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Role of Serotonin in Mammary Gland Development and Lactation Regulation in Dairy Animals: A Review

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Abstract:
The aim of this review was to look in to the role of serotonin in the of mammary gland development and lactation regulation in dairy animals. In dairy animals, the dynamic interplay of endocrine hormones and locally produced factors such as serotonin regulates udder gland development and lactation. Serotonin (5-hydroxytryptamine, 5-HT) is a central neurotransmitter that influences mammary development and lactation in a variety of mammals. Its action is mediated by receptors found in a variety of mammary tissues. Serotonin played a significant role in the dilatation of the mammary alveolar space. Mammary 5-HT is used to regulate lactation, initiate the shift from the early stages of involution, and accelerate calcium mobilization from the skeleton. 5-HT is a nearby or local signal that controls milk secretion and promotes the formation of parathyroid hormone–related peptide (PTHrP) in several animals. According to various studies, serotonin influences milk yield and composition. Intrinsic 5-HT, which is generated inside the mammary epithelium, is vital in managing milk volume homeostasis in many species of mammals. Furthermore, when the udder gland is full of milk, 5-HT sends a negative feedback signal to the mammary epithelium, inhibiting further milk supply. Serotonin can limit milk production via a negative feedback loop by countering prolactin synthesis of mammary gland growth and lactation. Cellular connections (adherens junctions, desmosomes, and gap junctions), TPH1 induction, secretory activation, and pharmacological effects all have an impact on serotonergic control of lactation. Thus, serotonins linked with their receptors and play a crucial role in mammary gland development and lactation regulation.

Keywords: Serotonin, mammary development, lactation

INTRODUCTION

Researchers set out to identify genes whose expression is influenced by prolactin in order to uncover possibly novel aspects of mammary gland physiology and development. Researchers focused their efforts on PRL-regulated genes that do not encode milk proteins or other milk-related gene products (Manabu et al., 2004). Serotonin (5-HT) is a peripheral (marginal) signaling chemical that impacts hemostasis, immune function, intestinal physiology, and other systems. 5-HT is a neurotransmitter that influences mood and cognition in both animals and humans (Hardman and Limbird, 2001). Because its receptors are found in a number of organs, including the endocrine, cardiovascular, immunological, and gastrointestinal systems, it is known as a marginal signaling molecule. Serotonin (5-HT) receptors are classified into four families (5-HTR1, 5-HTR2, 5-HTR3, 5-HTR4-7). Each serotonin receptor has its unique signaling pathways and physiological roles (Manabu et al., 2004). Serotonin (5-HT) is an old signaling chemical, although it is now frequently employed in mammary glands. The biological function of serotonin signaling and serotonin itself is complex, and extensive physiological, pharmacological, and molecular genetic studies on mammary process control have not been completed. For the first time, serotonin is extracted from the guts of several species, as well as their skins and serum. It was

named from two terms: serum-derived (sero-) vasoactive (tonic) chemical (Nelson and Robert, 2014).

The mammary gland's reactions to biosynthesis and secretion of serotonin are increased in response to alveolar space dilatation. Mammary serotonin has fulfilled two duties since its discovery some years ago; notably, it controls lactation and initiates the shift into the early phases of involution. Following that, serotonin stimulates the synthesis of parathyroid hormone–related peptide (PTHrP) via a local signal, causing the mammary gland to mobilize calcium from the skeleton (Nelson and Robert, 2014). Serotonin has a powerful role in both metabolism and physiology as a neurotransmitter, vasoconstrictor, gastrointestinal health regulator, and a mammary produced hormone that assists in lactation coordination (Horseman & Collier, 2014).

Furthermore, through performing on mammary epithelial cells (MECs), monoamine serotonin, a mammary-derived autocrine-paracrine signaling biomolecule, influence milk yield in many species. Bruschetta et al. (2020) discovered breed-specific serotonin concentrations in Italian Fresian and Brown Swiss cows during early lactation. Collier et al. (2012), in another cases, explored how serotonin ligands affect cow's milk output and composition. Serotonin also has a crucial metabolic function in the inhibition of the lactating mammary gland. Serotonin can also manage maternal metabolism without endangering maternal health (Hernández-Castellano et al., 2019). As a result, the main objective of this review paper was to examine the role of serotonin in mammary development and lactation regulation in lactating animals.

