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Review

Mechanism of antiplatelet action of hypolipidemic, antidiabetic and antihypertensive drugs by PPAR activation PPAR agonists: New antiplatelet agents

Eduardo Fuentes *, Iván Palomo *

Department of Clinical Biochemistry and Immunohaematology, Faculty of Health Sciences, Interdisciplinary Excellence Research Program on Healthy Aging (PIEI-ES), Universidad de Talca, Talca, Chile
Centro de Estudios en Alimentos Procesados (CEAP), CONICYT-Regional, Gore Maule, R09I2001, Chile

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ABSTRACT

Given the prevalence of cardiovascular disease in patients with cardiovascular risk factors (i.e., hypertension, diabetes, smoking and obesity) and that platelet activation plays an important pathogenic role in cardiovascular diseases, it is very important to identify the drugs that have multiple targets. In this sense, the present article describes the mechanism of antiplatelet action of hypolipidemic (statins and fibrates), antidiabetic (thiazolidinediones) and antihypertensive (nifedipine) drugs via peroxisome proliferator-activated receptor (PPAR) activation. The mechanism of antiplatelet action of the drugs is by direct activation of PPARs with the inhibition of cyclooxygenase-1, protein kinase C-alpha, calcium mobilization, thromboxane A2, sCD40L, platelet microparticles and cAMP-phosphodiesterase, and the stimulation of proteins kinase G and A. Thus, these observations highlight PPARs as a novel therapeutic target for the treatment and prevention of cardiovascular diseases.

Contents

1. Introduction

Cardiovascular diseases (CVD) (i.e., acute myocardial infarction, cerebrovascular disease and peripheral arterial thrombosis) have significantly increased in recent years [1,2]. The most frequent and independent risk factors for CVD are cigarette smoking, elevated blood pressure, elevated serum total cholesterol and diabetes, among others [3,4].

In most cases, CVD is the consequence of an atherosclerotic plaque rupture and thrombus formation. Accelerated atherosclerosis and an increased risk of thrombotic vascular events in diabetes may result from dyslipidemia, endothelial dysfunction and platelet hyperreactivity [5,6]. Platelets from patients with type 1 and type 2 diabetes exhibit enhanced platelet aggregation activity early in the disease course that may precede CVD development [7,8]. Thus, platelets adhere; secrete their granule contents, aggregate and initiate thrombus formation following an atheromatous plaque rupture, [9,10].

* Corresponding authors at: Immunology and Haematology Laboratory, Faculty of Health Sciences, Universidad de Talca, Casilla, 747, Talca, Chile. Tel.: +56 71 200493; fax: +56 71 20048.
E-mail addresses: edfuentes@utalca.cl (E. Fuentes), ipalomo@utalca.cl (I. Palomo).

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Given the central role of platelets in the atherosclerotic-related inflammatory response and the subsequent thrombotic event, a variety of antiplatelet agents have been developed [11,12]. Although antiplatelet drugs have been proven to be beneficial in patients with clinical evidence of CVD, outcomes still remain poor [13]. In this way, platelets from diabetic patients release greater amounts of thromboxane A2 (TXA2) than platelets from non-diabetic patients receiving treatment with low-dose aspirin [14]. This is because all the current available antiplatelet agents only target one signal pathway and moderately inhibit platelet activation (e.g. aspirin and clopidogrel) [15]. Therefore, there is much room for further improvement of antiplatelet treatment and the need to identify the mechanisms by which hypolipidemic (statins and fibrates), antidiabetic (thiazolidinediones) and antihypertensive (nifedipine) drugs inhibit platelet activation. It has also been observed that these drugs are ligands for peroxisome proliferator-activated receptors (PPARs) in cells which have a nucleus [16–18].

PPARs are involved in many biological processes, including lipid and energy metabolism inflammation responses, and atherosclerotic plaque formation [19–21]. Selective agonists through their action on nuclear receptors (e.g. PPARs) regulate platelet function despite the absence of a nucleus in platelets. [22]. In this sense, the present article describes the antiplatelet action mechanism of hypolipidemic, antidiabetic and antihypertensive drugs via PPAR activation.

2. PPARs and atherothrombosis

PPARs consist of a family of three nuclear receptor isoforms (γ, β/δ, and α) [23]. PPARs are the key regulators of metabolism and inflammation, and play an important role in chronic inflammatory disease processes [24,25]. Accumulating evidence suggests that PPAR activation is a key mechanism to reduce atherosclerosis and improve cardiovascular function [26–28].

Recent studies suggest that PPAR-γ activation decreases atherogenesis, not only by correcting metabolic disorders, but also through its direct effects on the vascular wall [29]. In addition, PPAR-α and PPAR-β/δ have also been suggested in the regulation of inflammation and slow atherosclerosis progression [20,30].

Ligands of PPAR-α are important regulators of lipid and lipoprotein metabolism, thereby positively affecting plasma lipid risk factors related to atherosclerosis [31]. In this context, the lipid-lowering effect of fenofibrate is achieved by activating PPAR-α and AMP-activated protein kinase (AMPK) signaling pathway that results in increasing lipolysis and fatty acid β-oxidation [32].

