European Journal of Pharmacology 669 (2011) 1–6

Contents lists available at ScienceDirect

European Journal of Pharmacology

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

Review

The promise of EPC-based therapies on vascular dysfunction in diabetes

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ARTICLE INFO

Article history:
Received 9 February 2011
Received in revised form 29 June 2011
Accepted 21 July 2011
Available online 5 August 2011

Keywords:
Diabetes
Vascular dysfunction
Circulating endothelial progenitor cell

ABSTRACT

Diabetes mellitus is one of the most common metabolic diseases in the world and the vascular dysfunction represents a challenging clinical problem. In diabetes, endothelial cells (ECs), lining the inner wall of blood vessels, do not function properly and contribute to impaired vascular function. Circulating endothelial progenitor cells (EPCs), the precursor of mature EC, actively participate in endothelial repair, by moving to the vascular injury site to form mature EC and new blood vessels. Knowing that the therapeutic interventions can improve only a part of EC dysfunction in diabetes, this review addresses recent findings on the use of EPCs for cell therapy. The strategies proposed in review are based on in vivo and in vitro studies and, thus, their physiological relevance is confirmed. EPC therapy shows great promise for the prevention and cure of diabetes-induced vascular dysfunction.

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1. Introduction

Diabetes mellitus is a clinical condition characterized by early and widespread endothelial dysfunction (McVeigh et al., 1992; Simionescu et al., 2005). By means of soluble factors, which can alternatively mediate vasoconstriction or vasodilation, the endothelium is crucially involved in the maintenance of adequate vascular tone and function. The term endothelial dysfunction refers to a condition in which endothelium loses its physiological ability to promote vasodilation, fibrinolysis and anti-aggregation. The responsible factors for the endothelial dysfunction are vasodilators: nitric oxide (NO), prostacyclin, endothelium-derived hyperpolarizing factor (EDHF), and vasoconstrictors and growth-promoting substances such as: superoxide anions, endoperoxides, thromboxane A2, endothelin-1, and angiotensin II. The contribution of each of these signals varies from a type of blood vessel to another.

In addition to well known mechanisms by which diabetes induces endothelial dysfunction, some evidences indicate that alterations in number or function of bone marrow-derived endothelial progenitor cells (EPCs) are involved in the pathogenesis of vascular complications in diabetes. EPCs are a heterogeneous subpopulation of bone marrow mononuclear cells with an enhanced potential for differentiation within the endothelial cell lineage. In response to vascular injury, EPCs are mobilized from the bone marrow to the peripheral circulation, and home to the sites of new vessel growth, where they

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doi:10.1016/j.ejphar.2011.07.035

become incorporated into the growing vasculature (Roncalli et al., 2008).

2. Endothelial physiology

The endothelial cells (ECs) line the internal lumen of blood vessels and serve as a biological barrier between the blood and vascular smooth muscle cell (VSMC) layer of the wall. The physiological function of ECs includes the modulation of vascular tone (vasoconstriction and vasodilation), hemostasis, regulation of growth and differentiation of VSMC, and modulation of inflammation (Singh et al., 2010). ECs modulate vascular tone by regulating the release of vasodilators such as NO and EDHF and vasoconstrictors such as endothelin-1, prostaglandin H2 (Fleming and Busse, 1999), reactive oxygen species (ROS), angiotensin II, and thromboxane A2 (Schiffrin, 2001). ECs express also a range of adhesion molecules such as ICAM-1, VCAM-1, and selectins (E, P and L-selectin) (Hwang et al., 1997). These molecules are modulated by ECs to regulate the dissociation of leukocytes (Miyamoto et al., 1997) and platelets from the vascular bed by release of NO (Colwell and Nesto, 2003). As a major regulator of local vascular homeostasis, the endothelium maintains the balance between vasodilatation and vasoconstriction, the inhibition and promotion of proliferation and migration of VSMCs, the prevention and stimulation of adhesion and aggregation of platelets, as well as thrombogenesis and fibrinolysis. Upsetting this tightly regulated balance leads to endothelial dysfunction (Davignon and Ganz, 2004).

3. Endothelial cell dysfunction

A lot of reports directly link the diabetic vascular complications to endothelial dysfunction. These studies are based on data from animal models, as well as from clinical trials. EC dysfunction occurs early in diabetes and insulin resistance condition (Madonna and De Caterina, 2011). The definition of endothelial dysfunction varies depending on the organ studied; however, in general, endothelial dysfunction is characterized by impaired endothelium dependent dilatation to agonists, to shear stress, or to local ischemia. In general, diabetic microvascular complications are typically associated with dysregulation of vascular remodeling and vascular growth, with decreased responsiveness to ischemic/hypoxic stimuli, and impaired or abnormal neovascularization. Lack of endothelial regeneration and impaired angiogenesis contribute to the progression of diabetic micro- and macrovascular complications. The presence of endothelial dysfunction was assessed also in hypertensive streptozotocin injected mice. The results demonstrated a diminished reactivity of the renal arteries in response to 10^{-4} M noradrenaline, 10^{-4} M acetylcholine, and 10^{-4} M sodium nitroprusside (Georgescu et al., 2007). Also, on the experimental model of simultaneously hyperlipemic–hyperglycemic hamster (Simionescu et al., 1996), the vascular reactivity of mesenteric resistance arteries was found to be modified, essentially in terms of an enhanced contractility to $PGF_{2\alpha}$ (Georgescu and Popov, 2003) and a diminished endothelium-dependent vasodilation (Georgescu et al., 2001).

