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Review

ACUTE PHASE BIOMARKERS OF DISEASES IN SMALL RUMINANTS: AN OVERVIEW

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Summary

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Acute phase proteins (APPs) are a large group of proteins synthesised mainly by the liver. Their production is stimulated in response to disturbances in the systemic homeostasis. It is known that each species has a specific set of APPs. Serum amyloid A and haptoglobin are the main APPs in small ruminants and their plasma concentration is changed most significantly in comparison with minor APPs such as ceruloplasmin. In general, APPs could provide valuable information on the general condition of the organism but cannot point at the exact disease. Therefore, APPs should be included as an additional indicator in clinical diagnosis. Knowledge of APPs behaviour in disease states has a remarkable potential for detecting animals with subclinical infections, determining the prognosis of clinical infection, differentiation between viral and bacterial disease, treatment monitoring, vaccine effectiveness and stress conditions. The aim of this review is to present data on APPs behaviour during some parasitic and infectious diseases as well as pathological conditions leading to aseptic inflammation and stress in sheep and goats.

Key words: acute phase proteins, sheep, goats, diseases

INTRODUCTION

Acute phase response (APR) refers to a nonspecific reaction of an organism and belongs to innate immunity. It occurs shortly after tissue injuries such as infections, burns, trauma, neoplastic growth, immunological disorders, surgery and stress conditions (Cray *et al*., 2009; Tothova *et al*., 2014). Its main purpose is to restore homeostasis and to remove the cause of disturbance (Ceciliani *et al.,* 2002). APR is expressed by increased or decreased synthesis of acute phase proteins (APPs) by the liver. Depending on changes in their concentrations during disease, APPs are divided into major, moderate and minor.

Haptoglobin (Hp) and serum amyloid A (SAA) are the main APPs in small ruminants (Gomez-Laguna *et al*., 2011). Hp belongs to a group of transporter plasma proteins that bind the free haemoglobin. This defines its bacteriostatic effect as well as antioxidant activity (Smith & Roberts, 1994; Murata *et al*., 2004; Ceciliani *et al*., 2012). SAA plays a role as an opsonin, prevents accumulation of cholesterol on the site of inflammation and modulates innate immune reactions (Ceciliani *et al.,* 2012). Other important APPs in sheep and goats are the α-1 acid glycoprotein (a moderate APP), fibrinogen (a minor APP in sheep but moderate in goats) and ceruloplasmin (a minor APP) (Gomez-Laguna *et al*., 2011). Changes in their concentrations occur early in the course of disease before manifestation of clinical signs. Therefore, they could be used as an early indicator in various pathological processes in small ruminants. Data concerning APPs in cattle and pets have been carried out establishing their usefulness in various diseases but information about APPs in small ruminants is limited. This overview presents the main points concerning the specificity and dynamics of the acute phase response in sheep and goats during the course of naturally or experimentally induced infectious and non-infectious diseases.

PARASITIC DISEASES

All data concerning the APPs behaviour in different disease states in sheep and goats are summarised and presented in Tables 1 and 2.

Parasitic diseases comprise a significant part of the pathology in small ruminants. In general, they can be divided into three main groups: parasitoses caused by parasitic insects and arachnids (arachnoentomoses), worms (helminthoses) and protozoa (protozoan infections).

O'Meara *et al*. (1995) have studied the protein content of the inflammatory exudate from myiasis wounds (blowfly strike) caused by *Lucilia cuprina* in susceptible and resistant sheep breeds. Six to twelve hours after *Lucilia* larvae implantation, the authors found that the exudate was rich in IgG and fibrinogen (Fb), and about the 24th h it has grown in complexity and contained 74 peptides such as plasminogen and albumin (Alb). For comparison, the exudates from wounds of resistant animals contained far more peptides in first 12 h than susceptible sheep which suggests a faster development of inflammatory response. According to this reserach, the exudate composition is likely to be influenced by local APPs synthesis. In a similar study, Colditz *et al*. (2005) investigated some physiological responses associated with reduced wool growth during blowfly strike in Merino sheep and established increasing values of plasma serum amyloid A (SAA), haptoglobin (Hp) and the pro-inflammatory cytokine interleukin-6 (IL6).

