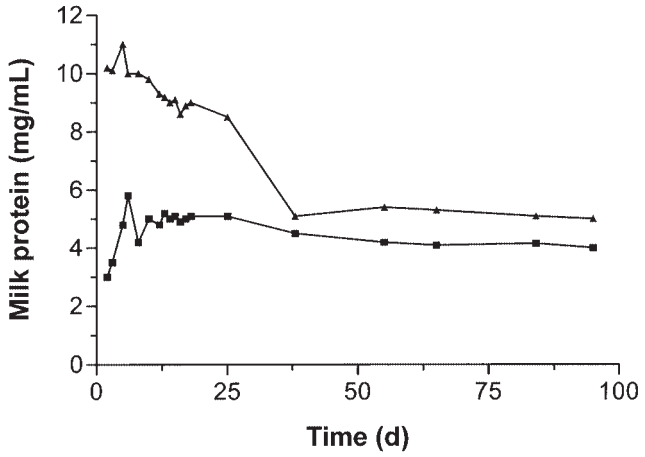

FIGURE 1. Changes in whey protein (▲) and casein (■) concentrations during lactation in one mother. Data from reference 4.

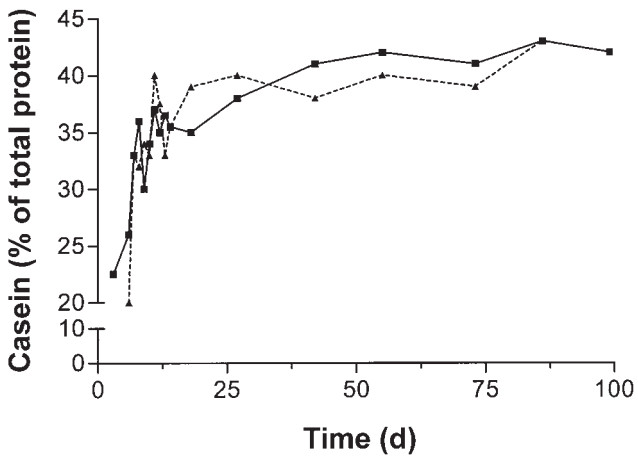

FIGURE 2. Changes in casein content as a percentage of total protein (ie, ratio of whey protein to casein) in 2 mothers during lactation. Data from reference 4.

NPN constitutes ≈20–25% of total nitrogen, and the use of the nitrogen content and a conversion factor will overestimate milk protein considerably. A more accurate approach is to determine the total nitrogen and NPN contents, subtract the NPN value from total nitrogen, and then multiply the value by the conventional Kjeldahl factor of 6.25 (6). This slightly underestimates the total amino acid equivalents because small peptides and free amino acids are included in the NPN fraction, but this amount is only a few percent of the total. It is, of course, possible to determine the precise amino acid content and the true protein content (α amino nitrogen) by amino acid analysis, but this procedure is expensive and time-consuming. True protein contents determined with the use of the "corrected Kjeldahl" method and amino acid analysis have been shown to agree closely (6).

The true protein content of breast milk, determined as described above, is 14–16 g/L during early lactation, 8–10 g/L at 3–4 mo of lactation, and 7–8 g/L at 6 mo and later (1, 4). It has been argued that these protein concentrations and, consequently, the corresponding intakes do not accurately reflect the utilizable amounts of amino acids provided to breastfed infants. This argument is based on the observation that intact breast-milk proteins can be found in the stool of breastfed infants; thus, they are incompletely digested and do not represent utilizable amino acids (7). It has therefore been suggested that such proteins [eg, lactoferrin and secretory immunoglobulin A (sIgA)] should be subtracted from the protein concentration of breast milk to derive a true digestible protein content. However, it is not correct to assume that these proteins are completely indigestible, even if they have properties that make them more resistant to proteolytic enzymes than are most other proteins. It is only a minor fraction that escapes digestion; for example, it has been estimated that 6–10% of lactoferrin is not digested by breastfed infants (7). The quantitatively most significant of the relatively indigestible human milk proteins are lactoferrin and sIgA. The total concentration of these 2 proteins in mature milk (> 30 d of lactation) is ≈2 g/L; assuming that 6–10% is undigested, there is a potential loss of ≈0.12–0.2 g/L (or ≈1.2–2.0% of total protein intake), which may be within the margin of error for the analysis used. Thus, whereas undigested, biologically active proteins may have physiologic significance for breastfed infants, the effect of the loss of these amino acids on the nutrition of infants may be insignificant.