When testing the effects of depolarizing K^+ (64.1 mM) both phasic and tonic components of K^+ stimulated contraction were diminished in the resistance arteries of hyperlipemic hamster, and were particularly reduced in hyperlipemic–hyperglycemic hamster (Georgescu and Popov, 2001). It was reported that both normal biological aging and diabetes induced in aged hamsters conduct to the dysfunction of resistance arteries (Georgescu et al., 2003). The endothelial dysfunction may generate various pathophysiological complications such as enhanced expression of adhesion molecules resulting in increased leukocyte–endothelial cell adhesions (Goldberg, 2009), promotion of a procoagulant state as a result of increased activation of platelets and clotting factors (Ding and Triggle, 2005), and impaired NO release (Georgescu et al., 2011). These conditions may conduct to defective modulation of vascular growth and remodeling in the vessel wall (Rudic and Sessa, 1999; Spinetti et al., 2008).

Currently, the clinical management of diabetic complications relies exclusively on pharmacological therapeutic that minimally affects the endothelial repair or regeneration. These treatments have modest influence on end organ dysfunction. Hence, there is a need for therapeutic interventions aimed to accelerate the repair of dysfunctional ECs and to restore the blood flow, resulting in the functional tissue generation. A rapid progression of EPCs from the "bench to the bedside" occurred via translational studies even in the absence of a consensus about the true identity of EPCs (Jarajapu and Grant, 2010).

4. Endothelial progenitor cells (EPCs)

The definition and biology of EPCs are complex and under a heavy debate. Today, the term EPCs is used for a heterogeneous group of cells including circulating and culture-differentiated cells. Protocols for enumeration and cultivation are as heterogeneous as the cells themselves (Steinmetz et al., 2010). Bone marrow derived EPCs play a critical role in vascular maintenance and repair. There is still great dispute about the most appropriate markers that define an EPC. EPCs can be isolated using cell sorting by surface phenotype selection or in vitro cell culture (Li Calzi et al., 2010).

Asahara et al. (1997) described first early EPCs that mainly consisted of CD34-derived cells. Today, it is known that EPCs could be released from bone marrow, fat tissue, vessel wall (especially adventitia) and possibly spleen, liver and intestine. EPCs enter the blood as circulating EPCs, where they express CD133 (at the early stage), then CD34/Flk-1, and also VEGFR2 (Xu, 2007). EPCs as defined by the depicted markers can be further mobilized to contribute to endothelial repair, but can also promote plaque growth, neovascularization and instability (Hristov and Weber, 2009). Clinically, the number and function of EPCs may reflect the balance between endothelial integrity and repair; both measures have been suggested as surrogate markers of endothelial function and cardiovascular diseases (Hamed et al., 2010).

5. The role of EPCs in vascular dysfunction in diabetes

The possible role for EPCs in diabetic vascular disease was first investigated in mice. Infusion of human CD34-positive leukocytes, as an EPC-enriched population, accelerated the blood flow restoration in diabetic nude mice with experimental hindlimb ischemia (Harraz et al., 2001). Decreased angiogenic potential of EPCs has been demonstrated in diabetic animals (Tamarat et al., 2004). Also, reduction in circulating EPCs and functional impairment of cultured EPCs have been reported both in type 1 and type 2 diabetic patients. It was showed that peripheral blood mononuclear cell (PBMC)-derived EPCs isolated from type 2 diabetic (Tepper et al., 2002) and type 1 diabetic patients (Loomans et al., 2004) displayed a reduced proliferation rate in culture, compared to control subjects, a weaker adherence to activated human umbilical vein endothelial cells (HUVECs) and a reduced incorporation into vascular structures in vitro. The rate of EPC proliferation from plated PBMCs in diabetic patients was inversely correlated with the levels of glycated hemoglobin, suggesting a possible relation between glucose control and EPC function. Reduced adhesion of EPCs to HUVECs demonstrated altered cell-to-cell interactions which could indicate that EPCs are recruited less avidly in vivo at sites of ischemia, as well that the reendothelization by means of bone-marrow derived cells is less likely to take place in the presence of EPC dysfunction. Lambiase et al. (2004) have shown that a poor coronary collateral development (typical for diabetes), may be related to low levels of circulating EPCs. Also, patients with diabetes mellitus and high high-sensitivity C-reactive protein (hs-CRP) levels showed a marked decrease in the number of EPCs compared with non-diabetic patients with low hs-CRP levels (Koshikawa et al., 2010).