

Factors Influencing Serum Amyloid Type A (SAA) Concentrations in Horses

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ABSTRACT

The acute phase response (APR) is the reaction that occurs in animals in response to disturbances in hemostasis following tissue damage. In horses, the APR is manifested in a variety of pathological processes of various origins, such as infections caused by bacteria, viruses, parasites, arthritis, burns, chemicals, trauma surgery and stress. Acute phase proteins (APPs) are considered those proteins that modify its plasma concentration at least 25% in inflammatory and infectious processes. In adult horses, various respiratory inflammatory processes, gastrointestinal tract, reproductive organs and musculoskeletal system are accompanied by increased levels of a specific APP, so-called serum amyloid type A (SAA). SAA is the most important major APP in the horse. This paper provides a review of physiological factors affecting SAA levels and their role in horses in defense of natural mechanisms, the pathways involved and their material components.

Keywords: Acute Phase Response; Serum Amyloid A; Equine

1. Introduction

The acute phase response (APR) is the reaction that occurs in animals in response to disturbances in hemostasis following tissue damage [1,2]. The main functions of this systemic response are to provide energy and substrates for the fight against invading pathogens, preventing the transfer of metabolites necessary to pathogens, limiting the damage caused by pathogens and/or remove damaged or infected tissue and restore it. During the development of APR release pro-inflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF- α) that act through different receptors on the membrane of hepatocytes, certain proteins synthesized in the so-called acute phase proteins (APPs), including: C-reactive protein, serum amyloid A (SAA), haptoglobin, fibrinogen, C-reactive protein, ceruloplasmin and α_1 -acid glycoprotein [1-4].

SAA is the major protein in horses and presents the following characteristics: they are present at very low or undetectable levels in the serum of healthy animals but increase rapidly from 10 to 1000 times during the APR. This level of response is related to the size of the damaged tissue and can be expressed in a wide dynamic range

and decrease rapidly in response to treatment, although not totally reduced in the absence of recovery. The periods of relapse or the presence of secondary complications lead to new elevation of SAA, and are brought about by non-inflammatory processes, nutritional status, exercise, manipulation or other forms of stress, such as transport [5] that should not affect the normal values. On the other hand, endurance horses with SAA levels higher than 1000 ng/mL may not complete the distance. Thus, high SAA concentration may indicate a poor condition of a horse, resulting in elimination during a competition [6,7]. Also, Kent [8] noted that the baseline should remain unchanged with age, sex or genetics of animals. These properties are the most interesting from a clinical perspective of the horse, and are represented by the SAA. Also, the SAA is involved in the defense of the animal in its adaptation or the body's defense against pathogens [9-11]. Thus, the SAA is the protein that responds quickly to stimuli in the horse. Serum concentration of reactant, ie SAA, increases a few hours after the onset of the stimulus, reaches a peak at 24 - 48 h, and then normalizes [12,13].

2. Serum Amyloid Type A

The SAA belongs to the family of apolipoproteins,

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whose molecular weight is estimated at around 9 and 11 kDa [14,15]. The complete sequence of equine SAA was published by Sletten *et al.* [16]. Three isoforms were identified by their isoelectric point electrophoresis and amino acid sequence [17,18]. SAA3 isoform has been isolated both in hepatocytes during the APR and in various cell types that are checked for extra hepatic synthesis in the digestive tract, airways, mammary gland, synovial tissue and articular cartilage chondrocytes [18-20]. Thus, the protein levels rise substantially in inflammatory arthritis and mastitis [13,18,21,22].

Normal plasma concentrations of SAA in horses range from 0.5 to 20 mg/L [15,23-27], although in most situations they exceed 7 mg/L [23]. It is noteworthy that the cytokine responsible for hepatic synthesis of SAA are released from inflamed tissues, regardless of the cause of the injury. For this reason, the SAA is a nonspecific marker of inflammation and therefore cannot be used for etiologic diagnosis. In fact, Hultén *et al.* [28] identified levels of SAA above 7 mg/L in both viral and bacterial infections, showing the non-specific nature of this protein. In response to tissue damage after inflammation or infection, these values increase rapidly and reach concentrations ranging between 100 - 200 and 1000 mg/L [13, 23]. This type of response develops after 6 - 8 hours of the onset of the stimulus, and reaches peak values within 36 - 48 hours and then decrease to baseline levels within 1 to 2 weeks in the absence of new stimuli [28]. The plasma clearance of SAA is very fast and is degraded in the liver between 30 minutes and 2 hours after synthesis. Thus, the levels decrease rapidly when the cause of tissue damage ceases [13]. These features make the SAA a suitable marker of real-time inflammatory activity and therefore a good indicator of the current health status of the horse [13,29].