A case could be made that biologically active peptides that are formed during the digestion of several human milk proteins, such as casein phosphopeptides, also represent indigestible protein and that they should not be included in the total protein content of breast milk. However, no such peptides have been detected in the stool of breastfed infants, and a likely scenario is that they are transiently formed during digestion in the upper gastrointestinal tract. It is possible that they may be formed in the duodenum or upper jejunum to exert their physiologic activity locally, to subsequently be completely digested and absorbed in the lower jejunum and ileum. Further experimental evidence is needed to support this scenario.

ROLE OF HUMAN MILK PROTEINS IN NUTRIENT ABSORPTION

It is well known that nutrients are utilized exceptionally well from breast milk. Several factors likely contribute to this high degree of utilization, and some of these factors may be proteins present in human milk. There are proteins that bind essential nutrients, help keep them in solution, and facilitate their uptake by the intestinal mucosa. Other proteins (protease inhibitors) may assist in this process by limiting the activity of proteolytic enzymes, thereby preserving the physiologic function of some relatively stable binding proteins. Furthermore, some enzymes can affect the digestion and utilization of macronutrients.

Activities related to digestive function

Bile salt–stimulated lipase

The presence of bile salt–stimulated lipase in human milk may aid in the digestion of lipids in newborns, particularly in preterm infants, who have low lipase activity and poor lipid utilization (8, 9). It has been shown that the heating of breast milk, which destroys the activity of bile salt–stimulated lipase, results in decreased lipid absorption in premature infants (10). It is also possible that bile salt–stimulated lipase aids in lipid digestion in term infants, because of its uniquely wide substrate specificity; it hydrolyzes mono-, di-, and triacylglycerols; cholesterol esters and

diacylphosphatidylglycerols; and micellar as well as water-soluble substrates (9).

Amylase

Breast milk contains a significant concentration of α-amylase (11). This enzyme is active also at a low pH and is relatively stable against pepsin degradation (12). Although there is no substrate for amylase in human milk, it has been suggested that amylase from breast milk may compensate for low salivary and pancreatic amylase activity in newborns and aid in the digestion of complex carbohydrates when complementary foods are being fed in close proximity to breastfeeding (13). Whether this contributes significantly to carbohydrate utilization in mixed-fed infants is not yet known.

α_1-Antitrypsin

The protease inhibitors α_1-antitrypsin and antichymotrypsin are present in human milk at concentrations that may be of physiologic significance (14). Together they may limit the activity of pancreatic enzymes in breastfed infants (12, 15), acting as natural "brake" molecules. It has been shown that some milk proteins, including α_1-antitrypsin, may escape digestion in part and are found in the stool of breastfed infants (7, 16). In vitro experiments show that the addition of α_1-antitrypsin to human milk results in a larger proportion of lactoferrin resisting proteolytic degradation (17). Although the protease inhibitor activity of α_1-antitrypsin and antichymotrypsin may have relevance for the reduced rates of digestibility of specific proteins, this may only delay their eventual breakdown because data on the total nitrogen balance of breastfed infants suggest that net protein utilization is not substantially affected.

