Pharmacology & Therapeutics xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

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

Associate editor: S. Kennedy

Dietary manipulation of platelet function

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ARTICLE INFO

Available online xxxx

Keywords:
Diet
Platelet function
Cardiovascular disease
Dietary fatty acids
Dietary polyphenols

ABSTRACT

Activated platelets contribute to plaque formation within blood vessels in the early and late stages of atherogenesis, and therefore they have been proposed as risk factor for cardiovascular disease. Anti-platelet drugs, such as aspirin, are now the most prescribed pharmacological treatment in Europe. Certain dietary bioactives also beneficially affect platelet function, and with less side effects, albeit that effects are generally more subtle. Therefore, consumption of dietary bioactives could play a role in the prevention of atherothrombotic vascular disease. Here we review the efficacy of dietary treatment strategies, especially those involving certain dietary fatty acids and polyphenols, to modulate platelet function in healthy subjects or in patients with cardiovascular disease. Variation in study populations, small study sizes and lack of comparability between methods to assess platelet function currently limit robust evidence on the efficacy of dietary bioactives in healthy subjects or specific patient groups. Also, limited knowledge of the metabolism of dietary bioactives, and therefore of the bioavailability of bioactive ingredients, restricts our ability to identify the most effective dietary regimes to improve platelet function. Implementation of uniform point-of-care tests to assess platelet function, and enhanced knowledge of the efficacy by which specific dietary compounds and their metabolites affect platelet function, may enable the identification of functional anti-platelet ingredients that are eligible for a health claim, or combined treatment strategies, including both pharmacological anti-platelet treatment as well as dietary intervention, to tackle atherothrombotic vascular disease.

Contents

1 . Role of platelets in cardiovascular disease development

Cardiovascular disease (CVD) remains the main cause of death worldwide. It is responsible for a large part of our disease burden including ischaemic heart disease, coronary heart disease, cerebrovascular disease, peripheral artery disease and hypertension (WHO, 2011). The main cause of CVD is atherosclerosis – a chronic inflammatory state in the arterial blood vessel walls – and subsequent thrombus formation in the arteries (Frayn & Stanner, 2005). Atherosclerosis is a product of increased lifespan, genetic susceptibility and an adverse environment and/or personal lifestyle that includes smoking, consumption of a high fat diet and lack of exercise, leading to dyslipidaemia and chronic inflammation, and ultimately atherosclerotic plaque formation (Berenson et al., 1998; Lusis, 2000).

The process of inflammation and atherosclerosis involves active participation of various cell types, including endothelial cells, monocytes and platelets (Lusis, 2000; Siegel-Axel et al., 2008). Platelet activation is a multilayered three-phase receptor-mediated process under a broad range of haemodynamic conditions (Jackson, 2007). This process is initialised during adhesion and activation of platelets by the simultaneous

Abbreviations: ADP, adenosine 5′-diphosphate; AA, arachidonic acid; CLA, conjugated linoleic acid; COX-1, cyclooxygenase-1; CVD, cardiovascular disease; DHA, docosahexaenoic acid; EFSA, European Food Safety Authority; EPA, eicosapentaenoic acid; GP, glycoprotein; ICAM-1, intercellular adhesion molecule-1; NDA, Dietetic Products, Nutrition and Allergies; NF-κB, nuclear factor kappa B; PAR, protease-activated receptor; PFA-100, platelet function analyser-100; PPARγ, peroxisome proliferator-activated receptor γ; PSGL-1, P-selectin glycoprotein-1; RANTES, regulated on activation, normal T cell expressed and secreted; TxA_2, thromboxane A_2; UGT, uridine diphosphate-glucuronosyltransferase; vWF, von Willebrand factor.

