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REVIEW

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Reflections about possible nutritional supplements in infant milk formula

Gedanken zu möglichen Supplementen der Milchnahrung im Säuglingsalter

Summary The composition of infant milk formula intends to mirror breast milk as close as possible. However, there are a variety of substances, like amino acids, fatty acids, polyamines, nucleotides, oligosaccharides, functional proteins, hormones, vitamins, and minerals, which are attributed effects in special situations. A concept is proposed to develop problem oriented "supplementation packages" for infant milk formula.

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Zusammenfassung Beim Versuch die Inhaltsstoffe von Säuglingsmilchnahrungen jenen der Muttermilch anzupassen ergibt sich eine Fülle von Einzelsubstanzen aus dem Bereich von Aminosäuren, Fettsäuren, Polyaminen, Nukleotiden, Oligosacchariden, Funktionsproteinen, Hormonen, Vitaminen und Mineralien, denen Bedeutung in besonderen Situationen zugewiesen werden kann. Es werden gedankliche Ansätze, für an definierte Problemsituationen angepaßte „Supplementierungspakete" für Formulamilchnahrungen entwickelt.

Schlüsselwörter Säuglingsmilchnahrungen – Supplemente – Problemorientierung

Key words Infant milk formula – supplements – problem orientation

Abkürzungen

AC/FC	acyl carnitine/free carnitine ratio
AGA-infants	appropriate for gestational age infants
β-*CM*	β-casomorphin
Ca/P	calcium/phosphorous ratio
CF	cystic fibrosis
EGF	epidermal growth factor
FAD	flavinadenine dinucleotide
GABA	γ-aminobutyric acid
GM-CSF	granulocyte-macrophage colony-stimulating factor
H. pylori	helicobacter pylori
IGF	insuline like growth factor
LCP	long chain polyunsaturated fatty acids
NAD	nicotinamide-adenine-dinucleotide
NGF	nerve growth factor
RDA	recommended daily allowances
ROS	reactive oxygen species
SGA-infants	small for gestational age infants

Introduction

A large British multicenter study of the consequences of early feeding regimen supplemented with protein, sodium, calcium, phosphorus, copper, zinc, vitamins D, E, and K, water-soluble vitamins, carnitine, and taurine for preterm infants with respect to short-term and long-term clinical and developmental outcome showed that after 18 months postnatally the infants who had received supplemented formula had major developmental ad- vantages (105). As a clear developmental advantage could be ascertained with the intake of breast milk one is faced with the question whether infant formula should be supplemented with defined compounds present in mothers milk (106).

Taurine in infant nutrition

Taurine is the major intracellular free amino acid of most tissues of mammals. Conjugation with bile acids to form bile salts is the best documented reaction in which taurine participates (191). It has been known for several decades that taurine concentrations in the brain are high, especially in neonatal brain, where they are several fold greater than in adult brain (170). In 1975 it was noted that the decrease in brain taurine concentration that occurs from birth to maturity was accomplished over the period of natural weaning for a variety of mammalian species (166). This observation focused attention on milk. A systematic study showed that taurine was present in milk of mammalian species, including humans, and often in high concentrations (141). Radiolabeled taurine injected intraperitoneally into lactating rats was expressed in their milk and accumulated in the brain and other tissues of the suckling pups, suggesting that nutritional taurine might be important (167). Cats fed diets containing little or no taurine suffered ophthalmoscopically visible retinal degeneration, accompanied by reduced retinal and plasma taurine concentrations (74). These results, being specific for felines, point however, to the importance of taurine as a neurotransmitter. Kittens raised with taurine deficient milk have several abnormalities, including a peculiar gait, retinal and tapetum degeneration, delayed cerebellar granule cell division and migration (129, 169). There is much debate about the necessity to supplement formulas with taurine even though there had been no obvious clinical evidence of retinal or other abnormalities during several decades of formula use. A nutritional study in which infant rhesus monkeys were raised either with or without formula supplemented with taurine showed that although the monkeys deprived of taurine showed no abnormalities on ophthalmoscopic examinations or with fluorescein angiograms, they showed significant retinal abnormalities on postmortem electron microscopic examination at 26 months of age. The outer segments of the cone photoreceptors showed extensive disorientation and vesiculation of the membrane arrays and disrupted and disorganized outer plasma membranes (168). One study, initiated several years before the taurine supplementation of formula, showed that the infants receiving taurine-supplemented formula had more mature brain stem auditory evoked responses and a significant reduction in the interval between stimulus and response associated with higher plasma taurine concentrations (183). In conclusion it can be stated that taurine is conditionally essential during infant development (61). Taurine is unique among amino acids in that its body pool size is largely regulated by the kidney (33). Unlike most amino acids, which are completely reabsorbed by the proximal renal tubule, taurine is not completely reabsorbed. At the proximal tubule brush-border membrane, the transporter activity is shared with other ß-amino acids and γ-aminobutyric acid (GABA) (32). The transporter activity is adaptively regulated by the taurine intake maintaining plasma and tissue taurine levels, particularly in several areas of the brain, where taurine is an important osmolyte (35). The synthesis of the transporter molecule is induced by low intracellular taurine concentrations. Northern blot test analysis indicated that the abundance of mRNA from the cDNA probe is increased in cells incubated in taurine-free medium (70). Therefore, in the case of the taurine pool a gene-nutrient interaction seems likely (70). The ultimate role of renal osmolytes, including sorbitol, betaine, and taurine, is to allow for regulatory cell-volume changes in the face of a hypertonic renal medulla. Taurine is preferentially localized to the medullary region of the kidney, where urine osmolarity varies between to 300 to 1300 mOsm/l. The transport of taurine into the distal tubule pertains to its function as an osmolyte; hence, it is important that transport is enhanced by hyperosmolar conditions, because for every taurine molecule one chloride and two sodium ions are taken up by the cell. Because taurine resides free in the intracellular water, it is an ideal osmolyte that increases intracellular osmolarity whenever extracellular osmolarity is increased, thereby maintaining cell volume (90). The state of cellular hydration is a basic signal for the regulation of proliferative-anabolism respectively of catabolism. Cellular swelling signals an increase of protein-, DNA- and glycogen synthesis and an inhibition of proteolysis (73, 160). Eight weeks of taurine depletion in cats seems to increase vulnerability to hypernatremic dehydration and results in significantly higher seizure activity and mortality rates, suggesting that this amino acid is an important cerebral osmoprotective molecule (178). Indeed, taurine constitutes nearly 50% of the adaptable intracellular osmolar pool whose concentration varies in the course of osmoregularity in response to perturbations in extracellular fluid toxicity (178). Hypernatremia induces the synaptosomal uptake of taurine (180). To summarize, taurine uptake into the brain is enhanced during chronic hyperosmolar states, such as hypernatremia or hyperglycemia, to expand the intracellular pool of this osmoprotective molecule and limit brain shrinkage. The nutritional consequences of renal immaturity of taurine transport is potentially harmful to the retina and brain of the very low birthweight preterm infant (201). The urinary taurine content of these neonates is markedly elevated with a fractional excretion ranging from 38% to 60% versus lower than 10% in term infants. The immature kidney failes to adapt to variations in dietary taurine intake and puts the preterm infant at risk for taurine deficiency (201). Oral administration of taurine to rats with puromycin aminonucleoside nephropathy, which induces a proteinuric renal disease similar to focal segmental glomerulosclerosis, protects against the progressive decline in renal function and alteration in renal structure found in this model (179). Taurine seems to prevent