Some studies have suggested that SAA is even more sensitive than classical markers of inflammation, such as white blood cell count and Fb [30,31], as stated previously. Various factors such as fear, excitement and infections, among others, mainly induce increased cortisol and neutrophilic leukocytosis type levels. Neutrophils have a very limited kinetics and, therefore, are not considered to be markers of the intensity of the trauma [32]. For this reason, to monitor certainly inflammatory or infectious process, the serum profiles of SAA reflect better the course of the inflammation, since they are correlated by the severity of the process. In contrast, fever and changes in the number of leukocytes, are generally considered as markers of inflammation and infection, and are not useful parameters for monitoring post-operatively, due to its non-specificity [29,31].

Until a few years ago and even today, the most widely used APP in equine clinics has been the Fb. Because research in recent years has shown that the APP of choice

is the SAA, as it responds more actively to inflammation and/or infection. Among the numerous advantages of the SAA to Fb cited, it is quicker responsiveness, the Fb peak occurs within 7 - 10 days, while the SAA occurs in 24 - 48 h, and evolves in parallel with the degree of injury and recovery and broader responsiveness. While the Fb reaches values between 1000 - 4000 and 11,500 mg/L, the SAA is significantly lower (0.5 - 20 mg/L), the Fb can be estimated at 1000 mg/L, which allows the degree of injury to be determined. In addition, Fb does not serve to monitor the effective of the treatment as the response and plasma clearance occur over time. By contrast, the levels of SAA after injury are independent of the values before the onset of the disease [32] and its half-life in blood is very short.

The Fb is present in high amounts in healthy horses, and decrease in situations of increased vascular permeability or excessive consumption and coagulation disorders which may mask the inflammatory or infectious process [13,31,32]. Finally, the standard method of measurement of Fb is insensitive to small changes, so it only detects changes above 100 mg/dL [33]. Furthermore, the levels of SAA rise when the inflammatory process is active, and fall after the cessation of the stimulus. Thus, relapse or exacerbation of inflammation must be accompanied by further increases, indicating the extent of tissue injury. Therefore, repeated measurements provide an objective assessment of the health status, and help to monitor the treatment, the degree of recovery and to decide when the patient is fit to return to perform their normal daily activity [13,34,35].

3. Factors Related to the Variations of Serum Amyloid Type A Concentration in Horses

3.1. Influence of Age and Sex

Several investigations have examined the effect of age and sex on concentrations of SAA in horses, showing conflicting results. Thus, while gender does not seem to affect basal levels of this protein, age exerts a significant influence on the protein profiles. In neonates, a significant increase occurred at 72 hours after delivery. This increase was related to the combined effect of tissue trauma induced by the passage of the fetus through the birth canal, as well as the release of cytokines from the maternal circulation which reflects on the inflammatory nature of the physical phenomenon of labor [15,36,37]. Also, Stoneham *et al.* [24] and Paltrinieri *et al.* [38] related this increase to the ingestion of immunoglobulins from the colostrum. These levels remain elevated until 2 weeks of age [15,36].

In several species, SAA3 isoform has been isolated from colostrum and milk [21,37,39]. Colostral levels of

this protein are closely related to serum levels in healthy foals at 48 hours after birth, suggesting that the protein can be absorbed intact through the intestine and alter the circulating levels. By contrast, other researchers have shown undetectable levels of this protein in healthy foals during this same time period [24,33,40]. These controversial results suggest that fluctuations in the levels of age-dependent SAA are so insignificant that no clinical significance in the horse. In fact, a recent study by Jacobsen *et al.* [32] showed no variations in this age-associated protein.

