REVIEW ARTICLE

C-reactive protein — biological functions, cardiovascular disease and physical exercise

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Abstract

C-reactive protein (CRP) is an acute-phase reactant that increases in response to noxious stimuli that inevitably induce cellular and/or tissue injury. The increased synthesis of CRP occurs predominantly in the liver and peaks 24 - 48 hours after the inciting stimulus. CRP forms an integral component of innate immunity and serves primarily to recognise potential pathogens and damaged cells. It facilitates the removal of these cells through opsonisation and activates the complement system. With increasing evidence supporting the classification of artherosclerosis as inflammatory in nature, CRP has received considerable attention as a marker, and in some cases a contributor towards this cardiovascular disease. Traditionally, CRP has been measured within exercise studies to provide evidence that an acute-phase inflammatory response can or has been initiated. Although the elevation in CRP following exercise has largely been attributed to muscle damage, evidence is mounting to contest this premise. Participation in chronic exercise has been associated with a reduced risk of cardiovascular disease. Numerous studies have now shown an inverse relationship between physical activity levels and resting concentrations of CRP. Thus, exercise may prove beneficial in lowering systemic inflammatory markers such as CRP, and consequently contribute towards preventing the progression of inflammatory disorders.

Introduction

C-reactive protein (CRP) was first discovered in 1930 by William Tillet and Thomas Francis.[48] In studying the blood of patients suffering from acute *Streptococcus pneumonia* infection, it was found that the sera of these patients formed a precipitin with an extract from the streptococcal bacterium. The extract was originally labelled Fraction C, and was later confirmed as a polysaccharide. Hence, as a result of its reactivity with the C-polysaccharide of the *Streptococcus* cell wall, the 'substance' in the sera was named CRP.

CRP ligand-binding is calcium dependent and binds with highest affinity to phosphocholine (PC), a constituent of the cell membrane phospholipid, phosphatidylcholine. Under normal conditions phophatidylcholine is not exposed, however, once a cell has been damaged it becomes 'accessible' to CRP.[7,52]

Synthesis and application

CRP synthesis was originally thought to be confined to the liver with no evidence supporting its production in cells other than hepatocytes.[35] Jabs *et al.*[15] have recently shown by real-time polymerase chain reaction (PCr) and immunohistochemistry, that in response to stimulation with interleukin-6 (IL-6), renal cortical tubular epithelial cells express CRP messenger ribonucleic acid (mRNA). Additional extrahepatic sites of CRP synthesis/gene expression have been identified and include the epithelial cells of the human respiratory tract and T-lymphocytes in culture.[13,14] It is still generally accepted that the liver is the primary site of *de novo* CRP production.

CRP concentration can increase dramatically up to 1 000-fold during the acute-phase response, and usually peaks 24 - 48 hours after an initial acute inflammatory stimulus.[20,34] The half-life of CRP is 19 hours and is independent of the circulating concentration of CRP.[1] Hence, the primary factor determining the serum level of CRP is the rate at which it is produced.[1]

Normal systemic CRP levels are classified as less than 5 mg/l with averages of the sedentary/general population being estimated at approximately 2 mg/l.[9] No difference in concentration exists between males and females, nor does CRP exhibit diurnal or seasonal variation.[6,34] Serum levels are not affected by food intake, however, Ganapathi *et al.*[10] have shown that the CRP levels in human hepatoma cell lines are potentiated by caffeine. In addition, Church *et al.*[5] have shown that CRP levels are reduced through the use of a multivitamin over a 6-month period.

Regardless of the nature and location of cellular/tissue damage, a non-specific, systemic acute-phase response is initiated. Although CRP has been identified as one of the most prominent acute-phase proteins that allows for quantification

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of an inflammatory state, its elevation cannot differentiate between damaged tissues, hence its measurement and diagnostic value has been questioned.[1] Thus, CRP is generally measured within a clinical setting to provide the physician with an indication of disease activity, the effectiveness of pharmacological treatment and to determine if intercurrent infections have manifested.[1] Whilst an increase in CRP has generally been accepted as a response to an inflammatory 'condition', Kushner has proposed that minor elevations of CRP are indicative of biological ageing, a non-inflammatory condition.[19]

Biological properties and functions of CRP

Recognition of pathogens and damaged cells

As part of the acute-phase response, CRP levels may rise dramatically in order to facilitate non-specific immune functions and assist with the repair process. The ability of CRP to recognise disease-causing agents and damaged cells, and to mediate their removal, in conjunction with the fact that there exists an absence of any documented human CRP deficiency, highlights its crucial role in innate immunity.