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enhanced lipid peroxidation and collagen synthesis induced by hyperglycemic conditions in renal glomerular mesangial cells grown in culture (181). As a sulfur containing compound, taurine is supposed to function as an endogenous antioxidant. It could be demonstrated that long-term taurine administration reduced oxidant damage to the kidney in streptozotocin-induced diabetes (182). Taurine is chlorinated by neutrophils and possibly by other tissues, a reaction that removes hypochlorous acid generated by the myeloperoxidase system. The resulting taurine-chloramine inhibits production of cell-damaging nitric oxide and cytokines, such as tumor necrosis factor, by activated macrophages, and may be one mechanism of antioxidant action (130).

Glutamine

Glutamine is the abundant amino acid in the intracellular pool of free amino acids in skeletal muscle. Glutamine constitutes 61% of the amino acid pool (excluding taurine) in skeletal muscle (9) and exists in humans at a concentration of 20 mmoles/l of intracellular water, which is approximately 30 times the concentration of glutamine in whole blood. This large gradient favors glutamine export from cells. Glutamine and alanine are the major compounds that transport amino nitrogen from skeletal muscle to visceral organs. Following the stress of an operation, accidental injury, or sepsis, glutamine is released by skeletal muscle at increased rates (93). The intracellular glutamine concentrations are depleted by 50 %, while plasma levels fall only 20 - 30% below normal during these catabolic states (195). Administration of corticosteroids results in accelerated efflux of glutamine from skeletal muscle (158). Cells of the immune system have very high energy needs, accelerated rates of protein synthesis, and high rates of nucleic acid synthesis for replication (121). Macrophages, lymphocytes, and thymocytes were shown to use glutamine as a major fuel source (122). This supports the general idea that glutamine is a nutrient necessary for cell proliferation. It plays a dual metabolic role in these cells, providing both an energy source via oxidation and carbon and nitrogen precursors for biosynthetic processes. Approximately 10 - 30% of the glutamine is oxidized to carbon dioxide, depending on whether the cells are resting or stimulated to proliferate. Glutamine is also a major respiratory fuel for the intestinal tract. Enterocytes and colonocytes were found to utilize glutamine to a greater extent than other fuel source, even glucose (197). The gastrointestinal tract is known to modulate the general protein catabolic response to stress, presenting an increased glutamine uptake during disease (196). A further hint is given by animal studies, the results of which showed that administration of glutaminase depleted plasma concentrations of glutamine. This process was associated with edema and ulcerations of the intestinal mucosa and with patchy areas of intestinal necrosis (7). Glutamine fullfills the requirements for a conditionally essential amino acid in at least critically ill patients. With the availability of stable glutamine dipeptides (L-alanyl-L-glutamine and L-glycyl-L-glutamine) a glutamine supplementation appears technically feasable.

