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Milk more than a nutrient: Hormones, growth factors, and bioactive factors

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Summary

Until recently, the biological role of milk has been viewed mostly as a source of nutrients for the newborn mammal, covering energy, protein and lipid demands as well as the supply of essential nutrients such as vitamins and minerals. However, in addition to the established nutritional value many different factors are present in milk, which exhibit specific physiological activities essential to growth and development of the neonate and to protect against diseases and infections. Milk thus represents a very valuable weapon for enhancing the immature immunologic system of the newborn and for strengthening its deficient host defense mechanisms against infective or other foreign agents and might modulate many physiological functions such as the maturation of gastrointestinal tract and the endocrine system of the neonate.

Keywords: milk, hormones, growth factors, bioactive components

Milch ist mehr als nur ein Nahrungsmittel: Hormone, Wachstumsfaktoren und bioaktive Bestandteile

Milch wurde für lange Zeit vor allem als eine gute Quelle von Nährstoffen für das Neugeborene gesehen. Sie liefert die für das Wachstum notwendige Energie, Eiweiß und Fett sowie die essentiellen Nährstoffe wie Vitamine, Mengen- und Spurenelemente. Neben diesen wichtigen Bestandteilen enthält Milch aber auch eine Vielzahl verschiedener Faktoren, die spezifische physiologische Funktionen wahrnehmen, die für Wachstum und Entwicklung des Neugeborenen sowie dessen Schutz vor Erkrankungen und Infektionen von Bedeutung sind. Milchbestandteile unterstützen das noch unzureichend ausgebildete Schutzsystem des Organismus gegenüber infektiösen und nicht infektiösen Ursachen und modulieren zahlreiche physiologische Funktionen wie die Reifung des Magen-Darm-Traktes und die Entwicklung des endokrinen Systems des Neugeborenen.

Schlüsselwörter: Milch, Hormone, Wachstumsfaktoren, bioaktive Bestandteile

Introduction

Milk contains a heterogeneous mixture of secreted components with wide ranging chemical, physical and functional activity. Until recently, the biological role of milk has been viewed mostly as a source of nutrients for the newborn mammal, covering energy, protein and lipid demands as well as the supply of essential nutrients such as vitamins and minerals. However, in addition to the established nutritional value, in milk many different factors are present, which exhibit specific physiological activities essential to growth and development of the neonate and to protect against diseases and infections *(Koldovsky, 1995; Schams, 1994; Schams and Karg, 1986; West, 1989)*. This protection is conferred through several mechanisms: specific antibody targeted protection against pathogens in the neonate's environment such as IgA, IgG and IgM and a broad spectrum of nonspecific protection provided by several distinct mechanisms. These are: bactericidal effects of lactoferrin; bacteriostatic effects of lactoferrin and lysozymes, lysis of microorganisms by lysozymes, antiviral effects of lactoferrin and products of lipolysis in the digestive system, antiprotozoan activity of free fatty acid produced during lipolysis and ligand action that inhibits the adhesion of pathogens to the mucosa as in the case of kappa-casein. Additional bioactive factors modulate one or more metabolic processes such as immunological responsiveness, circulation, cellular growth and repair or the uptake of nutrients.

Many of these factors are enriched in the milk of the very first few days, the colostrum. Differences between colostrum and mature milk are primarily due to changes in protein composition including hormones, growth factors and immunoglobulins *(LeBlanc et al., 1992; Rouse and Ingram, 1970; Sheoran et al., 2000; Shing and Klagsbrun, 1984; Zicker and Lonnerdal, 1994)* as well as fat-soluble vitamins, cholesterol and phospholipids *(Bitman and Wood, 1990; Macias and Schweigert, 2001; Newstead, 1976; Schweigert, 1990; Schweigert and Gottwald, 1999)*. The high concentration of immunoglobulins in colostrum is of importance for the passive transfer of immunity to the neonate, because in many farm animals the transfer via the placenta is limited. This aspect has been proposed as early as *1890* by *Paul Ehrlich* and has thoroughly been reviewed *(Korhonen et al., 2000; McFadden et al., 1997)*. This will not be the scope of this review but it will briefly summarize the current knowledge on hormones, growth factors and bioactive factors present in milk with most information available from experimental animals, humans and cattle.

Hormones

Milk contains a number of hormones that promote gastrointestinal maturation and might also contribute to the development of the neonate's own intestinal host defense. Because many of these milk borne hormones can be absorbed and demonstrate biological activity at distant sites a modulation of the neonate's endocrine system through these factors is

assumed *(Koldovsky, 1995)*. Absorption is favoured by a lower proteolytic activity than in adults and a higher "permeability" of the mucosa lining for macromolecules. Among the many hormones protein hormones such as prolactin, insulin, thyroxine and recently erythropoietin as well as steroid hormones such as gestagens, estrogens, corticoids and androgens as well as vitamin D and the retinoids have been detected. The concentration of these hormones in milk is either affected by the stage of lactation (high in colostrum) or by the ovarian cycle and the stage of gestation as in the case of estrogens and progesterone. Progesterone is used for the diagnosis of pregnancy *(Kling et al., 1998; Koskinen et al., 1990; Schams and Karg, 1986; West, 1989)*.

