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REVIEW ARTICLE

OVERVIEW OF C-REACTIVE PROTEIN AND TREATMENT OF CARDIOVASCULAR DISEASE

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ABSTRACT

C-reactive Protein (CRP) is an acute-phase protein that belongs to the pentraxin family of calcium dependent legend-binding plasma proteins. The human CRP molecule has five identical subunits. These subunits are made up of 206 amino acids and are non glycosylated polypeptide. This review focuses on the various biological roles of CRP, their normal values, methods of measurement, advantages and factors. CRP is closely related to cardiovascular disease and other diseases. Cardiovascular disease can be treated by both phytochemical and non phytochemical sources.

INTRODUCTION

Tillet and Francis identified a pneumonia in the sera of patients in 1930 that has the ability to precipitate polysaccharide fractions, designated as fraction C that is derived from *streptococcus pneumonia* (Tillet *et al*., 1930). This property quickly disappeared when patients recovered and was not identified in healthy volunteers. When the cause of this reaction was identified as a protein, it was named CRP. Inflammation that may increase several hundred fold about acute injury, infection or other inflammatory stimuli agent as tumor necrosis factor-a, interleukin-1 are characterized by CRP that is an acute marker (Ridker *et al.*, 1997; Kuller *et al*., 1996). CRP level as far below those found during inflammatory process can be determined by high sensitivity methods that have been recently developed. CRP is primarily produced by the liver where its synthesis is controlled by many cytokines (Pepys *et al*., 2003). During activation of CRP, it can clean up the cellular debris through its action as a pattern recognition receptor involving calcium-dependent legend binding (Garlanda *et al*., 2005).

Structure of CRP

Native CRP consists of five identical subunits, each composed of 206 amino acids with a molecular weight of 23000, that bind non-covalently to form a symmetrically shaped, pentameric molecule with a molecular weight of 118000.

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Emerging evidence showed that C-reactive protein (CRP) has at least two conformationally distinct isoforms, *i.e.*, pentameric CRP (pCRP) and monomeric CRP (mCRP or CRP subunit). Both CRP isoforms are proposed to play roles in inflammation and may participate in the pathogenesis of cardiovascular disease. However, the origin of mCRP *in situ* and the interplay among the two CRP isoforms under physiological/pathological circumstances remain elusive. Calcium-dependent binding of pCRP to membranes, including liposomes and cell membranes, led to a rapid but partial structural change, producing molecules that express CRP subunit antigenicity but with retained native pentameric conformation. This hybrid molecule is herein termed mCRPm. The formation of mCRPm was associated with significantly enhanced complement fixation. mCRPm can further detach from membrane to form the well-recognized mCRP isoform converted in solution (mCRPs) and exerts potent stimulatory effects on endothelial cells. Scenarios for mechanism of regulation of CRP function and mCRP formation are provided by membrane induced pCRP dissociation.

Biological roles of CRP

CRP activate vascular cells

From blood (Sun *et al*., 2005) CRP can be deposited in vascular wall and in the arterial wall (Kobayashi *et al*., 2003) CRP mRNA is detectable, that showed that within atherosclerotic plaque CRP is also produced locally in which one study has found higher CRP mRNA concentrations than those in liver tissue (Yasojima *et al*., 2001). CRP (Yasojima

et al., 2001) produces by macrophages with in plaque. Several factors can lead to the instability of a plaque and a subsequent acute coronary event (2–5) are shown in (Fig. 1) (Koenig, 2001).

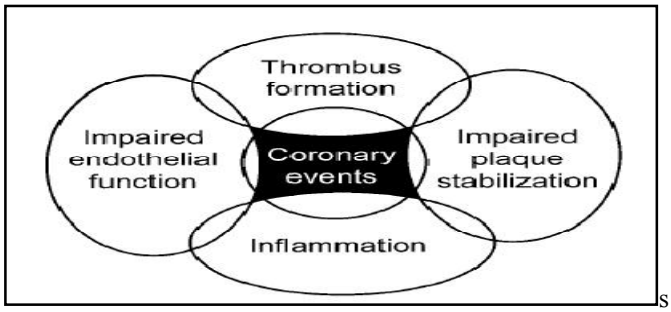

Fig.1: Potential mechanisms for plaque instability and coronary events.

