Balance between contaminants and antioxidants in breast milk

BALANCE ENTRE CONTAMINANTES Y ANTIOXIDANTES EN LECHE MATERNAL

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Abstract

This study provides information on the factors that affect the load of contaminants and antioxidant defenses in breast milk. It is important to understand the role of the balance between contaminants and antioxidants during breastfeeding.

This period of high vulnerability is due to the fact that the infant depends solely and exclusively on breast milk for its growth. Exposure to pollutants can affect brain development, an impact that cannot be measured in the short-term but would be expressed in the medium- and long-term. The way in which antioxidants and related enzymes in breastmilk contribute to detoxification is still unknown. This review suggests that a marine origin diet provides a significant advantage because of the large number of micronutrients it contains, including fatty acids that are important for brain development in infants, potentially providing balance against the amount of pollutants it may contribute.

Keywords: Antioxidants, breast milk, fish, marine diet, micronutrients.

Resumen

Este manuscrito proporciona información sobre los factores que contribuyen a la exposición de contaminantes y el beneficio de las defensas antioxidantes en la leche materna. Es importante comprender el papel del equilibrio entre los contaminantes y los antioxidantes durante la lactancia. Este período de alta vulnerabilidad se debe al hecho de que el neonato depende única y exclusivamente de la leche materna para su crecimiento. La exposición a contaminantes puede afectar el desarrollo del cerebro, un impacto que no se puede medir a corto plazo y se expresará a mediano y largo plazo. La forma en que los antioxidantes y las enzimas relacionadas en leche materna desempeñan el papel de la desintoxicación es aún desconocida. En esta revisión, sugerimos que la dieta de origen marino proporciona una ventaja significativa debido a la gran cantidad de micronutrientes que proporciona, incluyendo ácidos grasos que son muy importantes para el desarrollo del cerebro en los infantes, balanceando potencialmente la cantidad de contaminantes que podría aportar.

Palabras clave: Antoxidantes, dieta de origen marino, leche materna, micronutrientes, pescado.

Introduction

Breast milk as a nutrient for newbo

Regardless of the socioeconomic or health status of the mother, breast milk provides a unique and specific combination of nutrients and immune factors (Picciano, 2001). Colostrum, produced during the first week postpartum, is rich in proteins, antibodies, various nutrients and antioxidants, and is a good source of vitamins, such as vitamin A, vitamin E, and carotenoids (Neville, 1995; Saint et al., 1984). Transition milk is produced during the second week postpartum; protein and salt content is lower, but the concentration of lipids, carbohydrates (lactose), and vitamins is higher, than in colostrum (Shellhorn and Valdés, 1995). In the mature milk, produced after the second week postpartum and for the remainder of the lactation, vitamin and water content are increased (Lawrence, 2007).

Breast milk is rich in proteins. Casein stimulates the infant´s immune system, contributes to absorption of calcium ions, and possesses antithrombotic, antihypertensive, and opioid activities (Lönnerdal, 1985; Lönnerdal, 2003; Migliore-Samour and Jolles, 1988). Lactalbumin is one of the most abundant proteins in breast milk and contains enough cysteine and tryptophan to meet the infant's requirements; these amino acids are essential for growth and nitrogen balance, and are a limiting factor in formula and bovine milk (Hanning et al., 1992; Heine et al., 1991; Lien, 2003). Lactoferrin, found in elevated concentration in colostrum, can bind iron atoms such that microorganisms cannot use it to proliferate, exerting a bacteriostatic effect in the infant's intestine, in synergy with immunoglobulins (Giansanti et al., 2016). Immunoglobulins A, G and M are abundant in breast milk, particularly in colostrum, and provide the capacity to synthesize antibodies that bind microorganisms and, thus, prevent pathogens from crossing the infant's intestinal mucosa (de Ferrer, 2000; Hamosh, 1998; Xanthou, 1998). Functional proteins, enzymes, are also present in breast milk. Among them, lysozyme acts as a bactericide breaking the β-1,4 bonds in bacterial cell walls, and lipase contributes to lipid hydrolysis and absorption in the infant's gastrointestinal tract (Lönnerdal, 1985).

