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The Biochemistry, Functions, And Clinical Importance Acute Phase Proteins: A Review

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Abstract

Acute phase proteins (APPs) are a heterogeneous group of plasma proteins whose concentrations change markedly in response to inflammation, infection, tissue injury, and metabolic stress. Synthesized predominantly by the liver under the regulation of pro-inflammatory cytokines, APPs exhibit diverse biochemical structures and functions that extend beyond their traditional role as nonspecific inflammatory markers. They actively participate in innate immune defense, modulation of oxidative stress, regulation of protease activity, lipid and metal metabolism, and maintenance of tissue homeostasis. Key APPs—including C-reactive protein, serum amyloid A, haptoglobin, α1-antitrypsin, and ceruloplasmin—demonstrate distinct physiological roles and clinically relevant response kinetics that reflect underlying disease processes. Aberrant or persistent alterations in APP levels are implicated in the pathogenesis of chronic inflammatory disorders, cardiovascular disease, metabolic syndromes, infectious diseases, and organ dysfunction. Clinically, APPs remain indispensable tools for disease diagnosis, activity assessment, and prognostic evaluation, although limitations related to specificity and biological variability persist. This review synthesizes current advances in the biochemistry, physiological functions, and clinical significance of major acute phase proteins, emphasizing their evolving translational relevance in modern laboratory and clinical medicine.

Keywords: Acute Phase Proteins, CRP, SAA, fibrinogen, haptoglobin, α1-acid, ceruloplasmin

Introduction

The acute phase response (APR) is a key feature of the innate immune system, which consists of an immediate and coordinated systemic response to infection, tissue damage, neoplasia and other types of inflammation. A hallmark of this response is the modification of hepatic production of a set of plasma proteins known as acute phase proteins (APPs). These proteins undergo a significant increase or decrease in their concentration within the serum, following stimulation of inflammation

which is mainly induced by cytokines (IL-6, IL-1β and TNF-α) (Ceciliani et al., 2002).

APPS are a heterogenous group of molecules with unique biochemical identity and biologic functions, among which C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen, haptoglobin, α1-acid glycoprotein and ceruloplasmin. Once considered nonspecific markers of inflammation, APPs are now considered as active players in host defense. They are involved in the recognition and clearance of pathogens, activation of complement, modulation immune cell trafficking, control oxidative stress and tissue homeostasis. This functional diversity reinforces their relevance in addition to being useful as diagnostic aids, placing APPs at the core of inflammatory biology (Sproston & Ashworth, 2018).

In this review, we briefly summarize the historical development of APPs and provide an overview of recent progresses in the studies on molecular regulation and clinical significance of APPs published from 2015 to the present. IL-6-dependent activation of the JAK/STAT route has been recognized as the master regulator of hepatic APP gene expression, which can be synergistically or antagonistically modulated by other cytokines and hormonal factors (Schmidt-Arras & Rose-John, 2016). Furthermore, APP function is influenced by its post-translational modifications, particularly glycosylation, which are known to play key roles in modulating protein stability, receptor binding and immunomodulatory potential. These subtle biochemical differences emphasise the importance of taking into account qualitative, and not simply quantitative, changes in APP during disease (Reily et al., 2019).

In the clinical setting, APPs are still considered one of most commonly used laboratory biomarkers. High-sensitivity CRP (hs-CRP) is widely used to represent cardiovascular risk and evaluate chronic low-grade inflammation, SAA has also been studied as sensitive marker of infection severity and mortality, especially in sepsis and viral disease (Sproston & Ashworth, 2018). The COVID-19 pandemic highlighted the prognostic relevance of APPs, expressed by numerous reports of highly increased CRP and SAA levels that invariably correlated with disease severity, cytokine storm and unfavorable outcome. Read The study results further underpin the value of APPs in clinical decision making and patient selection (Liu et al., 2020).

