Dipeptidyl peptidase-4 (DPP-4) inhibitors are widely used in the management of type 2 diabetes worldwide. Despite amelioration of insulin secretion from pancreatic $\beta$-cells, DPP-4 inhibitors have very little hypoglycemia risk and do not promote bodyweight gain when compared with other insulin secretagogues, such as sulfonylureas (SU) and glinides. Furthermore, accumulating data from clinical trials shows that DPP-4 inhibitors exert greater glycated hemoglobin (HbA1c)-lowering effects in non-obese Asian type 2 diabetes when compared with diabetes in other ethnicities. This could be explained by the fact that Asian type 2 diabetes is characterized by impaired insulin secretion, particularly in the early phase after ingestion of glucose or mixed meals. Enhancement of the incretin system by DPP-4 inhibitors was found to ameliorate impaired early phase insulin secretion in clinical studies using DPP-4 inhibitors in patients with type 2 diabetes.

Although DPP-4 inhibitors alone are considered to have very little hypoglycemia risk based on the results of clinical trials, cases of severe hypoglycemia with DPP-4 inhibitor and SU combinations were reported when the first DPP-4 inhibitor sitagliptin emerged in Japanese clinical practice in November 2009 (Figure 1). The estimated incidence of hypoglycemic coma with sitagliptin during the first 6 months after its launch in Japan was 16.3 per million patients who received sitagliptin. The Goto-Kakizaki rat study clearly showed that activation of incretin signaling reduces production of reactive oxygen species, which then impairs glucose metabolism and reduces adenosine triphosphate (ATP) production in pancreatic $\beta$-cells. It was previously shown that SU-induced closure of K$_{ATP}$ channels is affected significantly by intracellular ATP levels. Reduced ATP production as a result of chronic hyperglycemia could thus make pancreatic $\beta$-cells less sensitive to SU, partly explaining ‘SU secondary failure’. The Goto-Kakizaki rat study clearly showed that activation of incretin signaling reduces production of reactive oxygen species in islets and increases ATP, an exchange protein directly activated by cyclic adenosine monophosphate (cAMP) 2A (EPAC2A) dependenty. Thus, initiation of DPP-4 inhibitors in patients with ‘SU secondary failure’ could result in hypoglycemia as a result of improved sensitivity of pancreatic $\beta$-cells to SU.

Another clue came from a study showing novel cross-talk between SU and incretin signaling through EPAC2A. Activation of incretin signaling in pancreatic $\beta$-cells increases intracellular levels of cAMP, which binds to EPAC2A and triggers its conformational change, thereby activating its downstream target
Ras-related protein 1 (RAP1) to enhance insulin secretion. They had previously shown that SU also bind to and activate EPAC2A, thereby promoting insulin secretion through activation of RAP1. Recently, they extended their study and showed through molecular docking simulation and fluorescence resonance energy transfer experiments using mutagenized EPAC2 that binding of SU to EPAC2A depends on both the concentration of cAMP and the structure of SU. Importantly, glibenclamide and glimepiride, but not gliclazide, binds to EPAC2A and induces a conformational change that activates RAP15. These results are suggestive of the cases in which SU is responsible for severe hypoglycemia. Among the 62 cases of severe hypoglycemia in patients treated with dipeptidyl peptidase-4 (DPP-4) inhibitor sitagliptin in each quarter (Sitagliptin Japanese early post-marketing vigilance data, Pharmaceuticals and Medical Devices Agency). The number was drastically reduced on announcement of the recommendation from the committee for appropriate use of incretin-related drugs (glucagon-like peptide-1 [GLP-1] receptor agonists and DPP-4 inhibitors). (b) Estimated incidence of severe hypoglycemia with sitagliptin and indicated sulfonylureas. The number of cases of severe hypoglycemia caused by sitagliptin and sulfonylurea combinations during the 6 months after the launch of sitagliptin was divided by the number of patients who received indicated sulfonylureas and sitagliptin simultaneously in the same period (Sitagliptin Japanese early post-marketing vigilance data between November 2009 and May 2010; National Prescription Audit™, IMS Japan KK). (c) An extract of the recommendation from the committee. 1Q, first quarter; 2Q, second quarter; 3Q, third quarter; 4Q, fourth quarter.
hypoglycemia after initiation of sitagliptin (Sitagliptin Japanese early post-marketing vigilance data between November 2009 and May 2010), most of the patients were taking glimepiride (67.7%) and glibenclamide (30.6%), whereas very few were taking gliclazide (3.2%). The estimated incident rates of severe hypoglycemia in patients who received sitagliptin with glimepiride (3.35 per 10,000) and glibenclamide (7.86 per 10,000) were more than twofold higher than in those who received sitagliptin with gliclazide (1.66 per 10,000) between November 2009 and May 2010 (Sitagliptin Japanese early post-marketing vigilance data between November 2009 and May 2010; National Prescription Audit™, IMS Japan K.K.). Although numerous factors including reduced glucose counter-regulation might affect the incident rates of severe hypoglycemia by the combinations of sitagliptin and each SU, these data complement the original observations in clinical settings and provide insight on the suitability of the various SU to be used in combination with DPP-4 inhibitors. These observations also have important implications for SU and GLP-1 receptor agonist use in combination. As was shown, a high level of cAMP inhibits binding of SU to EPAC2A, so cross-talk of SU and incretin signaling through EPAC2A might not be expected with GLP-1 receptor agonists, which appear to increase levels of cAMP in pancreatic β-cells more strongly than DPP-4 inhibitors. Indeed, no severe hypoglycemia cases were reported for combinations of SU and the GLP-1 receptor agonist liraglutide during the first 6 months after its launch in Japan (Liraglutide Japanese early post-marketing vigilance data from Pharmaceuticals and Medical Devices Agency). Although greater awareness of the recommendations among Japanese physicians at the time of launching the first GLP-1 receptor agonist, liraglutide, in Japan and the 21.6-fold higher number of prescriptions for sitagliptin as a combination drug with SU during 6 months after their launch (National Prescription Audit™, IMS Japan K.K.) must be taken into account, the very rare incident of severe hypoglycemia in combinations of SU and GLP-1 receptor agonists is in good accordance with these observations

Taken together, these critical findings explain why activation of incretin signaling by DPP-4 inhibitors enhances SU-induced insulin secretion from pancreatic β-cells, even in patients with ‘SU secondary failure’. With careful titration of SU doses and appropriate patient education on hypoglycemia, a combination of DPP-4 inhibitors and SU drugs can be effective therapy for type 2 diabetes. However, careful consideration is required when such combination therapy is initiated in the elderly and/or patients with renal insufficiency.

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REFERENCES
1. Seino Y, Yabe D. GIP and GLP-1: incretin actions beyond pancreas. J Diabetes Invest 2013; 4: 108–130.
2. Mukai E, Fujimoto S, Sato H, et al. Exendin-4 suppresses SRC activation and reactive oxygen species production in diabetic Goto-Kakizaki rat islets in an Epac-dependent manner. Diabetes 2010; 60: 218–226.
3. Mukai E, Ishida H, Kato S, et al. Metabolic inhibition impairs ATP-sensitive K+ channel block by sulfonylurea in pancreatic beta-cells. Am J Physiol 1998; 274: E38–E44.
4. Zhang CL, Katoh M, Shibasaki T, et al. The cAMP sensor Epac2 is a direct target of antidiabetic sulfonylurea drugs. Science 2009; 325: 607–610.
5. Takahashi T, Shibasaki T, Takahashi H, et al. Antidiabetic Sulfonylureas and cAMP Cooperatively Activate Epac2A. Sci Signal 2013; 6: ra94.

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