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Review

Platelet activating factors in depression and coronary artery disease: A potential biomarker related to inflammatory mechanisms and neurodegeneration

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ABSTRACT

The persistence of a depressive episode in coronary artery disease (CAD) patients not only heightens the risk of acute ischemic events, but it is also associated with accelerated cognitive decline. Antidepressant interventions for depression in CAD have only modest effects and novel approaches are limited by a poor understanding of etiological mechanisms. This review proposes that the platelet activating factor (PAF) family of lipids might be associated with the persistence of a depressive episode and related neurodegenerative pathology in CAD due to their association with leading etiological mechanisms for depression in CAD such as inflammation, oxidative and nitrosative stress, vascular endothelial dysfunction, and platelet reactivity. The evidence implicating PAFs in CAD, vascular pathology, and neurodegenerative processes is also presented. We also propose future directions for the investigation of PAFs as mediators of persistent depression. In summary, PAFs are implicated in leading mechanisms associated with depression in CAD. PAFs may therefore be associated with the persistence of depression in CAD and related to neurodegenerative and cognitive sequelae.

Contents

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1. Introduction

Coronary artery disease (CAD) is a leading cause of mortality in the developed world (WHO, 2011). CAD is characterized by inflammation with extravasation of immune cells into the subendothelial space contributing to the formation and/or progression of atherosclerotic plaques and thickening of the artery walls. Accordingly, circulating inflammatory mediators, in conjunction with vascular risk factors including hypertension, dyslipidemia, and diabetes, are associated with the presence of vascular endothelial dysfunction, atherogenesis in the coronary and peripheral vessels, and an elevated risk of thrombosis (Mizuno et al., 2011). These lead to progressive CAD-related morbidity and a heightened risk of acute ischemic events such as myocardial infarction or stroke (Mizuno et al., 2011).

Up to 20% of CAD patients experience a major depressive episode within the first year following an acute coronary syndrome (ACS), an incidence rate that is 2–3 fold greater than that in the general adult population. A further 30–45% of CAD patients suffer from clinically significant symptoms consistent with minor depression (Sowden and Huffman, 2009; Celano and Huffman, 2011) and these are a risk factor for future major depressive episodes (Patten et al., 2012). The presence of a depressive episode in CAD patients is associated with an elevated risk of secondary acute ischemic events, poorer compliance with risk factor interventions, and increased mortality independently of traditional cardiac risk factors (reported odds ratios between 1.64 and 2.59) (Januzzi et al., 2000; Barth et al., 2004; Carney et al., 2004; van Melle et al., 2004). In the setting of secondary ACS prevention; depression is associated with increased dropout from exercise-based cardiac rehabilitation programs and less cardiopulmonary benefit among program completers (Swardfager et al., 2011). Although a depressive episode can often be transient in CAD patients, it can also become chronic and may persist for one year or longer (Frasure-Smith et al., 1999; Lauzon et al., 2003). The persistence of a depressive episode is a strong risk factor for cognitive decline and transition to dementia in CAD patients (Saczynski et al., 2010; Barnes et al., 2012; Freiheit et al., 2012). Intervention trials have demonstrated that response rates to antidepressant pharmacotherapies are modest (number needed to treat [NNT] = 4–32) suggesting that, for those who seek treatment, relatively high numbers of patients are treated unsuccessfully for every successful treatment of a depressive episode (Dowlati et al., 2010a). Considering the negative cardiac and cognitive consequences of persistent depression in CAD patients, adequate antidepressant interventions are a clinically important unmet need in CAD (Carney et al., 2004; Freiheit et al., 2012).

The association between depression and CAD is complex and may be complicated by genetic, lifestyle, and metabolic factors (de Jonge et al., 2010) that may differentially contribute to transient or persistent depressive episodes. As such, the mechanisms responsible for the persistence of depression, related neurodegeneration, and associated cognitive decline in CAD have yet to be established; however, several reviews have proposed etiological mechanisms for depression in CAD that are consistent with proposed mechanisms of neurodegeneration associated with depression (Carney et al., 2005; de Jonge et al., 2010; Khan et al., 2010; Celano and Huffman, 2011; Sanner and Frazier, 2011; Stapelberg et al., 2011; Baune et al., 2012; Moylan et al., 2012). Evidence suggests that elevated peripheral concentrations of inflammatory biomarkers, vascular endothelial dysfunction, and heightened platelet reactivity may be important processes that contribute to depression in CAD patients (de Jonge et al., 2010; Celano and Huffman, 2011) (Table 1). Aberrant lipid metabolism and reduced tissue concentrations of polyunsaturated fatty acids have also been observed in CAD patients with and without depression (de Jonge et al., 2010; Stapelberg et al., 2011), as well as those with depression who are otherwise medically healthy (Maes et al., 1996, 1999), implicating lipid signaling in the comorbidity. While the directionality of these associations is likely heterogeneous, it is thought that repeated or prolonged activity of inflammatory processes and related pathophysiology can contribute to the persistence of depressive episodes and lead to neurodegeneration (as reviewed Maes et al., 2011; Moylan et al., 2012).

Here we review the evidence suggesting that the platelet activating factor (PAF) family of lipids may function as mediators, potentially being associated with the persistence of depression and related neurodegeneration and cognitive decline in CAD patients. We will review the synthesis and known signaling effects of PAFs with respect to the inflammatory response, oxidative and nitrosative stress, vascular endothelial dysfunction, and platelet reactivity; leading etiological mechanisms associated with depression and CAD. The evidence supporting PAFs as mediators of CAD, neurodegeneration, and cerebrovascular pathology will also be reviewed. Finally, we will propose future directions for the investigation of PAFs as biomarkers of persistent depression and associated neurodegeneration in CAD.

2. Methods

Supporting data used for this review were collected using the electronic databases PUBMED, EMBASE, and PsychInfo and were not limited by publication date or language. PAF data were searched systematically using the above databases using the keywords “platelet activating factor”, “platelet activating factor acetylhydrolase”, “PAF”, “alkyl-PAF” and “*lyso*-PAF” (Supplementary Fig. 1).

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2013.06.010.

3. Platelet activating factors

PAFs are a family of potent pro-inflammatory phospholipids that are released by several cell types participating in vascular and immune homeostasis such as macrophages, monocytes, and endothelial cells (Farooqui et al., 2007). PAFs were the first ether-linked lipid family identified by their biological activity and were shown to be released from histamine-stimulated rabbit basophils eliciting platelet aggregation (Benveniste et al., 1972). The structural diversity of PAF species has since been elucidated. For example, PAF lipids are members of the 1-alkyl-2-acylglycerophosphocholine (AAGPC) subclass (GP0102) of glycerophosphocholines (GP01) (LipidMAPS, 2012). Family members are defined by an alkyl ether linkage at the *sn*-1 position, an acetyl group at the *sn*-2 position, and a phosphocholine at