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Review article

Role of oxidative stress on platelet hyperreactivity during aging

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ABSTRACT

Thrombotic events are common causes of morbidity and mortality in the elderly. Age-accelerated vascular injury is commonly considered to result from increased oxidative stress. There is abundant evidence that oxidative stress regulate several components of thrombotic processes, including platelet activation. Thus oxidative stress can trigger platelet hyperreactivity by decreasing nitric oxide bioavailability. Therefore oxidative stress measurement may help in the early identification of asymptomatic subjects at risk of thrombosis. In addition, oxidative stress inhibitors and platelet-derived nitric oxide may represent a novel anti-aggregation/-activation approach. In this article the relative contribution of oxidative stress and platelet activation in aging is explored.

Contents

1. Introduction

Cardiovascular diseases (CVD) increase in incidence in the elderly, a tendency dependent on the age-related changes in vascular and hemostatic systems [1]. Age-accelerated vascular injury is commonly considered to result from increased oxidative stress [2]. In these conditions, aging is associated with immunosenescence and accompanied by a chronic inflammatory state which contributes to metabolic syndrome, diabetes and their cardiovascular consequences [3–5]. Age is a nonmodifiable risk factor for atherosclerosis. Older animals develop more extensive atherosclerosis than younger animals when both groups are fed an atherogenic diet [6, 7].

Platelets have a dynamic functional repertoire that mediates haemostatic function [8]. However, platelet function is altered in older adults [9–11]. Therefore in aging, the correlation between platelet aggregation in whole blood and platelet-arterial wall interactions (*in vitro* and *in vivo*) may contribute to CVD [12].

Nitric oxide (NO) in human is produced from L-arginine by three enzymes called nitric oxide synthases (NOS): inducible (iNOS), neuronal (nNOS) and endothelial (eNOS), which differ in their dependence on Ca^{2+}, as well as in their expression and activities. The eNOS and iNOS have been crucial in cardiovascular protection [13, 14].

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The NO is present in platelets and regulates their platelet function [15, 16]. NO stimulates cyclic guanosine monophosphate (cGMP) synthesis by activating soluble guanylyl cyclase (sGC), which plays a crucial role in preventing platelet activation [17, 18]. However, metabolic abnormalities as a result of aging cause platelet hyperaggregability involving enhanced intraplatelet reactive oxygen species (ROS) production and decreased NO bioavailability [19, 20].

NO is a reactive free radical that can participate in several types of redox reactions, some that mediated its biological effects and others that limit its activity. Inactivation of NO occurs largely through oxidative reactions mediated by ROS [21, 22]. Increased generation of ROS is found in a variety of vascular disorders and during aging [23–26].

The nitric oxide pathway plays an important role in the inhibition of platelet activation and thrombus formation. Yet, the role of oxidative stress on platelet function and thrombus risk during aging yet to be fully elucidated. In this article the relative contribution of oxidative stress and platelet hyperreactivity during aging is explored.

2. Aging and cardiovascular diseases

Most studies of older populations in developed countries show a decrease in the prevalence of disabilities, and an increase in chronic diseases over the past decades [27, 28]. The world population is rapidly aging. Between 2000 and 2050, the proportion of the world's population over 60 years will double from about 11% to 22% [29–31]. Although people are living longer, they are not necessarily healthier than before – nearly a quarter (23%) of the overall global burden of death and illness is in people aged over 60, and much of this burden is attributable to long-term illness caused by diseases such CVD [32–35].

The incidence and prevalence of CVD increase steeply with advancing age [36]. In this context, aging is one of the strongest and most prevalent risk factor for venous thrombosis [37]. Furthermore, venous thrombosis, which leads to pulmonary embolism (PE), is the third most common CVD after myocardial infarction and stroke [38, 39].

The increase of CVD in elderly people is because the aging process is associated with alterations of the structure and function of vascular components, such as the endothelium, vascular smooth muscle cells (VSMCs) and platelets [40, 41].

