



Acute phase proteins in cats

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ABSTRACT: *Acute phase proteins (APP) are proteins synthesized and released largely by hepatocytes upon the occurrence of cell damage or invasion by microorganisms. This article reviews the use of APP in feline diseases, identifying their usefulness in the clinical setting, analyzing 55 published papers. Serum amyloid A, alpha-1 acid glycoprotein, and haptoglobin are the indicators pointed out by the authors as useful in monitoring the acute inflammatory response in cats. Although, APP measurement is still not routinely used in veterinary medicine, together with clinical signs and other blood parameters, was of clinical interest and applicability in diseases such as feline infectious peritonitis, pancreatitis, renal failure, retroviral and Calicivirus infections. Although, there are commercially available kits for dosing feline APP, assay standardization aiming technical simplicity, more species specificity and with less associated costs will allow routine use in feline practice, as it is done in the human field.*

Key words: *inflammation, acute phase proteins, cat.*

Proteínas de fase aguda em gatos

RESUMO: *As proteínas de fase aguda (PFA) são proteínas sintetizadas e libertadas em grande parte por hepatócitos ao mesmo tempo da ocorrência de lesão celular ou invasão por microrganismos. Este artigo revê a utilização das PFA nas doenças do gato identificando a sua potencial utilidade no contexto clínico, analisando 55 artigos publicados. A amiloide sérica A, a alfa-1 glicoproteína ácida e a haptoglobina são os marcadores apontados pelos autores como úteis na monitorização da resposta aguda inflamatória nesta espécie. Embora o doseamento das PFA ainda não seja rotineiramente utilizado na medicina veterinária, o seu doseamento, em conjunto com sinais clínicos e outros meios complementares de diagnóstico, revelou interesse e aplicabilidade clínica em doenças tais como a peritonite infecciosa felina, pancreatite, insuficiência renal, infeções retrovirais e por Calicivírus. Apesar de existirem kits comercialmente disponíveis para dosear as PFA felinas, será necessária uma padronização de ensaios no sentido da melhoria da sua simplicidade técnica, da sua especificidade para o gato e com menores custos associados, para que sejam utilizados de forma rotineira, tal como são utilizados em medicina humana.*

Palavras-chave: *inflamação, proteínas de fase aguda, gato.*

INTRODUCTION

The acute phase response (APR) is an early, non-specific systemic innate immune reaction to local or systemic stimulus, which helps to heal and re-establish homeostasis and minimize tissue damage when the body is affected by trauma, infection, stress, surgery, neoplasia or inflammation (GRUYS et al., 2005; CRAY et al., 2009; ECKERSALL & BELL, 2010). In this reaction we observe several different systemic effects: fever, leukocytosis, hormone shifts—mainly cortisol and thyroxine concentrations, with a secondary catabolic state and muscle protein depletion, serum depletion of iron and zinc, among others (CERÓN et al. 2005, JAVARD et al. 2017).

Under the influence of IL-1 β , TNF- α , and especially IL-6, and about 90 minutes after injury, protein synthesis is increased on hepatocytes, lymph nodes, tonsils, and spleen as well as in blood leukocytes. Those newly produced proteins are called acute phase proteins (APP) (TIZARD, 2013b).

Acute phase proteins

The APP concentrations can increase (positive APP) or decrease (negative APP) (PALTRINIERI et al., 2008) in response to inflammation (JOHNSTON & TOBIAS, 2018). They can activate leukocytosis and the complement, cause protease inhibition, lead to clotting and opsonisation -a defense mechanism that lead to the elimination of infectious agents, tissue repair

and restoration of the healthy state (CRAY et al., 2009). The APP can have two functions, a pro-/and an anti-inflammatory effect, which must be delicately balanced to promote homeostasis (HOCHEPIED et al., 2003).

Three major groups of APP are recognized, based on response magnitude and duration secondary to stimulus (MURATA et al., 2004; PETERSEN et al., 2004; CERÓN et al., 2005). Positive APP can be divided in two groups: the first group, which includes APP with increases of 10 to 1000 times in humans or 10 to 100 times in domestic animals in the presence of inflammation—e.g. C-reactive protein (CRP) and serum amyloid A (SAA); and a second group, which corresponds to APP that increase 2 to 10 times in inflammatory response—e.g. haptoglobin and alpha-globulins. The last group included negative APP, where concentration decreases in response to inflammation—e.g. albumin (KANN et al., 2012).

