

Physiology Team 431
Reproductive Block

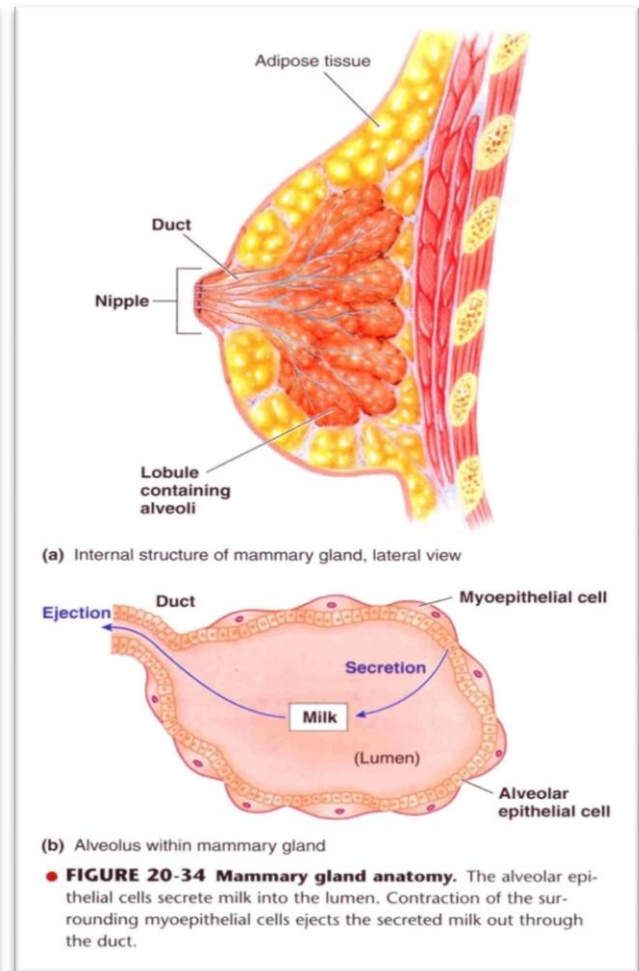
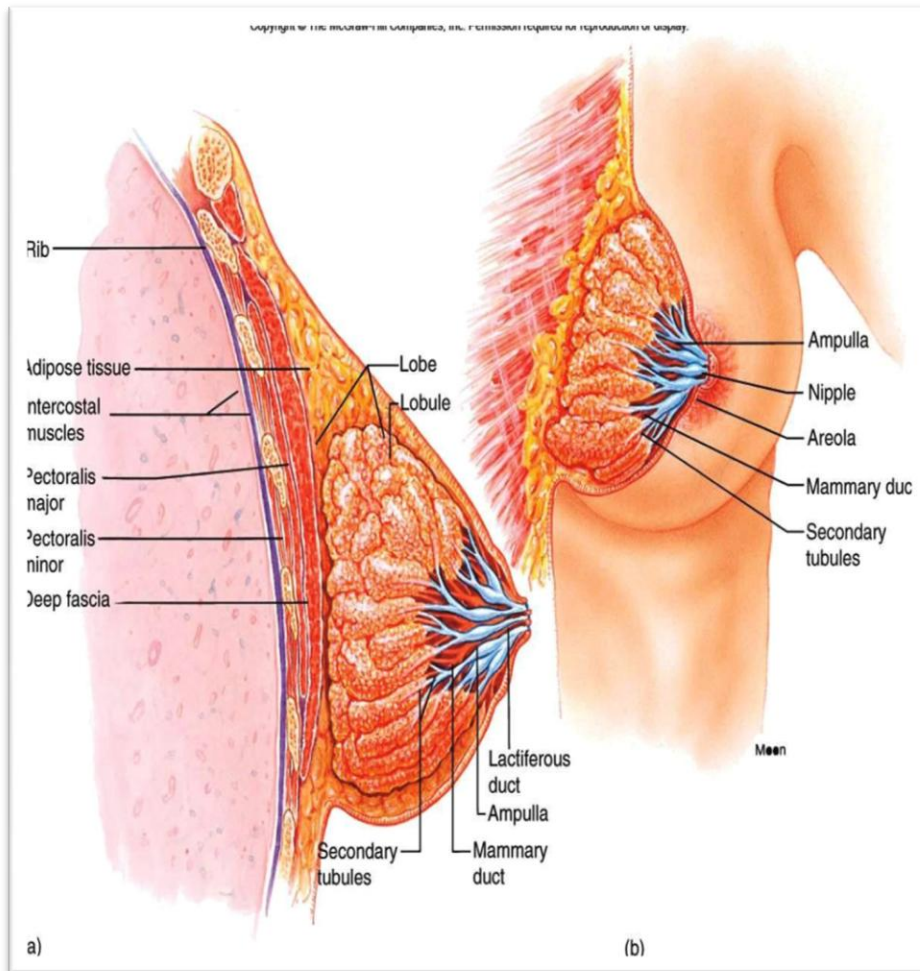
Lecture 8

