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The goat udder: mechanism of milk secretion, and protein/fat synthesis

La ubre de la cabra: mecanismo de secreción láctea y síntesis de proteínas/grasas

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ABSTRACT

In recent years, the shift in milk marketing towards a standardized price structure based on dairy components has placed greater emphasis on lipid and protein concentration over the quantity of L or kg of milk produced. The nutritional content of goat's milk exceeds the nutritional content of cow's milk, in terms of proteins and fats, and it is the lactocytes of the caprine mammary gland, which must replicate and synthesize these components dairy products. Therefore, this review initially considers the understanding of the anatomy and histology of the mammary gland as responsible for all the activities related to the milk ejection mechanism. The development of the mammary gland determines all aspects of cell behavior, so its development is reviewed through four stages: i) mammogenesis, ii) lactogenesis, iii) galactopoiesis, and iv) involution. The remainder of the review emphasizes milk lipogenesis and proteogenesis, due to their various roles within cellular metabolism and the production of the lipid fraction and protein fraction of milk.

Keywords: mammary gland, goat milk, lipogenesis, proteogenesis.

RESUMEN

En los últimos años, el cambio en la comercialización de la leche hacia una estructura de precios estandarizada a partir de los componentes lácteos ha puesto un mayor énfasis en la concentración lipídica y proteica sobre la cantidad de L o kg de leche producidos. En virtud de lo anterior, el contenido nutricional de la leche de cabra supera al contenido nutricional de la leche de vaca, en lo que respecta a proteínas y grasas, y son los lactocitos de la gandula mamaria caprina, quienes deben replicarse y sintetizar estos componentes lácteos. Por lo tanto, esta revisión considera de manera inicial la comprensión de la anatomía e histología de la glándula mamaria como responsable de todas las actividades vinculadas al mecanismo de eyección de la leche. El desarrollo de la glándula mamaria determina todos los aspectos del comportamiento celular, por lo que se revisa su desarrollo a través de cuatro etapas: i) mamogénesis, ii) lactogénesis, iii) galactopoyesis, e iv) involución. El resto de la revisión hace hincapié en la lipogénesis y la proteogenesis láctea, debido a sus diversas funciones dentro del metabolismo celular y la producción de la fracción lipídica y fracción proteica de la leche.

Palabras clave: glándula mamaria, leche de cabra, lipogénesis, proteogénesis.

ABBREVIATIONS

A	aminoacyl site
aa	amino acids
ACAT	acyl-CoA:cholesterol acyltransferase
ADH	antidiuretic hormone
DNA	deoxyribonucleic
mRNA	messenger ribonucleic acid
tRNA	transfer ribonucleic ribonucleic acid
ATP	adenosine triphosphate
$C_3H_3O_3$	pyruvate
$Ca_3(PO_4)_2$	tricalcium phosphate
CCT	CTP:phosphocholine cytidylyl transferase
CO_2	carbon dioxide
DAG	diacylglycerol
DGAT	acyl-CoA:diacylglycerol acyltransferase
E_1	estrone
E_2	17 β-estradiol
E_3	estriol
FAS I	fatty acid synthase I
GH	growth hormone
GPAT	glycerol-3-phosphate acyltransferase
HCO_3^-	hydrogenocarbonate anion
LFLAT	lysophospholipid acyltransferase
NADPH	nicotinamide adenine dinucleotide phosphate
O=C-N-H	peptide bonding
OXT	oxytocin
P	peptidyl site
p.p.	postpartum
P_4	progesterone
PAP	phosphatidic acid phosphatase
PLA	phospholipase A
Plin	perilipin
PRL	prolactin
TAG	triacylglycerols
UAA	uracil-adenine-adenine
UAG	uracil-adenine-guanine
UGA	uracil-guanine-guanine-adenine

INTRODUCTION

Goat milk has positioned itself as an important element in the human diet (Bauman *et al.*, 2006). Its nutritional relevance lies mainly in two components: i) the lipid fraction, formed by fatty acids (Harvatine *et al.*, 2009) and ii) the protein fraction, where caseins, whey proteins and fat globule membrane proteins are distinguished (Swaisgood, 2003). The nutritional content of goat milk exceeds that of cow milk in terms of protein (goat milk: 3.40 g/100 mL^{-1} vs cow milk: 3.30 g/100 mL^{-1}) and fat (goat milk: 4.30 g/100 mL^{-1} vs cow milk: 3.95 g/100 mL^{-1}) content (Davidson & Stabenfeldt, 2020). Current trends in milk production and consumption enhance lipid and protein concentration over the amount of L or kg of milk produced (Manterola, 2011), taking into account the eating habits of a growing urban population (Vidal, 2013). Goat milk collectors use this product mainly for cheese production (National Chamber of Industrial Milk, 2021). For this reason, it is necessary to increase our understanding of the metabolism involved in goat milk production and its lipid and protein contents (Heid & Keenan, 2005; Kumar *et al.*, 2009). Therefore, this review discusses the anatomy and histology of the mammary gland. Its development as a milk-producing organ through four stages: i) mammogenesis, ii) lactogenesis, iii) galactopoiesis, and iv) involution. Continuing with milk ejection and its hormonal control, and to substantiate the basic biochemistry of milk lipid and protein synthesis, information on the processes of milk lipogenesis and proteogenesis is presented at the end.

I. Anatomy and Histology of the Mammary Gland

Goats have two independent mammary glands, their location in the body of the animal is inguinal and they are: i) pear or elongated type, ii) oval or Alpine type, and iii) globular or Saanen type (Menzies, 2021). Histologically, each mammary gland is composed of two tissues: i) the parenchyma whose origin is embryonic ectoderm, and which includes lactocytes or lacteal exocrineocytes and myoepithelial cells (Lawhead & Baker, 2017), and ii) the stroma whose origin is embryonic mesoderm, and which includes blood vessels, lymphatic vessels, adipose tissue, connective tissue and nervous tissue (Baljit, 2017).

The parenchyma develops through the proliferation of lactocytes arising from the primary mammary cord (Menzies, 2021). Lactocytes present receptors for prolactin (**PRL**) (Baljit, 2017), and eventually form hollow circular structures with a length of 100 to 500 µm called alveoli (Lawhead & Baker, 2017). The outer wall of each alveolus is surrounded by arterial capillaries and venous capillaries along with a layer of myoepithelial cells with receptors for oxytocin (**OXT**) (Davidson & Stabenfeldt, 2020). The internal structure of the mammary gland consists of: i) parenchyma, ii) lactiferous ducts: intra and inter lobular and lobular depending on their connection within the mammary gland (Reese *et al.*, 2020), iii) glandular lobules (Figure 1), formed by lobules with 150 to 220 lacteal alveoli, iv) myoepithelial cells, v) venules, vi) arterioles, vii) capillaries, viii) gland cisternae (Figure 2), ix) teat cistern and x) nipple canal (Davidson & Stabenfeldt, 2020).

