Acta Scientific paediatrics (ISSN: 2581-883X)

Volume 6 Issue 10 December 2023

Review Article

Anti-Inflammatory Properties of Human Milk, An Ancient but Novel Concept

Enrique Chacón-Cruz[1]* and Eduardo Antonio Lara-Pérez[2]

[1]Independent Researcher/Consultant in Houston, Texas, USA and the Institute for Global Health, University of Siena, Italy

[2]Pediatrician, Retired from IMSS, Full Academician (Mexican Academy of Pediatrics) President and CEO of the Medical Fraternity for Health A.C. "Doctors United for Mexico"

***Corresponding Author:** Enrique Chacón-Cruz, Independent Researcher/Consultant in Houston, Texas, USA and the Institute for Global Health, University of Siena, Italy.

Received: March 15, 2023

Published: November 28, 2023

Abstract

As an evolutionary process acknowledging all its countless benefits, human milk (HM), has led to many types of studies: experimental (in vitro and in vivo), cohorts, etc., all with outcomes consistent on infant's protection. HM effects as neuroprotective, anti-infective, promotor of infant's development, and many more are known by everyone. The primary aim of this review is to inform the reader about this property in HM: Anti-inflammation. The document starts with a brief anthropological/historical glance of this property, following with in vitro and in vivo experimental studies done both in experimental animals, as well as in human cells, with emphasis on studies done by one of the co-authors. At the end, is expected that the reader recognizes HM anti-inflammatory effects as essential in the protection process of the infant against both infectious and non-infectious injuries, as well as to finally understand the leading mechanisms of action of HM anti-inflammation, such as its effects on neutrophils (polarization, phagocytosis, intra and extracellular response to calcium), on other inflammatory cells, interleukins, among others.

Keywords: Anti-Inflammatory; Human Milk, Breastfeeding

Introduction

Breastfeeding remains one of the most important strategies to protect infants against infectious diseases, both in terms of morbidity and mortality. Protection by human milk is established predominantly vs. gastrointestinal tract infections and diarrheal diseases due to both viral, bacterial and parasitic etiologies [1-5], but it has also been associated with protection vs. respiratory infections including otitis media [4-13], bacteremia/meningitis [4,14-17], and necrotizing enterocolitis [18,19]. All this enormous evidence of protection has already been explained by multiple mechanisms, such as optimal nutrition, reduced exposure to enteropathogens, increased growth of protective intestinal flora, immunological factors (lysozyme, lactoferrin, Immunoglobulin (Ig) A, presence of neutrophils and cells mononuclear cells, etc...), glycoconjugated substances that block the union of the pathogen with its receptor, increased thickness of the intestinal mucosa due to the presence of growth factors, among many others [18,20,21-28].

Exclusive breastfeeding during the first 6 months of life is a current universal recommendation, with minimal exceptions for its contraindication, such as maternal HIV infection or the intake of some drugs (such as fluoroquinolones) by the mother.

In this review we will delve into the anti-inflammatory properties of human milk, a concept little known by many, but obviously essential within the global role of immune protection of human milk.

Human milk and anti-inflammation

Observations consistent with anti-inflammatory properties of human milk are numerous. Clinically evident inflammation is ab-

sent in the early lactating breast, despite the presence of abundant neutrophils in the colostrum. Likewise, in some cultures erroneously called "primitive" (e.g., the Tarahumara) use human colostrum to manage neonatal conjunctivitis, an effect not only explained by its anti-infective activities.

There are already systematic reviews in which the different components or anti-inflammatory systems of human milk are analyzed [29,31], among which the following stand out, classifying them as soluble or cellular.

Soluble components

- Antiproteases: Essential function to unfold hydrolytic proteins released during the inflammatory response, and thus reduce tissue damage [29].
- Lysozyme: Present not only in tears, multiple anti-inflammatory mechanisms [29]. - Lactoferrin: Macromolecule that not only has anti-infectious activity, but also binds to some membrane receptors, thus preventing the penetration of enteropathogens [30]. - Secretory IgA: its non-opsonizing effect is well known, therefore it is not pro-inflammatory, unlike the IgG that predominates in cow's milk.
- Antioxidants: -tocopherol, cysteine, ascorbate and -carotenes, all of which confer activity vs. cell injury [31].
- Antibodies vs. Platelet Activation Factor (PAF): Said Factor is a potent pro-inflammatory [26].
- Presence of anti-inflammatory Interleukins (IL): Classically the presence of IL-10 [32]. - Presence of soluble factors: At least soluble receptors for IL-1 and for tumor necrosis factor-α (TNFα) have been isolated, which implies an "extramembrane" blockade of these strongly pro-inflammatory cytokines [35]. (see the following figure)

Cell components

Neutrophils with less lytic capacity: Point that we will discuss below

The sterile inflammation induced with acetic acid in the subcutaneous tissue of rats is dramatically decreased by previous contact with human colostrum, translated into a significant reduction in granulocytic presence [33] (see the following figure)