Carrier and absorption activities

β-*Casein*

The major constituent of the family of human caseins is β-casein, a highly phosphorylated protein (18). Clusters of phosphorylated serine and threonine residues are located close to the *N*-terminal end and are capable of complexing Ca^{2+} ions (19). During digestion, phosphopeptides are formed and have been shown to keep Ca^{2+} soluble, thus facilitating its absorption (20). It is therefore likely that phosphopeptides formed from β-casein contribute to the high bioavailability of calcium from human milk. Casein phosphopeptides may also affect the absorption of other divalent cations, such as zinc (21).

Lactoferrin

A major proportion of iron in human milk is bound to lactoferrin, an iron-binding protein capable of binding 2 ferric ions (22). Lactoferrin facilitates the uptake of iron by human intestinal cells in culture, which is most likely mediated by the presence of a specific enterocyte lactoferrin receptor (23, 24). This is supported by the observation that transfection of Caco-2 cells with complementary DNA for the lactoferrin receptor significantly enhanced cellular iron uptake (24). Clinical trials with bovine lactoferrin added to infant formula have not shown any enhancing effect on iron absorption or iron status (25, 26), which may be because bovine lactoferrin does not bind to the human lactoferrin receptor (27). Usually, little information is provided in these studies about the bioactivity of lactoferrin before it is added to the formula, how the lactoferrin was added to the formula (dry blended or dissolved), and how the formula was processed (the extent of heat treatment), all of which can affect the ultimate activity of lactoferrin when fed to infants. It is also possible that a positive effect of lactoferrin is found only when it is present in breast milk; when added to infant formula, other constituents of the formula may interfere with iron utilization from lactoferrin.

Haptocorrin

Virtually all of the vitamin B-12 in human milk is bound to haptocorrin, previously known as vitamin B-12–binding protein (28). There is considerably more haptocorrin than vitamin B-12 on a molar basis, resulting in the protein being largely in the unsaturated form (29), which may be important for its antimicrobial activity (*see* below). It was shown recently that holohaptocorrin binds in a saturable manner to human intestinal brush border membranes and that haptocorrin-associated vitamin B-12 is taken up by human intestinal cells in culture (30), suggesting that haptocorrin may be involved in vitamin B-12 absorption early in life. Intrinsic factor is present in the stool of breastfed infants at young age, but its concentration is low and it may not be adequate to facilitate the uptake of vitamin B-12 via the intrinsic factor receptor (30).

Folate-binding protein

A folate-binding protein (FBP) has been found in both particulate and soluble forms in human milk (31). The soluble FBP is glycosylated to ≈22%, which may help it to survive proteolytic digestion. Folate-binding proteins have been shown to tolerate low gastric pH and resist proteolysis in newborn goats (32), and it is possible that a similar function exists in human infants. Experiments using rat intestinal cells have shown that folate uptake was higher when it was complexed to FBP than when in the free form (33), suggesting that FBP facilitates folate uptake. It has also been proposed that FBP may actually slow the release and uptake of folate in the small intestine to allow a gradual release and absorption of folate, which may increase tissue use (34).

α-*Lactalbumin*

It is known that human α-lactalbumin binds Ca^{2+} (35) and that it can also bind Zn^{2+} (36). Although the amount of calcium bound to α-lactalbumin in breast milk is only ≈1% of the total calcium content (35), it is possible that α-lactalbumin has a positive effect on mineral absorption, possibly by the generation of peptides that facilitate the absorption of divalent cations. We observed that the supplementation of infant formula with bovine α-lactalbumin increased the absorption of zinc and iron in infant rhesus monkeys (37). Whether human α-lactalbumin has an effect on mineral absorption in breastfed infants has not yet been studied.

Insulin-like growth factor– binding proteins

Insulin-like growth factors (IGFs) I and II are present in human milk (*see* below) and are primarily found to be associated with IGF-binding proteins (38). These binding proteins may protect IGF-I and IGF-II from being digested, prolong their half-life, and modulate their interaction with intestinal receptors (39). After the binding of IGF-I and IGF-II to enterocytes, they may exert activity locally and, possibly, be transported and act systemically.