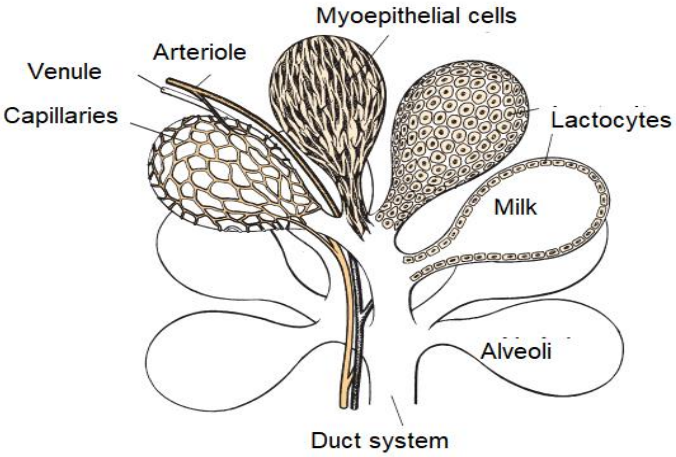

Figure 1. Representation of the glandular lobe in the mammary gland of a goat

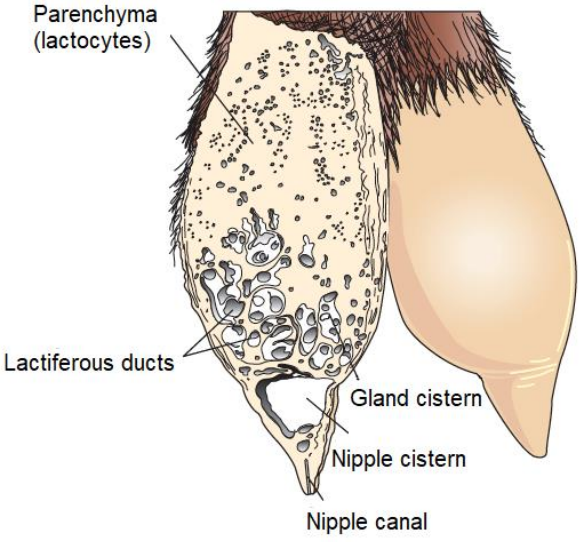

Figure 2. Representation of the mammary gland of a goat

The irrigation of the mammary gland is carried out by the external pudendal artery, which passes through the inguinal canal and divides into cranial and caudal branches (Davidson & Stabenfeldt, 2020). Venous circulation is mainly by the venous circle formed by the external pudendal vein, the caudal superficial epigastric vein and the perineal vein (Lérias *et al.*, 2014). Innervation of the mammary gland is mainly carried out by sympathetic nerve fibers in the first and second lumbar nerves and the inguinal nerves, their function is the control of blood flow in the udder and innervation of the smooth muscle tissue surrounding the lactiferous ducts, gland cistern muscles, teat cistern muscles and teat canal (Dee & Magee, 2018). Milk contained within the alveolar lumen empties into small intralobulillar ducts (Figure 3) that empty into a central collecting space, from which the interlobular ducts emerge (Davidson & Stabenfeldt, 2020).

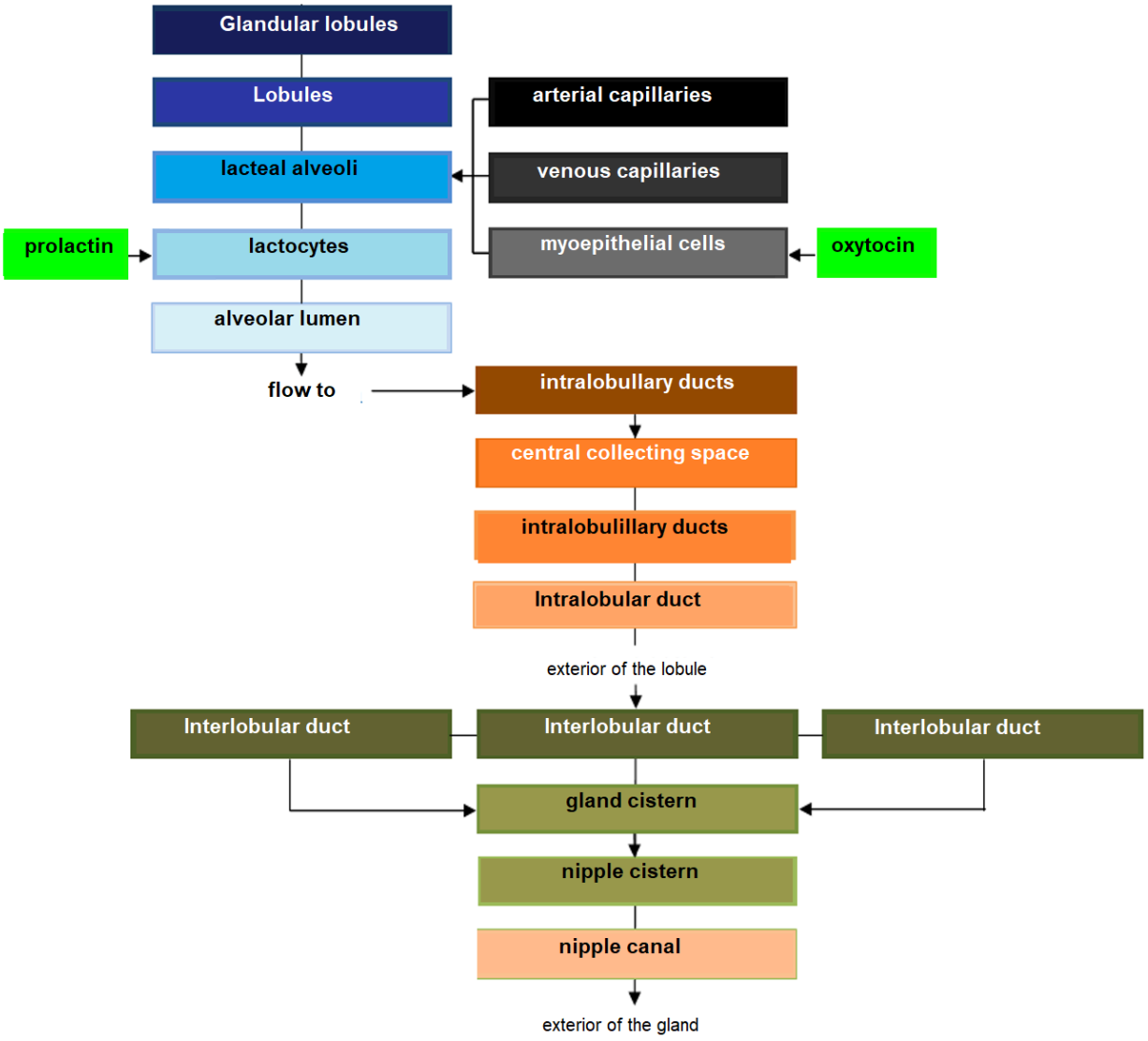

Figure 3. Lactiferous ducts of the mammary gland

Within the lobule the interlobular ducts join to form an intralobular duct, which upon exiting the lobule acquires the name interlobular duct; these ducts may lead directly into the cistern of the gland or join other interlobular ducts before reaching it (Dee & Magee, 2018). Reece & Rowe (2017b). noted that the ductal system connects the gland cistern to the teat cistern, which allows milk to pass from the formation area to the delivery area or nipple canal. The gland cistern in goats is larger in volume compared to that of cattle, and allows for almost 70 % of the milk produced between each milking (Martínez & Suárez, 2018). The anatomy and histology of the mammary gland are modified throughout lactation, by changes associated mainly with the neuroendocrine system (Dee & Magee, 2018). Therefore, there are three stages in mammary biology, characterized by gestation/lactation cycles: i) proliferation, ii) secretion and iii) involution (Lawhead & Baker, 2017). Although most of the proliferation occurs during gestation and most of the involution occurs after milk production, both stages overlap: parenchymal proliferation continues during early lactation (1/3 lactation) and its involution begins during late lactation (3/3 lactation) (Lérias *et al.*, 2014). Event that in goats is reached from 180 to 280 d, with peak production between 8 and 12 weeks postpartum (**p.p.**) (Menzies, 2021) (Figure 4).

