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Clinical Aspects Related to Plasma Serotonin in the Horse

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Abstract

Serotonin (5-HT) is a neurotransmitter that has important functions such as the physiological regulation of hemostasis, blood clotting, bone metabolism, cardiovascular growth, contractile activity and gastrointestinal motility, renal function, and stress and sexual behavior, among others. In this review, we consider the potential of 5-HT to contribute to the development of various pathological conditions, including metabolic, vascular, and nervous disorders in horses. The values of 5-HT in circulation are modified under common pathological conditions. Thus, laminitis, endotoxemia, surgical cramps, recurrent airway obstruction, Cushing's syndrome, central fatigue, and certain behavioral alterations such as stereotypes and other acute or chronic conditions can cause increased levels of 5-HT.

Keywords: horse, pathology, plasma serotonin

1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurocrine messenger that is synthesized from tryptophan (TRP) by tryptophan hydroxylase in the brain and mastocytes and enterochromaffin (EC) cells in the gastrointestinal (GI) tract [1]. TRP is able to cross the blood-brain barrier and metabolize into 5-HT in the raphe nuclei within the brain stem. In the intestinal tract, 5-HT is produced by EC and to a lesser extent by serotonergic neurons and released upon mucosal stimulation. The synthesis of 5-HT is identical in the central nervous system (CNS) and in the gut, where TRP is first converted to 5-hydroxytryptophan (5-HTP) via tryptophan hydroxylase (TPH), the rate-limiting enzyme in the biosynthesis of enzyme. 5-HT is eliminated from the interstitium by 5-HT transporters on enterocytes and neurons; 5-HT overflow from the gut reaches the intestinal lumen and portal circulation. In the circulation, it is quickly removed from the plasma by uptake into platelets (PLTs) or metabolized by monoamine oxidase (MAO) into 5-hydroxyindoleacetic acid (5-HIAA) in hepatic and lung endothelial cells. Plasma 5-HT is quickly transported into the PLTs via 5-HT reuptake transporter (5-HT transporter; SERT) on the PLT membrane. PLTs accumulate, store, and release 5-HT in an analogous manner to central serotonergic synaptosomes. The free plasma 5-HT exerts important systemic functions, modulating PLT aggregation, and has been reported to be also involved in vasomotor function [1, 2].

In GI tract, 5-HT interacts with receptors on afferent neurons, initiating peristaltic, secretion, and secretory reflexes. On the other hand, 5-HT induces smooth

muscle cell contraction and proliferation but stimulates endothelial cells to release vasodilating substances and acts as a “helper agonist” of PLT aggregation [2, 3].

Measurement of 5-HT in whole blood gives a reasonable approximation of 5-HT in PLTs [4], and the free 5-HT/whole blood-5-HT (f-5HT/WB-5-HT) ratio may be a marker of PLT activation [5]. The concentration of free 5-HT is typically measured in PLT-poor plasma (PPP), produced by prolonged or high-speed centrifugation of plasma and containing <10,000 PLTs/ μ l [6]. Several researchers reported PPP 5-HT values in healthy horses range from 2.5 ng/ml to 90 ng/ml, with a majority varying between 3 ng/ml and 30 ng/ml [7–16]. Plasma 5-HT is the fraction which shows the equilibrium state between synthesis by EC cells, the inactivation by liver and lung by MAO and PLT uptake.

5-HT plasma concentrations in horses are subject to physiological variations such as age [17, 18], exercise [7–9], stress [19], seasonal, circadian and nycthemeral rhythms [15, 20], altitude [21], reproductive status [22], and type of anticoagulant and laboratory technique [23–25]. In addition, these factors also influence the analytical results of this neurotransmitter. Even in healthy horses, reported reference values for 5-HT are not consistent, which hampers further research into the role of 5-HT in equine diseases. One possible explanation for this inconsistency is the use of different biological samples and analytical methods for 5-HT determination. Indeed, to determine the concentrations of 5-HT in whole blood high-pressure liquid chromatography (HPLC) [7] and in serum, commercially available enzyme-linked immunosorbent assays (ELISA) or radioimmunoassays (RIAs) [19] have been used. Torfs et al. [24] showed that for accurate determination of plasma levels of 5-HT, it is essential to use PPP. It is believed that 5-HT in PPP reflects the amount of 5-HT synthesized and recently secreted in EC cells. Although ELISA [23] and HPLC [18, 21] have been used, the tandem chromatographic mass spectrometry (LC-MS/MS) method is suitable for determining the plasma reference values of 5-HT and analyzing changes in 5-HT associated with pathological conditions.