Hormones affecting female breast

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General Anatomy of the Breast ;



It is formed of 15-20 **LOBES** → Each lobe is formed of a number of **LOBULES** and **ONE LACTIFEROUS DUCT** → Lobules contain the **ALVEOLI**; an alveolus is formed of two types of cells :

- **Alveolar Epithelial** → Milk-producing cell (to the lumen).
- **Myoepithelial Cell** → Muscle-like cell Contracts and ejects milk from alveolar lumen through the duct.

Ductal System:

Alveolar Tubule → Secondary tubule → Mammary duct → Ampulla (lactiferous sinus) → Lactiferous duct.

Blood capillaries surround the alveolus → Carry the nutrients that are required for milk production.

Breast Development (MAMMOGENESIS) ;

During Puberty :

- **ESTROGEN** stimulates proliferation of ducts and deposition of fat.
- **Progesterone** stimulate development of lobules

During Pregnancy :

- **Complete development of glandular tissue.**
- Only in pregnancy the breast reaches its full development.

Endocrine System Role in Mamogenesis ;

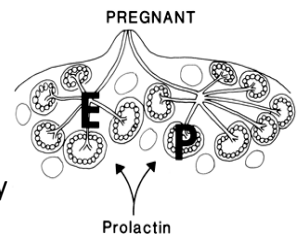
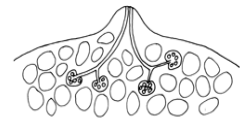
• Reproductive Hormones (Endocrine) :

1. **Estrogen** (placenta)

- **Growth & branching of ductal system**(with GH)
- **Fat deposition** in the stroma

2. **Progesterone** (placenta)

- **Growth of lobule-alveolar system**(budding of alveoli and secretory changes in epithelial cells)



Although estrogen and progesterone are essential for physical development of the breasts, **they INHIBIT actual secretion of milk.**

3. **Prolactin** (anterior pituitary)

- Its level **INCREASES during pregnancy** (10-20 times)
- Its main function is milk production
- **Sudden drop in E & P after delivery allows milk production**
- It is controlled mainly by hypothalamic hormone → **PIH(Dopamine)**

4. Human placental lactogen(placenta)

- Facilitate mammogenesis.
- Delay milk production.

Lactogenesis :

Cellular changes by which mammary epithelial cells are converted from a **NONSECRETORY** → **SECRETORY** state: 2 stages

Lactogenesis 1

(Cytologic and enzymatic differentiation of alveolar epithelial cells)

Starts in **MIDPREGNANCY** and characterized by expression of many genes involved in synthesis of milk components (**increases in uptake transport systems for amino acids, glucose, and calcium required for milk synthesis**).

Hormones involved:

1. **Progesterone** → suppresses milk secretion.
2. **Prolactin** and/or placental lactogen
3. **Growth hormone**
4. Glucocorticoids (**Cortisol**)

Breast Milk Immunoglobulins .. Take five basic forms, denoted as IgG, IgA, IgM, IgD and IgE. All have been found in human milk, but by far the most abundant type is IgA, which is found in great amounts throughout the gut and respiratory system of adults. It coats the lining of the baby's immature intestines, and helps to prevent pathogens from invading the baby's system. Secretory IgA also helps prevent food allergies.

Lactogenesis 2

(Copious secretion of all milk components).

