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Review Article

Pharmacological Modulators of Endothelial Progenitor Cell Therapy: Implications for Treatment with Thiazolidinediones

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Abstract

Endothelial progenitor cells (EPCs) play an important role in maintaining vascular health both by integrating in endothelium and by providing paracrine support to the resident vasculature. EPCs from patients with cardiovascular disorders and diabetic complications are typically reduced in number and dysfunctional. In an effort to restore EPC numbers and correct their dysfunction, a variety of commonly prescribed pharmacological agents such as statins, angiotensin converting enzyme (ACE) inhibitors, thiazolidinediones (TZDs) and erythropoietin (EPO) have been evaluated and found to be of benefit in both increasing EPC numbers and improving EPC function. This review will discuss several of these commonly used pharmacological agents and recent work in our laboratory highlighting some novel approaches to correct EPC dysfunction. Mechanism responsible for modulating EPC function by these agents is also briefly discussed.

INTRODUCTION

Endothelial Progenitor Cells (EPCs), first recognized in 1997 by Asahara et al., presented the new notion of postnatal neovascularization, which was earlier thought to be only limited to embryonic development [1]. EPCs exercise their vaso-reparative potential either by participating in new vessel formation or by providing paracrine support. Therapeutic effects of EPCs are reported in a variety of ischemic diseases including myocardial infarction, chronic wounds and diabetic retinopathy, among others [2-6]. A variety of diseases are associated with a decline in the number and function of EPCs, including obesity [7], renal failure and hemodialysis [8], hypertension [9,10], atherosclerosis [11], chronic obstructive pulmonary disease [12], and dyslipidemia [13].

Most notably, a negative alteration in the function and amount of EPCs is reported in diabetes and related complications. Both type I and II diabetes have decreased levels of EPCs. Diabetes also induces functional defects in EPCs, affecting EPC migration, adhesion, proliferation, and incorporation. Diabetes also induces bone marrow defects as implicated by reduced mobilization of progenitors from the bone marrow and selective depletion from bone marrow reservoirs. Moreover, diabetic microvascular complications like, retinopathy, nephropathy, and neuropathy are associated with impaired EPC numbers and function. This consistent impairment in both numbers and function of EPCs in several pathological disorders, including diabetes, suggests the importance of modulating EPCs for therapeutic purposes. In an attempt to correct EPC dysfunction, a variety of pharmacological agents have been tested either *in vivo* or in *vitro* before autologous transplantation in pre-clinical and clinical studies. Due to the important therapeutic potential of EPC, modulators of their function could fulfill an important role in modulation of a wide spectrum of diseases. Chemical modification of EPCs has been, and continues to be, intensely investigated. We reviewed Pub Med database on 4 July 2013 using search criteria as 'EPC and Pharmacology' which resulted in more than 1000 papers and for this review, pharmacological agents which produced adverse effects on EPC function and numbers were excluded. Following is the summary of important pharmacological modulators of EPC function; Table 1 provides a quick review of these agents.

PHARMACOLOGICAL MODULATION OF EPCS *IN VIVO*

Statins

In relation to correct EPC dysfunction and numbers, perhaps one of the most extensively investigated class of drugs is statins, or 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor [14,15]. While statins are widely prescribed for their cholesterol lowering effects, they have important EPC modulating effects that were first explored through *in vitro* studies of human mononuclear cells (MNCs) and *in vivo* studies in mice. Various statins, including atorvastatin, simvastatin, mevastatin [15], and rosuvastatin [16,17] were able to beneficially modify EPC function. Statins improve endothelial function by increasing the levels of bioavailable nitric oxide and correcting migratory defects [14]. Statins reduce oxidative stress via forkhead box O (FOXO) dependent mechanism [18] and possess anti-inflammatory properties which likely contribute towards correcting EPC dysfunction. Clinical studies show EPC numbers and function increase following treatment with statins, including a significant increase in EPC migratory function [19] and an increase in colony forming units [17].

