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THE MECHANISM OF IMMUNITY PROVIDED BY BREAST FEEDING

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Secretory IgA antibodies in human milk.

The mammary gland secretion has been known for a long time to contain factors of protective value for the suckling. Among these are unspecific factors including lactoferrin, lysozyme, complement factors, lactoperoxidase, bifidus factor and B-12 binding protein (14) as well as factors with specific immune functions such as immunoglobulins, phagocytes and T- and B-lymphocytes (2, 11). The dominating immunoglobulin in milk was shown to be IgA (8, 10) of the secretory type, SIgA (33).

The SIgA is composed of an IgA dimer stabilized by the polypeptide chain, the join chain (J-chain) and the secretory component (SC) (9, 33). The resulting molecule is more stable to pH-changes and enzymic degradation than the serum IgA antibodies (32). SIgA seems to provide efficient protection in variable millieux of different secretions and on various sites of mucous membranes in the body.

Early colostrum contains as much as 20 g/l of SIgA. The concentration of SIgA decreases to about 0.25-0.50 g/l in the so called mature milk. This rapid decrease in antibody levels is, however, compensated by a simultaneous increase in milk volume, so that the daily intake of IgA antibodies of the breast fed baby is relatively constant throughout the whole lactation period.

The SIgA concentration seems to be rather similar in groups of mothers from various socio-economic backgrounds. Inadequate dietary intake during gestation and lactation does not seem to reduce the production of SIgA. Women from rural and poor urban areas in Guatemala did not show significantly lower levels of SIgA as compared to more privileged groups of women in urban areas both in Guatemala and Sweden when one compensates for differences in volume produced per day (5). Corresponding results have also been shown when comparison was made between Swedish well fed women and under privileged women from Ethiopia and Pakistan (2, 11).

Milk antibodies in relation to intestinal exposure

The milk SIgA antibodies are directed against various structures on e.g. gram negative bacteria commonly colonizing the intestine. The explanation for this seems to be that these SIgA antibodies form a part of a specific defense system common to all mucous membranes. SIgA which is the dominating immunoglobulin in all exocrine secretions might originate from special lymphoid cells in the Peyer's patches which are primed by antigenic exposure in the intestine. These cells seem to be transferred via the lymph and the blood to various exocrine glands like the mammary, lacrymal and salivary glands, the in-

testine and possibly also to the urinary and respiratory tracts (12). Here they produce dimeric IgA antibodies which after combination with SC from the glandular epithelium form the SIgA molecule. There is preliminary evidence from studies in mice that this homing of lymphocytes to the mammary gland might be directed by Ia antigens on epithelial cells controlled by the major histocompatibility complex (35). The hormonal situation also seems to influence the homing of lymphocytes to the mammary gland (34).

There are also other possibilities to explain the presence of specific SIgA antibodies in milk. An antigen transport to the gland has not been excluded, although this explanation seems less likely since no serum antibody response has been observed in experiments where intestinal immunization has resulted in a milk antibody response (7, 23). A selective uptake of dimeric IgA from the blood might also occur in a similar way as shown in the liver (18). It remains to be seen whether this is a common phenomenon for several exocrine secretions or if it is only valid for some glands.

As a result of the gut-mammary link, the breast fed baby is provided with antibodies against a variety of bacteria found in the environment. SIgA antibodies have been found in milk against O antigens of a large number of E.coli strains. Antibodies against capsular K antigens are also frequently recorded, including the K1 capsule which is found in about 80% of E.coli causing neonatal meningitis. Furthermore, antibodies to V.cholerae and E.coli enterotoxins and Shigella, Salmonella, "enteropathogenic" E.coli and V.cholerae O antigens can be found in milk from women living in areas endemic for these organisms (1, 11). Antibodies against viruses like rotavirus (28) and poliovirus (15) as well as parasites like Entamoeba histolytica and Giardia lamblia (21) have also been demonstrated.

Dietary antigens also give rise to a milk antibody response. We have been able to demonstrate milk antibodies to various food proteins like different cow's milk proteins, soy protein and protein from black beans. Interestingly significantly lower levels of SIgA antibodies to cow's milk protein was found in mothers from Guatemala belonging to a social group who could not afford a regular cow's milk intake.