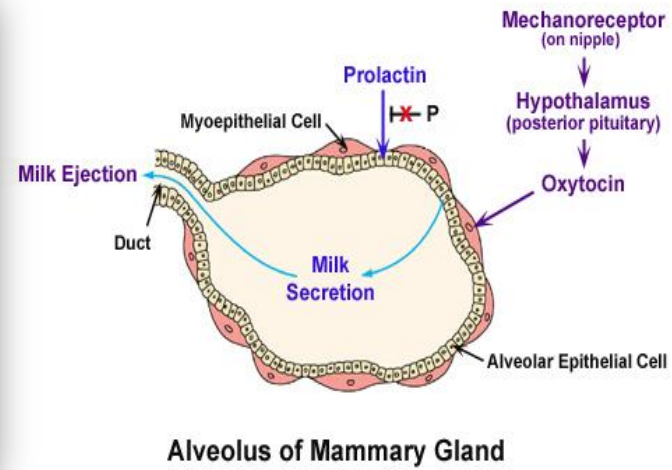
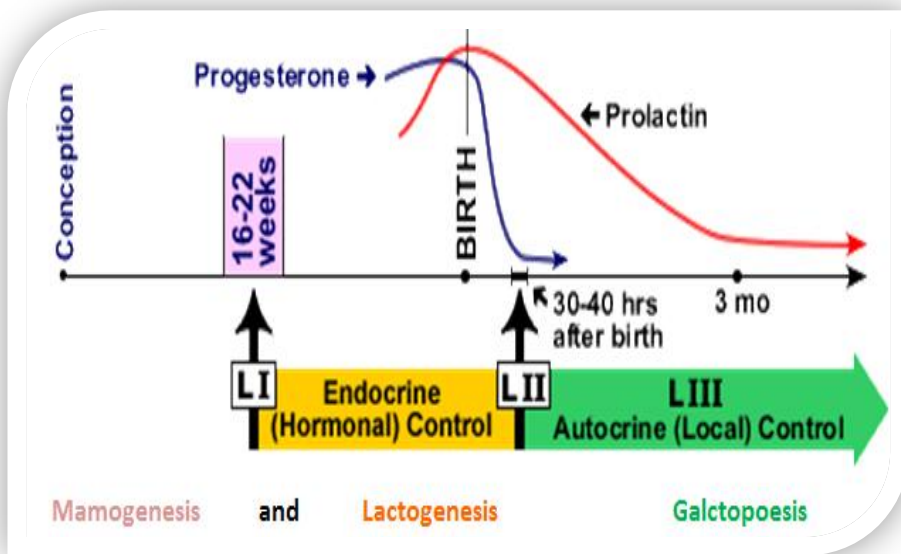
- **AROUND PARTURITION** withdrawal of **progesterone + high level of prolactin** leads to:
 - Further increase in expression of milk protein genes.
 - Glands absorb increased quantities of metabolic substrates from the blood.
 - **Movement of cytoplasmic lipid droplets and casein into alveolar lumina.**
 - Transfer of **IMMUNOGLOBULINS**
 - **SECRETION OF COLOSTRUM** followed by milk.
 - **Suckling stimulates further increase** in expression of genes involved in milk secretion with expansion of alveolar epithelium.
 - **Lactation is maintained by removal of milk.**

Hormones involved:

1. **Prolactin** → milk production.
2. **Oxytocin** → milk let-down.

What is COLOSTRUM ?

It is a form of milk produced by the mammary glands in day four of lactation. It contains antibodies to protect the newborn against diseases as well as being lower in fat and higher in protein than ordinary milk.



• Metabolic Hormones (Endocrine) :

• GH :

- Can be produced locally
- Its secretion is **stimulated by progesterone**
- Increases production of **IGF-1** by the liver
- Mediate **cell survival and ductal growth**

• Corticosteroids :

- **Increases during pregnancy** (fivefold)
- Involved in **breast development** (permissive action on milk protein synthesis)

• Thyroxin

- Essential for milk production
- **Thyroxin & TSH level decreases during lactation**
- **TRH increases leading to stimulation of PRL (nasal administration to treat inadequate lactation)**