Notwithstanding their general use, important concerns about the interpretation of APP measurements persist. Their nondisease-specificity, interindividual variability and sensitivity to comorbidities require cautious interpretation in relation to clinical data and to the presence of other biomarkers. In this context, growing interest in the multimarker strategy and combined inflammatory biomarkers APP ratios has been reported from current studies, but also longitudinal over individual measures for improved diagnostic and prognostic accuracy (Stanke et al., 2023).

Since our understanding of the biochemical diversity and functional pleiotropy of APPs increases it is an appropriate time to review these factors. The aim of this article is to review post-2015 evidence in biochemistry, physiology and clinical relevance of the acute phase proteins and to highlight novel molecular aspects with translational significance. Novel and known inflammatory markers that may contribute to stroke risk, burden or outcome are presented along with the potential of an improved understanding of APP biology for their rational use and enablement of pinpointing new inflammatory biomarkers in inflammation research.

Physiology and Clinical Significance of C-Reactive Protein

C-reactive protein (CRP) is one of the most commonly included APPs and remains as a cornerstone marker of inflammation in both clinical and research practice. It is a highly conserved, pentameric protein of the pentraxin family, primarily produced by hepatocytes following an inflammatory stimulus. CRP is normally present in blood at trace concentrations (< 1 mg/L), but levels can rise rapidly, up to 1000-fold within 24–48 h after infection, tissue damage or inflammatory stressor (Sproston & Ashworth, 2018).

Hepatic production of CRP is predominantly controlled by IL-6, acting in synergy with interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α). These cytokines trigger intracellular signal transduction pathways, in particular JAK/STAT3 pathway that induces transcriptional activation of the CRP gene (Schmidt-Arras & Rose-John, 2016). After release into the blood CRP has a relatively short half-life of 19 hours which is independent from the disease condition: accordingly serum CRP levels mainly reflect synthesis rather than clearance (Pepys & Hirschfield, 2003).

Functionally, CRP is a part of the innate immunity. It recognizes phosphocholine moieties exposed on the surface of pathogens, apoptotic cells and damaged host membranes in a calcium dependent fashion. Such binding allows opsonization and clearance by the classical complement pathway (via C1q) and interaction with Fcγ receptors on phagocytes. By these means CRP participates in host defense and modulates overactive inflammation by promoting clearance of necrotic material (Sproston & Ashworth, 2018).

Recent data demonstrate that some structural and functional heterogeinity exists with respect to CRP. Native pCRP can be disassembled into mCRP at inflamed locations, which possesses different and often stronger pro-inflammatory attributes such as endothelial activation and leucocyte tethering. This structural plasticity indicates that CRP is not a passive inflammatory marker but an active mediator whose actions are determined by its molecular form and local environment (Thiele et al., 2015).

In clinical use, C-protein is an established sensitive but nonspecific indicator of inflammation. Its fast kinetics render it of special interest for the diagnosis of acute infection, disease progression, and therapeutic evaluation. CRP levels are higher and elevate faster in bacterial compared to viral infections which may facilitate differential diagnosis and antibiotic stewardship when interpreted with clinic information (Sproston & Ashworth, 2018).

High-sensitivity CRP (hs-CRP) measurements now have broadened the use of CRP beyond acute inflammation to chronic, low-grade inflammation. Several prospective studies have reported that hs-CRP levels predict CV risk independent of other established CHD risk factors also in apparently healthy people. CRP is thus included in cardiovascular risk prediction algorithms, representing the contribution of inflammation to atherogenesis (Ridker, 2016).

Not only in autoimmune but also in inflammatory diseases (Rheumatoid arthritis, Inflammatory bowel disease and Vasculitis), it acts as an objective parameter to measure disease activity and treatment response. Nevertheless, the substantial personal variation in CRP responsiveness (reflecting genetic factors, cytokine composition and immune-modifying therapies) means that it is vital to interpret this information carefully, particularly when inflammation may be present even if CRP levels are normal (Pepys & Hirschfield, 2003).

