Potential of a glucagon-like peptide-1 receptor/glucose-dependent insulino tropic polypeptide receptor/glucagon receptor triagonist for the treatment of obesity and type 2 diabetes

Type 2 diabetes, which often accompanies obesity, is one of the major health-threatening diseases worldwide. Incretin-based therapies, such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor (GLP-1R) agonists, are used for the treatment of type 2 diabetes. The GLP-1R agonists have been shown to improve glycemic control and reduce bodyweight through its various actions, including glucose-dependent insulin secretion, suppression of glucagon secretion, and inhibition of gastric emptying and food intake. The GLP-1R agonists have been shown to improve glycemic control and reduce bodyweight through its various actions, including glucose-dependent insulin secretion, suppression of glucagon secretion, and inhibition of gastric emptying and food intake.

Recently, dual agonists of GLP-1R and glucose-dependent insulinotropic polypeptide receptor (GIPR), and those of GLP-1R and glucagon receptor (GCGR) have been developed. One of the dual agonists of GLP-1R and GIPR, named tirzepatide, has been shown to bind and activate both GLP-1R and GIPR in vitro and in vivo, its efficacy for the treatment of type 2 diabetes has been proven in a phase III trial, and it has recently been approved by the US Food and Drug Administration. In the phase III trial, once-weekly injection of tirzepatide (5, 10 or 15 mg) for 40 weeks reduced glycated hemoglobin (HbA1c) from baseline by 1.87, 1.89 or 2.07%, respectively, and reduced bodyweight from baseline by 7.0, 7.8 or 9.5 kg, respectively, in type 2 diabetes patients.

The most frequent adverse events with tirzepatide were gastrointestinal events. In the clinical trial that compared trizepatide (5, 10 or 15 mg) with once-weekly semaglutide (1 mg) in type 2 diabetes patients, trizepatide showed noninferior and superior reductions in HbA1c levels and in bodyweight. For both treatments, gastrointestinal events were the most common adverse events. The possible additional effects of GIP signaling in type 2 diabetes patients might depend on its augmentation of insulin secretion during hyperglycemic states.

The dual agonists of GLP-1R and GCGR specific for mice or monkeys have been developed and were investigated their effects in each species. In obese and diabetic cynomolgus monkeys induced by high-fat diet feeding, the monkey-specific dual agonist of GLP-1R and GCGR reduced total energy intake, decreased bodyweight and improved glucose tolerance. However, in another study using obese diabetic monkeys, glycemic control was worse when they were co-administered with both GLP-1R and GCGR agonists compared with that treated with an GLP-1R agonist alone. Therefore, the significance of the activation of GCGR signaling has not yet been fully clarified.

In 2015, Finan et al. created a triagonist that activates GLP-1R, GIPR and GCGR by selecting amino acids from the three peptide hormones, GLP-1, GIP and glucagon, and reported that the triagonist reduced bodyweight and improved glucose control in rodent models of obesity and diabetes.

More recently, Bossart et al. developed a novel GLP-1R, GIPR and GCGR triagonist, SAR441255. SAR441255 was confirmed to efficiently bind to and stimulate all three receptors in vitro studies. In a diet-induced obesity mouse model, subcutaneous injection of SAR441255 (0, 3, 1, 3, 10 or 30 μg/kg) showed a dose-dependent effect on bodyweight (+9.7%, +6.9%, +5.8%, −4.8% and −14.1%, respectively) compared with injection of vehicle (+11.5%). Non-fasted blood glucose levels were significantly lower in mice treated with SAR441255 at doses of ≥1 μg/kg when compared with vehicle-treated controls. In obese diabetic cynomolgus monkeys, treatment with SAR441255 (11 μg/kg) or a monkey-specific GLP-1R/GCGR dual agonist (4 μg/kg) significantly reduced the bodyweight by −12.6% or −8.1%, respectively, and decreased the HbA1c levels by −1.37% or −1.85%, respectively. Fasting plasma glucose and alanine aminotransferase levels were significantly reduced with SAR441255, but not with the dual agonist (Figure 1).