Positive acute phase proteins

Positive APP are glycoproteins in which serum concentrations increase by 25% upon stimulation by pro inflammatory cytokines during disease process, being released in the blood stream. These concentrations can be measured and used in the diagnosis, prognosis, to monitor treatment response, as well as for general health screening. They also can be considered quantitative biomarkers of disease, highly sensitive to inflammation but poorly specific, since elevation of APP can occur in non-inflammatory diseases as well (CERÓN et al., 2005; ECKERSALL & BELL, 2010).

Positive APP respond differently to cytokines, being these groups divided into two major classes. Type 1 APP, which include AGP, complement component 3, SAA, CRP, haptoglobin and hemopexin, are regulated by IL-1, IL-6 and TNF- α and also by glucocorticoids. Type 2 which includes the three fibrinogen chains (α -, β -, and γ -fibrinogen) and various inhibitory proteases, are regulated by IL-6 and glucocorticoid cytokines (BAUMANN et al., 1990; BAUMANN & GAULDIE, 1994).

In cats, SAA or alpha-1-acid glycoprotein (AGP) are the most relevant APP. Blood SAA levels can indicate inflammatory conditions such as feline infectious peritonitis (FIP) and other infectious diseases such as caliciviral infection, chlamydiosis, leukemia, and infectious immunodeficiency since it increases by 10- to 50-fold (TIZARD, 2013b). The SAA can also be elevated in other diseases like diabetes mellitus and cancer. Haptoglobin usually

increases 2- to 10-fold and is especially high in FIP (TIZARD, 2013b). Table 1 summarizes each positive APP in the context of feline disease.

Negative Acute Phase Proteins

Albumin is the most relevant negative APP, with blood concentration decreasing during APR, due to amino acid deviation towards the synthesis of positive APP (CRAY et al., 2009; PALTRINIERI, 2007a). Other negative APP are transferrin, transthyretin, retinol ligand and cortisol binding protein, proteins involved in vitamin and hormone transport (JAIN et al., 2011).

Acute phase proteins in feline disease

Unlike cytokines, which have a small size and are rapidly filtered by the kidney, the acute phase proteins have a higher molecular weight (greater than 45kDa), and subsequently a longer permanence in the plasma (SALGADO et al., 2011).

The APP levels can only assess inflammation and consequently their concentrations can assist in diagnosis and disease monitoring. APP can help to detect subclinical inflammation, differentiate acute from chronic disease and to predict its course (VILHENA et al., 2018; JAVARD et al., 2017). Since the APR begins before specific immunological changes occur, it can be used as an early marker for disease, before leucogram changes take place, being its magnitude related with the severity of disease (PETERSEN et al., 2004; CERÓN et al., 2005; VILHENA et al., 2018). For this reason, disease monitoring can be considered as one of the most interesting and promising applications of APP.

APP levels, together with clinical signs and blood tests have been evaluated in different animal diseases (i.e. FIP, canine inflammatory bowel disease, leishmaniasis, ehrlichiosis and canine pyometra), and proved to be useful in the diagnosis, treatment response monitoring and prognosis (ECKERSALL et al., 2001; MARTINEZ-SUBIELA et al., 2005; SHIMADA et al., 2002; JERGENS et al., 2003; GIORDANO et al., 2004; PETERSEN et al., 2004; DABROWSKI et al., 2009; VILHENA et al., 2018).

To obtain a complete information about APR, one major and one moderate positive, as well one negative APP should be done simultaneously (CERÓN et al., 2008). High concentrations of major APP are usually related with infectious diseases, usually a systemic bacterial infection or an immune-mediated disease (CERÓN et al., 2008; TROÏA et

Table 1 – Acute phase proteins studied in the context feline diseases.