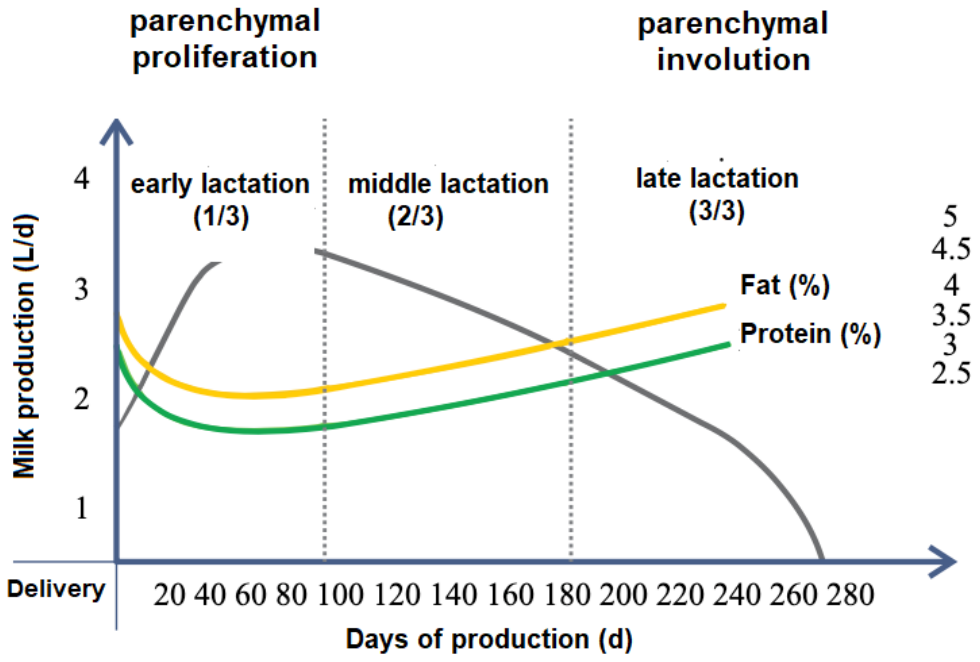

Figure 4. Parenchymal development and milk and solids production curve in goats

Reese *et al.* (2020) indicated that when the mammary gland is in a resting state, the lactocytes have a cubic appearance, whereas when the mammary gland is in milk production, their shape is cylindrical (Davidson & Stabenfeldt, 2020). Furthermore, it is important to note that higher milk production is negatively correlated with milk fat and protein, i.e. a decrease in milk L is equivalent to a higher milk solids content and vice versa (Martínez & Suárez, 2018).

II. Mammary gland development

Lactation proceeds through a cycle consisting of four stages: i) mammogenesis, ii) lactogenesis, iii) galactopoiesis, and iv) involution (Baljit, 2017). Mammogenesis initiates during fetal life in the embryonic ectoderm, forming the mammary band in the inguinal region after 30 d of conception (Reese *et al.*, 2020), the mammary gland at two months and the nipple cistern at three months of fetal life (Lawhead & Baker, 2017).

From birth to puberty, the mammary gland exhibits isometric growth with increased connective tissue and fat deposition (Dee & Magee, 2018). Cyclic ovarian activity results in the production of estrogens e.g., estrone (**E_1**), 17 β-estradiol (**E_2**) and estriol (**E_3**). E_1, E_2 and E_3 (Reece & Rowe, 2017a) (Figure 5), together with growth hormone (**GH**) and adrenal androstenedione, are responsible for the growth of lactiferous ducts (Maldonado *et al.*, 2018). In this regard Lérias *et al.* (2014) stated that the use of plastic implants with estrogens e.g., E_1, E_2 and E_3, directly and locally stimulates the growth of the lactiferous ducts and on the contrary the application of implants with anti-estrogenic activity, inhibits the growth of the lactiferous ducts within circumscribed areas (Reese *et al.*, 2020).

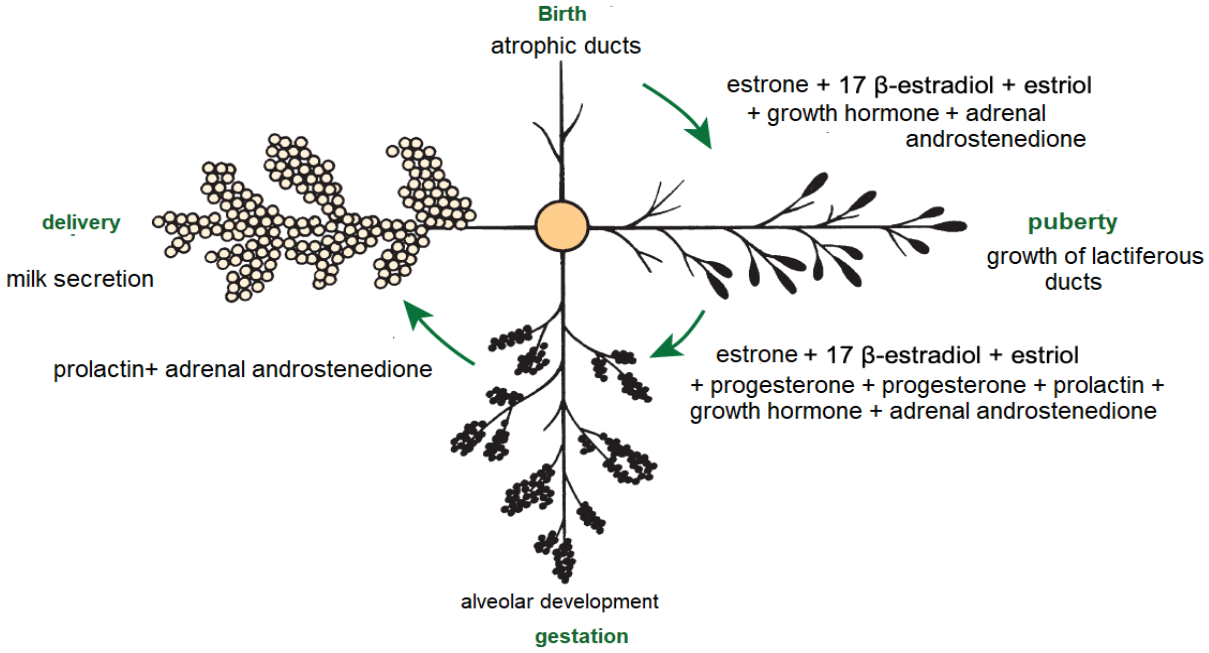

Figure 5. Hormones involved in mammary gland development

After puberty, the mammary gland shows allometric growth (Goff, 2015) and with each estrus there is a slight development of alveoli influenced by E_1, E_2 and E_3, progesterone (**P_4**) (Reece & Rowe, 2017a), GH and adrenal androstenedione (Lawhead & Baker, 2017). Information consistent with that reported by Reece & Rowe (2017b) who noted a synergistic stimulation of PRL, androstenedione, E_1, E_2 and E_3, and P_4 on mammary gland growth and alveolar lobe development (Neville *et al.*, 2002). Most parenchymal growth happens during gestation (Goff, 2015), induced by P_4, PRL and adrenal androstenedione

(Reese *et al.*, 2020). By day 35 (Figure 6) stroma is abundant, by day 92 glandular lobules form with several lobes clustered together; milk secretion is present within the alveolar lumen in some lobules, and considerable stroma is still present, by day 120 the lobes of the alveoli are almost fully developed (Svennersten & Olsson, 2005); the alveoli are filled with milk secretion and stroma is reduced to thin bands (Lawhead & Baker, 2017).

