Chapter 5

Physiology and Metabolic Anomalies of Dopamine in Horses: A Review

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Abstract

Dopamine (DA) is an important endogenous catecholamine that exerts generalized effects on both neuronal (as a neurotransmitter) and non-neuronal tissues (as an autocrine or paracrine agent). In the central nervous system (CNS), DA binds to specific membrane receptors present in neurons and plays a key role in the control of motor activity, learning, cognition, affectivity and attention. Horses can also present with hyper- and hypodopaminergic conditions, including stereotypic behaviors and pituitary pars intermedia dysfunction and Parkinsonian's syndrome, respectively. DA biosynthesis also occurs in peripheral tissues, and receptors in various organs such as the kidney, pancreas, lungs and blood vessels outside the CNS have been detected. DA emulates the actions related to the sympathetic nervous system (SNS), promoting the increase in heart rate, blood pressure, electrolyte balance and gastrointestinal (GI) motility. In fact, GI alterations in dopaminergic transmission have been directly or indirectly related to hypomotility and/or postoperative ileus (POI). On the other hand, there are physiological factors, such as breed, age, exercise and reproductive status that modify DA concentrations. In reproduction, the administration of DA antagonists in the middle/end of the spring and anestrus transition period advances the first ovulation of the year in mares. This chapter offers a brief description of the importance of DA as a neurotransmitter and peripheral hormone. Special attention is paid to: (1) functional alterations that occur in the brain and GI tract in various diseases and (2) current therapy to correct alterations in DA systems.

Keywords: dopamine, equine medicine, reproduction

1. Introduction

1.1. Biosynthesis, regulation, inactivation and degradation

Dopamine (DA) is synthesized in dopaminergic nerve terminals from the amino acid tyrosine. The majority of circulating tyrosine originates from dietary sources, but small amounts are derived from hydroxylation of phenylalanine by the liver enzyme phenylalanine hydroxylase. Hydrolysis of tyrosine to L-3,4 dihydroxyphenylalanine (L-DOPA) by the enzyme tyrosine hydroxylase (TH) and its subsequent decarboxylation by the enzyme DA decarboxylate leads to the formation of DA. The activity of TH is mainly controlled by the central nervous system (CNS) and the metabolic products of neurotransmitter synthesis (L-DOPA and DA) inhibit TH activity in brain tissue and minority by the catecholamines (serotonin, 5-HT), which act as regulatory factors through feedback mechanism [1, 2].

Although DA can be found in very different nerve pathways, there are four main dopaminergic nerve pathways that govern the synthesis and transmission of this catecholamine [3]:

- Mesolimbic (amygdala, hippocampus and prefrontal cortex). This pathway transmits DA from the ventral tegmental area (VTA) to the accumbens nucleus. VTA is located in the midbrain, while the accumulated nucleus is located in the limbic system.
- Mesocortical. This pathway transmits DA from VTA to the frontal and cerebral cortex.
- Nigrostriatal. This pathway transmits DA from the substantia nigra to the basal ganglia, specifically the striated nucleus. It is a neuronal pathway associated with motor control.
- Tuberoinfundibular. This pathway transmits DA from the middle hypothalamus to the infundibular region. The latter area connects different parts of the hypothalamus and the pituitary gland. It also controls the secretion of certain hormones, including prolactin (PRL) from the anterior pituitary gland. In the dopaminergic terminals the neurotransmitter is synthesized in the cytoplasm from where it can be released directly into the synaptic space or transported into the synaptic vesicles to be released by exocytosis. Once released into the synaptic space, the DA binds to the pre and post synaptic receptors.

Systemic DA is mainly derived from sympathetic nerve fibers, chromafine cells of the adrenal medulla, the gastrointestinal (GI) tract and neuroendocrine cells known as APUD (acronym for "amine precursor uptake and decarboxylation") [4]. These cell types are found in the kidney, pancreas, retina and peripheral leukocytes, among others, which are characterized by the synthesis of peptide hormones and amines with auto/paracrine functions [4–6]. It should be noted that some of these cells, such as those of the renal tubular epithelium, do not express the enzyme TH. Therefore, the synthesis of DA depends directly on the availability of L-DOPA and its transport into the cell, which increases in the presence of sodium [7]. In addition, the carotid body, an important peripheral chemo-receptor, releases DA under hypoxic conditions [8].

The dopaminergic receptors are grouped into two main families: D-1 and D-2. The first group, which includes subtypes D_1 and D_5, stimulate the activity of the adenylate cyclase enzyme and activate the protein kinase. The second group composed of subtypes D_2, D_3 and D_4 inhibits the

activity of this enzyme and alters the permeability of potassium channels [9]. In addition, when DA is present in high concentrations, it can act on adrenergic and serotoninergic receptors [7]. At the central level, D_1 receptors are widely expressed in the nigrostriatal, mesolimbic and mesocortical areas. While D_2 receptors are expressed in the stratum, black substance, hippocampus and hypothalamus, among others, highlighting their high concentration in the pituitary gland. In contrast, D_5, D_3 and D_4 receptors have lower levels, although they are also found in multiple brain regions. In general, at the peripheral level, DA receptors are found in the kidney, adrenal glands, sympathetic nodes, GI tract, blood vessels and heart [10]. Activation of the D_1 receptor causes dilation of the renal vasculature, heart, mesentery and brain, while the D_2 receptors inhibit secretion of aldosterone, PRL and renin. In addition, D_1 and D_2 receptors have been described in the ovarian cortex and corpus luteum (CL) and, to a lesser extent, in granulosa and teak cells [11] in the mare.

