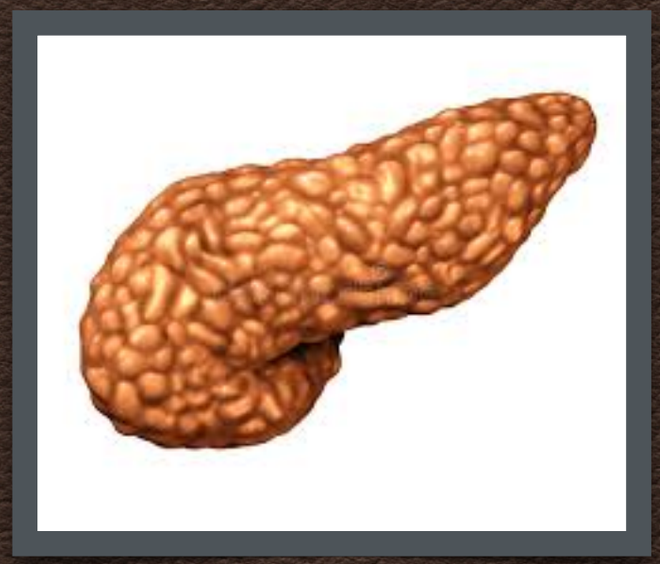

Diabetes Mellitus
The New Frontier

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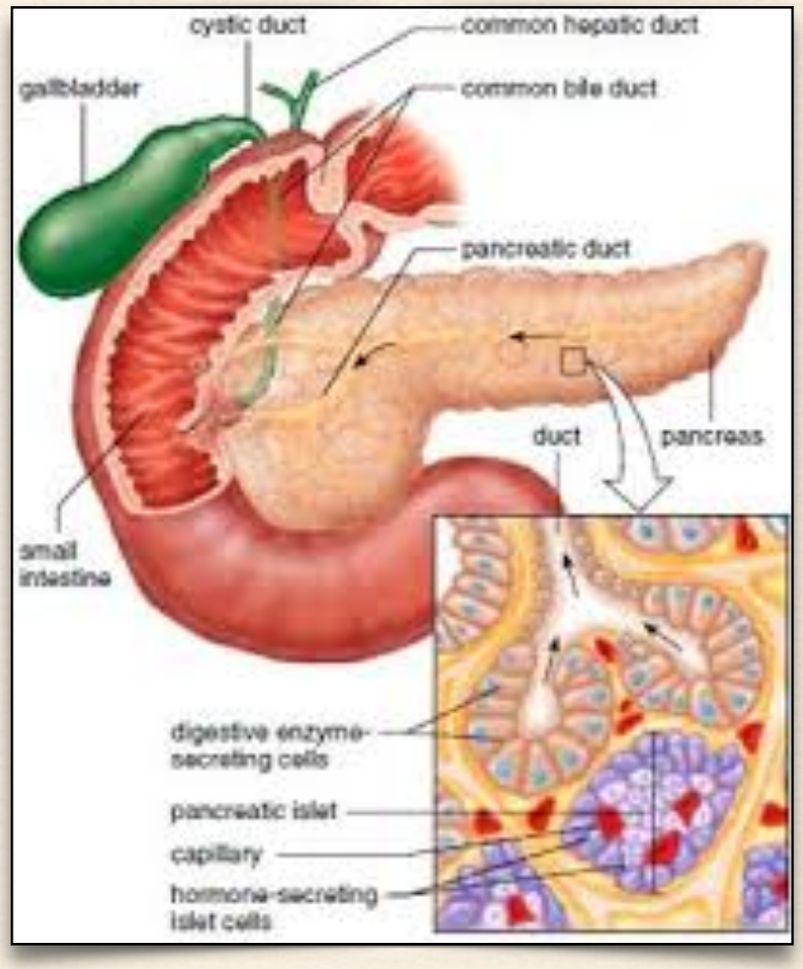
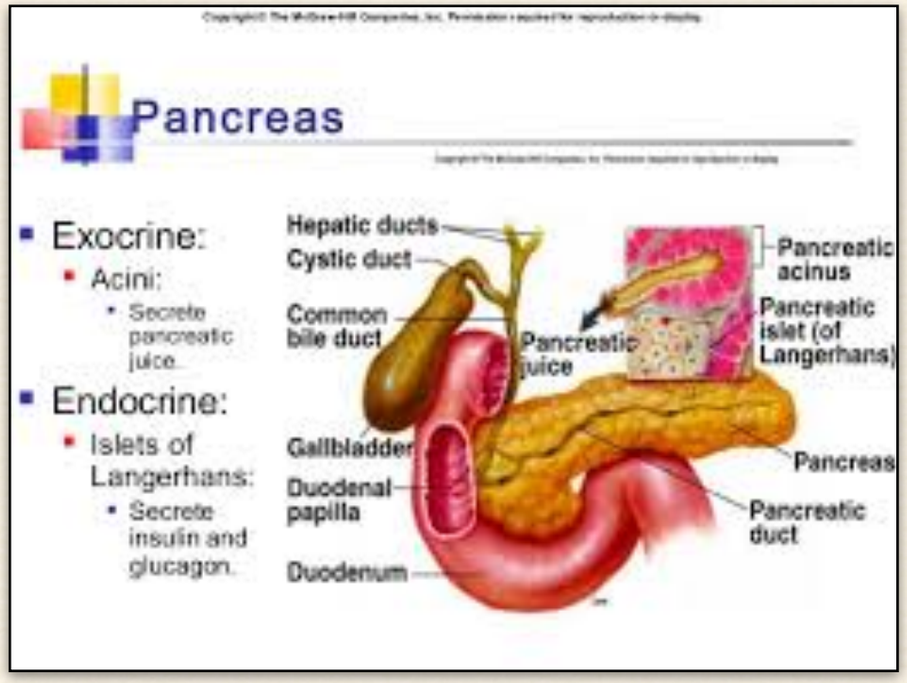
Diabetes Mellitus

