Neuroscience and Biobehavioral Reviews 37 (2013) 1611–1621

Contents lists available at SciVerse ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

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

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ARTICLE INFO

Article history:
Received 20 February 2013
Received in revised form 7 May 2013
Accepted 13 June 2013

Keywords:
Depression
Coronary disease
Platelet activating factor
Vascular endothelial dysfunction
Inflammation
Oxidative stress
Neurodegeneration
Cerebrovascular
Neuroprogression

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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0149-7634/$ – see front matter.
http://dx.doi.org/10.1016/j.neubiorev.2013.06.010

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

Table 1
Shared inflammatory and physiological characteristics in CAD and depression.

	CAD	Depression	PAFs
Inflammation	• ↑ CRP, IL-6, and TNF-α associated with increased risk of mortality (Bruunsgaard et al., 2000; Lindmark et al., 2001; Kaptoge et al., 2010)	• ↑ TNF-α, IL-6, IL-1β, CRP, sIL-2R in the serum of depressed patients (Howren et al., 2009; Dowlati et al., 2010b; Liu et al., 2011)	• Pro-inflammatory cytokines activate PLA_2 (Adibhatla et al., 2008)
	• TNF-α, IFN-γ, MMPs secreted by immune cells during atherosclerotic plaque development (Weber and Noels, 2011)	• ↑ IL-6 in CSF of suicide attempters associated with depressive symptom severity (Lindqvist et al., 2009)	• PLA_2 activation releases *lyso*-PAF and arachidonic acid (Kita et al., 2006)
	• Higher Lp-PLA_2 (PAF-AH) activity is associated with risk of CAD (Schmitz and Ruebsaamen, 2010)	• ↑ pro-inflammatory cytokine expression in the brains of depressed patients and suicide victims (Tonelli et al., 2008; Shelton et al., 2011; Pandey et al., 2012)	• PAFs activate $iPLA_2$ and COX_2 which metabolize arachidonic acid into inflammatory eicosanoids (Farooqui et al., 2007)
		• ↑ serum K/T ratio is associated with depressive symptoms (Swardfager et al., 2009)	• PAFs induce IL-6 and TNF-α release from leukocytes and platelets (Rola-Pleszczynski et al., 1992; Thivierge and Rola-Pleszczynski, 1992)
Endothelial dysfunction	• Independent risk factor for ACS in CAD patients (Hinderliter and Caughey, 2003)	• Impaired FMD is associated with severity of depressive symptoms (Cooper et al., 2011)	• Elevated $sPLA_2$ and Lp-PLA_2 activity associated with endothelial dysfunction and atherosclerosis (Farooqui et al., 2007; Adibhatla et al., 2008)
	• Increased risk of coronary artery restenosis after PCI (Munk et al., 2011)	• Impaired small artery dilatation in depressed patients (Paranthaman et al., 2012)	• PAFs induce surface expression of ICAM-1 and VCAM-1, facilitating leukocyte adhesion to endothelial cells (Farooqui et al., 2007)
	• Vascular risk factors associated with endothelial damage and dysfunction (Hinderliter and Caughey, 2003)	• Ineffective ischemic postconditioning in depressed patients (Zhuo et al., 2011)	• Associated with reduced NO bioavailability and enhanced peroxynitrite formation (Klabunde and Anderson, 2002; Yang et al., 2010)
Platelet reactivity	• Associated with increased risk of ACS (Celano and Huffman, 2011)	• ↑ β-thromboglobulin, platelet factor 4, P-selectin, and mean platelet volume in depression with and without CAD (Laghrissi-Thode et al., 1997; Piletz et al., 2000; Canan et al., 2011)	• Potent activators of platelet aggregation (Farooqui et al., 2007)
	• ↑ platelet-monocyte aggregates in CAD patients (Wang et al., 2007)	• ↑ plasma serotonin (Wulsin et al., 2009)	• PAFs can induce TNF-a release from platelets which then induces PAF release from endothelial cells and leukocytes (Montrucchio et al., 1994; Im et al., 1996)