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http://dx.doi.org/10.1016/j.pharmthera.2014.05.008
0163-7258/

action of more than one agonist, such as adenosine 5′-diphosphate (ADP), collagen or thrombin, that are coming from vascular cells, erythrocytes or leukocytes (Ruggeri, 2002), and bind to surface receptors, such as P_2Y_{12}, glycoprotein VI (GPVI) and protease-activated receptors (PAR), respectively (Varga-Szabo et al., 2008) (Fig. 1). The activation triggers an intracellular signalling cascade (Varga-Szabo et al., 2008), leading to the subsequent release of the platelet granules' contents, including P-selectin and ADP (Rendu & Brohard-Bohn, 2001; Flaumenhaft, 2013), as well as the production of thromboxane A_2 (TxA_2) from arachidonic acid (AA) by cyclooxygenase-1 (COX-1) and thromboxane synthase (Nakahata, 2008). In response to these platelet activation stimuli, the GPIIb/IIIa receptor becomes activated via so-called "outside-in signalling" (Shattil et al., 1998; Cosemans et al., 2008), leading to platelet–platelet cohesion and stabilisation of the platelet aggregate via covalently bound fibrinogen (Jackson, 2007).

Platelets and their secretion molecules, such as P-selectin, CD40 and RANTES (Rendu & Brohard-Bohn, 2001; Flaumenhaft, 2013), play a major role in the formation of plaques within the blood vessel, where they contribute to early inflammatory events and the progressive stages of atherogenesis (Gawaz et al., 2005). Indeed, platelets provide not only the inflammatory basis for plaque formation. They also physically obstruct the vessel lumen by a growing thrombus after plaque rupture (Moore & Tabas, 2011). In the early stages of atherosclerosis, the activated endothelium expresses P-selectin on the cellular surface (Wagner & Frenette, 2008). Activated platelets rolling along the endothelial monolayer form an initial attachment to damaged endothelial cells via P-selectin glycoprotein ligand-1 (PSGL-1)-P-selectin or GPIbα-P-selectin receptor binding. Platelets are then exposed to von Willebrand factor (vWF) and collagen secreted at the side of vascular lesion and bind via the membrane adhesion receptors GPIb/IX/V and GPVI. Subsequently, platelets firmly adhere to the endothelium via the integrin receptors α2bβ3 (GPIIb/IIIa, fibrinogen receptor) and α2β1 (collagen receptor) (Ruggeri, 2002; Nieswandt & Watson, 2003) Thereafter, adherent platelets recruit and bind circulating leukocytes via interaction of CD40 and its ligand CD40L (CD154) on the platelet surface. This causes the stimulation of these monocytes and macrophages which will ultimately lead to the production of inflammatory cytokines, proteases and adhesion molecules (Lusis, 2000; Flaumenhaft, 2013). This step is critical in the development of advanced lesions (Schonbeck et al., 2000). During the later stages of atherosclerosis, platelets bind to thrombogenic substances, e.g. collagen exposed from disrupted atherosclerotic plaques, leading to a growing thrombus (Gawaz et al., 2005). Considering the important role that platelets play in inflammatory events and the formation of plaques make them an effective target for anti-platelet therapies in the prevention of CVD. Indeed, for many years, anti-platelet therapies have been used in the prevention and management of atherothrombotic vascular disease (Ueno et al., 2011; Yeung & Holinstat, 2012; de Souza & Tricoci, 2013).

As activated platelets contribute to plaque formation within the blood vessels in the early and late stages of atherogenesis, they have been proposed as a risk factor for CVD, comparable to hypertension or diabetes (Assmann et al., 1999). Indeed, patients suffering from atherosclerosis have activated platelets circulating in their blood, and most risk factors for atherosclerosis like smoking, hypertension, hypercholesterolaemia and diabetes are associated with an increased number of activated platelets in the circulation (Huo & Ley, 2004). Furthermore, the risk for an ischaemic event after a patient has had a percutaneous coronary intervention increases significantly after a threshold of platelet reactivity to ADP is exceeded (Gurbel & Tantry, 2010). These findings, however, were not found sufficient to introduce platelet function as independent marker with a defined cut-off value associated with clinical CVD risk (Sharma & Berger, 2011). Over the years, a variety of techniques were developed and recommended in the clinical setting to test various endpoints of platelet function and for the diagnosis of platelet disorders