The degradation of the DA takes place in two phases. First, the enzyme monoamine oxidase (MAO) catalyzes its deamination, forming 3,4-dihydroxyphenylacetaldehyde (DOPAL). This aldehyde can be metabolized by aldehyde dehydrogenase to 3-4-dihydroxyphenylacetic acid (DOPAC) or by aldehyde reductase to 3,4-hydroxyphenylethanol (DOPET), resulting in its acid or alcoholic metabolite respectively. In addition, DOPAC can be inactivated by the enzyme catechol-O-methyltransferase (COMPT) which generates homovalinic acid (HVA). Both DA and its metabolites can be conjugated before urinary excretion by sulphation and glucuridation reactions [9].

1.2. Cellular effects of dopamine

1.2.1. Central nervous system and behavior

Dopaminergic neurons regulate important functions such as cognition, motor activity, vision, learning, pain perception, and sexual behavior, among others [4, 10, 12]. Several studies on horses have linked behavioral changes to changes in the central levels of DA. In fact, high concentrations of DA are associated with stereotypes such as shooting and bear dancing [3, 13], while decreased dopaminergic activity is accompanied by depression, lethargy and apathy [14]. In addition, there are racial variations in the expression of the dopaminergic D_4 receptor. This suggests their involvement in behavioral differences associated with the breed, such as alertness or curiosity [15].

On the other hand, DA controls circadian rhythms through the transport of light information in the retina and the synthesis of melatonin [4, 16]. In fact, DA can modify the synthesis of melatonin in the pineal gland by modulating the availability of 5-HT through its binding to DA-adrenergic receptors, D_4-α1 and D_4-β1 [17].

1.2.2. Endocrine system

As mentioned earlier, DA is a potent inhibitor of PRL secretion. In the presence of DA, the secretion of PRL is minimal. While when DA is absent, the rates of PRL secretion are high. PRL has self-regulating feedback on tuberous-infundibular DA neurons. Increased PRL concentrations due to lack of stimulation of the DA receptors in the lactotroposes cause a self-regulating feedback loop to the tuberous-infundibular DA neurons. These cells are activated to produce more DA, resulting in a reduction in prolactin secretion [18]. Melanotrophs of the pituitary

intermedia pars are innervated by periventricular hypothalamic periventricular dompaminergic neurons. The release of the neurotransmitter DA from these neurons causes tonic inhibition of the release of hormones from the surrounding melanotrophs. After release, DA binds to D_2 receptors in melanotropes that inhibit transcription of pro-opiomelanocortin (POMC) peptides, including adrenocorticotropic hormone (ACTH), α-melanocyte-stimulating hormone (α-MSH), and corticotrophin-like intermediate peptide (CLIP). Basic knowledge of the dopaminergic system is important to understand the pathogenesis and treatment of equine pituitary pars intermedia dysfunction (PPID). In fact, in horses with PPID, loss of inhibitory control of DA allows the cells of the intermediate pars to proliferate and produce and release higher levels of POMC protein derivatives [19].

1.2.3. Gastrointestinal system

DA plays an important role in the control of GI motility in horses. The agonist and antagonist receptors produce inhibitory (relaxation or inhibition of contractions) or excitatory (increased contractions, less frequently) effects on GI motility [20]. These effects are due to the fact that the D_1 receptor is mainly located in the effector cells (post-junctional) and the D_2 receptor is present both pre- and postjunctionally [21].

1.2.4. Renal function

The cells of the proximal tubule are the main source of DA synthesis, exerting natriuresis due to increased renal perfusion mediated by arteriolar vasodilatation and inhibition of tubular sodium reabsorption through the enzyme *sodium-potassium* adenosine triphosphatase (Na^+/K^+-ATPase) [22, 23]. For this reason, DA and its agonists are considered potential therapies for the treatment of renal hypotension, tubular obstruction, as they favor natriuresis and diuresis in horses. Although exogenous administration of DA does not significantly modify the fractionated excretion of sodium and potassium, it increases urine volume and decreases osmolarity [24]. In newborns, low-dose phenoldopam mesylate (D_1 agonist) increases urine output without causing systemic hemodynamic changes [25]. Additionally, stimulation of the D_1 and D_2 receptors promotes renin secretion and inhibits aldosterone. The administration of DA agonists such as bromocriptine inhibits the stimulation exerted by angiotensin II in Na^+/K^+-ATPase [26].

1.2.5. Cardiovascular system

Circulating DA, synthesized by the endothelial cells, alters the muscular contractility of the blood vessels. Thus, there is a negative correlation between this neurotransmitter and blood pressure [4]. However, exogenous administration of DA in horses has variable and dose-dependent effects depending on the general condition of the patient. Thus, infusion of high doses of DA increases blood pressure with an increased risk of arrhythmias [26]. However, there are no modifications at low doses (≤3 μg μg/kg/min) [24]. Under certain shock conditions, treatment with DA may increase blood pressure [27]. In fact, Trim et al. [28] demonstrated that infusion of DA in surgically operated endotoxic animals significantly improves

