

## Acute-Phase Proteins: The Biological Language of Inflammation

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### Abstract

Acute-phase proteins (APPs) are important components of the systemic inflammatory response and valuable biochemical indicators of inflammation in animals. Their synthesis is regulated mainly by cytokines particularly interleukin-6, interleukin-1 and tumour necrosis factor- $\alpha$ . Positive APPs including C-reactive protein, serum amyloid A, haptoglobin and fibrinogen increase during inflammation whereas negative APPs such as albumin and transferrin generally decrease. Beyond their diagnostic value APPs contribute to host defence, immune regulation, coagulation, iron metabolism and oxidative homeostasis. Their veterinary applications include inflammatory disease monitoring, treatment assessment, prognosis and detection of subclinical inflammation. Emerging biomarker panels, omics and artificial intelligence may enhance precision diagnostics.

**Keywords:** Acute-phase proteins, inflammation, C-reactive protein, serum amyloid A, haptoglobin, biomarkers, oxidative stress.

### Introduction

Acute-phase proteins (APPs) are a group of plasma proteins whose concentrations change markedly in response to inflammation, infection, tissue injury, trauma, stress and other physiological disturbances. They constitute an important component of the body's innate immune response and help restore and maintain homeostasis during inflammatory conditions. Inflammation may produce classical signs such as heat, redness, swelling, pain and loss of function but many inflammatory changes occur at molecular and systemic levels without obvious clinical manifestations. A major systemic response is the acute-phase response, characterized by altered concentrations of acute-phase proteins (APPs).

### Acute-Phase Response

Most APPs are synthesized predominantly by hepatocytes following stimulation by inflammatory cytokines particularly IL-6, IL-1 and TNF- $\alpha$ .

Recognition of pathogens or tissue damage activates macrophages and other immune cells which release these cytokines. The resulting hepatic response alters the synthesis of plasma proteins.

### APPs are broadly classified into:

- Positive APPs: concentrations increase during inflammation.
- Negative APPs: concentrations decrease during inflammation.

The magnitude and rate of change differ considerably among proteins and animal species. Therefore, species-specific characteristics are particularly important when interpreting APP concentrations in veterinary medicine.

### Hepatic Regulation

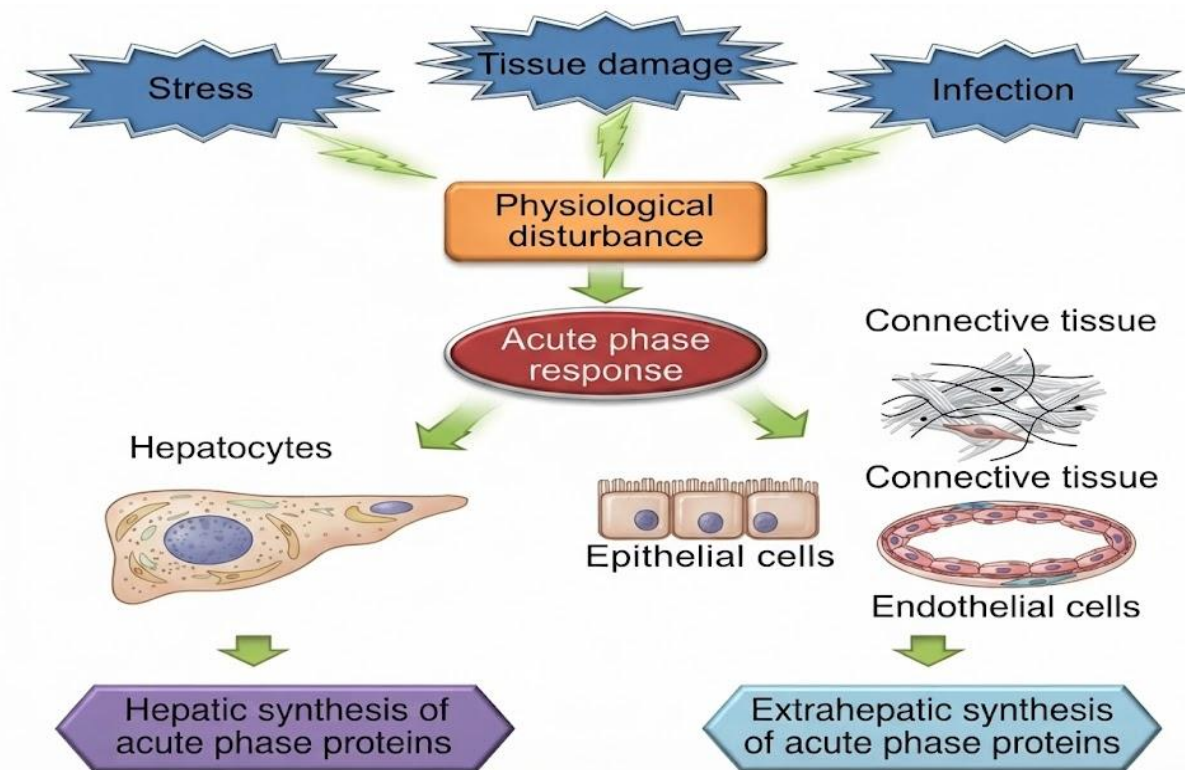
The liver acts as a major effector organ of the acute-phase response. Cytokine stimulation increases the synthesis of proteins such as C-reactive protein (CRP), serum amyloid A (SAA), haptoglobin, fibrinogen and complement components. At the same time, synthesis of proteins such as albumin,

transferrin and transthyretin may decline.

