Some newer approaches to the treatment of type 2 diabetes


Acrobat PDF file can be downloaded here.

The number of patients with type 2 diabetes has increased greatly during the past years. It is estimated that more than 220 million people will suffer from this disease within 2020. Because insulin and glucagon control energy metabolism, disturbances in lipid, carbohydrate and protein metabolism follow the development of diabetes.

Several good review articles have been published in Medscape this fall. A comprehensive review of the physiopathology and treatment of diabetes type 2 as well as a discussion of incretin hormone treatment of DT2 can be found here: (Diabetes and Intestinal Incretin Hormones: A New Therapeutic Paradigm, Medscape October 2004). This is a presentation from the Joslin Diabetic Center in Boston and should be a must for all practitioners treating diabetic patients. Remember, you must register with Medscape to use the service. This is gratis.

A second very informative article is: Getting to Goal in Type 2 Diabetes: Role of Postprandial Glycemic Control.

Both articles discuss shortcomings of current treatment and the possibilities offered by incretines. Among these are glucagon-like peptide-1 and exendin-4. Let us take a look at these.

Glucagon-like peptide 1 (GLP-1).

We have previously seen that glucagon and insulin secretion are linked. Low blood levels of glucose cause release of glucagon and inhibition of insulin secretion. Never the less, glucagon (or perhaps glutamate from glucagon-producing alpha cells) increases insulin release when a meal follows a fasting period. This is nothing new. However, during the past few years it has become evident many other hormones, known as incretins, regulate the functions of the endocrine pancreas. Recently, much attention has been given glucagon-like peptide 1 (GLP-1). This peptide is produced by and released from intestinal L-cells. It is a 37 amino acid peptide produced from proglucagon. GLP-1 is released from intestinal L-cells in response to dietary fat and carbohydrate. GLP-1 reduces food intake by inhibiting gastric emptying, increasing satiety through central actions and by suppressing glucagon release. GLP-1 lowers plasma glucose levels by increasing pancreas islet cell proliferation and increases insulin production following food consumption.

Note that the increased insulin secretion caused by GLP-1 is glucose-dependent. GLP-1 and related materials seem to work in beta cells by increasing K^+ levels following increased blood glucose levels. Therefore, GLP-1 appears to augment insulin secretion only when blood glucose is increased following a meal. Insulin levels fall in a normal manner following a reduction of blood glucose by uptake to tissues. GLP-1 and related peptides normalize blood glucose levels in diabetes type 2 patients without invoking hypoglycemia.

These are preliminary findings. Please go to the review articles listed above for more information.

Modification of GLP-1; Liraglutide

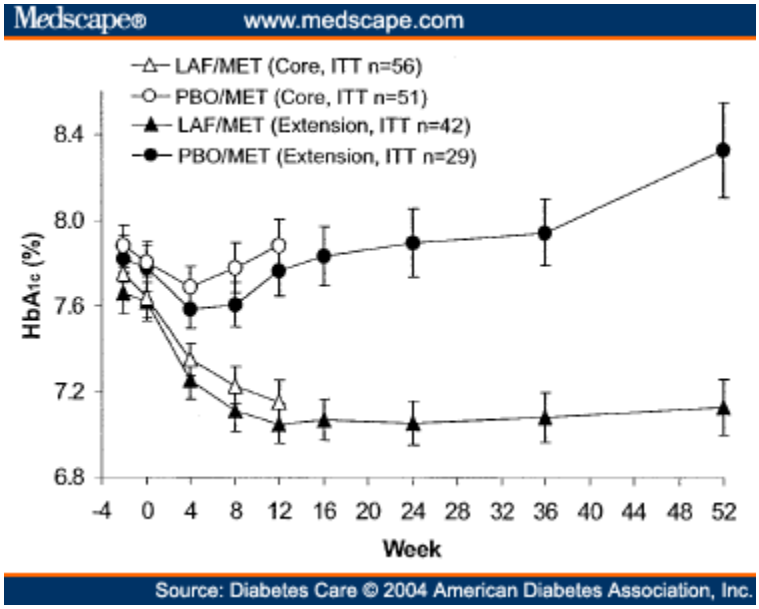
As mentioned above, GLP-1 is rapidly metabolized by a peptidase (dipeptidylpeptidase IV or DPP-IV). This results in a very short half-live and makes GLP-1 unsuitable as a therapeutic drug. One way to counter the rapid degradation of the hormone is to couple it to a fatty acid. Liraglutide is such a preparation. Liraglutide binds to serum albumin and is a poor substrate for the peptidase. Single injections of liraglutide give therapeutically active blood levels for 8 to 15 hours.

A recent clinical trial demonstrated that liraglutide reduced blood glucose levels postprandial and fasting, increased insulin secretion and decreased serum levels of glucagon. Thus, Liraglutide has the expected actions of GLP-1 and a much longer half-life.

A recent (June 2004) Medscape article presents data from another trial study of Liraglutide. The authors report a clear improvement in glycemic control following single daily injections of Liraglutide. Click here to pick up this article.

Inhibitors of dipeptidyl peptidase IV (DPP-4)

Another approach to extending the effectiveness of GLP-1 is to inhibit the hepatic dipeptidase responsible for its inactivation. Several compounds have been prepared and tested clinically. A recent (December 04) report presented a year-long study of the effects of a combination of metformin and LAF237 (a DPP-4 inhibitor) in 100 diabetes type 2 patients. The results were quite promising with a marked lowering of HbA1c levels in patients who received the combined therapy (figure to the left. Note that LAF/MET denotes the combination, PBO/MET the placebo therapy). [You can pick up the Medscape article by clicking here.]