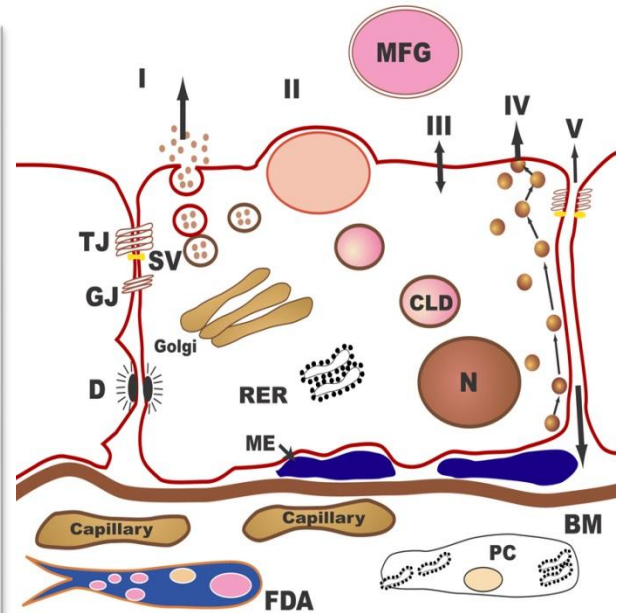
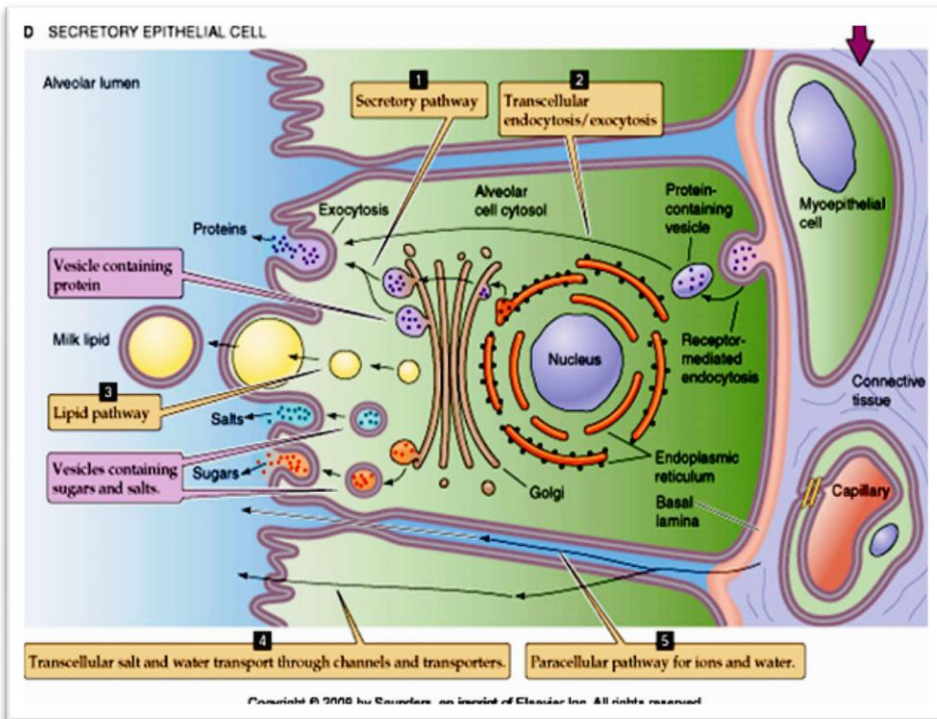
• Insulin

- **Low during lactation**
- Shunt of nutrients from storage depots to milk synthesis

Mammary Hormones (Autocrine) :

- **GH**
 - Progesterone stimulates its secretion
- **Leptin**
 - **Increases during pregnancy**(increase adipose tissue)
 - **Decreases with lactation**
- **PTHrP**
 - **Increases during lactation**
 - **Mobilizes bone calcium**
 - **Increase in alkaline phosphatase**

Milk Secretion Pathway ;



SV = Secretory vesicle. MFG = Milk fat globule
 FDA = Fat-depleted adipocyte TJ = Tight junction
 CLD = Cytoplasmic lipid droplet. GJ = Gap junction.
 D = Desmosome. ME = Myoepithelial cell.

Exocytosis of milk protein, lactose, and other components of the aqueous phase in Golgi-derived secretory vesicles → Milk fat secretion via the milk fat globule → Direct movement of monovalent ions, water, and glucose across the apical membrane of the cell → Transcytosis of components of the interstitial space → The paracellular pathway for plasma components and leukocytes.
***Pathway V is open only during pregnancy, involution, and in inflammatory states such as mastitis ..**

