Voglibose, an Alpha-glucosidase Inhibitor, to Increase Active Glucagon-like Peptide-1 Levels

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Abstract
Voglibose is an alpha-glucosidase inhibitor used for lowering post-prandial blood glucose levels in patients with diabetes mellitus. Voglibose is known for its ability to increase glucagon-like peptide-1 (GLP-1) secretion in humans. Our recent study demonstrated new mechanisms by which voglibose increases plasma active GLP-1 levels in diabetic ob/ob mice. As expected, the stimulatory effects of voglibose on GLP-1 secretion resulted in increased active GLP-1 levels in plasma in the 1-day dosing study. Unexpectedly, chronic but not 1-day treatment with voglibose decreased plasma dipeptidyl peptidase-4 (DPP-4) activity by reducing its circulating protein levels. We have also revealed that chronic dosing of voglibose increased Neurod1 and Glucagon gene expression, and GLP-1 content in the lower gut. Active GLP-1 levels in plasma achieved by chronic treatment with voglibose were higher than those achieved by 1-day treatment. In the present overview, by using acarbose, another alpha-glucosidase inhibitor with different selectivity, as a comparator, we demonstrated that inhibition of alpha-glucosidase induces a decrease in plasma DPP-4 activity in ob/ob mice. Notably, compared to acarbose, voglibose has demonstrated more favorable effects on DPP-4 activity, GLP-1 secretion and gut GLP-1 content, when glucose levels were equally improved, leading to higher plasma active GLP-1 levels. These findings provide new insights into the mechanism underlying the increases in active GLP-1 circulation by voglibose.

Keywords: Dipeptidyl peptidase-4; Glucagon-like peptide-1; Voglibose

Introduction
Alpha-glucosidase inhibitors delay the breakdown of carbohydrates in the small intestine and thus diminish the postprandial increase of blood glucose levels in animals and humans (1-3). Voglibose, acarbose, and miglitol are commonly used in clinical practice (1-3). One intriguing aspect of the alpha-glucosidase inhibitor is its ability to both increase and prolong glucagon-like peptide-1 (GLP-1) secretion in normal individuals and patients with type 2 diabetes (4-10). GLP-1 (7-36) amide and GLP-1 (7-37), both of which are active forms of GLP-1 and have similar activity, are secreted from gut L-cells (11). GLP-1 is now known to be involved in the regulation of insulin secretion (12), glucagon secretion (13), beta-cell turn-over (14), and extrapancreatic tissue functions (15). The active forms of GLP-1 are rapidly broken down by the enzyme dipeptidyl peptidase-4 (DPP-4) (16), leading to the generation of the inactive forms, GLP-1 (9-36) amide and GLP-1 (9-37) (16).

Preclinical and clinical studies have demonstrated that activating GLP-1 signals by administration of GLP-1 receptor agonists or DPP-4 inhibitors can improve diabetes in animals and humans (17-20). Alpha-glucosidase inhibitors delay carbohydrate absorption, which results in an increase in sugar absorption in the lower gut (21). Taking into account that sugar absorption plays a critical role on GLP-1 secretion (22, 23) and that...
GLP-1 producing cells are abundant in the lower gut (24, 25), delayed carbohydrate absorption is considered to be an acceptable contributing factor for stimulating GLP-1 secretion by alpha-glucosidase inhibition. However the mechanism by which alpha-glucosidase inhibitors increase GLP-1 secretion is poorly understood. In addition, limited data is available in regards to the effects of alpha-glucosidase inhibition on active forms of GLP-1 levels.

Results and Discussion

We recently found that voglibose has previously-unreported mechanisms by which it increases active GLP-1 levels in diabetic ob/ob mice (24). When administered in the diet to ob/ob mice for 1-day, voglibose at doses of 0.001% and 0.005% showed no effect on plasma DPP-4 activity as expected (24). This is consistent with the fact that voglibose had no effect on DPP-4 activity in vitro (24). However, 1-day treatment of voglibose resulted in increase in plasma active GLP-1 levels (0.001% voglibose, 8.0±2.0 pM; 0.005% voglibose, 16.6±7.8 pM; vehicle, 4.9±3.0 pM) in ob/ob mice (24). Taken together, these results indicate that a stimulatory effect on GLP-1 secretion but not a direct inhibition of the DPP-4 enzyme may contribute to the increase in active GLP-1 levels by voglibose.