Within the human body millions of cells die each day. Gershov *et al.*[11] have proposed that a key role of CRP is to facilitate the removal of these cells. They reported that in addition to binding to lysed or permeabilised cells, CRP binds to the membranes of intact apoptotic cells. The increased CRP was associated with enhanced phagocytosis of the apoptotic cells and would thus contribute towards their clearance.

Opsonisation

On binding to various cell membrane surfaces or necrotic tissue/debris, CRP then acts as an opsonin (from the Greek meaning 'prepare food for').[2] Opsonisation involves coating of the bacterial surface so that it can be recognised by other cells of the immune system, specifically macrophages and neutrophils. Thus, opsonisation by CRP promotes the uptake, and therefore removal of these cells by phagocytes.

Activation and regulation of complement pathways (pro v. anti-inflammatory role)

In addition to the binding and subsequent opsonisation of pathogens, CRP also serves to activate and modulate complement. CRP binds to C1q, the first component of the complement cascade, and thereby initiates activation of the classical pathway. The activation of complement serves to enhance opsonisation and increase local inflammation. Berman *et al.*[3] have shown that although CRP activates the classical pathway of complement, the terminal components (C5-C9) known as the membrane attack complex (MAC) are not activated. This was in contrast to immunoglobulin G (IgG) and immunoglobulin M (IgM) activation of the classical pathway, which formed the MAC. The non-activation of the MAC could be interpreted as an anti-inflammatory mechanism, since activation of these terminal components has been associated with cellular injury and the release of pro-inflammatory cytokines.

CRP also inhibits the alternate and lectin pathways of complement through the recruitment of factor H, a regulatory protein that promotes the degradation of the C3 and C5 convertase.[27] Thus CRP plays a dual pro and anti-inflammatory role in its regulation of the complement system.

The immunomodulating actions of CRP and its pro and anti-inflammatory effects are not restricted to complement. Pue[37] has shown that in response to lipopolysaccharide (LPS), the hosts' peripheral blood mononuclear cells (PBMC) respond to CRP in a pro-inflammatory manner. However, once the CRP has moved into the tissue and reacts with macrophages, inflammation is suppressed through the inhibition of interleukin-1b (IL-1b) and interleukin-1ra (IL-1ra). Additional anti-inflammatory properties exhibited by CRP include the ability to decrease the expression of cell adhesion molecule (L-selectin) *in vitro*, and reduce neutrophil superoxide production.[9,54]

CRP and cardiovascular disease

A plethora of studies have recently associated elevated serum CRP levels with an increased risk of developing cardiovascular disease (CVD). The increase in CRP is indicative of an inflammatory response, and it is now widely accepted that atherosclerosis (the underlying cause of most CVD) is a chronic inflammatory disorder.[38]

Atherosclerosis is in part characterised by the deposition and accumulation of lipids within arterial walls. These lesions can lead to ischaemia of the brain, heart and peripheral tissues resulting in infarction.[38] The oxidation of low-density lipoprotein (LDL) deposited on arterial walls is one of a number of factors contributing to what has been termed endothelial dysfunction,[38] a hypothesis proposing that vascular injury, and hence inflammation, is induced by a number of factors and possibly a combination thereof. Possible causes of endothelial dysfunction are elevated and modified LDL, diabetes, genetic alterations, cigarette smoking, hypertension, elevated homocysteine, and infectious microorganisms (e.g. *Chlamydia pneumoniae*).[38]

Although substantial evidence from numerous studies has identified CRP as a marker of CVD, increasing evidence is now implicating CRP as a risk factor directly involved in atherogenesis. Cermak *et al.*[4] have reported that CRP induced a 75-fold increase in tissue factor (TF) procoagulant activity of PBMC. It was suggested by the authors that the increase in monocyte TF expression (during infection/necrosis) induced by CRP could contribute towards the development of intravascular coagulation. This could arguably exacerbate the inflammatory state already present in 'injured' vessels. Nakagomi *et al.*[29] also reported increases in PBMC TF concentrations in response to stimulation with CRP. The authors proposed that their findings shed light on the link between inflammation and coagulation, a connection 'which may contribute to the progression and outcome of

thrombotic events associated with atherosclerosis'.