CRP, C-reactive protein; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; MMP, matrix metalloproteinase; CAD, coronary artery disease; Lp-PLA_2, lipoprotein phospholipase A_2; $sPLA_2$, secreted phospholipase A_2; $iPLA_2$, Ca^{2+}-independent phospholipase A_2; PAF, platelet activating factor; COX_2, cyclo-oxygenase 2; PAF-AH, platelet activating factor acetylhydrolase; CSF, cerebrospinal fluid; ACS, acute coronary syndrome; PCI, percutaneous coronary intervention; FMD, flow-mediated dilation; sIL-2R, soluble IL-2 receptor; NO, nitric oxide; ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

the *sn*-3 position. Related PAF-like lipids include the acyl-PAFs, phosphatidylcholines (PCs) with a short chain acetyl group at the *sn*-2 position, ethanolamine-PAFs (GP0202) (LipidMAPS, 2012), inositol-PAFs (GP0602) (LipidMAPS, 2012), and oxidized alkylacyl- and phosphatidyl glycerophosphocholines (Watson et al., 1995; Chen et al., 2007). PAF lipids have many diverse physiological actions, including bronchoconstriction (Kasperska-Zajac et al., 2008), vessel dilation (Kuebler et al., 2010), and in the CNS, facilitation of long-term potentiation (Arai and Lynch, 1992; Wieraszko et al., 1993; Chen et al., 2001).

3.1. The PAF synthesis pathway

Two pathways for production of PAF lipids have been described; the de novo synthesis pathway and the remodeling pathway. The de novo synthesis pathway is a minor pathway for PAF synthesis regulating homeostatic levels whereas the remodeling pathway is the primary avenue for PAF production in response to cellular activation (as in the inflammatory response) (Snyder et al., 1996; Shindou et al., 2009). Plasma PAF-acetylhydrolase (PAF-AH), also known as lipoprotein-associated phospholipase A_2 (one of three PAF-AH subtypes), is secreted into circulation by both endothelial and hematopoietic cells (Asano et al., 1999) and inactivates PAFs into their *lyso*-PAF intermediates through a deacetylation mechanism (Arai et al., 2002) (Fig. 1). As PAFs are acute response signaling lipids, the plasticity of this pathway allows for homeostatic regulation of their concentrations in plasma.

3.2. PAF signaling

In the periphery, PAF lipids are synthesized predominantly by activated endothelial cells and they are displayed at the cell surface for intercellular communication (McIntyre et al., 1985; Balestrieri et al., 2003) or released from monocytes/macrophages, basophils, and activated leukocytes acting, in part, to signal platelet aggregation (Elstad et al., 1988; Cluzel et al., 1989). While both PAF receptor (PAFR)-dependent and independent signaling pathways have been elucidated in the central nervous system (CNS) (Chen et al., 2001; Ryan et al., 2007), the majority of actions of PAFs and related analogs in the periphery have been attributed to the activation of the G-protein coupled PAFR (Ishii and Shimizu, 2000). Species identity, differentiated by heterogeneity in linkage, degree of unsaturation, and carbon chain length of the alkyl or acyl chains at the *sn*-1 position, partially dictates signaling specificity by eliciting various signal transduction pathways following PAFR activation (Satouchi et al., 1981; Ryan et al., 2008). PAFR is highly expressed by cells within the innate immune and cardiovascular systems (McIntyre, 2012), pointing to a role for PAFs as pleiotropic communicators in plasma (Montrucchio et al., 2000). Under normal circumstances, PAF concentrations in plasma are tightly regulated.