Interestingly when administered chronically (3-4 weeks), voglibose showed an unexpected effect on plasma DPP-4 profiles. Chronic administration of voglibose resulted in a 40-51% decrease in plasma active GLP-1 levels (0.001% and 0.005% voglibose, respectively). The 40-51% decrease in plasma DPP-4 activity resulted in the corresponding decrease in voglibose to decrease the circulating DPP-4 protein concentration revealed that voglibose decreased its plasma concentrations by 31-43% (24). These results indicated that it was the ability of voglibose to decrease the circulating DPP-4 protein that resulted in the corresponding decrease in plasma DPP-4 activity. The 40-51% decrease in plasma DPP-4 activity, which was observed in voglibose-treated ob/ob mice, was likely to be sufficient to increase plasma active GLP-1 levels. In fact, around 30% DPP-4 inhibition by the DPP-4 inhibitor alogliptin significantly increased plasma active GLP-1 levels in ob/ob mice (20). As expected, the chronic treatment of voglibose produced higher levels of plasma active GLP-1 (11.4±3.9 and 24.4±6.7 pM by 0.001% and 0.005% voglibose, respectively. 6.0±1.4 pM by vehicle) compared with the 1-day treatment with voglibose (8.0±2.0 and 16.6±7.8 pM by 0.001% and 0.005% voglibose, respectively, 4.9±3.0 pM by vehicle) (24). A similar treatment with 0.001% and 0.005% voglibose for 3-4 weeks had no effects on plasma DPP-4 activity in normal control mice, which showed lower plasma DPP-4 activity compared with ob/ob mice, indicating that the voglibose-induced decrease in plasma DPP-4 activity may be specific to diabetic ob/ob mice. Administration of pioglitazone (0.03% in the diet), a peroxisome proliferator-activated receptor gamma agonist, resulted in significantly improved glucose levels that were comparable to the glucose levels achieved by voglibose (0.005% in the diet) (24). However, pioglitazone was unable to alter the DPP-4 concentration and activity (24), indicating that improving glucose control is not the primary means by which plasma DPP-4 concentration and activity are altered in ob/ob mice. Thus, the mechanism by which voglibose decreases plasma DPP-4 concentration remains to be determined.

Chronic treatment of voglibose also had an impact on enteroendocrine cells, which may contribute to the observed increase in plasma active GLP-1 levels (24). Once again, it was unexpectedly observed that chronic treatment with voglibose resulted in an increase in active GLP-1 content in the lower intestine (1.5- to 1.6-fold increase) and colon (1.4- to 1.6-fold increase) (24). The increased active GLP-1 content in the colon was positively correlated with an increase in gut gene expression levels of Neurod1 (1.3- to 1.4-fold increase) and Glucagon (2.6- to 3.1-fold increase) (24). The increased gene expression of Neurod1, which is known to be an essential regulator for enteroendocrine cell differentiation (26), suggests that voglibose may induce differentiation of enteroendocrine cells. A recent study has shown that oligofructose, a dietary nondigestible carbohydrate, promoted L-cell differentiation as evidenced by the increased number of L-cells, elevated Glucagon gene expression, and a doubling of GLP-1 content in the proximal colon in rats (27). Thus, voglibose-generated undigested carbohydrates may play a role in the increase in gene expression of Neurod1 and Glucagon, and GLP-1 content in the lower gut. Further analysis into the complete mechanism is still warranted.

To assess whether our observations are a class effect by alpha-glucosidase inhibitors, the effects of acarbose, another alpha-glucosidase inhibitor, were compared with those of voglibose in ob/ob mice. The doses for acarbose were 0.05% and 0.5% in the diet, which exhibited comparable efficacy at lowering glucose levels to that of 0.001% and 0.005% of voglibose in ob/ob mice. Although it was weaker...
than the effect of voglibose, chronic treatment with acarbose also dose dependently decreased plasma DPP-4 concentration (-27 to -37%) and activity (-27 to -43%) in ob/ob mice. In addition, in vitro DPP-4 assay revealed no direct inhibition of acarbose on DPP-4 activity. Taken together with the voglibose results, alpha-glucosidase inhibition may result in decreased plasma DPP-4 concentration and activity in ob/ob mice by some common mechanisms.

