

Peripheral serotonin: An unraveled metabolite in bovines

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ABSTRACT

Serotonin is an omnipotent molecule in the brain and rest of the body and plays a pivotal role in the gut-brain axis. Serotonin's role in neurotransmission and its function at molecular levels with different genetic variants has been widely covered across the animal kingdom. Although the digestion process in ruminants is pillared on anaerobic microflora present in the rumen, the impact of the rumen microbial population on serotonergic activity is seldom explored. Besides its principal effect on the gastrointestinal, it regulates the excretion of bile acids, glucose and lipid homeostasis, energy balance, immunomodulation, and various other vital processes in the animal system. However, the studies on part of peripheral serotonin are moderate and very few in bovines. The objective of this review is to appreciate research conducted on the basics of serotonin, triallelic polymorphism in SLR6A4 gene polymorphism, receptors and its role in GI, liver, pancreas, adipocytes, and to a little extent in other organs like uterus, mammary gland, etc. in different species and look forward to expanding the information in bovines.

Keywords: Cattle, Contractions, Energy, Peripheral, Ruminants, Tryptophan

Serotonin's role as a neurotransmitter has drawn much attention because of its clinical importance in regulating mood, appetite, reproductive drives, sleep, and gastrointestinal functions. The focus on serotonin as a neurotransmitter focussed on peripheral serotonin (Alcaino *et al.* 2018). Peripheral serotonin is separate from neuronal serotonin as each is incapable of passing the blood-brain barrier (Walther and Bader 2003). The gastrointestinal is the leading site producing 95% of the serotonin and is essential in its luminal mechanical stimuli. Major work reported on serotonin was the human studies, followed by other mammals, but a very few studies are available on bovines. The plasma serotonin levels are used to evaluate the animal welfare on the farm (Bruschetta *et al.* 2010). However, the studies carried out in other species may be helpful in the perceptive role of serotonin in bovines. This paper reviews the fundamental aspects of serotonin precursors, synthesis, secretion, action, etc., and serotonin's physiological function in the various organs.

Serotonin secretion

Serotonin secretion can be portioned between the brain/central nervous system (CNS), gastrointestinal and other organs. It is produced in the raphe nuclei of the brain stem, Merkel or tactile epithelial cells (Woo *et al.* 2015) located in the touch-sensitive areas of the skin such as whisker follicles, hairless skin surface, gustatory cells in the upper surface

of the tongue and touch domes and are mechanosensitive (Morrison *et al.* 2009). Serotonin produced in the CNS or epithelial mechanosensor cells accounts for only 1 to 2% of its total production in the body. The majority of serotonin, approximately 95%, is produced in the enterochromaffin cells in the gastrointestinal (GI) tract and is involved in many physiological functions (Marrero *et al.* 2020). GI serotonin is involved in transformation of the enteric nervous system (ENS), neurogenesis, motility, secretion, inflammation, sensation, and epithelial development (Terry and Margolis 2017). The remaining serotonin 2 to 3% is found in the immune tissue, pancreatic β cells, adipocytes, mammary tissue, osteoclasts, etc. and is omnipotent in the body (Kim *et al.* 2010, Stunes *et al.* 2011, Chabbi-Achengli *et al.* 2012, El-Merahbi 2015). Serotonin in the GI tract can act locally or enter into the blood circulation and only 2% is present in free form to act as a hormone (Berger *et al.* 2009). In the blood, 98% of gut serotonin is taken up and stored by platelets and released during blood coagulation (Berger *et al.* 2009). Platelets can only store the serotonin as they lack the enzyme to synthesize it. Hence, the blood serotonin levels indicate its production in GI (Foley *et al.* 2011).