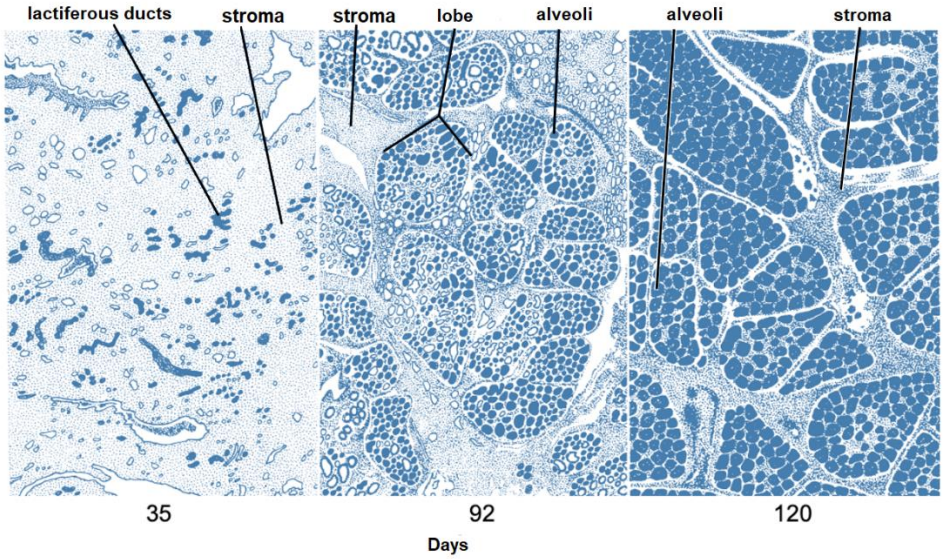

Figure 6. Goat mammary gland parenchyma during gestation
Source: (Dee & Magee, 2018)

After parturition and with the placenta expulsion, P_4 levels fall, initiating lactogenesis (Saipin *et al.*, 2020). The initial phase of lactation is characterized by the positive regulation of milk production, cell proliferation, and a decrease in the apoptosis process in the mammary gland (Henna *et al.*, 2021). During this process the adenohypophyseal endocrine tissue intervenes with the secretion of PRL in its lactotrope cells (Dee & Magee, 2018). PRL is a peptide of 199 amino acids (**aa**) and atomic mass of 23,000 Da, which binds to its tyrosine kinase family receptors located on lactocytes and activates signal transducers and activators of transcription associated with proliferation, differentiation, and lactogenesis (Lawhead & Baker, 2017). Therefore, PRL is indispensable in milk production (Svennersten & Olsson, 2005). In relation to the topic, an investigation that aimed to evaluate the effect of long-term inhibition of PRL, reported that administration for nine weeks of a dopaminergic agonist called quinagolide decreased milk production, confirming the importance of PRL in the functioning of the mammary gland (Lacasse *et al.*, 2011).

III. Milk ejection

Milk from the cistern (70 % of the milk produced between each milking), can be extracted independent of hormonal processes, by a passive mechanism (only by gravity) (Menzies, 2021). For its part, alveolar milk ejection begins with afferent induction (Lérias *et al.*, 2014), by sensory cells in the teat skin and udder base (Martínez & Suárez, 2018) and mechanical stimuli on the teat (Reece & Rowe, 2017b). It can also be triggered by visual stimuli e.g., milking from other females, auditory stimuli e.g., noise from buckets or the milking machine, olfactory stimuli e.g., the milk itself, and even become a conditioned reflex (Lawhead & Baker, 2017).

The ejecto-lacteal reflex, becomes an electrical impulse that travels up the inguinal somatic nerves to the spinal cord (Figure 7), reaching the paraventricular nucleus of the hypothalamus (Davidson & Stabenfeldt, 2020), where action potentials are produced in intermittent pulses, releasing 9 aa OXT [peptide (cysteine-tyrosine-isoleucine-glutamine-asparagine-asparagine-cysteine-proline-leucin e-glycine)] (Svennersten & Olsson, 2005) stored in the neurohypophysis (Dee & Magee, 2018).

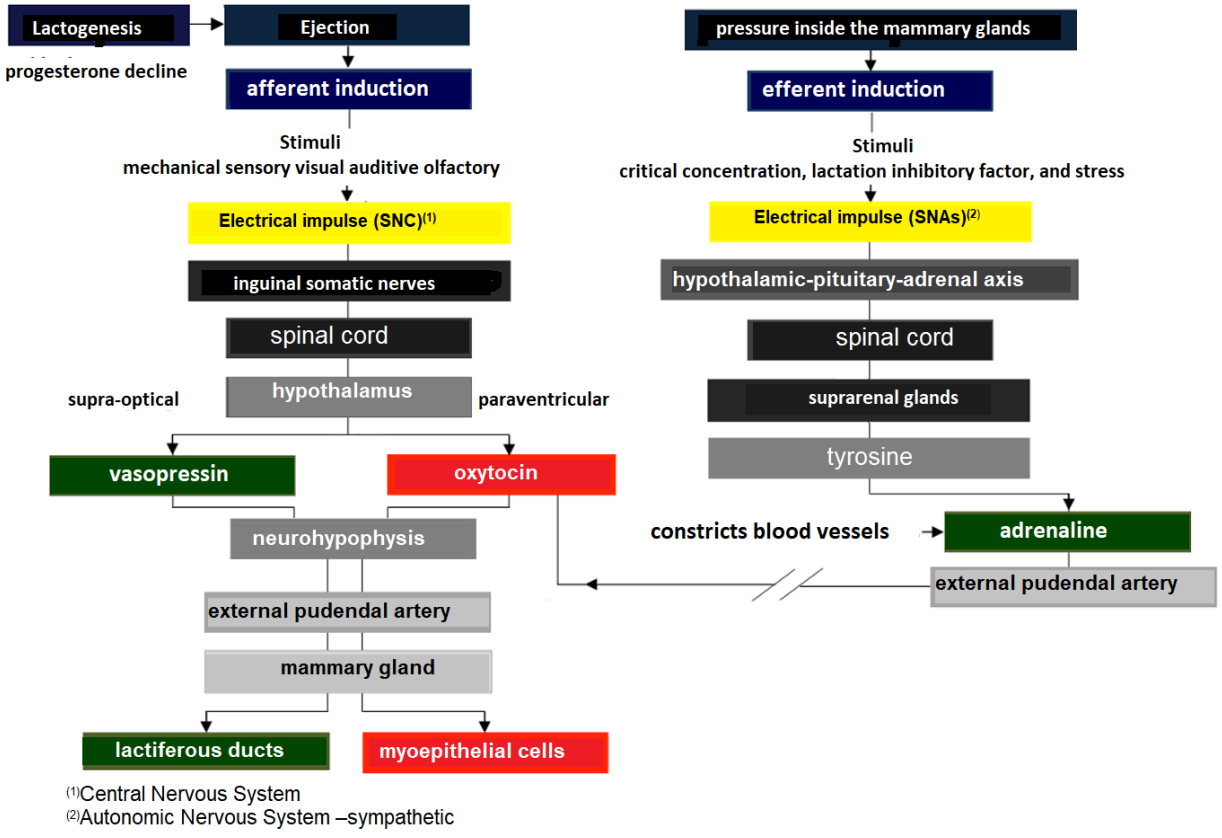

Figure 7. Mechanism of milk ejection and inhibition

The electrical impulse that travels up the somatic inguinal nerves to the spinal cord also reaches the supraoptic nucleus of the hypothalamus (Reese *et al.*, 2020),, where action potentials are produced in intermittent pulses, which release the antidiuretic hormone (**ADH**) also called vasopressin [peptide of 9 aa (cysteine-tyrosine-tyrosine-phenylalanine-glutamine-asparagine-asparagine-cysteine-proline-arginine-glycine)] stored in the neurohypophysis (Thul *et al.*, 2020).

