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Cardiovascular Research 56 (2002) 15–21

Cardiovascular Research

www.elsevier.com/locate/cardiores

Review

Molecular and cellular interface between behavior and acute coronary syndromes

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Received 28 August 2001; accepted 8 May 2002

Abstract

This review article integrates empirical findings from various scientific disciplines into a proposed psychoneuroimmunological (PNI) model of the acute coronary syndrome (ACS). Our starting point is an existing, mild, atherosclerotic plaque and a dysfunctional endothelium. The ACS is triggered by three stages. (1) Plaque instability: Pro-inflammatory cytokines (IL-1, IL-6, TNF-α) and chemoattractants (MCP-1, IL-8) induce leukocyte chemoattraction to the endothelium, and together with other triggers such as the CD40L–CD40 co-stimulation system activate plaque monocytes (macrophages). The macrophages then produce matrix metalloproteinases that disintegrate extra-cellular plaque matrix, causing coronary plaque instability. Acute stress, hostility, depression and vital exhaustion (VE) have been associated with elevated pro-inflammatory cytokines and leukocyte levels and their recruitment. (2) Extra-plaque factors promoting rupture: Neuro-endocrinological factors (norepinephrine) and cytokines induce vasoconstriction and elevated blood pressure (BP), both provoking a vulnerable plaque to rupture. Hostility/anger and acute stress can lead to vasoconstriction and elevated BP via catecholamines. (3) Superimposed thrombosis at a ruptured site: Increases in coagulation factors and reductions in anticoagulation factors (e.g. protein C) induced by inflammatory factors enhance platelet aggregation, a key stage in thrombosis. Hostility, depression and VE have been positively correlated with platelet aggregation. Thrombosis can lead to severe coronary occlusion, clinically manifested as an ACS. Thus, PNI processes might, at least in part, contribute to the pathogenesis of the ACS. This chain of events may endure due to lack of neuroendocrine-to-immune negative feedback stemming from cortisol resistance. This model has implications for the use of psychological interventions in ACS patients.

Keywords: Coronary disease; Cytokines; Immunology; Thrombosis/embolism

1. Introduction

The acute coronary syndrome (ACS) includes unstable angina and Q-wave and non Q-wave acute myocardial infarction (MI). Most ACS patients develop occlusions in coronary arteries not severely occluded in prior angiograms [1]. This suggests that rapid and more transient processes lead to an arterial occlusion and to an ACS, rather than long-term atheroslcerotic processes related to typical risk factors (e.g. cholesterol). Indeed, during the past decade, the understanding of the etiology of the ACS has shifted from emphasis on the role of the major risk factors alone (e.g. lipids, smoking, hypertension) to the inclusion of immune factors and the inflammatory response [2,3]. This thought shift and introduction of multiple systems in the etiology of ACS allows researchers to seek a broader explanation of previous links between psychological factors and the ACS. The field of psychoneuroimmunology (PNI), as described below, provides such a broad framework. Endothelium dysfunction and injury are the basis of the onset of the atherosclerotic process [3] and psychological stress has been associated with the dysfunction of the coronary endothelium [4,5]. However, the

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Time for primary review 18 days.

0008-6363/02/$ – see front matter
PII: S0008-6363(02)00537-0

starting point of the present article is an existing moderate atheroslcerotic plaque with a dysfunctional endothelium, continuing with how PNI processes may lead to further deterioration and to the ACS. This review will first present studies linking psychological factors with the ACS, and present the current three-stage immunobiological model of the ACS. After introducing the field of PNI, we then present the PNI of the ACS. Finally, additional points and suggestions for future research and clinical implications will be suggested.