- Educational objectives:
- The pancreas: structure and function.
- The different types of diabetes.
- Treating ketoacidosis
- Teaching yourself and your patient how to think like a pancreas to gain better diabetic control.
- How insulin works.
- Metabolic syndrome.
- How drugs work to control diabetes
- Duration of effect of drugs
- The bodies response to the presence of a drug.
- New Monitoring tools.

The pancreas gland



The pancreas gland
Structure and function



- Exocrine function
- Trypsin and chymotrypsin to digest proteins.
- Amylase to digest carbohydrates.
- Lipase to digest fats.

The pancreas gland
Structure and function

Endocrine function.

Alpha cells produce glucagon, a catabolic hormone that mobilizes glucose from storage in the liver, fatty acids and amino acids. This hormone functions to raise serum glucose when it is low.

Beta cells produce insulin, an anabolic hormone that mobilizes serum glucose into cells, and promotes the storage of glucose, fatty acids and amino acids into cells and tissues. This hormone functions to lower serum glucose.

The pancreas gland
Structure and function

Endocrine function.

D cells produce somatostatin which may regulate, locally, the secretion of the other pancreatic hormones.

In the brain (hypothalamus) and spinal cord it may act as a neurohormone and neurotransmitter.

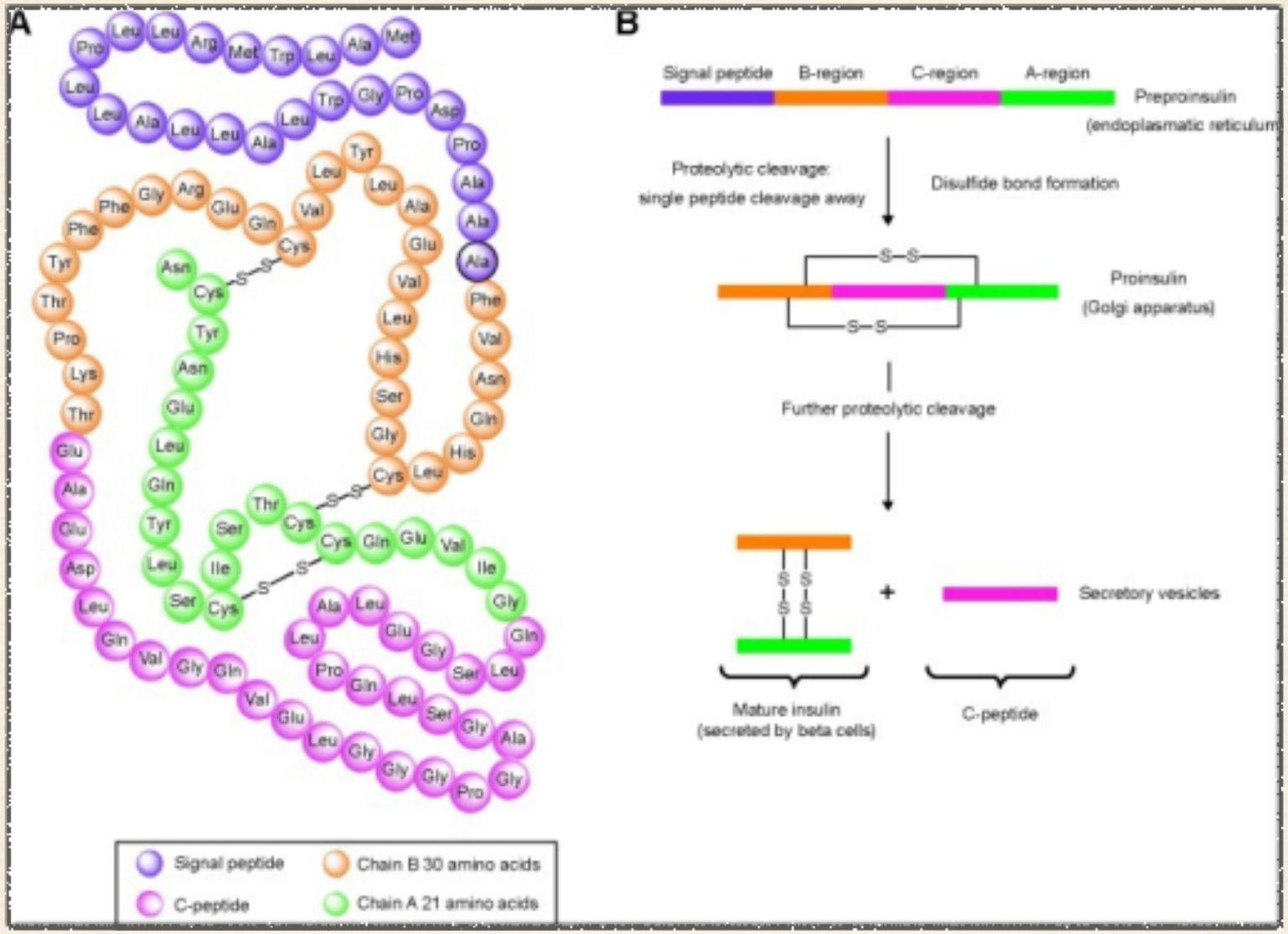
F or D1 cells produce pancreatic polypeptide, a hormone that may influence gastrointestinal function and promote intra-islet homeostasis.

The pancreas gland
Structure and function