Amino acids, nucleotides, carbohydrates and other molecules are also found in breast milk. Nucleotides contribute to modulation of the immune system, development of bifidobacteria and maturation of the gastrointestinal tract (Uauy, 1994). Free fatty acids have antimicrobial and anti-inflammatory activities, thus protecting the infant from protozoa, bacteria and viruses (Hamosh, 1998) The amino sulfonic acid taurine is abundant in breast milk; its deficiency affects the function of the retina (Gaull, 1989). Lactose, a disaccharide synthesized from glucose, contributes to the energetic requirements of the infant, favors build-up of acidophilic bacteria and promotes intestinal calcium absorption, due to the catalytic function of intestinal lactase (Cochet et al., 1983; de Ferrer, 2000). Oligosaccharides, because their structure is similar to that of epithelial intestinal cell receptors, can compete with pathogenic microorganisms, contribute to maintain an acidic pH, and have a prebiotic effect in the infant; over 20 oligosaccharides in breast milk have the capacity to bind competitively to pathogens in the digestive, respiratory and urinary systems (Gudiel-Urbano and Goñi, 2001; Kunz and Rudloff, 1993; Uauy, 1994; Yamashita et al., 1977).

Breast milk as carrier of contaminants (trace elements and pesticides) – maternal detoxification, infant contamination?

A number of contaminants and xenobiotics (substances that are foreign to the body), including trace elements and pesticides, that the mother obtains from food, water, air, and the environment in general, can make their way to breast milk (Esteban and Castaño, 2009). Because of their lipophilic characteristic, many contaminants can be bioaccumulated and their concentration can increase throughout the trophic chain (a phenomenon known as biomagnification) (Sonawane, 1995). The concentration of lipids in breast milk depends mainly on lipase enzymes; however, the lipid composition is determined by the mother's storage of lipids in the adipose tissue and her diet during pregnancy and lactation (Mena and Milad, 1998). Migration of lipids during lactation can function as a detoxification mechanism for the mother, but can favor the transference of lipophilic contaminants to the infant, via breast milk. Some of the lipophilic contaminants can be humoral antagonists or endocrine disruptors and can induce, amongst other complications, abnormalities in the reproductive system, damage to tissues such as brain, liver, kidney or the immune system of the infant (Colborn et al., 1993).

Trace elements in breast milk

Trace elements are found in breast milk. Some of these elements are nutrients required in the diet, weather in small amounts to fulfill physiological functions, or acting as either structural components or cofactors in enzymes. These elements, also known as microelements, contribute to the maintenance of the immune defenses, the antioxidant system and the genetic expression (Strachan, 2010). Iron (Fe) is required for erythrocyte (red blood cell) production, oxygen transport and cognitive development (Beard and Connor, 2003). Zinc (Zn) is essential for the infant's growth and development, contributes to the development of the immune system and in other physiologic processes, is a structural part of some hormones, and acts as cofactor of certain enzymes that participate in metabolic processes. Copper is necessary for the optimal function of Fe, is a cofactor in glucose metabolism and in the synthesis of hemoglobin, connective tissue and phospholipids (Lonnerdal, 1997).

However, some of the trace elements can also have toxic effects. Elements such as cadmium (Cd), lead (Pb), arsenic (As) and mercury (Hg) can be integrated as part of the trophic chain and, depending on the element's speciation, the type of diet and nutritional state of the individual, can induce toxicity (Gaxiola-Robles et al., 2014) . Trace element toxicity depends mainly on their transport across cell membranes, which can be affected by solubility, volatility, molecular weight, and the presence of specific transport mechanisms (Ferrer, 2003).

The main source of exposure to As is food, including fish, shellfish, mushrooms, poultry and, in smaller amounts, meat, milk and vegetables (Jomova et al., 2011). Permissible limits for As in breast milk and drinking water are between 1 and 25 μg L^{-1} (Gaxiola-Robles et al., 2014). Most studies report As concentration in breast milk under the permissible limits. For example, breast milk As levels were reported at 0.68 μg L^{-1} in Taiwan (Chao et al., 2014), at 3.2 μg L^{-1} in the Andean region of Colombia (Alonso et al., 2014), and at 0.67 μg L^{-1} in Baja California Sur (Castillo Castañeda, 2017).