2. Psychological factors associated with the ACS

Many studies have demonstrated a relation between psychological factors and onset and prognosis of the ACS. Hostility is defined as the tendency to behave antagonistically, think cynically and feel anger [6] and has been found to be the most toxic element of the previously assumed 'coronary prone' type-A behavior pattern [7]. Hostility has been associated with unstable angina [8] and with onset of MI [9,10], and significantly predicts coronary heart disease (CHD), independent of known risk factors [7,11,12]. Vital exhaustion is defined as a state of unusual tiredness, irritability and demoralization, and significantly predicts cardiac events [13]. Finally, depression and hopelessness significantly predict ACS onset and post-MI mortality [14–16]. The few articles that related PNI factors to the ACS provide important information for understanding the PNI of CHD [17–21]. However, these previous reviews did not integrate PNI processes with the three fundamental biological stages of the ACS described below. That is the purpose of the present article.

3. The three-stage immunobiology of the ACS

3.1. Immunobiology of plaque instability

An unstable and subsequently ruptured atherosclerotic coronary plaque with superimposed thrombosis constitutes the most common general pathological background of the ACS [2]. In most cases, plaque rupture is the major cause of ACS, yet in 18–37% of ACS cases, thrombosis takes place on an eroded but not ruptured plaque [22].

The precise chronological order of the events leading to plaque instability is not entirely known. Several factors including oxidized low-density lipoprotein (OX-LDL) cholesterol [23,24], *Chlamydia pneumoniae* (CP) [25] cytomegalovirus (CMV) [26] and the co-stimulatory pair CD40L–CD40 (see below) may act as triggers leading to plaque instability. Adherence of activated polymorphonuclear cells, monocytes and lymphocytes to a dysfunctional coronary endothelium takes place in response to the activity of chemoattractants such as monocyte chemoattractant protein 1 (MCP1), interleukin-8 (IL-8), and the secretion of the pro-inflammatory cytokines IL-1, IL-6, tumor necrosis factor-α (TNF-α) and OX-LDL [2,23]. On the side of the coronary vessel, cytokines initiate the expression of endothelial adhesion molecules such as vascular cellular adhesion molecule (VCAM) and intercellular adhesion molecule (ICAM) [27], which increase binding of the leukocytes described above to the endothelium. High levels of IL-6 and IL-8 have been found in unstable angina [28,29], possibly supporting their role in ACS. Cytokines induce their own autocrine expression and the expression of such adhesion molecules via the cellular transcription factor NF-κB [27]. Support for the role of NF-κB in the instability of coronary plaques can be derived from a study finding its activation in 82% of unstable-angina patients compared to only 12% of stable-angina patients [30]. However, given the retrospective design of the latter study, it is unclear whether differences in NF-κB activity represent the antecedent or consequence of coronary instability. Monocytes adhering to the endothelium and penetrating into the plaque (macrophages) are activated by several paracrine/autocrine mediators such as macrophage colony-stimulating factor (MCSF) and by pro-inflammatory cytokines. Another important extra-plaque factor activating macrophages in the plaque is the co-stimulatory pair CD40 ligand (CD40L)–CD40. The CD40L on T-cells binds to the CD40-receptor on macrophages and this activates macrophages [31]. The CD40L–CD40 system may reflect a link between the general circulation and the coronary plaque. At this crucial stage, activated macrophages then synthesize and secrete matrix metalloproteinases (MMPs) [31]. Metalloproteinases degrade vascular extra-cellular collagen matrix, thereby weakening the cap of the coronary plaque [2,32]. Supporting their role in the ACS, these degrading factors were found to be active in a higher proportion of unstable angina cases compared to stable angina cases [33]. Furthermore, interferon (INF)-γ (of activated T-cell origin) may directly induce degradation (possibly necrosis) of smooth muscle-cells (SMC), another path by which the coronary plaque becomes weak and unstable [34]. Plaque cap weakening contributes to coronary plaque instability and vulnerability towards rupture.

3.2. Immunobiology of plaque rupture

Several factors external to the coronary plaque are thought to increase the chance of plaque rupture, particularly given a weak plaque cap occurring in the former stage. Two of these factors, vasoconstriction and elevated blood-pressure (BP) [2] are detailed in the present article given their demonstrated relation to psychological factors detailed below. Both TNF-α and IL-6 have been found to experimentally induce arterial vasoconstriction [35]. One possible pathway by which cytokines cause spasms may be by the regulation of nitric oxide (NO) production [36].

