



Review:

Acute phase reactants, challenge in the near future of animal production and veterinary medicine*

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Abstract: The future of acute phase proteins (APPs) in science is discussed in this paper. Many functions and associated pathological processes of APPs are unknown. Extrahepatic formation in local tissues needs attention. Local serum amyloid A (SAA) formation may be involved in deposition of AA-amyloid induced by conformational change of SAA resulting in amyloid formation, having tremendous food safety implications. Amyloidogenesis is enhanced in mouse fed beta pleated sheet-rich proteins. The local amyloid in joints of chicken and mammary *corpora amylacea* is discussed. Differences in glycosylation of glycoproteins among the APPs, as has been shown for α 1-acid glycoprotein, have to be considered. More knowledge on the reactivity patterns may lead to implication of APPs in the diagnostics and staging of a disease. Calculation of an index from values of several acute phase variables increases the power of APPs in monitoring unhealthy individuals in animal populations. Vaccinations, just as infections in eliciting acute phase response seem to limit the profitability of vaccines because acute phase reactions are contraproductive in view of muscle anabolism. Interest is focused on amino acid patterns and vitamins in view of dietary nutrition effect on sick and convalescing animals.

When inexpensive methodology such as liquid phase methods (nephelometry, turbidimetry) or protein array technology for rapid APPs measurement is available, APPs have a future in routine diagnostics. Specific groups of patients may be screened or populations monitored by using APPs.

Key words: Acute phase protein, Amino acid, Joint, Mammary gland, Mastitis, Serum amyloid A (SAA), Vitamin A

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INTRODUCTION

The systemic acute phase reaction known to occur on infection, inflammation, trauma, burns, malignancies and tissue damage in general, has been studied by scientists from various disciplines. In the last decade, emphasis has been laid on application of blood tests for acute phase reactants to monitor ani-

mal health in general, as well as for human patients suffering from specified classes of diseases (Gruys *et al.*, 2005). However, basic mechanistic patterns associated with biological reaction mechanisms, such as local production of acute phase proteins by cells of organs involved in specific physiological mechanisms and disease processes which may be associated with defence functions and with development of, even worse, tissue alteration, still remain to be uncovered.

Precolostrum mammary tissue (McDonald *et al.*, 2001) and mastitic mammary epithelium have been

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shown to form mammary serum amyloid A (mSAA) (Vivanco *et al.*, 2003; Nguyen *et al.*, 2003). Moreover, haptoglobin (Hp) and other acute phase reactants are found in the milk. These factors are supposed to have functions in regulating the inflammatory process and to be beneficial for the enteric milieu of the young mammal including protection of the gut mucosa by mucus formation (Gruys *et al.*, 2005).

In birds with chronic arthritis the synovial cells may reveal SAA upregulation, SAA protein formation (Ovelgönne *et al.*, 2001; Upragarin *et al.*, 2002; 2005a) and amyloid formation (Landman, 1998; Upragarin *et al.*, 2005b).

This paper on the expected future developments of acute phase protein (APP) science and APP-related disorders is based on (1) present scientific activities concerning basic mechanistic patterns not discovered so far, (2) development of technology for quantitative measurement of APPs or the cellular upregulation of their formation, and (3) assessment of disorders, health and welfare with APP values. Some topics in these fields will be mentioned.

BASIC MECHANISTIC PATTERNS

Specific organs

Differentiated reactivity patterns of parenchymal cells in the organ involved, such as mammary gland, depend on locally active cytokines and are unraveled in this paper. Moreover, cell specific factors may be revealed. Just like enzymes known from clinical enzymology, specific cell proteins such as the fatty acid-binding gut protein (Niewold *et al.*, 2004), may be discovered and have applications in diagnostics and therapy.

Functional aspects of acute phase reactants in milk and blood need further attention. Knowledge of the activities which activate or just mitigate the inflammatory reaction can lead to new ways for therapy and prevention of inflammatory processes in organs involved, such as lung or mammary gland.

Extrahepatic, local SAA formation (Landman, 1998) and its possible precipitation as amyloid (Upragarin, 2005) as has been found in avian amyloid arthropathy, needs further investigations. From the pathogenetic mechanisms preventive measures may be developed. Once the beta-pleated sheets of amy-

loid have been formed, the substance has tremendous food safety implications. In murine studies orally administered AA-amyloid appeared to enhance inflammation-/acute phase reaction-induced amyloidosis, where the administered material served as nidus for amyloidogenesis. This indicates that like prions, this pathological material should be banned for risk groups of consumers (Lundmark *et al.*, 2002 & 2003). In mammary tissue, colostrum and fresh milk *corpora amylacea* may occur which contain amyloid (described to be derived from casein (Niewold *et al.*, 1999)). Recently this amyloid was found to be positive for SAA (Toussaint *et al.*, 2005) and this possibly originates from mammary epithelium after in situ hybridization results (Toussaint *et al.*, 2005). By others the local formation of mSAA has been mentioned (Larson *et al.*, 2005). The amyloidotic corpora should be regarded as unwanted beta pleated factors in colostrum and milk and the relationship to this mSAA is recommended for further investigation.

