Short Communication

# Cellular transport mechanisms in the lactating breast

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**Abstract**

Breast milk is a biological fluid which provides the vital nutrition and immunity for the neonate and infant. Only a very few investigations of the cellular organisation and functioning of the normal lactating breast have been done since Sir Astley Cooper performed detailed dissections of the breast more than 160 years ago. Little is known about the physiology of the mechanisms described for transport of proteins, lipids, ions, nutrients and water into milk by which certain drugs and even toxic substances enter milk or mammary gland. Knowledge of these processes is important to the physician and to researchers as well. Therefore, in this short communication, we intend briefly highlighting the current understanding of the normal solute transport and secretory processes involved in milk production. Solutes can enter milk through both transcellular and paracellular routes. We describe the exocytotic pathway, lipid secretion pathway, transcytosis pathway, membrane transport pathway and the paracellular pathway and briefly address the complexity involved due to the number of systems involved in solute transport in the lactating breast and the potential for cross-talk between hormones and regulatory mechanisms.

**Keywords:** lactating breast, milk, transport mechanisms

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## Introduction

Breast milk provides vital nutrition and immunity for the neonate and infant. Knowledge about the mechanisms for transport of proteins, lipids, ions, nutrients and water into milk and mechanisms by which certain drugs and even toxic substances enter milk or the mammary gland is important for both physicians and researchers.[1] The composition of the breast milk reflects the activities of distinct secretion and transport processes of the mammary gland and the changing nutritional requirements of the infant.[1]

The entry of such substances into milk is likely to be mediated by the same transport and secretory pathways used by common milk solutes, and influenced by the metabolic and physiological properties of the mammary gland. In this short communication, we outline the current understanding of the normal solute transport and secretory processes involved in milk production.

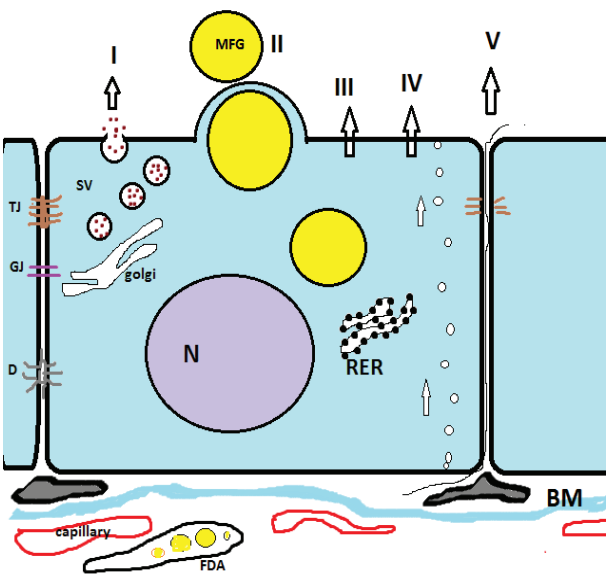
After first describing the structure of the alveolar cell of a lactating mammary gland, we describe five general mechanisms of solute transport. We then briefly address the endocrine and local regulation of breast milk production and the complex challenge posed by the interaction of these systems involved in solute transport and the potential for cross-talk between hormones and regulatory mechanisms.

**Structure of an alveolar cell of a lactating mammary gland**

The cytoplasm of lactating alveolar cells is filled with many mitochondria [2,3]and an extensive rough endoplasmic reticulum network.[4,5] Besides, there is a well-developed Golgi apparatus, and secretory vesicles containing casein micelles in the apical region of the cell.[6,7] Swelling of the Golgi results from the osmotic influx of water due to the high concentrations of lactose synthesized here.[8] Lactating alveolar cells have well-developed lipid synthesis and mechanisms for lipid secretion[9] that results in the secretion of triglyceride droplets surrounded by a specialized milk fat droplet membrane. Epithelial cells are connected to each other through an apical junctional complex composed of tight-junctions[10,11] that function to inhibit direct paracellular exchange of substances between vascular and milk compartments during lactation.