A notable difference was, however, observed in the plasma active GLP-1 levels between voglibose and acarbose after 1-day and chronic treatment. Acarbose increased plasma active GLP-1 levels after 1-day treatment with 0.05% and 0.5% doses while this regimen had no effect on plasma DPP-4 activity as expected. The active GLP-1 levels produced by acarbose (6.5±1.3 pM by 0.05% acarbose and 7.8±1.0 pM by 0.5% acarbose) were unexpectedly lower
compared to voglibose (0.001% voglibose, 8.0±2.0 pM; 0.005% voglibose, 16.6±7.8 pM; vehicle, 4.9±3.0 pM). When administered chronically, low-dose acarbose (0.05%) administration produced 9.0±6.1 pM of plasma active GLP-1 levels (6.0±1.4 pM by vehicle). While high dose administration of acarbose (0.5% in the diet) resulted in superior glucose control compared with the lower dose, it still resulted in only 9.0±5.4 pM of plasma active GLP-1 levels. These results indicate that voglibose may have a more favorable effect on increasing active GLP-1 levels compared with acarbose. When total amide GLP-1 levels (intact plus N-terminal-degraded amide GLP-1) were measured, 0.001% and 0.005% voglibose induced 1.3- and 1.5-fold increases in plasma amide GLP-1 levels, respectively, compared with vehicle alone (24). The administration of 0.05% acarbose increased amide GLP-1 levels by 1.2-fold, whereas 0.5% acarbose induced only 1.1-fold increase in amide GLP-1 levels, compared with vehicle alone. Consistently, in normal control mice, administration of 0.5% acarbose decreased amide GLP-1 levels by 46%, compared with vehicle-treated normal mice. These results indicate that voglibose may have a stronger effect on GLP-1 secretion compared with acarbose in ob/ob mice.

We speculate that the differences in enzymatic specificities of voglibose and acarbose against several types of glucosidase enzymes (2), leading to the different composition of undigested carbohydrates in the gut, may be a possible reason for the variability in GLP-1 secretion. When animal feces were compared, voglibose-treatment produced black feces, similar to that of vehicle treated mice, although somewhat smaller. The feces of acarbose-treated ob/ob mice were brown in color and little larger than vehicle-treated mice. Acarbose inhibits alpha-amylase thereby inhibiting the degradation of chow-derived starch, whereas voglibose has a much weaker effect on alpha-amylase when given in a pharmacologically effective range (2). Thus undigested starch is likely to be included in the brown feces in acarbose-treated mice. In a previous report, complex carbohydrates, like boiled brown rice or barley, were unable to stimulate GLP-1 secretion in contrast to a glucose meal, which clearly enhanced GLP-1 secretion in healthy human subjects (28). By contrast, sucrose and maltose, both of which are disaccharides, had stimulatory effects on GLP-1 secretion in the ileal loops of anaesthetized dogs (29). Thus, the lack of inhibitory activity of voglibose on alpha-amylase activity, which seems to generate more disaccharides in the lower gut than acarbose, may contribute to the increase in GLP-1 secretion in ob/ob mice.

In addition, unlike voglibose, acarbose was unable to increase active GLP-1 content in the lower-intestine in our ob/ob mouse study (vehicle, 106±28; 0.05% acarbose, 114±18; 0.5% acarbose, 116±12; 0.001% voglibose, 158±21; 0.005% voglibose, 166±31 pmol/g gut weight). Furthermore, our study demonstrated that colon active GLP-1 content in acarbose-treated mice was lower compared to voglibose-treated ob/ob mice (vehicle, 194±11; 0.05% acarbose, 246±46; 0.5% acarbose, 256±38; 0.001% voglibose, 279±45; 0.005% voglibose, 307±25 pmol/g gut weight). This corresponded with the results that suggested that acarbose had lower efficacy at increasing Glucagon gene expression in the colon (1.8- to 2.3-fold increase by acarbose, and 2.6- to 3.1-fold increase by voglibose). Taken together, these results suggest that the ability of voglibose to increase GLP-1 secretion and gut GLP-1 content accompanied with decreasing plasma DPP-4 activity may explain the reason why voglibose exhibits a more favorable effect on increasing plasma active GLP-1 levels compared to acarbose in ob/ob mice (Figure 1).

In conclusion, our studies showed that the acute and chronic effects of voglibose on DPP-4 differ; chronic but not 1-day administration of voglibose decreased plasma DPP-4 activity by reducing its circulating levels in plasma. In addition, chronic treatment with voglibose increased GLP-1 secretion and elevated GLP-1 content in the lower gut. Collectively, chronic administration of voglibose resulted in an increase in plasma active GLP-1 levels, which were higher compared with those achieved by acarbose. These observations suggest that voglibose may have additional utility in the management of type 2 diabetes.

Acknowledgements
The authors would like to thank Michelle Kujawski for writing support and comments on the manuscript.

Conflicts of Interest
No potential conflicts of interest to disclose.

References