However, SAA concentrations have been reported in foals less than 12 months of age and older than 18 months of 21.23 ± 12.20 and 14.93 ± 9.07 $\mu\text{g/mL}$, respectively, according to Satoh *et al.* [36] and 19.37 ± 9.41 and 21.53 ± 9.81 $\mu\text{g/mL}$, respectively, according to Nunokawa *et al.* [15]. In addition, both studies showed significantly lower levels in foals and horses aged 18 months to over 21 years. This evolution experienced by the SAA with age confirmed previous results from research in human [41]. The higher incidence of diseases of diverse origin with advancing age seems to be the source of the increase of this protein in older animals, although not all researchers agree with this theory [33].

3.2. Reproductive Status

These proteins are diagnostically useful tools to study several diseases, such as endometritis, in mares [42,43] and bitches [44] and mammary tumor disorders [45], among others. Specifically in the mare, in the authors' knowledge, the scientific literatures is very scarce and fragmentary, and have focused primarily on the peripartum period [15,36], estrous cycle [25] and pregnancy [26, 27]. The studies of Nunokawa *et al.* [15] and Satoh *et al.* [36] showed that during the last four months of gestation the levels of SAA remained within the physiological range of reference, ranging from 16.6 to 23.6 mg/L. Serum concentrations were increased 2 days before partum (23.81 $\mu\text{g/mL}$), reaching levels of 56.74 ± 136.78 $\mu\text{g/mL}$ [15] and 101.29 ± 98.82 $\mu\text{g/mL}$ [36] three days after delivery. This dynamic suggests that birth is an inflammatory event in horse breeding, which could be due to tissue damage induced by the passage of the fetus through the birth canal. However, this increase is modest and the levels of SAA return to normal one month after delivery [15].

Satué and Calvo [25] and Satué *et al.* [26,27] showed that SAA could not be used to diagnose heat or pregnancy in mares. On the contrary, an increase in SAA in early pregnancy has been related with early embryonic death [46].

Later, Duggan [47] found no significant differences in concentrations of SAA between mares and pregnant women. These same researchers showed significantly

higher levels of the SAA3 isoform in colostrum and milk in the serum of pregnant mares in peripartum period. SAA3 levels of colostrum have been associated such features as protection, growth, development and maturation of intestinal cells, immune system and other tissues in the neonate [48-50]. Although it is not precisely known, perhaps the endocrine pattern present in the mare during this period could be responsible for the elevated levels of this protein, since prolactin levels increase rapidly in the last week of gestation [51] and therefore, the production of colostrum, as previously shown in women [52,53].

3.3. Inflammatory Processes

As mentioned previously, the concentrations of SAA become very evident in horses with clinical signs of inflammation. Thus, in horses with experimentally induced inflammation, Nunokawa *et al.* [15] and Satoh *et al.* [36] showed that concentrations of SAA increased in 2 days after induction, reaching values of 4 to 40 times higher than pretreatment values. Subsequently, these values returned to baseline levels in 10 days to 4 weeks, which coincided with to the disappearance of clinical signs. To monitor the responsiveness of SAA aseptic arthritis in Standardbred horses, serial blood samples were taken by Hultén *et al.* [30] using the following protocol: before induction (0 h), at 8, 16, 24, 36 and 48 hours and then at 3, 4, 5 and 15 days post-induction. SAA concentrations increased at 16 hours, reached a peak at 36 - 48 h (227 times higher than the baseline), and remained elevated for two weeks. In complicated septic arthritis situations, SAA remains elevated both in serum and synovial fluid, so it can be used to monitor treatment effect, and that decreases simultaneously with the action of the treatment [22,54].

Henriksen *et al.* [55] and Labelle *et al.* [56] monitored the levels of SAA in the eye and in the local and systemic inflammatory processes accompanying uveitis and corneal ulcers in adult horses and foals with hypopyon. The observed values of SAA in serum and vitreous were significantly higher in foals than in adult animals. Although it was found that this protein does not cross the blood ocular barrier in uveitis and corneal ulcers, the local levels increased significantly in the process of hypopyon. Finally, these same researchers showed that uveitis does not seem to cause an acute phase response.