Serotonin precursors

Tryptophan is the precursor for serotonin synthesis (Fig.1). Tryptophan content in a few widely used feed stuffs in dairy rations is given in Table 1. The immediate precursor to serotonin synthesis, 5-hydroxy-L-tryptophan infusion, resulted in elevated circulating serotonin in prepartum cows (Weaver *et al.* 2016). Tryptophan content in most diets would be less than 1%; therefore, its ratio with other

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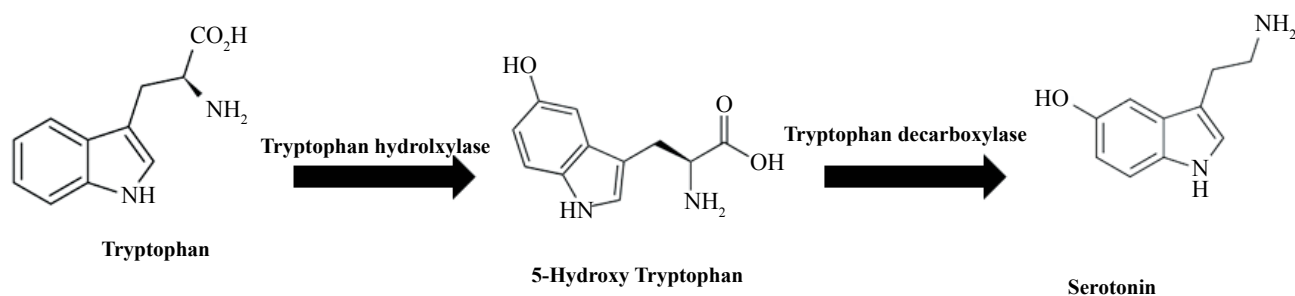


Fig. 1. Serotonin synthesis from tryptophan.

neutral amino acids in the diet is essential (Markus 2008). Tryptophan is also an initiation molecule for serotonin but also kynurenines and melatonin. Kynurenine is used in the production of niacin (vitamin B₃), which plays a vital role in the complete oxidation of acetyl Co-A in the liver and plays a role in energy balance (Longo *et al.* 2016). Serotonin is a precursor for melatonin. It is acetylated and methylated to yield melatonin which is known for its sleep-wake cycle and circadian rhythm (Hickman *et al.* 1999).

Serotonin synthesis

Although tryptophan hydroxylase (TPH) mediates the catalysis of tryptophan to 5-hydroxy tryptophan, it has two variants; TPH1 and TPH2. Tryptophan hydroxylation is catalyzed by the TPH using 6R-L-erythro-5,6,7,8-tetrahydrobiopterin and molecular oxygen (Tidemand 2017). TPH is a rate-limiting enzyme and unstable. TPH1 is expressed in the body, and acts mainly in the polygonal enterochromaffin cells located along the epithelium lining the lumen of the digestive tract but, particularly in the crypts between the intestinal villi, colon, and distal appendix as well throughout the ductile system of the pancreas. TPH2 is expressed in the brain and neurons of ENS and CNS. TPH1 is responsible for producing 90% of the intestinal serotonin, while the rest is produced through TPH2 (Terry and Margolsi 2017). TPH2 has a 71% sequence similarity to TPH1, but in addition to later, it has 41 amino acids. TPH1 is inhibited by the substrate concentration but not the TPH2. Both play significant and distinctive roles in intestinal function. As an action of TPH1 or TPH2, a hydroxyl group is added to tryptophan, and it is rapidly decarboxylated to 5-hydroxy tryptamine or serotonin (Höglund *et al.* 2019). The structure of tryptamine (without

the 5-hydroxyl group) is common between melatonin and serotonin.

Only a small part of tryptophan is used to synthesize serotonin, but the major portion is diverted to kynurenines synthesis (Höglund *et al.* 2019). Tryptophan at the metabolic junction can divert to kynurenine more than the serotonin pathway, especially during stress. Stress conditions divert tryptophan availability to the synthesis of kynurenine which in turn plays a neuroprotective role against neurotoxin quinolinic acid produced down the pathway (Jeon and Kim 2015). Bruschetta *et al.* (2010) reported negative correlation between plasma tryptophan and plasma cortisol ($r = -0.83$ $P < 0.005$); plasma serotonin and plasma total protein ($r = -0.72$, $P < 0.05$). Hence, tryptophan conversion to serotonin demands stress-free conditions; otherwise, there are more chances of reduced conversion of tryptophan to serotonin. Diet, physical activity, infection, changes in the gut microbiome, stress, and immune system activation affect plasma tryptophan concentration and tryptophan metabolism to serotonin (Höglund *et al.* 2019). Approximately 1% of available tryptophan metabolizes into serotonin (Mittal *et al.* 2017). There is a growing impetus on the role of gut microbiota in regulating the tryptophan pathway to serotonin or kynurenine; thus, playing an important role in the gut-brain axis and gastrointestinal function (O'Mahony *et al.* 2015).