Function of SIgA antibodies

Native SIgA antibodies are inefficient at activating complement and stimulating phagocytosis (12). The main function seems rather to be to neutralize viruses, bind antigen and agglutinate bacteria. It is possible that SIgA antibodies can play an important role in the protection of the breast fed baby against different diarrheal infections. Protection against enterotoxin-producing organisms like V.cholerae and certain E.coli may be accomplished by SIgA antibodies through binding the toxins as well as the bacteria thus preventing epithelial attachment (16). Pili may confer the capacity to attach to epithelial cells to the bacteria and antibodies to pili could therefore be of importance for protection. Human milk has also been shown to inhibit bacterial binding to epithelial cells (31). Milk SIgA antibodies were also recently demonstrated against E.coli pili antigens indicating that intestinal exposure to E.coli pili may be common (30). Several studies have shown that infection related morbidity is lower in infants fed human milk compared with those fed on cow's milk for-

mulaes (3, 36). Breast fed babies in countries where Shigella and enterotoxigenic E.coli are endemic are rarely infected or colonized with these pathogens (19, 20). On weaning the intestinal flora changes and the children get diarrhea from various infectious agents. There are also indications that treatment with colostrum and milk of newborns with gastroenteritis due to "entero-pathogenic" E.coli has effect (17). Since the infant's own local production of SIgA antibodies seems to be rather insufficient during early part of life, the milk antibodies may be required as a supplementary source of SIgA to help the child in the defense against infections. Besides the anti-infectious capacity human milk also seems to have anti-allergic effects. Breast feeding does not only diminish exposure to food allergens but provides also antibodies against e.g. cow's milk proteins which may diminish the exposure of the infant's intestinal mucosa to food introduced during the weaning period especially in atopic infants.

Possible improvement of milk protection through maternal vaccination

Studies have shown that parenteral cholera vaccination gave a significant titer increase of milk and saliva IgA antibodies as well as serum antibodies in earlier non-vaccinated women living in endemic areas. No increase was shown in milk antibody levels in Swedish women after parenteral vaccination and boosting. This suggests that a primary SIgA response cannot be induced by a parenteral vaccination, but an existing local response can be boosted via parenteral immunization (13). Simultaneously a dose of oral poliovaccine was given to Pakistani women. Instead of an increase of milk antibody levels a decrease was noted. The decrease was especially striking if the polio vaccine was given together with a cholera vaccine. These data suggest the possibility to improve breast milk-mediated immunity for the infant simultaneously with induction of protection for the mother. Further studies are, however, needed to investigate optimal timing and doses, as well as type of vaccine, to improve the effects of the vaccination. The data obtained with the oral vaccination might be due to induction of immunological tolerance in the gut and could be related to the unsatisfactory results sometimes seen with such vaccines in some developing countries.

The cellular immune response

Colostrum contains large numbers of leucocytes ranging from 1.1 x 10^5 - 10^7 cells/ml (4). The number decreases rapidly to about 10^5 cells/ml at the end of the first week of lactation. Macrophages constitute 30-80% of the total cell counts and the remaining cells are lymphocytes of both T and B character and neutrophil granulocytes. Macrophages are involved in the defense against microorganisms in the infant's gut through their content of IgA, lysozyme, C4 and transferrin (26). Data also indicate that the macrophages might help to amplify the T-cell reactivity via cellular cooperation or by processing the antigen (24). About 50% of the lymphocytes in colostrum or milk can be characterized as T-lymphocytes (6, 29). These cells which are able to produce interferon may partly differ in reactivity to mitogens and antigens from T-cells in the blood (25) which indicates that milk T-lymphocytes represent a selected cell population different from peripheral blood lymphocytes.

There is some evidence for a transfer of cell-mediated local

immunity from mothers to their breast fed infants. Tuberculin positivity has been demonstrated in babies of positive mothers (22, 27). Partly digested cells or smaller molecules transported by T-cells, like transfer factor or migration inhibitory factor, may also be transferred to the breast fed baby via breast milk (6). More studies are required before we fully can explain the biological significance of the ingested lymphocytes in the intestine of the infant.

SUMMARY

Human milk contains antibodies of the SIgA type against a variety of enterobacteria viruses and food proteins. There seems to be a close link between the specific immune response in the mammary gland and the antigenic exposure in the intestine.

As a consequence of this connection, the milk SIgA antibodies can possibly provide protection for the child against microorganisms in the environment and also give some epidemiological information. Vaccination experiments suggest that the milk antibody response can be boosted by parenteral vaccination in endemic areas. With a live peroral polio vaccine a decrease of the milk SIgA polio antibody levels were noted. There are also a large number of cellular elements like macrophages, neutrophils and T and B lymphocytes present in milk. The biological significance of these cells has not yet been settled.

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