Anti-diabetic Drug Development from Natural Resources

Sunmin Park

Dept. of Food & Nutrition, Hoseo University

Type 2 diabetes is a heterogeneous metabolic disorder characterized by increased insulin resistance in peripheral tissues such as liver, skeletal muscle, and adipose tissue and the impairment of insulin secretion from pancreatic β-cells. In most cases, insulin resistance mostly precedes the impairment of insulin secretion in humans. Until insulin secretion compensates for insulin resistance in peripheral tissues, diabetes does not appear. Anti-diabetic drugs require satisfying 1) to attenuate insulin resistance in liver, adipose tissues and muscles, 2) to improve glucose stimulated insulin secretion with β-cell mass expansion, and/or 3) to inhibit α-glucoamylase activity to decrease post-prandial serum glucose levels.

Troglitazone was approved as the first drug of an insulin sensitizer from FDA in 1999. It was discovered from a Japanese herb as cholesterol lowering agent at first. However, it was revealed as a potent insulin sensitizer, peroxisome proliferator-activated receptor-γ agonist. Another anti-diabetic drug developed from natural resources is exendin-4, glucagon like peptide (GLP)-1 agonist. It was isolated from lizard Heloderma and it is now under investigation for use as a therapeutic agent in the treatment of type 2 diabetes mellitus. It mainly exerts insulinotropic actions and it somewhat improves insulin sensitivity. Thus, there are great potentials to develop anti-diabetic drugs from natural resources.

To investigate anti-diabetic drugs to satisfy three categories, natural resources traditionally used as hypoglycemic agents are selected and extracted with 70% ethanol. The extracts are fractionated with Dianon-HP or XAD-1 column. The fractions are screened for all three categories in vitro. Insulin sensitizing action is determined as stimulation of insulin stimulated glucose uptake and triglyceride accumulation in 3T3-L1 adipocytes. The modulation of insulin signaling cascade is investigated in the fractions to modulate them. Insulinotropic action is screened by measuring glucose-stimulated insulin secretion and β-cell function and mass via insulin/insulin like growth factor-1 signaling cascade in Min6 cells, beta

cell line. The inhibitor of α-glucoamylase is selected by suppression of α-glucoamylase activity to digest maltose and dextrin in vitro. According to the results, fractions are selected to meet three categories in vitro. Selected fractions are further isolated and repeated to discover the effective compounds. Simultaneously, indicative compounds of the effective herbs are screen for anti-diabetic drugs. The physiological activity of effective compounds is determined in diabetic animals such as 90% pancreatectomized and streptozotocin induced rodents and db/db mice. In animal studies, the compounds or fractions are treated for 2 months and at the end of experiment, hyperinsulinemic euglycemic clamp and hyperglycemic clamp are performed to investigate insulin resistance and insulin secretion capacity, respectively. From hyperinsulinemic euglycemic clamp, it is determined which tissues have major impact on developing or alleviating insulin resistance. The α-glucoamylase activity is determined by modified oral glucose tolerance test with maltose or dextrin in experimental animals. In addition, pancreatic β-cell growth and survival is determined. The effective compounds or fractions (herb extracts) in animal studies are investigated in toxicity in GLP facility. The selective compounds or herb extracts proceed to clinical trials to become anti-diabetic drugs Clinical trials are categorized into 4 steps. In phase 1 trial, pharmacological action and safety of the new drugs are estimated in healthy volunteers. In phase 2 trial, therapeutic effects are determined in diabetic patients. Phase 3 trial is the final stage to receive approval from Food and Drug Administration to estimate dosage, effects, efficacy and safety of the new drug in the patients. Post-marketing surveillance of the drug is phase 4 trial to investigate side effects of new drug after marketing. In conclusion, anti-diabetic drugs can be developed from herbs to relieve insulin resistance, have insulinotropic action, and/or suppress α-glucoamylase activity.