Using human umbilical vein endothelial cells, Pasceri *et al.*[31] showed that CRP induced the expression of monocyte chemoattractant protein-1 (MCP-1), a chemokine that attracts monocytes, natural killer (NK) cells and activates macrophages. The same group reported a CRP-induced increase in the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in umbilical vein as well as coronary artery endothelial cells.[32] Inhibiting the expression of cellular adhesion molecules has been shown to decrease phagocytic activity within atherosclerotic plaque.[33] Pasceri *et al.*[32] concluded that CRP is not just a marker of inflammation, but rather that it may contribute to enhancing the progression of inflammation/ atherosclerosis.

In keeping with the role that CRP plays in contributing towards atherogenesis, Zwaka *et al.*[55] demonstrated that CRP facilitates the phagocytosis of native LDL by macrophages. The uptake of LDL particles by macrophages results in the formation of lipid peroxides, promotes the accumulation of cholesterol esters and eventually forms foam cells.[38] Zwaka *et al.*[55] suggested that the binding of CRP to LDL within arterial walls might promote the onset of arteriosclerosis.

Nitric oxide (NO) plays an integral role in inflammation and immune regulation with lowered levels associated with adverse cardiac events. Verma *et al.*[51] incubated endothelial cells with a concentration of recombinant CRP known to predict adverse cardiovascular events. They measured the production of NO and cyclic guanosine monophosphate (cGMP), the second messenger for NO. CRP elicited a dose-dependent, significant decrease in both NO and cGMP production. The authors concluded that the inhibitory effect that CRP exerts on NO production may facilitate the development of cardiovascular disease. Similarly, Venugopal *et al.*[50] investigated the effects that CRP had on endothelial nitric oxide synthase (eNOS) expression. Human aortic endothelial cells (HAEC) were incubated with recombinant CRP, and in a finding mirroring that of Venugopal *et al.*,[50] eNOS and eNOS mRNA protein levels were inhibited by CRP. This finding further supports the role of CRP in the artherogenic process.

Yasojima *et al.*[53] used a reverse transcriptase-polymerase chain reaction to detect mRNA for CRP and complement proteins (C1-C9) in arterial and atherosclerotic plaque. They found evidence of CRP as well as C1-C9 being synthesised within the arterial tissue of 10 postmortem cases. In addition, mRNA and the respective proteins were elevated in atherosclerotic plaque. Since complement proteins have been associated with atherosclerotic plaque,[39] and CRP is instrumental in potentiating local inflammation by binding with C1q it seems tenable that CRP may be involved in the pathogenesis of atherosclerosis.

Inflammation and exercise

It has been proposed that physical activity may serve as a model for studying the inflammatory response,[41] and it is well established that an acute bout of exercise may alter the circulating levels of a number of pro-inflammatory cells including cytokines, acute-phase proteins and white blood cells.[25,40,45] Although there is general consensus regarding the induction of an acute-phase inflammatory response following strenuous, unaccustomed or prolonged bouts of exercise, there is some degree of uncertainty surrounding the precise stimuli responsible for this response. The majority of authors have attributed the rise in inflammatory markers following physical activity to muscle damage. Evidence suggesting a possible role of other factors/stimuli involved in inducing or exacerbating the inflammatory response following exercise may include haemolysis,[21] endotoxaemia,[16] and the production of reactive oxygen species.[17] In addition, psychological stress, which may be more prevalent in elite athletes, has also been shown to cause an increase in pro-inflammatory cytokines.[22] Invariably, the mode, duration and intensity of the exercise, as well as the subject's level of conditioning may all affect the magnitude of the inflammatory response as well as resting concentrations of inflammatory markers such as CRP. In keeping with this, King *et al.*[18] have proposed that certain activities such as jogging, may be more beneficial in terms of lowering inflammatory markers than other modes of exercise.

