Human Milk

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Human milk is considered the most advantageous source of nourishment for infants. Even though there is no ideal composition of human milk, it still contains a unique combination of components that contribute to brain development.

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1. Introduction

Previous research has shown that human milk, as well as the act of breastfeeding, induce both short-term benefits such as optimal colonization of the intestinal microbiome, protection against infectious diseases, decreased infant mortality from all causes, and long-term benefits such as the reduced risk of obesity and type 2 diabetes, and improved cognitive performance [1][2][3]. respectively, HM contains a large range of bioactive components such as growth factors, hormones, antimicrobial components, digestive enzymes, transporters, and maternal cells (e.g., stem cells, leucocytes). Moreover, many studies have shown that HM helps the neurodevelopment of both term and preterm babies and these benefits may stem from the different composition of HM compared to artificial infant formula [4][5]. Moreover, further studies are needed to identify specific mechanisms of action of components of human milk involved in the neurodevelopment of the infants.

2. Human Milk Composition

HM is characterized by its optimal adaption in composition to infant needs providing nutritional and bioactive factors [6]. The variations in the HM composition are dependent on lactation stage, gestation, maternal diseases, and diet [7][8][9]. HM is made up of 87% water and the rest consists mainly of macronutrients such as carbohydrates, proteins and lipids [4][10].

In addition to the nutritional components, there are many bioactive components in HM such as antimicrobial factors, cytokines and anti-inflammatory substances, hormones, growth modulators and digestive enzymes, which influence biological processes or substrates, playing an important role in the health of the infants. Due to the immaturity of the digestive and immune system, these components have an important role, especially in neonatal life [11][12]. Among the bioactive components, breast milk is rich in miRNAs, small non-coding RNA that within membranous vesicles, such as exosomes, are present in body fluids and can mediate intracellular communication. Many studies have revealed that breast milk miRNAs, through the infant's systemic circulation, can perform tissue-specific immunoprotective and developmental functions in a newborn.

Furthermore, its composition varies according to the lactation stage and between preterm and term breast milk [13][14]. The first form of milk produced in the early days after birth is colostrum. A delayed onset can occur in the event of preterm birth or caesarean section. After five days to two weeks after giving birth, the milk will be considered largely mature.

3. Macronutrients in Human Milk Involved in Neurodevelopment

HM contains macro- and micronutrients that are essential during the neonatal period [15] .

Lactose, a disaccharide and an excellent source of slow-release energy is the main carbohydrate in HM and seems to exert modeling effects on the intestinal microbiota and promote brain development [16].

Proteins act as nutritional support and as carriers of other nutrients. The most abundant proteins are casein, α-lactalbumin, lactoferrin, secretory immunoglobin A (IgA), lysozyme and serum albumin. Non-protein compounds of HM such as urea, uric acid, creatinine, amino acids and nucleotides comprise about 25% of nitrogen.

The main energy source in HM is lipids, providing polyunsaturated fatty acids (PUFA), fat-soluble vitamins, complex lipids and bioactive compounds. The composition of HM fatty acids, especially long-chain polyunsaturated fatty acid (LCPUFA), is widely influenced by the maternal diet. The omega-6 fatty acid (linoleic acid) and the omega-3 fatty acid (α-linolenic acid) are dietary precursors of LCPUFA and most abundant HM fat. LCPUFAs include docosahexaenoic acid and arachidonic acid, which are involved in important physiological processes such as growth and immune response and are critical for brain development [17][18][19][20].

Among the components of HM, oligosaccharides (HMOs) are the third most abundant components after lipids and lactose, and differ significantly between HM and infant formula in concentration [21]. Most HMOs can be synthesized de novo by the mother and transferred to the fetus through the umbilical cord or later via breast milk. recently showed that at equivalent lactation stage and post-menstrual age the composition of the preterm and the term breast milk differs in HMO concentration. Since HMOs are absent in infant formula, causing newborns not to receive the same health benefits as breastfed infants, a mixture of galactooligosaccharides (GOS) and fructoligosaccharides (FOS), also called inulin, has been developed and is added to certain products.

Conjugant sialic oligosaccharide concentration in human colostrum undergoes marked changes in the first 3 days of lactation, following the physiological needs of newborns [22], demonstrating the importance of dynamic changes in the composition of maternal milk for brain development. compared the SA concentration in the frontal cortex of 25 infants who died of sudden infant death syndrome by using high performance liquid chromatography. Dietary supplementation with SL induces positive functional brain effects and increases the expression of genes related to SA metabolism, myelination and ganglioside biosynthesis in the hippocampus at 3 weeks of age, suggesting that SL may represent an important supplement for infant formula to promote the development of the preterm neonatal brain [23]. Identifying the specific "effects" of HM components on infant brain development is currently a complex research field.