Studies have been conducted to investigate the acute phase reaction in mange. In this connection Rahmann *et al*. (2010) evaluated the acute phase response in the Alpine ibex (*Capra ibex*) with sarcoptic mange through examination of the concentrations of SAA, Hp, acid glycoprotein (AGP) and ceruloplasmin (Cp) after *Sarcoptes scabiei* infestation. The authors found increased concentrations of all investigated acute phase proteins (APPs) in animals with clinical sings compared to healthy ones. They also reported that SAA and AGP elevatation was more than 10-fold while that of Hp and Cp: 2 to 5-fold. In this regard, Wells *et al*. (2013) examined the behaviour of SAA and Hp after primary and secondary infestation with *Psoroptes ovis* in sheep and the effect of treatment. During primary infestation, SAA and Hp concentrations were significantly elevated at post infestation week 4 and reached a peak about the 5th week. After treatment, the SAA and Hp concentrations decreased within 3 days and 1 week respectively and returned to the pre-infestation level for 10 to 14 days. The SAA and Hp profiles during second *P. ovis* infestation has shown that their plasma levels increased rapidly within the first 24 h compared to the primary infestation followed by gradual decrease and then reached pre-infestation levels for about 2 and 3 weeks, respectively.

Studies on APPs in helminthic diseases also have been done. Ulutas *et al*. (2008) examined APPs changes during a mixed helminth infestation by *Trichuris* spp., Trichostrongylidae and *Fasciola* spp. in goats and determined increased Hp and SAA levels. A similar survey on some APPs in sheep with experimental *Haemonchus contortus* infection has been reported (Zhong *et al*., 2014). The authors measured plasma SAA, Hp, lipopolysaccharide binding protein (LBP) and AGP and found increased concentration of SAA (10- to 150-fold), Hp (10- to 30-fold), LBP (2 to 6-fold) and AGP (2 to 10-fold). With the exception of SAA, all other APPs exhibtied two peaks, the first on day 3 and the second on day 28; while the first and second SAA peaks occurred on post infection days 1 and 28, respectively. The authors explained those APPs peaks as a combined effect of larval and adult *H. contortus* parasitising.

It is known that some protozoa cause significant tissue damage to the host as compared to helminthic infections. In this connection, Hashemnia *et al*. (2011) reported changes of APPs and inflammatory mediators during experimental caprine coccidiosis. In their study two groups of newborn kids were inoculated by different doses of *Eimeria arloingi* sporulated oocyst and serum levels of Hp, SAA, tumour necrosis factor-α (TNF-α), interferon-γ (IFN-γ) were measured. The authors found significantly increased APPs concentrations on post inoculation day 7 compered to pre-inoculation Hp and SAA levels. The highest Hp concentration was measured on days 14 and 21 for the first and second tested groups respectively. A peak in SAA level was detected on days 35 and 21 after inoculation. The authors concluded that APPs could be used as non-specific markers for predicting the prognosis and treatment monitoring. They concluded that the increased APP concentrations occur before clinical disease manifestation and that the magnitude and duration of the Hp and SAA responses correlated with inoculation doses and severity of the clinical signs. Acute phase response in sheep durung chronic *Trypanosoma vivax* infection was conducted by Sousa-Almeida *et al*. (2012). Four APPs have shown a significant reduction which was more marked for Cp and haemopexin (Hpx). An early reduction of plasma antitrypsin and transferrin (TF) on post inoculation day 5 was noted and then an increase above baseline in the chronic phase with highest levels especially for antitrypsin.