As outlined above, CRP is involved in the activation of the classical pathway of complement. Complement proteins are intimately involved in opsonisation, inflammation and cell lysis,[28,42] and have been investigated in response to exercise of varying mode and duration. Similar to CRP, the specific stimuli that upregulate complement proteins following exercise are controversial. However, as with CRP the resting concentrations of selected complement proteins have been shown to be lower in athletes compared with sedentary individuals.[30] More specifically, Nieman *et al.*[30] reported lower levels of C3 in athletes compared with sedentary controls. Interestingly, elevated C3 has recently been proposed as a marker to identify the progression of atherosclerosis.[46]

Effects of acute exercise on CRP

The acute response of CRP to physical activity has been published extensively, and the following section outlines a few of the common findings. Increases in CRP have been observed following acute strenuous, prolonged bouts of running,[40] triathlon,[16,47] bench stepping[12] and anaerobic exercise.[26] Since eccentrically based exercise is more commonly associated with muscle damage, and CRP serves to bind damaged cells, it seems reasonable to assume that this type of activity would be associated with pronounced elevations in CRP. Results contradicting this assumption have been documented by Sorichter *et al.*[44] and Malm *et al.*[23] In both studies no significant elevations were observed for CRP following eccentric exercise (70 eccentric quadriceps contractions, and 45 minutes of downhill running respectively). These results suggest that elevations in CRP following exercise may not be solely due to muscle damage. Supporting this would be the findings of Smith *et al.*[43] In this study, CRP was significantly

($p < 0.04$) elevated in 75% of active-untrained subjects, 24 hours after performing 60 minutes of cycling at only 60% of maximal oxygen uptake. Similarly, Meyer *et al.*[26] reported a significant ($p = 0.02$) increase in CRP 24 hours after 12 trained males performed an anaerobic cycle ergometer test.

Effects of chronic exercise on CRP

Pitsavos *et al.*[36] used a sample of 891 men and 965 women older than 18 years, to determine the association of leisure-time physical activity on CRP and other inflammatory markers. The results revealed that CRP levels were 33% lower in the subjects who partook in high-physical activity levels compared with the sedentary group (high-physical activity was defined as expended calories > 7 kcal/min). Similarly, our laboratory has observed (unpublished data) that CRP resting levels are significantly lower in professional cyclists compared with active-untrained individuals.

Tomaszewski *et al.*[49] have reported 'strikingly' low CRP levels in runners. Sixty-seven male ultra-marathon runners were compared with sedentary individuals. They were all categorised into groups having a body mass index (BMI) less than 25 kg/m^2 or greater than 25 kg/m^2. Although non-significant, the resting levels of CRP were markedly lower in the marathon athletes compared with the controls. Even though there were differences in BMI, the CRP levels were similar amongst the marathon runners. Thus, the authors suggested that lowered CRP levels can be attained by intense regular exercise, and that this suppression is independent of adiposity levels.

An interesting study by Mattusch *et al.*[24] revealed changes in CRP concentration following 9 months of training. Fourteen males (25 - 40 years) preparing for the Cologne Marathon provided blood samples before and after 9 months of training for the event. The mean CRP concentration before the training began was 1.19 ± 1.63 mg/l for athletes, and after 9 months was significantly ($p < 0.05$) reduced to 0.82 ± 0.94 mg/l. There were no significant changes reported for the control group. The authors suggested that an anti-inflammatory effect is induced by endurance exercise performed over 9 months. Similarly, Fallon *et al.*[8] reported significantly ($p < 0.05$) decreased levels of CRP following 9 months of soccer training in elite women, from a resting level of 2.68 (± 1.70 mg/l) to 1.62 (± 1.32 mg/l). It was suggested that systemic anti-inflammatory mechanisms, associated with regular intense exercise were behind this finding. The proposed anti-inflammatory effect of chronic exercise suggests that physical activity may impart favourable health benefits on individuals by lowering CRP, a key role player in cardiovascular disease.

In conclusion, CRP is an acute-phase protein that is upregulated in response to injury, infection or antigen exposure. CRP usually peaks 24 hours after exercise, and is more pronounced following longer more strenuous activity. The elevations in CRP following exercise have largely been attributed to muscle damage, however, it seems plausible that muscle damage does not have to be elicited by exercise in order for CRP to be elevated. The alterations in CRP are closely related to exercise-induced inflammatory sequelae and are more pronounced following activity that is longer or more aerobically challenging than exercise that is not. The supposed lower resting levels and adaptations associated with chronic physical activity may be more prominent following aerobic exercise although studies are lacking in which the effects of resistance training are investigated. Numerous studies have shown that an inverse relationship exists between CRP and fitness levels, and that elevated CRP may be seen as a significant risk factor for CVD. In addition, resting CRP concentrations seem to be higher in sedentary versus active individuals. This supports the notion that exercise may 'downregulate' systemic inflammatory markers and thus prove beneficial in opposing chronic inflammatory disorders such as cardiovascular disease.

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