Endocrine function.

Insulin is synthesized in B cells as part of a larger preprohormone - preproinsulin - which includes a 23 amino acid leader sequence attached to proinsulin; this leader sequence is lost upon entrance of the molecule into the endoplasmic reticulum leaving the pro-insulin molecule. Kallikrein, an enzyme present in the islets, aids in the conversion of proinsulin to insulin. In this conversion, a C peptide chain is removed from the proinsulin molecule producing the disulfide connected A and B chains that are insulin.

Pre pro Insulin



The pancreas gland
Structure and function

Endocrine

Background or basal insulin is secreted constantly.
Insulin secretion is pulsatile.

Insulin secretion is stimulated by high blood glucose levels, several amino acids, intestinal hormones, acetylcholine and others.

Insulin secretion is inhibited by: somatostatin, norepinephrine and other hormones.

The pancreas gland
Structure and function

Endocrine

Once in circulation, insulin is metabolized by the liver and eliminated and metabolized by the kidneys or utilized by binding to insulin receptors.

As the kidneys fail, endogenous and exogenous insulin may last longer.

This explains why many diabetics can use less exogenous insulin as their kidneys get progressively worse.

The pancreas gland
Structure and function

The major actions of insulin are:

Facilitation of glucose transport through membranes (e.g. adipose and muscle cells).

Stimulation of the enzyme system for conversion of glucose to glycogen (liver and muscle cells).