3. Nitric oxide pathway and platelet inhibition

The primary function of circulating platelets during the hemostatic process is to stop blood loss after tissue trauma [42, 43]. However, the barrier between physiological hemostasis and pathological thrombosis is very narrow, and it has been increasingly recognized that platelets are at least partially liable for the pathological development of atherothrombosis [44–46]. In this context, nitric oxide pathway plays an important role in the inhibition of platelet activation (Fig. 1) [47].

Although NOS is mainly localized to the endothelium, platelets have also been reported to possess a functional L-arginine/NO pathway [48]. Both eNOS and iNOS have been identified in human platelets and megakaryocytic cells [49–51]. In fact, platelet-derived type eNOS and iNOS have been shown to regulate platelet function [52]. The incubation of platelets with NOS substrate L-arginine inhibits platelet aggregation, whereas the NOS inhibitor NG-monomethyl-L-arginine enhances platelet reactivity [53, 54]. Even, platelet agonist-induced NO production is significantly reduced in iNOS-knockout platelets [55]. Meanwhile statins inhibit platelet activation independently on serum cholesterol levels by upregulation of type eNOS [56]. Thus this upregulation of the platelet L-arginine–NO pathway by statins may attenuate the risk of thromboembolic events [57].

The NO in human platelets plays a role in the modulation of platelet function [58, 59]. The antiplatelet effects of NO are mediated through of an increase in levels of both cAMP and cGMP, leading to further signaling events, including phosphorylation of vasodilator-stimulated phosphoprotein (VASP) [60–63]. The actions of cGMP and cAMP are terminated by phosphodiesterases expressed in platelets, which hydrolyzes active cGMP to inactive GMP, and cAMP to AMP [64, 65]. Moreover, other antiplatelet activity of NO is the inhibition of thromboxane receptor in platelet membranes, where activation of kinase G catalyzes phosphorylation of the cytoplasmic carboxyl-terminal domain of the thromboxane receptor [66]. In addition, NO release from platelets

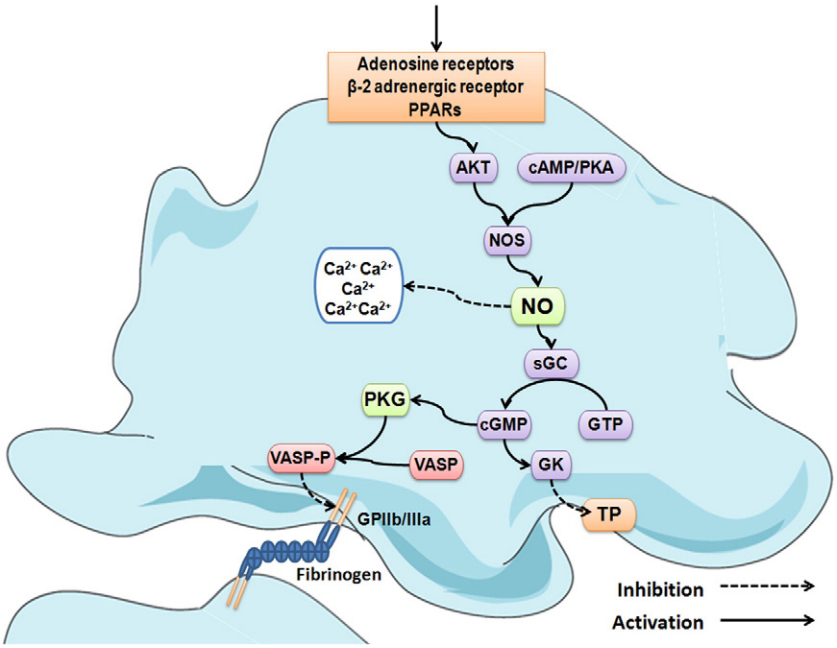

Fig. 1. Platelet inhibition by nitric oxide pathway. AKT = known as protein kinase B; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; GTP = guanosine triphosphate; GK = G kinase; GP = glycoprotein; NO = nitric oxide; NOS = nitric oxide synthase; PKA = protein kinase A; PKG = protein kinase G; PPARs = peroxisome proliferator-activated receptors; sGC = soluble guanylate cyclase; TP = thromboxane receptor; VASP = vasodilator-stimulated phosphoprotein; VASP-P = vasodilator-stimulated phosphoprotein phosphorylation.