SEROTONIN

Serotonin is an ancient signaling chemical found in a wide range of plants, animals, and unicellular creatures. Before 750 million years ago, the first serotonin receptor subtypes were found. Serotonin, a biogenic amine group, has affected the development and elasticity of many tissues in diverse animal species throughout the previous 2 billion years of development from protozoa to mammals. Serotonin is found in 5-hydroxytryptamine, Enteramine, Thrombocytin, 3-(ßAminoethyl)-5-hydroxy indole, and Thrombotonin (Raymond et al., 2001).

Serotonin regulates a variety of physiological functions including homeostasis, nutrition, immunity, energy control, cardiovascular function, behavior, intestinal motility, and reproduction (Horseman and Collier, 2014; Wyler et al., 2017). The serotonin system's extra-neuronal role in the mammary gland functions was recently revealed. Serotonin is present in numerous organs' epithelial cells, including the mammary gland (Marshall et al., 2014). Intrinsic 5-HT is produced by the mammary epithelial cells of mice, cows, and humans. The intrinsic 5-HT generated by mammary epithelial cells is employed to regulate milk volume homeostasis. Since the mammary gland was full of milk, Serotonin suppressed milk production by delivering negative feedback to mammary epithelial cells (Lauder, 2004; Matsuda, 2004).

During lactation, fifty percent (50%) of the circulating serotonin is produced and released. Serotonins have a strong influence on mammary homeostasis inside mammary epithelial cells (Weaver et al., 2017). However, in non-lactating animals, the bulk of serotonin is produced and secreted by enterochromaffin cells in the intestine (Gershon & Tack, 2007).

The Role of Serotonin in Mammary Gland

Matsuda et al. (2004) identified an unexpected function of serotonin in mammary gland development Serotonin is a neurotransmitter produced locally by the mammary epithelium that

plays a key role in the negative feedback loop opposing prolactin stimulation of mammary gland growth and lactation. In response to gland fullness, this feedback loop suppresses milk excretion. Serotonin is widely recognized for its several activities, including the early development of oocytes and embryos in a wide range of animals, including sea urchins, starfish, mollusks, Drosophila, and rodents (Buznikov et al., 2001).

Similar to big animals, serotonin regulates preimplantation embryo development in mice (Vesela et al., 2003). In a range of animal species, including mice, cows, and humans, intrinsic serotonin (5-HT) generated within the mammary epithelium plays a significant physiological function in milk volume homeostasis. During lactation, the production of 5-HT (TPH1) increases due to the activation of tryptophan hydroxylase 1 by mammary epithelial cells. The TPH1 catalyzes the 5-HT production in the mammary gland. Serotonin is produced in mammary epithelial cells and transferred into the apical (milk) and basolateral spaces via the vesicular monoamine transporter. Suckling affects the quantity of serotonin in milk because serotonin levels in milk decrease during suckling (Chiba et al., 2018).

Serotonergic Regulation of Lactation

Tryptophan Hydroxylase 1 (TPH1) Induction:

The production of 5-HT in the mammary gland was identified using PRL-knockout (PRL-KO) mice (Matsuda et al., 2004). TPH1 was undetectable in PRL-knockout mice, but it was increased at the mRNA level when these mice were given large doses of PRL. TPH1 induction and 5-HT biosynthesis were both modulated by alveolar distension. TPH1 induction and 5-HT biosynthesis are triggered by mammary epithelial secretory activity. However, TPH1 induction and 5-HT biosynthesis are ultimately dependent on PRL. The period of time influences milk 5-HT secretion. The biggest rise in milk 5-HT occurred between 10 and 18 hours, when udder engorgement was at its maximum, as indicated in the figure below (Zia et al., 1987). As a result of the TPH1 regulatory pattern, 5-HT may play a role in the homeostatic control of milk secretion during milk stasis.