Table 1: Pharmacological modulators of EPCs.

Drug Class	Example	Outcome/End Point
Statins [14-17,19]	Atorvastatin [14,15,19] Simvastatin [15] Rosuvastatin [16,17] Mevastatin [14,15]	↑ Migration [14] ↑ Number [16,19] ↑ Mobilization [19] ↑ Neovascularization [19] ↑ Differentiation [15] ↑ CFU [17]
Thiazolidinediones [20-22]	Rosiglitazone [20] Pioglitazone [21,22]	↑ Number [20] ↑Migration [21,22] ↓ Apoptosis [22] ↑ Neo-angiogenesis [22] ↑ Colony formation [20]
Erythropoietin [28]	Darbepoietin [28]	↑ Proliferation [28] ↑ Differentiation [28] ↑ Number [28]
GM-CSF/G-CSF [29-31]		↑ Number [29] ↑ Mobilization [29] ↑ Neovascularization [29]
Calcium channel blockers [32,53]	Benidipine [32] Nifedipine [53]	↑ Number [32,53] ↑ Differentiation [32,53] ↑ Migration [53] ↑ Oxidative stress resistance [53] ↓Apoptosis [53]
PDE-5 inhibitors [34]	Sildenafil [34] Tadalafil [35]	↑ Number [34,35] ↑ Migration [34] ↑ Adhesion [34]
DPP-IV inhibitors [24]	Sitaglipin [24]	↑ Number [24] ↑ Mobilization [24]
Modulators of RAAS system [36,37]	Ramipril, Enalapril Valsartan [37] Ang-(1-7) [39,54]	↑ Number [37] ↑ Survival [39] ↑ Proliferation [39]
Ebselen [41]		Number [41] ↑ Oxidative stress resistance [41] ↓Apoptosis [41]
Cytokines [29,42]	VEGF [29,42] FGF [29] Angiopoietins [29] SDF-1 [29] PIGF [29,42]	↑ Mobilization [29] ↑ Incorporation [29] ↑ Recruitment [42] ↑ Vessel Formation [42]
Hormones [44-47]	Insulin [44,45] 17 beta-estradiol [45-47]	↑ CFUs [44] ↑ Clonogenic capacity [44] ↑ Angiogenic capacity [44] ↑ Number [46] ↑ Differentiation [47] ↑ Migration [47] ↑ Proliferation [45,47] ↓Apoptosis [47] ↑ Adhesion [45]
Lifestyle change [47,50], [52] [49]	Exercise [47] Diet: Vegetables [50] Diet: Green Tea [52] Mediterranean diet [49]	↑ Number [47] [50] [49,52]
TGF- β 1 [40]		↑ Migration [40] ↑ Survival [40] ↑ Reparative function [40] ↑ Recruitment [40]
Mineralocorticoid receptor antagonist [55]	Eplerenone [55]	↑ Number [55] ↑ Colony forming [55] ↑ Migration [55]
Alkylating agent [56]	Cyclophospha-mide [56]	↑ Number [56] ↑ Mobilization [56]
Angiotensin Receptor Blockers [57]	Telmisartan [57]	↑ Colony Formation [57] ↑ Proliferation [57]
Osteopontin [58]		↑ Neovascularization [58]
Vitamin [59]	Niacin [59]	↑ Mobilization [59] ↑ Differentiation [59] ↓Apoptosis [59]
Urotensin II [60]		↑ Proliferation [60]
β2 adrenergic agonist [61]	Isoproterenol [61]	↑ Number [61] ↑ Migration [61] ↑ Proliferation [61]
Anti-oxidant [33,62]	Resveratrol [62] Benfotiamine [33]	Maintain CFUs [33] Recovery from high glucose effects [33] Delay in senescence [62]