System	Functions	References
Central nervous	Motor control and movement (nigrostriatral pathway)	[4, 10, 12, 14, 16, 17]
	Behavioral effects: alertness, curiosity, cognition, learning and memory (mesolimbic pathway)	
	Modulation of circadian rhythms	
Endocrine	Mare:	[18, 29–32]
	• Modulation of reproductive seasonality (inhibition of pituitary PRL secretion - tonic inhibition on reproductive activity during seasonal anoestrus-tuberoinfundibular pathway)	[33, 34]
	• Regulation of luteal function	
	Stallion:	
	• Modulation of sperm viability, acrosomal integrity, capacitation and motility	
Gastrointestinal	Regulation of GI motility:	[20, 21]
	• Inhibitory effects (relaxation or inhibition of contractions)	
	• Excitatory effects (increased contractions, observed less frequently)	
Renal function	Increased renal perfusion and arteriolar vasodilatation	[22, 23]
	Inhibition of tubular sodium reabsorption (natriuresis)	[25, 26]
	Increase renin and inhibition aldosterone secretion	
Cardiovascular	Dose-dependent effects:	[26–28]
	High doses increases blood pressure and cardiac output	[24]
	Low doses: no modifications	
	Vasodilation (relaxation)	

Table 1. General functions of DA in the horse.

cardiovascular function. These studies have shown an increase in cardiac output and blood pressure. **Table 1** summarizes the main functions of DA in the horse.

2. Physiological modifications of dopamine in the horse

2.1. Age

Similar to PPID animals, aging decreases the concentrations of DA in the spinal cord of adult mares compared to pre-pubertal females [35]. In fact, the activity of the dopaminergic and serotonergic systems is reduced in these animals, decreasing plasma concentrations of DA and 5-HT [36, 37]. McFarlane et al. [14] verified that the number of dopaminergic nerve terminals in the periventricular intermediate peripheries and in the cell bodies associated with the hypothalamus is reduced in animals with PPID compared to healthy animals of the same age.

2.2. Breed

Podolak et al. [38] showed that Arabian horses have higher concentrations of DA at rest and after exercise compared to thoroughbred horses. In horses, the D_4 DA receptor gene (DRD_4) is found on chromosome 12, and two types of polymorphisms have been found. They are variable number of tandem repeats (VNTRs) consisting of 18 base pairs (six amino acids) and some single nucleotide polymorphisms (SNPs) in the exon region 3. One of these SNPs, G292A, was reported to be associated with horse personality. The *A* allele in G292A is associated with low curiosity and high vigilance in thoroughbred horses. A previous study reported that a Kiso horse, a native Japanese horse breed, had shorter repetitions in the VNTR region than thoroughbred horses [39]. However, it has not yet been verified whether the allele frequency of this polymorphism differs between races. However, samples from more breeds are needed to validate the differences in DRD4 in horses of different breeds.

2.3. Transport

In stallions, Medica et al. [40] observed an increase in plasma DA after 100 km transport, with a decrease after 300 km. This response is related to the process of adaptation during transport. This is due to the fact that neurotransmitters are necessary for maintaining the homeostatic process and balancing the effects of perceived stress during transport.

2.4. Seasonality

The concentrations of DA also vary with the season. In normal mares, the concentrations of DA in the cerebrospinal fluid are minimal in summer, medium in autumn and winter and maximum in winter anestrus [41]. However, this pattern is not maintained in ovariectomized females, suggesting the influence of gonads on dopaminergic seasonality [35]. Nevertheless, Haritou et al. [36] showed a decrease in plasma levels during the spring and early fall months in horses with PPID.

3. Clinical implications of domanine in horses

3.1. Hypothalamic: pituitary dysfunction

As noted earlier, knowledge of the dopaminergic system is important for understanding the pathogenesis and treatment of fescue equine toxicosis and PPID [19]. In mares grazing on land rich in *Acremonium coenophialum*, an endophytic fungus that grows on the stem, leaves, pods and seeds of the fescue, the alkaloid ergopeptine and, mainly, the ergovaline, appear to be responsible for most of the abnormalities associated with toxicosis in pregnant mares. The symptoms that characterize the clinical picture include, among others, an increase in gestation duration, abortion, birth of weak or dead foals, agalactia, thickening and retention of the placenta, and infertility [42, 43]. Because AD is the main inhibitor of PRL secretion, agalactia occurs first, because of the agonistic effect of ergopeptine on D_2 DA receptors. Second, ergoalkaloids inhibit ACTH secretion, reducing fetal cortisol, thereby reducing placental

progesterone (P_4) secretion. Third, these alkaloids reduce the binding of estrogens to tissues, raising serum estradiol levels. It is important to note that blood estrogen levels usually drop around parturition. Interaction between PRL, P_4 and estrogens plays an important role in preparing the mammary gland for lactation. Low levels of PRL and P_4 and high levels of estrogen induce agalactia prevent the development of the mammary gland. The gestation period may be prolonged due to blockage of the fetal corticotropin-releasing hormone (CRH) by ergopeptine. This fact causes the lack of production of ACTH and fetal cortisol and the prolongation of gestation in the affected mares. It is also hypothesized that placental anomalies are associated with vasoconstriction, edema, fibrosis and mucoid degeneration of the placental arteries secondary to anoxia [43]. The administration of bromocriptine (D_2 dopaminergic agonist) in ponies at the end of pregnancy leads to a decrease in plasma concentrations of PRL and P_4 and induces clinical signs similar to this type of poisoning [42]. In addition, exogenous DA receptor antagonists (domperidone and metoclopromine; D_2 receptor antagonists, sulpiride; D_2 and D_3 receptor antagonists, and phenothiazines; DA) receptor antagonists during the last 30 days of gestation may reverse the inhibitory effects of DA by increasing PRL secretion [14, 19], udder development and lactation. After parturiton, the same dose of domperidone, given twice daily for several consecutive days, stimulates milk production [43].