Fatty acids

During late pregnancy cord blood lipids reveal a fatty acid composition different from that of maternal plasma (80). The percentage of polyunsaturated precursors of 18-carbon chains is relatively small, whereas the derivatives of the n-6 series and of docosahexaenoic acid (22:6 n-3) are relatively greater. As suggested by Hoving et al. (80), the trapping of long chain polyunsaturated fatty acids (LCP) by proteins in the feto-placental circulation followed by the receptor mediated uptake in the growing tissues may explain the observed “biomagnification” (41) and subsequent deposits of LCP in specific fetal organs during the last trimester of pregnancy. Fetal autopsy studies have confirmed the progressive accumulation of arachidonic acid (20:4 n-6) and docosahexaenoic acid (22:6 n-3) in brain tissues during the last trimester of pregnancy (36). It is now accepted knowledge that the preterm neonate is particularly at risk to develope a deficit of these long chain polyunsaturated fatty acids. An early and adequate dietary supply of 22:6 n-3 is essential for optimal retinal function, as retarded visual development, which was measured by electroretinographic studies and specific visual acuity tests, was shown to correlate with 22:6 n-3 in the diet (185). Data support a cause and effect relationship between early dietary 22:6 n-3 and later neurodevelopmental performance in preterm infants (27). A possible growth factor like role has been suggested for 20:4 n-6, as circulating arachidonic acid concentrations have been shown to correlate positively with birthweight among preterm infants (98). A low concentration of plasma arachidonic acid has been correlated with growth deficit in preterm infants fed formulas supplemented with fish oil (26). The fatty acids in milk fat of European women comprise 0.2% to 1.2% of arachidonic acid and 0.1% to 0.6% of docosahexaenoic acid. The milk of women who delivered before term already contains optimal contents of these essential fatty acids but shows higher medium chain fatty acid contents compared to the milk of women who gave birth at full term (13). It has to be realized that the supplementation of LCPs strongly influences the requirement of the antioxidative vitamin E. The additional requirement of vitamin E amounts to 0.6, 0.9, 1.2, 1.5, and 1.8 mg α-tocopherol per gram dienoic-, trienoic-, tetraenoic-, pentaenoic- and hexaenoic acid (6), respectively. The relevance of this recommendation is supported by the knowledge that the

intake of highly unsaturated fish oils may cause vitamin E deficiency (119).

On the whole, we recognize that the complex biochemical variables that affect the development of the infant's central nervous system seem to stress the need of an adequate supply of at least prematures with long chain polyunsaturated fatty acids.

The supplementation with selected long chain polyunsaturated fatty acids will be of increasing importance in special disease entities as there are for instance:

Insulin resistant state in obesity.

Insulin secretion has been found to correlate inversely with serum concentrations of linoleic acid (18:2 n-6) (133). As insulin stimulates Δ-6-desaturase activity (20), more linoleic acid gets converted into arachidonic acid under normal conditions. In case of insulin resistance the synthesis of 20 and 22 carbon fatty acids is decreased. Further assessment of supplementation with long chain polyunsaturated fatty acids, of the n-3 series in particular, in obese subjects who are beginning to develop resistance to insulin is still needed.

γ-linolenic acid in atopic disease.

During the last years there is increasing evidence of a relationship between fatty acids and the development of atopic dermatitis. These first observations of this kind date back to 1963 when Hansen et al. (71) reported about low essential fatty acid concentrations in the blood of atopic children. More than 10 years ago Manku et al. (110) compared the pattern of n-6 plasma phospho lipid fatty acids of patients with eczema with those of healthy controls. They demonstrated the linoleic acid concentrations to be increased whereas those of the fatty acids following the Δ–6-desaturase step were decreased. On this observation is based the discussion that atopic eczema develops on the basis of a decreased Δ-6-desaturase activity, which leads to a decreased formation of antiinflammatory and vasodilative prostaglandins of the E1 series (109). The supplementation of γ–linolenic acid (18:3 n-6), the fatty acid following Δ-6-desaturation, seems therefore warranted in formula used in atopic infants. On the basis of the amount of γ–linolenic acid found in breast milk, it should represent 0.5 - 1.0% of total fatty acids. Our own results with an eczema prevention study with γ–linolenic acid supplemented formula show at the moment promising results.

Adrenoleukodystrophy.

X-linked adrenoleukodystrophy is a peroxisomal disease characterized by the progressive demyelination of cerebral white matter through impaired degradation of the >24 C polyunsaturated fatty acids in the peroxisomes. As we had to learn recently the formation of docosahexaenoic acid (22:6 n-3) is realized via the peroxisomal shortening of C 24:6 n-3. It is, therefore, obvious that peroxisomal problems are accompanied by 22:5 n-3 deficiency. There is first evidence that the supplementation of adrenoleukodystrophic patients with 22:6 n-3 seems to be favorable for the further development, whereas trials with glycerol trioleate and trierucate oil (Lorenzo's oil) have not demonstrated a reduction of the deterioration in the clinical situation (5).

Cystic fibrosis.

Pediatric patients with cystic fibrosis often present a fatty acid status similar to that of patients with essential fatty acid deficiency (131). Patients with CF have a significantly lower molar percentage of linoleic acid (18:2 n-6) in serum phospholipids. The ratio linoleic acid to oleic acid also differs significantly from healthy controls. There is significant indication that the essential fatty acid deficiency is related to the genotype of the patients, but not always to pancreatic insufficiency (162). As a result of a nutritional intervention polyunsaturates should be adequately available. A parenteral emulsified soya lipid infusion improves retinal function, in addition to balancing the fatty acid status, through the mediation of prostaglandin metabolism (163). Enteral supplementation with eicosapentaenoic acid (20:5 n-3) has been tried with success and has been attributed to the inhibitory activity of 20:5 n-3 on leukotriene B4 synthesis (103).

Phenylketonuria.

Patients with phenylketonuria have to avoid proteins of animal origin; but herewith the dietary availability of arachidonic acid (n-3) and n-3 fatty acids especially the preformed LCPs is decreased. This could be demonstrated in several studies (59).