Moreover, CRP has also been further highlighted in the prognosis of critically ill and newly emerging infectious diseases. During the COVID-19 outbreak, high CRP levels were consistently associated with the severity of illness, respiratory failure, and death indicating extreme systemic inflammation and cytokine disarray These results further support the appropriateness of CRP as an easily available risk stratification tool in acute health care facilities (Liu et al., 2020)..

Physiology and Clinical Significance of Haptoglobin

Haptoglobin (Hp) is a major positive acute phase protein having several functions in hemoglobin scavenging, antioxidant defence and immune modulation. It is a glycoprotein mainly produced by hepatocytes with observed expression in adipose tissue, lung and immune cells. Physiologically, sHPT concentrations are 0.3e2 g/L but increase greatly during inflammation, infection, trauma and malignancies, consistent with the categorization of haptoglobin as an acute phase reactant (Ceciliani et al., 2002).

The major biological role of haptoglobin is to bind the free hemoglobin (Hb) that is released into the bloodstream during intravascular hemolysis. Free Hb is a strong pro-oxidant that induces the generation of reactive oxygen species and causes endothelial dysfunction and tissue damage. Haptoglobin prevents iron-induced oxidative damage and ensures that iron-loaded Hb is cleared safely through the macrophage CD163 scavenger receptor, by stable formation of Hp–Hb complexes (Schaer et al., 2013).

The Hp–Hb complex is endocytosed by CD163+ macrophages and induces heme degradation via the transcript of the heme oxygenase-1 (HO-1). This pathway not only drives iron recycling but also has anti-inflammatory and cytoprotective effects by generating carbon monoxide and biliverdin. It is in this context that haptoglobin centrally operates at the crossroads of redox biology, iron and immune regulation (Schaer et al., 2013).

The expression of haptoglobin is enhanced predominantly by IL-6, and also stimulated by IL-1β and glucocorticoids through JAK/STAT and MAPK signaling. Structural and functional variation in antioxidant capacity and hemoglobin-binding affinity between

haptoglobins Hp1, Hp2-1 is imposed by genetic polymorphism within the haptoglobin gene (Hp, with 1 allele and 2 alleles); these engender three principal phenotypes of the protein species: Hp 2-2; wait shout! must be reflecting "bonded multinuclear complexes"? or maybe... oh yeah will find out soon so assist may do sound complex but there are easy tests nowadays). These polymorphisms carry important consequences for disease risk and biomarker interpretation (Langlois & Delanghe, 1996).

Haptoglobin is clinically used as a diagnostic marker for intravascular hemolysis. Free haptoglobin is quickly neutralized by free hemoglobin in case of hemolytic anemias, where serum concentrations are greatly decreased and may be undetectable. Haptoglobin, along with lactate dehydrogenase (LDH), indirect bilirubin and reticulocyte count are essential for the laboratory diagnosis of hemolysis; (Stanke et al., 2023).

As an acute phase reactant, the concentrations of haptoglobin rise in inflammation and infection such as bacterial infection, immune diseases and carcinoma. Nevertheless, this paradoxical variation—namamicronegatively with hemolyses and mega-positively during inflammation—should be interpreted cautiously in the clinical setting when a patient also has both processes. A high level of haptoglobin is also associated with persistent iron sequestration, in chronic inflammatory diseases and may be involved in the aggravation of anemia of inflammation (Ceciliani et al., 2002).

There is also emerging evidence pointing at haptoglobin's role in cardiac metabolic disorders. Hp genotype is known to be associated with cardiovascular risk, especially in diabetics. Hp2-2 subjects have decreased antioxidant protection against Hb-driven oxidative stress and ultimately increased risk for atherosclerotic complications, indicating that Hp polymorphisms have demonstrable clinical relevance beyond that associated with traditional biomarkers (Levy et al., 2010).

Increased haptoglobin levels in infectious and critical illness have been shown to be related with severity of disease and prognosis. In sepsis, haptoglobin helps to contain haemoglobin mediated oxidative injury and regulate macrophage activity, with low levels suggesting extensive hemolysis or poor hepatic function. Recently published studies have suggested that haptoglobin could be a member of multi-marker panels to enhance risk stratification and prediction of outcome in patients with critical illness (Stanke et al., 2023).