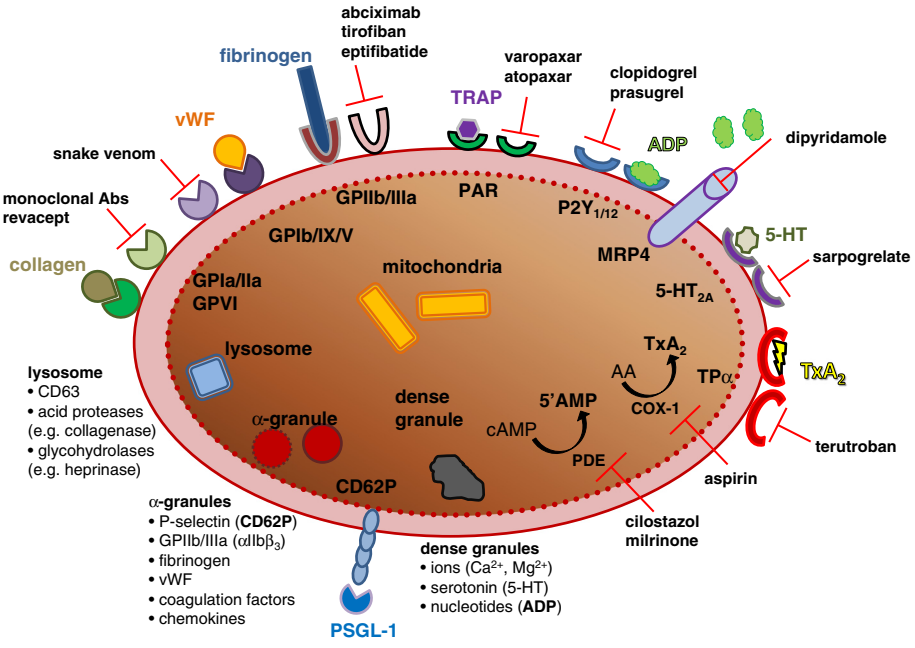

Fig. 1. Platelet morphology, main anti-platelet drugs and their targets. Platelets consist of three principal components: a phospholipid bi-layer membrane with surface receptors, cytoskeleton, and organelles in the cytosol, which are all involved in platelet function. Platelet activation is induced by collagen or ADP and receptor-mediated via several redundant pathways. This leads to secretion from platelet granules and expression of further surface receptors, such as P-selectin and CD63, and fibrinogen binding on activated GPIIb/IIIa forming bridges which contribute to the stabilisation of the blood clot. Circulating leukocytes bind and roll over activated platelets via PSGL-1–P-selectin interactions promoting local inflammation. AA from the phospholipid membrane is converted to TxA_2 by COX-1 and thromboxane synthase and released from the platelet cytosol. After binding to thromboxane receptor TPα, TxA_2 further stimulates platelet granule secretion leading to an amplification of the activation and aggregatory process. Various receptor- or enzyme-specific pharmacological compounds are known to inhibit platelet function. 5′AMP, adenosine 5′-monophosphate (inactive); 5-HT, serotonin; AA, arachidonic acid; Abs, antibodies; ADP, adenosine 5′-diphosphate; cAMP, cyclic adenosine 5′-diphosphate; COX-1, cyclooxygenase-1; GP, glycoprotein; MRP4, multi-drug resistant protein 4 or ATP-binding cassette protein 4; PAR, protease-activated receptor; PDE, phosphodiesterase; PSGL-1, P-selectin glycoprotein ligand-1; TPα, thromboxane receptor α; TRAP, thrombin receptor-activating peptide; TxA_2, thromboxane A_2; vWF, von Willebrand factor.

Please cite this article as: Bachmair, E.M., et al., Dietary manipulation of platelet function, *Pharmacology & Therapeutics* (2014), http://dx.doi.org/10.1016/j.pharmthera.2014.05.008