Impaired endothelial function can result in the loss of endothelial cells, the exposure of collagen and tissue factor, and superficial thrombosis over a plaque are some of the proposed mechanisms (Davies, 1995). With stable atherosclerotic plaques, the risk of vascular events in patients is lower than that for patients with unstable plaque is not surprisingly (Libby , 1995).In vascular smooth muscle cells (VSMCs) within human atherosclerotic plaques, CRP mRNA and protein are present that showed that VSMCs synthesize CRP *in vivo* (Jabs *et al*., 2003 ; Yasojima *et al*., 2001). Inflammatory cytokine can induce CRP expression when they are cultured in human coronary artery VSMCs (Calabró *et al*., 2003).CRP inhibits nitric oxide synthase expression and up regulates expression of interleukin-8, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 by exposure of cultured vascular endothelial cell (Venugopal *et al*., 2002 ; Devaraj *et al*., 2005). Except phosphocholine residues CRP have the ability to bind with a member of IgG Fc receptor family as Fcγ receptor-I (FcγR I CD64) that is expressed on macrophages (Crowell *et al*., 1991 ; Mold *et al*., 2002) . CRP can activate intracellular signaling pathways when it binds with FcγR-II a (CD32), that is expressed by macrophages and platelets that plays an important role in the pathophysiology of immune-mediated thrombocytopenia (Bharadwaj *et al*., 1999 ; Chi *et al*., 2002 ; Stein *et al*., 2000) .

Effect of CRP on blood platelets

CRP receptor FcγR(CD16) and FcγR-II a are expressed by platelets (Filep , 2009). Platelet aggregation induced by variety of agonists including thrombin, PAF and immune-globulin are prevented by CRP that have observed during several studies (Cheryk *et al*., 1996; Filep *et al*., 1991; Fiedel *et al*., 1976).Platelet aggregation that is induced by PAF can be prevented by CRP when it is bind to the phosphocholine residues of PAF (Kilpatrick *et al*., 1985). However, interaction between platelet adhesion to endothelial cells and monocytes (Yaron *et al*., 2006; Danenberg *et al*., 2007) by CRP ultimately promote thrombosis. Binding of platelet to neutrophils can be prevented by pentameric CRP when it bind to the FcγR-□a (Filep, 2009; Koreas *et al*., 2004)On the other side, platelet capture by neutrophils are promoted by monomeric CRP when it binds to FcγR-□ (Filep, 2009). Pentameric CRP is converted into monomeric form by activated platelets (Koreas *et al*., 2004; Eisenhardt *et al*., 2009).

Effect of CRP on fibrinolytic system

Plasminogen is converted to plasmin, the enzyme that degrades fibrin clots by tissue-type plasminogen activator (t-PA). Plasminogen activator inhibitor-1 (PAI-1) is the main physiological inhibitor of t-PA and urinary-type PA. PAI-1 is present in plasma, platelets, endothelial cells, VSMCs, and extracellular matrix. From vascular endothelial cells there is stimulated release of PAI-1 when CRP prevent release of t-PA (Devaraj *et al*., 2003 ; Singh *et al*., 2005). Therefore, CRP can alter the fibrinolytic balance of endothelial cells so as to promote intravascular fibrin formation.

Regulation of blood coagulation factors by CRP

Thrombosis after vascular injury by binding with factor-VIIa is initiated by TFs that have a molecular weight of 44,000 along with membrane bound glycoprotein (Marmur *et al*., 1996). The TF (Tissue factor) VIIa complex activates factor X and IX, thereby begining proteolytic cascades that result in thrombin formation and blood clotting. In the adventitia of normal blood vessels (Wilcox *et al*., 1989), TF is synthesized, where it functions to maintain hemostasis after vascular trauma. In the intima of normal arteries, TF is not detectable, but is detectable in the lipid rich cores of atherosclerotic plaque attribute to the presence of TF in lot of abundancy (Marmur *et al*., 1996; Thiruvikraman *et al*., 1996).TF expression by blood monocytes stimulates by CRP in vitro (Cermak *et al*., 1993) and it has been proposed that the monocyte is an important target cell of CRP that mediates its prothrombotic effects. TF expression by VSMCs induces by CRP can also be done both *in vitro* and *in vivo* (Cirillo *et al*., 2005; Wu *et al*., 2008), that provides a mechanism by that CRP can promote fibrin formation after endothelium-denuding vascular injury.

