Bioactive Proteins in Human Milk—Potential Benefits for Preterm Infants

Bo Lönnerdal, PhD

KEYWORDS

• Bioactive proteins • Protein digestibility • Human milk • Preterm infants

KEY POINTS

- Preterm milk contains high concentrations of several bioactive proteins.
- Significant amounts of these bioactive proteins survive digestion and are found intact in the stool.
- Bioactive proteins are likely to explain several of the advantageous outcomes described for preterm infants fed breast milk.

INTRODUCTION

Many components of breast milk are shown or suggested to provide bioactivities that are important for optimal health and development of the preterm infant. Among these are long-chain polyunsaturated fatty acids, complex oligosaccharides, bacteria with proposed beneficial effects provided with breast milk, nucleotides, and growth factors. The largest variety of bioactivities, however, is provided by proteins in breast milk (**Table 1**).[1,2] This article discusses these bioactivities and gives some examples of how milk proteins can improve infant outcomes. Clinical studies showing some of these benefits are presented and discussed.

PROTEIN DIGESTION IN TERM AND PRETERM INFANTS

To exert bioactivities in the gastrointestinal tract of infants, proteins need to retain an intact structure, or a significant portion thereof, that is, some resistance toward complete proteolysis for at least some time in the digestive process. Several human milk proteins have such resistance, among them secretory IgA (sIgA), lactoferrin, and lysozyme, which are present in significant quantities in the stool of breast-fed infants.

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Department of Nutrition, University of California, One Shields Avenue, Davis, CA 95616, USA
E-mail address: bllonnerdal@ucdavis.edu

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Table 1
Bioactive human milk proteins

Protein	Bioactivity
Lactoferrin	Bacteriostatic; bactericidal; immunomodulatory; cell proliferation and differentiation
α-lactalbumin	Prebiotic; antimicrobial; immunostimulatory; enhanced Fe and Zn absorption
sIgA	Transfer of maternal immunity; antibodies against bacteria and viruses
Lysozyme	Antibacterial activity; degradation of bacterial cell wall glycans
BSSL	Hydrolysis of triglycerides; fat absorption
Osteopontin	Immunomodulatory activity; brain function; intestinal development
Haptocorrin	Vitamin B12 absorption; antimicrobial activity
α_1-antitrypsin	Limit/slow down protein digestion
β-casein	Opioid activity; enhancing calcium absorption
κ-casein	Antibacterial activity by acting as structural analogues
MFGM proteins	Antibacterial and antiviral activities

Schanler and colleagues[3] found that very low-birth-weight infants fed pasteurized, lyophilized, mature human milk had markedly greater quantities of lactoferrin, lysozyme, and IgA in their stool than those fed cow's milk formula. Concentrations of total and sIgA were significantly correlated, and 95% of total IgA was sIgA. Fecal concentrations of specific sIgA antibodies to *Escherichia coli* O antigens correlated with the concentration of these antibodies in their milk. The investigators suggested that the larger quantities of these immune factors in the stool of infants fed breast milk is caused by increased ingestion but also raised the possibility of breast milk stimulating their endogenous synthesis. The same group also measured concentrations of these proteins in serum and found no difference between infants fed breast milk or cow's milk formula.[4] However, urinary excretion of these immune factors was significantly higher in infants fed breast milk than in those fed cow's milk formula, raising questions about the genesis of these proteins in the urine of infants fed breast milk. The authors of this report analyzed the presence of these immune factors in term, exclusively breast-fed infants and found significant quantities of lactoferrin and sIgA, which decreased with the age of the infant, but no detectable amounts of lysozyme.[5] Remarkably, during the first 2 weeks of age, nearly 70% of all soluble proteins in the feces consist of sIgA and lactoferrin, and this proportion decreases to about 20% to 30% at 4 to 5 months. In a carefully conducted nitrogen balance study on low-birth-weight infants,[6] the authors were able to calculate the survival rate for the major human milk bioactive proteins and found that these quantities were quite substantial and higher than what was observed in term infants.[7] As much as 25% and 9% of intake, respectively, of sIgA and lactoferrin were found in the fecal samples, whereas lysozyme and serum albumin (component of breast milk) were detected at lower amounts (~1% of intake). Immunoelectrophoresis and gel filtration chromatography confirmed that sIgA and lactoferrin were present in the stool in largely intact form, although there is a possibility of smaller peptides being formed, which are not immunoreactive. When comparing infants fed preterm milk only with those that received both preterm milk and cow's milk formula (50:50), the authors found that excretion of bioactive proteins was higher when formula was given and also that insoluble fecal nitrogen excretion was higher. This finding suggests that some cow milk proteins in formula which are difficult to digest form aggregates with breast milk