Both hormones travel via the external pudendal artery to the mammary gland (Davidson & Stabenfeldt, 2020). Main functions of OXT in the mammary gland are: i) to cause contraction of the myoepithelial cells surrounding the alveoli, to empty milk from the lactocytes into the alveolar lumen (Belo & Bruckmaier, 2010), and ii) to cause contraction of the intra- and inter-lobular milk ducts, forcing the flow of milk into the cistern of the gland (Neville *et al.*, 2002; Svennersten & Olsson, 2005).

For its part, ADH acts on vascular smooth muscle causing vasoconstriction and osmotic and oncotic pressure changes in the lactiferous ducts facilitating milk outflow (Goff, 2015). The increase in pressure within the mammary gland is evident at the minute of the ejection reflex, as milk is expelled from the alveoli and lactiferous ducts due to contraction of the myoepithelial cells (Lérias *et al.*, 2014). The term used in mammals to describe this phenomenon is milk "let-down" (Davidson & Stabenfeldt, 2020).

Milk flow increases the gland cistern size, originating an increase in pressure (Lawhead & Baker, 2017). Thus, the ejection rate presents an autocrine control at the glandular level by lactation inhibitory factor (Dee & Magee, 2018). This protein is produced by the same lactocytes of the glandular parenchyma and it is secreted together with the milk into the lacteal alveoli (Davidson & Stabenfeldt, 2020). In this regard Bruckmaier & Wellnitz (2008) indicated that lactation inhibitory factor exhibits two modes of action: i) it accumulates in milk until it reaches a critical concentration that inhibits ejection, and ii) when milk accumulates within a lacteal alveolus, it extends its surface exposing potential receptors for lactation inhibitory factor, allowing its binding and triggering inhibition.

Simultaneously, the ejecto-lacteal reflex can be temporarily inhibited by the release into the bloodstream of adrenaline also called epinephrine (Svennersten & Olsson, 2005) (Figure 7), as a result of increased pressure generating stress (Reese *et al.*, 2020). Adrenaline constricts blood vessels including the external pudendal artery, making it impossible for OXT to reach the myoepithelial cells surrounding the lacteal alveoli and indirectly inhibiting their contraction (Reece & Rowe, 2017b).

The maintenance period, or galactopoiesis, occurs when constant suckling at the teat continues to stimulate milk production (Bruckmaier & Wellnitz, 2008), main hormones controlling this physiological stage are PRL and GH (Lawhead & Baker, 2017). Both hormones are important for galactopoiesis, but one predominates in importance relative to the other depending on the species (Baljit, 2017). In rodents as in humans PRL is more important and in ruminants GH has a more active participation (Goff, 2015).

IV. Milk lipogenesis

Milk lipogenesis takes place in different cellular compartments (Gartner, 2018). It starts in the mitochondria of lactocytes (Friedman & Nunnari, 2014), with the production of acetyl-CoA from fatty acid oxidation (Nelson & Cox, 2017b), pyruvate (**$C_3H_3O_3$**) oxidation (McDonald *et al.*, 2011) and catabolism of aa carbonaceous skeletons (Rodwell, 2018) (Figure 8).

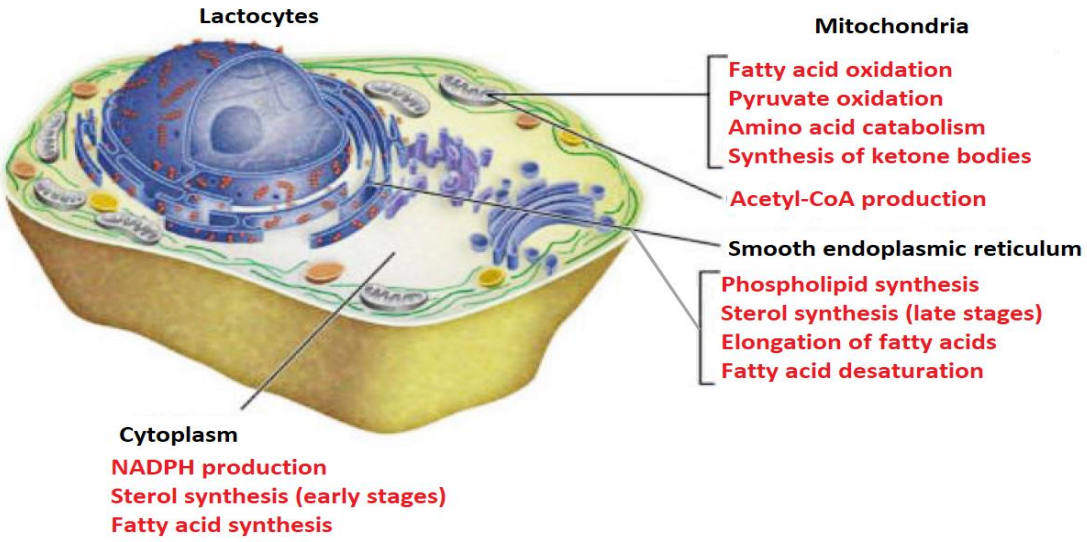

Figure 8. Subcellular localization of lipid metabolism

Like other metabolic pathways, fatty acid synthesis is endergonic and reductive (Botham & Mayes, 2018b). Therefore, the process uses adenosine triphosphate (**ATP** as an energy source (Botham & Mayes, 2018a) and nicotinamide adenine dinucleotide phosphate (**NADPH**) as a reduced electron carrier (Madigan *et al.*, 2019a). Consequently, fatty acid synthesis continues in the cytoplasm (Appleton *et al.*, 2013d), where NADPH is available for reductive synthesis [i.e., where the (NADPH)/(NADP+) ratio is high] (Cooper, 2019a). However, the inner mitochondrial membrane is impermeable to the passage of acetyl-CoA (Ellis *et al.*, 2015; Mas, 2018), so a shuttle for transfer of acetyl-CoA (acetyl groups) from the mitochondrial matrix to the cytoplasm is required (Nunes *et al.*, 2013) (Figure 9).

Intra-mitochondrial acetyl-CoA first reacts with oxaloacetate to form citrate (Nelson & Cox, 2017a), in the citric acid cycle reaction catalyzed by citrate synthase (Appleton *et al.*, 2013b). Citrate passes through the mitochondrial membrane on its transporter (Nunes *et al.*, 2013). In the cytoplasm, citrate cleavage catalyzed by citrate lyase regenerates acetyl-CoA and oxaloacetate in an ATP-dependent reaction (Ellis *et al.*, 2015; Verschueren *et al.*, 2019). Oxaloacetate cannot return directly to the mitochondrial matrix, as there is no transporter for it (Nelson & Cox, 2017a). So, malate dehydrogenase catalyzes its reduction to malate, and this passes through the mitochondrial membrane on its transporter (Nunes *et al.*, 2013).

