JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
JDI UPDATES

New prospects for incretin-related drugs in the treatment of type 2 diabetes

Currently, incretin-based therapies focusing on glucagon-like peptide-1 (GLP-1) mimics and dipeptidyl peptidase-4 (DPP-4) inhibitors are the major tool for the treatment of type 2 diabetes worldwide. In the background, the unique action of incretin-related drugs can be mentioned in comparison with pre-existing glucose-lowering agents. Incretin preparations that regulate both insulin and glucagon secretion in a blood glucose-dependent manner have a low risk of hypoglycemia and weight gain. DPP-4 inhibitors act by inhibiting the enzyme that breaks down incretin hormones, thus maintaining the circulating GLP-1 at a physiological level (~10 pmol/L). In contrast, GLP-1 receptor agonists act at supraphysiological concentrations, inducing a more potent effect on glycemic control, and resulting in weight loss due to delayed gastric emptying and increased central satiety.

Recently, a concentration-dependent mechanism of GLP-1 was advocated as a new concept of GLP-1 signaling pathway on pancreatic insulin secretion[1]. Although a pharmacologically high concentration of GLP-1 (~100 pmol/L) stimulates insulin secretion through the cyclic adenosine monophosphate–protein kinase A pathway, a physiologically low concentration of GLP-1 (~10 pmol/L) without a significant increase of intracellular cyclic adenosine monophosphate mainly acts through the phospholipase C–protein kinase C-dependent pathway[2]. This concept might support that a picomolar concentration of GLP-1 induced by DPP-4 inhibitor is sufficient to stimulate insulin secretion.

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Received 29 October 2020; revised 1 November 2020; accepted 4 November 2020

Incretin-related drugs are more effective in Asian patients with type 2 diabetes than other ethnic groups, DPP-4 inhibitor is reported to be more effective at a lower body mass index and GLP-1 receptor agonist is also more effective at body mass index <30 kg/m^2[3]. Each DPP-4 inhibitor has a similar glucose-lowering effect despite different pharmacokinetics. The HbA1c lowering efficacy is thought to be up to 0.5~1.0% when used for a long period. In addition, safety in administration to the elderly has been established[4]. DPP-4 inhibitors can be safely and effectively used, even in end-stage renal disease with appropriate dose reduction[5], the exceptions being linagliptin and teneligliptin, which can be freely used due to its non-renal clearance. Currently, two once-weekly DPP-4 inhibitors – trelagliptin and omarigliptin – are available mainly in Japan and several Asian countries.

DPP-4 inhibitors are widely used in daily clinical practice due to excellent efficacy and convenience, but they rarely cause serious side-effects, such as vesicular pemphigoid[6-8], and caution should always be taken. In addition, the risk of pancreatitis and pancreatic cancer among patients taking DPP-4 inhibitors cannot be completely excluded[9]. At present, the possibility should be taken into account by checking sudden increases in pancreatic enzymes and blood glucose when using DPP-4 inhibitors. In contrast, positive results for a certain type of cancer are also beginning to be reported. Nishina *et al.*[10] recently reported that DPP-4 inhibitors suppress hepatocellular carcinoma through activating lymphocyte chemotaxis in a rodent model.

Meanwhile, treatment with GLP-1 receptor agonists lowers HbA1c by 1~2% in a dose-dependent manner. Theoretically, GLP-1 receptor agonist can be used with all antidiabetic drugs, except DPP-4 inhibitor, in the treatment of type 2 diabetes[11,12]. Combination use of GLP-1 receptor agonist and sodium–glucose cotransporter 2 inhibitor is considered to have a significant effect on improving blood glucose levels and weight loss[13]. The role of GLP-1 on the modulation of appetite and weight is managed by a complex brain–gut relationship. The activation of GLP-1 receptors present in the central nervous system and the gut is further modulated by cholinergic signals from the vagus nerve. However, at present, liraglutide is the only approved drug for the treatment of obesity in the USA, Europe and South Korea. The first phase III clinical study of semaglutide against obesity has just completed, and the results showed the significant effect of weight loss.