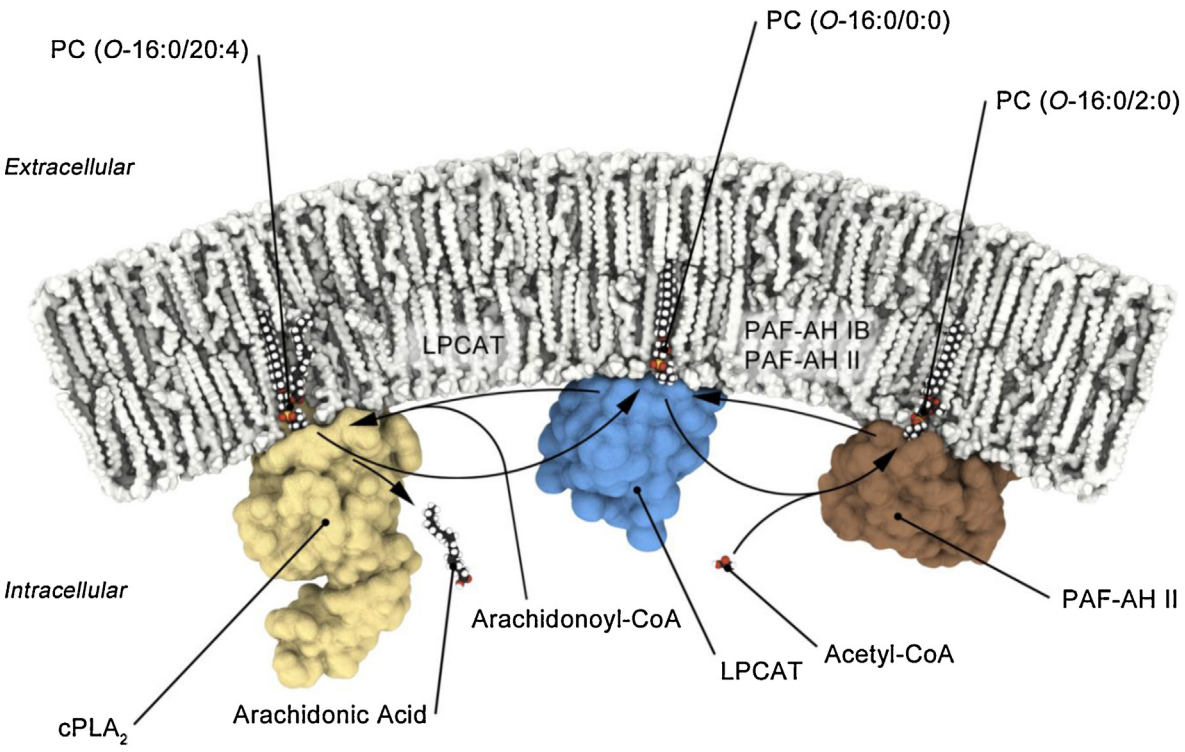

Fig. 1. The alkylacylglycerophosphocholine remodeling pathway. Also known as Lands' cycle, this two-step pathway is the primary PAF synthesis pathway during an inflammatory response. In this example, arachidonic acid is cleaved from a membrane AAGPC, PC (O-16:0/20:4), by $cPLA_2$ at the inner plasma membrane. The *lyso*-PAF intermediate, PC (O-16:0/0:0), is remodeled to a PAF, PC (O-16:0/2:0) using acetyl-coA as a donor. Synthesized PAFs can then flip to the outer plasma membrane where they are released into the extracellular space. PAFs that are not released may be remodeled back to the parent AAGPC through a PAF-AH mediated deacetylation mechanism, followed by the addition of arachidonic acid to the *lyso*-PAF intermediate via the LPCATs. *Abbreviations*: AAGPC, alkylacylglycerophosphocholine; $cPLA_2$, cytosolic phospholipase A_2; LPCAT, *lyso*phosphatidylcholine acyltransferase; PAF, platelet activating factor; PAF-AH, PAF acetylhydrolase.

However, production of PAFs can become elevated and/or dysregulated during extended periods of immune activation (Callea et al., 1999) and this been observed in CAD (Zheng et al., 2012) and in the CNS (Farooqui et al., 2007).

4. Emerging mechanisms in depression and CAD: a role for PAFs?

4.1. Inflammation

The association between elevated pro-inflammatory activity and CAD is well established (Ridker, 2007). Pro-inflammatory mediators, including many cytokine and lipid species, induce endothelial expression of cellular adhesion molecules (e.g. vascular cell adhesion molecule; VCAM-1) involved in recruiting monocytes to the vascular endothelium (Weber and Noels, 2011). Once recruited, monocytes become activated and participate in the formation of atherosclerotic plaques by releasing matrix metalloproteinases, nitric oxide (NO), and pro-inflammatory cytokines such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α (Weber and Noels, 2011). Type 1 helper T (Th1) cells also infiltrate the developing plaque and are activated by oxidized low density lipoprotein (Weber and Noels, 2011). Active Th1 cells secrete additional pro-inflammatory cytokines such as IFN-γ and TNF-α which are found abundantly in atherosclerotic lesions and exacerbate atherogenesis (Weber and Noels, 2011). Emerging evidence further suggests that interleukin (IL)-17 expressing lines of helper T cells might also contribute to atherogenesis and ischemic reperfusion injury by enhancing neutrophil and monocyte recruitment (Butcher et al., 2012; Liao et al., 2012). Elevated levels of circulating pro-inflammatory mediators such as C reactive protein (CRP) (Kaptoge et al., 2010), VCAM-1 (Blankenberg et al., 2001), IL-6 (Lindmark et al., 2001) and TNF-α (Bruunsgaard et al., 2000) are associated with an increased risk of mortality in CAD patients.