BACTERIAL DISEASES

Bacterial infections represent a significant part of sheep and goat pathology. A number of studies concerning APPs during corynebacterial infections in small ruminants are available. Pepin *et al*. (1991) investigated the changes in APPs profile in lambs experimentally infected by *Corynebacterium pseudutuberculosis*. After subcutaneous inoculation, the authors reported a rapidly increasing Hp concentration in the plasma with peak between the

Table 1. Studies of some diseases in sheep that have investigated APPs

Pathology	Examined APP(s)	Reference
Parasitic diseases		
Myiasis (*Lucilia cuprina*)	Fb, Alb, plasminogen	O'Meara *et al*. (1995)
Myiasis	SAA, Hp	Colditz *et al*. (2005)
Scab (*Psoroptes ovis*)	SAA, Hp	Wells *et al*. (2013)
Helminths (*Haemonchus contortus*)	SAA, Hp, LBP, AGP	Zhong *et al*. (2014)
Protozoa *(Trypanosoma vivax)*	Cp, Hpx, TF, antitrypsin	Sousa Almeida *et al*. (2012)
Bacterial diseases		
Corynebacterium pseudutuberculosis	Hp	Pepin *et al*. (1991)
Caseous lymphadenitis (*Corynebacterium pseudutuberculosis*)	Hp, SAA, AGP	Eckersall *et al*. (2007)
Caseous lymphadenitis	Hp, Fb	Bastos *et al*. (2011)
Intrauterine bacteria (*Escherichia coli*, *Staphylococcus aureus*, *Streptococcus uberis*, *Enterococcus* spp.,*Clostridum* spp.)	Hp, Cp, seromucoid	Regassa & Noakes (1999)
Bacterial peptidoglycan-polysaccharide (PG-PS)	SAA, Hp	Dow *et al*. (2010)
Mannheimia haemolytica	Hp, Cp, SAA, Fb	Ulutas & Ozpinar (2006)
Endotoxaemia (*Escherichia coli* lipopolysaccharide)	SAA, Hp	Chalmeh *et al*. (2013)
Vaccination	SAA	Eckersall *et al*. (2008a)
Subclinical mastitis	SAA	Winter *et al*. (2006)
Mastitis (*Staphylococcus epidermidis)*	SAA	Winter *et al*. (2003)
Viral and prion diseases		
Ovine rinderpest (*Paramyxoviridae*)	SAA, Hp	Arslan *et al*. (2007)
Scrapie	Cp, Hp, SAA	Meling *et al*. (2012)
Internal diseases, aseptic inflammation, stress		
Pregnancy toxaemia	SAA, Hp	Gurdogan *et al*. (2014)
Intrathoracic injection of yeast	Cp, Fb, Hp, Alb	Pfeffer *et al*. (1993)
Non-surgical mulesing (cetrimide)	Hp	Colditz *et al*. (2009)
Non-surgical mulesing (sodium lauryl sulfate)	Hp	Colditz *et al*. (2010)
Transport stress	Hp, SAA, Fb	Piccione *et al*. (2012)
Obstetrics and surgery		
Dystocia	Hp	Scott *et al*. (1992)
		Aziz & Taha (1997)
		Georgieva *et al*. (2011)
Mulesing	Hp	Paull *et al*. (2008)
	Fb, Hp, SAA	Lepherd *et al*. (2011)
Castration	Hp	Price & Nolan (2001)
		Paull *et al*. (2009)
Maxillofacial surgery	Hp	Abu-Serriah *et al*. (2007)
Pulmonary damage and surgery	Hp	Pfeffer & Rogers (1989)

1st and 5th day. In a similar survey, Eckersall *et al*. (2007) explored the differences in plasma levels of Hp, SAA and AGP during experimental ovine caseous lymphadenitis induced by *C. pseudotuberculosis*. The results showed significantly raised SAA and Hp concentrations on day 7 after inoculation; furthermore, these values were statistically significant until the 15th day. A similar response was shown by AGP which also increased on day 7 and then showed a gradual increase on post inoculation day 13. After this period a gradual decline occurred with still significant difference between infected and control groups on day 29. The authors concluded that Hp and SAA increased in the post infection period, returned to normal after 2 weeks while AGP increased more slowly and its levels persisted for 4 weeks after the infection. In another study, Bastos *et al*. (2011) have also investigated APPs during caseous lymphadenitis in Santa-Ines ewes. According to the results, serum Hp and Fb concentrations were not significantly different in seropositive and seronegative sheep. Later, in 11 sheep which have not developed peripheral abscesses, a significantly higher Hp concentration was shown. A similar study concerning caseous lymphadenitis was also conducted by Colom-Cadena *et al*. (2014) in Iberian ibex (*Capra pyrenaica*). The researchers found that during the study period, all values of SAA and Hp were under the limit of detection and attributed this fact to the sampling frequency.

