The discovery of insulin at the beginning of this century was a major breakthrough in medicine, and initiated a new era in our understanding and treatment of diabetes. Nonetheless, diabetic patients who require insulin are still confronted with the discomfort of multiple subcutaneous injections or continuous insulin infusions. Recently, Moller’s group (1) has discovered a small molecule that binds to the intracellular β-subunit of the insulin receptor and mimics the effects of insulin. This compound is a non-peptidyl fungal metabolite of the insulin receptor and mimics the effects of insulin. It can be given orally, and exerts antidiabetic effects in mice. These findings, even though preliminary, raise the hope for new insulin-like oral drugs.

During the past 77 years over which insulin has been given to diabetic patients, there have been many improvements in the preparation and the mode of administration. Molecular biology made the production of recombinant human insulin possible, and modern chemistry enabled the development of long-acting, and recently of very short-acting insulin formulations. These advances proved to be very useful in order to achieve tight glycemic control. Additionally, insulin pens provide patients with convenient injection devices and external insulin infusion pumps help control type 1 diabetic patients more easily and reduce the number of injections. Over the last few years, an increasing number of patients have undergone pancreas transplantation for a definitive cure of their type 1 diabetes. However, significant risks due to surgery and to lifelong immunosuppression are associated with this major invasive procedure.

For type 2 diabetic patients, several different classes of oral antidiabetic drugs have been developed including the new class of insulin sensitizer, thiazolidinediones. These drugs have provided glycemic control for many non-insulin-dependent diabetic patients. But once type 2 diabetic patients progress to a more advanced stage of the disease and require insulin, they are left with the same limited options of insulin administration as type 1 diabetic patients.

There have been a number of efforts to find novel routes for insulin administration in order to provide more comfort to the patient and to ensure higher compliance. At this year’s American Diabetes Association meeting in San Diego, California, major approaches such as the development of inhaled insulin and of oral insulin by chemical modification and the screening for insulin mimetic substances were presented. A variety of inhaled insulin systems have been tested with the major problem of precision and bioavailability (2). Nevertheless, inhaled insulin will likely be approved in the next few years (3) since recent studies look promising. In type 1 diabetic patients, inhaled insulin was comparable to subcutaneous insulin in reducing postprandial glucose levels (4). In a multicenter phase II trial with type 2 diabetic patients failing oral agents, adjunctive inhaled insulin was able to reduce hemoglobin A1c significantly compared to placebo (5).

Chemical modification of the peptide insulin could potentially lead to better oral absorption and reduce its degradation after ingestion. In this connection, hexyl insulin seems to exhibit these characteristics in animal studies, and was able to increase serum insulin levels in a dose-dependent manner in healthy volunteers (6). However, the duration of this effect was limited to the first 30 min after ingestion, suggesting that there may still be a problem with stability and bioavailability. Studies in diabetic patients are planned and should determine whether these compounds will be clinically useful.

The group of Nag at Calyx is currently working on a series of plant-derived substances that lower blood glucose levels when given orally to several different rodent models of diabetes including ob/ob and db/db mice as well as fa/fa rats and streptozotocin-induced diabetic rats (7, 8). While some of these compounds seem to mediate their effects via the insulin receptor, others show no competitive binding to the receptor. All of them share the ability to up-regulate the glucose transporters, GLUT 1 and 4. In addition, they were reported to reduce plasma levels of triglycerides, free fatty acids and cholesterol.

Moller’s group at Merck screened over 50,000 natural and synthetic substances in a cell-based assay for insulin-like activity. They recently discovered a small non-peptidyl molecule (L-783,281) from a fungal (Pseudomassaria) extract (1). Surprisingly, purification of the active compound revealed that L-783,281 structurally is a quinone. No other currently known antidiabetic drugs belong to this substance class. L-783,281 seems to bind directly to the intracellular β-subunit of the insulin receptor containing the insulin receptor tyrosine kinase activity. Binding leads to a conformational change resulting in activation of the kinase and induction of the insulin signaling cascade downstream of the receptor at micromolar concentrations. L-783,281 leads to phosphorylation of a number of proteins of the insulin signaling pathway including...
the β-subunit of the insulin receptor, the insulin receptor substrate-1 and the Akt-kinase (or PKB). In addition, it stimulates phosphoinositid-3 kinase. L-783,281 was also shown to increase glucose uptake in primary adipocytes and in soleus muscle.

In rodent models of diabetes oral administration of L-783,281 improved glycemic control significantly. In db/db mice suffering from severe hyperglycemia it decreased plasma glucose levels, and in the hyperinsulinemic ob/ob mice, it reduced insulin levels and improved glucose tolerance in a dose-dependent manner. These effects were seen after a single oral dose as well as during a 7 day treatment period. Oral administration of L-783,281 for up to 15 days did not cause any changes in food intake, body weight, blood chemistry or liver function tests.

In contrast to the non-selective effects of the insulin mimetic phosphatase inhibitor vanadate, L-783,281 seems to bind specifically to the insulin receptor. No activation of the platelet-derived growth factor receptor could be detected and weak activation of the epidermal growth factor receptor and the insulin-like growth factor-I receptor was only found at a more than ten times higher dose.

From a molecular point of view this paper (1) introduces the new concept that substances which can bind to membrane-bound receptors at sites different from the original ligand binding domain can still mimic the effects of the cognate ligand of the receptor. Potentially, there also might be endogenous factors modulating the activity of receptors by this mechanism. These recent findings open up a wide field for the development of activating compounds. From a molecular point of view this paper (1) introduces the new concept that substances which can bind to membrane-bound receptors at sites different from the original ligand binding domain can still mimic the effects of the cognate ligand of the receptor. Potentially, there also might be endogenous factors modulating the activity of receptors by this mechanism. These recent findings open up a wide field for the development of activating compounds.

Clinically, the discovery of L-783,281 or similar insulin mimetic compounds could be an important breakthrough in the treatment of diabetes and insulin resistance. Obviously, the present data are only based on in vitro and mouse models and the safety and efficacy of L-783,281 have to be tested more extensively in animals and ultimately in humans. But the recent findings at least raise the hope for an oral drug with insulin-like effects that would reduce the necessity of multiple injections in type 1 and late-stage type 2 diabetic patients. In addition to the convenience of oral administration, substances like L-783,281 could have advantages in different states of insulin resistance due to their different mechanism of action. In type 2 diabetic patients, glycemic control could potentially be achieved at much lower insulin levels and thereby the vicious cycle of hyperglycemia and hyperinsulinemia could be interrupted as suggested by the results in ob/ob mice (1). In patients with severe insulin resistance due to mutations in the insulin receptor, ligand binding is often abrogated. Since these new agents can activate the insulin receptor at a different site, they also may be helpful in the treatment of this rare disorder. Finally, patients suffering from insulin resistance caused by antibodies against insulin itself or against the extracellular α-subunit of the insulin receptor may benefit from drugs that are able to mimic the effects of insulin and do not require either insulin or the extracellular domain of the insulin receptor. Taken together, it is not surprising that diabetic patients and endocrinologists await with great anticipation future studies and the answer whether L-783,281 or similar agents will provide novel therapies for diabetes.

References