The intermediate pars of the pituitary gland receive direct innervation from the dopaminergic neurons of the periventricular nucleus of the hypothalamus. These axons project through the infundibular stem, travel along the periphery of the nerve pathway and then branch off into the intermediate pars where they end in the peach groves. At this site, the DA released by the periventricular nerve terminals interacts with the dopaminergic D_2 inhibitor receptors causing a decrease in hormone synthesis and release as well as an inhibition of cell division [44]. The lack of inhibition of DA may also result in multiclonal expansion. However, the neuronal cell bodies producing DA in lactotrophes are located in the arcuate nucleus while those of melanotrophs are in the periventricular nucleus. For this reason, a highly specific regional loss of these DA-producing cells may explain the monoclonal expansion of melanotrophs. In fact, there is good evidence that PPID is a neurodegenerative disorder characterized by a lack of dopaminergic input to melanotrophs in the intermediate pars [45].

PPID is one of the most common diseases of horses and ponies over 15 years of age. The pathological features of PPID are hypertrophy, hyperplasia and adenoma formation in the middle pars of the pituitary gland. Horses with PPID develop enlarged pituitary glands up to five times their normal weight. As the middle pars expand, it compresses the adjacent pituitary lobes and hypothalamus. This often results in a loss of periventricular dopaminergic nerve terminals and cellular bodies which decreases the concentrations of DA and DA-metabolite by eight times [14]. However, the intermediate pars remain active, secreting relatively large amounts of POMC derived peptides into the peripheral circulation (40-fold increase), α-MSH, ACTH, β-endorphin, β-lipotropin and CLIP. In fact, increased secretion of ACTH and CLIP results in hyperadrenocorticism [46].

While no initiating events causing neurodegeneration in PPID have been identified, evidence suggests that oxidative damage to dopaminergic neurons occurs in horses with PPID [14]. Oxidative stress results in the modification of cellular components including proteins, DNA

and lipids of the cell membrane due to excessive exposure to exogenous or endogenous sources of free radicals. This damage eventually leads to cell death or, in the case of neurons, to neurodegeneration. Dopaminergic neurons are particularly vulnerable to oxidative damage, since the metabolism of DA itself produces free radicals. Chronic oxidative stress is considered to be a factor in the development of other diseases associated with dopaminergic neurodegeneration, such as Parkinson's disease [47].

By immunohistochemical evaluation of pituitary and hypothalamic tissue, McFarlane et al. [48] showed that the immunoreactivity of TH is reduced in affected horses. This finding supports the role of dopaminergic neurodegeneration in PPID. In addition, immunohistochemical evaluation revealed an increase in the oxidative stress marker, 3-nitrotyrosine and in the nerve end protein, α-synnuclein, located in the intermediate pars of horses with this disease. These authors have also suggested a role for nitration of the overexpressed α-synuclein in the pathogenesis of neurodegeneration in PPID [47].

Loss of hypothalamic dopaminergic innervation appears to be an important mechanism for the development of PPID. For this reason, the use of DA agonists is a logical approach to treatment [47–49]. In fact, pergolide mesylate, in a daily dose (1 mg of PO/day h for 2 months, followed by 2 mg of PO/day for 4 months) is probably appropriate for most horses and ponies. This drug is a first-generation D_2 receptor agonist based on ergolinapara, restores dopaminergic inhibition of melanotrophs and regulates plasma ACTH [48]. A lower initial dose of 0.002 mg/kg body weight (range 0.002–0.01 mg/kg daily body weight) can also be calculated for small ponies or miniature horses. Systemic supplementation of DA or a DA agonist to horses with PPID results in a decrease of POMC peptides in plasma, ACTH and cortisol concentration.

Classic signs of PPID include hirsutism, polyuria/polyidipsia, lethargy, excessive sweating, loss of muscle mass, repeated infections, infertility, and bulging eyes as result of supraorbital fat redistribution [47]. However, insidiously onset chronic laminitis is the most significant clinical complication of PPID in horses (50%). PPID-induced laminitis is due to two factors: (1) alteration of helmet perfusion by excess catecholamines acting directly on vascular smooth muscle (vasoconstriction and limited blood flow) and (2) indirectly by overproduction of circulating cortisol causing insulin resistance. Castro et al. [50] showed that oral administration of domperidone at 1.1 and 5.5 mg/kg increased lamellar microvascular blood flow (LMBF). This effect begins 4 h after administration and the effect persisted for at least 8 h. Intravenous administration of 0.2 mg/kg domperidone increased the LMBF at 10 and 12 h after administration. In horses with laminitis, domperidone may be helpful in preventing vasoconstriction and reduction of LMBF. However, further research into the effects of the drug on horses with laminitis may be needed.

3.2. Behavioral alterations: stereotipies

The neurobiological consequences or regulations of equine stereotypes focus on neurotransmitter systems, specifically the serotoninergic and dopaminergic pathways. Various studies have reported that the DA and reward systems are the underlying mechanisms for the development of stereotypes [51, 52]. Stereotypes can act as a rewarding behavior and help the horse to fight in a suboptimal environment.