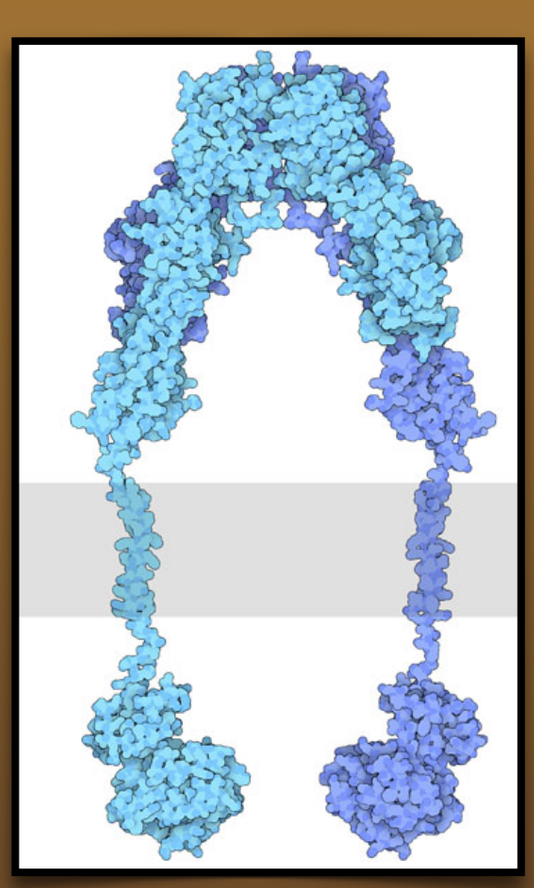
Slow-down of gluconeogenesis (liver and muscle cells).

Regulation of lipogenesis (liver and adipose cells).

Promotion of protein synthesis and growth (general effect).

The pancreas gland
Structure and function

Insulin initiates its action by binding to a glycoprotein receptor on the surface of the cell. This receptor consists of two alpha subunits and two beta subunits, which bind the hormone.



The pancreas gland
Structure and function

This binding of insulin causes translocation of the glucose transport protein GLUT4 to move to the surface of the cell to transport one molecule of glucose into the cell.

Negative cooperativity: the higher the concentration of insulin secreted and the higher the number of insulin receptors bound, the less afinity the receptor has for insulin.

The number of insulin receptors per cell can be up regulated or down regulated.

What is insulin?

- Glucose is transported into the beta cell by facilitated diffusion; elevated concentrations of glucose in extracellular fluid lead to elevated concentrations of glucose within the beta cell.
- Elevated concentrations of glucose within the beta cell ultimately leads to membrane depolarization and an influx of extracellular calcium. The resulting increase in intracellular calcium is thought to be one of the primary triggers for exocytosis of insulin-containing secretory granules. The mechanisms by which elevated glucose levels within the beta cell cause depolarization is not clearly established, but seems to result from metabolism of glucose and other fuel molecules within the cell, perhaps sensed as an alteration of ATP:ADP ratio and transduced into alterations in membrane conductance.
- Increased levels of glucose within beta cells also appears to activate calcium-independent pathways that participate in insulin secretion.

Insulin Elimination

Insulin that is secreted by the pancreas has a circulating half-life of approximately 6 minutes, which is to say that every 6 minutes, the amount of insulin in the blood declines by 50%. In fact, after it is released from the pancreas, insulin is no longer detectable in the bloodstream within 30 minutes.

Insulin is removed from the body by enzymes in the kidney and the liver, as well as by its interaction with insulin receptors.

Decreased function of the kidneys can cause a prolonged effect of endogenous and/or exogenous insulin.

Types of diabetes

- Diabetes insipidus.
- Dysfunction of the hormone anti diuretic hormone.
- Either malfunction of secretion or at the receptor..

Types of diabetes

Insulin dependent. Also known as juvenile onset.
These patients lack production of insulin and have an absolute demand for exogenous insulin administration. C-peptide level will be low or non existent.

Insulin requiring diabetic. These patients have beta cell burn out. They require insulin injections to augment insulin production by their own pancreas.

Non insulin requiring diabetic. These patients make less insulin than needed. Their insulin production may be modulated by pills or injection.