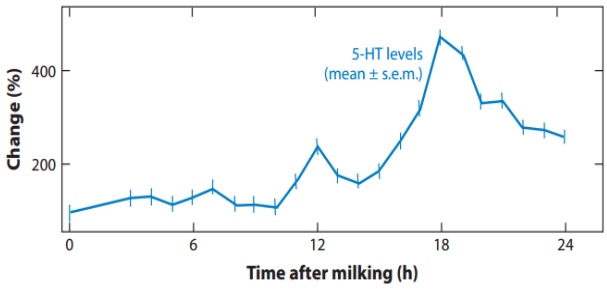

Figure 1: Milk serotonin (5-HT) during 24 h after milking (Zia et al., 1987)

Cellular Junctions:

Cellular junctions preserve the membrane integrity between epithelial cells and the extracellular matrix. Because cellular connection features are critical in recognizing mammary epithelial physiology (Linzell and Peaker, 1971). Four junctions are involved in the serotonergic control of lactation. Adherens junctions (formerly known as intermediate junctions), desmosomes, gap junctions, and tight junctions are all types of junctions. These junctions were important in the control of serotonergic lactation. Adherens and desmosomes junctions join cells and give strength and rigidity to the epithelial membrane, whilst gap junctions enable substances to flow selectively between cells. Tight junctions also regulate the movement of molecules between the

luminal and serosal compartments by producing the z-axis barrier that divides the apical membrane from the basolateral membrane (Steed et al., 2010; Sawada, 2013).

During milk stasis, 5-HT dynamically modifies mammary epithelial tight junctions. Hernandez et al. (2011) employed FLX, an SSRI, to produce an in vivo tight junction response to 5-HT in milking cow udders. Serum lactose levels, a measure of tight junction leakiness, were significantly higher 24 hours after FLX infusion compared to values in mice given only the vehicle (Hernandez et al., 2011). Mammary epithelial cells were cultivated on permeable membranes to assess solute transport and transepithelial electric resistance. To validate the measurement, the Serotonin type-7 receptor (5-HT7) system was employed as a mediator of 5-HT tight junction responses. 5-HT agonists and antagonists can alter the basolateral membrane, but they have no effect on the apical membrane (Stull et al., 2007). Because of their strong constitutive activity as well as homologous and heterologous desensitization, 5-HT7 receptors are employed as tight junction mediators (Pai et al., 2008; Krobert and Levy, 2002).

Secretory Activation:

Milk production is restricted during pregnancy due to placental steroid (particularly progesterone), which is part of endocrine signals (Freeman et al., 2000). However, no further study was conducted to determine specific local factors inhibit secretory activation. While research on mice mammary glands using pituitary grafting found that local serotonin, in concert with endocrine factors, can decrease mammary gland secretory activity when the gland is exposed to high amounts of lactogenic hormones (Matsuda et al., 2004).

Drug Effects:

Pharmacological drugs can be used to investigate mammary gland serotonin systems. Serotonergic drugs are commonly used as antidepressant medicines in therapeutic agents (Wong et al., 2005). They were commonly used to treat depression, anxiety, migraine headaches, fibromyalgia, and smoking cessation. These medications worked by decreasing the reuptake of released 5-HT, resulting in a longer-lasting 5-HT signal. In general, the concentration of Selective Serotonin Reuptake Inhibitors (SSRI) determines the drug effect on mammary gland serotonin, because low concentrations of SSRI increase tight junction resistance, whereas high concentrations of SSRI open a tight junction, resulting in decreased transepithelial resistance and tight junction protein disorganization (Marshall et al., 2010).

Delayed Secretory Activation in New Mothers Taking SSRI:

When a new mother is given an SSRI, the secretory stimulation of mammary gland serotonin into the udder might be delayed, which is contrary to laboratory findings. Lactation is delayed as a result of this occurrence. Because of the delayed lactation, mom/cow is at a considerable risk of failing to breast/udder feed their babies/calves (Marshall et al., 2010).