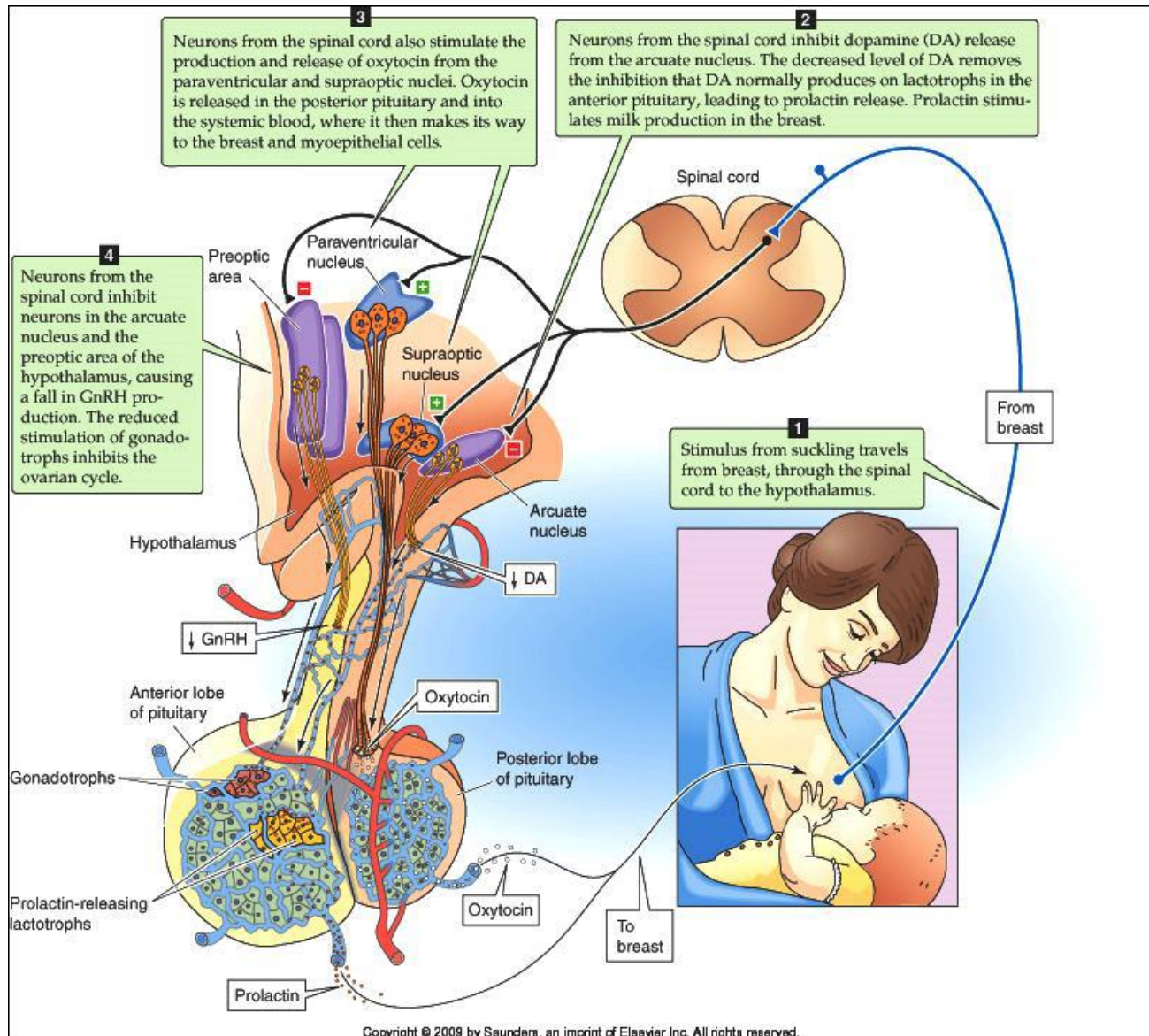
GALACTOPOESIS ;

Galactopoeisis is defined as the maintenance of lactation once lactation has been established.

- **Role of Hormones :**
 - **Prolactin:**
milking-induced surge is a direct link between the act of nursing (or milk removal) and the galactopoeitic hormones involved in maintaining lactation.
 - **Growth Hormone:**
support **increase in synthesis of lactose, protein, and fat in the mammary gland**
 - **Glucocorticoids:**galactopoeitic in physiological doses
 - **Thyroid Hormones:**galactopoeitic
 - **Ovarian Hormones :**
 - Estrogen in very **LOW** doses is galactopoeitic
 - Progesterone alone has **NO** effect on galactopoeisis because there are no progesterone receptors in the mammary gland during lactation.

- If a woman is lactating and she wants to take contraceptives (Progesterone) it won't affect milk production (It won't inhibit the action of prolactin) why? Because once lactating has been established progesterone receptors will disappear.