Various proteins

In birds acute phase proteins such as (ovo)transferrin appear to have special characteristics differing from those of mammals. In mammals and possibly in avian species as well, some acute phase proteins may reveal differences in glycosylation patterns associated with different diseases and stages of those diseases, as had been shown for feline α 1-acid glycoprotein (AGP) (Ceciliani *et al.*, 2004; Pocacqua *et al.*, 2005). Further analysis may unravel basic biological mechanisms and indicate specificity of the glycosylation patterns for disease and reveal new concepts for therapy.

Reaction of different analytes in various situations, separate and combined

Viral, bacterial, and protozoal infections may be associated with different patterns in cytokine release and acute phase reactivity. Inflammatory processes in internal organs appeared to result in more severe reactivity patterns than diseases of the skin and the enteric system (Alsemgeest, 1994). Specific knowledge of pattern details may lead to implication of the parameters in diagnostics and staging of the disease.

Calculation of an index from values of rapid- and slow-reacting positive and negative APPs had been reported (Gruys and Toussaint, 2001; Gruys, 2002;

Toussaint *et al.*, 1995; 2002; 2004; Niewold *et al.*, 2003), because it appeared to increase statistical sensitivity and specificity for detecting unhealthy subjects. It covers a broad time span and includes changes in blood values resulting from the body's reactivity as well as starvation. In layer chickens, on contact with *Staphylococcus aureus* or turpentine, an acute phase protein reaction was induced. Measurement of values for SAA, transferrin, serum albumin and apolipoprotein A-1 in blood samples of these birds (Upragarin, 2005; Upragarin *et al.*, 2005b) showed that calculation of an acute phase index for this species offers promising results in this species. Outcome was as has been calculated for cows with various diseases (Toussaint *et al.*, 1995) and for pigs with a *Streptococcus suis* infection (Toussaint *et al.*, 2002).

Infections and vaccination

To prevent spontaneous disease frequent vaccination is recommended. It has been shown, however, that upon vaccination an acute phase protein reaction may develop. This appears to limit the advantages of vaccines, because acute phase reactions are known to be contraproductive in view of muscle anabolism. Future interest will be more on amino acid pattern differences in muscle and APPs (Table 1) and on the negative acute phase reactants.

Table 1 Major amino acid composition differences between muscle protein and two major acute phase proteins after a gross amino acid composition list (in arbitrary units) (Reeds *et al.*, 1994)

Amino acid	Muscle protein	CRP	SAA
Phe	40	105	103
Tyr	36	50	67
Trp	13	42	45
Arg	69	36	116
Ala	59	31	106

CRP: C-reactive protein; SAA: serum amyloid A

On starvation and negative energy balance associated with most diseases, muscle proteins are catabolised for amino acid supply of the hepatic APP formation and as source of energy. Especially for those APPs which rapidly and quantitatively increase in blood, their formation may have amino acid impact. An increased hindquarter protein catabolism exceeding the hepatic protein synthesis, and efflux of

glutamine and alanine from the hindquarter was measured during a porcine induced endotoxemia study (Bruins *et al.*, 2003). For growth during and after recovery from a disease, food requirements for amino acids thus may differ from the formula in ordinary food. Some pig studies indicate positive influences of additional dietary tryptophan (Le Floc'h *et al.*, 2004) or L-arginine (Bruins *et al.*, 2002).

Negative APPs may be associated with a change in concentration of bound compounds. A decrease of retinol-binding protein and of vitamin A values may be vice versa interrelated, vitamin A-deficiency being well known to decrease immune reactivity of children in developing countries. It is astounding to encounter a huge negative variation from normal blood vitamin A values of around 1~0.75 $\mu\text{mol/L}$ to around $<0.1 \mu\text{mol/L}$ in fattening pigs, as was revealed in a local investigation by a Dutch veterinarian (Hogendoorn, 2004).

Association of APPs with parturition, starvation and ketosis in cattle has been described. Rise in non-esterified fatty acids (NEFAs) occurs; their level increase might parallel those of some APPs. It is to be expected that due to negative APPs, blood vitamin A levels decrease as suggested for the pig. The NEFAs are toxic and have negative influence on metabolism. It is hypothesized that the NEFAs may decrease with increased muscular activity (walking). An inverse association with walking activity had been shown (Adewuyi, 2004).