Polyamines

Spermine, spermidine, and putrescine are polycationic amines that assume a key role in virtually all prokaryotic and eukaryotic cells. To meet the needs of division processes and protein synthesis, the intracellular concentrations of polyamines are critically regulated; the rate limiting enzymes for their synthesis are ornithine decarboxylase and S-adenosyl-methionine decarboxylase (132). Rapidly proliferating tissues, such as the intestinal epithelium, are also dependent upon exogenous sources of polyamines supplied by food, secretions, and microbial flora (127). When given orally at high doses (3 - 10 μmoles per day), exogenous polyamines can directly influence epithelial cell renewal, enterocyte maturation, and intestinal enzyme expression (24). Human milk contains

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substantial quantities of polyamines, mainly spermine, and spermidine with much less putrescine (ratio spermidine/spermine 0.78). The profile of concentrations established for the three polyamines in human milk is spermine >spermidine >putrescine (137). Spermine and spermidine concentrations markedly increase during the first three days of lactation. Semi-elemental diets have a very high polyamine content. They are prepared by hydrolysis of the original protein using an extract of pancreatic enzymes, which is extremely rich in polyamines, as are in vivo exocrine pancreatic secretions. Several studies have shown that endoluminal polyamines derived from milk or food can be absorbed by selective transport mechanisms into enterocytes and can exert direct trophic effects, including enhanced enzyme expression and DNA and protein synthesis (1, 83). Assuming that neonates and young infants consume 500 - 700 ml of human milk per day it can be calculated that this volume would represent an oral load of =/ >3.5 µmoles polyamines per day (25).

Nucleotides

Among the reported biological effects of nucleotides in animals, there has been a trophic influence on the small intestinal mucosa. SGA infants have impaired intestinal absorptive function probably caused by intrauterine malnutrition. Nucleotide supplementation of an infant formula improved catch-up growth of a group of SGA infants. In the first month of life mean weight gains were 117 vs. 103 g/kg/week, $p < 0.05$ and length 25.3 vs. 22.3 mm/week, $p < 0.02$ (39).

Nucleotides are the phosphate esters of nucleosides. Nucleosides are formed by addition of a pentose to a purine or pyrimidine base. Nucleotides play important roles in major cellular functions. They act as precursors for nucleic acid synthesis (DNA and RNA) and are also fundamental to cell metabolism. ATP, an adenine nucleotide is the major molecule responsible for the transfer of chemical energy. Other nucleotides such as nicotinamide-adenine dinucleotide (NAD), flavin adenine dinucleotide (FAD), and coenzyme A play key roles as activated intermediates in the synthesis of lipids, carbohydrates, and protein and are responsible for the transfer of reducing equivalents in cellular oxidative processes. Nucleotides account for a significant proportion of the non-protein nitrogen of human milk (2 -5%) and have been incorporated into infant formula in some countries, because they are considered by some as semiessential nutrients for the neonate (62). The contribution of the non-protein nitrogen fraction to the total nitrogen content of milk is at least three times greater in human milk than in the milk of other species used in infant feeding such as cow's milk. Human milk is relatively richer in nucleotides than ruminant milk. Nucleotides were first isolated from human milk more than 30 years ago (45). Since that time at least 13 acid-soluble nucleotides have been identified of which cytidine, adenine, and uridine are found in relatively higher concentration, whereas orotate, in contrast to cow milk, is absent. Most of the data available show that cytidine and uridine nucleotides comprise the first and second largest fractions of the total nucleotide content (97). Values for adenosine monophosphate are the most variable, whereas guanosine is found in lesser amounts. Janas and Picciano were first to report the presence of inosine monophosphate in human milk (85). More recently an increasing number of clinical research has suggested various roles for dietary nucleotides, including enhancement of the normal host defense system (91, 92, 187), effects on neonatal lipid metabolism (63, 148), and influence on iron bioavailability (50). Most dietary nucleotides are readily metabolized and excreted; however, a significant proportion of retained nucleotides are found in gastrointestinal tissues. Gut-associated lymphoid tissue can initiate and regulate T-cell development and may act as a thymus analogue (118). There is one report about a better weight gain with nucleotide supplemented formula (96). A careful review of human controlled clinical studies of nucleotides shows no detectable effects of nucleotide supplementation of formula on weight gain, linear growth, head circumference or any other anthropometric index. Thus, most likely de novo nucleotide synthesis under conditions of a full gestation and an otherwise complete diet is sufficient to support normal growth (184). However, it remains to be determined whether nucleotide supplemented formula can optimize growth, immune function or gut development in premature infants or in special disease entities like short bowel syndrome, on the one hand, or special inborn errors of purine metabolism, on the other. Patients receiving a ribonucleic acid supplemented diet after a cancer operation showed better immune function as determined by higher T lymphocytes and their subsets, activated T cells (CD 3), and helper T cells (CD 4) (94). The inborn defects of adenosine deaminase deficiency or PNP-deficiency indicate the biological impact of nucleotides on normal immune function. Dietary nucleotide enhancement of immunity may be particularly important for individuals at increased risk of acquiring infections. Infants, particularly those born prematurely, and individuals with decreased immunosuppression are included in this category.

Lactoferrin

Lactoferrin is an iron-binding glycoprotein that was first isolated from human milk in 1960 by Johanson (87). It is present in the whey fraction of milk (76). Human milk is particularly rich in lactoferrin, concentrations ranging from 5 to 7 mg/ml in colostrum to about 1 mg/ml in mature milk. Approximately 30% of milk iron is lactoferrin bound. Lactoferrin is surprisingly resistant to pro-

teolytic degradation by trypsin and trypsin-like enzymes. Until recently, it was thought that the main bacteriostatic activity of lactoferrin was due to apoprotein competition with enteric bacteria for ferric iron in the lumen. Today we believe that mechanisms other than simple iron competition may be involved in the antibacterial action of lactoferrin (84). Ellison and coworkers showed that whereas lactoferrin and lysozyme alone are bacteriostatic, together they could be bactericidal for strains of V. cholerae and Salmonella typhimurium in a dose dependent manner (46). The important role that lactoferrin plays in host defense is shown by the observed susceptibility of subjects with congenital or aquired lactoferrin deficiency to recurrent infections (18). Lactoferrin has also been shown to have anti-inflammatory properties by suppressing cytokine responses. It may play a major regulatory role in preventing the recruitment and activation of leukocytes to sites of intestinal inflammation (40).