2. Role of serotonin in the equine clinic

In horses, changes in 5-HT levels are associated with gastrointestinal pathologies such as ileus, colic or endotoxemia, vascular dysfunctions such as digital hypoperfusion causing laminitis, recurrent airway obstruction and endocrine disruption such as intermediate equine pituitary dysfunction (PPID) or Cushing syndrome, and behavioral alterations such as stereotypes [26, 27].

2.1 Gastrointestinal diseases: ileus, colic, and endotoxemia

In the intestine, there are three types of cells that produce 5-HT, such as immune cells, nerve cells and EC cells [26]. Free plasma 5-HT concentration is a potential predictive parameter for postoperative ileus, since it may reflect intestinal integrity, as well as the circulatory effects associated with inflammation or endotoxemia. Therefore, 5-HT quantitation might be an aid in prognosticating the outcome in horses with postoperative colic. The knowledge of plasma 5-HT changes in colic horses is also important in the quest for an effective treatment for ileus, since certain classes of prokinetic drugs target 5-HT receptors [26]. A risk of receptor desensitization [27] might exist when these drugs are used in patients with already elevated 5-HT levels.

5-HT contractile receptors have been identified in the longitudinal and circular layers of the smooth muscle [28] and myenteric neurons of descending colon, ileum and submucosal neurons of ileum, and duodenum in horses [29, 30], in which 5-HT

exerts local actions, causing the activation of intrinsic and extrinsic afferent neurons. This initiates secretory and peristaltic responses to transmit the information to the CNS [27]. While the interaction of 5-HT with 5-HT₂, 5-HT₃, and 5-HT₄ receptors stimulates contractility, 5-HT₁ and 5-HT₇ receptors induce relaxing effects in the GI tract [31]. Among these types of receptors, 5-HT₄ exerts important control over intestinal motility. Indeed, a prokinetic effect occurs following the administration of 5-HT₄ agonists, such as Tegaserod and Mosapride [32].

In horses with intestinal hypomotility, the agonist of 5-HT₄ receptor Prucalopride can increase motor contractility of the duodenum, cecum, and colon, 30–90 minutes after oral administration. This motor activity is maximal in the duodenum, with a minimal increase in the cecum and left colon related with other intestinal segments [33]. Tegaserod is other selective agonist of 5-HT₄ receptor that induces increase in the frequency and amplitude of contractions in equine ileum and pelvic flexion [34], speeding up GI transit time and increases frequency of bowel sounds and defecation [29]. In this way, Tegaserod can offer therapeutic potential in horses suffering from impaction or paralytic ileus. Cisapride is an indirect cholinergic prokinetic agent that acts by promoting the release of acetylcholine from intramural nerve terminals (myenteric plexus) through stimulation of 5-HT₄ receptors [35]. Mosapride is other selective agonist of 5-HT₄ receptors. The use of this agonist improves gastric, jejunal, and cecal motility in horses [36]. A disadvantage of this medication is the oral administration route. This complicates the use in horses with postoperative ileus. Unfortunately, the availability of this drug is also limited. On the other hand, Tegaserod with a higher risk of cardiac events in humans has been suspected (as for cisapride), its availability is limited, as well as its application in equine practice, explaining the lack of more clinical reports. This drug is a potent dopamine D2 receptor antagonist, a moderate 5-HT₃ receptor antagonist, and 5-HT₄ receptor agonist [29] that increases the contractility of smooth muscle [37] and improved *in vivo* motility of the jejunum [36].

The final effects of 5-HT in the intestine will depend on plasma concentrations and the balance between activation and desensitization of these receptors. The concentrations of 5-HT in the intestinal mucous membrane and its association with postoperative bowel recovery may better reflect the net effects of 5-HT on intestinal motility [38].

5-HT is a very potent proinflammatory, vasoconstrictor, and immunomodulatory agent. Although Delesalle et al. [11] reported an increase in plasma concentrations of 5-HT in horses with intestinal strangulation, Ayala et al. [19] showed a decrease in serum concentration of 5-HT in horses with acute abdominal pain.

