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The Effects of GLP-1 Receptor Agonists on Endothelial Function: Do They Function Directly or Indirectly?

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Glucagon-like peptide 1 (GLP-1) receptor agonists, as well as dipeptidyl peptidase-4 inhibitors, have recently been widely used as therapeutics of type 2 diabetes [1]. According to the accumulation of clinical experience, cardiovascular protective effects of GLP-1 receptor agonists have been focused [2,3]. Although these effects may partly be due to their indirect glucose-lowering and weight-losing effects [4], recent evidence has indicated their direct effects on endothelium.

GLP-1 receptor, a seven-transmembrane G-protein coupled receptor consists of 463 amino acids, is not only expressed in pancreatic islets, but also in broad range of organs including endothelium [5]. A GLP-1 receptor agonist liraglutide has been demonstrated to stimulate endothelial nitric oxide (NO) synthase (eNOS) phosphorylation at Ser-1177/NO production via AMP-activated protein kinase (AMPK) activation in human umbilical vein endothelial cells (HUVEC) [6]. Another GLP-1 receptor agonist exenatide also induced eNOS phosphorylation at Ser-1177 in HUVEC, indicating that the effect is mediated via GLP-1 receptor [7]. However, GLP-1(9-36), which has a weak affinity for GLP-1 receptor, also stimulated eNOS phosphorylation at Ser-1177 in HUVEC [7]. Additionally, NO-mediated vasodilatory effects by GLP-1 and GLP-1(9-36) were maintained in Glp-1r$^{-/-}$ mice [8]. Therefore, the existence of GLP-1 receptor-independent pathway for eNOS phosphorylation/NO production is also speculated.

Regarding the signal transduction of GLP-1-mediated eNOS phosphorylation/NO production, involvement of protein kinase A (PKA) has also been demonstrated in bovine aortic EC [9]. Recently, GLP-1 receptor/cyclic AMP/PKA/liver kinase B1 (LKB1)/AMPK/eNOS cascade has been proposed for the GLP-1-stimulated NO production [10]. The phosphoinositide 3-kinase (PI3K)/Akt cascade is also recognized as an important pathway for eNOS phosphorylation [11]. Although exenatide has been shown to induce eNOS phosphorylation at Ser-1177 via both PKA and PI3K/Akt pathways in human coronary artery EC [12], the significance of PI3K/Akt cascade in the GLP-1-mediated NO production remains uncertain. We therefore performed DNA microarray analyses to examine the effect of liraglutide on human coronary artery EC gene expression. Interestingly, we observed that liraglutide significantly up-regulated (3.2-fold) the expression of p87 (PIKAP), which is a novel regulatory subunit of PI3K p110gamma [13] (Kudo et al. unpublished data). Further studies are needed to define the importance of PI3K/Akt pathway and its crosstalk with PKA/LKB1/AMPK cascade in the GLP-1-mediated eNOS phosphorylation/NO production.

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