The association between depression and pro-inflammatory activity has been well characterized including increased peripheral blood concentrations of TNF-α (Howren et al., 2009; Dowlati et al., 2010b; Liu et al., 2011), IL-6 (Howren et al., 2009; Dowlati et al., 2010a; Liu et al., 2011) IL-1β (Howren et al., 2009), CRP (Howren et al., 2009) and the soluble IL-2 receptor (Liu et al., 2011). Pro-inflammatory activity in the CNS has also been documented (Levine et al., 1999; Lindqvist et al., 2009). For instance, elevated concentrations of IL-6 were detected in the cerebrospinal fluid (CSF) of suicide attempters when compared to controls and these concentrations were related to the severity of depressive symptoms (Lindqvist et al., 2009). Elevated gene expression of pro-inflammatory cytokines in the brains of depressed patients (Shelton et al., 2011) and suicide victims (Tonelli et al., 2008; Pandey et al., 2012) also implicates neuroinflammation.

Immune activation and PAF synthesis are closely linked. During an immune response, pro-inflammatory mediators such as cytokines may initiate the PAF synthesis cascade by activating several isoforms of phospholipase A_2 (PLA_2) (Adibhatla et al., 2008). Cytosolic PLA_2 is primarily responsible for the liberation of the PAF intermediate, *lyso*-PAF, and arachidonic acid from membrane phospholipids and it plays an important role in potentiating the inflammatory eicosanoid cascade (Kita et al., 2006). Other isoforms, such as secreted PLA_2 and lipoprotein-associated PLA_2, are also associated with PAF activity and have been implicated in the development of endothelial dysfunction and atherosclerosis (Farooqui et al., 2007; Adibhatla et al., 2008). PAFs potentiate local pro-inflammatory cascades by promoting the expression of Ca^{2+}-independent PLA_2 and cyclo-oxygenase 2 (COX_2) that metabolize

free arachidonic acid into various eicosanoid metabolites (Farooqui et al., 2007). PAFs further contribute to a pro-inflammatory state by inducing the release of cytokines such as IL-6 (Thivierge and Rola-Pleszczynski, 1992) and TNF-α (Rola-Pleszczynski et al., 1992) from leukocytes upon binding to PAFR (Farooqui et al., 2007).

4.2. Oxidative and nitrosative stress

The activity of oxidative and nitrosative stress pathways is implicated in the pathophysiology and progression of depression (Maes, 2008; Maes et al., 2009; Miller et al., 2009) and CAD (Maes et al., 2011; Rajesh et al., 2011). Briefly, reactive oxygen species (ROS), such as the superoxide anion, can combine with NO to form the powerful oxidant, peroxynitrite, a reactive nitrogen species (RNS) (Beckman et al., 1990). Heightened activity of ROS and RNS mediators can lead to oxidative and nitrosative damage to proteins and lipids, not only potentially modifying their signaling capacity but also perpetuating the inflammatory response in depression (Maes et al., 2010; Leonard and Maes, 2012; Stefanescu and Ciobica, 2012). Peroxynitrite and other oxidative/nitrosative agents in the vascular endothelium adjacent to brain tissue may induce neurotoxic cascades in brain tissue leading to depressive symptoms and neurodegeneration (reviewed Maes et al., 2009).

In addition to pro-inflammatory cytokine and eicosanoid pathways, PAFs stimulate the activity of oxidative and nitrosative stress pathways. PAFs are well known stimulators of ROS, such as the superoxide anion and hydroxyl radical, and nitrosative stress pathways (Kubes et al., 1991; Schmidt et al., 1992; Schwappach et al., 1995; Kurose et al., 1996; Pinckard and Prihoda, 1996; Klabunde and Anderson, 2002), which is implicated in the onset of neuroinflammation in depressed patients (Leonard and Maes, 2012). PAFs have been shown to induce vascular endothelial permeability through the formation of RNS metabolites such as peroxynitrite (Klabunde and Anderson, 2002). Peroxynitrite can also deactivate PAF-AH under oxidative stress conditions (MacRitchie et al., 2007), thus impeding PAF inactivation.