ANTIMICROBIAL ACTIVITY OF HUMAN MILK PROTEINS

A multitude of proteins in human milk have inhibitory activities against pathogenic bacteria, viruses, and fungi. Some of these

proteins are likely to act independently, whereas others may act synergistically. There appears to be considerable redundancy, with several components acting on the same pathogen; this suggests a multilayered defense system that may explain the lower prevalence of infection in breastfed infants than in formula-fed infants (40).

Immunoglobulins

Several of the immunoglobulins in serum are also found in human milk, but the major type in human milk is sIgA (>90%)—a dimer of IgA linked together with a secretory component and a joining chain (41). This molecular arrangement renders the molecule relatively resistant to intestinal proteolysis (42) and, as noted above, modest amounts of sIgA have been found intact in the stool of breastfed infants (7). Concentrations are remarkably high, ≈1–2 g/L in early lactation, and remain at 0.5–1 g/L up to 2 y of lactation (41). The mother's immunity against several general pathogens can be transferred to her breastfed infant in the form of sIgA, mediated via the so-called enteromammary pathway (43). This allows the immature immune system of newborns to be "boosted" by acquired immunity in the mother. sIgA antibodies against bacterial pathogens such as *Escherichia coli*, *Vibrio cholerae*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Clostridium difficile,* and *Salmonella*; against viruses such as rotavirus, cytomegalovirus, HIV, influenza virus, and respiratory syncytial virus; and against yeasts such as *Candida albicans* have been found in breast milk (41), illustrating the breadth of this defense.

Lactoferrin

Several antimicrobial activities have been ascribed to lactoferrin (22). Originally, it was believed that lactoferrin, being largely unsaturated with iron, could withhold iron from iron-requiring pathogens because of its high affinity for iron, thereby exerting bacteriostatic activity. Although this is possible, several studies have also shown a strong bactericidal activity of lactoferrin against several pathogens, which is not dependent on the degree of iron saturation of lactoferrin (44). Some, if not all, of this activity may be the result of the formation of lactoferricin, a potent bactericidal peptide formed during the digestion of lactoferrin (45). Recent studies also showed that lactoferricin inhibits the attachment of enteropathogenic *E. coli* (EPEC) to intestinal cells (46), which appears to be mediated by the serine protease activity of lactoferrin (47). By degrading the protein structures of EPEC that are needed for the attachment and invasion of the bacteria, infection may be blocked. It therefore appears that several activities of lactoferrin contribute to the defense against bacterial infection. Lactoferrin was also shown in vitro to have activity against viruses, such as HIV (48), and fungi, such as *C. albicans* (49), but the mechanisms behind these activities are not known.

Lysozyme

One of the major components of the human milk whey fraction is lysozyme, an enzyme capable of degrading the outer cell wall of gram-positive bacteria by hydrolyzing β–1,4 linkages of *N*-acetylmuramic acid and 2-acetylamino-2-deoxy-D-glucose residues (50). Recent studies show that the addition of recombinant human lysozyme to chicken feed would serve as a natural antibiotic (51), possibly suggesting that it could replace currently used antibiotic drugs.

Lysozyme has also been shown to kill gram-negative bacteria in vitro, in a synergetic action with lactoferrin (52). By binding to lipopolysaccharide and removing it from the outer cell membrane of bacteria, lactoferrin will allow lysozyme to access and degrade the inner proteoglycan matrix of the membrane, thereby killing the microorganism.

Lysozyme has also been shown to inhibit the growth of HIV in vitro (53), but in human milk it may act on the free virus and not on cell-associated virus. The mechanism of antiviral activity is not yet known.