The rate of postpartum uterine involution was monitored in 13 ewes and presented by Regassa & Noakes (1999). Four animals were positive for intrauterine bacteria such as *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus uberis*, *Enterococcus* spp. and *Clostridum* spp. The results have shown that the presence of intrauterine bacteria have not affected the time for completion of uterine involution. In bacteria-free ewes, Hp concentration has increased after lambing with a peak on postpartum day 1 and then has decreased slowly as uterine involution progressed. In contaminated ewes, Hp response was significantly greater. In addition, the concentration of seromucoid has increased. The authors explained that statistically higher plasma levels of Cp were not observed in animals during uterine involution.

Dow *et al*. (2010) designed an experiment to evaluate the acute phase response in ewes challenged with peptidoglycan-polysaccharide (PG-PS) as a part of Gram positive bacteria at day 5 after mating. The ewes exhibited increased SAA and Hp concentration. In addition, PG-PS injected animals on day 5 after mating reduced their pregnancy rate.

The role of colostrum feeding on the magnitude of APP response during *Mannheimia haemolytica* infection in sheep was reported by Ulutas & Ozpinar (2006). The results demonstrated Hp peak on day 10 in the colostrum breast milk-fed sheep while in the colostrum-deprived group, Hp peak has occurred on day 13 after infection. The mean Cp level was also significantly increased in groups until day 10 but the peak occurred on day 7 in colostrum-fed group and on day 1 in colostrum-deprived group. The plasma levels of C-reactive protein (CPR) and Fb significantly increased during infection and reached a peak on day 1 in both groups. In a later study, Chalmeh *et al*. (2013) found a rapid elevation in SAA and Hp levels during experimentally induced endotoxaemia in sheep by lipopolysaccharide from *Escherichia coli*.

The effect of vaccination on the immune response in sheep has also been investigated. According to Eckersall *et al*.

Table 2. Studies of some diseases in goats that have investigated APPs

Pathology	Examined APP(s)	Reference
Parasitic diseases		
Sarcoptic mange *(Sarcoptes scabiei*	SAA, Hp, AGP, Cp	Rahman *et al*. (2010)
Helminths (*Trichuris* spp., *Fasciola* spp., *Trichostrongylidae* family)	Hp, SAA	Ulutas *et al*. (2008)
Caprine coccidiosis (*Eimeria arloingi*)	Hp, SAA	Hashemnia *et al*. (2011)
Bacterial diseases		
Caseous lymphadenitis	SAA, Hp	Colom-Cadena *et al*. (2014)
Mastitis (*Staphylococcus aureus*)	Fb, Hp	Fasulkov *et al.* (2014)
Viral and prion diseases		
Lentiviral infections	Hp	Kaba *et al*. (2011)
Lentiviral infections	Fb	de la Concha-Bermejillo *et al*. (2000)
Retroviral arthritis	SAA	Sack & Zink (1992)
Border disease (*Flaviviridae*)	SAA, Hp	Balikci *et al*. (2013)
Internal diseases, aseptic inflammation		
Pregnancy toxemia	Hp, SAA, ASG, Fb, Alb	Gonzalez *et al*. (2011)
Injection of turpentine oil	Hp, SAA, ASG, Fb, Alb	Pfeffer *et al*. (1993)

(2008) and Ceciliani *et al*. (2012) in lambs born to ewes on a diet that did not exceed the maintenance requirements, lower SAA concentration were detected after vaccination compared with those on a balanced diet, indicating that maternal undernutrition prior to parturition affected the innate immune system in the offspring. Furthermore, acute phase reaction caused by vaccination of lambs could have a role in the assessment of vaccine efficacy (Dowling *et al*., 2004).