Serotonin release and response

Chemical synaptic transmission between neuron cells was reasonably elucidated by Günther (2019). Serotonin is released at chemical synapse packed into synaptic vesicles, but the release is regulated by the voltage-dependent calcium channels. This channel is permeable to sodium

Table 1. Tryptophan content in a few common feeds used in bovine diets

Grains	Protein (%)	Tryptophan (mg/100 g)	Oilseed meals	Protein (%)	Tryptophan (mg/100 g)	By-products	Protein (%)	Tryptophan (mg/100 g)
Cowpea	24	280	Soya	47	710	Rice bran	16	260
Rice	9	160	Groundnut	47	630	Wheat Bran	14	230
Broken								
Wheat	13	150	Cottonseed	38	570	Rice hulls	4	220
Barley	13	140	Linseed	33	550	Soy hulls	13	110
Oats	17	140	Canola	40	500	Oat hulls	6	80
Sorghum	10	110	Rapeseed	40	470	Cottonseed hulls	6	70
Maize	8	60	Sunflower	33	450	Maize bran	8	70

*Tryptophan expressed as mg per 100 g of feed on a dry matter basis. Data source from the work of the author and web sources. All the values were adjusted to decimals.

many folds lesser than the calcium, referred to as the $\text{Ca}^{2+}\text{-Na}^{+}$ channel. Calcium influx into the cells activates sensitive potassium channels, muscle contraction (Alcaino *et al.* 2018), and the release of serotonin by exocytosis, followed by endocytosis and reusing synaptic vesicles in presynaptic terminals. The presynaptic segregation of vesicle trafficking pathways at chemical synapses mediates spontaneous and synchronous evoked release of serotonin that enables postsynaptic signaling (Li and Kavalali 2017). Immediately after reacting with presynaptic and postsynaptic receptors, serotonin removal from the synapse is essential. Failure to remove serotonin from the synaptic cleft (~20 nm wide) not only prevents further signaling but also causes intestinal inflammation, low-grade irritable bowel syndrome, and celiac diseases (Terry and Margolsi 2017). Serotonin from the synaptic cleft is removed rapidly by active transport than diffusion and allows recycling for further use. Transporter protein helps in the re-uptake of serotonin from the cleft.

Serotonin transporter

After postsynaptic signaling, Na^{+} and Cl^{-} dependent transporter proteins pump the serotonin into the presynaptic cell. Serotonin transport protein (SERT) is a crucial regulator for removing serotonin from the synaptic cleft and maintains extracellular serotonin at tonic concentrations for regulating appetite (Baudry *et al.* 2019). It consists of approximately 600 amino acids and shares a structural motif of 13 putative transmembrane domains. Bovine SERT has high homology to ovine origin (Mortensen *et al.* 1999). SERT is a monoamine transporter (MW 60 to 80 kDa) located peri-synaptically. SERT first binds to Na^{+} followed by Cl^{-} at the tail end. The Na^{+} and Cl^{-} bound SERT spin inside the cell due to membrane potential created by the $\text{Na}^{+}/\text{K}^{+}$ -ATPase ubiquitously found in all animal cell membranes, thus, resulting in the release of serotonin in the cytoplasm. After releasing the serotonin, K^{+} (potassium) ions bind to the transporter to spin the SERT outside the cell, and the cycle repeats approximately a dozen times. Mortensen *et al.* (1999) compared the K_m , $V_{\max}$, and $B_{\max}$ of SERT in cows, humans, and rats and reported that K_m was 0.63, 0.28, and 0.29 μM while $V_{\max}/B_{\max}$ was 51, 60, and 48 per min, respectively. Approximately one molecule of serotonin is translocated per second.