Several authors have observed higher concentrations of 5-HT after ischemia-reperfusion in the peritoneal fluid intestinal lumen and mesenteric, portal, and hepatic veins [11, 39]. Increased plasma of 5-HT can have important consequences in colic horses. It has been shown *in vitro* and *in vivo* that 5-HT is an important and very powerful vasoconstrictor agent [16]. The accumulation of 5-HT in the systemic circulation of horses that have colic may reinforce continuous intestinal ischemia. Both local lesions in the intestinal wall and the associated inflammatory and endotoxemic systemic reactions promote the development of ileus. The concentration of free 5-HT in plasma is a possible predictive parameter in cases of postoperative ileus, as it may reflect the integrity of the intestine, as well as the circulatory effects associated with inflammation or endotoxemia. For this reason, the quantification of 5-HT in horses could be an important tool to predict postsurgical evolution as a consequence of colic [26, 40].

Coagulation of circulating PLTs, as well as EC from necrotizing intestinal segments, could serve as a source of 5-HT. In horses, it is argued that intestinal ischemia makes the mucosa more permeable. This event leads to an important

translocation of endotoxins and amines from the diet, among which 5-HT passes from intestinal contents to systemic circulation [28]. Indeed, Davis et al. [41] showed liver lesions in horses suffering from proximal duodenitis-jejunitis. In addition to the lesion caused by the ascending bile duct infection, these authors also propose the absorption of endotoxins or inflammatory mediators of portal circulation. In addition, hepatic hypoxia resulting from systemic inflammation and endotoxemic shock may be possible causes of liver injury.

Intestinal microorganisms are also important for the 5-HT synthesis. Yano et al. [42] estimated that 90% of peripheral 5-HT is produced by the intestinal microbiota. These authors found that in germ-free mice, the production of 5-HT was approximately 60% less in comparison to mice with normal intestinal bacteria. Indeed, when bacterial colonies were restored in the intestines of germ-free mice, 5-HT levels are recovered. Several metabolic byproducts of the intestinal microbiota are controlled by the mixture of spore-forming bacteria acting on EC to alter 5-HT production. However, bacteria are capable to produce 5-HT on their own. In fact, *Lactobacillus spp.* produce acetylcholine and GABA; *Bifidobacterium spp.* produce GABA, *Escherichia* produce norepinephrine, 5-HT, and dopamine; and *Streptococcus* and *Enterococcus* produce 5-HT. *Bacillus* species have also been shown to produce norepinephrine and dopamine [43].

Torfs et al. [24] showed that the plasma concentrations of 5-HT are significantly lower in horses with small bowel surgical colic compared to healthy animals. In addition, it was demonstrated that 5-HT concentrations remained low until at least the first morning after surgery. A previous study on horses with signs of acute colic showed significantly lower concentrations of 5-HT compared to healthy ones [19]. However, this earlier study focused on serum concentration of 5-HT used the ELISA method of analysis. This situation complicates the comparison of these results with the current ones. In contrast to these achievements, Delesalle et al. [11] indicated an increase in plasma concentrations of 5-HT, measured by HPLC, in a small group of horses undergoing small bowel surgery. In addition to the analytical differences between these studies, there are multiple possible physiological and pathological explanations for variations in the results obtained.

2.2 Vascular dysfunctions: Laminitis

The GI flora produces relatively high concentrations of dietary amines by fermenting the consumed amino acids [44, 45]. It is thought that the link between the GI system and the equine foot occurs through dietary amines.

The bacteria responsible for the fermentation of carbohydrates produce enzymes (amino acid decarboxylase) that convert free amino acids to monoamines. Then, the fermentation of large amounts of carbohydrates in the large intestine is associated with a greater number of Gram-positive bacteria (*Streptococci* and *Lactobacilli*) and elevated production of dietary amines [12]. These bacteria increase in the production of lactate, which is responsible for the decrease in intraluminal pH causing death of Gram-negative bacteria and therefore an increase in endotoxin release (lipopolysaccharide, LPS). Tryptamine is the most potent amine in the cecum. It causes vasoconstriction both *in vitro* and *in vivo* through direct activation of serotonergic receptors and 5-HT displacement of PLTs. Monoamines found in the horse's cecum could potentially induce hemodynamic disturbances in the hoof resulting in lamellar ischemia and therefore laminitis [46–50]. Besides, these monoamines present in the cecum can also be detected at much lower concentrations in blood plasma.