Lysozyme

Lysozyme is a protein found in significant amounts in human milk. In one study, the mean concentrations in milk and infant samples were 3.24 and 2.15 mg/dl, respectively (125). Lysozyme represents an important component of host defence mechanisms in that it lyses bacteria by hydrolyzing ß-1,4 linkages between N-acetylmuramic acid and 2-acetylamino-2-deoxy-Δ–glucose residues in bacterial cell walls (34). As lactation progresses and after the first month, there is a rise in the quantity of lysozyme ingested by infants (157). The amount of lysozyme excreted in the stools of human milk-fed low birth-weight infants in about eight times that in cow's milk-fed infants (151).

Oligosaccharides

There are many types of oligosaccharides in human milk that compete with receptors on epithelial cells for the binding of certain bacterial pathogens or their toxins (72, 77). They are excreted into the urine of breast fed infants. This situation may even present a pitfall when oligosaccharide screening is performed in the case of suspected metabolic disease (99). The physiological role of these oligosaccharides is to protect against diarrhea in infants colonized by pathogenic bacteria. In vitro assays have shown the ability of these molecules to competitively inhibit microbial adhesion and enterotoxin binding by acting as receptor analogues (72). Traditionally intestinal infections have been treated with carots. As we learned in the meantime the carot oligosaccharides effectively inhibit bacterial binding to intestinal mucosa cells (65). Selective fermentation of oligo- and polysaccharides by bifidobacteria may be one method to suppress pathogenic bacteria (199). Feeding of liquid elemental diets causes atrophy of colonic tissue, in particular, the colonic mucosa (86). Maintenance of the colonic mucosal layer requires fermentable substrate (64). Diets containing the highly fermentable substrate pectin were fed to rats and produced enhanced colonic healing after surgery: this effect was attributed to short-chain fatty acids, which are produced by microbial fermentation of pectin (144). Of the short chain fatty acids produced during fermentation, butyrate appears to be the most effective stimulant of cell proliferation (147). Fructooligosaccharide is readily fermentable and results in short chain fatty acid production. They have a growth promoting activity on bifidobacteria populations as well as on colonic mucosa (81).

Inositol

Inositol is a six-carbon sugar alcohol present in biologic systems primarily as myo-inositol; other inositols with different structural configurations are also present but are much less abundant. It is a component of membrane phospholipids, and compounds containing inositol are important in signal transduction (108, 194). A deficiency of inositol can result from a deficiency in the diet (78) or in endogenous synthesis (49). Breast milk (270 - 360 mg/l), especially colostrum (540 - 720 mg/l), has a high concentration of inositol. Infant formula has a lower concentration of inositol (23, 134). Serum concentrations of inositol are higher during fetal development than during postneonatal growth (139). In a study of 74 premature infants with respiratory distress syndrome, inositol supplementation increases survival without increasing the frequency of bronchopulmonary dysplasia (68), and in a trial in 221 patients (80 mg inositol/kg/day) inositol supplementation lead to a significantly lower requirement for inspiratory oxygen, to increased survival without bronchopulmonary dysplasia, and a decreased incidence of retinopathy of prematurity (69). Therefore, inositol supplementation has to be reflected in infants with immature lung function.

L-Carnitine

L-carnitine (trimethylamino-β-hydroxybutyric acid) is the basis of the fatty acid transfer system across the inner mitochondrial membrane. It is synthesised mainly in the liver from the amino acids lysine and methionine. The concentration in mothers milk is at a constant mean level of about 60 µmoles/l during the first weeks postpartum. Thereafter, the concentration falls to about 35 µmoles/l (30, 150). In comparison the carnitine content in cow's milk amounts to about 200 µmoles/l (150). Soy formula

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is carnitine free and has to be supplemented for to avoid carnitine deficiency (124). There is a dynamic equilibrium between free and acylated carnitine on the one hand and free and acylated intramitochondrial CoA on the other hand. This situation makes carnitine interesting for supplementation in even pharmacological amounts in situations of enhanced intramitochondrial accumulation of acylated CoAs and a reduced availability of free carnitine. This state of carnitine insufficiency is characterized by an increased acyl carnitine/free carnitine ratio (AC/FC >0.4 in the fed state and >0.7 in the fasted state). Carnitine supplementation leads to the liberation of intramitochondrial free CoA and, therefore, supports the normal reactions of intramitochondrial intermediary metabolism (143, 198).

During inflammatory processes, white blood cells are in an energetically activated state and show an increased fatty acid uptake (47). As could be demonstrated in cases of bacterial infection as well as inflammatory bowel disease, there are major distributory changes of carnitine in white blood cells reflecting a massively increased requirement (43).