SERT is expressed in most bovine tissue and possesses high-affinity uptake with increased K_m compared to rat or human SERT (Mortensen *et al.* 1999). Plasma serotonin levels differ between breeds, and it was 334 ± 81 ng/ml in Brown Swiss in contrast to 170 ± 50 in Italian Friesian (Bruschetta *et al.* 2010).

Serotonin receptors

Serotonin (5-HT) action is mediated by 14 receptors outside and within the brain (Berger *et al.* 2009, Mittal *et al.* 2017, Terry and Margolis 2017). These are separated into 7 classes, 5HT1 to 5HT7. The 5HT1 class is further sub-divided into subscripts A, B, D, E, and F (e.g. 5HT1_A)

and is more abundant among all other receptors. The 5HT2 class is divided into 3 sub-classes A, B, and C (e.g. 5HT2_C). The other receptor classes contain 2 sub-classes, 5HT_A and 5HT_B. Receptor classes without sub-classes are 5HT3, 5HT4, 5HT6, and 5HT7. All classes of receptors are G-protein coupled receptors or serpentine receptors except 5HT3. The 5HT3 receptor is a ligand-gated channel or ionotropic receptor that allows Na^{+} , K^{+} , Ca^{2+} , and Cl^{-} ions to bind to serotonin. It is the main receptor mediating signals to CNS. All other receptors are cell surface receptors located outside the cell and detect the molecules. In the intestine, 5-HT1, 5HT2, 5HT3, 5HT4, and 5HT7 are expressed. 5HT1_A and 5HT1_B are presynaptic and modulate peristaltic and serotonin release (Gershon 2004). Snider *et al.* (2018) reported the presence of 5HT2_A receptors in bovine ruminal and mesenteric vasculature. Increased expression of 5HT7 receptors was reported in cows with elevated serotonin levels in whole blood, but increased expression of 5HT4 was observed after 24 h (Connelly and Hernandez 2021). O'Mahony *et al.* (2015) summarized the location of serotonin receptors and their sub-types spread across the CNS and GI tract and are instrumental in serotonergic system-inducing effects across the gut-brain axis.

SERT gene and polymorphism

Serotonin transporter proteins are encoded by the gene SLC6A4, which is responsible for the expression of SERT in the brain as well as peripheral blood cells (Beikmann *et al.* 2013). It belongs to a solute carrier family 6 members 4. The SLC6A4 is a single gene located on chromosome 19 in bovines with 13/14 exons (Mortensen *et al.* 1999) in contrast to chromosome 17 in humans with 40 kilobase pairs and consists of 14/15 exons (Ramamoorthy *et al.* 1993, Margoob *et al.* 2008). The variation in the SERT promoter region (5-HTTLPR) located ~1.2 kb upstream of the transcription site on SLC6A4 in human cells modulates SERT expression (Baudry *et al.* 2019). Hence, SERT expression and function are governed by epigenetic regulation, including DNA methylation, histone modification, and microRNA (Bauder *et al.* 2019). These effects depend on the 5-HTTLPR genotype. 5-HTTLPR has a polymorphism with long (L) and short (s) alleles. The short allele has 448 base pairs with 14 tandem repeats, and the long allele has 528 base pairs with 16 tandem repeats. This difference in base pairs is probably why 's' allele reduced transcription and functional capacity. Higher levels of CpG methylation are reported in the s allele (Kinnaly *et al.* 2010). Further, functional polymorphism studies indicated 2 subtypes of long alleles, A and G; L_A and L_G. G allele is in phase with the L allele and is functionally similar to the s allele. Thus, the 5-HTTLPR is a triallelic polymorphism; L_A, L_G, and s (Wendland *et al.* 2006, Kobiella *et al.* 2011). Increased SLC6A4 transcription increased SERT levels in the brain, and other tissues are ascertained on the L_A allele. Elevated serotonin in plasma may alter the mRNA of serotonin metabolism, transport,