APP	Diseases	References
	FIP	DUTHIE et al., 1997; GIORDANO et al., 2004; HAZUCHOVA et al. 2017;
	Induced inflammation and surgery	KAJIKAWA et al., 1999;
SAA	Various diseases (Pancreatitis, Renal failure, FLUTD, Tumors, Diabetes mellitus; renal disease, injury, etc.)	SASAKI et al., 2003; KANN et al., 2012; TAMAMOTO et al., 2013; TAMAMOTO et al., 2013; JAVARD et al., 2017;
	Sepsis	TRÓIA et al., 2017;
	FeLV; Hemotropicmycoplasmas infections	VILHENA et al., 2018;
	Infection by Hepatozoonfelis and Babesia vogeli	VILHENA et al., 2017;
	Dirofilariaimmitis	SILVESTRE-FERREIRA et al., 2017;
	FIV cats treated with recombinant feline interferon	LEAL et al., 2014;
	Infection by <i>Chlamydomphila psittaci</i> ;	TERWEE et al., 1998;
	Pancreatitis and pancreatic tumors	MEACHEM et al., 2015;
AGP	Feline infectious peritonitis	DUTHIE et al., 1997; CECILIANI, et al., 2004; GIORDANO et al., 2004; BENCE et al., 2005; PALTRINIERI et al., 2007b; GIORI et al., 2011; HAZUCHOVA et al., 2017;
	Lymphoma and other tumors	SELTING et al., 2000; CORREA et al., 2001; WINKEL et al. 2015;
	Induced inflammation and surgery	KAJIKAWA et al., 1999;
	FIV cats treated with recombinant feline interferon	LEAL et al., 2014
	Abscesses, pyothorax, Fat necrosis	OTTENJANN et al., 2006;
	Various diseases (FLUTD, Tumors, Diabetes mellitus; renal disease, injury, etc.)	KANN et al., 2012;
	Feline infectious peritonitis	DUTHIE et al., 1997; GIORDANO et al., 2004; HAZUCHOVA, K. et al. 2017;
	Induced inflammation and surgery	KAJIKAWA, T. et al. 1999
Haptoglobin	Abscesses, Pyothorax, Fat necrosis,	OTTENJANN et al., 2006;
	Various diseases (FLUTD, Tumors, Diabetes mellitus; renal disease, injury, etc)	KANN et al. 2012
	Infection by Hepatozoonfelis and Babesia vogeli	VILHENA et al., 2017;
	FeLV, Hemotropicmycoplasmas	VILHENA et al., 2018;
CRP	Dirofilariaimmitis	SILVESTRE-FERREIRA et al. 2017;
	FIV cats treated with recombinant feline interferon	LEAL et al., 2014
	Induced inflammation and surgery	KAJIKAWA et al., 1999;

Legend: Serum Amyloid A (SAA), α 1-Acid Glycoprotein (AGP), Systemic Inflammatory Response Syndrome (SIRS) Feline Lower Urinary Tract Disease (FLUTD), Feline Infectious Peritonitis (FIP), Feline Leukemia Virus (FeLV), Feline Immunodeficiency Virus (FIV); Feline Calicivirus (FCV).

al., 2017). Even though APP should be analyzed together with white blood cell and neutrophil counts, they are the most sensitive in detecting inflammation and infection earliest in time (CERÓN et al., 2008; ALVES et al., 2010). However, the specificity of these proteins is low in detecting the cause of the process, being also increased in physiological states, such as pregnancy (PALTRINIERI et al., 2008).

Figure 1 illustrates the expected behavior of positive acute phase proteins based of the studies revised. The AGP, SAA and haptoglobin were pointed as useful indicators for monitoring the acute inflammatory response in cats (WINKEL et al., 2015; PALTRINIERI et al., 2007a,b; KAJIKAWA et al.,

1999). The APP in cats were firstly identified after comparative serum measurements in clinically normal and diseased animals, in experimentally induced inflammation studies, and in post-operative studies (KAJIKAWA et al., 1999). The SAA concentration was reported to be the first to increase, with AGP and haptoglobin increasing thereafter, opposing to a less significant increase of CRP (KAJIKAWA et al., 1999). One study showed that CPR behaves similarly to SAA and AGP in feline inflammation (LEAL et al., 2014).