The different anatomical regions of the brain, the basal ganglia, have been identified as critical to the performance of stereotypes. Recent studies have focused on the striatum of the basal ganglia, which are related to neurophysiological processes during stereotyped activities. Basal ganglia have been identified as a critical region in relation to the performance of stereotypes [51]. DA is suggested as an activator and modulator of basal ganglia motor programs that reinforce behavior through a reward system. Neurological studies in cradle-biting horses have shown that the subtypes of D_1 and D_2 receptors in the nucleus accumbens were significantly higher and D_1 receptors in the caudate putamen (dorsomedial stratum) were significantly lower [51, 53]. Therefore, increased neural transmission within the striatal region of the basal ganglia appears to be associated with oral stereotypes, including crib biting [51].

Chronic stress resulting from weaning or lack of ability to carry out specific behavioral needs often resulting from living in a domestic environment can result in decreased or increased secretion of deoxyribonucleic acid. This fact develops depression or cradle bite, respectively. Depressed horses have little reaction to stimuli, and they can also fall into a state of learned helplessness. As a result, the horse makes no effort to learn, understand or give natural responses to the stimuli [51].

Because of the links between stress and DA, anxious horses may be more sensitive to environmental stressors. These factors such as restricted feeding or social isolation are common stressors faced by stable horses [54]. In animals kept under the same environmental conditions, behind this increased ability to respond to stress, anxious individuals may have a high striated DA compared to less anxious animals. This may allow the initiation of active coping in an attempt to gain control over the environment, similar to the elevated DA levels seen in the active coping DBA mouse strain [55]. A similar process can occur with anxious horses, as demonstrated by the increased rate of spontaneous blinking in these individuals [13].

From the neurobiological perspective of stereotypes, an alternative hypothesis is based on the activation of the mesoaccumbens pathway by highly motivated events. Highly motivated activity restrictions are known to initiate high dopaminergic transmission of mesoaccumbens. Therefore, the development of stereotypes can occur in environments where goal-directed behaviors are restricted [51]. Pharmacological treatment of these alterations focused especially on the neurotransmitters DA and serotonin, and opioid systems. The use of medications such as tryptophan, naloxone, naltrexone, dextromethorphan, acepromazine maleate, and clomipramine [56, 57] has been reported for the treatment of stereotypic behaviors.

On the other hand, chronic ingestion of yellow star thistle (*Centaurea solstitialis*) or Russian wolf mint (*Acroptilon repens*) causes nigropallidal encephalomalacia (NPE) in horses. Neurological signs are characterized by an abrupt onset of dystonia of the lips and tongue, inability to prehend food, depression and locomotor deficits. The transmission of DA plays an important role in four main pathways: nigrostriatal, mesolimbic, tuberous-infundibular and mesocortical. Lesions located within the substantia nigra pars reticulata, sparing the cell bodies of the dopaminergic neurons in the substantia nigra pars compacta, and in the rostral portion of the globus pallidus, with partial disruption of dopaminergic fibers passing through the globus pallidus. These findings indicate that equine NPE can serve as a large animal model of environmentally acquired toxic Parkinsonism. The clinical phenotype is directly attributable

to lesions in the globus pallidus and substantia nigra pars reticulata rather than to the destruction of dopaminergic neurons [58].

In horses experimentally infected with Westnile virus, central levels of DA are significantly decreased due to imbalance in expression of the enzyme TH and MAO. In these infected animals, TH and MAO decrease and increase, respectively. The decrease in dopaminergic activity, accentuated by the decrease in dopaminergic receptor expression, is associated with the characteristic clinical symptoms of the disease and resembles the motor alterations observed in Parkinson's disease in humans [59].

3.3. Hypomotility gastrointestinal

GI motility abnormalities in horses may be due to different conditions. These include equine herb disease, gastroduodenal ulceration, intraluminal obstruction or retention, excessive wall strain, strangulation obstruction, peritonitis, duodenitis, proximal jejunitis, colitis and postoperative ileus (POI) [60].

DA plays an important role in the control of GI motility in horses. Receptor agonists induce inhibitory (relaxation or inhibition of contractions) and excitatory (increased contractions, less frequently) effects in various portions of the GI tract [20]. These effects are possible since the D_1 receptor is mainly located in the effector cells (postjunctional) and the D_2 receptor is present both pre and postjunctional [21]. However, receptor antagonists affect intestinal motor activity from the stomach to the colon [61]. For the treatment of intestinal hypomotility in horses, prokinetic drugs such as D_1 and D_2 receptor antagonist and domperidone have been used as a competitive antagonist in peripheral D_2 receptors [62–64].

Metoclopramide is an antagonist of CNS and systemic D_2 dopaminergic receptors and blocks the inhibitory effect of DA on GI smooth muscle [65]. In a model of POI in horses, continuous infusion of metoclopramide restored coordinated gastroduodenal activity and GI transit. In a retrospective study also conducted in horses, the clinical use of metoclopramide (continuous infusion at 0.04 mg/kg body weight/h) after small bowel resection and anastomosis was evaluated. Although the horses treated in this study had decreased total volume, duration, and rate of gastric reflux, previously reported side effects were again noted [66]. In another study conducted on horses [67], metoclopramide increased contractility of the smooth muscle strips of the antrum pyloricus, duodenum and jejunum. When used as a pretreatment, metoclopramide has also been shown to improve gastric emptying in horses receiving endotoxin [68].