Calcium and phosphorus

During the last trimenon the fetal calcium and phosphorus accretion is very high. The fetal calcium accretion at about 30 weeks of gestation is 3.0 mmoles/kg/day (125 mg/kg/day) and that of phosphorus is 2.5 mmoles/kg/day (70 mg/kg/day). With birth this maternal supply is interrupted with the consequence that the calcium and phosphorus demand of the premature infant is not adequately covered by the milk intake (136). The fetal accretion rates are the basis for the calculation of recommended intakes of immature infants. When the calcium and phosphorus supply of the young and especially immature infant is discussed, the Ca/P ratio in hydroxyapatit in the bone should be taken into consideration. The molar Ca/P ratio is 1.67 whereas by weight it is 2.16. The daily recommended intake of calcium is about 200 mg/kg/day (5 mmoles/kg/day) and of phosphorus 90 mg/kg/day (2.8 mmoles/kg/day). With mothers milk about 20 mg (0.5 mmoles) calcium/kg/day and 25 mg (0.9 mmoles) phosphorus/kg/day are obtained. With formula it is about 80 mg (2 mmoles) calcium/kg/day and about 50 mg (1.8 mmoles) phosphorus/kg/day.

Because osteoporosis has been recognized as a major cause of morbidity, it has become a concern of public health authorities. Variation in bone mass accumulation during childhood and adolescence is now considered as the important determinant of the risk of osteoporotic fractures during adult life. Maximizing bone mass during growth constitutes one of the best preventive strategies. Calcium and phosphate are the essential dietary nutrients as a major constituent of bone mineral. The earliest data suggesting an influence of dietary calcium on the achievement of peak bone mass found a difference in bone mass and fracture rate in two Croatian populations with substancially different calcium intakes (111). The difference in bone mass was clearly visible in this study at 30 years of age, suggesting that the greatest effect of dietary calcium probably occurred during growth rather than at adulthood. A 3 year intervention study was conducted in 45 pairs of monozygotic twins, 6 to 14 years old at entry, whose usual calcium intake was about 900 mg/day (88). One of each twin pair received supplemental calcium raising overall daily calcium intake to 1600 mg. No significant differences in bone mineral density were found in subjects having already entered puberty; however, in the prepubertal twins taking 1600 mg calcium daily, midradius bone density gains were significantly greater from 6 months up to 3 years of supplementation. Therefore, a continued high calcium intake throughout infancy and childhood may be required for the achievement of a maximal peak bone mass, as has been suggested from a number of retrospective studies (135, 149, 161). Calcium requirements have been reported to be greatest during infancy and adolescence (112). For infants with adequate vitamin D status, RDAs are set at 400 mg/day for up to 6 months and 600 mg/day from 6 to 12 months. During childhood, dietary intakes of approximately 800 mg/day, the current RDA, may allow sufficient calcium retention to cover the skeletal requirement of about 100 mg calcium/day (112). During the accelerated skeletal growth of adolescence, calcium retention has been estimated to range from 360 to 400 mg/day (75), which would be achieved with intakes of 1200 mg, corresponding to the RDA (Recommend Daily Allowance) for this age group (112).

Iron

The American Academy of Pediatrics Committee on Nutrition has recommended that infant formulas should be supplemented with iron. Presently many formulas in the USA are iron fortified, usually 12 mg/l. This level of supplementation influences infant development scores (128, 192). As there are concerns about interactions of iron with other nutrients, in particular copper and zinc, some authors suggest a level of 6 mg/l as being adequate (156). There has been a case report of copper deficiency in an infant fed iron-fortified formula (153). Claims that iron supplementation may cause an increased rate of infection by interfering with the bacteriostatic effect of lactoferrin appear to be unfounded (2). However, there is increasing knowledge about the origins of oxidative stress and the formation of reactive oxygen species (ROS). Iron is clearly involved in the formation of $OH^{\cdot}$ according to the Fenton reaction. At birth, plasma transferrin is lower and much more highly loaded with iron than in later life

(152). In fact, non-protein-bound iron has been measured in the plasma of borth preterm and term babies (104). High vitamin C levels in cord blood can reduce ferric iron and thereby antagonize the ferroxidase activity of ceruloplasmin (66). Ceruloplasmin is also decreased in cord blood, and the occurrence of ferrous iron in plasma has indeed recently been demonstrated (9). Not only the concentrations of the iron binding and ferroxidase proteins are decreased in cord blood plasma but also their in vitro antioxidant activity to protect against iron induced lipid peroxidation (116). In babies the transferrin antioxidant capacity has been demonstrated to correlate positively with its latent iron-binding capacity and negatively with the plasma non-protein-bound iron concentration (104). Taking into account all these facts about iron metabolism, iron supplementation, at least in formulations designed for the premature infant, should be reconsidered and very cautiously handled. From the point of view of oxidative stress the low iron concentration in breast milk may be quite meaningful. The importance of maintaining very low iron levels in plasma is evident, as in healthy subjects there is a three-fold excess of transferrin binding capacity relative to the amount of iron normally transported. The brain has a high content of bound iron, which if released cannot readily be resequestered because of the absence of significant iron-binding capacity in the cerebrospinal fluid. This relatively low iron binding capacity might explain the ease with which certain neurotoxic drugs are able to damage nerval terminals, the suggested role for ROS in the pathogenesis of several neurological diseases, and why vitamin E deficiency or other free radical-based insults lead to a variety of neurological symptoms (42). Although iron deficiency is a health problem in much of the world, recent studies indicate that the typical western diet leads to body iron stores that are significant risk factors for myocardial infarction and other major disease (38).