and signaling genes in the whole blood of lactating dairy cows (Connely and Hernandez 2021). Reduced levels of SERT mRNA are observed because of methylation of CpG island near untranslated exon 1A of the SLC6A4 gene (Philibert *et al.* 2007, Baudry *et al.* 2019). The polymorphism of 3'-untranslated regions of the SERT gene may influence mRNA's translation, localization, and stability (Baudry *et al.* 2019). Compared to the L allele, SERT mRNA expression levels are 60 to 70% lesser on the s allele leading to reduced serotonin uptake by lymphocytes (Wankerl *et al.* 2014).

Uptake of serotonin and storage by platelets

The bovine peripheral leukocytes express all known serotonin receptors, and can synthesize, uptake, and degrade serotonin due to the expression of serotonin metabolism-related genes (Marrero *et al.* 2020). SERT mediates the serotonin uptake by platelets from the plasma by a saturable mechanism and controls its levels in plasma. Approximately 8% of total serotonin is stored in platelets, and 2% of the blood serotonin is free, equal to 1 to 2% produced in the brain. Failed uptake of serotonin from extracellular solution into lymphocytes indicated minimal SERT function (Beikmann *et al.* 2013). Subsequently, serotonin in platelets is either segregated or degraded by vesicular monoamine transporters or monoamine oxidase, respectively. The primary inactivation of serotonin is carried by monoamine oxidase-A (Mohammad-Zadeh *et al.* 2008). The serotonin uptake capacity of platelets is directly proportional to SERT molecules located in the plasma membranes (Mercado and Kilic 2010). Serotonin in platelets is stored in dense granules at a high concentration of 65 mM. Serotonin molecules per platelet are 8.52×10^{-19} . According to the average volume of platelets, such as 9 fL,

the concentration of serotonin in single platelets is 95 μ M (Lee *et al.* 2020). Extracellular serotonin concentration, in turn, controls the SERT molecules, where SERT is regulated by the genotypes of SLC6A4 (Kinnaly *et al.* 2010, Baudry *et al.* 2019). Plasma membrane SERT levels and serotonin uptake initially rise as platelets are exposed to increased serotonin concentration, but subsequently, SERT levels diminish with higher serotonin concentration. Thus, dynamic relationships exist between blood serotonin concentrations, SERT molecules' expression, and platelet serotonin (Mercado and Kilic 2010). A diminished serotonin platelet uptake is directly related to diastolic and mean arterial blood pressure and plasma cholesterol (Jafri *et al.* 1992). Systolic and diastolic arterial blood pressure (ABP) in cattle varies with the body size. In cattle with less than 150 kg body weight, ABP ranges from 71 to 116, whereas in large cattle, it would be 88 to 140 (Aarnes *et al.* 2014). Bovine pulmonary hypertension (BPH) or right heart failure affects cattle above altitude of 7,000 feet, but is also noticeable in grazing cattle at 2,000 to 4,000 feet altitudes. Diurnal variation in serotonin content of platelets shows 1.91 to 1.97 nM/mg platelet protein in the morning (0800 hrs) compared to 1.70 to 1.77 nM/mg platelet protein in the evening (1600 hrs).

Serotonin and gastrointestinal

Serotonin plays a role in intestinal motility and secretions (Alcaino *et al.* 2018). Serotonin's influence on GI and associated organs is shown in Fig 2. Serotonin is released by enterochromaffin cells into the intestinal lumen and interstitial space. Intestinal serotonin regulates the secretion of pancreatic enzymes based on gastrointestinal contents. Human SERT mRNA expression is highest in the ileum. It was about 40% less in the duodenum and 80%