Serum amyloid a

The SAA is one of the major APP in several species, important in both Humans and

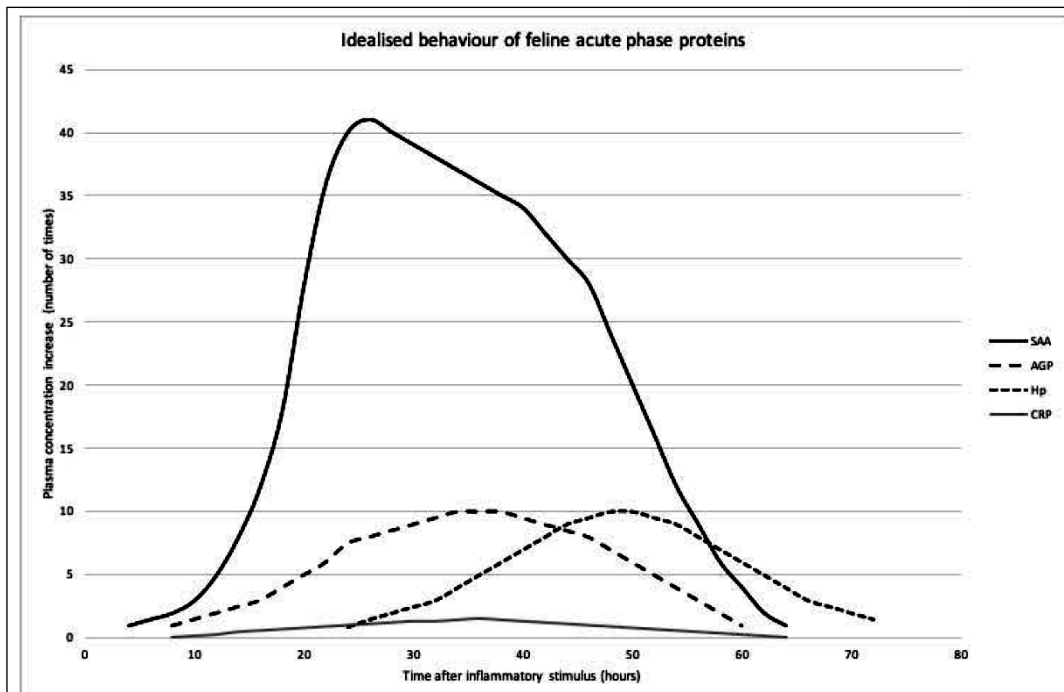


Figure 1 - Idealized behavior of acute phase proteins in the cat after an inflammatory stimulus. The values depicting the changes cannot be taken as absolute. Serum Amyloid A (SAA) increase 3 to 6 h after the stimulus, peak at 21 to 24 h, magnitude at peak 10 to 50 times its basal plasma concentration. α 1 acid-glycoprotein (AGP) increase 8 h after the stimulus, peak at 36 h, magnitude at peak 2 to 10 times its basal plasma concentration. Haptoglobin (Hp) increase 24 h after the stimulus, peak at 36 to 48 h, magnitude at peak 2 to 10 times its basal plasma concentration value. C-Reactive protein (CRP) increase 8 h after the stimulus, peak at 36 h, magnitude at peak 1.5 times its basal values.

cats (KAJIKAWA et al., 1999). Modulates the immune response by attracting inflammatory cells to tissues and leading to the production of multiple inflammatory cytokines (GRUYS et al., 2005; TIZARD, 2013a). Its concentration may rise more than 1,000-fold in inflammatory status, consequently perceiving inflammation (TAMAMOTO et al., 2013). Such increase; however, is also seen in non-inflammatory diseases in inflammatory diseases and in neoplasia (TAMAMOTO et al., 2013). According to a study performed in cats undergoing surgery, SAA concentration begins to increase at approximately 3 to 6 hours, achieving the highest value 21 to 24 hours postoperatively (SASAKI et al., 2003).

Alpha 1-acid glycoprotein

Alpha 1-acid glycoprotein (AGP) is an acute phase reactant protein reported in the seromucoid portion of the serum (SELTING et al., 2000; WINKEL et al., 2015). As most positive APP, AGP is a glycoprotein synthesized mostly

by hepatocytes upon APR and released into the bloodstream (CÉRON et al., 2005).

AGP can be used to monitor early interferon treatment in cats infected with Feline immunodeficiency virus (FIV) (GIL et al., 2014). AGP, as well as haptoglobin (Hp) is increased in anemic cats suffering from pyothorax, abscesses or fat necrosis (OTTENJANN et al., 2006).