NB: October 2004:

The latest article concerning GLP-1 and Exenatide has men cited earlier. This gives the most up-to-date information available today. Click on ([Diabetes and Intestinal Incretin Hormones: A New Therapeutic Paradigm, Medscape October 2004]) if you have not already done so.

Exendin-4

Strangely enough, we find a peptide resembling GLP-1 (exendin-4) in the saliva of the Gila monster, a poisonous lizard that lives in the Southwestern United States. Now, the Gila monster eats large amounts of food, but does that quite seldom. These lizards eat as few as four times each year, storing large amounts of fat in their tails and living off that in longer periods of time. When the lizard eats, the exendin-4 in the spit of the animal "wakes" pancreatic islet activity, giving rise to beta-cell activity, insulin release and control of glucose and fat metabolism. Exendin-4 has a longer half-life than GLP-1 and has very recently been shown to have a hypoglycemic effect in humans when given twice a day for one month. Like glucagon and glucagon-like-peptide 1, exendin-4 increases insulin release only following meals. Exendin-4 is presently being tested by several pharmaceutical firms and may possibly be used in treatment of type 2 diabetes.

Picture taken at night with Black and White film.

Gut hormones and diabetes were a subject of interest at the recent ADA 63rd annual sessions. "More than two dozen gut hormones have emerged that affect processes in the brain and elsewhere in the body that control appetite and energy metabolism," said Peter J. Havel, DVM, PhD, Associate Professor of Nutrition at the University of California at Davis and moderator of today's symposium on GI Signals and Energy Balance, in a recent interview. "These represent promising pathways for developing new treatments for obesity and type 2 diabetes." Click here for more information.

Exenatide, a synthetic version of Exendin-4

Exenatide is a 39-amino acid peptide which closely resembles exendin-4. It is DPP-4 resistant and has many of the actions of GLP-1. That is, it slows stomach emptying, increases satiety and decreases food intake and leads to increased release and synthesis of insulin. Exenatide is now (May 2005) approved by the FDA for treatment of type 2 diabetes. If you click here you will go to Medscape and find the details.

Fat tissue and thiazolidinediones (TZDs), a new class of medicaments in the fight against diabetes type 2

Insulin's mechanism of action in our organs has been studied since Banting's work in 1922. In spite of this, the hormone's way of working is still somewhat of a mystery. We know that adipose tissue, especially central fat depots, is related to glucose intolerance and development of diabetes type 2. Furthermore, the production of so many peptide hormones in fat tissue suggested that control of protein production might help in regulation of metabolism and counteract insulin resistance. About ten years ago, one found a new class of controlling elements in the nuclei of liver and fat cells, the so-called PPAR's or peroxisome proliferator-activated receptors. The alpha form is most common in the liver, while the gamma form is found in fat depots. The thiazolidinediones troglitazone, rosiglitazone and pioglitazone activate PPAR-gamma and were tried out as hypoglycemic agents in diabetes type 2. All of these improve the diabetic picture, reducing blood glucose and lowering blood lipid levels. Troglitazone was found to adversely affect hepatic metabolism and has been withdrawn from the market. The others are used in clinical practice today.

The mechanism of action of the TZDs is not clear. While they do combine with the PPARs, this may not be their sole working mechanism. Fat cells are rich in PPAR-gamma. Originally, it was hypothesized that these drugs acted in fat cells, changing the secretion of one or more of the many peptide hormones produced there, and that these in some way altered muscle metabolism and insulin sensitivity. That is, an altered adipocyte protein synthesis controlled muscle glucose uptake.

It has as been recently shown that muscle cells also have PPAR-gamma, although at quite a bit lower level than that found in fat cells. Muscle cells have been shown to respond directly to TZDs. While PPAR independent mechanisms have been demonstrated in muscle, specific blocking of PPAR-gamma in skeletal muscle has now been shown to duplicate "insulin resistance" in mice. These data indicate that skeletal muscle PPAR-gamma may underlie development of glucose intolerance and diabetes type 2. The link between obesity and increased blood lipids and skeletal muscle PPAR is not known. See A. I. Hevener et al, Nature Medicine, 9, 1491-1497 (2003) or click here to go to the original article.

Are thiazolidines safe?

Rosiglitazone has become one of most commonly utilized drugs in treatment of type 2 diabetes. Recently, several large studies have suggested that rosiglitazone may be cardiotoxic and may be involved in hundreds of instances of cardiac failure. In contrast to this, pioglitizone has not been reported to affect the heart and may be a better choice for treatment of type 2 diabetes. As of February 2010 the FDA has not withdrawn rosiglitazone from the market. Check Medscape.com or the FDA for more and current information.

Which medicine should I choose?

There is an increasing number of new approaches and drugs for treatment of type 2 diabetes during the past few years. It is expected that this tendency will continue.

Which drugs shall a doctor suggest for patients? How can diabetic patients follow developments? One possibility can be found at clicking one of the following links:

http://www.drugwatch.com is comprehensive a Web site featuring extensive information about thousands medications and drug side effects.

http://www.medscape.com is an excellent source for up-to-date information concerning diabetes and many other medical areas.

Central (brain) control and integration of metabolism.

The involvement of central neural mechanisms in homeostasis has become increasingly evident during the past few years. Even insulin resistance has been suggested to be controlled in the brain. This offers new approaches to treatment of type 2 diabetes. **You can click here to go to a discussion of this topic.**