Finally, platelets circulating near the plaque, release thromboxane A_2, which causes vasoconstriction as well.

Immunological factors are also associated with elevated BP. Hypertensive patients were found to have higher levels of IL-1β than various controls, and IL-1β is positively correlated with BP ($r=0.38$) in hypertensive patients [37]. Furthermore, injection of IL-1β was found to increase sympathetic discharge and BP in anesthetized rats [38] suggesting a causal role of IL-1β in elevated BP. If sufficiently strong or enduring, vasoconstriction and elevated BP will lead to plaque rupture [2].

3.3. Immunobiology of thrombosis

Under normal conditions, the endothelium maintains balance between cell surface-associated coagulants such as tissue factor (TF), one of several molecules inducing the coagulation pathway and anticoagulant proteins (thrombomodulin, protein S). The anticoagulant pathway including protein C and protein S and cytokines (such as IL-8) have been proposed as the common link between coagulation and the inflammatory response [39,40]. Studies have shown that IL-1, IL-6 and TNF-α have been found to have a role in activation of platelets [41]. These cytokines induce the expression of adhesion molecules (e.g. VCAM) on endothelial cells as mentioned above, and also attract platelets to the ruptured site. TNF-α is capable of inducing expression of TF on monocytes and on endothelial cells and down regulating thrombomodulin and protein S [42]. TF then begins the coagulation cascade [43]. Furthermore, following stimulation by IL-1 or TNFα, endothelial cells can switch from anticoagulant to procoagulant participants [44], and the balance between pro and anticoagulation factors may be then impaired, leading to hypercoagulation. The CD40L–CD40 system could also affect thrombosis as it induces macrophages to secrete TF [31]. Hypercoagulability at a site of plaque rupture may then cause severe coronary occlusion in a previously moderately occluded plaque. Severe coronary occlusion may in turn result in any form of ACS—unstable angina or MI potentially leading to death as well.

4. The field of psychoneuroimmunology

The field of psychoneuroimmunology (PNI) investigates the relations between psychological factors and immune and neuroendocrine pathways, and the implications of such relations to illness and health. Psychological factors have been repeatedly related to enumerative and functional indices of the immune system (for meta-analysis, see Refs. [45,46]), to the common cold and wound healing rate [47–49], and to people's immune response to vaccinations [50]. Psychological interventions were found to affect various immune parameters such as lymphocyte proliferation [51] and cytokine patterns in asthmatic children [52]. Psychological factors have also been associated with factors construed as 'antigens' in the etiology of ACS such as oxidated LDL [53] and activation of viral and microbial agents [54].

How does the brain communicate with the immune system? The brain affects immune responses via the hypothalamic–pituitary–adrenal (HPA) axis. The HPA axis enhances the inflammatory response by secreting corticotrophic releasing hormone and adrenocorticotrophic hormone from the hypothalamus and pituitary gland, respectively, while the adrenal gland secretes cortisol that suppresses the inflammatory response. Cells of the immune system express receptors for these hormones. The immune to brain pathway is less evident. The brain receives signals about a local visceral immune response, and thereafter orchestrates a systemic inflammatory response in the following manner. Peripheral IL-1 at local inflamed visceral sites triggers vagal afferents to the central nervous system (CNS). More specifically, the vagal nerve sends neural signals to the hypothalamus via the nucleus tractus solitarius [55–57]. The hypothalamus and the HPA axis have been shown to be activated as a function of time and dose of peripheral IL-1 stimulation [58,59], and to orchestrate the inflammatory response. Two other brain regions, namely the amygdala and medulla, modulate the effects of IL-1 on the HPA axis [59,60]. This may be crucial to PNI since the amygdala has a prominent role in various psychological states such as helplessness [61] and depression [62], and the medulla is cardinal to breathing and to hypertension.