4.3. Endothelial dysfunction

Endothelial dysfunction describes a state of impaired vasodilatory response that is characterized by the reduced bioavailability of NO due to either decreased formation, increased utilization, or both (Hinderliter and Caughey, 2003). Inflammation or vascular risk factors such as hypertension can increase superoxide production which combines with NO, reducing its bioavailability (Hinderliter and Caughey, 2003; Forstermann and Munzel, 2006) and instead forming the longer-lived oxidative/nitrosative agent peroxynitrite. This can exacerbate damage to the vascular endothelium, further impairing endothelial function (Forstermann and Munzel, 2006). Endothelial dysfunction may be a pathophysiological link between depression and CAD (Celano and Huffman, 2011). Many depressed patients demonstrate impaired flow-mediated vessel dilation (FMD) and, in a recent meta-analysis, the degree of endothelial dysfunction, as measured by FMD, was positively associated with the severity of depressive symptoms (Cooper et al., 2011). Another study reported that small artery dilation to acetylcholine, a measure of endothelial function, was impaired in depressed patients compared to controls (Paranthaman et al., 2012). That study also found that endothelial function worsened in a gradient from controls to depressed antidepressant responders to depressed non-responders, although the difference between responders and non-responders did not reach significance. Ischemic postconditioning, a protective strategy used to minimize endothelial dysfunction following ischemic-reperfusion injury, was shown to be ineffective in depressed patients when compared to non-depressed controls (Zhuo et al., 2011). In that study, greater endothelial impairment was associated with greater depression severity and lower NO bioavailability. Taken together, these studies suggest that endothelial dysfunction may account for at least some of the association between depression and increased CAD-related morbidity, particularly since endothelial dysfunction is an independent risk factor for ACS in CAD patients (Hinderliter and Caughey, 2003), and it is associated with coronary artery restenosis after percutaneous coronary intervention (Munk et al., 2011).

The pro-inflammatory properties of PAF lipids contribute to vascular endothelial inflammation and may potentiate endothelial dysfunction. PAF activity is associated with leukocyte adhesion and infiltration across the vascular endothelium by promoting the surface expression of endothelial cellular adhesion molecules such as VCAM-1 (Farooqui et al., 2007). Endothelial derived PAFs can also facilitate leukocyte-endothelial interactions through a PAFR-based mechanism (Zimmerman et al., 1990). Elevated PAF signaling within the vascular endothelium has been implicated in reduced NO bioavailability, a core feature of endothelial dysfunction, through the acid sphingomyelinase pathway (Yang et al., 2010). Pre-clinical models have shown that local production of PAFs is associated with the development of endothelial dysfunction during cerebral ischemia and systemic elevations in PAFs can induce leukocyte-endothelial interactions in cerebral vessels (Uhl et al., 1999a, 1999b). Furthermore, PAFs are thought to mediate increased endothelial permeability, in part via peroxynitrite (Klabunde and Anderson, 2002), leading to greater extravasation of leukocytes into the perivascular spaces and, if occurring at the blood-brain barrier, the possible induction of neuroinflammatory cascades, implicated in the etiology of depression (Montrucchio et al., 2000).

4.4. Platelet reactivity

Platelet reactivity, the degree to which platelets become activated in response to an agonist, is associated with an increased risk of thrombosis and the release of pro-inflammatory mediators (Franchini et al., 2007). Platelet reactivity and endothelial function are intimately linked through several pathways. For example; platelet-released serotonin, a stimulator of NO secretion and vasodilation in healthy endothelium, increases platelet reactivity in cooperation with other, more potent platelet agonists such as adrenaline or arachidonic acid (Ziegelstein et al., 2009). NO is an inhibitor of platelet reactivity and it is instrumental in maintaining platelet-endothelial homeostasis (Gkaliagkousi and Ferro, 2011). In dysfunctional vessels, NO bioavailability is reduced and the NO response to serotonin released by activated platelets is suppressed (Celano and Huffman, 2011). The suppression of NO, and consequential persistence of platelet activation, may facilitate the development of pro-thrombotic platelet-monocyte interactions, leading to increased secretion of inflammatory mediators (Passacquale et al., 2011), and exacerbation of endothelial dysfunction (Gkaliagkousi and Ferro, 2011).

Elevated platelet reactivity is associated with depression and with an increased risk of ischemic events in those with CAD (Musselman et al., 1996; Celano and Huffman, 2011). In a large community-based study (Canan et al., 2011), mean platelet volume, an indicator of platelet activity, was significantly elevated in patients with major depressive disorder compared to those without depression. Platelet reactivity markers such as β-thromboglobulin, platelet factor 4, and P-selectin are reportedly higher in depressed patients with CAD than in their non-depressed counterparts (Laghrissi-Thode et al., 1997), as well as in depressed patients without CAD compared to non-depressed controls (Piletz et al., 2000). The heightened expression of platelet surface receptors such as P-selectin helps to facilitate the platelet-monocyte interactions that contribute to thrombosis and endothelial dysfunction (Gkaliagkousi and Ferro, 2011). Higher levels of platelet-monocyte

aggregates have been observed in CAD patients and they are associated with an increased risk of ACS when compared to controls (Wang et al., 2007). Elevated platelet reactivity is also associated with the secretion of pro-inflammatory mediators through the PLA_2 and COX pathways (Aukrust et al., 2010). Other contributors to increased platelet reactivity in depressed patients might include elevated production of adrenaline, due to overactivity of the hypothalamic-pituitary-adrenal (HPA) axis, or high concentrations of arachidonic acid – both elevated in depression (Gold et al., 2005; Dinan et al., 2009).