Suckling Reflex ;



• Secretory Activation:

The most critical time in the establishment of lactation is its onset, during the transition from pregnancy to lactation, a period now called secretory activation (previously termed lactogenesis stage II). Secretory activation takes place after birth in women. Most lactation problems arise during this period as the result of stress of childbirth or problems with the mechanics of suckling. If unresolved these problems can lead to lactation failure.

The major inhibitor of milk production during pregnancy is **PROGESTERONE**.

- Once birth occurs, a developed mammary epithelium, the continuing presence of high levels of prolactin, and **a fall in progesterone are necessary for the onset of copious milk secretion.**

- Thus **removal of the placenta**, the source of progesterone during pregnancy in women, has long been known to be necessary for the initiation of milk secretion.

- **Conversely, retained placental fragments with the potential to secrete progesterone have been reported to delay secretory activation.**

- **Progesterone receptors are lost in lactating mammary tissues.**

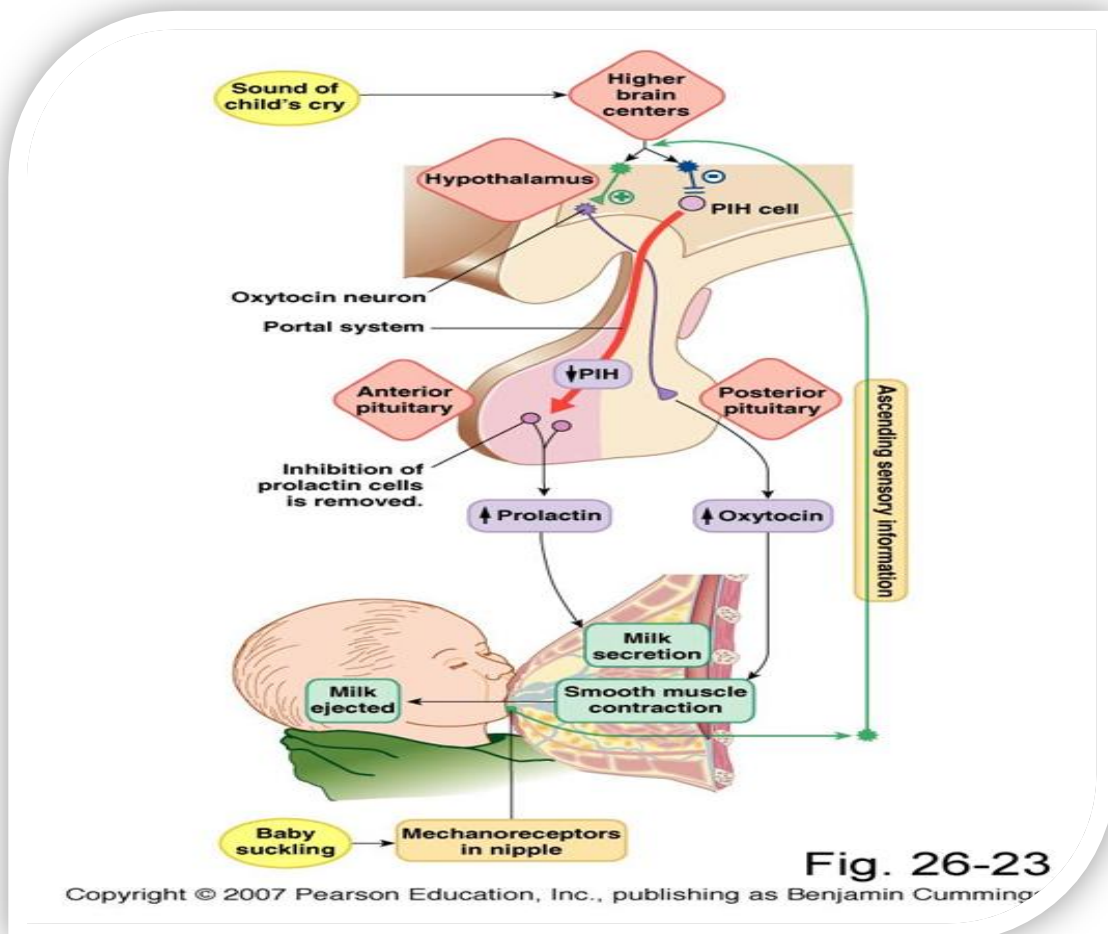
• Milk Letdown :