Leukocytes can be indirectly activated by PLTs and mainly by LPS. Therefore, endotoxin may contribute to the initiation of early inflammatory changes observed in experimental models of acute laminitis [13]. This may occur because the amines

are able to mimic and potentiate the effects of the biogenic amines (5-HT, epinephrine, norepinephrine, and dopamine) in the circulation. Gut-derived amines mimic the actions of the endogenous biogenic amines by displacing 5-HT from PLTs or norepinephrine from sympathetic nerve ending or by directly activating the receptors for these amines on the vasculature [49]. The potentiation of the action of endogenous amines is produced by two processes: inhibition of absorption in endothelial cells and PLTs [47, 48] or by competition between amines derived from the intestines and endogenous amines by the metabolism of the enzyme amine oxidase [12, 47, 48].

Dietary amines are similar to substances normally produced by the body, including catecholamines and 5-HT. Since 5-HT is a potent vasoconstrictor that is mainly stored in PLTs, it helps to maintain low plasma concentrations that reduce its effects. Bailey et al. [46] reported that the absorption of 5-HT by PLTs is a saturable process in horses. The most efficient way to work is at substrate concentrations below the micromole. The noncompetitive inhibition of 5-HT absorption by other natural monoamines may result in increased plasma concentrations of 5-HT and endotoxin release. The amines present in the diet inhibit the uptake of 5-HT from the PLTs. As a result, plasma concentration of 5-HT would increase above the level at which digital vasoconstriction occurs [44, 51]. However, other peripheral blood vessels are unaffected, since digital vessels are much more sensitive to the vasoconstriction effects of 5-HT [52, 53]. Dietary amines can also cause digital vasoconstriction directly [49]. The overall result is the digital ischemia and subsequent reperfusion, which could lead to the activation of metalloproteinases.

Endotoxins act as a mechanism that triggers laminitis. These substances activate the coagulation cascade directly through the Hageman factor (factor XII, in the intrinsic coagulation pathway). They are called the contact factor because the activation occurs by contact with nonendothelial and foreign surfaces. In addition, endotoxins are the initial stage of intrinsic plasma coagulation. They also cause damage to endothelial cells and favor the addition of PLTs, thereby establishing a blood profile compatible with disseminated intravascular coagulation (DIC). As a result, peripheral vasoconstriction initially results in decreased capillary perfusion of the hoof with some degree of ischemia [47, 48].

The aggregation of PLTs and the formation of microthrombi in the capillaries of the hoof contribute to maintain vascular occlusion ischemia. In addition, a potent vasoconstrictor such as thromboxane A₂ is released from PLTs, which adds to increase the process. At the same time, the inflammatory response begins with the release of autacoids such as histamine, 5-HT, bradykinin, prostanoids, leukotrienes, and interleukin 1. Histamine plays a very important role in acute inflammation. It has a vasodilatory action on arterioles, but the role in inflammation is more important, since it improves the action of other mediators such as histamine and bradykinin. This results in arteriolar dilation, increased capillary permeability, and hyperalgesia. Leukotriene B₄ is also involved in the passage of leukocytes to inflammatory exudate [16].

The relationship between the appearance of digital hypoperfusion and increases in plasma concentration of 5-HT is consistent. This is because PLTs-derived mediators are associated with LPS-induced laminitis. These experimental data support the use of antiPLT therapy in the prevention of laminitis related to endotoxemic diseases [16].

2.3 Endocrine diseases: pituitary pars intermedia dysfunction

Pituitary pars intermedia dysfunction (PPID) or Cushing's disease is characterized by hypertrophy and hyperplasia of the Pituitary Pars Intermedia and is argued

to be due to a reduction in dopamine synthesis or degeneration of periventricular pituitary dopaminergic neurons [54]. PPID is more frequent in adult horses and result of a progressive loss of the neurotransmitter at central and peripheral level as result of the degeneration of the pineal gland [15].