PAFs are potent stimulators of platelet reactivity through the PAFR, leading to increased aggregation and release of inflammatory and platelet activity mediators (Farooqui et al., 2007). These platelet-released mediators can then induce the release of TNF-α and inflammatory eicosanoids from endothelial cells and leukocytes, contributing to a feed-forward mechanism that ultimately generates more PAF release from these cells and therefore greater platelet activation (Montrucchio et al., 1994; Im et al., 1996). It has been shown that PAF-mediated platelet activation is heightened in hypertensive patients compared to normotensive controls (Gabbasov et al., 1998), suggesting that PAFs may interact with vascular risk factors to contribute to the development and progression of CAD.

5. PAFs and CAD

PAFs have been established as participants in the onset of myocardial ischemia in animal studies (Nemcsik et al., 2004; Penna et al., 2011). Clinically, elevated concentrations of PAFs in the peripheral blood have been associated with an increased risk of CAD (Zheng et al., 2012) and the presence of CAD when compared to healthy controls (Chen et al., 2010); however, species specificity has yet to be determined. Recent studies have reported that plasma activity levels of PAF-AH were higher in CAD patients than in controls and that PAF-AH activity was independently associated with CAD severity (Samsamshariat et al., 2011; Zheng et al., 2012). PAF-AH has also been suggested as a potential risk marker (Winkler et al., 2007) and therapeutic target for CAD (Carlquist et al., 2007). As PAF-AH is responsible for inactivating PAFs, it is possible that higher PAF-AH activity is a compensatory response to elevated PAF concentrations. Collectively, these findings implicate the PAF metabolism pathway in the onset and/or progression of CAD.

6. PAFs in the CNS: a role in neurodegeneration

At present, the relationships between plasma and CNS PAF concentrations are not well understood; however, PAFs are important mediators of long-term potentiation when present at physiological concentrations in the CNS (Arai and Lynch, 1992; Wieraszko et al., 1993; Chen et al., 2001). PAFs may accomplish this by acting as retrograde messengers by which they diffuse from the post-synaptic site where they are synthesized to the pre-synaptic terminal where they promote the vesicular release of pre-synaptic glutamate (Kato et al., 1994; Kato and Zorumski, 1996; Kornecki et al., 1996). During heightened inflammatory activity, elevated PAF production can promote glutamate excitotoxicity (Bennett et al., 1998; Xu and Tao, 2004) as one mechanism of their neurodegenerative effects at elevated concentrations (Bazan, 2006; Farooqui et al., 2007; Frisardi et al., 2011). Other mechanisms of PAF-mediated neurotoxicity stem from their pro-inflammatory effects and previously mentioned interactions with ROS and RNS mediators. Finally, PAFs can exert neurodegenerative effects on neurons via PAFR-dependent and independent mechanisms (Zhu et al., 2004; Ryan et al., 2007, 2008). They may also be important mediators of neurodegeneration associated with amyloid-β and hyperphosphorylation of tau (Ryan et al., 2009). These effects implicate PAFs as amplifiers of the neuroinflammatory cascades implicated in depression and neurodegeneration.

7. A role in vascular pathology

Cerebrovascular pathology has consistently been observed in older adults with depression and is the foundation of the vascular hypothesis of depression in late-life as first described by Alexopoulos and colleagues (Alexopoulos et al., 1997) and since reviewed (Alexopoulos, 2006; Naarding and Beekman, 2011). Cerebrovascular pathology has also been observed in patients with CAD (Ozeren et al., 1998; Hoshide et al., 2001; Vlek et al., 2009; Geerlings et al., 2010), suggesting an etiopathological link.