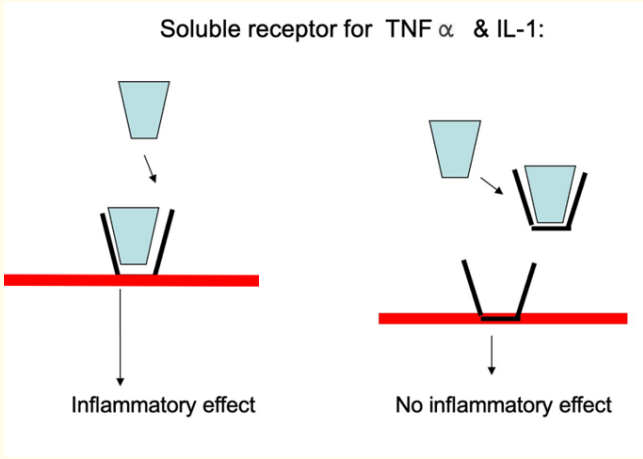

Figure 1

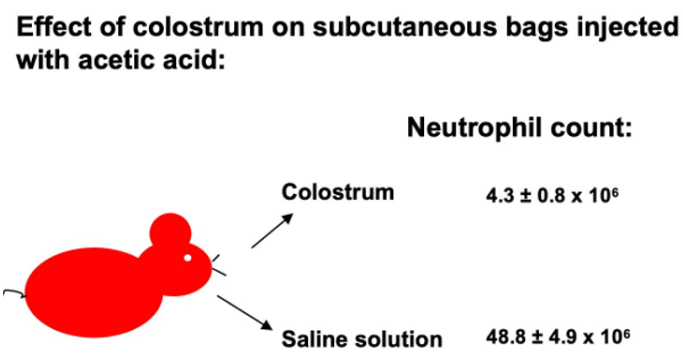

Figure 2

Enteral feeding with mature human milk significantly decreases colonic inflammation induced by acetic acid in the animal model, with also a significant decrease in the presence of granulocytes [34]. Many functions and capacities of neutrophils are negatively altered by pre-exposure with human milk, including Staphylococcus aureus clearance, adherence, deformability, chemotaxis, enzyme release, oxygen free radical release, actin assembly, and L-selectin release [35-38].

The vast majority of all granulocytic functions, if not all, depend on increases in cytoplasmic calcium concentrations.

Under normal conditions, after a physiological stimulus (bacterial formyl-peptide, IL-8, etc...), cytoplasmic calcium concentrations rise due to the release of calcium from intracellular stores, later calcium channels open, which allow an influx of this divalent cation into the cytoplasm, which allows a greater response, and at the same time restores intracellular stores to later be able to respond to a new stimulus (see the following figure)

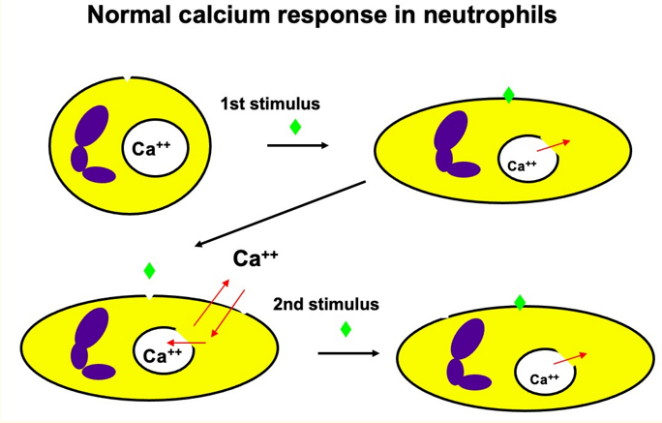

Figure 3

Exposure to human milk causes at least two independent effects on neutrophils, the first consisting of a partial release of intracellular calcium stores with partial depletion thereof, and later a block on the entry of this ion, leading to a even greater depletion of stores, and a generally diminished functional response [39,40] (see the following figure).

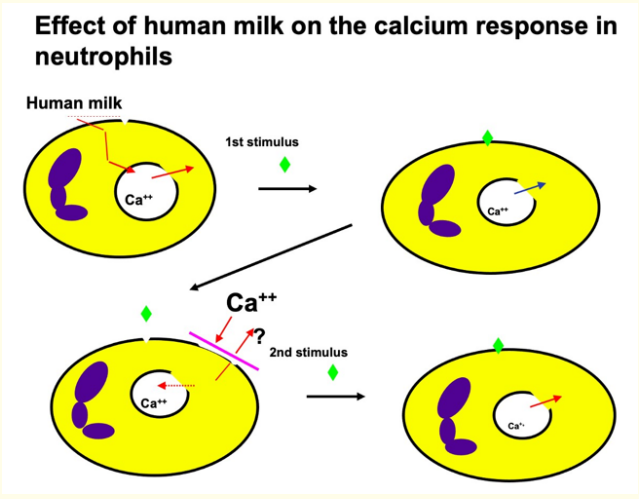

Figure 4

This explains the most viable mechanism of action of the antagonistic effects of human milk on granulocyte function: partial inhibition of calcium metabolism in at least two ways, leading to the presence of a hypofunctional neutrophil, with much less capacity for injury. tissue and pro-inflammatory. The aforementioned effects were observed with human milk concentrations as low as 0.1%, and such effects were not present with exposure to placebo or formulas (commercial milks) [36,39-41].

Conclusion

The inflammatory response, after an infection, is responsible for tissue, cellular and systemic damage, and the classic examples are serious infections such as sepsis, bacterial meningitis and osteomyelitis, where the participation of neutrophils and pro-inflammatory cytokines are responsible for multiple cases of morbidity and mortality.

The dilemma that is required as an approach is how, being anti-inflammatory, is human milk protective? Nobody has the answer, but there are two reasons that indirectly justify these effects: 1) all these anti-inflammatory properties have been around for thousands of years and 2) the evidence, to date, demonstrates an inhibitory/modulatory rather than an ablatory effect. Undoubtedly, much remains to be learned about human milk, which is more than a nutrient, it is an immunological/nutritional transplant that has evolved from an eventration of reptiles to what we know today [42], thus concluding that it does not breastfeeding implies going against the very evolution of the human species.

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