5. The psychoneuroimmunology of the ACS

5.1. PNI of plaque instability

Many of the immune/inflammatory factors playing a role in plaque instability have been correlated with psychological factors. Appels et al. [54] found that subjects high on vital exhaustion (VE) had significantly higher titers to CMV than those low on VE. In a meta-analysis of methodologically sound studies, depression was correlated with cellular immune suppression [63], which is critical to activation of agents including CMV and CP. Elevations of plasma pro-inflammatory cytokines (e.g. IL-1) and decreases in anti-inflammatory cytokines (e.g. IL-4) have been associated with acute stress [64–66], with VE among cardiac patients [17] and with depression [67,68]. Vital exhaustion has also been associated with reduced activity of plasminogen activator inhibitor I, which may lead to increased fibrinolysis [69]. The latter may then lead to further instability of the plaque by breaking extra-cellular plaque components and by enhancing additional immune activity. It has recently been found that hostility and life-events were positively correlated with percentage of monocytes, while perceived control and social support

were inversely correlated with percentage of monocytes in the blood of ACS patients [70]. Together, these relations suggest that psychological factors may affect synthesis of pro-inflammatory cytokines, recruitment of monocytes, activation of viral agents and oxidation of LDL. In the context of a moderate atherosclerotic plaque and a dysfunctional endothelium, such psychologically induced immune and inflammatory activation may contribute to plaque instability via one of the triggers described above (see Table 1).

5.2. PNI of plaque rupture

Degree of anger while recalling an annoying event was strongly correlated with vasoconstriction ($r=0.82$) in narrowed CAD vessels [71]. Hostility is positively correlated with sympathetic arousal [72], and vasoconstriction is sympathetically mediated [73]. Narrowed arteries with dysfunctional endothelium appear to be sensitive to sympathetic arousal [74], making such arterial segments more prone towards anger-induced vasoconstriction. Psychological states have been associated with TNF-α and IFN-γ as mentioned above [17], which may increase the vasoconstrictor endothelin-1 [75]. Finally, platelets, which are also correlated with anger/hostility (see below), release thromboxane A_2, which causes vasoconstriction as well.

Hostility may be causally related to BP since reductions in hostility were significantly positively correlated with, and preceded in time, reductions in diastolic-BP in a randomized-controlled hostility-reduction trial [76]. An immunological pathway linking psychological stress to elevated BP was also identified since stress-induced elevations in BP were found to be strongly correlated (between $r=0.63$ and 0.70) with stress-induced changes in IL-6 and IL-1 receptor antagonist [66].

Hostility-induced vasoconstricton and elevations in epinephrine and norepinephrine [72] may result in high cardiac-output, blood-flow and BP, which may increase shear stress. High shear stress also increases the risk of rupturing a vulnerable plaque [2] (see Table 1).

5.3. PNI of thrombosis

Anger-expression and hostility have been found to be significantly and positively correlated with platelet aggregation [73], platelet activation as indexed by β-thromboglobulin (BTG) [74], and with activation of fibrinogen receptors and fibrinogen binding [80]. Epinephrine, associated with anger and hostility [72], was found to enhance thrombosis as well [76]. Depression is associated with enhanced activation of platelets and with enhanced release of BTG [77,78]. Depression is also associated with elevated IL-6, which as mentioned above, can activate platelets as well [41] (see Table 1).

In summary, all three basic stages of the ACS (plaque instability, plaque rupture, and thrombosis) can be partly explained by converging multidisciplinary evidence, modeled by a PNI framework (see Table 1). These processes can be explained by linking events taking place at the level of the central nervous system (e.g. brain secretion of norepinephrine), systemic immune and neuroendocrine level (e.g. recruitment of T-cells), and at the molecular and cellular level of the coronary plaque (e.g. macrophage release of MMP), all contributing to the probability of an ACS. Table 1 depicts the entire proposed PNI model integrated into the three phases of the ACS. We believe that this model not only partly explains previously demonstrated relations between psychological factors and the ACS [9–11,13–16], but may add to and broaden the biological model of the ACS.