Thiazolidinediones

Another class of drugs that has been explored in modulating EPCs is glitazones or thiazolidinediones (TZD). TZDs are peroxisome activated proliferator receptor agonists with anti-diabetic properties. Like statins, several types of glitazones have been shown to similarly modulate EPCs, including pioglitazone and rosiglitazone [20,21]. *In vivo* experiments in mice showed an increase in EPC levels in the bone marrow when treated with rosiglitazone [20]. Moreover, in humans, EPC numbers and functions were increased when treated with pioglitazone [21]. Beneficial effects of TZDs are attributed to several mechanisms. TZD treatment corrects EPC migratory defects, improves clonogenic potential and decreases EPC apoptosis by enhancing endothelial nitric oxide synthase (eNOS) activity [21,22]. We used TZDs to correct the dysfunction in diabetic EPCs; *in vitro* treatment of diabetic EPCs with pioglitazone enhanced their

migration to the gradient of stromal derived factor 1 (SDF-1). Restoration of migratory potential in diabetic EPCs was attributed to an increase in nitric oxide levels (Figure 1). We also observed a decrease in reactive oxygen species after treatment with pioglitazone (Figure 2). Interestingly pioglitazone also increases the levels anti-inflammatory protein [23], adiponectin. This may result in an improvement of EPC number and function.

Thus we believe that there are multiple facets to the beneficial effects of pioglitazone treatment and that TZDs can be used effectively to correct dysfunctional diabetic EPCs for autologous transplantation.

DPP-IV inhibitors

Dipeptidyl peptidase-4 (DPP-IV) inhibitors are a class of anti-diabetic drugs which block the enzyme DPP-4 and reduce glucagon levels [24]. In addition to glucose lowering effects, DPP-IV inhibitors also show cardio-protective action. DPP-IV inhibitor sitagliptin promotes an increase in EPC numbers and adhesion, both in animal [24] and human studies [25] Multiple mechanisms, such as an increase in NO production [24], reduction in inflammation [26] and reactive oxygen species [27] are suggested in the therapeutic benefit of DPP-IV inhibitors.

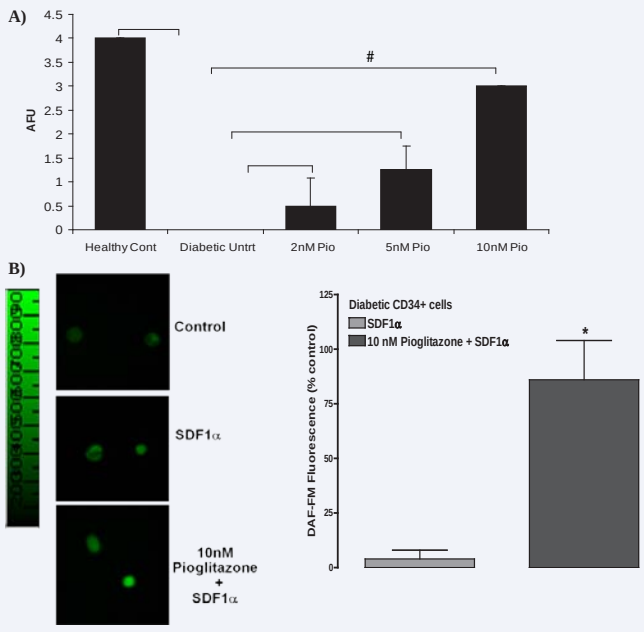

Figure 1 Pioglitazone corrects migratory defects by increasing nitric oxide in diabetic EPCs cells

(A) Healthy and diabetic EPCs were allowed to migrate to SDF-1 gradient in a modified Boyden chamber assay. Diabetic EPCs cells failed to migrate towards SDF-1 while pioglitazone treatment corrected migratory defects (#P<0.05). (B) Imaging of NO-sensitive 4-Amino-5-Methylamino-2',7'-Difluorofluorescein Diacetate (DAF-FM) fluorescence in human diabetic EPCs. Shown in the extreme left was the color scale for arbitrary fluorescence units and images were shown in pseudo color. Cells that were non-treated served as time-control and effect of SDF1-α without and with pioglitazone (10 nM) pretreatment were expressed as percent increase compared to the time-control in a bar chart on right. Production of NO in response to SDF1-α was significantly increased by pretreatment with Pioglitazone (*P<0.0001). Scale bar measuresv 20 microns and is applicable for all images.