4. Micronutrients in Human Milk Involved in Neurodevelopment

Iron, folate and zinc have a critical role in brain development and function. Total HM iron concentrations reach a maximum in colostrum and subsequently decrease during the first year of lactation; after 6 months of age, iron supplementation has been recommended because the concentrations in HM are insufficient for infant requirements [24]. The predominant form of folate in HM is 5-methyltetrahydrofolate; its concentration is low in colostrum with progressive increase after childbirth, reaching a peak at 2–3 months and then remaining stable [25]. Zinc concentrations in HM decrease abruptly from colostrum to transitional milk, followed by a gradual reduction during lactation.

Choline is an essential micronutrient for the development of the fetus and newborn. It is the precursor of many important compounds such as phospholipid, phosphatidylcholine, and sphingomyelin membranes, and a precursor of the acetylcholine neurotransmitter. Choline deficiency leads to persistent cognitive and memory deficits [26]. Breast milk choline concentrations increase between 7 and 22 days postpartum and remain stable in mature milk [27].

Iodine is a micronutrient that plays a vital role in the production of thyroid hormone (TH); a severe iodine deficiency is associated with mental retardation in newborns. Pregnant women are prone to iodine deficiency due to the double iodine requirement during pregnancy. Iodine concentrations reach a maximum in colostrum, and then decrease over the next few weeks until they reach a plateau at 100–150 µg/L in mature milk. The use of iodized salt during breastfeeding allows the transfer of adequate amounts of iodine to newborns through mother's milk, preventing iodine deficiency [28].

Calcium plays a vital role as a second messenger in signal transduction, which controls the production of neurons and glial cells. Total calcium concentrations in breast milk increase abruptly in the first 5 days of breastfeeding and then gradually decrease throughout breastfeeding [24].

Vitamin B-6 is an essential cofactor for more than 100 enzymes involved in amino acid metabolism, glycolysis, and gluconeogenesis. Vitamin B-6, especially in form of pyridoxal, increases in the first few weeks postpartum, followed by a gradual decline in late lactation; after 6 months of age, supplementation of Vitamin B-6 is needed because the concentration in human milk appears insufficient for infants' vitamin B-6 requirements. Deficiency of vitamin B-6 is associated with neurological and behavior abnormalities [29].

Vitamin B-12 plays a fundamental role in the preservation of the myelin sheath around neurons and the synthesis of neurotransmitters, and its deficiency can cause damage to the myelin sheath leading to syndromes such as myelopathy, neuropathy, and neuropsychiatric disorders. The total concentration of vitamin B-12 in breast milk decreases at the beginning of lactation, then remains stable for up to 12 weeks and then slowly decreases [30][24].

Vitamin C plays an important role in developing neurons through their maturation and differentiation, and in forming myelin. The total concentration of ascorbic acid (AA) in breast milk is greater in colostrum and decreases during lactation depending on the difference in maternal status and food intake [30][24].

Vitamin D plays an important role in brain development, inducing the nerve growth factor (NGF), promoting neurite growth, and inhibiting neuronal apoptosis in the hippocampus [30]. The levels of vitamin D, regardless of the maternal diet, are low, suggesting a necessary supplementation of vitamin D to the infants [13][31].

Detailed concentrations of micronutrients in human milk are shown in Table 1.

Table 1. Micronutrient concentration in human milk.

Micronutrient	First Weeks of Lactation		References
	Preterm Group	Term Group	
	33 w (27–37 w)	40 w (39–41 w)	
	(Mean ± SD)	(Mean ± SD)	
Iron [mg/L]	1.35 ± 0.42	1.02 ± 0.37	[32][33][34]
Folate (Vitamin B-9) [ng/mL]	21 ± 14	30.4 ± 10	[35]
Zinc [mg/L]	2.25 ± 0.95	2.6 ± 1.1	[32][36][37]
Choline [mg/L]	158 ± 10	258 ± 10	[37][38]
Iodine [mg/L]	0.092 ± 0.67	0.087 ± 0.41	[32]
Calcium [mg/L]	289 ± 25	279 ± 30	[32][39][40]
Vitamin B-6 [ng/mL]	33 ± 0.30	53 ± 0.40	[29][35]
Vitamin B-12 [ng/mL]	0.55 ± 0.11	0.33 ± 0.20	[29][35]
Vitamin C [mg/L]	53 ± 18.7	45 ± 15.8	[41][42][43]
Vitamin D [ug/L]	1.36 ± 0.16	0.86 ± 0.10	[44]

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