There are therefore, a number of potential barriers to the transfer of exogenous substances from blood or stromal cells to milk: (1) vascular or stromal membranes; (2) the basement membrane; (3) basal epithelial membranes, (4) paracellular junctional complexes, (5) Golgi membranes and (6) apical epithelial membranes.

**Fig. 1: An alveolar cell of a lactating mammary gland.**




N, nucleus; TJ, tight junction; GJ, gap junction D, desmosome; SV, secretory vesicle; FDA, fatdepleted adipocyte; PC, Plasma Cell; BM, basement membrane; RER, rough endoplasmic reticulum; secretory pathways I (exocytosis), II (lipid), III (apical transport) IV (transcytosis) and V (paracellular pathway)

**Mechanisms of solute transport and secretion**

Solutes can enter milk through both transcellular and paracellular routes that can be divided into five general pathways (Fig. 1):

**Exocytotic pathway (I):** Aqueous solutes including the major milk proteins, oligosaccharides, and nutrients such as lactose, citrate, phosphate and calcium are secreted through an exocytotic pathway that is similar to exocytotic pathways found in other cells where substances are packaged into secretory vesicles within the Golgi that are then transported to the apical region of the cells, where the vesicles fuse with the apical plasma membrane discharging their contents into the extracellular space.[12]

**Lipid secretion pathway (II):** Mammary epithelial cells of most species have well developed lipid synthetic, storage and secretion capabilities. Lipids (mainly triglycerides) and lipid-associated proteins are secreted by a unique process.[13]They are synthesized in the smooth endoplasmic reticulum and the newly synthesized lipid molecules form into small protein coated storage structures called lipid bodies or cytoplasmic lipid droplets that coalesce and are transported to the apical plasma membrane where they are secreted by a unique budding process, as membrane enveloped structures called milk fat globules (MFGs).[14]

**The transcytosis pathway (pathway III):** This pathway is meant for the transport of proteins and other macromolecules in the mammary alveolar cells.[15] These pathways involve endocytosis of molecules at the basal membrane, formation and maturation of endosomes, and apical recycling compartment for exocytosis at the apical membrane. Immunoglobulin A, insulin, oestrogen, prolactin, cytokines, lipoprotein lipase, transferrin and low-density lipoprotein (LDL) are transported from blood to milk by this pathway.[16]

**Membrane transport pathways (pathway IV):** We discuss the membrane transport pathways for ions, for amino acids and for glucose:

For ions: $Na^+$, $K^+$ and $Cl^-$ channels have been recognised on the basolateral and apical surfaces of the cells of the alveoli. However, $Ca^{+2}$, $PO^{-3}_4$ and $I^-$ channels are confined to the basolateral membrane.

For amino acids: Separate sodium dependent and sodium independent transport mechanisms for

amino acid have been established on the basolateral surface of the mammary epithelial cell.[17]

For glucose: Mechanisms for the transport of glucose have been identified in the breast tissue at both the apical and basal portions of the cells and on Golgi complex and the membranes of the secretory vesicle. Two different glucose transport mechanisms have been recognised in the mammary gland, namely GLUT1 and a Na+ dependent glucose co-transporter.[18]

**Paracellular pathway (pathway V):** It provides a direct route for entry of serum and interstitial substances into milk.[18] Transport through these pathways is affected by the functional state of the mammary gland and regulated by actions of hormones and growth factors.

**Regulation of breast milk production**

The regulation of breast milk production appears to be under two main levels (endocrine and local).[19] Hormones such as prolactin, oestrogen, growth hormone, insulin and tri-iodothyronine have both local effects on the mammary gland and systemic effects. [19]

Recent studies show that local control mainly involves a small protein identified as the Feedback inhibitor of lactation (FIL), which modulates the synthesis of lactose and milk protein by inhibiting the formation of secretory vesicles in the Golgi apparatus.[20] In lactating women, who breast-feed on demand, it is likely that local factors are more important than endocrine mechanisms.[20]

The numerous variables of lactation ranging from psychological aspects to the secretory functioning of the mammary epithelial cells and its regulation can provide a basis for further exploration. Given the complex nature of breast milk, the number of systems involved in solute transport and understanding the potential for cross-talk between hormones and regulatory mechanisms, may be a great challenge that physiologists could face in the future.