Antioxidants

It is now well established that free radicals and other reactive oxygen species are continuously produced in vivo. In consequence, organisms have evolved antioxidant defense systems to protect against them. Among the antioxidant defense strategies mammals use enzymes (superoxide dismutase, catalase, glutathione peroxidase) (58, 89, 177), lipophilic (α-tocopherol, ubiquinol 10, ß-carotene, bilirubin) (35, 57, 159), and hydrophilic compounds (ascorbate, glutathione, urate, amino acids, and plasmaproteins) (3, 123, 193). Oxidative stress is defined as a lack of antioxidative capacity to balance ongoing oxidative processes. Oxygen radical diseases of the premature, as coined by Sullivan in 1988 (171), is considered in encephalopathies (189), necrotizing enterocolitis (107), retinopathy of the premature (31), and bronchopulmonary dysplasia (138). Which neonate has to be considered at risk for oxidative stress is one of the most challenging tasks of neonatology. Supplementation with antioxidative compounds in pharmacological amounts should be taken into consideration. In the case of iron supplementation the additional supply with antioxidants has to be considered a must. It must be realized however, that mixtures of ascorbate and iron salts themselves generate $OH^{\cdot}$ radicals and can accelerate lipid peroxidation. The message is that vitamin C acts as a prooxidant in the presence of iron (68, 113). However, as can be shown for the case of glutathione, not only the addition of the directly active compound has to be considered, but also the adequate supply with precursor substances. Cystine for instance is the limiting amino acid for glutathione synthesis and an adequate cystine supply has, therefore, direct importance for the stabilization of glutathione availability. Glutathione has to be considered not only as a redox-active substance but has recently also been shown to be important in regulating the folding of proteins as they pass through secretory pathways (82). Under these aspects the clinical importance of cysteine supplementation could be demonstrated in the reduction of total parenteral nutrition induced hepatic lipid accumulation (120).

Special design of milk proteins

Several human milk proteines have been suggested to exert physiological functions in milk or the recipient infant. Some proteins have primarily nutritional functions, e.g., bile-salt stimulated lipase, which promotes efficient digestion of milk lipids or lactoferrin, which assists in iron absorption, while others have antimicrobial properties such as sIgA and lysozyme. A common denominator of these proteins is that they belong to the whey proteins, i.e. the soluble protein fraction remaining after precipitation of the caseins. Among the caseins it was suggested that κ-casein may function as a growth stimulator of B. bifidum (12). Because B. bifidum has been shown to produce and secrete a large set of highly specific glycosyl hydrolases, probably including endo-ß-GlcNac'ase (51, 79), this could be explained by enzymatic release of the bifidus factor or other growth-promoting GlcBac-containing saccharides present on the κ-casein molecule (54, 100). For attachment of H. pylori to the gastric mucosa it is suggested that fucose residues are required (52). Boren et al. extended this observation by showing that the fucosylated Le^b blood group antigen expressed on human gastric surface mucous cells acts as a receptor for H. pylori (17). The monofucosylated blood group H type I antigen is bound by the bacteria (17). Human κ-casein oligosaccharides are reported to be fucosylated via an α-1,4-linkage to N-acetylglucosamine and differ in this respect from bovine κ-casein (188). In addition it could be demonstrated that the human κ-casein

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carries the Le^b-antigen but that bovine κ-casein does not (165). 15% of the population are "nonsecretors", not carrying this antigen (165). In addition casein fractions have adhesion inhibitory properties on H. influenzae and S. pneumoniae (4). This is an effect specific to human but not to bovine casein.

Brantl et al. reported the presence and characterization of a material with opioid activity in the enzymatic casein digesta (19). It was shown that it is a heptapeptide and is a fragment of bovine ß-casein; therefore, they called it ß-casomorphin (ß-CM). The ß-CM compounds seem to be generated and absorbed in a gradient-like fashion from the gastrointestinal tract after ingestion of milk under certain conditions (176). The peptide ß-CM7 is not readily degraded because it was found in plasma some 4 h after milk ingestion, whereas other ß-CMs are rapidly degraded with their half-life estimated to be shorter than 5 minutes (157). It is noteworthy that ß-CMs from bovine milk are more potent than those from human milk. They seem to influence gastric emptying and gut motility as well as general behavior and pain sensation. Effectiveness against pain is mediated through central opioid pathways (14). The postabsorptive quality of mother's milk causes a protracted change in the infant state and the brain is obviously able to detect changes in circulating levels of ß-CM.

Growth factors in human milk

A particular class of substances in breast milk has been the subject of considerable study over the past few years. These are commonly referred to as growth factors, peptides capable of stimulating the proliferation of cell growth. A diversity of growth factors is present in human milk and they are enriched especially in colostrum. Included among these are, for instance, several polypeptide growth factors like epidermal growth factor (EGF), nerve growth factor (NGF) or insulin like growth factors 1 and 2 (IGF) (142). In 1978, Klagsburn (95) first reported that human milk contained a mitogenic factor able to stimulate DNA synthesis and cell division in mouse and human fibroblasts in vitro, 1% milk having the relative potency of 10% fetal calf serum. Increasing numbers of results suggest that growth factors consumed in milk are biologically active and important at various developmental stages.