Measurements of CRP

Latex enhanced immunoturbidometry assay is used for the detection of concentration of CRP with a lower limit of detection of 0.02mg/l (Roche diagnostics) (Roberts *et al*., 2001). According to Centers for Disease Control and the American Heart Association CRP cut-off values is 1.0 and 3.0 mg/l (Pearson *et al*., 2003). CRP Reagent is a suspension of polystyrene latex particles of uniform size coated with rabbit IgG anti human CRP. When a sample containing CRP is mixed with the reagent, a clear agglutination occurs, that can be measured by turbidimetry. High-sensitivity C-reactive protein (CRP) was measured with the Roche particle enhanced immunoturbidimetric assay (Roche Diagnostics GmbH, Mannheim, Germany) at one site and with the Dade-Behring nephelometric assay (Dade-Behring, Deerfield, IL) at the other. For the good concordance between these 2 assays regression analysis shows excellent results (Hamwi *et al*., 2001).The Reynolds Risk Score, that takes into account hs-CRP readings, has been shown to improve global CV risk prediction as compared with the previous assessment of traditional CV risk factors and represents a practical and simple method of risk assessment in the clinical setting.

Clinical Significance

Elevated CRP levels and higher BP in adults, mainly higher systolic blood pressure show positive association among it (Ridker *et al*., 2003).In the recent, more prospective study (Sesso *et al*., 2003), elevated CRP levels were associated with increased risk of developing hypertension. Other significant factors associated with abnormal albuminuria include the duration of diabetes and GFR (Glomerular filteration rate). During several studies in adults (Saito *et al*., 2003) and children (Cook *et al*., 2000) there is consistent association between CRP and adiposity has been observed. It has been assumed that interleukin-6 production (Fried *et al*., 1998) that is induced by adipose tissue releases tumour necrosis factor stimulates hepatic production of CRP. High sensitivity CRP levels that are examined in adults shown that these are associated with an increase of several symptom of cardio vascular disease, including myocardial infarction (Danesh *et al*., 2004), stroke (Rost et al., 2001), sudden cardiac death (Albert *et al*., 2002) and peripheral artery disease (Ridker *et al*., 2001). Cardiovascular risk is increased by CRP, but it is not correlated with lipoprotein levels such as TC (Total Cholestrol), HDL-C (High Density Lipoprotein- Cholestrol) or LDL-C (Low Density Lipoprotein- Cholestrol) are weakly correlated with CRP in adults (Ferranti *et al*., 2002).Surgical infections or complications that is a early sign of post-surgical complications in gastric cancer patients are showed by increase level of CRP (Mustard *et al*., 1987; Sakaguchi et al., 2004).

Factors Affecting CRP

Serum CRP levels can be reduced by smoking cessation, exercise and weight loss (Nicklas *et al*., 2005; Nissen *et al*., 2005). Serum levels of high-sensitivity C-reactive protein (hs-CRP) have been found to be a strong predictor for increased cardiovascular disease risk associated with type-2 diabetes independent of traditional risk factors. Yorulmaz *et al*., 2006 evaluated the non-metabolic factors affecting hs-CRP levels and their frequency and they concluded that at least one of the non-metabolic factors capable of increasing hs-CRP levels was found in one's of every six patients with type-2 diabetes, suggesting a limited use of hs-CRP for predicting cardiovascular risk.

Advantages of CRP

Firstly it is a stable compound and second it can be measured at any time of the day without regards to biological clock. In contrast to results for cytokines such as IL-6, no circadian variation appears to exist for hsCRP. Hence without regard for time of day clinical testing for hsCRP can be accomplished (Meier-Ewert *et al*., 2001).

Treatment of Cardiovascular Disease

Garlic

The enzyme Allinase is inactivated by heat leaving behind alliin as the main constituent present in the water extract of heat-treated garlic. Garlic bulb contains an average 0.9% g-glutamylcysteines and up to 1.8% alliin (Lawson *et al*., 1998). Similarly, a commonly used preparation of garlic in the form of AGE (aged garlic extract) extract of 7.2 g daily for 6 months also showed the beneficial effects on the lipid profile of moderately hypercholesterolemia subjects. Its efficiency was confirmed on the basis of fact that it can decrease 6.1% in cholestrol levels and 4% decrease in LDL levels (Steiner *et al*., 1996). AGE (age garliac extract) can inhibit platelet aggregation at dose concentration of 7.2 g that is recommended by trial of using age garliac extract preparation for detection of dose dependent inhibition for platelet aggregation however fibrinolytic activity was inhibited at all doses among hypercholesterolemia patients (Steiner *et al*., 2001).