This redistribution of hepatic protein synthesis represents a physiological adaptation in which metabolic resources are directed toward host defence and restoration of homeostasis.

**Pathological stimulus → innate immune activation → cytokine release → hepatic response → altered plasma proteins → systemic inflammatory response**

Serum amyloid A (SAA) is a highly responsive positive APP that can increase substantially during inflammatory conditions. It is involved in innate immunity, lipid metabolism and inflammatory regulation and has applications in the monitoring of inflammatory disorders in companion animals and livestock. Persistent elevation of SAA is clinically important because prolonged inflammatory stimulation can contribute to amyloidosis in which amyloid derived from SAA accumulates in tissues



### Major Positive Acute-Phase Proteins C-Reactive Protein

C-reactive protein (CRP) is one of the best-characterized positive APPs. It participates in innate immunity by recognizing structures associated with damaged cells and microorganisms and interacting with the complement system. CRP concentrations can increase rapidly during inflammation, making CRP particularly useful for detecting and monitoring systemic inflammatory activity. Canine CRP has received considerable attention in veterinary medicine because of its responsiveness to inflammatory stimuli. However, CRP is not disease-specific. Increased concentrations can occur with infection, trauma, surgery, tissue injury, immune-mediated disease and neoplasia. Therefore, CRP should be interpreted as an indicator of inflammatory activity rather than as a definitive diagnostic marker.

### Serum Amyloid A

and may impair organ function.

### Haptoglobin

Haptoglobin binds free haemoglobin released during erythrocyte destruction. By facilitating its removal from circulation, haptoglobin helps limit the pro-oxidant effects of free haemoglobin. Its biological function therefore links the acute-phase response with haemoglobin metabolism, iron homeostasis and oxidative stress making it both a functional protein and a useful inflammatory biomarker.

### Fibrinogen

Fibrinogen connects inflammation with coagulation. Its concentration generally increases during inflammatory conditions and contributes to the body's response to tissue injury. Increased fibrinogen can enhance erythrocyte aggregation and influence the erythrocyte sedimentation rate. It has consequently been used as an inflammatory indicator, particularly in large-

animal veterinary practice.

### Negative Acute-Phase Proteins

Important negative APPs include albumin, transferrin and transthyretin. Albumin is the major plasma protein and plays essential roles in maintaining colloid osmotic pressure and transporting numerous substances. During systemic inflammation, hepatic albumin synthesis may decrease as protein production is redirected toward positive APPs. However, hypoalbuminemia is not specific for inflammation. It may also result from altered nutritional status, hydration, hepatic dysfunction, gastrointestinal or renal protein loss and other pathological conditions. Therefore, albumin should always be interpreted in a broader clinical context.

### APPs as Functional Components of Inflammation

APPs perform diverse biological functions beyond serving as biomarkers. These include:

- Recognition of pathogens and damaged cells
- Regulation of innate and adaptive immunity
- Complement activation and regulation
- Transport and sequestration of biologically important molecules
- Regulation of haemoglobin and iron availability
- Participation in coagulation
- Modulation of oxidative processes
- Protection of tissues and restoration of homeostasis.

Thus, the acute-phase response represents an integrated interaction between the immune, hepatic, haematological, metabolic, coagulation and antioxidant systems.

### APPs and Oxidative Stress

Inflammation and oxidative stress are closely interconnected. Activated immune cells generate reactive oxygen and nitrogen species for antimicrobial defence but excessive production can damage lipids, proteins and nucleic acids. Conversely, oxidative stress can stimulate inflammatory signalling and creating a cycle of inflammation and oxidative injury. Haptoglobin helps limit this damage by binding free haemoglobin and reducing haem-associated oxidative effects. This interaction is particularly relevant in chronic inflammatory, infectious, metabolic and degenerative diseases.

### Acute and Chronic Inflammation

Although the term acute-phase response is commonly associated with acute inflammation. APPs concentrations can remain altered during chronic inflammatory conditions. Persistent inflammation may contribute to metabolic disturbances, oxidative imbalance and tissue dysfunction.

Consequently, serial measurement can sometimes provide more useful information than a single determination. A single APP measurement provides a snapshot of inflammatory status whereas repeated measurements reveal the trajectory of the response.

A declining APPs concentration may support resolution of inflammation while persistent or increasing concentrations may suggest continuing inflammatory stimulation or complications. Such interpretation should always be combined with clinical findings.

### Clinical Importance in Veterinary Diagnostics

**APPs are valuable tools in veterinary clinical biochemistry for:**

- Detecting systemic and subclinical inflammation
- Assessing disease severity and progression
- Monitoring treatment response
- Supporting prognosis and postoperative monitoring
- Evaluating resolution or persistence of inflammation.

However, APP responses vary among animal species. Therefore, species-specific reference intervals and appropriate clinical interpretation are essential.

### Recent Developments

Veterinary APP research is increasingly shifting from individual biomarkers toward multimarker approaches. Combining CRP or SAA with haptoglobin, fibrinogen, haematological, metabolic or oxidative-stress markers may provide a broader assessment of inflammatory status.

Advances in proteomics, metabolomics, automated assays and artificial intelligence (AI) are enabling identification of complex biomarker patterns. These developments may improve disease detection and support precision veterinary medicine by integrating species, disease stage and treatment-response information.

### Conclusion

Acute-phase proteins are important biomarkers and functional components of the inflammatory response in animals. Their measurement supports the detection, monitoring and prognostic assessment of inflammatory diseases. Species-specific interpretation and serial measurements can improve their diagnostic and clinical value. Future integration with omics, multiplex biomarkers and AI may strengthen precision veterinary diagnostics.