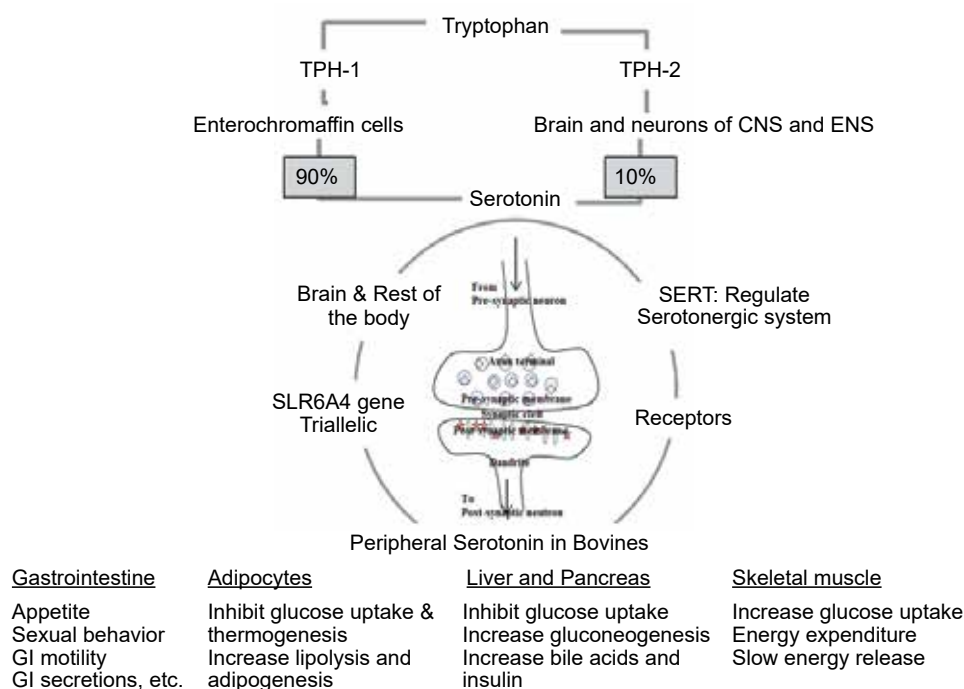


Fig. 2. Peripheral serotonin: Synthesis, regulation, functions in GI and associated organs.

less in the jejunum but almost absent in the colon (Gill *et al.* 2007). The relative abundance of SERT mRNA has been reported 16 folds higher in the small intestine (100%) than colon ($6.0 \pm 0.5\%$). More SERT activity in the human intestine was found by Gill *et al.* (2007) in the apical brush-boarder membrane and intracellular compartments of ileal epithelia and distributed throughout the crypt-villus axis but not detected at basolateral membranes. Serotonin is critical in signal-regulating gut-brain axis and plays a role in body temperature control. *Lactobacillus lactis* and *L. planetarium*, and a few other firmicutes produce serotonin in the gut (O'Mahony *et al.* 2015).

The intestinal microbes also utilize tryptophan and break tryptophan to indole by tryptophanase. Thus, optimum intestinal microflora is also necessary for appropriately expressing serotonin in the gut. More accumulation of serotonin in the gut worsens the intestinal pathological manifestation and enhances the production of pro-inflammatory cytokines (Mittal *et al.* 2017). Therefore, the expression of SERT in the gut is important for the re-uptake of serotonin and preventing its accumulation. In bovines, where pre-gastric fermentation plays a significant role, the microbial protein flow to the abomasum is important besides dietary protein that partly escapes or by-pass fermentation in the rumen. Net degradation of 1 mM of L-Tryptophan by rumen bacteria, protozoa and a combination of the two has been reported to be 47%, 9%, and 80%, respectively (Mohammed *et al.* 2003). The microbial protein production in small, medium, and large breeds of bovines is directly proportional to rumen size, and it may range from 80 g to 280 g/d (Srinivas and Gupta 1997, Singh and Srinivas 2018). Diet plays a vital role in the quantity of rumen microbial protein production (Srinivas and Krishnamoorthy 2013). Rumen microbes can also synthesize the tryptophan, but a small population of *Lactobacillus* strains found in rumen produce a range of indolic compounds from L-tryptophan during anaerobic fermentation. Tryptophan is converted to indole acetic acid, which further decarboxylates to skatole, which is toxic to rumen microorganisms (Attawood *et al.* 2005). Rumen bacteria and protozoa produce tryptophan and phenylalanine from p-hydroxyphenyl pyruvic acid and indole pyruvic acid (Khan *et al.* 2002). Rumen bacteria and protozoa conserved 47 to 50% of the p-hydroxyphenyl pyruvic acid to tryptophan in 6 to 12 h of incubation. Thus, rumen microbes contain 65% true protein, and tryptophan is 975 mg/100 g of rumen microbial biomass. Tryptophan content in rumen microbial protein is higher than any popular feedstuffs used in bovine rations. It was also reported that the K_m value of SERT is higher in cows than in humans or rats (Mortensen *et al.* 1999). As per the range of rumen microbial protein, tryptophan from rumen microbial protein flowing to the duodenum may vary from 3.8 to 13.4 mM.