κ-Casein

κ-Casein, a minor casein subunit in human milk, is a glycoprotein with charged sialic acid residues (54). The heavily glycosylated κ-casein molecule has been shown to inhibit the adhesion of *Helicobacter pylori* to human gastric mucosa (55). *H. pylori* infection has been shown to occur in increasingly younger age groups, but breastfeeding seems to provide some protection. It is likely that the carbohydrate component of κ-casein is responsible for this activity because sIgA, which is also glycosylated, had similar activity, and both proteins lose their activity when deglycosylated (55). κ-Casein has been shown to prevent the attachment of bacteria to the mucosal lining by acting as a receptor analogue (56). Oligosaccharide structures on the glycans of these glycoproteins act as decoys for similar surface-exposed carbohydrate structures on the gastric mucosa, thereby inhibiting adhesion.

Lactoferrin has been shown to inhibit the growth of *H. pylori* in vitro, and it is thus possible that lactoferrin, κ-casein, and sIgA work together to limit the growth, proliferation, and adhesion of this pathogen.

Lactoperoxidase

Lactoperoxidase, in the presence of hydrogen peroxide (formed in small quantities by cells), catalyzes the oxidation of thiocyanate (part of saliva), forming hypothiocyanate, which can kill both gram-positive (57) and gram-negative (58) bacteria. Thus, lactoperoxidase in human milk may contribute to the defense against infection already in the mouth and upper gastrointestinal tract. Human milk contains active lactoperoxidase (59), but its physiologic significance is not yet known. For cow milk, however, the lactoperoxidase system has been used by the dairy industry in developing countries for decades to preserve microbial quality.

Haptocorrin

Only a small percentage of the vitamin B-12–binding capacity of haptocorrin is occupied in human milk (*see* above), leaving it in a very unsaturated form. It has been suggested that vitamin B-12–binding protein (haptocorrin) inhibits bacterial growth by tightly binding and withholding the vitamin from the bacteria (29). The structure and activity of haptocorrin was maintained after in vitro digestion with pepsin and pancreatin, indicating that haptocorrin may resist digestion in the gut. Whether this is the inhibiting mechanism, how broad its antimicrobial activity is, and whether haptocorrin quantitatively contributes to the defense against infection in breastfed infants remain to be explored. Recent studies in vitro show that both apo- and holo-haptocorrin can inhibit the growth of EPEC, but the mechanism of this vitamin B-12–independent activity is not yet known (60).

α-Lactalbumin

Few studies have focused on the potential antimicrobial activity of α-lactalbumin. However, 3 polypeptide fragments from α-lactalbumin were recently found to have antimicrobial activity

against *E. coli*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Staphylococcus epidermis*, *Streptococci*, and *C. albicans* (61). These peptides were generated after exposure to proteases known to be present in the gastrointestinal tract. This may explain our finding of an inhibitory effect of α-lactalbumin–supplemented infant formula on EPEC-induced diarrhea in infant rhesus monkeys (37). The primary structure of bovine and human α-lactalbumin is similar, but whether the same antimicrobial peptides are being formed during digestion has not yet been studied.

STIMULATION OF A BENEFICIAL GUT MICROFLORA

The bacterial flora of breastfed infants is different from that of formula-fed infants; breastfed infants have fewer potentially pathogenic bacteria such as *E. coli*, *Bacteroides*, *Campylobacter,* and *Streptococci*, but more *Lactobacilli* and *Bifidobacteria* (62). Although it is likely that antimicrobial components in human milk inhibit the growth of pathogenic bacteria, it is also likely that some substances stimulate the growth of beneficial bacteria, ie, they have prebiotic activity. This factor, originally called the bifidus factor, may promote the growth of *Lactobacilli* and *Bifidobacteria*, which can limit the growth of several pathogens by decreasing intestinal pH. One possible substance identified was *N*-acetyl-glucosamine (63). Subsequently, several oligosaccharides have been shown to have this activity (56), but it is also possible that milk proteins also have such prebiotic activity.

Lactoferrin and secretory component

Recently, bifidogenic peptides were purified by chromatography after in vitro digestion of human milk with pepsin (64). Two of these peptides were found to originate from lactoferrin and 1 from the secretory component of sIgA; the peptides were found to be stable on further digestion with pepsin, trypsin, and chymotrypsin. They were active at low concentration; the bifidogenic effect was ≈100 times stronger than that of *N*-acetyl-glucosamine, a known bifidus factor. A synthetic lactoferrin-derived peptide was shown to have as strong a bifidogenic activity as the native peptide, which verifies the results from the in vitro generation of peptides.