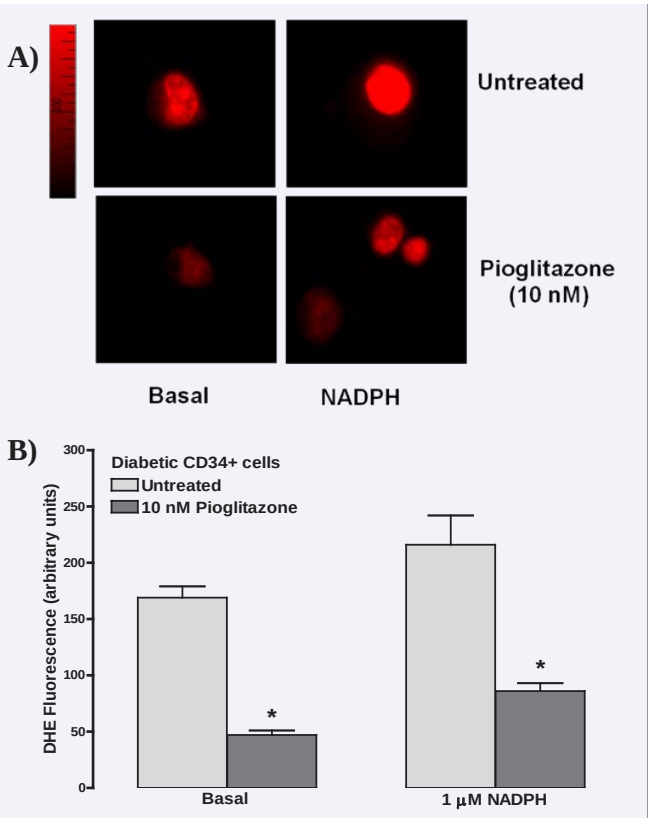

Figure 2 Pioglitazone treatment reduces reactive oxygen species (ROS) production in diabetic EPCs. (A) Images of ROS-sensitive dye dihydroethidine (DHE) showing basal and NADPH-stimulated ROS production. Images were obtained by Till Photonics system with 40x W objective (Zeiss) at 2x2 binning. Shown in the left was color scale. Scale bar measures 20 microns and applicable to all images. Images are representative of 17 to 41 cells in a group. (B) Pretreatment with 10 nM pioglitazone significantly reduced basal and NADPH stimulated ROS production (P<0.0001).

Erythropoietin

Erythropoietin (EPO) is a cytokine that controls erythropoiesis; some studies show that EPO is effective in enhancing EPC numbers and function. A study using darbepoietin (a synthetic form of erythropoietin) in renal failure patients showed enhanced EPC proliferation and differentiation potential [28].

GM-CSF

Granulocyte-colony stimulating factor (G-CSF) and granulocyte monocyte colony-stimulating factor (GM-CSF) are also cytokines shown to be effective in promoting bone marrow release of EPCs [29]. In humans, when G-CSF-mobilized $CD34^+$ cells were injected intramuscularly in patients with ischemia, improvements were observed [30,31].

Calcium channel blockers

Calcium channel blockers induce vasodilation by blocking the influx of calcium ions into vascular smooth muscle cells, leading to a decrease in systemic blood pressure. *In vivo* treatment with benidipine, a calcium channel blocker, promotes endothelial differentiation of EPCs [32]. Another calcium channel blocker,

nifedipine, not only increases EPC numbers, but also enhances several EPC functions, including migration, differentiation, and resistance to oxidative stress [33]. Beneficial effects of calcium blocker treatment are attributed to anti-oxidant defense mechanisms.

