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Brief Commentary

On the heart, the mind, and how inflammation killed the Cartesian dualism. Commentary on the 2015 Named Series: Psychological Risk Factors and Immune System Involvement in Cardiovascular Disease

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ABSTRACT

The 2015 Named Series on "Psychological Risk Factors and Immune System Involvement in Cardiovascular Disease" was conceived with the idea of drawing attention to the interdisciplinary work aimed at investigating the relationships between the heart, metabolic system, brain, and mental health. In this commentary, we provide a brief overview of the manuscripts included in this Named Series and highlight how a better understanding of immune regulation will help us to move forward from the current "dualistic" perspective of the heart as separate from the mind to a more comprehensive understanding of the physiological links between cardiovascular and mental disorders. The manuscripts included in this Named Series range across a wide spectrum of topics, from understanding biological mechanisms explaining comorbidity between cardiovascular disease and psychiatric disorders to new insights into the dysregulation of inflammation associated with cardiovascular risk factors. Clearly, inflammation emerges as a cross-cutting theme across all studies. Data presented in this Series contribute to putting an end to an era in which the heart and the mind were considered to be separate entities in which the responses of one system did not affect the other.

1. Introduction

During the last decade, links between physical and mental illnesses have been increasingly described and acknowledged. This has led not only to implementation of a more holistic therapeutic approach for patients, but it has also raised new research questions about etiopathogenesis that has led to investigations of novel diagnostic and therapeutic strategies. Of note, the relationship between the heart, metabolic system, and brain has become a particularly strong focus of this research in the past few years. We conceived the 2015 Named Series on "Psychological Risk Factors and Immune System Involvement in Cardiovascular Disease" to draw attention to interdisciplinary work carried out to investigate this relationship. Manuscripts included in this Named Series are wonderful ambassadors of the wide spectrum of studies conducted in this area, ranging from understanding biological mechanisms explaining comorbidity between cardiovascular disease and psychiatric disorders to new insights in the dysregulation of inflammation associated with cardiovascular risk factors. Indeed, inflammation emerges as a cross-cutting theme across the studies, which finally starts to clarify associations between cardiovascular diseases and mental illnesses. In this commentary, we aim to give a brief overview of the manuscripts included in this Named Series and highlight how a better understanding of immune regulation will help us to move forward from the dualistic perspective of the heart and the mind to a more comprehensive view in which cardiovascular and mental disorders are closely interlinked.

2. Looking for a biological link between cardiovascular diseases and depression

Cardiovascular diseases and depression have often been found to coexist and their comorbidity has been acknowledged to be associated with poorer prognosis for patients with cardiovascular disease (Meijer et al., 2011). Identification of possible common risk factors has been suggested to be fundamental for a better understanding of common underlying etiopathogenesis and development of effective treatments.

Lagraauw et al. (2015) provide a comprehensive overview of both human and animal studies supporting the contribution of

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acute and chronic stress (well known risk factors for development of depression) to increased cardiovascular risk. The authors review how the biological systems activated in the stress response, such as the hypothalamus–pituitary–adrenal (HPA) axis, sympathetic adrenomedullary system, renin–angiotensin–aldosterone system, and the cholinergic system, affect the cardiovascular system directly or indirectly through modulation of the immune system. This summary is particularly relevant in the context of increasing evidence showing the effects of childhood adverse events on adult physical and mental health (Baumeister et al., 2015a). Lagraauw et al. (2015) highlight the potential role of therapeutic modulation of psychosocial risk factors in patients with cardiovascular diseases. Indeed, it still remains to be established if current psychological treatments and psychotropic medications can influence some of the biological systems involved in the response to stress (Baumeister et al., 2015b) and consequently improve cardiovascular health. Nikkheslat et al. (2015) found increased levels of the inflammatory markers C reactive protein (CRP), interleukin-6 (IL-6) gene expression and vascular endothelial growth factor (VEGF) in coronary heart disease patients with depression when compared with coronary heart disease patients without depression. Interestingly, coronary heart disease patients with depression also presented with reduced glucocorticoid receptor expression and sensitivity, as well as increased activation of the kynurenine pathway. These findings greatly contribute to a better understanding of the biological pathways, and in particular of inflammation, that link these two disorders. Gouweleeuw et al. (2015) review the role of the inflammatory marker neutrophil gelatinase associated lipocalin (NGAL) in cardiovascular disease and depression, reporting evidence form both animal and human studies. Increased circulating levels of NGAL have been previously associated with depression in patients with heart failure (Naude et al., 2014). In this review (Gouweleeuw et al., 2015), we learn about factors that modulate the function of NGAL as well as its function in the central nervous system. The authors propose mechanisms through which NGAL may mediate the link between peripheral disease and onset of depression by focussing on the effects of NGAL on microglial activation, astrocytosis and neuronal migration and apoptosis. We believe that this research may uncover important target pathways for future therapeutic strategies for patients experiencing comorbidity of cardiovascular disease with depression.