In the mitochondrial matrix, malate is re-oxidized to oxaloacetate catalyzed by malate dehydrogenase to complete the shuttle (Friedman & Nunnari, 2014). The pyruvate produced is sent to the mitochondrion by its transporter, and then converted back to oxaloacetate catalyzed by pyruvate carboxylase (Nelson & Cox, 2017a). In the resulting cycle, two molecules of ATP are consumed (by citrate lyase and pyruvate carboxylase) for every molecule of acetyl-CoA supplied for lactate lipogenesis (Appleton *et al.*, 2013c).

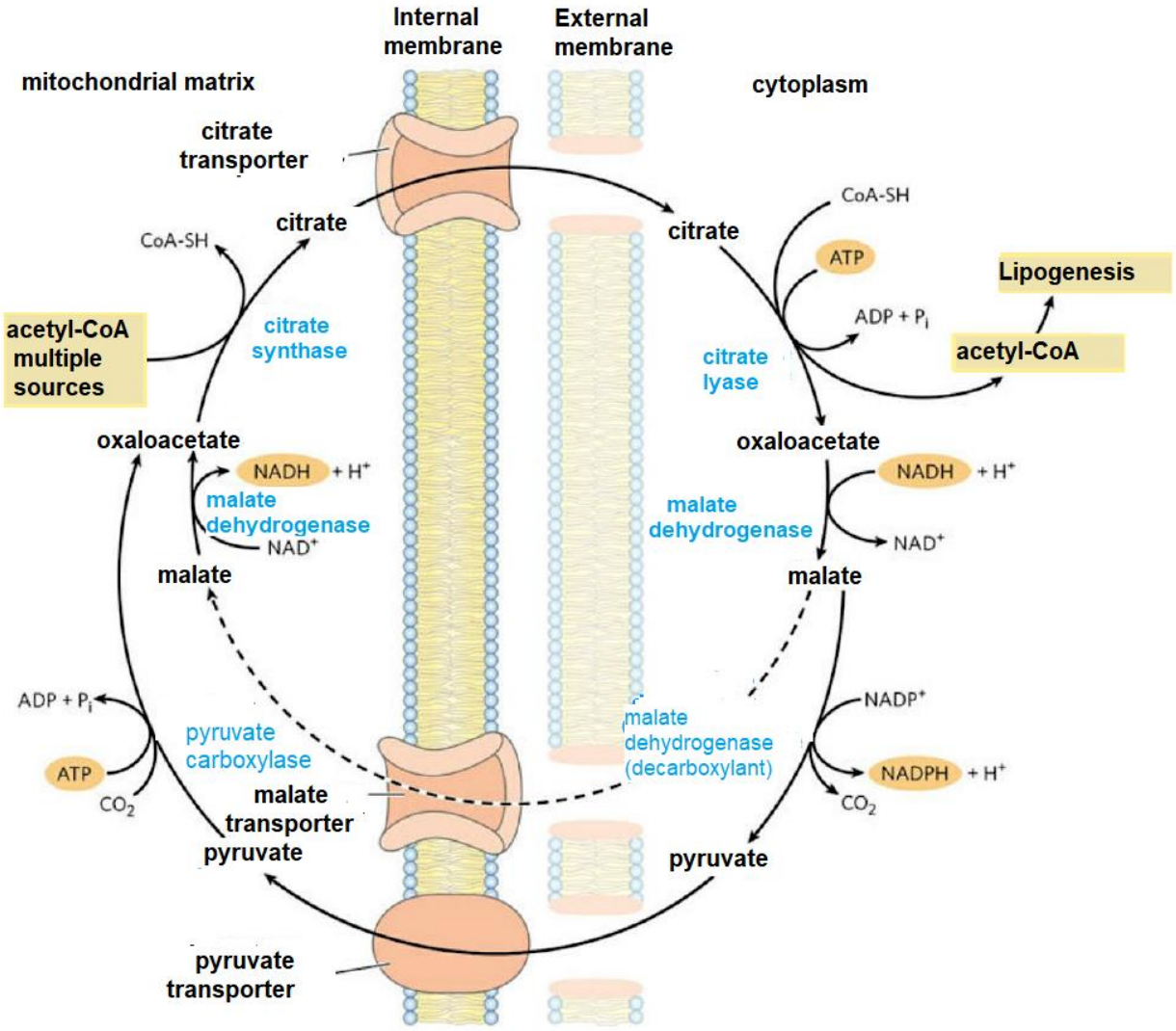

Figure 9. Shuttle for acetyl group transfer

In the cytoplasm, fatty acid biosynthesis begins with the participation of a three-carbon intermediate called malonyl-CoA (Mas, 2018) (Figure 10).

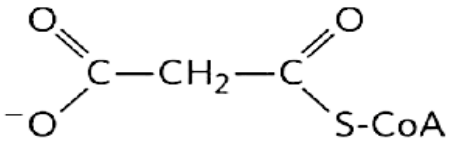

Figure 10. Malonyl-CoA

The formation of malonyl-CoA is from acetyl-CoA in an irreversible process catalyzed by biotin carboxylase (Nunes *et al.*, 2013). In this two-step reaction a carboxyl group derived from the hydrogenocarbonate anion (**HCO_3^-**), binds to a nitrogen of the biotin ring in an ATP-dependent reaction (Botham & Mayes, 2018a), activating carbon dioxide (**CO_2**) (Mas, 2018). The biotinyl group serves as a temporary CO_2 carrier (Nelson & Cox, 2017a), and part of the transporter protein and the long flexible biotin arm turn to transport activated CO_2 from biotin to acetyl-CoA producing malonyl-CoA (Cooper, 2019a).

From malonyl-CoA lipogenesis is performed by the fatty acid synthase I (**FAS I**) protein complex (Suburu *et al.*, 2014). This system performs synthesis, reduction, dehydration and again reduction by concentrating malonyl-CoA groups with acetyl-CoA, with loss of CO_2 at each step (Belew *et al.*, 2019). After each two-carbon addition, reductions convert the growing chain to a four-carbon fatty acid, then six, then eight carbons, and so on (Song *et al.*, 2018) (Figure 11). Fatty acid synthesis in FAS I always reaches 16 carbons (palmitic, C16:0) and no intermediates are released (Chandel, 2021).

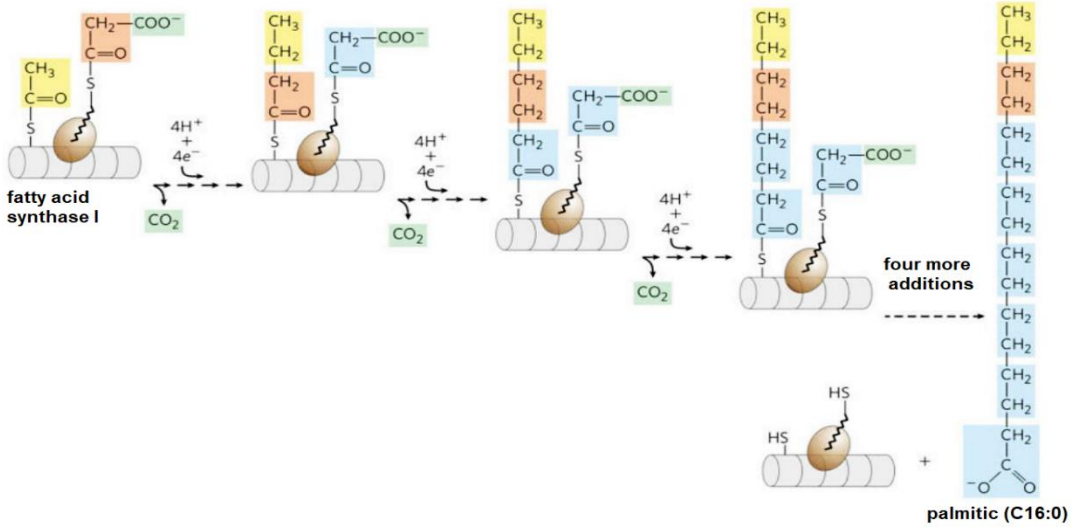

Figure 11. General process for the synthesis of palmitic acid

Palmitic, leaves FAS I and can enter the endoplasmic reticulum (Olarte *et al.*, 2020), to be elongated (coupling new carbons to lengthen the chain) (Balla *et al.*, 2019) and desaturated (introducing *cis* double bonds between its carbons) to form polyunsaturated fatty acids (Rowland & Voeltz, 2012). At this time the mammary gland parenchyma undergoes a functional and morphological differentiation termed lactogenesis I (Reese *et al.*, 2020; Menzies, 2021), and initiates the accumulation of lipid microdroplets (Ashdown