Epidermal growth factor (EGF)

One of the most extensively studied growth factors is EGF (28). EGF induces proliferation and functional maturation in the small intestine (11, 56). It has been hypothesized that luminal EGF may play a regulatory role in intestinal proliferation and ontogeny, because EGF is the most potent mitogen in breast milk (11, 186). The mechanisms involved in EGF-stimulated changes in physiological function are suggested to be stimulated by ligand-dependent tyrosine phosphorylation of substrates of the EGF receptor tyrosine kinase (21). Because the levels of circulating EGF are low (about 1 ng/ml), the milk to plasma ratio of EGF is higher than other reported milk hormones and ranges up to several hundred-fold. Beardmore et al. (8) detect highest levels of EGF in mouse milk in the middle of the suckling period. The pioneering study of Cohen and Taylor demonstrating that oral administration of EGF to newborn mice causes precocious eyelid opening was published in 1972 (37). Absorption of "intact" EGF was demonstrated in rats, mice, and sheep. In studies in humans, the potential significance of presence of EGF in breast milk is further stressed by its absence in infant formulas. Britton et al. showed the stability of 125 I-human recombinant EGF against gastric degradation (22). These data support the concept of substantial gastric survival of ingested EGF in a potentially biologically active form in preterm infants. EGF has been shown to be one of the major growth-promoting factors in human milk, since most of its mitogenic activity on cultured human fibroblasts is lost after addition of antibodies against EGF (29). Feeding of EGF was followed by an increase in DNA synthesis, RNA transcription, and a stimulated subsequent protein synthesis (28) as well as a stimulation of glucose, water, and electrolyte transport (126), as Milovic et al. (115) showed in Caco-2 cells, which have close morphologic and functional characteristics of normal enterocytes. EGF is followed by an increased polyamine uptake as well as it increases the activity of ornithine decarboxylase, a crucial enzyme for polyamine syntheis (55). The importance of external polyamine uptake is emphasized by the fact that in cells with a high demand for polyamines, polyamine uptake can completely substitute for synthesis (154). EGF has also been shown to affect gastrointestinal motility (173). EGF receptors were found in the stomach wall of suckling rats (140) and in cultured myocytes from newborn rabbit gastric fundus (200). Recently, Shinohara et al. (155) presented evidence that EGF delays gastric emptying and small intestinal transit in suckling rats.

Granulocyte-macrophage colony-stimulating factor (GM-CSF)

In breast milk are present significant amounts of GM-CSF (100.4 ± 193.9 pg/ml)(160). As the GM-CSF production by neonatal T-cells is diminished (48) and the cord serum concentrations are decreased (160), the GM-CSF in breast milk could represent a compensatory mechanism and have, for instance, favorable effects on

neutrophil chemotaxis that is impaired in neonatal granulocytes (145).

Thyroxine

The developoment of the thyroid gland size during the first months of life shows that infant formulas, despite their supplementations with adequate amounts of iodine (6-11.5 µg I/dl) (16), still lead to a significantly larger thyroid gland volume than alimentation with mothers milk (16). As suggested by Böhles et al. (16) this difference may be caused by the significant amounts of thyroid hormones present in breast milk. According to the literature about 10 µg thyroxin/dl and 10 - 400 µg triiodothyronin/dl have been measured in breast milk (117, 164, 190). It is, therefore, understandable that breast feeding can deliver sufficient amounts of thyroid hormones to mitigate even hypo thyroidism, as reported by several authors (15, 146, 174, 175). As transient neonatal hypothyroidism is very common in preterm infants, the results of a study presented by Den Ouden et al. (44), relating neonatal thyroxin blood levels with neurodevelopmental outcome at age 5 and 9 years, may be of future importance. Both neurologic dysfunction at age 5 years and school failure at age 9 years were significantly related to lower neonatal thyroxine levels even after adjustment for other perinatal factors (odds ratio 1.3).

Microbes

For centuries, fermentation of milk products using specific bacteria has been a way to preserve dairy foods. In 1908, Metchnikoff suggested that ingested lactobacilli could displace toxin producing microorganisms in the gastrointestinal tract and, thus, promote health (114). It was also recognized that germ free animals are more susceptible to infection than animals colonized with microflora (172). Since most diarrheal disease is secondary to enteric infection by viral or bacterial pathogens, it makes sense that modifying the intestinal flora by exogenously providing “good bacteria” could help prevent or treat infectious diarrhea. The most commonly used and reported germs include lactobacilli (L. acidophilus, L. casei, L. bulgaricus) and bifidobacteria (B. bifidum, B. longum, B. breve, B. infantis, B. animalis). There is evidence that L. acidophilus and related strains can adhere to the intestinal mucosa (102). Adherence is believed necessary for adequate, long-term colonization of the gut. A study published by Langhendries et al. (101) were able to achieve colonization with bifidobacteria in infants receiving a whey adapted acidified formula containing 10^6 viable B. bifidum organisms/g powder. Fehlandt et al. (53) confirmed these results demonstrating bifidobacteria colonization after administration of lyophilized germs (9 x 1.25 x 10^8 bifidobacteria). In the group of infants with bifidobacteria dominance fewer cases of septicemia were observed. Bifidobacteria supplementation may be of special interest in newborns delivered by cesarian section because their pattern of bacterial colonisation is dominated by hospital germs whereas in those delivered vaginally maternal germs of the vagina and the skin are leading.

Conclusion

There is an almost innumerable amount of substances present in breast milk. Only with respect to some compounds have we hitherto reached certainty about their importance for supplementation. Regarding many substances present in breast milk we are unable to distinguish whether they are mere byproducts of the mammary gland or whether they play a teleological role in infant nutrition. We would, therefore, like to suggest the promotion of problem oriented supplementation packages which can be added to the basic formula according to the defined developmental or clinical situation like for instance:

Problem:	*Supplementation package:*
Short bowel syndrome	EGF, nucleotides, polyamines, glutamine, vitamins
Chronic inflammation:	ω-3-fatty acids, vitamin E, carnitine, antioxidants, cysteine
Infections:	antioxidants, cysteine, oligosaccharides, lysozyme, lactoferrin
Diarrhea:	LCP, taurine, antioxidants, cysteine, nucleotides, lactoferrin, lysozyme

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