Mercury is found in nature; sources of exposure to Hg are, among others, fossil fuels, metallurgy, processing of petroleum and cement, waste water treatment (Behrooz et al., 2012). Increased Hg concentrations have been reported in association to diets rich in fish and shellfish, especially marine fish (Acosta-Saavedra et al., 2011). Permissible limits for Hg in food are in the range of 0.001 to 1 mg kg^{-1} (Gaxiola-Robles et al., 2014). In breast milk, Hg concentrations were reported to be on average in Spain 0.53 μg L^{-1} and 0.62 μg L^{-1} in women with high fish and shellfish consumption (134 g d^{-1})(García-Esquinas et al., 2011); in Iran, 0.4 μg Hg L^{-1} (Behrooz et al., 2012); in Austria, 1.59 μg L^{-1} (Gundacker et al., 2002); in Taiwan, 2.03 μg L^{-1}, with no difference between women who live in the city or near fishing camps (Chien et al., 2006) and in Baja California Sur 1.54 μg L^{-1} with no effect due to including fish in the mother's diet (Castillo Castañeda, 2017; Gaxiola-Robles et al., 2014). Elements such as selenium (Se) interfere with Hg metabolism by either forming a Hg-Se complex or competing for binding sites, decreasing its bioavailability and toxicity (Gaxiola-Robles et al., 2014). In Taiwan, Hg concentration was lower in breast milk from women who included Se from. The elevated content of vitamin E and Se in food of marine origin, besides providing an antioxidant defense, contribute to maintain relatively low levels of Hg (Chien et al., 2006; Gundacker et al., 2002).

Organochlorine pesticides in breast milk

Pesticides contribute to maintain human health by controlling vector-borne diseases and eradicating pests from agriculture. Because increased reproductive and neuronal issues, as well as increased incidence of diseases such as diabetes and cancer in humans were reported in association with persistent organochlorine pesticides (POPs), their use was banned in developed countries >40 years ago, and in Mexico 17 years ago (Ramírez et al., 2003). The use of POPs for agricultural application, as well as the presence of POPs in tissues from several mammal species in the Baja California peninsula have been reported (Nino-Torres et al., 2009).

Along with biomolecules, POPs are mobilized through the mother's body during lactation and, because of their lipophilic character, are excreted in breast milk (Waliszewski et al., 2000). Several factors, such as age, body mass index (MBI), diet and number of pregnancies (parity) have been related to POPS concentration in breast milk. Presumably because of accumulation of POPs in the mother's adipose tissue, age is associated to increased POP levels in breast milk (Chávez-Almazán et al., 2014). Eating foods of animal origin, preferentially those rich in fat, has been associated to a higher concentration of POPs (Azeredo et al., 2008). Parity has been negatively correlated to POP concentrations in breast milk; this is assumed to be related to the elimination of contaminants in every reproductive event and subsequent lactation period (Sudaryanto et al., 2008).

In breast milk of women from Veracruz, elevated concentrations of dichlorodiphenyltrichloroethane (DDT) (0.651 mg kg^{-1}) and of its main metabolite dichlorodiphenyl-ethylene (pp´DDE) (3.997 mg kg^{-1}) were reported (Waliszewski et al., 2001). Higher concentrations of β-hexachlorocyclohexane, dieldrin, aldrin, heptachlor, DDT and DDE were reported in breast milk from women of urban areas than those of rural zones; this is assumed to be due to the continuous use of pesticides in urban homes (Prado et al., 2004). In 2008, over 30% of the breast milk samples collected from women in Yucatán, were reported to contain POPs, including DDT, at levels above the acceptable daily ingestion established in 2006 by the Food and Agriculture Organization of the United Nations (FAO) (0.1 μg kg^{-1}) for POPs (Rodas-Ortíz et al., 2008). In Guerrero in 2014 lower POP concentrations were reported in comparison to those found in previous years in other areas of the country (Chávez-Almazán et al., 2014). Therefore, it is suggested that POP levels in the overall population are decreasing since the prohibition of production and use of POPs in Mexico of 1991, ratified in 2001 (eliminated: aldrin, hexachlorocyclohexanes, chlordanes, dieldrin, endrin, heptachlor, hexachlorobenzene, lindane; restricted: DDT) in the Stockholm Convention (Ramírez et al., 2003).

Factors that affect trace elements and organochlorine pesticides concentrations in breast milk

The mother's age is related to pollutant concentrations found in breast milk. A positive relationship between maternal age and POPs levels in breast milk was reported (*ANOVA,* $p < 0.002$) (Zhou et al., 2012). Significant correlations have been found between age and POPs, specifically HCHs and DDTs ($r = 0.36$ y $r = 0.34$, respectively) concentrations in adipose tissue in humans (Aulakh et al., 2007). However, there are also reports where no significant differences in POPs content in breast milk were found associated to age, but were related to marine-origin food, particularly contaminated fish (Azeredo et al., 2008). In Baja California Sur, no significant correlations were found between mother's age and POP content in breast milk (Castillo Castañeda, 2017). Concentration of POPs in adipose tissue is product of exposure and bioaccumulation, while in breast milk POPs derive from mother's adipose tissue and her diet during lactation (Migliore-Samour and Jolles, 1988).