Serotonin influence on liver and pancreas

Serotonin infusion in rats ameliorated the phosphoenol pyruvic decarboxylase enzyme in the liver. Increased

expression of phosphofructokinase in the liver with serotonin administration is evidence of its role in glycolysis. Sumara *et al.* (2012) suggested that serotonin provides glycerol from the adipose tissue mediated by 5HT_{2B} receptors. This receptor is highly expressed in the liver and doubles during fasting. Blood glucose and insulin levels are reported to increase post ruminal infusion of L-tryptophan in cattle (Valente *et al.* 2021). Serotonin regulates lipid metabolism in the liver both directly and indirectly. Peripheral serotonin also directly operates on hepatocytes and helps in liver regeneration (El-Meharabi *et al.* 2015). Serotonin stimulates the contraction of the gall bladder's smooth muscles, resulting in the excretion of bile acids into the duodenum and again facilitating the absorption of bile acids from the ileum (Watanbe *et al.* 2017). Serotonin reduces triglycerides, cholesterol, and non-esterified fatty acids in plasma. The available literature needs to be strengthened to arrive at a definite conclusion on regulating hepatic glucose and lipid metabolism by serotonin. Serotonin is synthesized in pancreatic β cells and circulating serotonin influences the function of pancreatic β cells. TPH1 and TPH2 both are expressed in pancreatic β cells. Serotonin promotes insulin granule exocytosis in β cells in an autocrine, receptor-independent manner (El-Merahbi *et al.* 2015). The only ligand-gated cation channel receptor 5HT₃ is necessary to maintain glucose-regulated insulin secretion from the pancreatic β cells by the serotonin. In contrast, 5HT_{2C} inhibits insulin secretion from pancreatic β cells (Watanbe *et al.* 2017).

Serotonin and energy metabolism

Peripheral serotonin's influence on energy balance, various other metabolic processes, and physiological stages in the life cycle is least focussed on until recently. Often energy imbalance in periparturient cows results in extended inter-calving periods. Thibeault *et al.* (2019) hypothesized that from the mechanistic point of view, estrogen regulates the serotonergic system, and serotonin, in turn, affects estrogen synthesis to retrieve homeostasis.

Serotonin levels in the CNS respond to both energy deficiency and excess. Serotonin is also expressed in adipocytes and requires the differentiation of preadipocyte cells (Kinoshita *et al.* 2010, Stunes *et al.* 2011). Serotonin stimulation of white adipose tissue leads to impaired insulin action and reduced glucose uptake (Li *et al.* 2013) but induces lipolysis. However, high levels of serotonin in blood again reduce free fatty acids in the blood. Peripheral serotonin accelerates lipid metabolism by increasing the bile acids in circulation (Watanabe *et al.* 2010). Gut derived serotonin is required for stimulation of lipolysis in fasting or during energy deficiency, while locally produced serotonin in adipocytes promotes differentiation (El-Meharabi *et al.* 2015). Serotonin in adipocytes degrades to 5-hydroxy-indole acetate and 5-hydroxy-methyl acetate, which act as peroxisome proliferator-activated receptor- γ agonists to promote differentiation of adipocytes. Simultaneously 5HT_{2A} receptors suppress adiponectin as an adipokine that

promotes peripheral insulin sensitivity and lipogenesis (Oh *et al.* 2015). El-Merahbi (2015) concluded that peripheral serotonin in adipocytes promotes lipolysis and insulin resistance and suppresses glucose uptake and adiponectin production, while serotonin produced locally in adipocytes suppresses thermogenesis in brown adipocytes.

