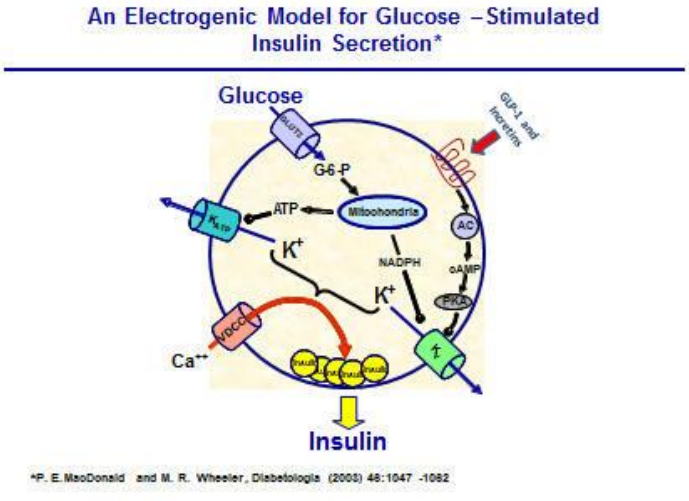
Some newer approaches to the treatment of type 2 diabetes

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, globally, more than 220 million people will suffer from this disease within 2020. In the United States, approximately one third of those over 65 years of age are diabetic: type 2 diabetes represents a huge medical problem! Treatment during the past decades has been largely based on metformin initially, with sulfanilamides and insulin as a follow-up when metformin no longer provided metabolic control. Many newer medications have been released for clinical use during this period. Let's look as some of these drug classes.

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 that other compounds released from the intestine and 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.



GLP-1 and related compounds are known as incretins. These interact with receptors on pancreatic beta cells, stimulating production of cAMP and activating protein kinase A. Phosphorylation of the voltage-dependent K^+ channel reduces its activity, leading to increased intracellular potassium levels after exposure of beta cells to increased plasma glucose. Note that stimulation of beta cells by incretins alone does not lead to release of insulin. Increased cAMP "primes" beta cells such that they release more insulin when activated by increased levels of circulating glucose. That is, the increased insulin secretion caused by GLP-1 is glucose-dependent.

To repeat; GLP-1 and related materials seem to work in beta cells by increasing K^+ levels following increased blood glucose levels. GLP-1 and other incretins 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 reduce blood glucose levels in diabetes type 2 patients without invoking hypoglycemia.

Unfortunately, GLP-1 is rapidly metabolized and inactivitated by a hepatic dipeptidase, resulting in a very short half-life. Therefore, GLP-1 is not suitable as as a medication.

Modification of GLP-1; Liraglutide

As mentioned above, GLP-1 is rapidly metabolized by a peptidase (dipeptidylpeptidase IV or DPP-IV) resulting in a very short half-live. 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.

Exendin-4

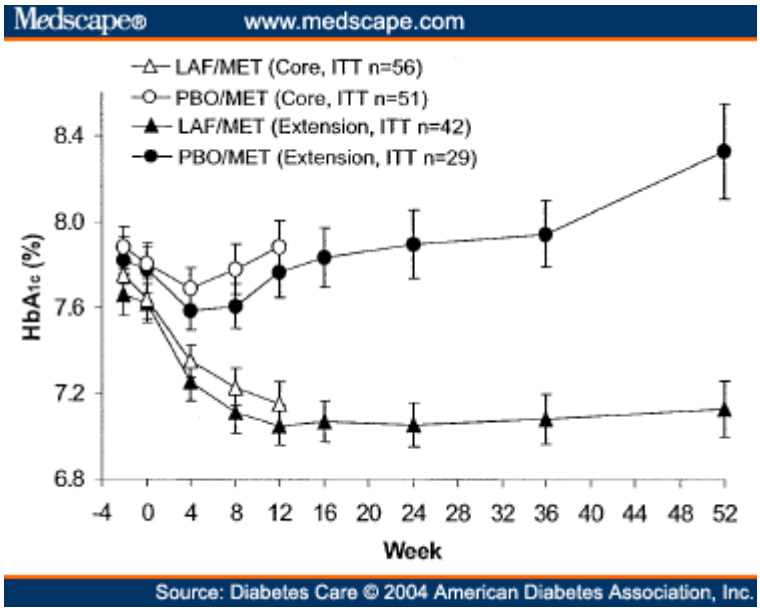
Strangely enough, we find a peptide resembling GLP-1 (exendin-4) in the saliva of the Gila monster, a poisonous lizard that lives in the Southwestern United States. These lizards eat as few as four times each year, storing large amounts of fat in their tails and living off that in longer periods of time. 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.

Picture taken at night with Black and White film.

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 has been approved by the FDA for treatment of type 2 diabetes.

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 are available for clinical use. An early report presented a year-long study of the effects of a combination of metformin and LAF237 (a DPP-4 inhibitor) in 100 type 2 diabetes 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).

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 for my patients?" or "old are best".

There are now eleven classes of drugs used in the United States for treatment of type 2 diabetes. All have been shown to somewhat reduce hyperglycemia and HbA1c. Surprisingly, none of the newer medications are as effective (or cost-effective) as metformin as the initial drug in monotherapy for type 2 diabetes. Metformin is also suggested as one of two or three elements in further treatment.

Click on the following titles for detailed discussions. (Inclusion of interesting figures from these sites would be too expensive for MedBio).

1. Current (2014) American Diabetes Association "Standards of Medical Care in Diabetes" .

2. The American College of Physicians: Clinical Guidelines for 2012: Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus.

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.