Data published by Winter *et al*. (2006) demonstrated that the milk SAA levels could serve as a marker of subclinical mastitis in sheep and had good diagnostic value in individual animals. In an earlier study Winter *et al*. (2003) indicated that *Staphylococcus epidermidis* mastitis in sheep led to increased serum and milk SAA but the mean serum SAA peak occurred earlier than that in milk. In addition, there was no correlation between serum and milk SAA concentrations.

Fasulkov *et al*. (2014) investigated plasma Fb and Hp concentrations during experimentally induced *Staphylococcos aureus* mastitis in goats and showed an increase of the Hp as early as the 8th hour with the most significant differences from baseline values by the 24th and 48th h after infection. It was observed that plasma Fb concentration increased earlier (4th h) and then on the 8th h but the highest level of statistically significance differences were found 24 and 48 h post infection.

VIRAL AND PRION DISEASES

Experimental data indicate that bacterial infections induce a strong systemic APR due to the effects of bacterial toxins on the monocyte-macrophage system, however, viral infection response is relatively less pronounced (Gruys *et al*., 2005). Some investigations on the APPs expression during lentiviral infections in goats demonstrated no enhancement of serum Hp (Kaba *et al*., 2011) and Fb (de la Concha-Bermejillo *et al*., 2000). Sack & Zink (1992) reported a local synovial cell expression of SAA genes in arthritic joint tissue from Lentivirus infected sheep and goats. According to Balikci *et al*. (2013), SAA and Hp considerably increased in goats with Border disease (Flaviviridae), furthermore, there was a significantly higher difference of SAA and Hp levels in aborting than in non-aborting goats. The authors believed that these findings can provide a more accurate assessment of disease prognosis. An earlier study performed by Arslan *et al*. (2007) showed increased serum SAA and Hp levels in ovine rinderpest infected sheep (peste des petits ruminant virus, Paramyxoviridae). A study concerning APPs response during the prion disease scrapie in sheep found an increased Cp, Hp and SAA values at the clinical stage but many individual variations in Hp and SAA concentrations before the clinical stage were also observed (Meling *et al*., 2012).

INTERNAL DISEASES, ASEPTIC INFLAMATION AND STRESS

APPs behaviour was investigated in other noninfectious pathological conditions. In this connection, Gonzales *et al*. (2011) aimed to study the behaviour of Hp, SAA, acid soluble glycoprotein (ASG), Fb and Alb in goats with fasting-induced pregnancy toxaemia. Only Hp was found to be elevated, but changes in other mentioned APPs have not been recorded. However, a significant increase in Hp was not observed until the appearance of clinical sings. According to the authors, APPs seem not to have an advantage over traditional markers in diagnosis of fasting-induced pregnancy toxaemia in goats. In a more recent study, Gurdogan *et al*. (2014) also investigated SAA and Hp in sheep with clinical and subclinical pregnancy toxaemia. The results showed a significantly increased APPs levels in both groups and the authors concluded that SAA and Hp can be used for the diagnosis of pregnancy toxaemia in pregnant ewes.

Pfeffer *et al*. (1993) demonstrated the changes in APPs of in sheep after intrathoracic injection of yeasts. The yeasts caused acute pleuritis followed by fibrous adhesions and abscesses. This pathological process led to increasing levels of Cp, Fb and Hp and decrease in Alb concentration. Those changes were expressed as well between the 5th and 7th day for the positive APPs and on the 12th day for Alb. Causing aseptic inflammation by subcutaneous injection of turpentine oil in goats, Gonzales *et al*. (2008) demonstrated increases in Hp, SAA, ASG, Fb and decreased Alb concentration.