DEVELOPMENT OF TECHNOLOGY TO QUANTATIVELY MEASURE PROTEINS OR CELLULAR UPREGULATION OF THEIR FORMATION

Several groups, after many laboratories used radio-immunoassays (RIA) and enzyme-linked methodology (ELISA) for APP measurement in particular of C-reactive protein (CRP) in human hospitals, are developing methods for rapid measurements of APP values. Multiple immunoassays with simultaneous analysis of various different serum analytes have been recommended (Lukacs *et al.*, 2005; Ray *et al.*, 2005; Petrou *et al.*, 2002). Different nephelometry systems are compared during application for human CRP (Maggiore *et al.*, 2005). Turbidimetry is developed

for APP in the dog (Kjelgaard-Hansen *et al.*, 2003), horse (Jacobsen *et al.*, 2005a; 2005c) and for the cat (Kjelgaard-Hansen *et al.*, 2005). Other methods of liquid phase analysis with the option of recycling of the sample (Philips, 2001), such as those possible with Surface Plasmon Resonance (Biacore® system), have been tested for APP in bovine milk (Åkerstedt *et al.*, 2005). Two-dimensional electrophoresis with mass spectrometry has been shown to be applicable to animal samples with the aim to measure acute phase reactants (Miller *et al.*, 2004; 2005a) as has been done by others for analytes of human cancer growth and activity (Mian *et al.*, 2005; Wang *et al.*, 2005). A protein chip has been developed for measurement of haptoglobin and SAA in human patients (Tolson *et al.*, 2004). Protein microarray methodology on slides has been proposed for APP in pigs (Toussaint *et al.*, 2004). Preliminary experiments with a monoclonal anti porcine CRP and pig acute phase sera using methodology as described (Timmerman *et al.*, 2004), offered the possibility to measure more than 1000 pig blood sample spots on a single slide.

Indirectly, acute phase protein formation may be measured in biopsies by methods to assess upregulation of protein synthesis (quantitative PCR). Especially the technique may be applied on samples after slaughter, or in histopathology and together with assessment of cytokines.

These technological developments may have crucial importance in the future if done rapidly, and at low costs, many samples can be handled, the APPs have a good future in diagnostics. This technique is for general assessment just as the erythrocyte sedimentation rate is used in internal medicine, but more sensitive, and for special groups of patients such as horses after castration (Jacobsen *et al.*, 2005c) or laparotomy (Miller *et al.*, 2005b).

ASSESSMENT OF DISORDERS, HEALTH AND WELFARE

Specific groups (Petersen *et al.*, 2004; Murata *et al.*, 2004), such as castrated horses (Alsemgeest, 1994; Jacobsen *et al.*, 2005b), cows with inflammatory processes including mastitis (Alsemgeest, 1994; Eckersall *et al.*, 2001), peri-parturient cattle (Alsemgeest *et al.*, 1993; Alsemgeest, 1994; Koets *et al.*,

1998), periparturient sows (Zhu *et al.*, 2005), or dogs and cats with infectious disorders (Ceron *et al.*, 2005) benefited from acute phase reactant measurement. In milk samples of cows (McDonald *et al.*, 2001; Eckersall *et al.*, 2001; Jacobsen *et al.*, 2005d) and sheep and goats (Winter *et al.*, 2005) mastitis may be monitored.

Combination of various APP values in an index increases the diagnostic power of the APPs to discern between normal animals in a population and non-healthy ones. After it was shown that an index combining values of fast and slow, positive and negative APPs can be used to assess human cancer patients (Ingenbleek and Young, 1994), such an index has been mentioned to assess health in populations of cattle, pig, dog and chicken (Toussaint *et al.*, 1995; 2000; Martinez-Subiella and Ceron, 2005; Upragarin *et al.*, 2005a; 2005b; Upragarin, 2005). Not only blood or milk samples can be used, meat juice (Petersen *et al.*, 2005) and other body fluids such as saliva (Parra *et al.*, 2005), are tested and found useful.

Involvement of multi-analysis technology in measuring the APPs and when coupled with pattern recognition software, the power of selective diagnostics of the APPs can increase.

Finally, because with respect to reaction of acute phase analytes in slaughter pigs (Heegaard *et al.*, 2005) and in cows with experimental induction (Jacobsen *et al.*, 2005d) individual variability is striking, in the future the APP reactivity pattern of an individual breeding animal may be used for selection on robustness.

CONCLUSION

Future possibilities for acute phase reactants depend on basic new mechanistic findings of known proteins, new discoveries such as organ specific components, and on technological possibilities for rapid immunological or chemical multi-analyses coupled with computer analysis of the patterns found. A shared cost European Union (EU) project (No. QLK5-2001-02219) on porcine acute phase proteins has helped to spread the knowledge to scientists of member states involved, and to develop a base for practical applications. For other species such as cattle, horse, dog and cat, but also chicken and even human,

a similar field is open for development of clinical and health management applications. Finally, new fields of research and application are in the negative metabolic influences of acute phase processes and their relationship with growth and nutrition.

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