Furthermore, the oral daily GLP-1 receptor agonist, semaglutide, was just approved for the treatment of type 2 diabetes in Japan. The glucose-lowering effect and weight loss are dose-dependent, and its efficacy is similar to existing injectable GLP-1 receptor agonists in Japanese patients with type 2 diabetes[14].

It is meaningful to know what kinds of clinical characteristics patients who are prone to side-effects have. Gastrointestinal adverse events are known to be positively associated with age and renal function. Recently, it was reported that patients who are taking proton pump inhibitor or histamine-2 receptor antagonist are more likely to experience gastrointestinal events after the induction of GLP-1 receptor agonist, although the detailed mechanism is still unclear[15].

After 15 years of clinical application, it has been found that incretin-related drugs have various effects in addition to the glucose-lowering action (Figure 1). An anti-cardiovascular effect is one of

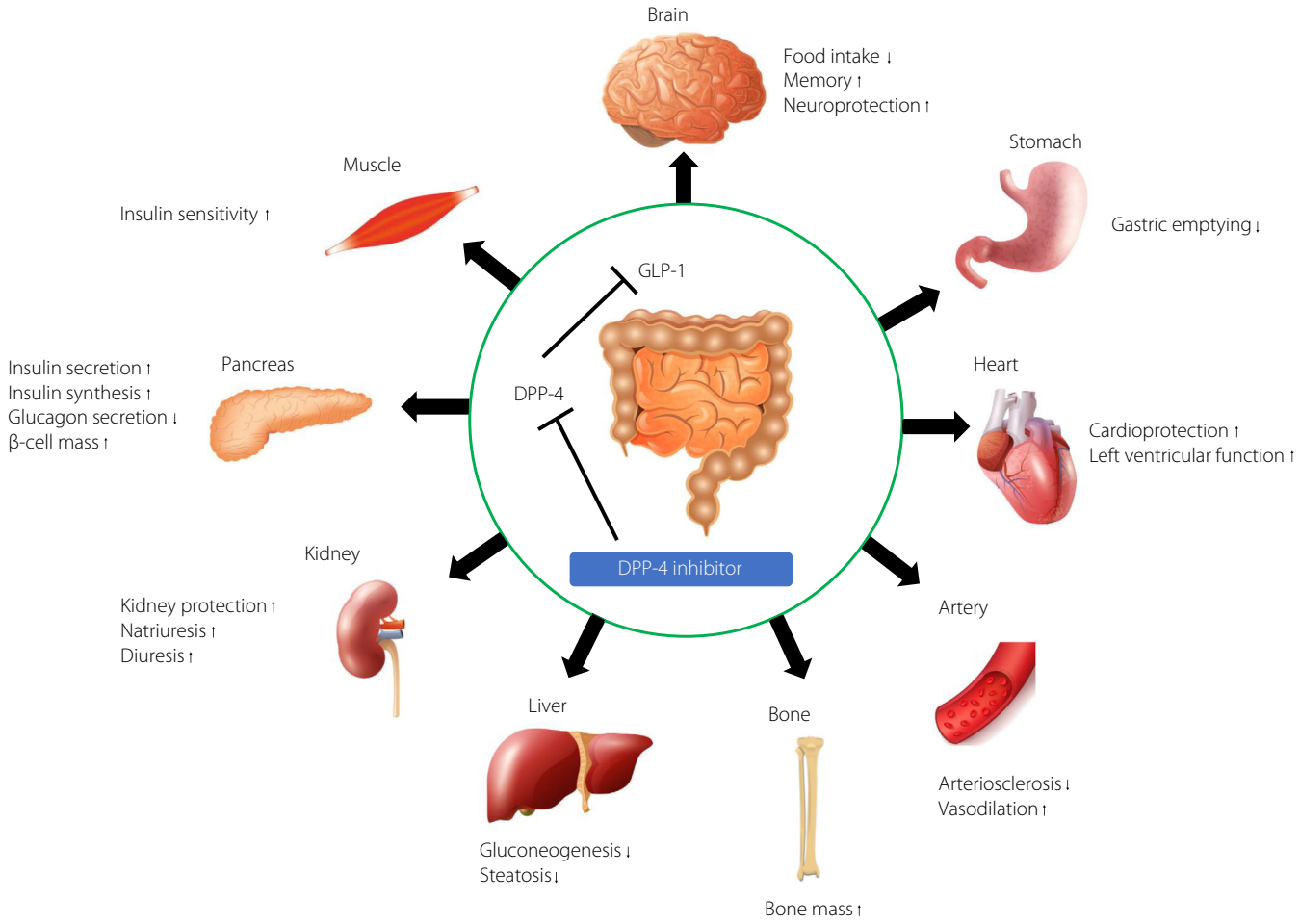

Figure 1 | The potential action of glucagon-like peptide-1 (GLP-1) on each organ. The action of GLP-1 on each organ including indirect effects through the improvement of the metabolic profile. GLP-1 exerts a variety of intra- and extrapancreatic effects suggested by animal and human studies. Some of them might be beneficial in the prevention and treatment of diabetes-related complications and comorbidities that are shown independently of glycemic control. Dipeptidyl peptidase-4 (DPP-4) inhibitors inhibit DPP-4 activity, resulting in the maintenance of circulating GLP-1 at physiological levels. Note that the physiological GLP-1 concentration caused by the DPP-4 inhibitor does not have some beneficial effects, which are shown by GLP-1.

the most outstanding benefits related to GLP-1 receptor agonists. Unfortunately, there are currently no reliable results that positively support anti-arteriosclerotic effects in DPP-4 inhibitors. The cardiovascular outcome trials have provided useful information that has helped to shape changes in American Diabetes Association/European Association for the Study of Diabetes consensus guideline for the management of type 2 diabetes. At the