3.4. Surgery

Generically, surgery induces a marked APR, characterized by a biphasic pattern of SAA [23,31,33]. In particular, after castration, SAA levels have been identified above 7 mg/L, with a peak at 2 - 3 days followed by a second rise 4 or 5 days after surgery [23]. This pattern had also previously been shown in mares experimentally

infected with equine herpesvirus type 1 (EHV-1), although in this case, a second rise occurred later, *i.e.*, at 10 - 12 days from the onset of the process, an expected phenomenon during the inflammatory process [34]. In both cases, the second increase was not accompanied by a worsening of clinical signs and the values returned to the normal reference ranges for 7 - 15 days after surgery [23,32].

In response to surgical stimulus, Satoh *et al.* [36] and Pollock *et al.* [33] showed a narrow range for this protein (from 0.0 to 0.1 µg/mL), which increased rapidly (from 16.1 to 27.29 µg/mL) compared with other markers of inflammation, such as HP or Fb, suggesting that the SAA is useful in the diagnosis and monitoring of disease with surgical intervention in horses.

In three types of surgery, arthroscopic surgery, correction of the recurrent laryngeal nerve neuropathy, and laparoscopic ovariectomy, Jacobsen *et al.* [32] affirmed the induction of the APR, and an increase of SAA. The concentrations of IL-6 were higher in the postoperative period after conventional open surgery, which is a minimally invasive process.

Therefore, this cytokine seems to be a sensitive indicator of the intensity of surgical trauma, since it is the main inducer of the hepatic synthesis of APPs. Jacobsen *et al.* [32] also described the nature of the surgical trauma that could affect the inflammatory response after surgery. Both the length of the surgical incision, as the degree of tissue disruption and the type of tissue, may influence the magnitude of the inflammatory response. In fact, levels of IL-6 after abdominal and thoracic surgery are superior to those of a skeletal muscle. Moreover, peritoneal cells produce different types of cytokines, including IL-6, so that laparotomy may result in an increase of these cytokines in the peritoneal fluid, which affect the APR postoperative process [57]. By contrast, the type of anesthetic and the time of exposure to it seem to influence the levels of APPs [32].

The postsurgical inflammatory and infectious complications are also accompanied by significantly higher values of SAA [31], that correlate with the severity of symptoms. Thus, monitoring the SAA allows making quick decisions about the treatment to apply, and thus decrease the discomfort and postoperative complications [22,29].

3.5. Bacterial and Viral Infections

Serum levels of SAA were significantly elevated within hours of the establishment of infection, thus behaving as an immediate indicator of the disease. This type of response occurs with infections caused by bacteria [24,28,34,38] and viruses [23,28,34]. Specifically, in adult horses with bacterial infections, SAA levels have been reported levels above 2000 mg/L [13], but there was a

more moderate increase associated with viral infections. Thus, the degree of response will help to differentiate the type of microorganisms involved. Hultén *et al.* [28] showed that although an increase in SAA is not a specific indicator of influenza or other viral infection is it an important diagnostic tool for the control, management and monitoring of viral infections in horses. The SAA response against the influenza virus occurs within 48 hours, and returns to baseline levels after 11 - 22 days, in the absence of complications. Therefore, persistent elevations of SAA beyond the 11 - 22 days could be related to severe infections, infectious complications or tissue damage secondary to another source that goes unnoticed. Thus, the SAA can be used as a prognostic marker in bacterial and viral respiratory diseases on a large scale in herds, indicating the clinical severity and recovery status of the animals [28,34].

Recurrent airway obstruction (RAO) is an inflammatory, obstructive airway disease that becomes clinically evident in middle-aged horses. The disease, also known as heaves, is most prevalent in the northern hemisphere where horses are stabled for large parts of their lives and are fed hay. Attacks of airway obstruction are induced by exposure of susceptible animals to organic dust (typically hay dust). Following dust exposure, there is massive influx of neutrophils into the airways. This is accompanied by bronchospasm and mucus accumulation [58].