PDE5 inhibitors

Phosphodiesterase 5 (PDE-5) inhibitors also play a role in correcting EPC dysfunction [34]. Sildenafil, a PDE-5 inhibitor, increases EPC levels [34]. Moreover, EPC functions, including migration and adherence, were also improved upon treatment with sildenafil [34]. Modified angiogenic factor expression and reduced oxidative stress were observed with sildenafil treatment and are implicated as the mechanism for its effects [34]. Tadalafil, another PDE-5 inhibitor, also modulates EPCs, with increasing cell numbers [35].

Modulators of renin angiotensin aldosterone system (RAAS)

Modifying the RAAS influences EPC numbers [36]. Angiotensin converting enzyme (ACE) inhibitors such as ramipril and enalapril, and AT-II inhibitors such as valsartan, – increase EPC numbers [37]. These drugs reduce oxidative stress by decreasing NADPH oxidase expression [38]. Currently, our laboratory is exploring the role of RAAS in modulating EPC function by evaluating (ACE-2)/Angiotensin-(1-7), the vasoreparative axis of the RAAS. We observed that *in vitro* treatment with Ang-(1-7) repairs the migratory defects of diabetic EPCs and improves EPC proliferation and survival [39].

IN VITRO EPC TREATMENT FOR AUTOLOGOUS TRANSPLANTATION

Transforming growth factor-β1 (TGF-β1) is involved in differentiation, proliferation, and quiescence of hematopoietic stem cells [40]. In diabetic patients, TGF- β1 levels are increased in EPCs and this negatively influences cellular function [40]. Our studies have shown that pre-treatment with TGF-β1-PMOs (phosphorodiamidate morpholino oligomers) reduces these high levels back towards normal, corrects EPC migratory dysfunction and promotes their homing to areas of injured retina [40]. Inhibition of TGF-β1 restores bioavailable NO in EPCs of diabetic origin and increases their expression of CXCR4, a critical receptor involved in EPC migration. Ongoing work in our laboratory indicates that plasminogen activator inhibitor-1, the main target of TGF- β1 action, may also represent a novel target for improving EPC function. In addition, the randomized placebo-controlled ENACT-AMI trial is evaluating similar *in vitro* priming of EPCs using overexpression of eNOS in patients with diabetes and hypertension.

OTHER PHARMACOLOGICAL AGENTS

Some investigational pharmacological agents have shown beneficial effects in correcting EPC dysfunction in animal studies; for example, Ebselen, a synthetic anti-oxidant, reduces EPC apoptosis and increases EPC numbers [41]. Another strategy for EPC modulation is the use of various cytokines and hormones [29] including vascular endothelial growth factors (VEGF), fibroblast growth factor (FGF), angiopoietins, SDF-1, placental growth factor (PIGF), and others [29,42,43]. When treated with insulin, EPCs from patients with type 2 diabetes showed an increase in EPC colony forming units (CFUs) [44]. Similarly, treatment with 17 beta-estradiol promoted EPC proliferation and adhesion [45-47]. Improved lifestyle such as increased exercise [48] and balanced nutrition such as a Mediterranean diet [49] increases EPC number [50,51]. Some specific dietary components that improve EPC conditions include green tea [52].

CONCLUSION

In conclusion, a variety of pharmacological strategies have been found to be effective in modulating EPCs to i) stimulate their proliferation; ii) enhance their release from the bone marrow; or iii) to "prime" the cell *in vitro* before autologous transplantation. The choice of well-accepted pharmacological agents (e.g. statins, TZDs, EPO) provides the advantage of modulating EPC function in addition to the agent's primary therapeutic benefit. Our studies suggest that pioglitazone is a promising candidate in correcting diabetes induced EPC dysfunction. It is worth noting that some pharmacological agents like paclitaxel, sirolimus, everolimus, and zotarolimus produce adverse effects on both EPC numbers and function, which were not discussed in this review, but should be considered when prescribing to patients with established vascular disease. Overall, EPC modulation continues to be an area of intense investigation and a promising therapeutic option in treating a wide variety of diseases.

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