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

Masataka Kudo¹, Akiko Saito-Hakoda², Ken Matsuda³, Kyoko Shimizu⁴, Ikuko Sato⁵, Akira Uruno⁶, Takeo Yoshikawa⁷, Yuko Ikī⁸, Kaori Sugawara⁹, Naotaka Kogure¹⁰, Takako Saito-ito¹¹, Sadayoshi Ito¹² and Akira Sugawara¹³

¹Division of Nephrology, Endocrinology, and Vascular Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan
²Department of Molecular Endocrinology, Tohoku University Graduate School of Medicine, Sendai, Japan
³Department of Medical Biochemistry, Tohoku University Graduate School of Medicine, Sendai, Japan
⁴Department of Pharmacology, Tohoku University Graduate School of Medicine, Sendai, Japan

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 due to their indirect glucose-lowering and weight-losing effects [4], recent evidence has indicated their direct effects on endothelium.

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 (LK/B1)/AMPK/eNOS cascade has been proposed for the GLP-1-stimulated NO production [10]. The phosphoinositide 3-kinase (PI3K)/Akt cascade is also proposed as an important pathway for 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.

Upregulation of nitric oxide production in vascular endothelial cells by all-trans retinoic acid through the phosphoinositide 3-kinase/Akt pathway. Circulation 112: 727-736.

Received December 27, 2012; Accepted December 28, 2012; Published December 27, 2012


Copyright: © 2013 Kudo M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

References