INVOLVEMENT OF HUMAN MILK PROTEINS IN IMMUNOCOMPETENCE

Several human milk proteins are involved in the immunocompetence of breastfed infants, either directly as described above for sIgA, or indirectly.

Cytokines

Human milk has been shown to contain several cytokines, such as interleukin (IL) 1β, IL-6, IL-8, IL-10, tumor necrosis factor α, and transforming growth factor β (65). Although all of these cytokines are immunomodulatory, it appears that most of them are antiinflammatory, thereby possibly lessening the effect of infections. The cytokines can be released from cells in breast milk but are also found in their free form. The concerted action of the potent signal molecules on the immature immune system and its variation among infants needs to be studied further, as does the suggested effect on the switch from T helper cell subset 1 (Th1) to subset 2 (Th2) and the development of allergies.

Lactoferrin

The capacity of lactoferrin to bind to its receptor in the small intestine may explain its effect on cytokine expression. Lactoferrin has been shown to increase the production and release of cytokines such as tumor necrosis factor α, IL-1β, IL-8, nitric oxide, and granulocyte-macrophage colony stimulating factor (66), which may affect the immune system. It is possible that this is caused by signaling events triggered by the interaction with the receptor, but it is also possible that internalized lactoferrin can bind to the nucleus, affecting nuclear transcription factor κB and subsequently cytokine expression (67). Recently, human lactoferrin was shown to activate the transcription of IL-1β (68), suggesting that lactoferrin may directly interact with the nucleus. The released cytokines may then have effects on immunomodulation, similar to what was described above for cytokines in milk.

DEVELOPMENT OF THE GUT AND ITS FUNCTIONS

Growth factors

Several growth factors, such as IGF and epidermal growth factor (EGF), have been found in human milk (69). IGF-I and IGF-II were shown to stimulate DNA synthesis and to promote the growth of various cells in culture (70–72), suggesting that they may promote the development of the neonatal gastrointestinal tract. Effects on intestinal mucosal growth have been shown and the development of function may be affected, as shown by stimulation of intestinal enzyme expression and maturation (73, 74). EGF has also been shown to affect the maturation of intestinal function in newborns (75), possibly by interacting with EGF receptors in the small intestine (76).

Lactoferrin

Administration of lactoferrin has been shown to increase cell proliferation in the small intestine of experimental animals and to affect crypt cell development (77). This mitogenic effect of lactoferrin has been hypothesized to be responsible, in part, for the rapid development of the intestinal mucosa of suckling newborns (78, 79). Weight gain in infants fed formula supplemented with bovine lactoferrin has been shown to be higher than in infants fed regular formula (80), which agrees with this proposed function of lactoferrin. Further studies on the potential growth-stimulating effect of lactoferrin are needed.

Casein-derived peptides

Several peptides with physiologic activity have been generated from human casein, particularly β-casein. Most of these peptides have been generated in vitro, but some have also been isolated from intestinal contents, suggesting that they are also formed in vivo. Peptides have been shown in experimental systems to have antithrombotic, antihypertensive, and opioid activities (81–84). Whether these activities are also exerted in infants is not known, but opioid peptides have been implicated to have both local effects (eg, effects on fluid transport in the small intestine) and systemic effects (eg, effects on sleeping behavior) (81).

CONCLUSIONS

Human milk contains a wide array of proteins, which provide biological activities ranging from antimicrobial effects to immunostimulatory functions. In addition, the proteins in human milk provide adequate amounts of essential amino acids to growing infants. This suggests a highly adapted digestive system, which allows the survival of some proteins and peptides in the

upper gastrointestinal tract and amino acid utilization from them further down in the gut.

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