Growth factors

Growth factors, highly potent hormone-like polypeptides, are found in milk of many species. Colostrum contains higher levels of growth factors than mature milk does. Among these factors the epidermal growth factor (EGF), nerve growth factor (NGF), transforming growth factor (TGF) and insulin-like growth factor (IGF´s) have been described. Many of these factors originate from the mammary gland itself and constitute less than 0.1% of total milk protein but have specific biological functions in the local and possibly systemic regulation. Most important is their role in the proliferation and maintenance of the lactating gland. With regard to their effects in the neonatal, IGF is increasing in rats the activities of lactase and sucrase but did not stimulate intestinal cellular growth. TGF is suspected to inhibit cell proliferation but supports the differentiation of villus enterocytes. EGF might play a role in the healing of ulcer. *(Blum and Hammon, 1999; Koldovsky, 1995; Murphy, 1998; Murray et al., 1992; Schams, 1994)*.

Bioactive factors

Lactoferrin is a 80 kDa glycoprotein found in high concentration in milk. It has been shown to inhibit bacterial growth in vitro. The bacteriostatic activity is not only due to its iron-scavenging ability and it's binding to specific receptors on the bacterial surface causing a release of lipopolysaccharides from the cell wall resulting in permeability alteration and cell death. Additionally lactoferrin supports the absorption of iron in the duodenum as indicated by the presence of specific receptors for lactoferrin at the apical side of the enterocyte and affects the neonatal intestinal growth, hepatic protein synthesis and intestinal recovery from injury possible as a result of transcriptional regulation *(Steijns and van Hooijdonk, 2000; van Hooijdonk et al., 2000)*.
Fragments obtained during the intestinal hydrolysis of lactalbumin are involved in the modulation of both B lymphocyte and T helper cells *(Gill et al., 2000)*.
β-Lactoglobulin, the most abundant whey protein is a carrier of small hydrophobic molecules including retinoic acid, which is a potent modulator of lymphocyte response *(Perez and Calvo, 1995)*.

Enzymes

Among the many different enzymes found in milk antiproteases, milk bile salt-dependent lipase, platelet-activating factor acetyl hydrolase and peroxidase are important bioactive components that might either inhibit uncontrolled proteolysis or protect the intestine from inflammatory diseases.
Lysozyme in conjunction with lactoferrin is bactericidal. It lyses bacteria by hydrolyzing β-1,4 linkage between n-acetyl muramic acid and 2-acetylamino-2-deoxy-D-glucose residues of the bacterial wall *(Haezebrouck et al., 1992)*. It is stable to digestive processes in the gastrointestinal tract. The biological function of the lactoperoxidase system is that of defense through bacteriostatic and bactericidal effects against a broad spectrum of microorganism as well as antiviral activities *(van Hooijdonk et al., 2000)*. Additionally, several other enzymes present in milk might provide protection by generating components that are bactericidal (bile salt dependent lipases, peroxidases), prevent inflammatory reactions (platelet-activating factor acetylhydroxilase), or protect the integrity of milk proteins (antiproteases).

Bioactive factors resulting from digestion of proteins

From the individual protein fractions of milk, bioactive peptides have been identified that are the result of hydrolytic reactions catalyzed by digestive enzymes. These peptides directly influence numerous biological processes evoking behavioural, gastrointestinal, hormonal, immunological, neurological and nutritional responses *(Clare and Swaisgood, 2000)*.
Casein represents the majority of milk proteins *(Zicker and Lonnerdal, 1994)*. Although its primary function is nutritional, some casein fractions itself (kappa-casein) or fragments of caseins are bioactive components *(Schams and Karg, 1986)*. In experimental animals it was possible to show that the β-casomorphins, derived from the limited proteolysis of kappa-casein, induce analgesia and modulate the social behaviour. In addition several proteolytic fragments of α- and ι-casein subunits have been isolated that show immunstimulatory effects. The bioactivity of casein-derived phosphopeptides is their ability to sequester minerals such as calcium and form organophosphate salts with trace elements such as iron, manganese, copper and selenium and might thus function as carriers for these minerals *(Gill et al., 2000)*.

Oligosaccharides and glycoconjugates

Milk contains a huge number of different complex carbohydrates including glycoproteins, glycolipids, glycosaminoglycans, mucins and especially oligosaccharides. Complex carbohydrate moieties of glycoconjugates and oligosaccharides are synthesized by glycosyltransferases in the mammary gland. Some of them act as receptor analogs that inhibit the binding of certain enteric bacterial pathogens and their toxins to the host receptor and are known to be selective growth promotors of bifidus *(Newburg, 1996)*.

Lipids and fat-soluble vitamins

Fatty acid and monoglycerides released during lipolysis of milk fat in the gastrointestinal tract have been shown to disrupt as potent detergents herpes simplex virus and other enveloped viruses such as measles virus and vesicular stomatitis virus, bacteria and protozoa in infants *(van Hooijdonk et al., 2000)*. Fat-soluble vitamins that modulate genetic expression through the nuclear receptors such as vitamin D and retinoids might not only be of importance for the metabolism of calcium as in the case of vitamin D *(Goff et al., 1982; Schams and Karg, 1986)* but might influence the development of the endocrine system as has been postulated for the retinoids *(Gaal and Csaba, 1998)*. Additionally both retinoids and vitamin E are potent immunmodulators *(Bendich, 1992)*. Vitamins such as vitamin E and vitamin C as well as carotenoids are important antioxidants present in milk *(Lindmark-Mansson and Akesson, 2000)*.
In conclusion, a steadily increasing number of biological factors are isolated and characterized from colostrum and milk. For many of these factors the physiological role has to be assessed. Furthermore it remains to be studied if some of these factors can be used therapeutically in newborns with disturbances in different functions attributed to host defense or maturation and development of the gastrointestinal tract.

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