6. Maintenance of a psychoneuroimmunologically induced ACS

Two processes may explain how PNI-induced effects may endure and lead to an ACS. The first concerns

Table 1
Psychological, neuroendocrine, immunological and hemodynamic factors in the acute coronary syndrome

Psychological factors	Neuroendocrine factors	Immune and cell factors	Hemodynamic factors	Acute coronary syndrome stage
Hostility, depression, acute stress and vital exhaustion	Norepinephrine, CRH, ACTH, Cortisol	IL-1β, IL-6, TNF-α, IFN-γ, monocytes, MMPs		Plaque instability
Hostility and acute stress	Norepinephrine Epinephrine	IL-1β, IL-6, TNF-α	Vasoconstriction, elevated BP, shear stress	Plaque rupture
Hostility, depression	Epinephrine	IL-1β, IL-6, TNF-α,	Pro-coagulant and anti-coagulant factors (C-protein)	Thrombosis⇒ acute coronary syndrome

CRH, corticotrophic releasing hormone; ACTH, adrenocorticotrophic hormone; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; BP, blood pressure; MMPs, metalloproteinases.

relations between the three proposed stages. It is possible that superimposed thrombosis may actually amplify plaque instability in the following manner. Activation of platelets may induce leukocyte-platelet adhesion units, which have been found to markedly increase levels of IL-1, IL-8 and MCP-1 [79]. These elevations may then restart a continuous cycle of monocyte recruitment and macrophage-induced plaque instability. Under conditions of vasoconstriction or elevated BP, plaque rupture may then occur, resulting again with thrombosis, and further increase the probability of an ACS.

Second, persistence of immune processes thought to be critical in the etiology of the ACS may result from an imbalance between neuroendocrine factors that enhance and factors that inhibit immune responses. Over-activity of the immune response requires lack of the usual negative feedback induced by cortisol on immune/inflammatory responses. This feedback is expected to occur due to the immune to brain communication described earlier, involving the vagal nerve. Chrousos [80] proposed that 'cortisol-resistance' can lead to lack of attenuation of the inflammatory response. Certain psychological factors linked to ACS such as depression (atypical depression) and certain physical illnesses linked to ACS such as rheumatoid arthritis [81] are indeed characterized by cortisol resistance [80]. Such cortisol resistance (insufficient cortisol-induced immune suppression) may account for the persistence of PNI processes and of the inflammatory response etiologically important in the ACS as described above.

7. Future directions and implications for treatment

Several issues need to be clarified in future research in relation to the proposed model. First, do different psychological states (hostility/anger, acute stress, vital exhaustion and depression) lead to ACSs of different severity mediated via different elements of the model, or is the combination of psychological traits/states necessary for an ACS? Given the multiple roles of OX-LDL and the CD40L–CD40 co-stimulatory system, future studies need to examine whether drug treatments targeting them may minimize a PNI-mediated ACS. Finally, more work needs to be done on the role of cortisol resistance in the maintenance of PNI processes potentially leading to an ACS.

The proposed model may explain the effects of psychological interventions on reducing mortality in ACS [82]. Certain behavioral techniques such as relaxation and guided imagery have been found to reduce inflammatory responses [83] and to positively affect post-MI patients [84]. The medulla and amygdala modulate the effects of peripheral IL-1 on the HPA axis [60]. Accordingly, one may speculate that relaxation techniques, which affect breathing and sympathetic arousal, may regulate a centrally orchestrated inflammatory response associated with the ACS. Should relaxation reduce inflammatory responses in ACS patients, this may reduce adverse outcomes following inflammatory responses in ACS [85,86]. These issues are currently under investigation by our research team and by others. Finally, beta-blockers, such as nadolol, which reduce aggression and suspiciousness [87], may also be tested for their effectiveness in reducing hostility.

Acknowledgements

The authors wish to thank Professor Charles Dinarello and Dr Hava Golan for providing their comments on earlier versions of this manuscript.

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