Acceleration of Dry-off in the Dairy Cow:

The obvious significance of 5-HT in natural lactation homeostasis and the effects of SSRI medication in new cows compelled researchers to investigate the system of serotonin mammary gland in dairy cows (Marshall et al., 2010; Hernandez et al., 2011). The cow, like humans and mice, expressed serotonin receptors (5-HT7) in its mammary epithelium. Cows, on the other hand, have an extra receptor that mice and humans do not have. When serotonin receptors (5-HT7) are activated, tight junctions in the cow mammary epithelium opened and milk protein gene production is suppressed. The secretory activation of the cow is delayed when it is given an SSRI.

In addition, the drying process in dairy cows is hastened. This means that the serotonin system, through the action of serotonergic drugs, might impact lactation performance of cow (Hernandez et al., 2011).

Integration of Calcium Mobilization and Lactation Physiology by 5-HT

The physiological integration of tissue, cellular function, and lactation physiology at the organismal level can be modulated by mammary serotonin systems. Tryptophan hydroxylase 1(TPH1) expression is induced by secretory material in the alveolar lumen and is controlled by lactational dilatation and contraction. Because of its unique mode of regulation, serotonin is a reliable source of information for the dynamic change that occurs during lactation within the mammary gland (Hernandez et al., 2012).

Serotonin, alveolar filling, and calcium mobilization are all connected to the induction of parathyroid-Hormone Related Peptide (PTHrP). During lactation, serotonins play a significant role in PTHrP expression. As a result, its activity is directly mediated in epithelial cells via the 5-HT2B receptor type. PTHrP regulates serotonin's participation in whole-body calcium metabolism. The researchers begin by inducing PTHrP via serotonin signaling systems in order to solve the issue of why dairy cows are particularly sensitive to hypocalcemic crises whereas other animals are not (Horst et al., 2005). A big cisternal udder has been intentionally selected in dairy cows to drain the alveolar gaps efficiently. This reservoir must fill before the alveolar gaps may be completely distended. Inflating milk was the traditional therapy for milk fever a century ago. Figure 2 depicts, in a simplified form, the feedback loop through which milk secretion drives PTHrP.

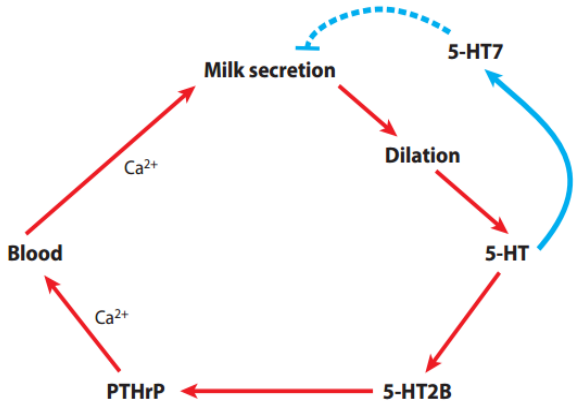

Figure 2. Linkage between serotonin mechanisms that regulate milk secretion via and 5-HT7

CONCLUSIONS

This review was concluded by underlining the importance of serotonin in the development and lactation of dairy animals' mammary glands. In order to function on mammary tissues, serotonin is mediated via receptors located in a number of tissues. The intrinsic and mammary gland 5-HT signaling systems have paved the way for new study into the local regulation of physiology in lactating mammary glands, as well as communication between mammary glands. The 5-HT system in the mammary gland plays a significant role in the physiological integration of tissue and cellular activities, as well as lactation physiology at the organismal level.

Therapeutic 5-HT drugs can have an effect on lactation, either favorably or adversely. Pharmacological medications work by decreasing the reuptake of produced 5-HT in mammary

tissue, allowing for the generation of a longer-lasting 5-HT signal. As a result, for a long time, serotonin has been employed in mammary gland growth and milk yield advancement with few negative implications, as it prolonged the 5-HT signal to be generated by decreasing the rate of released 5-HT reuptake from mammary tissues.

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Ethics Approval
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Availability of Data and Material (Data Transparency)
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Code Availability (Software Application)
As per the review article, no software was used

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The author prepares this work entirely on his own, with no assistance from anyone

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