Novel Therapeutic Approach of Type 2 Diabetes Mellitus

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Type 2 diabetes (T2DM) is a heterogeneous disorder resulting from interaction between genes and environment. Currently, this disease is the most common of all metabolic disorders and the incidence is increasing. There are approximately 110 million people with diabetes at present but this number will reach over 220 million by the year 2010.

Current treatments which focus on insulin deficiency and insulin resistance have been proved to be effective. However, they are frequently associated with many side effects especially hypoglycemia and weight gain. Moreover, they fail to preserve or stop the loss of β-cell function which is a hallmark characteristic of this disease. Hence, a novel therapy is required.

The observation that food (glucose) ingestion can provoke a greater stimulation of insulin secretion than intravenous infusion of glucose with similar amount of energy has guided the researcher to study the role of gastrointestinal tract in glucose homeostasis. It was hypothesized that gut-derived signals stimulated by enteral administration of nutrient are powerful insulin secretagogues. Recently, there is considerable evidence supports the role of Glucagon-like pepetide (GLP)-1 and glucose-dependent insulinotropic polypeptides (GIP) as dominant peptides involving in nutrient stimulating insulin secretion. GLP-1 and GIP are members of the glucagon peptide superfamily and share substantial aminoacid identity. GLP-1 is mainly synthesized within L-cells located predominantly in the ileum and colon whereas GIP is secreting from enteroendocrine cells in the duodenum and proximal jejunum.

In contrast with their structural similarity information from animal models and human studies have indicated that these proteins have some differences in biological actions. GLP-1 and GIP stimulate insulin secretion and promote expansion of β-cell mass. In T2DM GIP secretion in response to nutrient ingestion is approximately normal but its action is markedly diminished. In contrast, GLP-1 secretion in response to nutrients is significantly decreased. Although GLP-1 action is preserved in T2DM but its effect at each glucose concentration is less than normal. Only GLP-1 inhibits gastric emptying and glucagon secretion. Moreover, food intake and weight gain were also repressed. Therefore GLP-1 has more advantages as a tool to treat T2DM. However, the main impediment in developing this novel therapeutic agent is due to the fact that GLP-1 has extremely short plasma half-life because it is degraded by ubiquitous enzyme dipeptidyl peptidase IV (DPP-IV) by cleaving at the position 2 alanine of GLP-1 peptide. There are two possible ways to overcome this issue: by creating stable GLP-1 analogues or GLP-1 receptor activators or by making inbitors of the DPP-IV enzyme.

Until recently, a novel peptide has been discovered from venom of the Gila monster, *Heloderma suspectum*, a poisionous lizard from the desert of Arizona. This peptide, exendin-4, acts as a high potency agonist at the GLP-1 receptor of insulin-secreting β-cells. The synthetic exendin-4, now known as exenatide is in phase III clinical trials involving more than 1,400 T2DM patients inadequately controlled with sulfonylurea or metformin or a combination of both, in whom exenatide was given by subcutaneous injection as an add-on therapy for 30 weeks. The overall decrease in HbA1c was 0.8% and the proportion of patients with HbA_{1c} below 7% were 41%, 45% and 34% in sulfonylurea-, metformin- and combined drug-treated group, respectively. Mild hypoglycemia occurred in 28-36% of patients receiving sulfonylurea. An interesting finding was a significant dose-dependent and progressive weight loss of 1.6 kg in sulfonylurea-treated group (monotherapy or in combination) and 2.8 kg in metformin-treated group. Adverse effects were mild and generally gastrointestinal. Finally exenatide has been approved for the treatment of diabetes by the FDA in April 2005. Another GLP-1 analogue currently under development is liraglutide. Palmitic acid was attached to GLP-1 molecules and protect it(liraglutide) from DDP-IV and renal elimination. Subcutaneous injection of liraglutide to T2DM patients for 3 months lowered HbA1c in a dose-dependent manner (up to 0.75% from a baseline level of 7.6%) and body weight was significantly decreased. There were very few side effects. Liraglutide also reduced fasting plasma glucose from 13 mmol/l to 9 mmol/l and resulted in weight loss of 2.4% in patients already on metformin treatment. Developments of others GLP-1 analogues are ongoing.

DDP-IV inhibitor completely inhibits the N-termial degradation of GLP-1. A study in animal model of diabetes have shown that chronic administration of oral DDP-IV inhibitor improved glucose tolerance, insulin

sensitivity, β-cell responsiveness and even delayed the onset of hyperglycemia in these animals. These effects can be explained, at least in part, by the increase in level of intact GLP-1. Recently, vildagliptin, a long-acting oral DDP-IV inhibitor has been studied in 52-week clinical trial in patients already on metformin treatment. It significantly lowered HbA1c from 7.7% to 7% after 3 months of treatment and was maintained for the remaining period which was 1.1% lower compared to the placebo group. Meal-induced insulin secretion was impaired in placebo group but remained unchanged in vildagliptin-treated group. No change in body weight was observed and side effects were trivial. Many other DDP-IV inhibitors are under vigorous development.

The interaction between nutrient ingestion and plasma glucose regulation has led to inventions of new and promising therapeutic agents for T2DM. Since most of the patients are obese, the weight-losing effect of GLP-1 analog is very attractive in paradigm of disease management. However, the fact that this analog can only be administrated by subcutaneous injection can make oral DDP-IV inhibitor a more appealing drug especially when compliance to treatment comes into consideration.

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