PAF synthesis is induced during ischemia where PAFs act as pro-inflammatory messengers and, during cerebral ischemia, neurodegenerative agents (Chen and Bazan, 2005). Animal (Frerichs et al., 1990; Lindsberg et al., 1990) and clinical (Satoh et al., 1992) studies have found higher levels of PAFs in ischemic tissue and PAF concentrations have been linked to greater infarct size (Belayev et al., 2008, 2009, 2012) and greater severity in stroke (Adunsky et al., 1999). PAF concentrations have been shown to rise early on in ischemia, suggesting that PAF activity might be an instigator for cerebrovascular damage (Lindsberg et al., 1990). In models of cerebral ischemia, the use of selective PAFR antagonists, such as LAU-0901 or BN 50739, is associated with reduced infarct size, greater local cerebral blood flow, reduced microglial infiltration, and greater astrocytic and neuronal survival post-ischemia (Frerichs et al., 1990; Liu et al., 2001; Belayev et al., 2008, 2009, 2012). In keeping with the established vascular and inflammatory effects of PAFs, these studies implicate PAFs as potent mediators of vascular pathology. Combined with their known role in neurodegeneration, the effects of PAFs on cerebral vasculature during ischemia, and their associations with inflammation, oxidative and nitrosative stress, and vascular endothelial dysfunction, it is possible that PAFs mediate vascular pathophysiology sub-acutely during periods of persistent inflammatory activity, observed in depression.

8. Summary and perspective

Persistent depression in CAD patients is associated with accelerated cognitive decline and neurodegeneration (Maes et al., 2010; Freiheit et al., 2012). We have proposed the PAFs as potential mediators of persistent depression and related cognitive decline in CAD patients due to their known association with CAD, their neurodegenerative effects when elevated in the CNS, and their roles within vascular pathology and leading etiopathological mechanisms of depression in CAD (Fig. 2). Accordingly, PAFs may be particularly relevant to the persistence of depression and associated cognitive sequelae in patients with CAD rather than the persistence of depression in those who are otherwise medically healthy, or the development of depression per se in CAD patients. However, this mechanism of cognitive decline may reasonably be active in other populations characterized by alternations in PAF and vascular pathology. PAFs may also be associated with the elevated risk of ACS in CAD patients experiencing a persistent depressive episode, due to their role in the inflammatory pathways associated with depression and their associations with the presence of CAD.

Recent advances in mass spectrometry allow for a comprehensive 'lipidomics' approach to the investigation of the lipid metabolism pathways (Bou Khalil et al., 2010). This approach enables the characterization of the spectrum of lipids present in plasma from each patient. Indeed, a recent lipidomics study found a cross-sectional association between greater depressive symptoms