According to Nieto et al. [67], metoclopramide (0.2 mg/kg PO) improved jejunal motility, but there was no effect on cecal motility [61]. In addition, when evaluating gastric emptying, the researchers found that metoclopramide had less time needed to reach a peak than the control group. This suggests an improving effect of metoclopramide on gastric emptying. Complementary to these results, another *in vitro* study on equine smooth muscle strips derived from the pyloric antrum, proximal duodenum and mid-jejunum showed a significant increase in contractile amplitude of the muscle strips in the three locations, caused by metoclopramide. An interesting finding here is the observation that lower concentrations of the drug were needed in the proximal parts of the GI tract to obtain a response (10^{-9} M in the pyloric antrum compared to 10^{-5} M in the mid-jejunum). This may be because metoclopramide is believed to work by restoring gastroduodenal coordination.

However, due to motility disorders in horses such as POI and colic, the question arises whether metoclopramide can be considered a reliable drug in equine practice. The agent indeed has been found to be effective in cases of both natural and experimentally induced POIs [67, 69]. It has also been successful in the fight against experimentally induced colic [70]. However, the ability to cross the blood-brain barrier and cause serious central side effects should prompt professionals to use this drug with caution in equines. Recommended dosages include 0.125–0.250 mg/kg, diluted in 500 mL of polyionic solution for slow infusion (more than 60 min); 0.05 mg/kg (IM, four times daily); 0.1–0.25 mg/kg (SC, 3 or four times daily) or 5 mg/kg (PO, four times daily) [71].

Domperidone is a dopaminergic D_2 receptor antagonist present in both the center and periphery (including the GI tract) of the neural system [72]. Unlike metoclopramide, which crosses the blood-brain barrier easily, domperidone causes minimal extrapyramidal central side effects. This is because it interacts only slightly with central dopaminergic receptors. A recent study used oral administration of the drug at 1.1 and 5.5 mg/kg both in vivo and in vitro, the influence of domperidone therapy on gastric emptying, and motility of the intestinal tract in horses [64]. However, no effect was detected on the rate of gastric emptying at a dose of 1.1 mg/kg PO, which was previously effective in the treatment of fescue toxicosis in pregnant mares [73].

On the other hand, the higher dose of 5.5 mg/kg PO significantly increased the area under curve (AUC) and maximum concentrations (Cmax) in the acetaminophen test. Both test parameters have been postulated to increase gastric emptying. *In vitro* assembly of the same study showed no effect on the contractile response of the longitudinal and circular smooth muscle strips obtained from the duodenum, jejunum, ileum and equine colon (pelvic flexure) [50]. In addition, domperidone was found to decrease the contractile activity induced by DA of smooth muscle strips in the mid-jejunum. Therefore, more research is needed to elucidate the potential beneficial effects of domperidone *in vivo*, as well as to obtain more knowledge about its pharmacokinetic properties.

On the other hand, equine ileocolonic aganglionosis, also called lethal white colt syndrome (LWFS), is a severe congenital condition characterized by failed colonization of the neural crest in the caudal part of the small intestine and the entire large intestine. The LWFS, which is attributable to a mutation in the endothelin B receptor gene, results in intestinal akinesia and due reduction of colic in enteric neurons [74]. This evidence highlights the involvement of the dopaminergic system in the control of GI motility.

In addition, in horses under anesthesia with isoflurane, Dancker et al. [75] showed that DA increased cardiac output but decreased blood flow in the colon, as well as systemic vascular resistance and mean blood pressure compared to baseline values.

4. Role of dopamine in equine reproduction

4.1. Neuroendocrine basis

It is generally accepted that the primary controllers of gonadal function are various endocrine/paracrine mechanisms including the hypothalamic-pituitary-gonadal axis. However, there is evidence of additional components that control gonadal function. These additional elements

involve autonomic neuronal (catecholaminergic) activity and, possibly, endocrine-like effects produced by neurotransmitter chemicals secreted by non-neural ovarian cells [76, 77].

Earlier studies (reviewed in [78]) showed that decreased photoperiod during the fall and winter suppresses gonadotropin-releasing hormone (GnRH) secretion. This effect is mediated by changes in melatonin secretion from the pineal gland. Low levels of GnRH reduce gonadotropin secretion which in turn leads to reduced follicular growth and anovulation. The increase of the photoperiod during the spring induces a gradual increase of the hypothalamus-pituitary axis that allows the initiation of follicular growth and eventually ovulation [79].

Like other females with seasonal reproduction and relatively long gestation periods, the environmental control of reproduction in the mare is mainly through the photoperiod [80]. In addition to the photoperiod, environmental factors and associated neural pathways are involved in the neuroendocrine control of the mare's reproductive seasonality [81]. Therefore, the functions of several classical neurotransmitters, including opioid peptides, catecholamines and neuro-exciting amino acids and their relationship to their potential functions in regulating seasonal reproduction in mares, have been examined [81].

Substances released by catecholaminergic nerves can directly influence through their interaction with a variety of receptors in target tissue cells. They can also be internalized and converted to other catecholamines within the tissue to exert their action on other cells [77].

In the 1990s, some studies have reported on the role of DA in the control of reproduction in mares or stallions [82, 83]. In the mare, the concentration of DA in the CSF fluid is lower during the period of reproductive activity compared to the anovulatory period. In addition, it appears to be inversely correlated with plasma concentrations of luteinizing hormone (LH) [82]. Beyond seasonal variations, the concentrations of DA in the CSF appear to depend on the presence of gonads. Although ovariectomized mares show a seasonal variation in the secretion of LH, these females do not express a seasonal variation in the concentrations of DA in the CSF. This suggests a functional relationship between DA secretion and ovarian function [35].