The role of 5-HT in the regulation of the PPID it is not clear. Treatment of PPID in horse includes 5-HT antagonists [55], such as cyproheptadine. Antagonist of 5-HT is potent secretagogue of ACTH in pituitary rat tissue, and it was used effectively in human Cushing's disease. Cyproheptadine decreases the 5-HT-induced stimulation to the pituitary pars intermedia, the synthesis of pro-opiomelanocortin (POMC), and finally, ACTH secretion. Cyproheptadine (0.25–0.5 mg/kg PO, SID, or BID) was used for the treatment of PPID result in an improvement in clinical status and normalization of laboratory parameters within 1–2 months of treatment initiation, being effective in 28–60% of cases [56]. However, similar improvements were achieved with improved nutrition, preventive care, and management alone [57].

Additionally, Bailey et al. [46] measured peripheral plasma concentrations of 5-HT in summer, autumn, winter, and spring in clinically normal ponies and those predisposed to laminitis, and no significant differences were observed. Although light/dark differences were not investigated in the latter work, nycthemeral increases in serum 5-HT in the healthy, athletic horse have been reported [20]. Later, Haritou et al. [15] reported seasonal changes in circadian peripheral plasma concentrations of melatonin, 5-HT, dopamine, and cortisol in aged horses with PPID. Six horses and ponies with PPID were matched with six controls to test the hypothesis that aged horse responds differently to changes in season because of deficiency in melatonin production. They also examined the link between the presence or absence of the clinical signs of PPID and peripheral plasma concentration of 5-HT, dopamine, and cortisol. Results showed that the 24-h pattern of plasma melatonin concentrations during the four seasons of the year was similar in both groups, indicating that impaired melatonin output is unlikely to play a role in PPID. However, 5-HT profiles were affected by season, with lower 5-HT detected in PPID horses in the summer and winter. Although the reasons for this reduction remain unknown, enhanced conversion of 5-HT to melatonin could account, at least in part, for the lowered circulating level. The total amount of dopamine released was dependent on season and markedly lower in PPID horses versus controls. These results implicate both serotonin and dopamine in the pathogenesis of the disease [15].

2.4 Behavioral alterations: stereotypes

Most frequently observed stereotypies in domestic horses are crib biting, weaving, box walking, wind sucking, and wood chewing. However, there is no scientific consensus as to whether wood chewing is definitely a stereotypy [58]. More recently, some morphological variations of these stereotypic activities have also been identified as equine stereotypies, such as licking the environment, lip licking, sham chewing or teeth grinding, self-biting, and rubbing self, as well as locomotion stereotypies, including pawing, tail swishing, door kicking or box kicking, and head tossing/nodding [59]. The most common forms of equine stereotypies are within two general categories, oral and locomotion stereotypic behaviors.

The neurobiological consequences of equine stereotypies focus on neurotransmitter systems, specifically the serotonergic and dopaminergic pathways [59, 60]. 5-HT is implicated in the underlying pathology of stereotypies. Indeed, Lebelt et al. [61] found a trend for lower basal 5-HT levels in crib-biting compared to nonstereotypic horses, suggesting that the serotonergic system of crib-biters may differ from

that of noncrib biting horses (mean 201.5 vs. 414.3 nmol/l). The precise role of 5-HT in the development or maintenance of the behavior remains unclear however, and the results obtained by these authors have yet to be confirmed or refuted through additional experimental studies of the serotonergic system in crib-biting horses.

However, blood levels of 5-HT in horses with weaving is more than triple compared to healthy horses. Thus, 5-HT is recognized as the “happiness hormone” or “pleasure hormone” [62]. It can be assumed that during the demonstration of stereotypical disorder, horses are “happy,” and that repetitive disturbance is a means of increasing 5-HT levels in the blood and therefore the feeling of comfort [63].

Serotonin reuptake inhibitors (SRI) are a type of drug which acts as a reuptake inhibitor of the neurotransmitter serotonin (5-hydroxytryptamine (5-HT)) by blocking the action of the serotonin transporter (SERT). This in turn leads to increased extracellular concentrations of serotonin and, therefore, an increase in serotonergic neurotransmission. Although administration of SRIs drugs has been associated with the reduction of stereotypies, it was dubious if such medications decreased stereotypic behaviors due to general sedative effects or selectively influenced stereotypic behavior. These uncertainties were due to general sedative effects or selective influence on the type of behavior. As previously expressed, the specific role of 5-HT in the development or maintenance of behavior remains uncertain [60, 61, 64, 65], and further studies are needed to provide a more accurate interpretation of stereotypies.

