Basic Science

GLP-1 analog liraglutide protects against oxidative stress and albuminuria in streptozotocin-induced diabetic rats via protein kinase A-mediated inhibition of renal NAD(P)H oxidases

Hari Hendarto a, b, Toyoshi Inoguchi a, c, *, Yasutaka Maeda a, Noriko Ikeda a, Jing Zheng a, Ryoko Takei a, Hisashi Yokomizo a, Eiichi Hirata a, Noriyuki Sonoda a, c, Ryoichi Takayanagi a, c

a Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan
b Faculty of Medicine and Health Sciences, Syarif Hidayatullah State Islamic University (UIN) Jakarta, Indonesia
c Innovation Center for Medical Redox Navigation, Kyushu University, Fukuoka, Japan

ABSTRACT

Accumulating evidence has implicated that GLP-1 may have a beneficial effect on cardiovascular and renal diseases but the mechanism is not fully understood. Here we show that GLP-1 analog, liraglutide, inhibits oxidative stress and albuminuria in streptozotocin (STZ)-induced type 1 diabetes mellitus rats, via a protein kinase A (PKA)-mediated inhibition of renal NAD(P)H oxidases. Diabetic rats were randomly treated with subcutaneous injections of liraglutide (0.3 mg/kg/12 h) for 4 weeks. Oxidative stress markers (urinary 8-hydroxy 2′-deoxyguanosine and renal dihydroethidium staining), expression of renal NAD(P)H oxidase components, transforming growth factor-α (TGF-α), fibronectin and urinary albumin excretion were measured. In vitro effect of liraglutide was evaluated using cultured renal mesangial cells. Administration of liraglutide did not affect plasma glucose levels or body weights in STZ diabetic rats, but normalized oxidative stress markers, expression of NAD(P)H oxidase components, TGF-α, fibronectin in renal tissues and urinary albumin excretion, all of which were significantly increased in diabetic rats. In addition, in cultured renal mesangial cells, incubation with liraglutide for 48 h inhibited NAD(P)H-dependent superoxide production evaluated by lucigenin chemiluminescence in a dose-dependent manner. This effect was reversed by both PKA inhibitor H89 and adenosyl cyclase inhibitor SQ27536, but not by Epa2 inhibition via its small interfering RNA. Liraglutide may have a direct beneficial effect on oxidative stress and diabetic nephropathy via a PKA-mediated inhibition of renal NAD(P)H oxidase, independently of a glucose-lowering effect.

© 2012 Elsevier Inc. All rights reserved.

Abbreviations: DPI, diphenylene iodonium chloride; GLP-1, glucagon-like peptide-1; MDA, malondialdehyde; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; PKA, protein kinase A; ROS, reactive oxygen species; STZ, streptozotocin.

* Corresponding author. Department of Internal Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan. Tel: +81 92 642 5284; fax: +81 92 642 5287.
E-mail address: toyoshi@intmed3.med.kyushu-u.ac.jp (T. Inoguchi).

0026-0495/ - see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2012.03.002