same time, the mechanisms that might explain the cardiovascular benefits are still being explored. Recently, the presence of GLP-1 receptor in the vascular endothelial cells is becoming more certain[16,17]. The anti-arteriosclerosis effect of GLP-1 is considered to be due to both the direct effect through GLP-1 receptors on vascular endothelial cells and indirect effects related to improvement of metabolic profile[18].

Furthermore, accumulated evidence further suggests that the cardiovascular benefits of GLP-1 receptor agonists might not be a class effect, with GLP-1 analogs having a greater benefit rather than exendin-based agents. However, it is still controversial whether the cardiovascular effect of GLP-1 receptor agonists is different between drugs, because the background of each clinical study is not necessarily the same as others. At the beginning of the clinical application for GLP-1 receptor agonists, it was a concern that a large amount of ligand might cause the downregulation of GLP-1 receptors, which could lead to "secondary failure." Long-term administration of GLP-1 receptor agonist, however, did not cause decreased GLP-1 receptor expression on pancreatic β-cells in a rodent model[19]. Thereby, it is unlikely that the secondary failure of the GLP-1 effect is clinically problematic.

Another noteworthy point is the protective effect against chronic kidney disease. GLP-1 receptor agonists, as well as

sodium–glucose cotransporter 2 inhibitors, are defined as second-line drugs for patients with type 2 diabetes accompanied with chronic kidney disease[20]. It is reported that GLP-1 protects the function of glomeruli and tubules in diabetic rats through protein kinase C and protein kinase A[21]. Whereas the effect of DPP-4 inhibitors on kidney function is considered to be neutral at present.

Here, we have examined the current situation for incretin-related drugs, DPP-4 inhibitors and GLP-1 receptor agonists. Both drugs will continue to be key players in the treatment of type 2 diabetes in the future. That is why the evidence must be carefully considered and selected to maximize the benefits of each drug.

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Doi: 10.1111/jdi.13460