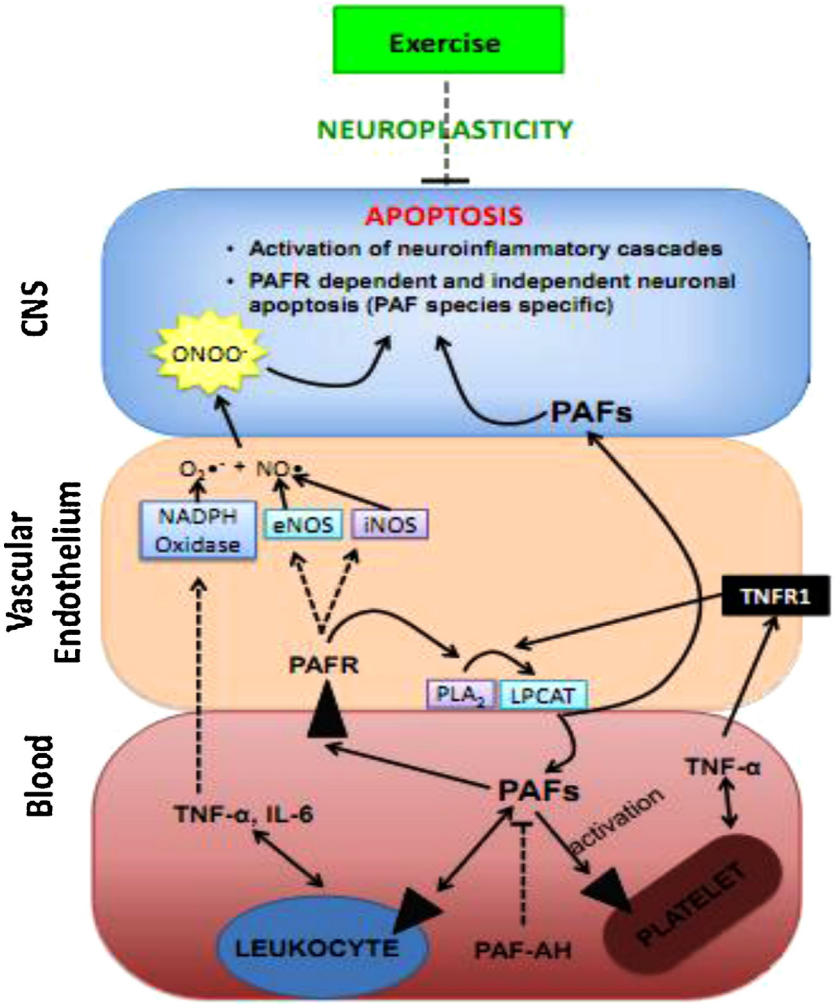

Fig. 2. Mechanisms linking PAFs to inflammation, platelet activation, and the production of reactive oxygen and nitrogen species such as peroxynitrite (ONOO-). PAFs can be released by vascular endothelial cells and leukocytes and they can activate the PAF receptor (PAFR) present on endothelial cells, leukocytes, and platelets. PAFR activation leads to greater PAF release and the release of pro-inflammatory cytokines (TNF-α, IL-6) and eicosanoids (not shown). PAFs in the blood can be degraded by PAF acetylhydrolase (PAF-AH). Collectively, PAFs and other pro-inflammatory mediators, including peroxynitrite, can activate neuroinflammatory cascades in the central nervous system (CNS), implicated in the progression of depression and other neurodegenerative diseases. *Abbreviations*: LPCAT, *lyso*phosphatidylcholine acyltransferase; TNF-α, tumor necrosis factor α; TNFR1, TNF receptor 1; IL-6, interleukin 6; PLA_2, phospholipase A_2; eNOS, endothelial nitric oxide synthase; iNOS, inducible NOS; NADPH oxidase; nicotinamide adenine dinucleotide phosphate-oxidase.

and lower plasma concentrations of the AAGPC species PC O 36:4, a potential PAF parent (Demirkan et al., 2013). That finding suggests that AAGPC metabolism is elevated in depressed patients, supporting the rationale for investigating the effects of downstream mediators in the etiology of depression. PAFs may be particularly involved in the co-morbidity between depression and CAD due to their effects on cerebral vasculature during ischemia and the clinical similarities between vascular depression and CAD (Alexopoulos et al., 1997). Furthermore, characterizing the fluctuations in the lipid profile of depressed CAD patients during antidepressant interventions may elucidate the role of PAFs and upstream precursors such as *lyso*-PAFs as biomarkers and/or therapeutic targets in depression and CAD.

PAFs have yet to be investigated as biomarkers of depressive symptoms or interventional response in CAD; however, previous literature has described interactions between some antidepressants and PAF-mediated inflammatory and vascular modifications (Svens and Ryrfeldt, 2001; Strumper et al., 2003; Yang et al., 2010). Although the clinical association between antidepressants and PAFs has yet to be explored, we cannot rule out the possibility that PAFs interact with antidepressant response in CAD patients. SSRIs, which have been found to be safe and effective treatments for depression in patients with cardiovascular disease (Strik et al., 2000; Glassman et al., 2002; Lesperance et al., 2007), not only act on neurotransmitters, but may also act as anti-inflammatory agents (Maes et al., 2009) and may decrease platelet hyperaggregability (Serebruany et al., 2001) suggesting possible interactions with PAFs. In addition, a greater concentration of PAFs in plasma prior to treatment may be associated with a benefit from augmentation of pharmacotherapy using exercise interventions based on the anti-inflammatory effects of exercise (Swardfager et al., 2012), the positive association between high concentrations of inflammatory biomarkers and antidepressant effects of exercise (Rethorst et al., 2012), and the limited treatment efficacy of SSRI pharmacotherapies in patients with high levels of inflammatory biomarkers (Lanquillon et al., 2000; Eller et al., 2008).

Further investigation might confirm a role for PAFs in the underlying pathophysiology linking depression with neurodegeneration and negative cognitive outcomes in CAD patients.

9. Conclusion

PAFs are potent inflammatory phospholipids that are elevated in CAD, associated with leading mechanisms underlying depression

in CAD, cerebrovascular pathology, and with neurodegeneration when elevated in the CNS. Therefore, PAFs are potentially important markers of pathophysiology central to the persistence of a depressive episode and related to cognitive decline in CAD patients. Future investigation of PAFs in this context is warranted.

Conflict of interest

No conflict of interest exists for any of the authors.

Funding

This work was supported by the Ontario Mental Health Foundation and by funding from the Strategic Training Initiative in Health Research/CIHR Training Program in Neurodegenerative Lipidomics and CIHR Institute of Aging to SF, SALB, and KL (TGF 96121). GM, NV, and HX received Institute of Aging and CIHR Training Program in Neurodegenerative Lipidomics graduate, post-professional, and post-doctoral fellowships, respectively. GM and HX also received an Ontario Graduate Scholarship and MITACs internship, respectively. WS received a post-doctoral fellowship from the Toronto Rehabilitation Institute.

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