AGP changes in feline neoplasia seems to be inconsistent among studies. Some describe no changes in cats bearing lymphoma (CORREA et al., 2001). On the contrary, others show increase of both AGP or SAA in cats with sarcomas, carcinomas or other round cell tumors (SELTING et al., 2000; TAMAMOTO et al., 2013; MEACHEN et al., 2015; HAZUCHOVA et al., 2017).

The AGP has been important as an indicator test for FIP, specially used in Europe (CECILIANI et al., 2004).GIORI et al. (2011) studied the specificity and sensitivity of several tests in 12 cats, where 33.33% were FIP negative

by histopathology and immunohistochemistry, and 66.66% of the cats were FIP positive confirmed by histopathology and immunohistochemistry. This author concluded that immunohistochemistry must always be performed to confirm FIP, but high concentrations of AGP may help to support the diagnosis of FIP in case where immunohistochemistry is not possible to perform, and histopathology is not conclusive.

Haptoglobin

Haptoglobin (Hp) is one of the most important acute-phase proteins in cattle, sheep, goat, horses and cats (TIZARD, 2013a), synthesized mostly by hepatocytes but also by other tissues, like skin, lung and kidney (JAIN et al, 2011). The Hp binds to iron molecules and makes them unavailable to invade bacteria, consequently inhibiting bacterial proliferation and invasion. Consequently it also binds to free hemoglobin, preventing its oxidation with lipids and proteins (TIZARD, 2013a), justifying the reduction of Hp in case of hemolysis.

In cats, Hp usually increases 2- to 10-fold in inflammatory conditions, being especially high in FIP (TIZARD, 2013a). However, both Hp and SAA did not provide enough support to differentiate between FIP and other causes of effusion, compared with AGP (HAZUCHOVA et al., 2017).

App measurement

The serum is composed by a large number of individual proteins, in which detecting changes in its fractions can provide important diagnostic information (ECKERSALL, 2008).

Ideally, measurement of all serum proteins should be available to be used as a diagnostic tool in the context of inflammatory diseases.

Nowadays, APP (Table 2) can be determined using Enzyme-Linked Immunosorbent Assay (ELISA), radioimmunoassay, nephelometry, immunoturbidimetry (IT), Western blot, and messenger ribonucleic acid (mRNA) analysis (CÉRON et al., 2005; PALTRINIERI et al., 2008; SCHREIBER et. al, 1989). Although, some APP assays for Humans have been automated also for veterinary medicine, species-specific tests are still limited. Interspecies APP variations and the limited availability of cross-reactive reagents have contributed, for now, to a low routine determination of APP in veterinary labs, especially for cats. Regardless, technology is evolving, and it is possible to foresee in the near future routine monitoring of the clinically relevant APP in cats.

CONCLUSION

Acute phase proteins in cats are useful biomarkers to monitor inflammation, together with other clinical and laboratory findings, being useful in diagnosing subclinical changes, monitoring the evolution and the effect of a disease in the organism, as well as evaluate treatment response.

In the cat, SAA is the APP expressing the highest magnitude in response to inflammation, followed by AGP and haptoglobin, contrarily to CRP as observed in other species.

Although, there are commercially available kits for dosing feline APPs, assay standardization aiming technical simplicity, more

Table 2 – Advantages and disadvantages of possible techniques in measuring APP.

Analyses	Advantages	Disadvantages	References
Radioimmunoassay		24 to 48 hours to get results, specific skills from the operator	WHICHER et al., 1983
ELISA	Commercially available kits, species specific	Lack automation, expensive, some imprecision between-run	JACOBSEN et al. 2006 TECLES et al. 2007 MARTÍNEZ-SUBIELA, S. et al. 2005
Immunoturbidimetry	30 minutes to get results, adaptable to biochemical analyzers		WHICHER et al., 2003, KURIBAYASHI et al., 2003 BENCE et al. 2005
Western Blot		Long period to process immunoblots	CALLAHAN & YATES 2014
Nephelometric immunoassays		Depend on cross-reactivity of antiserum raised	WEIDMEYER & SOLTER, 1996

species specificity with less associated costs will allow routine use in feline practice, as it done in human medicine.

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DECLARATION OF CONFLICT OF INTERESTS

The authors declare no conflict of interest. The founding sponsors had no role in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results.

AUTHORS' CONTRIBUTIONS

The authors contributed equally to the manuscript.

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