Bromelain

The crude aqueous extract from stem and fruit of pineapple is known as bromelain. Bromelain includes a grouping of sulfhydryl proteolytic enzymes obtained from the pineapple plant (*Ananas comosus*). Several protease inhibitors, carbohydrates, glycoproteins, cellulases, peroxidases, glucosidase, phosphatases are mixture of different thiol endo-peptidases wich is present in bromelain. About 12 g/day of bromelain can be consumed significantly by the body without causing any major side effects (Castell *et al*., 1997). Inhibition of platelet aggregation, fibrinolytic activity, anti-inflammatory activity and cytokine modulation as well as producing mucolytic effects and cardiovascular and circulatory improvements are done by whole bromelain extract whereas it is interesting to note that the purified proteolytic fraction has been shown to be physiologically inactive (Kelly *et al*., 1996).

Aspirin Drug

British pharmacologist John Vane in 1971 first described the mechanism of action of aspirin that involves inhibition of platelet activation and aggregation (Vane, 1971). Platelet become an excellent target for antithrombotic therapy because platelets do not have nucleus and thus cannot regenerate COX (Cyclooxygenase), while aspirin shows both immediate and long-term effects on platelets (Vane *et al*., 2003).The formation of COX-dependent vasoconstr-ictors, that contribute to endothelial dysfunction in atherosclerosis is blocks by aspirin (Husain *et al*., 1998). Furthermore, the inflammatory response in patients with coronary artery disease (Ridker *et al*., 1997) reduces by aspirin and by protecting low-density lipoprotein from oxidation may inhibit the progression of atherosclerosis (Steer *et al*., 1997).

Red yeast rice

The HMG-CoA reductase activity of red yeast rice comes from a family of naturally occurring substances called monacolins. HMG CoA (3-hydroxy-3-methyl-glutaryl-CoA)- reductase inhibitors, the drugs known as statins, reproducibly reduce CRP values, independently of their effects on lipid profiles (Ridker *et al*., 1999). Monacolin K, also known as mevinolin or lovastatin, is the ingredient in red yeast rice that Merck & Co., pharmaceutical manufacturer of Mevacor, (lovastatin), asserts is a patented pharmaceutical. Red yeast rice has one of the anti-hyperlipidemic actions attribute to consequence of an inhibitory affect on cholesterol biosynthesis in hepatic cells

showed by the results (Man *et al*., 2002). 20-40 mg daily dosages of lovastatin are daily used in clinical trials (Bradford *et al*., 1994).

Conclusion

From the liver an inflammatory marker that is known as CRP is produced to an acute infection or inflammation and its concentration in plasma can increase as much as 1000-fold during injury and infection (Schultz *et al*., 1990). CRP appears to play an important role in regulating the function of blood platelets, the extrinsic blood coagulation cascade, and the fibrinolytic system. In vivo, CRP enhances the thrombotic response to vascular injury. Inflammation upregulates CRP expression; hence, CRP appears to be an important mechanistic link between inflammation and thrombosis. Activation of the blood clotting system - specifically, activation of platelets - regulates CRP structure and biological function. Therefore, the CRP-dependent crosstalk between inflammation and thrombosis is bidirectional. Farther studies are necessary to define more precisely the pro-thrombotic functions of CRP. Elevated level of CRP increased the risk of hypertension and cardio-vascular disease. Determination of CRP is a cheap, consistent and reproducible test and is available in almost every hospital. Phytochemical treatments for cardiovascular disease offer good methods for reducing unfavorable blood-related cardiovascular risk factors. Aspirin remains the cornerstone of antiplatelet therapy in patients with cardiovascular disease. Natural-based medicines may be used both before and following actual clinical diagnosis of heart disease and, with newer cardiovascular risk factors being identified and validated, nutritional treatments can play a major role in reducing these risk factors. Monacolins are potent cholesterol lowering drugs to be administered under medical supervision.

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