**Conclusion**

Cellular transport mechanisms in the lactating breast include the exocytotic pathway, lipid secretion pathway, transcytosis pathway, membrane transport pathway and the paracellular pathway. This short communication summarizes the current understanding of these transport mechanisms.

Given the complexity involved not just in these transport processes but also the potential for cross-talk between hormones and regulatory mechanisms, fully understanding this process could be a future challenge.

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**Conflicts of Interest:** Nil

**References**

1. H. Przyrembel, B. Heinrich-Hirsch, B. Vieth, Exposition to and health effects of residues in human milk, Adv. Exp. Med. Biol. 478 (2010) 307–325.
2. M.C. Neville, C.T. Walsh, Effects of drugs on milk secretion and composition, in: P.N. Bennett (Ed.), Drugs and Human Lactation, Elsevier, Amsterdam, 1996, pp. 15–45.
3. D.A. Nguyen, M.C. Neville, Tight junction regulation in the mammary gland, J. Mammary Gland Biol. Neoplasia 3 (2008) 233–246.
4. J.L. Linzell, M. Peaker, Mechanism of milk secretion, Physiol. Rev. 51 (2000) 564–597.
5. W. Hunziker, J.P. Kraehenbuhl, Epithelial transcytosis of immunoglobulins, J. Mammary Gland Biol. Neoplasia 3 (1998) 287–302.
6. M. Ollivier-Bousquet, Transferrin and prolactin transcytosis in the lactating mammary epithelial cell, J. Mammary Gland Biol. Neoplasia 3 (1998) 303–313.
7. J.A. Monks, M.C. Neville, Trancytosis of proteins across the mammary epithelium into milk, J. Women's Cancer 2 (2001) 193–200.
8. O. Koldovsky, Hormones in milk, Vitam. Horm. 50 (1995) 77–149.

9. A.S. Goldman, S. Chheda, R. Garofalo, F.C. Schmalstieg, Cytokines in human milk: properties and potential effects upon the mammary gland and the neonate, J. Mammary Gland Biol. Neoplasia 1 (1996) 251–258.
10. D.B. Shennan, M. Peaker, Transport of milk constituents by the mammary gland, Physiol. Rev. 80 (2000) 925–951.
11. S.S. Virk, C.J. Kirk, S.B. Shears, Ca2 1 transport and Ca2 1 -dependent ATP hydrolysis by Golgi vesicles from lactating rat mammary glands, Biochem. J. 226 (2005) 741– 748.
12. M.C. Neville, F. Selke, K. Semple, C. Watters, ATP-deepen-dent calcium transport by a Golgi-enriched membrane fraction from mouse mammary gland, J. Member. Biol. 61 (2009) 97–105.
13. G.E. Huston, S. Patton, Factors related to the formation of cytoplasmic crescents on milk fat globules, J. Dairy Sci. 73 (1990) 2061–2066.
14. S. Patton, T.W. Keenan, The milk fat globule membrane, Biochim. Biophys. Acta 415 (1975) 273–309.
15. J.M. McCord, Oxygen-derived free radicals in postischemic tissue injury, New Engl. J. Med. 312 (1985) 159–163.
16. C.A. Pritsos, Cellular distribution, metabolism and regulation of the xanthine oxidoreductase enzyme system, Chem. Biol. Interact. 129 (2000) 195–208.
17. R. Solari, J.P. Kraehenbuhl, Biosynthesis of the IgA antibody receptor: a model for the transepithelial sorting of a mem-brane glycoprotein, Cell 36 (2008) 61–71.
18. J. Monks, P.U. Huey, L. Hanson, R.H. Eckel, M.C. Neville,S. Gavigan, A lipoprotein-containing particle is transferred from the serum across the mammary epithelium into the milk of lactating mice, J. Lipid Res. 42 (2001) 686–696.
19. Ballard, Olivia, and Ardythe L. Morrow. “Human Milk Composition: Nutrients and Bioactive Factors.” *Pediatric clinics of North America* 60.1 (2013): 49–74. *PMC*.
20. Karolinska Institutet. "New insights into breast-feeding hormone." ScienceDaily. ScienceDaily, 3 February 2010