Higher content of DDE and total chlordanes (528 ng g^{-1} lipid, 45 ng g^{-1} lipid, respectively) were reported in people with a BMI > 25.6 kg m^{-2} (Hardell et al., 2010). Positive correlations have been found between BMI and concentrations of βHCH ($r = 0.171$, $p = 0{,}044$) and ∑HCH ($r = 0.171$, $p = 0{,}044$) in breast milk samples (Lu et al., 2015). In Baja California Sur, a positive correlation was reported between BMI and ∑HCH ($r = 0.23$, $p > 0.05$). This can be due to the lipophilic characteristic of HCH and consequent persistence in tissues with elevated lipid content (Lu et al., 2015).

Antioxidants, reactive oxygen species and oxidative damage in breast milk

Antioxidant capacity, defined as the capacity of neutralizing the reactivity of or inhibiting the production of ROS (Thornalley and Vašák, 1985), in breast milk is higher as compared to formula (Hanna et al., 2004). Antioxidants (enzymes and other proteins, vitamins, and low molecular weight molecules) in breast milk contribute to avoid oxidation of lipids and proteins, and serve as an additional defense for the infant (Lindmark-Månsson and Åkesson, 2000).

The antioxidant enzyme superoxide dismutase (SOD) catalyzes the dismutation of superoxide radical to hydrogen peroxide (H_2O_2). In biology, three types of SOD, depending on the metal (Fe, manganese (Mn), or copper and zinc) bound to the enzyme, are known (Fridovich and Freeman, 1986). In breast milk, the main isozyme is Mn-SOD (Lindmark-Månsson and Åkesson, 2000). Catalase (CAT) subsequently decomposes H_2O_2 into water and oxygen (Gaetani et al., 1996; Halliwell, 2007). Glutathione peroxidase (GPx) also metabolizes H_2O_2 as well as other peroxides; one of the GPx isoforms has selenium (Se) bound to its functional site; Se is oxidized by H_2O_2 and is then reduced by glutathione (GSH), which is converted to its oxidized form (GSSG). Glutathione reductase (GR) reduces GSSG is back to GSH in a redox cycle (Halliwell and Gutteridge, 2007). The antioxidant enzyme glutathione S-transferase (GST) participates in the process of detoxification of biomolecules and xenobiotics, in reaction that also utilize the GSH-GSSG redox cycle (Halliwell, 2007).

Vitamin A and vitamin E content is three times higher, while carotenoid level is ten times higher in colostrum than mature milk (Stoltzfus and Underwood, 1995).

The main function of vitamin C (or ascorbic acid) is as an antioxidant and as cofactor in enzymatic reactions that occur during bone and cartilage development (Iqbal et al., 2004). Vitamin A participates in different biological functions, is part of the visual pigment rodopsin which allows for vision under low light (Zile and Cullum, 1983) and is needed for growth and immune response (Sun, 2012); its concentration varies in breast milk, for it is dependent on the mother's diet (Khachik et al., 1997). Vitamin E is a potent antioxidant; this is relevant in breast milk given its elevated concentration of polyunsaturated fatty acids, which are highly susceptible to oxidative damage (Sun, 2012) .

Oxidation of molecules such as lipids, proteins, and nucleic acids can originate an oxidative stress state; that is, an imbalance between prooxidants and the antioxidant defenses in favor of the former, generating molecular and cellular damage (Castillo Castañeda, 2013). Oxidant agents can be exogenous (xenobiotics) or endogenous (ROS) (Castillo Castañeda, 2017). Reactive oxygen species (ROS) are molecules, including free radicals, that are highly reactive, have a very short half-life and can oxidize all types of molecules (Halliwell and Gutteridge, 2007). In mammals, ROS participate in a suite of physiological and pathological processes, such as defense against microorganisms (Halliwell and Gutteridge, 2007).

