Relevance of Incretins in treatment of type2 diabetes in Asia

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Type 2 diabetes is characterized by various degrees of insulin resistance and pancreatic β-cell dysfunction. In Europe and the USA, insulin resistance with obesity is the predominant pathological manifestation of diabetes; in Asia, impaired insulin secretion is predominant. This difference was noted more than 30 years ago, when the insulin response to glucose was found to be impaired even in mild diabetic patients in Japan. Our first papers describing the phenomenon appeared in 1974-8 in Horm Metab Res, Acta Diab Lat, and Diabetes, and were confirmed in studies of Japanese living abroad. Studies in Western countries at that time were generally finding that the insulin response to glucose was rather somewhat exaggerated. Our results from Japanese subjects as well as findings from Korean and other Asian populations showing a defective insulin response in type 2 diabetic patients were seemingly ignored. However, as β-cell research continued to develop and the centrality of the K\text{ATP} channel in glucose metabolism became clear, the putative insulinotropic substance in the gut called “incretin” became more intriguing. The incretins are hormones released from the gut upon ingestion of meal that stimulate cAMP production and potentiate early phase insulin secretion. Our work on the physiology of GIP was first published in JCEM, Clin Endocrin, and Endocrinol Jpn in the 1980s. We have since identified GIP genes, cDNA and receptors in Mol Endocrinol, PNAS, and BBRC that make advanced incretin research possible.

Both GLP-1 and GIP have been well-characterized using KO mice. While both Asian and Western type 2 diabetes patients generally exhibit incretin defects, these may be more dramatic in Asian patients. In addition, it has recently been demonstrated that both GIP and GLP-1 have extrapancreatic effects. We have found in studies first published in PNAS, Nat Med, and Mol Endocrinol that GIP stimulates nutrient uptake into adipocytes and bone, and that inhibition of the GIP signal reduces meal-induced adiposity. On the other hand, as we have published recently in Endocrinology, GLP-1 controls bone formation in addition to its suppressive effect on glucagon secretion and food intake, and slows gastric emptying in human and promotes beta cell neogenesis and proliferation in animal models. Thus, GLP-1 and GIP receptor agonists and dipeptidy1-IV DPP-IV inhibitors that enhance endogenous incretin activity may be therapeutically useful in type 2 diabetes with impaired insulin secretion. It is noteworthy that while the effectiveness of GLP-1 is generally preserved, that of GIP is markedly reduced in type 2 diabetes. We have recently confirmed this phenomenon in isolated islets of GK rats, a model of non-obese type2 diabetes in Diabetes. The reasons for the failure of GIP to stimulate insulin secretion under certain conditions remain to be clarified, but several possible mechanisms have been proposed. Because native GLP-1 is degraded immediately by DPP-IV, both GLP receptor agonists (also called GLP-1 mimetics) or analogues and DPP-IV inhibitors have been developed. GLP-1 analogues/agonists in comparison with DPP- IV inhibitors have been found to achieve a greater insulin response with superior glycaemic control, improved weight loss, and comparable levels of adverse effects. Moreover, the beneficial effects of DPP-IV inhibitors are dependent on the endogenous GLP-1 level, which may render them less effective than GLP-1 analogues/mimetics that elicit higher pharmacological GLP-levels. On the other hand, GLP-1 mimetics and analogues require administration by injection while DPP-IV inhibitors can be administered orally. Recently, the results of a clinical trial of GLP-1 derivatives in Japanese has appeared that allows comparison of the relative effects of DPP-IV inhibitors with those in Caucasians. Sitagliptin and vildagliptin both improve HbA1c in Caucasian and Japanese diabetic patients, but the reduction in HbA1c at the same dosages is 1.5 fold greater in Japanese. The use of the GLP-1 analogue, liraglutide, in Japanese type 2 diabetes patients revealed that monotherapy with once-daily administration achieved significant improvements in glycaemic control, with HbA1c reductions of 1.9% compared to placebo. Even though the dosage used was less than half that used in Caucasians, the reduction in HbA1c was more prominent in Japanese type2 diabetes patients. These findings indicate that GLP-1-targeted agents may be more effective in Asian than in Caucasian type2 diabetes patients due to their improvement of early phase insulin secretion.