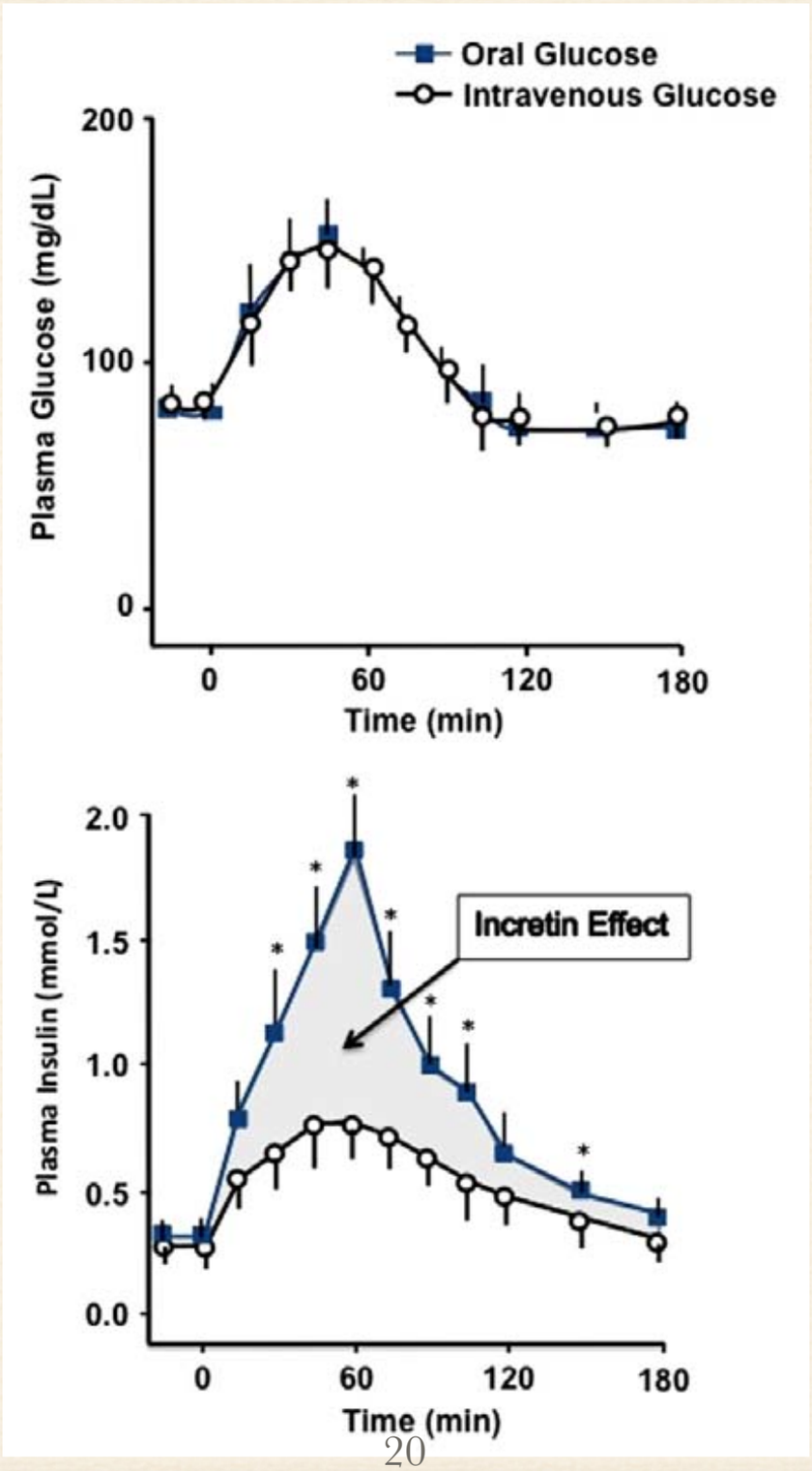
Incretin Effect

Scientists noted that injecting gastric tissue into subjects lowered glucose levels.

The incretin effect suggests that an oral nutrient load stimulates a much higher secretion of insulin than a similar load given by IV and lead to the discovery of gastric inhibitor polypeptide (GIP) and Glucagon Like Peptide Type 1 (GLP-1).

New Interpretation of Glucose Tolerance. Lancet 1964 July. 4;2: 20-1

Incretin Effect



Glucagon Like Peptide Type 1

Glucagon like peptide type 1 is a 30 amino acid long peptide hormone derived from the tissue specific post translational processing of the proglucagon peptide. It is produced and secreted by intestinal enteroendocrine L cells and certain neurons within the nucleus of the solitary tract in the brainstem upon food consumption.

The peptide is metabolized and inactivated by Dipeptidyl peptidase 4 (DPP4).

It's duration of effect is less than 2 minutes.

Glucagon Like Peptide Type 1

Promotes insulin secretion from the beta cells in a glucose dependent manner.