On the other hand, there is also a regulatory function on seasonality due to the presence of synapses between dopaminergic and GnRH neurons in the median of pituitary eminence. In addition, suppression of these receptors increased LH during the anestrus period [84].

DA has been identified in the ovaries of laboratory experimental animals [85, 86], cows [87], sows [88] and mares [77]. The actions of DA are mediated through specific receptors found in the cell membrane. Five different DA receptors have been identified [84, 89], which according to their physiological, pharmacological and biochemical properties have been grouped into two general families: D_1 and D_2 [90]. Therefore, even within the same ovary, different functions can be controlled by the DA depending on whether it binds to D_1 or D_2 type receptors. Both types of receptors have been reported in ovarian tissues in mares [77].

It has been suggested that DA may act through the D_2 receptor to inhibit follicular growth [84]. This theory is based on the fact that dopaminergic antagonists such as sulpiride and domperidone have a positive effect on follicular growth in anovulatory mares. Also, in the fact that treatment with these antagonists does not increase FSH secretion in this type of

mares [29, 41, 84, 91]. These findings are supported by the observation that cortical samples appear to have a higher incidence of D_2 receptor mRNA compared to D_1 receptor mRNA [77].

DA is also present in equine follicular fluid. Higher concentrations of DA have been found in small follicles (<25 mm in diameter) compared to medium and large follicles. This suggests a role in early follicular recruitment. It has been reported that in mares during the breeding season, the mRNA of the DA D_1 and D_2 receptors is present in the germinal epithelium of the ovarian cortex and in some granular tissues of the antral follicles [91]. It was also hypothesized that the direct dopaminergic contribution in the ovary may affect follicular growth. It has also been described that the effects of DA on mare follicular growth can be mediated through the regulation of *follicle-stimulating hormone* (FSH) secretion. It has been observed that neither the amount of the message changes during seasonal fluctuations in the ovarian activity of the mare [91].

Like DA, PRL has also been shown to play a role in the ovarian function of the mare. DA acts to influence follicular dynamics by indirectly affecting the ovary and influencing circulating PRL concentrations [92, 93]. PRL is found in follicular fluid [94] and can be produced by granulosa cells [95]. PRL has been associated with seasonal follicular growth [83], ovulation [93] and CL [77, 96]. In mares, PRL levels are lower in autumn and winter compared to spring and summer when follicular activity resumes [92]. In addition, there is a positive correlation between PRL and follicular diameter during the spring transition in mares [83].

As mentioned earlier, PRL appears to be associated with follicular growth. PRL receptors (PRLr) are at the highest concentration in the antral follicles, where it has been shown that PRL is manufactured by granular cells [94]. Once PRL is produced, it is presumably accumulated in the follicular fluid, which suggests a paracrine/autocrine function for PRL within the follicle [95]. The DA is sent to the target organs through the dopaminergic nerves. In the pituitary gland, dopaminergic neurons of hypothalamic origin deliver DA to lactotrophs to inhibit PRL production. Dopaminergic nerves have also been shown to provide a source of DA to the equine ovary. Unlike other species, DA neurons in the mare's ovary do not appear to be associated with reproductive structures. DA neurons, as well as DA receptors in ovarian blood vessels, suggest a role for DA in the regulation of ovarian vascular compliance. But they can also serve as a method of local distribution of DA to vascularized reproductive structures. DA D_2 and PRLr are evenly distributed through the large and small luteal cells of CL [92]. The regulation of luteal function is not well described in the mare, but the PRL and DA appear to have some role [96].

4.2. Luteal function

DA also plays a role in the regulation of luteal function. For example, D_1 and D_2 DA receptor proteins have been detected in mares in CL [77]. In rats, DA produces stimulating effects on P_4 secretion from luteinized granular cells through interaction with D1 [97]. In the cow, DA has been reported to control luteal endocrine function [77]. In addition, in luteal tissue in mares, an increased incidence of gene expression of DA receptors was reported. Both types of receptors appear to be homogeneously distributed throughout the tissue [77].

In mares, systemic concentrations of DA increase from basal levels in summer to peak levels during the winter anestrus season [82]. During this seasonal change, but before detectable changes in the patterns of secretion of LH or FSH, the average P_4 concentrations during the luteal phase undergo a linear decrease [98–100]. This decrease in the function of CL can be regulated by DA in the ovary since DA results from a seasonal decrease in PRL [30]. The treatment of cycling mares during this transition period with the specific D_2 antagonist did not alter the seasonal change in luteal secretion of P_4, suggesting that this function may be under the control of D1 [30].

4.3. Pharmacologic control of reproduction in mares

4.3.1. Cyclicity

DA antagonists have been used of as an alternative of artificial photoperiod, progestogens, GnRH and its analogues, and gonadotropins to induce early cyclicity and ovulation in anovulatory mares [30]. However, differences in environmental factors, such as photoperiod and temperature, or stress have been recognized to exert an influence on the efficacy of these treatments [31].

The most commonly used DA antagonists in horses were sulpiride [29, 32] and domperidone [91]. Two other antagonists also used were fluphenazine [101] and perphenazine [102]. All these compounds have been documented to induce follicular growth or ovulation in seasonal anovulatory mares. However, there is a wide variation in the results between studies [84].