Physiology and Clinical Significance of α1- Antitrypsin

α1- Antitrypsin (AAT) is one of predominant circulating serine protease inhibitor and key positive acute phase protein that mediates critical role in protection of tissue from proteolytic damage during inflammation. It is a 52-kDa glycoprotein that is the product of the SERPINA1 gene and a member of the serpin superfamily. AAT is mainly synthesized in hepatocytes, however extrahepatic synthesis occurs by monocytes, macrophages, neutrophils and pulmonary epithelial cells especially under inflammatory situations (Greene et al., 2016).

Immunomodulating properties AAT's primary modulatory function is the inhibition of neutrophil elastase and other serine proteases such as proteinase-3 and cathepsin G. In an acute inflammatory response, activated neutrophils release these proteases to help break down pathogens and damaged tissue. Uninhibited protease activity can, however, also cause substantial host tissue damage, in particular in the lung. AAT inhibits these enzymes by irreversibly binding to form an enzyme–antienzyme complex and is essential for the protease-antiprotease balance that allows tissue integrity (Sandhaus et al., 2016).

AAT is a moderate acute phase reactant, its serum levels are elevated two- to four-fold during inflammation. Its hepatic production is mainly controlled by interleukin-6 (IL-6), which partially interacts with the effects of interleukin-1β and tumor necrosis factor-α, through JAK/STAT and NF-KB signal transduction pathways. In addition to protease inhibition, AAT has anti-inflammatory and immunomodulatory functions that include suppression of pro-inflammatory cytokine release, reduction in neutrophil chemotaxis and protection from apoptosis in endothelial and epithelial cells (Janciauskiene et al., 2018).

Novel non-enzymatic activities of AAT were also reported recently. It can regulate adaptive immune response, induce macrophage polarization towards anti-inflammatory phenotype and display antimicrobial activity not related to enzymes inhibitory effects. These results have broadened the potential paradigm of AAT as not only a passive antiprotease but also as an active

mediator for regulation of immune homeostasis (Janciauskiene et al., 2018).

Clinically, AAT is most commonly associated with its deficient state which represents a frequent inherited condition with decreased circulating levels or defective protein. α1-Antitrypsin deficiency (AATD) arises from mutant SERPINA1 alleles, particularly PiZZ variant, causing misfolding of the protein, intracellular retention in hepatocytes and decreased plasma concentrations. AATD is highly related to early-onset pulmonary emphysema and chronic obstructive pulmonary disease (COPD) as well as liver disease caused by hepatocellular injury (Sandhaus et al., 2016).

Serum AAT measurement forms part of diagnostic pathways for unexplained COPD, bronchiectasis and chronic liver disease. Because AAT is an acute phase protein, inflammatory conditions can produce a transient rise in serum levels that obscures underlying deficiency, and suspected cases require genotypic or phenotypic validation (Greene et al., 2016).

Apart from genetic deficiency, increased levels of AAT can also be recorded in acute and chronic inflammatory responses as that occurring during infections, autoimmune diseases, neoplasia and trauma. Elevated serum AAT is a marker of acute phase response activation and may limit protease mediated tissue damage. Elevated AAT levels in sepsis or acute lung injury are linked with inhibition of neutrophil-mediated damage and better outcome, implicating a protective function for AAT during systemic inflammation (Janciauskiene et al., 2018).

Purified plasma-derived AAT is approved for augmentation therapy in severely deficient patients with proven emphysema. Similarly, newer investigations have begun examining AAT as a therapeutic intervention for inflammatory and immune-mediated disorders such as graft-versus-host disease, type I diabetes and toxic viral infections, given its wide-ranging anti-inflammatory activity (Sandhaus et al., 2016).