Inhibits gastric emptying and gastric acid secretion and motility.

Promotes satiety by stimulating the satiety center in the brain.

Decreases secretion of glucagon from the pancreas.

Increases beta cell proliferation

Ensures that beta cell stores of insulin are quickly replenished during secretion by promoting insulin gene expression.

Glucagon Like Peptide Type 1

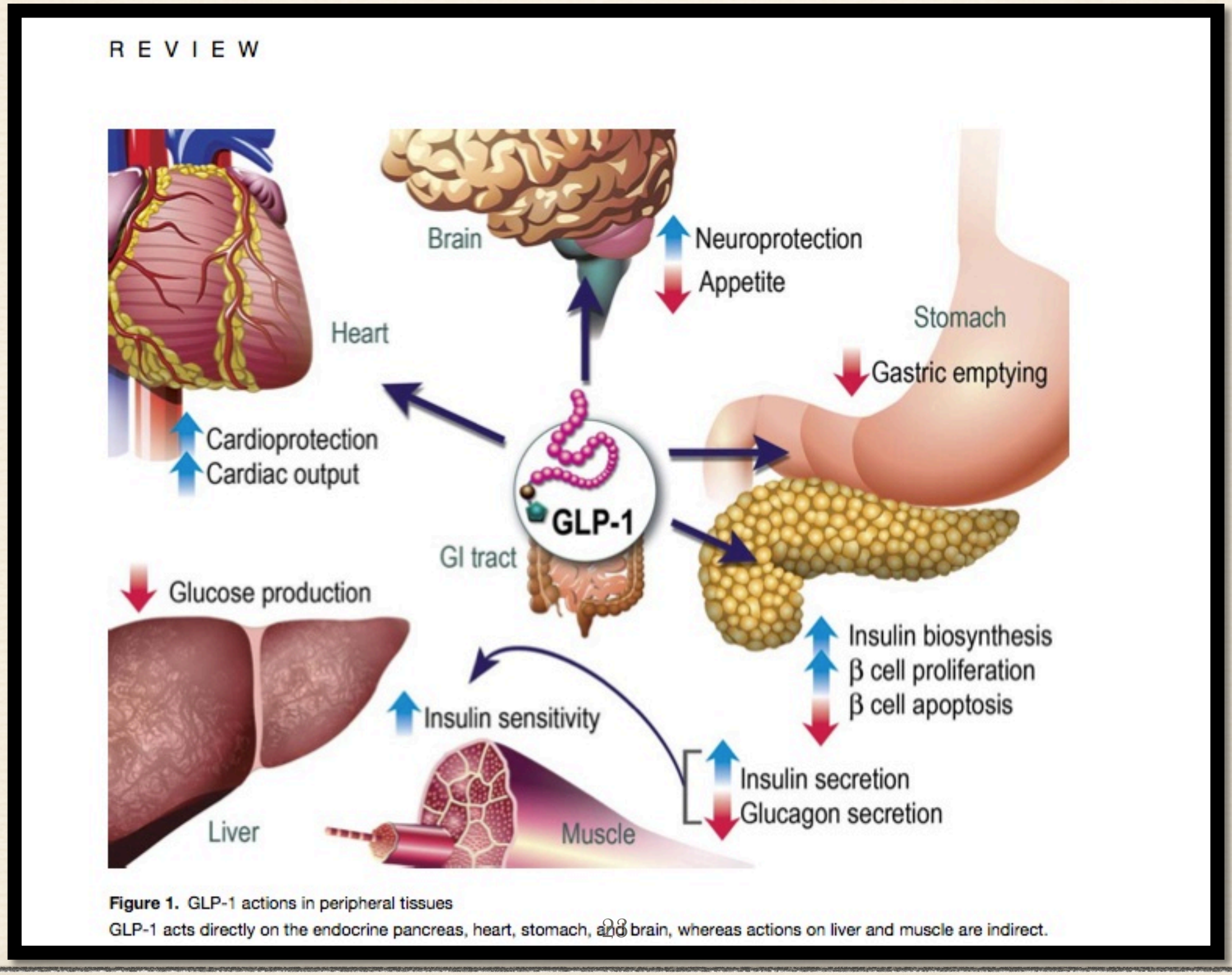


Figure 1. GLP-1 actions in peripheral tissues

GLP-1 acts directly on the endocrine pancreas, heart, stomach, and brain, whereas actions on liver and muscle are indirect.