Systemic inflammation in horses with heaves is poorly characterized. In a study done by Lavoie-Lamoureux *et al.* [59], serum haptoglobin concentrations were significantly higher in heaves-affected horses compared with healthy controls. They were also significantly increased by antigen challenge in both controls and horses with heaves. Serum SAA was detected more frequently in heaves-affected horses compared with healthy controls. Thus concluded in heaves, haptoglobin is a marker of both acute and chronic systemic inflammation, while high concentrations of SAA indicate acute inflammation.

3.6. Neonatal Diseases

Generically, in newborn foals the manifestations of clinical signs of disease usually are non-specific, so diagnosis is often made with difficulty. For this reason, the accuracy and reliability of the measurement of SAA can provide positive results. In neonates, the SAA rises in the presence of sepsis and infection [24,29,40]. Certain investigations on the evaluation of SAA in foals by non-infectious causes, such as prematurity, failure of passive transfer of immunity, neonatal maladjustment syndrome, isoerythrolysis, meconium impaction, have given conflicting results. In some of these cases the levels of SAA remain within the physiological range of reference [24,29], while in other situations they are elevated [37,40]. Chronic infections in foals also lead to an increase of

SAA, although at lower levels than in acute infections [29].

High concentrations of SAA in foals often are indicative of infection. It has also been suggested that values above 100 mg/L could distinguish infectious from non-infectious causes [24]. In fact, to distinguish these processes, the SAA is more accurate than traditional analytic markers (Fb and leukocyte count) [29]. Neonatal sepsis is a serious problem and a delay in starting treatment can be fatal. Therefore, the SAA measurement can aid in the diagnosis and most appropriate treatment setting in less time [24]. Like in adult horses, localized infections, such as abscesses in umbilical cord of foals, the SAA may remain low or undetectable. This response is related to the location of these abscesses and the removal of the hepatic synthesis [24].

3.7. Respiratory Processes

Elevated levels of SAA have been detected in horses infected with influenza [28] and pneumonic processes of unknown etiology [15,34]. The SAA in horses with influenza is a more sensitive marker of acute infection detected by nasal swabs. In addition, the SAA is positively correlated with the severity of the clinical disease and decreases or becomes undetectable in horses recovering from viral infection [28]. High concentrations of SAA were detected in foals infected by *Rhodococcus equi* which decreased after initiating treatment [29]. However, a study conducted in foals younger than 1 month showed no variations in the concentrations of SAA among foals with pneumonia caused by *Rhodococcus equi* at the time of onset of clinical signs and clinically healthy foals.

Thus, SAA should not be used as a source of reliable diagnosis, but as a tool to assist in the early detection of respiratory tract infections [60].

SAA is also a useful tool to monitor the response to treatment of respiratory tract infections. Secondary bacterial complications or severe influenza processes induce persistent elevations in the levels of SAA [28]. For this reason, the SAA can be used as a marker of the degree of recovery and determine the appropriate convalescence period, avoiding the detrimental effects of a return to daily activity [61].

The responsiveness of SAA has been used to monitor vaccinations against influenza, and tetanus. Generically, vaccination causes a moderate increase of SAA, which begins at 24 hours, persists for 96 hours and decreases in 3 - 4 days [62,63]. The A2 influenza virus produces a type of local response which in some cases is systemic and is due to the synthesis of IL-6 and TNF- α [64]. Similarly, inoculation of endotoxins produced by *Escherichia coli* induces a marked release of IL-1 [65].

It has been hypothesized that the measurement of SAA in horses with respiratory disease could distinguish between infectious and noninfectious type caused by allergic reactions. This justification is based on extrapolating from human situations in which immune-mediated diseases, such as systemic lupus eritematoso, polymyositis and ulcerative colitis that are associated with a low release of SAA [66,67]. At present, it remains to be clarified if allergic or immune-mediated processes develop alterations in the levels of SAA in horses.

Tables 1 and 2 describe the pathological causes commonly associated with elevated levels of SAA in horses.

Table 1. Description of the pathological processes infectious bacterial, septic and aseptic joint inflammation and surgeries that lead to elevated levels of SAA in horses.