Milk letdown is the evacuation of milk from the alveolar lumen to the duct system

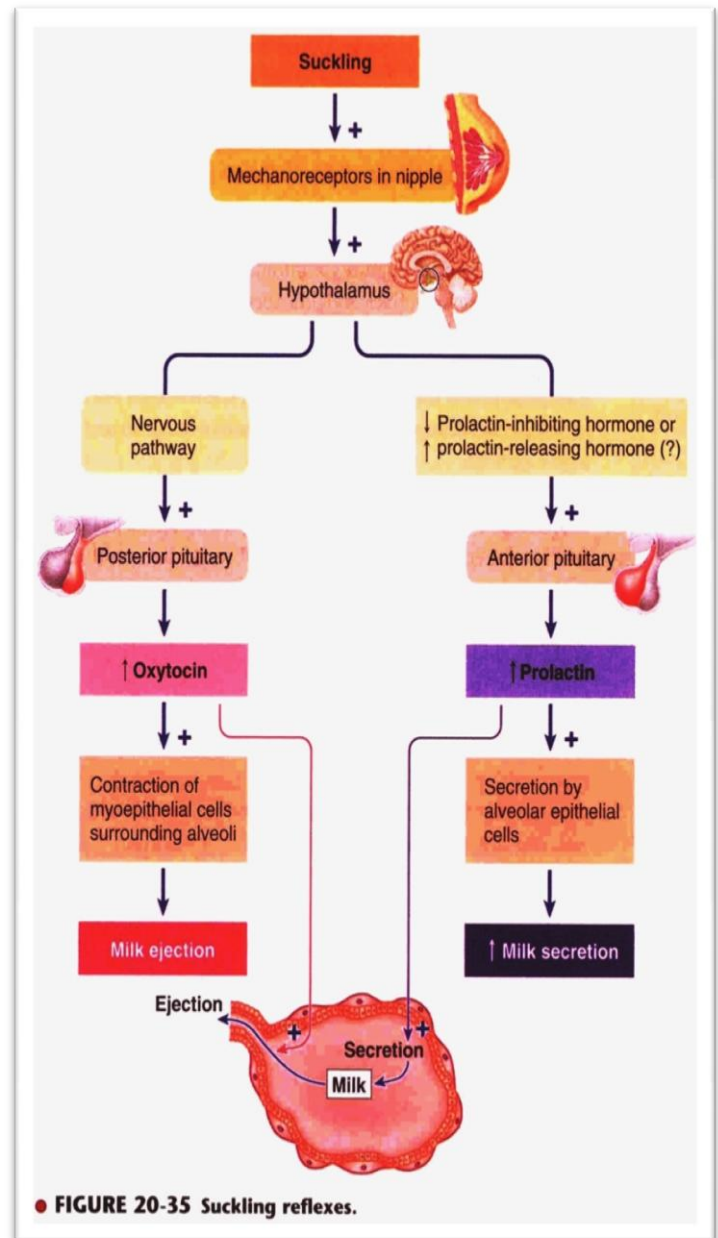
Nerves receive stimuli at the end of nipple → Stimuli is received in the posterior pituitary → Oxytocin is released from pituitary into blood →

Blood circulation brings oxytocin to mammary tissue →

Targets are the myoepithelial cells that contract.



- Milk production is a **"use it or lose it"** process. The more often and effectively the baby nurses, the more milk will be produced
- Milk production <100 ml/day in day 1 postpartum
- Milk production by day 3 reaches 500 ml/day
- Milk composition changes dramatically ($\downarrow \text{Na}^+$ & Cl^-) due to closure of tight junctions that block paracellular pathway.



AAP Recommendations: (American Academy of Pediatrics):

1. Exclusive breastfeeding for the first six months of life.
2. Continued breastfeeding for at least one year, as long as is desired by mother and child.

Questions

Q1: All of the following will not stimulate milk production except:

- A- Prolactin
- B- Suckling
- C- Oxytocin
- D- Progesterone
- E- Milk let-down reflex

Q2 : regarding Prolactin hormone choose the incorrect statement

- A- it has action in breast development
- B- it has action in milk production
- C- it has an action in milk ejection
- D- sucking is a factor that can control it
- E- A and B

Q3 : Which ONE of the following is released by suckling the nipple?

- A. Cortisol
- B. Dopamine
- C. Oxytocin
- D. Gonadotropin Releasing Hormone

Answers : 1-A , 2-C , 3-C