Obesity and Diabetes

Obesity is a chronic inflammatory process that stimulates the release of the inflammatory molecule LTB4 that can cause insulin resistance.

Extra fat cells, especially in the liver, stimulate the release of LTB4

Removing the cell receptor that responds to LTB4 or blocking the receptor with a drug improves insulin resistance.

Nature Medicine, 2015; DOI: 10.1038

Treating ketoacidosis

Diabetic ketoacidosis (DKA) is a serious condition that can occur in diabetes. DKA happens when acidic substances, called ketones, build up in your body. Ketones are formed when your body burns fat for fuel instead of sugar, or glucose. That can happen if you don't have enough insulin in your body to help you process sugars.

This state represents that the body has an absolute deficiency of insulin.
Without insulin, the human can not burn glucose efficiently and depends on fat metabolism producing ketones.
The patient needs insulin infusion to recover.

Treating ketoacidosis

As long as ketones are present in circulation, the patient will continue to need IV insulin administration.

Treating ketoacidosis

Make the diagnosis.
Admit to ICU.
Replace fluids and electrolytes.
May need bicarbonate drip to treat acidosis.
Insulin drip.
Look for causes. Infection etc.

Treating ketoacidosis

Continue IV insulin drip until ketones are absent.
If glucose drops below 250 mg/dl, start 10% glucose until ketones are absent.

Once the patient is stable and eating without nausea, you can begin to return to their usual insulin program.

Thinking like a pancreas

The pancreas secretes background insulin around the clock.
The pancreas also secretes insulin upon demand under stress (counter regulatory hormones) or consumption of food.
A patient using insulin needs to understand this concept if they are able.
Any consumption of food should be covered by additional coverage with insulin.

Metabolic Syndrome

Metabolic syndrome is a cluster of conditions. This includes:
Increased blood pressure.
High blood glucose.
Central obesity.
Elevation of cholesterol and triglycerides.

Known causes:
Obesity
Inactivity
Insulin resistance

Metabolic Syndrome

Risk factors
Age
Mexican American
Obesity
Gestational diabetes mellitus
Cardiovascular disease
Non alcoholic fatty liver disease (think of high fructose corn syrup)
Polycystic ovarian syndrome

Metabolic Syndrome

Ectopic fat (fat deposited outside of fat cells) causes insulin resistance.

20% of obese individuals may NOT have insulin resistance and have normal metabolic profiles.

Insulin is required to convert excess calories into fat and also to sustain it as fat.

Hyperinsulinemia underlies all of the metabolic syndrome and it's consequences and forms a large portion of the toxicity of insulin.

Hyperinsulinemia stimulates the formation of atherosclerosis.

Metabolic Syndrome

Real world records from the the United Kingdom General Practice Research Database from 1986 to 2008, identified over 20,000 patients who had added insulin to their diabetes medication. Patients with the lowest A1C expected the best survival, but the exact opposite was true!

Patients with the ‘best’ blood glucose control had the worst outcomes. Patients achieving an A1C of 6.0%, considered ‘excellent’ control, fared just as poorly as those patients with an A1C of 10.5%, considered ‘uncontrolled’ diabetes. The glucotoxicity paradigm utterly failed to explain this phenomenon. If most of the damage from diabetes was being caused by the high blood glucose, then those with the lowest A1C should have the best outcomes. But they did not.

Metabolic Syndrome

Remember the C peptide we talked about?
Checking C peptide levels will help you understand if the pancreas in over producing insulin.

See, you are beginning to think like a pancreas already!!!

Insulin Toxicity

May lead to diabetes.
Increased risk of polycystic ovarian syndrome.
Leads to increased synthesis of VLDL.
Hypertension.
Sodium retention.
CAD (increased insulin damages endothelial cells) and plaque.
Associated with early Alzheimer's disease.
Increased incidence of stroke.
Metabolic syndrome.
Non alcoholic fatty liver.
Leads to obesity
Makes cells resistant to the function of insulin
Decreases the function of sex hormones.
Increases the risk of prostate and breast cancer.
Prevents the body from storing magnesium.

So, where did we go wrong?
Food for Googling

Genetically modified wheat.
High fructose corn syrup.
Sodium as a preservative.
Growth hormones

We are what we eat!!

How Medications Work to Treat Diabetes

Diabetes was first described in 1552 BC by Hesy-Ra. He noticed a wasting disease and that ants were attracted to urine from patients with this disease.