Skeletal muscles, forming about 35 to 50% of body mass, also play an important role, especially in periparturient cows where bodyweight loss is inevitable owing to negative energy balance in close-up and fresh cows. Bodyweight loss is further aggravated after parturition due to reduced appetite. To meet milk production's energy and protein requirements, energy is mobilized from adipocytes and protein from skeletal muscle. This state represents a physiological maximum in protein anabolism with high protein export to the mammary gland (Cloves *et al.* 2005). Serotonin increases glucose intake by muscle fibers. During pregnancy, when muscle fiber sensitivity decreases to insulin, it increases the glucose uptake by the gravid uterus/fetus. Contrary to reduced energy expenditure in white and brown adipose tissue, serotonin transforms skeletal muscle fiber into slow energy release and increases energy expenditure (Watanabe *et al.* 2017). Increased serotonin levels in serum in pregnant women have been reported (Bolte *et al.* 2001).

Serotonin and other organs

According to El-Meharab *et al.* (2015) serotonin has unique features, unlike classical hormones. It is produced in many locations in the system. Serotonin regulates several different aspects of cardiac function, controls breathing and respiratory drive, renal metabolism, mammary gland development, and development and regeneration of endocrine organs, uterus, and immune system (Berger *et al.* 2009, O'Mahony *et al.* 2015, Watanabe *et al.* 2017, Kaur and Krishnan 2020). In organs where mechanical contractions are important, such as uterine contraction, uterine involution, sperm ejaculation, micturition, etc. serotonin's function is supported by serotonin (Cordeaux *et al.* 2008, Riggan and Koren 2015). Serotonin is a feedback inhibitor of lactation in the Holstein cows and expressed in bovine mammary cells *in vitro* and unregulated by prolactin (Hernandez *et al.* 2008). Mammary epithelial cells synthesize ~50% of the circulating serotonin during lactation (Weaver *et al.* 2016). Serotonin also increases circulating calcium in lactating cows and helps mitigate hypoglycemia in dairy cows (Connelly *et al.* 2021). Serotonin also controls the T-cell mediated immune system. Marrero *et al.* (2020) observed serotonin bioavailability enhanced gene expression of serotonin receptors and immune-related genes in dairy calves. Serotonin modulates immune cell trafficking, chemotaxis, activation, and proliferation (Terry and Margolis 2017). It alters the many leukocytes' functions ranging from immune response activation to memory cell generation. The serotogenic components expressed in the immune system encompass complex proteins that coordinate the synthesis and degradation, transport and storage,

and response to serotonin stimulation (Arreola *et al.* 2015).

Conclusion

Serotonin plays a broad role in the brain and other organs of the body, regulating movements in different organs through epithelial mechanosensor cells that include the release of serotonin from the enterochromaffin cell, energy metabolism, glucose, lipid metabolism, etc. in almost all the organs in the system. The information surveyed to the extent of the aim of this review from different species and elaborative reviews also exists in the scientific domain to understand further details. However, the work and literature on bovine serotonin are minimal. In bovines, tryptophan content in popular feedstuffs used in bovine rations is more, besides tryptophan present in microbial protein flowing to the duodenum, yet studies on peripheral serotonin molecules in nutrigenetic and nutrigenomic perspectives are none. Negative energy balance in periparturient cows is a significant caveat in extended inter-calving periods in bovines, and knowing the implications of serotonin in energy regulations is essential. Stress affects serotonin levels in the blood, and its precursor levels in plasma are negatively correlated with cortisol. Henceforth, the role of peripheral serotonin in bovine reproduction and milk production may be more significant than what it is portrayed! Nutritional interventions to change expression levels of SLC6A4 genetic variants can provide many clues on the role played by peripheral serotonin in bovines.

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