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Anti-inflammatory effects of liraglutide by ectodomain shedding of RAGE in human aortic endothelial cells

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Objectives: Glucagon-like peptide-1 (GLP-1) stimulates insulin secretion, inhibits glucagon secretion, stimulates beta-cell proliferation and differentiation, and delays gastric emptying. Therefore, GLP-1 receptor agonist is widely used for treatment of type 2 diabetes and obesity. GLP-1 receptor agonist also showed cardiovascular benefits in diabetic patients, but the mechanisms of this anti-inflammatory effect are not well defined.

Methods: In this study, we investigated the mechanism by which liraglutide attenuates advanced glycation end product-bovine serum albumin (AGE-BSA)-induced inflammation on human aortic endothelial cells (HAECs).

Results: Treatment of AGE-BSA on HAECs increases ICAM-1 expression in Western blot. However, ICAM-1 expression was decreased when HACEs were treated with liraglutide and AGE-BSA. To examine whether liraglutide causes ectodomain shedding of RAGE, HAECs were incubated with various concentrations of liraglutide and various durations, after which whole-cell lysates and conditioned media were collected. Cellular RAGE was decreased in a concentration- and time-dependent manner. Also, RAGE in the culture supernatants was also increased in the same manner (Figure 1). However, in the presence of BAPTA-AM and verapamil, ectodomain shedding of RAGE by liraglutide was decreased suggesting that this is calcium-dependent mechanism. Calcium influx activates ADAM10. When we examined the change in the localization of ADAM10 by immunofluorescent staining and confocal microscopy, ADAM10 at the cell surface was markedly increased after liraglutide treatment. Liraglutide-induced cell surface ADAM10 expression was inhibited by BAPTA-AM. Inhibition of ADAM10 by siRNA also suppressed liraglutide-induced ectodomain shedding of RAGE and effect of liraglutide on AGE-BSA induced ICAM-1 expression.

Conclusions: These findings suggest that liraglutide attenuated the effects of AGE-BSA on HAECs by inducing ADAM10-mediated ectodomain shedding of RAGE. This explains a mechanism which liraglutide has anti-inflammatory effect on endothelial cells in diabetes patients.

Figure 1. Liraglutide induces ectodomain shedding of RAGE

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