

PORCINE ACUTE PHASE PROTEINS IN EXPERIMENTAL MODELS OF INFECTIOUS DISEASES

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Introduction

We have studied the porcine acute phase protein (APP) response in a number of infection models for bacterial and viral infections through collaboration with Danish and European groups, especially in the EU funded Shared Cost project Acute Phase Proteins in Pigs (QLK5-2001-02219). This has led to the identification and characterisation of a number of new negative pig acute phase proteins (some of which are being presented at this meeting) and the description of concentration changes of a selection of positive and negative pig APPs during various experimental infections.

Materials & Methods

A typical infection experiment entailed a group of pigs being infected at the same time by well-described infection methods aimed at reproducing the corresponding natural infection. The pigs were then followed daily to inspect for clinical signs of disease. Blood samples were obtained before infection and at regular intervals after infection, sampling several times from the same animal. At the end of the experiment animals were euthanised and autopsied to record pathological changes and to recover tissue for demonstration of the presence of the infective agent and other microorganisms, if present. Serum samples were analysed by immunochemical methods and calibrated whenever possible with porcine acute phase protein standards from the EU concerted action "Animal Acute Phase Proteins" (QLK5-CT-1999-153). Data from a number of such experiments will be presented together with the methods used for statistical treatment of the data.

Results

Strongly reacting positive pig APPs include serum amyloid A (SAA), C-reactive protein (CRP), pig major acute phase protein (pig MAP) and haptoglobin; SAA is often undetectable in normal pig serum but its big incremental change during the acute phase reaction makes it one of the most prominent of the acute phase proteins. Hemopexin and complement C3 are weakly reacting positive acute phase proteins and transthyretin (TTR) and alpha-1 apolipoprotein (apo A1) are strong negative acute phase proteins, while albumin, although negatively reacting is quite inconsistent in doing so. Surprisingly, alpha-1-acid glycoprotein is nonresponsive in pigs while in most other species it is a prominent positive APP. Comparing different infections, in many cases SAA was not increased and albumin was not decreased, while generally, CRP, haptoglobin, pig MAP and transthyretin and apoA1 reacted strongly to the infections studied. Using the most sensitive and specific of these APPs a good reflection of the severity of infection could generally be obtained.

Discussion

It can be concluded that certain APPs are rather insensitive to infection, either by not reacting (SAA, albumin) or by showing a pronounced baseline variation that lowered the sensitivity for detecting an acute phase condition (haptoglobin, TTR). Furthermore, the specificities of some APPs may be hard to establish (SAA) because pre-infection levels are undetectable. Using a selection of APPs with rapid and prolonged AP changes and low prechallenge variations a composite parameter could be constructed that was investigated statistically for general responsiveness to infections. In conclusion, it is possible by using such a parameter to gain precise information on the AP status of an animal. A number of basic questions might be investigated by the use of such a combination of measurements, including the possibility of detecting subclinical infections by APP reactions, the differentiation if possible between acute vs. chronic infection and the influence of physical and psychological stress on APP reactions. This will then lay the foundation for the practical use of APP measurements as a clinical and surveillance aid.

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THE ACUTE PHASE RESPONSE IN CLINICAL PRACTICE: THE FIRST 75 YEARS

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Study of the acute phase response started with the discovery of C-reactive protein (CRP) 75 years ago. Clinical interest in and use of acute phase proteins in human medicine has waxed and waned over the years since then for technical, cultural and educational reasons. Although CRP is overwhelmingly the best systemic marker of the acute phase response in humans, clinicians in different specialties and in different countries have shown, and still show, remarkable differences in their capacity to understand and apply the profound clinical utility of measuring this exquisitely sensitive, precise, and quantitative but non-specific, non-diagnostic, marker of disease. Nevertheless, routine use of CRP assays is now firmly embedded as an established part of investigation and management in most parts of the world, and properly standardised on the WHO International Reference Standard that I produced 20 years ago. The only other human acute phase protein that merits routine measurement as a marker of inflammation is serum amyloid A protein (SAA), monitoring of which is essential in management of reactive systemic, AA, amyloidosis, in which the aim is reduction, to normal if possible, of the circulating SAA concentration, in order to arrest amyloid deposition and allow amyloid regression with associated clinical benefit. We also made the WHO standard for this analyte.

Following our original demonstration in 1994 that high sensitivity measurements of CRP provide significant prognostic information in patients with acute coronary syndromes, there has been an explosion of interest in CRP and cardiovascular disease, greatly enhanced by the finding that baseline CRP values in the general population also predict future atherothrombotic events. The avalanche of publicity and hype about this has generated a bandwagon of enthusiasm for such measurements in risk assessment that is not well supported by the epidemiological evidence. There have also been enormously exaggerated claims, based on very poor experimental evidence, that CRP is pro-atherogenic. In fact no rigorous studies to date support these claims. In marked contrast, after ischaemic necrosis of tissue has occurred, we have robustly demonstrated that human CRP can be pro-inflammatory and enhance tissue damage *in vivo*. CRP is thus a valid therapeutic target and we are designing and developing novel CRP-inhibitory drugs that may have cardioprotective and neuroprotective effects after myocardial infarction and stroke.

In the past my laboratory has also studied various acute phase proteins in different animals, identifying and/or characterising them in detail for the first time, in particular mouse serum amyloid P component (SAP), rat CRP, dog CRP and horse SAA. Although both the pentraxin proteins, CRP and SAP, and the SAA family are stably conserved in evolution, there are notable differences between species in their circulating concentrations and behaviour as acute phase reactants. Mouse SAP is an exquisitely sensitive acute phase protein with important and, as yet, largely unrealised potential for use in toxicological screening. The accelerating recent progress of clinical applications of animal acute phase protein measurement in veterinary medicine and in food production is both timely and appropriate, and will surely continue to yield wide ranging benefits