Factors that affect antioxidant defenses in breast milk

The concentration of antioxidants in breast milk depends on the mother's diet, her place of residence and her lifestyle (Sadeghi et al., 2009). Activity of SOD is 10 to 25 times higher in breast milk than serum (L'abbe and Friel, 2000), its activity changes throughout lactation, being higher in colostrum and decreasing after 4 months (Kasapović et al., 2005). In Baja California Sur, increased activities of SOD (45.6%), CAT (65%), GPx (205%), and GST (117%) were found in breast milk from women with 3 or more pregnancies as compared to women with 1 pregnancy (Castillo Castañeda, 2013).

The presence of toxic trace elements and pesticides can increase production of reactive oxygen species (ROS), such as superoxide radical ($O_2^{\bullet-}$) and hydroxyl radical ($^{\bullet}OH$), and lead to an imbalance between these pro-oxidants and the antioxidant defenses which can result in oxidative stress (Halliwell, 2007). Therefore, the content of trace elements and pesticides in breast milk will affect the antioxidant capacity and the biomarkers of oxidative damage. Positive relationships have been reported between concentration of pesticides (α-HCH, γ-HCH and total HCHs) and the concentration of malondialdehide (MDA; biomarker of oxidative damage to lipids), as well as a negative relationship between POPs concentration and the content of the antioxidant GSH, in human placenta (Agarwal et al., 2012). POPs affect metabolism (glucose transport, glycolysis, mitochondrial activity and oxidation of fatty acids) and are associated to an increase in lipid and protein oxidation due to increased ROS production via induction of the cytochrome P450 complex (Androutsopoulos et al., 2013). In breast milk from women from Baja

California Sur, a weak correlation between POPs content and oxidative damage to lipids (quantified as TBARS levels) and proteins (quantified as protein carbonyls concentration) was observed (Castillo Castañeda, 2017). This can be the product of antioxidants (enzymatic and non-enzymatic) in breast milk neutralizing ROS and their effects.

Discussion

Balance between contaminants and antioxidants in breast milk – advantages for the neonate.

The main source of exposure to contaminants is suggested to be through the diet, especially animal food products with elevated fat content (Nag and Raikwar, 2011). A marine diet has been related to the presence of high concentrations of POPs in populations around the World (Fujii et al., 2012). For instance, in Brasil, POP content in breast milk was associated to the type of diet, characterized by a high consumption of marine fish as the main source of protein; fish in which the presence of POPs has been reported (Azeredo et al., 2008). In the coasts of the Gulf of California, 13 POPs (aldrin, dieldrin y δ-HCH (100%), endosulfan 1, endrin, heptachlor epoxide and y methoxychlor (80%)) were reported in different fish species of commercial value (Reyes-Montiel et al., 2013). Fish may be exposed to waste water and residues from agriculture drained into lakes, rivers and/or directly into the ocean, leading to storage and bioacumulation of trace elements and POPs in fish tissues. Further, these contaminants can be transferred to humans by ingestion of contaminated products (Pazou et al., 2013). However, food of marine origin (fish and shellfish) also have an elevated content of proteins, of enzymatic and non-enzymatic antioxidants (including carotenoids and vitamins), of elements and minerals that contribute to enzyme activity (such as Fe and Se), as well as of ω-3 and ω-6 fatty acids (Corredor and Landines, 2009) which may contribute to avoid or alleviate the effects of contaminants and xenobiotics (Hamre, 2011).

Recommendations

Many coastal communities, such as those in Baja California Sur, base their diet on fish and other staple products such as rice, beans and corn. However, consumption of staple products by themselves represents an exposure to contaminants almost comparable to fish intake without the beneficial antioxidants and micronutrients associated with seafood. Therefore, the potential risk of toxicity to the unborn fetus and neonates is higher from consumption of rice beans and corn than fish or shellfish.

World-wide, the population has been exposed to different contaminants, including heavy metals, pesticides, plastics and electronic and pharmaceutical waste. Until now, there are few comprehensive studies, making it difficult to assess the global load of contaminant exposure through food intakes. In this review we suggest that a diet of marine origin provides a significant advantage because of the large number of micronutrients it provides, greater than the amount of pollutants it may contribute. Fatty acids that are found in fish are of great importance for brain development in infants, so the intake of marine products should be recommended during pregnancy and lactation. Therefore, in this study we addressed the influence of consumption of fish and shellfish, particularly of marine origin. In this type of studies, it is relevant to assess not only the contaminant load, but also the levels of antioxidants and other nutrients that food items may provide to the mother and, via breastmilk, to the infant. We suggest that a diet of marine origin provides micronutrients, fatty acids, vitamins and antioxidants that are important for the appropriate development of infants.

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