Pharmacological preparations containing TRP are marketed worldwide as relaxing agents for treating excitable horses. The few studies in which TRP has been administered to horses suggest that low doses cause mild excitation. However, high doses reduce endurance capacity and cause acute hemolytic anemia when given orally due to the presence of a toxic metabolite in the intestine [65, 66]. Despite questions about its effectiveness, TRP is marketed as an equine sedative and is related to sedation, inhibition of aggression, fear, and stress.

Because TRP competes with other amino acids to bind to protein transport and cross the blood-brain barrier, researchers are now using a ratio of TRP with other large neutral amino acids (ANNALs) to estimate the production of 5-HT in the CNS [67]. Besides, previous researchers showed that the age, breed, and gender modify the response of serotonergic system due to changes in dietary TRP [17, 68]. While all of these factors may play a role in the permeability of the blood-brain barrier, the effectiveness of supplemental TRP on 5-HT biosynthesis, it is also worth considering that these types of treatments may be most effective in horses with dysfunctioning serotonergic system.

Although the safety of TRP doses should be confirmed, there is no evidence to suggest that a single dose is an effective analgesic in horses. In fact, given that TRP continues to be used as a tranquilizer, there is an urgent need for research to confirm its efficacy and establish a range of safe therapeutic doses. In the meantime, available data suggest that it would be unwise to rely on the TRP to calm the excitable horse. Instead, more efforts should be made to identify the underlying causes of excitability and explore other more appropriate nonpharmacological solutions. Indeed, when evaluating the use of calming supplements or drugs, it is important to consider the welfare of the horse. While calmative compounds may be beneficial in alleviating short-term stress and anxiety, the cause of such emotions should also be evaluated. Horses kept in unnatural environments, managed poorly, or asked to perform beyond their level of training may show signs of stress and anxiety. Chronic health issues, such as ulcers or lameness, may also be the culprit. Sedative drugs and supplements are often utilized to limit unwanted behaviors such as spooking, bolting, rearing, or bucking. Looking into the potential causes of unwanted behaviors should be the first step before owners turn to calming drugs or

supplements. Providing more training, turnout time, or treatment for an underlying disease or condition could result in a more sustainable way to reduce a horse's unwanted behaviors and could improve welfare for the animal [65].

Equine self-mutilation syndrome (ESMS) includes glancing or biting at the flank or pectoral areas, bucking, kicking, vocalizing, rubbing, spinning, or rolling. Eight flank-biting horses with ESMS were enrolled for a behavioral study, and the effects of drugs that either stimulate or inhibit central opioid, dopamine, norepinephrine, and 5-HT neurotransmitter systems were reported. Behaviors were recorded hourly during the study and were compared with those of a saline control baseline to determine whether there were significant differences among the treatments. The suppression of ESMS activities with Buspirone (0.5 mg/kg) suggests a role for serotonergic modulation of the behavior. However, the clomipramine, a preferential 5-HT reuptake blocker, does not produce any significant effect on ESMS behavior in horses [69].

Horses with compulsive disorder may help the fluoxetine at dose of 0.25–0.5 mg/kg/day PO. Fluoxetine is a selective serotonin reuptake inhibitor (SSRI) that increases 5-HT levels within CNS by preventing the reuptake of 5-HT at level of the presynaptic neuron. This allows 5-HT to accumulate in the synaptic cleft and affect the postsynaptic neuron. While no cases of fluoxetine-induced colic have been reported in horses being treated for behavior problems and because there are many 5-HT receptors in the gut, it is advisable to begin administering the drug at the lowest dose and increase it gradually in horses that do not improve and have not exhibited adverse effects [70].

The ability to train and control horses is an important behavioral trait for the handling and training of animals. Hori et al. [71] inform that horses carrying allele A located at c. 709G > A had a lower capacity to be handled. These results provide the first evidence that a polymorphism in a 5-HT-related gene may affect the management of horses with a partially different sex-related effect.

2.5 Recurrent airway obstruction

Based on the results reported in humans, in which PLTs contribute to the pathogenesis of allergic airway disease, Hammon et al. [14] compared PLT aggregation induced by the activating factor PLTs (PAF), thromboxane (Tx), plasma Tx, and 5-hydroxytryptamine (5-HT) production in ponies with recurrent airway obstruction (RAO) before and after antigen exposure. Plasma 5-HT was significantly higher in ponies with RAO but did not increase more by exposure to the antigen. There were also no differences between the aggregation of PLTs induced by PAF or the production of Tx or plasma Tx before or after exposure. These evidences suggest that there may be a difference between 5-HT uptake of PLTs in RAO and normal ponies. However, they do not provide evidence of PLTs activation after exposure to the antigen. This bronchoconstriction can be mediated by 5-HT. However, the effect or pathway of 5-HT may be deactivated during the development of small airway disease [72].