Colditz *et al*. (2009) studied some clinical and paraclinical parameters in lambs after non-surgical mulesing by intradermal injection of cetrimide and found raising Hp concentration for at least 7 days after treatment. The same authors carried out a similar study in which they tested sodium lauryl sulfate as an alternative approach for non-surgical mulesing in lambs and the results again indicated highly elevated Hp after 2–7 days (Colditz *et al*., 2010).

As mentioned earlier in this review, the stress can also trigger an acute phase reaction by neural signals, although the exact mechanism activating macrophages and Kupffer cells to produce pro-inflammatory cytokines and therefore to provoke

APPs synthesis by liver is unknown (Murata *et al*., 2004). However, changes in APPs during a variety of stress factors have been described before. Piccione *et al*. (2012) evaluated the effect of transport stress in sheep on serum Hp, SAA and Fb values. The results showed statistically significant differences between transported and unaffected groups with respect to SAA and Hp while the transport had no effect on Fb concentration. In addition, SAA increased significantly after 24 and 48 h of road transport, while Hp increased after 48 h. These data are in agreement with those published by Colditz *et al*. (2005) and Eckersall *et al*. (2007) summarising that SAA increased more rapidly than Hp during APR in sheep.

OBSTETRICS AND SURGERY

In reproductive conditions, APPs can be used as prognostic indicator of ovine dystocia (Ceciliani *et al*., 2012). According to Scott *et al*. (1992), Hp concentration was significantly elevated in sheep where dead lambs were presented *in utero* and when ewes died following caesarean surgery compared to those which delivered live lambs. Aziz & Taha (1997) also examined the effect of dystocia on serum Hp in ewes and reported a significant elevation in cases treated 24 h after labour compared to ewes treated during the first 24 hours, as well as between surgically and manually treated ewes. Georgieva *et al*. (2011) researched the behaviour of plasma Hp after normal parturition and caesarean surgery in ewes with dystocia. According to this study, Hp concentrations gradually increased in sheep with a normal parturition on the first hour of labour to the 14th day postpartum. In ewes with dystocia, Hp level increased on the 4th and 8th days after the parturition, while in operated sheep Hp significantly increased on the 2nd day and reached a peak on the 4th day after caesarean surgery.

The mulesing of lambs and young sheep (removal of strips of wool-bearing skin from around the breech area to prevent flystrike) is a well known practice in Australia (Lepherd *et al*., 2011). According to Paull *et al*. (2008) mulesed lambs demonstrated a major increase in Hp. In a recent study Lepherd *et al*. (2011) found that the surgically mulesed lambs had the most marked increases in concentration of Fb, Hp and SAA and concluded that the mulesing led to the greatest systemic effect in terms of magnitude and duration of APPs increase.

Price & Nolan (2001) examined the effect of analgesia on plasma Hp after castration and tail docking by rubber rings in lambs and found that the Hp concentration following the manipulation remained close to the detection limits of the assay, and that they were similar to those recorded in control animals during the study period (48 h). Another study performed by Paull *et al*. (2009) demonstrated that knife-castrated lambs had higher peak of circulating Hp than ring-castrated lambs. According to Abu-Serriah *et al*. (2007) the concentration of Hp in sheep increased significantly one day after experimental maxillofacial surgical procedure, indicating the presence of a significant acute inflammatory response, and returned to pre-surgical concentrations by the 7th day.

The concentrations of plasma APPs were monitored in sheep with pulmonary damage and subsequent surgery (Pfeffer & Rogers, 1989). The authors found significant changes during APR including increased concentration of plasma Cp, Fb and Hp.

CONCLUSION

This review presents data on the acute phase response in small ruminants to various pathological conditions. A large variety of proteins with different reaction patterns have been studied. In general, the most indicative changes were exhibited by blood levels of haptoglobin and serum amyloid A, irrespective of the pathological stimulus. The changes in the other APPs were less noticeable. The presented data convincingly demonstrate that haptoglobin and serum amyloid A are the main components of the acute-phase response in small ruminants. They are more pronounced in bacterial infections, in contrast to parasitic and viral infections. Although the APP response is non-specific, it could be used as an early diagnostic marker, and for prediction of outcome of the disease.

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