Physiology and Clinical Significance of Serum amyloid A

Serum amyloid A (SAA) apolipoproteins are a family of evolutionarily conserved proteins and constitute major positive acute phase reactants in man. The major acute phase isomers are SAA1 and SAA2 after which family members were classified, the expression of both encoded in liver cells being stimulated by inflammatory signals. At physiological conditions the concentration of SAA in circulation is low (< 10 mg/L), while during acute inflammatory state its serum level can raise over 1000-fold within 24–48 h and may exceed several fold the increase observed with other acute phase proteins like CRP (Sack, 2018).

The expression of acute phase SAA is strictly controlled by pro-inflammatory cytokines, especially IL-6, IL-1β and TNF-α. These cytokines trigger intracellular signaling pathways like JAK/STAT and NF-κB, which in turn prompts quick transcriptional induction of the SAA genes in hepatocytes. Extrahepatic synthesised SAA has also been reported in macrophages, adipocytes, endothelial cells and synovial fibroblasts indicating its role in local inflammatory responses (Eklund et al., 2012).

Functionally, SAA is intimately related to lipid metabolism. In the acute phase response, SAA is the major apolipoprotein of HDL, which replaces A-I and in so doing changes structure and function. This remodelling induces reverse cholesterol transport from inflammatory sites and immune cells regulation (Sack, 2018). SAA carries out its profound immunomodulatory action via scavenger receptors, toll-like receptor (TLR2 and TLR4) and formyl peptide receptor- like 1 (FPR2) interaction leading not only to neutrophil and monocyte chemotaxis, but also cytokine/chemokine induction, and inflammasome activation (Eklund et al., 2012).

These effects are part of host defense, but prolonged or excessive SAA expression can be detrimental. Persistent increasing SAA is a major pathogenic factor for AA amyloidosis, which is defined as extracellular amyloid fibrils stemming from fragments of SAA that deposit in organs and subsequently disrupt their functions, especially the renal. Such a dual protective–pathogenic role emphasizes the requirement for finely-tuned SAA expression (Westermark et al., 2015).

Clinically, SAA is considered one of the most sensitive markers for acute inflammation. When compared with CRP, SAA can increase more readily and more so even in response to minor insults and is especially useful for the detection of early inflammation as well the assessment disease activity and treatment response. Increased SAA has been associated with bacterial and viral infections, autoimmune disorders, cancer, and trauma (Sack 2018).

In rheumatologic diseases including rheumatoid arthritis (RA), ankylosing spondylitis, and systemic lupus

erythematosus, SAA is significantly associated with disease activity and radiographic progression even more effectively than CRP in representing subclinical inflammation. Chronic SAA elevation in these diseases is not only strongest risk factor for AA amyloidosis but also highlights its prognostic value (Eklund et al., 2012).

The attention paid to SAA has been growing in the fields of infectious diseases and critical care. In sepsis and severe viral infections, including COVID-19, extremely high levels of SAA has been correlated with the severity of disease and cytokine storm, as well as unfavorable clinical outcomes. A number of research have suggested SAA as a prognostic marker for early risk stratification and inflammatory burden monitoring in hospitalized patients (Li et al., 2020).

In CVD/metabolic disease, persistent low-grade elevation of SAA was associated with atherosclerosis and insulin resistance (ie, obesity-related inflammation). HDL particles that are enriched with SAA display diminished cholesterol efflux and antioxidant capacity, which may lead to endothelial dysfunction and plaque destabilization. These data suggest that SAA is not only a marker but also an effector of chronic inflammatory disease (Sack, 2018).

Physiology and Clinical Significance of Ceruloplasmin

Ceruloplasmin (Cp) is a multifunctional copper-containing glycoprotein and one of the major positive acute phase proteins which takes part in copper metabolism, iron homeostasis, antioxidant defense and inflammation. It is synthesized predominantly in hepatocytes and released into the blood, where it represents about 95% of total plasma copper. Serum ceruloplasmin concentrations are usually between 20 and 40 mg/dL under physiological conditions, but they increase substantially with acute and chronic inflammatory diseases, infection, pregnancy, or malignancy (Hellman & Gitlin, 2002).