Domperidone has a high affinity for D_2 receptors and a half-life of about 7 h. It is metabolized predominantly in the liver and intestine [84]. It is usually given by mouth, but can also be given by injection. It is often used to treat agalactia and fescue toxicity. It is also increasingly popular for inducing cyclicality and follicular growth in anovulatory and transitional mares [84].

Sulfiride is selective for D2 receptors and also, although with some inconsistent results, has been used in the mare to induce cyclicality. Besognet et al. [103] described successful treatments using both a high dose (1.0 mg/kg body weight once daily) and a low dose (200 mg/mare). Daels et al. [104] used a dose of 0.5 mg/kg to decrease the time interval at first ovulation. However, other studies have shown no influence on the date of first ovulation [29]. Therefore, the results have been mixed, with some researchers reporting increased follicular development and earlier onset of ovarian cycles and others who have reported no effect [80].

The use of DA antagonists in noncyclic mares was mainly performed in the northern hemisphere and treatments generally began in January and February. A comparison between these studies indicates that the most favorable environmental conditions for mares coincide with an earlier response to treatment with DA antagonists [31]. For example, mares housed indoors and photo-stimulated ovulated earlier [104] compared to mares kept outdoors [83, 104]. When treatment with domperidone, for 12–17 days, in mares, kept outdoors and subjected to natural photoperiod began in April [105], treated females did not ovulate earlier compared to control females (31.6 days vs. 31.0 days). It should be noted that in this study, the treatment started with an average follicular diameter of 16.7 mm.

Information on the fertility of mares treated with DA antagonists is scarce and, in most cases, with a low number of animals. In these studies [103, 104] pregnancy rates of 57% (4/7) and 60%

(4/6) were reported at 18 and 14 days after ovulation, respectively. Mari et al. [106] reported a pregnancy rate of 40% (4/10) and 70% (7/10) for mares treated with sulpiride or domperidone, respectively, and all pregnant mares were foaled. Differences in efficacy in the use of DA antagonists may be due to the FSH secretion status of the anestro mare and the presence or absence of functional FSHr in the ovaries. A hypothesis of this assumption could be that the direct dopaminergic ovarian contribution may affect follicular growth through the regulation of FSHr populations [41].

DA also appears to be associated with some aspects of ovarian follicular growth in mares. DA antagonists have been able to stimulate follicular recruitment in anestrus mares [91, 104]. In opposition, the administration of the DA agonists delayed the spring transition to the breeding season [102]. However, the use of DA antagonists in mares during the breeding season did not change the timing of the estral cycle events [83].

If AD through the D_2 receptors inhibits ovarian follicular growth, blocking of these receptors in the preantral follicles of the anestrus mares by the DA antagonists would presumably interfere with inhibition and allow follicular development. However, follicular growth may occur only if other stimulating factors, such as FSH secretion and ovarian responsiveness, are present [29].

4.3.2. Lactation

DA is the most important factor inhibiting the release of prolactin. In mares, different DA D2 receptor antagonists have been used to prevent the plasma PRL decrease induced by ergot alkaloids [101]. This decrease in PRL is an agalactia cause in mares during the lactation period [107]. Therefore, D_2 DA antagonists may be used to restore lactation in affected mares.

Two different studies demonstrate that lactation can be induced successfully in the summer, in intact, cyclic mares using a D_2 DA antagonist sulpiride, after steroids treatment administered by vaginal sponges. Thus, Chavatte-Palmer et al. [108] have demonstrated the induction of lactation in non-pregnant cyclic mares. Therefore, is possible to use these mares as foster mothers for foals separated from their mother, for a short time after the birth [109].

In ovariectomized mares, the PRL secretion induced by the D_2 DA antagonist is lower than in treated intact mares; this fact indicates that ovarian steroids increased plasma PRL levels. Thus, when lactation is induced in mares with a D_2 DA antagonist to increase PRL, steroids secreted by the ovary are necessary. Therefore, treatment with exogenous steroid is not necessary in intact mares. So, this induction is possible at the end or the beginning of the breeding or foaling season [108].

4.4. Stallion

In stallions, Urra et al. [33] documented that DA acts as a physiological modulator of viability, capacitation and sperm motility. Indeed, the acrosome integrity and thyrosine phosphorylation is significantly reduced at high concentrations of this catecholamine in equine sperm. Bromocriptine (DA agonist) on PRL secretion and subsequently on gel-free seminal volume are consistent with the hypothesis that PRL is involved with the sexual stimulation-induced

rise in seminal volumes in stallions. The number of mounts, sperm concentration, motility, pH of gel-free semen, number of spermatozoa per ejaculate, and PRL concentration in gel-free semen were not affected by treatment of bromocriptine and sulpiride during period of sexual stimulation. The lack of effect of sulpiride (AD antagonist) treatment indicates that PRL alone does not mediate the effect of sexual stimulation on seminal volume [34].

5. Conclusion

This chapter analyzes the physiological mechanisms of secretion, regulation, cerebral functions and extracerebral self/paracrine of DA in equids, the physiological factors that modify the profile of DA, such as age, breed, exercise and reproductive status and the importance of DA in the reproductive seasonality in the mare. Likewise, the implication of DA and the effects exerted by the agonists and antagonists of the dopaminergic receptors used in equine clinic in PPID and stereotypies, microvascular blood flow of the hoof, fescue poisoning in pregnant mares and GI hypomotility have been described.

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