& Done, 2011). These droplets are obtained from NEFA, released from circulating lipoproteins by lipoprotein lipase located in the vascular bed of the mammary gland (Davidson & Stabenfeldt, 2020) or by circulating fatty acids derived from adipose tissue bound to ALB (Fox *et al.*, 2015).

After parturition lactogenesis II begins (Baljit, 2017), this process requires: i) coordination and activation of fatty acids by acyl-CoA synthetases (Fernandez & Ellis, 2020), ii) de novo synthesis of medium-chain fatty acids from GLU (Jones, 2016; Cooper, 2019a), and iii) synthesis of neutral lipids e.g., triacylglycerol (**TAG**), COL and diacylglycerol (**DAG**) esters (Sanhueza *et al.*, 2012; Nelson & Cox, 2017b), which provide binding for accessory proteins (Reece & Rowe, 2017b), e.g., CTP:phosphocholine cytidylyl transferase (**CCT**) and perilipins (**Plin**) (Henry *et al.*, 2015).

In general, milk fat globules are thought to form from tubular microdomains of the smooth endoplasmic reticulum (Pol *et al.*, 2014). However, unlike other lipogenic cells e.g., hepatocytes and adrenocortical cells (Saheki & De Camilli, 2017), mammary gland parenchyma is highly enriched in rough endoplasmic reticulum with enzymes for neutral lipid synthesis (Sturley & Hussain, 2012).

This process begins with the esterification of fatty acids to a glycerol molecule to form TAG (Tortora *et al.*, 2019), in four reactions catalyzed by members of glycerol-3-phosphate acyltransferase (**GPAT**), phosphatidic acid phosphatase (**PAP**) and acyl-CoA:diacylglycerol acyltransferase (**DGAT**) enzyme families (Monks *et al.*, 2020). Monks et al., 2020). The final step in this pathway is the esterification of DAG to TAG (Chandel, 2021). In turn, the synthesis of COL esters is mediated by acyl-CoA:cholesterol acyltransferase (**ACAT**) (Sanhueza *et al.*, 2012).

Once these elements are structured, they are incorporated into the fat globule (Figure 12), together with carotenoids, fat-soluble vitamins and phosphatidylcholine (Mas, 2018). Two main pathways contribute to phosphatidylcholine synthesis: i) the Kennedy pathway for de *novo* synthesis of phospholipids, a reaction catalyzed by CCT and ii) the Lands cycle (Appleton *et al.*, 2013d; John *et al.*, 2022). In the latter, the remodeling of phospholipids in the fat globule membrane takes place in deacylation/reacylation reactions (Henry *et al.*, 2015; Guoyao, 2017a), catalyzed by phospholipase A (**PLA**) and lysophospholipid acyltransferase (**LFLAT**) (Seoane *et al.*, 2018). Botham & Mayes (2018b) established that, thanks to these phospholipids, the apolar tails project to glycerides and the polar heads project to water.

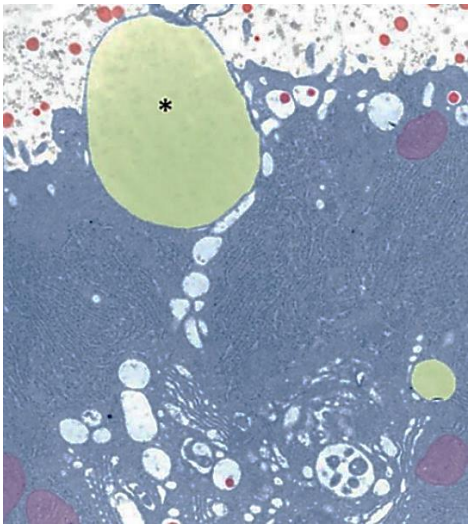

Figure 12. Electron micrograph of a milk fat globule (asterisk) attached to the apical plasma membrane; casein micelles (red)

Fuente: (Dee & Magee, 2018)

Regulation of lipolysis appears to be the main function of the five Plin proteins (Lundquist *et al.*, 2020), which prevent access of lipases to the fat globule (Zhang & Liu, 2019). Unlike lipoproteins, milk lipids are not packaged into vesicles in the Golgi apparatus (Wilson *et al.*, 2011), nor are they secreted by an exocytic mechanism (Lowe, 2011). Instead, they advance unidirectionally toward the apical pole of the lactocyte (Davidson & Stabenfeldt, 2020) and once there, they pass into the alveolar lumen via an apocrine mechanism (Figure 12), in the form of Plin-coated milk fat globules (Lundquist *et al.*, 2020), to continue their transit into the intralobulillar ducts and flow into a central collecting space (Davidson & Stabenfeldt, 2020).

V. Milk proteogenesis

Usually a portion of the dietary protein resists bacterial proteolysis in the rumen and passes into the abomasum without being catabolized (Appleton *et al.*, 2013a), along with ruminal bacteria attached to the fermented feed (Guoyao, 2017b). Pancreatic acinar cells translate hydrolases e.g., peptidase or protease, aminotransferase and nuclease (Philipps, 2018). In the duodenum, these enzymes soak the food bolus and its proteins lose their peptide bonds by hydrolysis (Lozano *et al.*, 2005). This process, releases the aa from their polymeric structure to be absorbed at the intestinal level (Piña & Flores, 2018), transported to the liver and redirected to the cytoplasm of lactocytes (Ahern, 2019).

Milk proteogenesis begins in the lactocyte nucleus with transfer ribonucleic acid (**tRNA**) transcription (Madigan *et al.*, 2019b). RNA polymerase carries out the transcription of messenger ribonucleic acid (**mRNA**) (Cooper, 2019b), starting from a segment of deoxyribonucleic acid (**DNA**) that serves as a template (Singh & Rajeev, 2020). This DNA segment contains exons (coding regions) and introns (non-coding regions) (Nelson & Cox, 2017c). Before leaving the nucleus, segments corresponding to introns are cut (Weil, 2018b) and segments corresponding to coding exons are spliced (Madigan *et al.*, 2019b).