PPARs appear to play a major role in the regulation of atherogenesis by countering the inflammation-provoking action of platelet adhesion and activation [33].

3. Mechanism of antiplatelet action by PPAR activation

Nuclear receptors are transcription factors that are activated by ligands and subsequently bind to regulatory regions in target genes; allowing the organism to integrate signals coming from the environment [34]. While steroid/nuclear receptors are recognized via for their role in gene regulation, increasing evidence supports nongenomic actions of these receptors [35,36]. Thus, although platelets lack a nucleus, they express a number of transcription factors including steroid/nuclear receptors such as PPARs [37,38], glucocorticoid receptor (GR) [39], retinoic X receptor (RXR) [41], estrogen receptor (ER) [40] and nuclear factor kappa B (NF-κB) [42]. Thus, selective ligands for these receptors regulate platelet aggregation and activation [22,43].

While many reports focus on PPAR expression in the nucleus [44,45], in this article we focus on the role of PPAR-cytoplasm in platelet function. Recent studies have provided the first evidence that human bone marrow megakaryocytes and human platelets express PPAR-γ [37]. PPAR-γ activation decreases platelet aggregation and delays intra-arterial thrombus formation in rats, at least partially, by an increase in the expression of nitric oxide synthase (NOS) and thrombomodulin [46]. PPAR-γ activation also inhibits platelet function induced by collagen through the modulation of early glycoprotein (GP) VI signaling, at the level of Syk and LAT [47]. In addition, platelet incubation with a natural PPAR-γ agonist (15d-PGJ(2)) or with a potent synthetic PPAR-γ ligand (rosiglitazone) not only attenuates platelet activation, but also decreases the release of platelet proinflammatory and procoagulant mediators (sCD40L and TXA2) [33,37].

Agonists of PPAR-β, including GW0742 and L-165041, inhibit platelet activation after 5 min of incubation. Clearly with such acute exposure and as platelets have no nucleus, PPAR-β is an active antithrombotic pathway in platelets, whose effects are independent of the nucleus [38].

Moreover, PPAR-α activators may exert vasculo-protective action through suppression of PDGF-BB production in a megakaryocyte/platelet pathway [48]. Prostacyclin formed by the consecutive actions of cyclooxygenase-1 (COX-1) and prostacyclin synthase is arguably the most important endogenous antiplatelet hormone identified to date [49]. Prostacyclin inhibits platelet function via stimulation of a surface prostanoid receptor linked to the activation of adenylyl cyclase and increased intracellular levels of cyclic adenosine monophosphate (cAMP) [50]. Moreover, prostacyclin activates PPAR-β/δ in human platelets in the low 10^{-9} M range. Therefore, an additional mechanism of antiplatelet action by prostacyclin occurs by activation of PPAR-β/δ and its effects on platelet aggregation is synergistic with nitric oxide (NO) [38,51].

4. Drugs and platelet inhibition: role of PPAR activation

Given the prevalence of CVD in patients with cardiovascular risk factors (i.e., hypertension, diabetes, smoking and obesity) and that platelet activation plays an important pathogenic role in atherothrombosis [3,52], it is very important to identify the drugs that have multiple targets. In this sense, the present article describes the mechanism of antiplatelet action of hypolipidemic (statins and fibrates), antidiabetic (thiazolidinediones) and antihypertensive (nifedipine) drugs by PPAR activation.

4.1. Statins and fibrates

The 3-hydroxy-3-methylglutaryl-coenzyme (HMG-CoA) reductase inhibitors, also known as statins, are the most effective class of drugs for lowering serum low-density lipoprotein cholesterol (LDL-C) concentrations [53]. In this way, another class of drug called fibrates reduces triglycerides and increases high-density lipoprotein cholesterol (HDL-C) [54]. In this article, we discuss how statins and fibrates appear to have more biological effects than those originally targeted. Statins and fibrates can exert beneficial anti-inflammatory and antithrombotic effects in after patients with a high risk of coronary artery disease as early as 3 days after therapy [55]. Thus, statins (simvastatin, atorvastatin, or cerivastatin) decrease morbidity and mortality in patients with CVD by their effects on proinflammatory cytokines: interleukin 6 (IL-6), IL-8, and monocyte chemoattractant protein-1 (MCP-1) [56]. Meanwhile, fibrates by PPAR-activation may inhibit atherosclerosis development *in vivo* [57].

Interestingly both statins and fibrates inhibit platelet function [54]. Inhibition of platelet aggregation by simvastatin involves the activation of the cAMP-eNOS/NO-cGMP pathway, resulting in the inhibition of the PLC-γ2/PKC/p38 MAPK/TXA2 cascade [58,59]. Therefore, the direct inhibitory effects of statins and fibrates on platelet activation are mediated by PPAR activation and this new finding reveals some of the pleiotropic effects of these drugs [60]. In platelets, PPAR signaling pathway activation involves binding and repression of PKC, and increasing of cAMP and cGMP levels [60]. The increase of intraplatelet levels of cAMP is due to the fact that the repression of PKC allows greater activity of adenylyl cyclase, which converts ATP to cAMP [61,62]. In addition, cAMP induced inhibition of platelet P-selectin expression, platelet