Process	Description	References
Joint diseases	Experimentally induced aseptic arthritis	Hultén <i>et al.</i> [23] Hultén and Demmers [29] Jacobsen <i>et al.</i> [18,22]
	Naturally induced infectious arthritis	Pepys <i>et al.</i> [34] Jacobsen <i>et al.</i> [24]
	IM injection of turpentine oil	Nunokawa <i>et al.</i> [15]
Surgery	Laparotomy	Nunokawa <i>et al.</i> [15]
	Different procedures (laryngoplasty, ventriculectomy, ovariectomy)	Hultén <i>et al.</i> [17] Pepys <i>et al.</i> [34] Pollock <i>et al.</i> [33] Jacobsen <i>et al.</i> [32]
	Castration	Nunokawa <i>et al.</i> [15] Hultén <i>et al.</i> [23] Jacobsen <i>et al.</i> [24]
	Arthroscopy	Jacobsen <i>et al.</i> [32]
Bacterial infections	Sepsis in foals	Chavatte <i>et al.</i> [40] Hultén <i>et al.</i> [17] Stoneham <i>et al.</i> [24] Hultén and Demmers [29]
	<i>Rhodococcus equi</i> pneumonia	Chavatte <i>et al.</i> [40] Hultén and Demmers [29]
	Focal (abscesses, septic arthritis in foals)	Stoneham <i>et al.</i> [24]
	Strangles (<i>Streptococcus equi</i>)	Pepys <i>et al.</i> [34] Hultén <i>et al.</i> [17]
	Endometritis by experimental infection of <i>E. coli</i>	Chistoffersen <i>et al.</i> [42]
	Pyæmia, abscesses, post-operative infections	Jacobsen <i>et al.</i> [32]
Unknown etiology abortion	Nunokawa <i>et al.</i> [15]	

Table 2. Description of the virus-like disease processes, gastrointestinal, non-infectious, reproductive and metabolic disorders, leading to elevated levels of SAA in horses and describe the processes.

Process	Description	References
Viral infections	Herpes virus type 1 in foals	Pepys <i>et al.</i> [34] Chavatte <i>et al.</i> [40] Hultén and Demmers [29]
	Herpesvirus type 1 in adults	Pepys <i>et al.</i> [34]
	Influenza virus	Hultén <i>et al.</i> [23,28]
	Diarrhea and enteritis in foals	Nunokawa <i>et al.</i> [15]
Gastrointestinal diseases	Colic in adult horses	Nunokawa <i>et al.</i> [15] Vandeplas <i>et al.</i> (2005)
	Peritonitis	Jacobsen <i>et al.</i> [32]
Neonatal non-infectious diseases	Weakness, prematurity, neonatal maladjusted syndrome, birth trauma and meconium colic retention	Chavatte <i>et al.</i> [40]
	Hypoxic-ischemic encephalopathy	Duggan [47]
Reproductive diseases	Foaling induction	Duggan <i>et al.</i> [37] Paltrinieri <i>et al.</i> [38]
	Abortion of unknown etiology	Nunokawa <i>et al.</i> [15]
Metabolic diseases	Laminitis	Hultén <i>et al.</i> [17]
Other diseases	Hyperlipidemia, anemia, weight loss, idiopathic edema of unknown origin and ciatostomiasis	Jacobsen <i>et al.</i> [32]

3.8. Amyloidosis

Recurrent inflammatory processes with sustained elevations of SAA can lead to reactive amyloidosis. This term covers a variety of diseases involving the deposit of SAA in the muscle fibers of the liver, spleen and kidney. Systemic amyloidosis can have fatal consequences, as verified in horses with repeated immunization for the production of antiserum [17,68].

4. Conclusion

The APPs determination of the physiological factor which modifies the APR offers a biological effect mechanism appropriate to assess the health in equine patients. Despite the nonspecific nature of the APR, the estimation of plasma levels of SAA can be useful as a diagnostic aid, helping to differentiate inflammatory from non-inflammatory conditions. Levels of SAA can also be important for management of patients, since they generally reflect the extent and intensity of the inflammatory process and the response to, and need for, therapeutic interventions and prognostic value, that ensures the return to normal healthy condition in the shortest amount of time.

5. Conflict of Interest Statements

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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