Next, tRNA and mRNA exit the nucleus and enter the cytoplasm (Weil, 2018a). At this point, protein translation is promoted on ribosomes with three main steps: i) initiation, ii) elongation and iii) termination (Nelson & Cox, 2017c) (Figure 13). 2

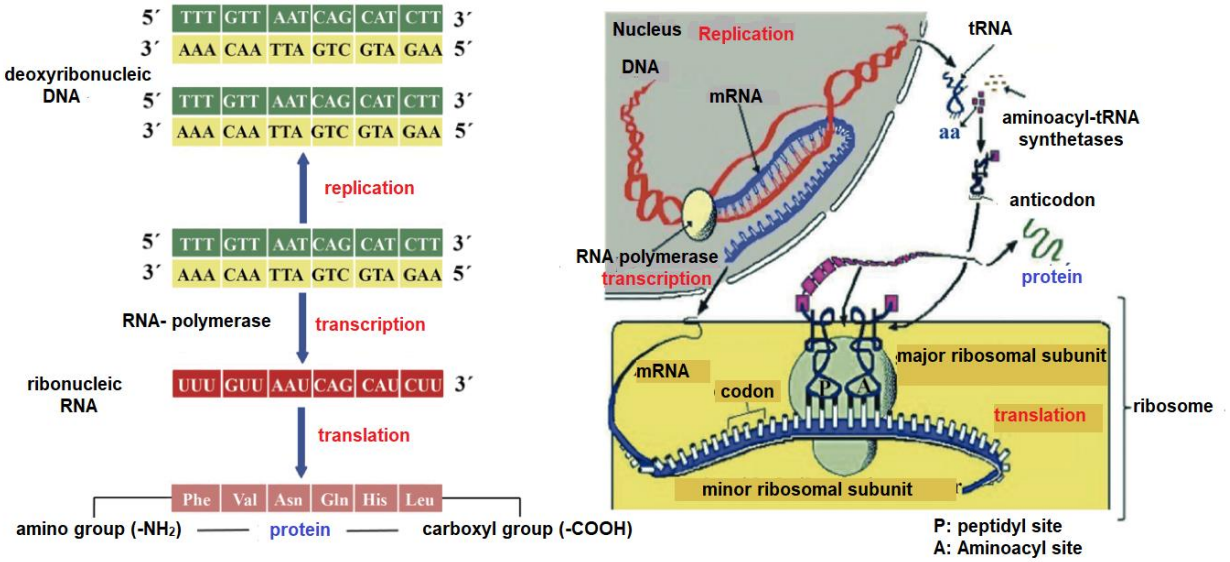

Figure 13. Proteogenesis, transcription and protein translation
Source: (Pacheco *et al.*, 2021)

tRNA transports aa from the cytoplasm to the ribosomes (Weil, 2018b) and to ensure that the tRNA carries the correct aa, each tRNA contains a specific sequence of three nitrogenous bases called an anticodon (Lozano *et al.*, 2005). In the case of mRNA its specific sequence of three nitrogenous bases is called a codon (Angov, 2011). Ribosomes contained in the lactocytes of the glandular parenchyma are the organelles responsible for the translation of different types of caseins e.g., αS1-CN, αS2-CN, β-CN, and κ-CN (Doherty & Doudna, 2000). A lactocyte can have thousands of ribosomes (Ingolia, 2014), and their number increases with the proliferation of the glandular parenchyma during early lactation (1/3 lactation) (Reese *et al.*, 2020) and their involution begins during late lactation (3/3 lactation) along with the decrease in milk (Davidson & Stabenfeldt, 2020).

Each ribosome consists of two subunits the peptidyl (**P**) site and the aminoacyl (**A**) site (Ingolia, 2014), which associate for codon-anticodon base pairing (Weil, 2018a) and dissociate during translation termination (Swaisgood, 2003). The A site is where the first aa-loaded tRNA is docked (Madigan *et al.*, 2019b). P site is where the growing polypeptide chain binds to the preceding tRNA (Piña & Flores, 2018). During peptide bond formation (**O=C-N-H**) the growing chain moves toward the tRNA at the A site (Nelson & Cox, 2017c). After elongation the tRNA containing the polypeptide translocates from the A site to the P site (Madigan *et al.*, 2019b), thus freeing the A site for a new aa-loaded tRNA (Lozano *et al.*, 2005) (Figure 13). In each translocation, the ribosome advances three nucleotides (one codon) along the mRNA (Appleton *et al.*, 2013a), exposing a new codon at the A site (Weil, 2018a). Accuracy in translocation is essential for the accuracy of dairy

proteogenesis (Weil, 2018a). That is, the ribosome must move exactly one codon at each step or the fidelity of translation would be compromised (Angov, 2011).

Protein translation ends when the ribosome reaches a termination codon e.g. uracil-adenine-guanine (**UAG**), uracil-adenine-adenine (**UAA**) and uracil-guanine-adenine (**UGA**) (Weil, 2018a), as no tRNA binds to a codon of these (Piña & Flores, 2018). Instead, release factors recognize UAG, UAA and UGA (Nelson & Cox, 2017c) and cleave the attached polypeptide from the final tRNA (Lozano *et al.*, 2005), releasing the finished caseins (Davidson & Stabenfeldt, 2020). mRNA is then released and can be re-read by other ribosomes (Madigan *et al.*, 2019b), and the ribosomal subunits dissociate and become free to form new initiation complexes and repeat the process (Pacheco *et al.*, 2021). Finally, in the Golgi apparatus, glycosylation of caseins (binding with lactose) takes place (Wilson *et al.*, 2011) and during their movement through the cytoplasm tricalcium phosphate [$\mathbf{Ca_3(PO_4)2}$] and other ions are coupled to form a structure called a micelle (Reese *et al.*, 2020), which will be exported to the alveolar lumen (Dee & Magee, 2018), to continue its transit to the intralobulillar ducts and flow into a central collecting space (Davidson & Stabenfeldt, 2020).

The protein fraction is divided into 20 % for soluble or serum proteins where the following stand out: i) β-lactoglobulin (retinol and fatty acid binding and possible antioxidant) (McKerchar *et al*., 2023), ii) α-lactoalbumin (lactose production, calcium transport, immunomodulatory and anticancer) (Diao *et al*., 2022), iii) immunoglobulins IgA, IgM and IgG (immune protection) (Nayik *et al*., 2022) iv) lactoferrin (antibacterial, antioxidant, immunomodulatory, iron absorption and anticarcinogenic) (Sansi *et al*., 2022), and v) lactoperoxidase (antibacterial) (Lérias *et al.*, 2014). All soluble proteins present a higher proportion of leucine, isoleucine and valine (Ahern, 2019).

Eighty percent of the protein fraction corresponds to insoluble proteins or caseins whose function is to transport and bind minerals, mainly calcium and phosphorus (Dhasmana *et al*., 2022). The concentration of αs1-casein and αs2-casein is lower in goat milk than in cow milk, the fraction of β-casein is higher and the amount of and κ-casein is equal to that of cow milk (Saikia *et al*., 2022). The αs-casein is the main protein found in cow's milk, whereas the main protein factor found in goat's milk is β-casein (Dhasmana *et al*., 2022). All insoluble proteins have a higher proportion of histidine, methionine and phenylalanine (Ahern, 2019).

CONCLUSIONS

In recent years, the shift in milk marketing towards a standardized price structure based on lipid and protein concentration requires a better understanding of the anatomical and physiological processes occurring in the mammary gland. Goats appear to be the least affected species with respect to emotional stress and milk ejection. Because of the morphological and physiological characteristics of the goat mammary gland, 70 % of the milk produced between milkings can be extracted independently of hormonal processes. The development of the mammary gland through its four stages: i) mammogenesis, ii)

lactogenesis, iii) galactopoiesis, and iv) involution, determines all aspects of the behavior of the lacteal glandular parenchyma. Lactocytes possess a high metabolic complexity and a robust microscopic organization to develop their systems of extraction, utilization of polysaccharides, lipids and proteins and transformation into milk fat and protein. Knowledge of the anabolic and catabolic processes of these molecules will allow understanding the basic biochemistry of milk production.

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Errata Erratum
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