To further understand engagement of the different receptors in vivo, receptor occupancy of SAR441255 at the GLP-1 and the GCG receptors was studied with the use of positron emission tomography imaging after radiotracer administration in lean cynomolgus monkeys. A subcutaneous injection of 11 μg/kg SAR441255 together with radiotracers specific for GLP-1R and GCGR showed the significant signals of both receptors in the liver and pancreas of monkeys, suggesting the binding of SAR441255 to both receptors.

Correspondence
Eiichi Araki
Tel: +81-96-373-5169
Fax: +81-96-366-8397
E-mail address: earaki@gpo.kumamoto-u.ac.jp
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existing in these organs. Cardiovascular safety of SAR411255 was further confirmed in lean cynomolgus monkeys. Finally, a phase I study with SAR411255 in lean to overweight healthy participants was carried out to assess the safety, tolerability, pharmacokinetics and pharmacodynamics. After subcutaneous administration, SAR441255 concentration reached the median maximum serum concentration by 3.0–3.5 h, and was eliminated with a mean elimination terminal half-life of 3.5–6.1 h. After administration of single doses (80 and 150 mg) of SAR441255 in the fasting state, maximal reduction in blood glucose levels were observed at 1 h post-dose. At this time point, three of six participants who received the 80 mg dose and all six participants who received the 150 mg dose showed hypoglycemia (<70 mg/dL) without any clinical signs or symptoms. No further low blood glucose values were observed in either dose group. Blood glucose levels subsequently returned to baseline levels within 1–2 h. In contrast, fasting insulin and C-peptide levels were relatively stable, and showed no correlation with the glucose levels. Therefore, the mechanisms of this early phase hypoglycemia have not yet been clarified. After the mixed-meal test 3 h after the SAR441255 administration (80 and 150 mg), a dose-dependent reduction in postprandial plasma glucose was observed. Because insulin and C-peptide levels were also reduced during mixed-meal test, postprandial plasma glucose reduction was suggested to be due to inhibition of gastric emptying, as observed with GLP-1R engagement.

Gastrointestinal disorders (nausea, vomiting, dry mouth and mouth ulceration) were the most frequent treatment-emergent adverse events after treatment with SAR441255. All events were mild in severity, and occurred between 3 and 4 h after SAR441255 administration.

To clarify the effects of SAR441255 on GIPR and GCGR in humans, specific biomarkers for each receptor were measured. As expected, a biomarker for GIPR activation, C-telopeptide of cross-linked type I collagen, which is a marker of bone turnover, was significantly reduced by >50% in participants who received SAR441255 administration (80 and 150 mg). Likely, plasma amino acids levels, which are sensitive biomarkers of GCGR activation, were reduced after SAR441255 administration in these individuals.

As aforementioned, the dual agonists of GLP-1R and GIPR might have comparable or even more stronger effects in reductions of HbA1c and bodyweight in obese type 2 diabetes patients; the significance of the activation of GCGR signaling should be evaluated to confirm the benefits of the triagonists of GLP-1R, GIPR and GCGR. In this regard, the effects of glucagon to enhance energy expenditure partly through enhancement of fat and glucose oxidation could cover some of the benefits, but further investigations should be necessary. In addition, it has recently been reported that GLP-1R agonists have clinically significant cardiovascular benefits in type 2 diabetes patients. Therefore, it should be clarified if the dual or triagonists also have comparable cardiovascular benefits, as observed in GLP-1R agonists in type 2 diabetes patients.
Because triagonists have been shown to have better profiles in weight loss and glycemic control in animal models of obese type 2 diabetes compared with GLP-1R agonists and dual agonists of GLP-1R and GIPR or GLP-1R and GCGR, clinical studies that investigate the efficacy in type 2 diabetes patients should be of great interest.

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