The major physiological role of ceruloplasmin as a ferroxidase is the catalytical oxidation of Fe^{2+} to Fe^{3+}. This reaction is required for iron to be loaded on transferrin and thereby transported systemically. Ceruloplasmin promotes efflux of iron from macrophages, hepatocytes, and enterocytes and is essential for avoiding intracellular iron overload as well as iron-mediated oxidative stress (Vashchenko & MacGillivray, 2013; Hellman & Gitlin, 2002).

Ceruloplasmin is also one of the major antioxidant agents in plasma. It scavenges the active oxygen species and prevents lipid peroxidation utilising its copper dependent enzymatic activity, thus protecting tissues against oxidative damage during inflammation. Moreover, ceruloplasmin regulates the nitrogen/nitric oxide metabolism and endothelial function evidently sustaining vascular homeostasis (Skjørringe et al., 2012).

Ceruloplasmin synthesis is increased in the acute phase response mainly by IL-6 (interleukin-6) with partial regulation by IL-1β and glucocorticoids, possibly through the JAK/STAT pathways. Such cytokine-mediated induction parallels the response of ceruloplasmin with other acute-phase proteins acting to promote homeostasis and minimize tissue injury during systemic inflammation (Ceciliani et al., 2002).

Structurally, ceruloplasmin has both a secreted soluble form as well as a glycosylphosphatidylinositol (GPI)-anchored membrane bound form. The membrane-bound isoform, which is active in astrocytes and other cells, appears to be particularly significant for regional export of iron and neuroprotection, emphasizing tissue-specific physiological roles beyond the systemic circulation (Skjørringe et al., 2012).

Ceruloplasmin has been most widely known for its clinical significance as a diagnostic marker of copper metabolism disorders to date, especially Wilson's disease. Wilson's disease is a rare autosomal recessive disorder of defective copper excretion and incorporation of copper into ceruloplasmin, leading to low serum ceruloplasmin and toxic accumulation of copper in liver, brain, and other organs. Serum ceruloplasmin concentration is consequently a mainstay of Wilson disease screening and diagnosis, along with urinary copper excretion and hepatic copper content determination (Roberts & Schilsky, 2018).

Apart from copper disorders, ceruloplasmin is an inflammatory biomarker. Acute infections, autoimmune power diseases, cardiovas-cular illnesses and malignances are the causes of increased ceruloplasmin in serum. Its raising levels indicate hepatic acute phase response and increased need of antioxidants during inflammation. The chronicity of inflammation as reflected by persistently high ceruloplasmin may also result in disturbed iron trafficking and promotion of oxidant stress, thereby perpetuating pathology (Ceciliani et al., 2002).

Ceruloplasmin has also been implicated in cardiovascular and metabolic disorder studies. Higher ceruloplasmin levels are related to atherosclerosis, endothelial dysfunction and cardiovascular risk by possible mechanisms involving lipoprotein oxidation and iron metabolism. Despite being an antioxidant, ceruloplasmin can paradoxically promote oxidative modification of LDL under certain conditions and hence its role in vascular disease is complex and context dependent (Skjørringe et al., 2012).

The involvement of ceruloplasmin deficiency or malfunction in neurodegenerative diseases. Aceruloplasminemia, an autosomal recessive, disorder is characterized by the absence of ceruloplasmin activity resulting in iron overloaded brains and progressive neurodegeneration which demonstrates that this protein is essential for neural regulation of iron (Hellman & Gitlin, 2002).

Conclusion

Acute phase proteins are a key link between inflammation, immunity and systemic balance. Their tight control of synthesis and overwhelming number of biological activities go clearly beyond their historical eufunction as inflammation markers. Proteins like CRP, SAA, haptoglobin, α1-antitrypsin and ceruloplasmin are involved in host defense, oxidation equilibrium and tissue protection. They are still, clinically, invaluable for diagnosis, prognosis and therapy monitoring, in a wide range of pathological conditions. The ability to interpret them in the clinical setting has been further developed with the molecular characterization and integration of biomarkers. Increased knowledge of the biology of acute phase proteins will improve them as translational tools and foster development of more specific inflammatory diagnostics.

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