Chang et al. (2015) focussed on another known link between the two disorders, the omega-3 polyunsaturated fatty acids (N3 PUFAs) pathway. Previous studies have shown lower levels of N3 PUFAs both in cardiovascular diseases and depression (Peet et al., 1998; Whelton et al., 2004), and that administration of N3 PUFAs helps prevent depression (Su et al., 2014). In their short report, Chang et al. (2015) evaluated levels of N3 PUFA in patients with cardiovascular diseases comorbid with and without depression. Their data establish that patients with cardiovascular diseases and comorbid with moderate or severe depression have lower N3 PUFAs levels than patients without depression. Interestingly, this difference is not present in patients with mild depression, suggesting a possible role of N3 PUFAs in patients who present with more severe depressive symptoms.

Another cardiovascular disorder that is associated with increased prevalence of depression and anxiety, the cardiac syndrome X, appears characterised by the presence of increased inflammation. Cardiac syndrome X is usually defined by the presence of angina pectoris despite normal epicardial coronary arteries. In our Named Series, Dollard et al. (2015) show increased CRP levels in patients with cardiac syndrome X compared with healthy controls. Moreover, they show that CRP levels change prospectively in these patients according to other functional measures of disease severity, suggesting a possible role for CRP as state marker of this syndrome.

3. Is depression associated with heart disease different from other depressive syndromes?

One question that indirectly arises from all these studies is whether depression in patients with cardiovascular disease is biologically and phenotypically different from other types of depression observed in psychiatry. Of note, this is of particular interest at a stage where the Research Domain Criteria (RDoC) research framework proposed by NIH for the study of mental disorders has underlined the need to look at molecules and biological circuits, which could explain functional dimensions of behaviour rather than tying ourselves to diagnostic classifications based on symptoms. In this context, Granville Smith et al. (2015) have produced an excellent review examining the notion that depression associated with acute coronary syndrome may constitute a subtype of depression that may be qualitatively different from other depression syndromes present in psychiatric patients. The authors report inconclusive findings from previous literature, suggesting a certain degree of heterogeneity, which may depend on additional factors such as genetic and acquired vulnerabilities or abnormalities in the stress response. Interestingly, given the presence of individual differences in inflammatory responses across patients with acute coronary syndrome, the authors also suggest the possibility that individuals with specific inflammatory marker profiles might express different depression phenotypes.

In a subsequent paper from the same group, Vollmer-Conna et al. (2015) try to directly address this issue by examining a wide range of immunological, autonomical and nutritional markers in a large sample of patients with acute coronary syndrome, who either had developed depression before developing acute coronary syndrome, or developed depression afterwards, or were not depressed. The authors report that the regression model using immunological, autonomical and nutritional markers fails to predict being part of the group with depression associated with acute coronary syndrome. However, using an alternative data-driven approach, they identify a subgroup of patients with acute coronary syndrome who are characterised by increased inflammation, low heart rate variability and poor nutritional status. Their findings appear to support again that depression associated with acute coronary syndrome is not a distinct subcategory of depression, but, on the other hand, identify a combination of biological pathways, which appear to be involved in increased vulnerability for developing depression during acute coronary heart syndrome.

4. Not only depression: the link between inflammation and cardiovascular risk in psychosis

Cardiovascular disease has not been associated only with depression, but it is increasingly acknowledged as a leading cause of mortality in patients with psychosis (Brown et al., 2010). The increased cardiovascular risk for patients with psychosis has been largely attributed to the increased prevalence of obesity and related antipsychotic induced weight-gain and metabolic abnormalities. Despite the severe consequences of metabolic abnormalities and cardiovascular diseases in these patients, still very little has been done so far to understand biological mechanisms that underlie the association between psychosis and cardiovascular risk. Indeed, inflammation is one of the biological mechanisms recently proposed to play a role.

In our Named Series, two papers investigated possible predictors of metabolic and cardiovascular abnormalities in patients with psychosis by focusing in particular on inflammatory markers. Miller et al. (2015) found that lymphocyte and monocyte counts are a significant predictor of total-to-HDL cholesterol ratio in subjects with non-affective psychosis and that white blood cell count