Tetrahydrobiopterin (BH4), an essential cofactor for diverse cellular processes, is present in almost every cell or tissue of higher organisms. BH4 has well-defined functions in terms of enzymatic activities (BH4 is a crucial cofactor for the aromatic amino acid hydroxylases and all isoforms of nitric oxide synthase [NOS]) but has other less-defined functions in cells. BH4 is a growth or proliferation factor for various mammalian cells, including hematopoietic and endothelial cells.1,2 Epidermal growth factor and nerve growth factor act to increase proliferation of rat PC12 cells by elevating BH4 levels.3 However, BH4 is also a powerful antioxidant4 and has scavenging capabilities, reacting with superoxide anion radicals peroxynitrite and hydrogen peroxide.5 BH4 bioavailability is, thus, potently influenced by oxidative stress in cells.

GTP cyclohydrolase I (GTPCH), 6-pyruvoyltetrahydropterin synthase, and sepiapterin reductase act in sequence to generate BH4 de novo in endothelial cells.5 The first enzyme, GTPCH, is thought to be the rate-controlling enzyme. GTPCH activity can be controlled at the transcriptional level by a number of mediators, including nutritional (phenylalanine and arginine), hormonal (insulin and estrogen), immunologic (inflammatory cytokines including interleukin1, interferon-γ, and tumor necrosis factor-α), therapeutic (statins and cyclosporin A), and endothelium-derived (basic fibroblast growth factor and H2O2) factors.5 These agonists act via different mechanisms but all lead to the increased generation of BH4.

BH4 regulates NO synthesis in both mature endothelial cells and endothelial progenitor cells (EPCs). Bone marrow–derived EPCs have the potential to give rise to circulating vascular progenitor cells that home to damaged vessels and differentiate into mature endothelial cells, thereby contributing to vascular repair, remodeling, and maintenance of endothelial function. Mobilization and recruitment of these cells, for example, play a key role in postischemic tissue repair. EPCs isolated from bone marrow aspirates or peripheral blood can be reintroduced into the circulation or ischemic tissue where they participate in blood vessel growth at sites of ischemia or vessel injury and improve blood circulation in ischemic disease. A growing number of studies have investigated the feasibility of using autologous EPCs to induce therapeutic revascularization and tissue repair in patients with a variety of ischemic conditions. Unfortunately, the vascular regenerative potential of EPCs is impaired in some disease conditions, such as hypertension or diabetes mellitus. This impairment is manifested as reduced EPC number and function. Interestingly, hyperglycemia-induced EPC dysfunction can be reversed by treating EPCs with BH4.

In this issue of Hypertension, He et al6 report that the ligand-activated transcription factor peroxisome proliferator-activated receptor–δ (PPARδ) enhances the regenerative capacity of human EPCs by stimulating BH4 biosynthesis. Using the high-affinity ligand for PPARδ, GW501516, these authors demonstrate that PPARδ activation increases EPC proliferation and migration by stimulating phosphoinositide 3-kinase/AKT/GTPCH–mediated BH4 synthesis and reducing PTEN-mediated dephosphorylation of phosphatidylinositol (3,4,5)-trisphosphate, which would decrease activation of AKT. The proproliferative effect of PPARδ activation is abolished by inhibiting GTPCH activity but not by inhibiting endothelial NOS (eNOS) activity, illustrating that BH4 has direct effects on EPC proliferation that are independent of its ability to enhance NO synthesis (Figure). These human EPCs helped to repair denuded endothelium in a mouse model of carotid injury. Pretreatment with GW501516 or GTPCH knockdown significantly enhanced or inhibited, respectively, the re-endothelialization brought about by injected EPCs.

Our understanding of the role of PPARδ in vascular cells is limited. In this study, He et al6 demonstrate that PPARδ activation can regulate AKT signaling in EPCs by decreasing PTEN action, effectively reducing PTEN’s antagonism of the phosphoinositide 3-kinase pathway, increasing AKT activation, and boosting the production of BH4 via GTPCH.6 This effect of PPARδ appears to be direct and not attributed to activation of the phosphoinositide 3-kinase-Akt-nuclear factor κB pathway. However, this does not rule out other indirect mechanisms to support GTPCH activity in EPCs, such as activation of AMP-activated protein kinase. Wang et al7 demonstrated that activation of AMP-activated protein kinase

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suppresses 26S proteasome-mediated degradation of GTPCH linked to endothelial dysfunction in diabetes mellitus. He et al acknowledge that GW501516 has been shown to phosphorylate AMP-activated protein kinase, which could potentially support BH4 synthesis indirectly by maintaining GTPCH levels for BH4 synthesis in EPCs.

Reduced BH4 levels in endothelial cells with resultant uncoupling of eNOS is becoming a well-accepted mechanism responsible for endothelial dysfunction in a number of disease states, including hypertension and diabetes mellitus. The current study by He et al helps us to understand something about the dynamic regulation of BH4 availability in endothelial precursors. These authors demonstrate a high basal level of BH4 in EPCs. Interestingly, there is a low expression of eNOS in these cells. Activation of PPARδ increased both BH4 synthesis and eNOS phosphorylation.

The effect of increased BH4 availability on EPC proliferation in the current study does not appear to be related to changes in ROS and, thus, not attributed to the antioxidant effect of BH4. However, it is likely that the actions of BH4 on cells may differ in disease states. For example, Xie et al demonstrated that the GTPCH/BH4 pathway regulated EPC number and function in deoxycorticosterone acetate-salt hypertensive mice, at least in part, by suppression of oxidative stress. EPC number and function are also decreased in diabetes mellitus. Wenzel et al demonstrated that atorvastatin treatment significantly elevated circulating EPCs in streptozotocin-induced (type I) diabetic rats and increased EPC numbers to an even greater extent in control animals. These authors concluded that this consequence of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibition normalizes endothelial function and reduces oxidative stress in diabetes mellitus by inhibiting NADPH oxidase activation and by preventing eNOS uncoupling. Importantly, Dimmeler et al demonstrated that statins can activate the phosphoinositide 3-kinase/AKT/eNOS pathway in EPCs, but inhibition of NO synthesis (blocking eNOS activity) did not prevent the statin-induced increase in EPC numbers. Because statins also increase GTPCH activity and thus BH4 levels, their effect on EPC number and function may indeed be brought about, at least partially, by BH4-mediated eNOS-independent pathways.

The results of the current study by He et al offer additional insight into an important role for BH4 in the functional integrity of EPCs that is only partially dependent on its ability to support eNOS-mediated production of NO. At present, it is unknown how BH4 stimulates EPC proliferation. However, therapies that can bring about increases in BH4 availability may have important disease-preventing effects. We have shown that dietary supplementation with L-arginine can upregulate GTPCH expression and BH4 synthesis in endothelial cells. This may be a simple, nonpharmacological means of modulating EPC number and function in disease states, such as obesity, diabetes mellitus, and hypertension, but remains to be tested in clinical studies. In the meantime, the eNOS-dependent and eNOS-independent effects of PPARδ agonists should be studied further to assess the therapeutic efficacy of PPARδ agonists for treating vascular conditions associated with endothelial injury and/or loss of normal function.

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