2.6 Central fatigue

Accordingly, the synthesis and metabolism of 5-HT in the CNS increase in response to exercise [73]. Increased 5-HT concentration in the brain is associated with central fatigue markers, such as decreased motivation, lethargy, fatigue, or loss of motor coordination [74].

It has been shown that nutritional status can alter cerebral neurochemistry, especially carbohydrates and 5-HT [75]. Therefore, it has been hypothesized that

infusion of TRP may increase the ratio of fTrp (free TRP) and fTrp to BCAA while decreasing the resistance of endurance horses to treadmill. Therefore, central fatigue may limit resistance in horses, and by manipulating fTrp and BCAA, exercise capacity could be altered in a predictable way [76]. However, TRP infusion results are consistent with the central fatigue hypothesis where an increase in plasma fTrp concentration is related to the early onset of fatigue during prolonged exercise [77]. Piccione et al. [20] reported that if exercise is performed at the time of the rhythmic acrophase of the TRP (18:45, 18:16), it is likely that exercise performed at the time of the acrophase of the TRP rhythm (18:45, 18:16) affects the onset of physiological fatigue, thus turning on the body's exercise adaptation mechanisms in order to maintain better physical performance.

2.7 Other conditions

Virus of Borna's disease (BDV) can enter into the brain and infect neurons, often the limbic system. It can also remain active for long periods of time in the CNS without generating neuronal lysis. The BDV virus is unique in the order of mononegavirals because it replicates in the cell nucleus. Alterations include falling, tremor, abnormal posture, hyperactivity or hypoactivity, increased aggression, and paralysis. In some rodent species, BDV can cause mild or asymptomatic symptoms, while in other animal species such as horses, it can cause severe CNS symptoms that often lead to death. In humans, a common treatment for psychiatric illnesses such as depression or anxiety disorders is the use of SSRIs. The function of these drugs is to increase extracellular 5-HT. Interestingly, there are viruses that can exert the opposite action and reduce levels of 5-HT and therefore theoretically have an opposite effect to SSRI [78].

Equine hepatic encephalopathy is caused by direct damage to the liver or by toxins derived from the intestine that overwhelm or evade this organ. These toxins act on the CNS, giving rise to signs of encephalopathy. Secondary hepatic encephalopathy in horses occurs more often than liver failure. This may be due to megalocytic liver disease caused by ingestion of plants containing pyrrolizidine alkaloid (*Senecio*, *Crotalaria* and *Amsinckia*), Theiler's or Tyzzer's disease, cholangiohepatitis, chronic active hepatitis, liver neoplasia, toxic liver disease, and portosystemic shunts [79]. Because the liver is incapacitated, normal detoxification activities cannot be performed in all these conditions. Therefore, toxins derived from IG enter the CNS through the bloodstream.

In horses, hyperammonemia has been linked to clinical signs of encephalopathy without evidence of liver disease, which promotes the formation of Alzheimer's cells II [80]. It is also suggested that alteration of amino acid metabolism with upward regulation of aromatic amino acids and downward regulation of BCAA lead to direct neuronal inhibition secondary to effects on CNS. Alteration of *gamma aminobutyric acid* (GABA) and glutamate during liver failure plays an important role in the physiopathology of hepatic encephalopathy. Liver impairment leads to an increase in substances similar to endogenous benzodiazepines that inhibit neuronal excitation. Therefore, the most likely scenario is that there are multiple mechanisms working in synergy with each other to create signs of encephalopathy.

3. Conclusions

Serotonin is a neurotransmitter associated with important physiological, digestive, and vascular functions of the central nervous system. This review describes the involvement of serotonin in the most common pathological processes of equine

clinic. Deficiencies or excesses in plasma serotonin concentrations may predispose to endocrine, vascular, or nervous disorders in the horse. Therefore, new additional studies are needed to continue showing the physiopathological mechanisms with implications of serotoninemia in other organs of the horse.

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