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PERSPECTIVE

Further Possible Mechanisms of Dipeptidyl Peptidase-4 Inhibitors to Decrease Blood Glucose in Subjects with Type 2 Diabetes

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Abstract: Recently, dipeptidyl peptidase-4 (DPP-4) inhibitors have been launched into clinical use for type 2 diabetes in Japan. Shortly after its use, several cases have been reported, in which the co-administration of DPP-4 inhibitors with sulfonylureas caused severe hyperglycemia in Japan. Additionally, the efficacy to improve glycemic control was greater than expected. Taken together, it is suggested that DPP-4 inhibitors may have other action mechanisms than to stimulate insulin secretion in glucose-dependent manner. I present here several possible mechanisms of DPP-4 inhibitors to reduce blood glucose in type 2 diabetes; first, to inhibit glucagon secretion, second, to stimulate glucose-dependent insulinotropic peptide (GIP) secretion, which may regain its action to stimulate insulin secretion when hyperglycemia has been improved, third, to recover the response to sulfonylureas by restoring pancreatic ATP levels, fourth, to stimulate glucagon-like peptide 1 (GLP-1) secretion directly from the intestine, and finally to inhibit the action of DPP-4 as an adipokine.

Keywords: DPP-4, GLP-1, inhibitors

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In December 2009, dipeptidyl peptidase-4 (DPP-4) inhibitors, "incretin enhancers"[1,2] were launched into clinical use for type 2 diabetes in Japan.[3] Shortly after its use, several cases with severe hypoglycemia were reported in Japan, in which the DPP-4 inhibitors were administered with sulfonylureas, necessitating a statement by the Japanese Diabetes Society to reduce the dose of sulfonylureas properly. Furthermore, the efficacy of DPP-4 inhibitors was much greater than expected in improvement of glycemic control in Japanese subjects with type 2 diabetes.

These findings suggest that DPP-4 inhibitors may have other action mechanisms than to stimulate insulin secretion in glucose-dependent manner. I propose here several possible mechanisms of DPP-4 inhibitors to reduce blood glucose in type 2 diabetes.

First, DPP-4 inhibitors are known to inhibit glucagon secretion.[1–4] It is plausible that a decrease in glucagon secretion is involved in the improvement of glycemic control of subjects with type 2 diabetes after DPP-4 inhibitors.

Second, DPP-4 inhibitors stimulate glucose-dependent insulinotropic peptide (GIP) secretion.[1,2] Although the incretin effect of GIP is abolished in type 2 diabetes, GIP is reported to restore its action to stimulate insulin secretion, after the glycemic control has been improved both in rats and humans.[1,5,6]

Third, it has recently been indicated that exendin-4, an "incretin mimetic", which is in fact a GLP-1 paralog,[7] causes an elevation of impaired ATP production by high glucose in islets of diabetic rats.[8] Therefore, it is plausible that DPP-4 inhibitors may recover the response to sulfonylureas by restoring pancreatic ATP levels.

Fourth, it has very recently been reported, in an abstract form, that sitagliptin, one of the DPP-4 inhibitors, may stimulate glucagon-like peptide 1 (GLP-1) secretion directly from the intestine.[9] Further studies are required to evaluate whether this effect is due to DPP-4 inhibition, and it has clinical effect in humans.

Fifth and finally, DPP-4 has been reported to act as an adipokine, which may be positively linked to insulin resistance.[10] Although the physiological significance of these findings remains to be elucidated, it is possible that DPP-4 inhibitors may inhibit the action of DPP-4 as an adipokine, resulting in an improvement of insulin resistance.

Further studies are justified to investigate whether the possible mechanisms of DPP-4 inhibitors presented here may have clinical significance in the treatment of type 2 diabetes with DPP-4 inhibitors.

Conflict of Interest

The author received research grants from MSD, Daichi-Sankyo Co. and lecture fees or consultation fees from MSD Japan, Daichi-Sankyo Co. Pfizer Co., Novartis Co. Novo Nordisk, Eli Lilly Co. Bohringer-Ingelheim Co., Tanabe-Mitsubishi Pharma Co., and Astellas Co.

Disclosure

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

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