In 150 AD, the Greek physician Arteus described "the melting down of flesh and limbs into urine". Urine tasters were developed to diagnose diabetes.

How Medications Work to Treat Diabetes

The first treatment used was exercise.
During the Franco-Prussian war of the 1870's, Apollinaire Bouchardat noticed that food rationing during the war helped control diabetes.

In 1916 Boston scientist Elliott Joslin wrote a text about combining diet and exercise.

How Medications Work to Treat Diabetes

In 1889 Oskar Minkowski and Joseph Von Mering in France showed that removing the pancreas from a dog caused diabetes.

In 1904, a German scientist, George Zuelzer injected pancreatic extracts into diabetic patients.

Fredrick Banting, a Canadian physician began experimenting in 1920 and was successful at treating diabetes with insulin in 1922.

How Medications Work to Treat Diabetes

Sulfonylureas work by stimulating the pancreas into producing more insulin.

Can only be used in patients with functioning islet cells.

Continued use of this group of drugs can cause progressive beta cell burnout.

Acetohexamide
Tolazamide
Tolbutamide

Glimeperide (Amaryl)
Glyburide (Diabeta, micronase)
Glipizide (Glucatrol)

How Medications Work to Treat Diabetes

Biguanides.

Metformin

Primary effect is to decrease glucose release from the liver.

It also increases sensitivity to insulin.

It also decreases the amount of glucose absorbed from meals.

FDA recently approved use of Metformin at eGFR as low as 30 ml/min. Do not start if eGFR < 45 ml/min.

JAMA Internal Medicine (2018;178(7):903-910)

How Medications Work to Treat Diabetes

Dopamine agonist

Bromocriptine

May help treat insulin resistance.

How Medications Work to Treat Diabetes

DPP4 inhibitors
Dipeptidyl peptidase 4
This enzyme metabolizes glucagon like peptide-1.

Blocking this enzyme prolongs the effect of the endogenous hormone.
The "gliptin group.

Sitagliptin (Januvia)
Vildagliptin (Galvus)
Saxagliptin (Onglyza)
Linagliptin (Tradjenta)

How Medications Work to Treat Diabetes

Other DPP4 inhibitors being investigated
Gemigliptin. LG life Sciences. Korea
Anaglipitin. Sanwa Kagaku Kenkyusho. Japan
Teneleglíptin. Japan
Alogliptin. Takeda
Trelagliptin. Japan
Omarigliptin. Japan
Evogliptin. South Korea
Gosogliptin. Russia
Dutogliptin. Phenolic corp.

How Medications Work to Treat Diabetes

Glucagon like peptide type 1 agonists.

Simulate the action of GLP-1.

Stimulates the pancreas to release insulin.

Stimulate the satiety center and decreases appetite.
Slow stomach emptying.
Reduces pancreatic production of glucagon thus reducing the release of storage glucose from the liver.

Recent data suggests that they also stimulate beta cell growth, reduce beta cell apoptosis, Protect the heart and protect the brain

How Medications Work to Treat Diabetes

Meglitinides
Stimulate the release of insulin in the presence of glucose after eating.

Similar to sulfonylureas.

They have a weaker binding affinity than sulfonylureas.

Nateglinide (Starlix)
Rapaglinide (Prandin)

How Medications Work to Treat Diabetes

Sodium glucose transporters - 2 (SGLT2) inhibitors.
Prevent the kidneys from reabsorbing glucose after being filtered through the glomerulus.

Canaglifozen (Invokana)
Dapaglifozen (Farxiga)
Empaglifozen (Jardiance)
Ertugliflozin (Steglatro)
Ipragliflozin. (Suglat)
Luseogliflozin. (Lusefi)
Remogliflozin
Tofogliflozin (Apleway and Deberza)
Sotagliflozin (dual SGLT-1 and SGLT-2 inhibitor to treat type 1 DM. refused by the FDA)

How Medications Work to Treat Diabetes

Thiazolidinediones

Decrease liver glucose.
Increases fat cell sensitivity to insulin reducing insulin resistance.
Modifies adipocyte differentiation
Decreases leptin levels (causing increased appetite)
Reduces interlukin 6

Pioglitazone (Actos)
Rosiglitazone (Avandia) (may also be effective in treating Alzheimer's disease)
Lobeglitazone (Duvie-avaliable only in Korea)

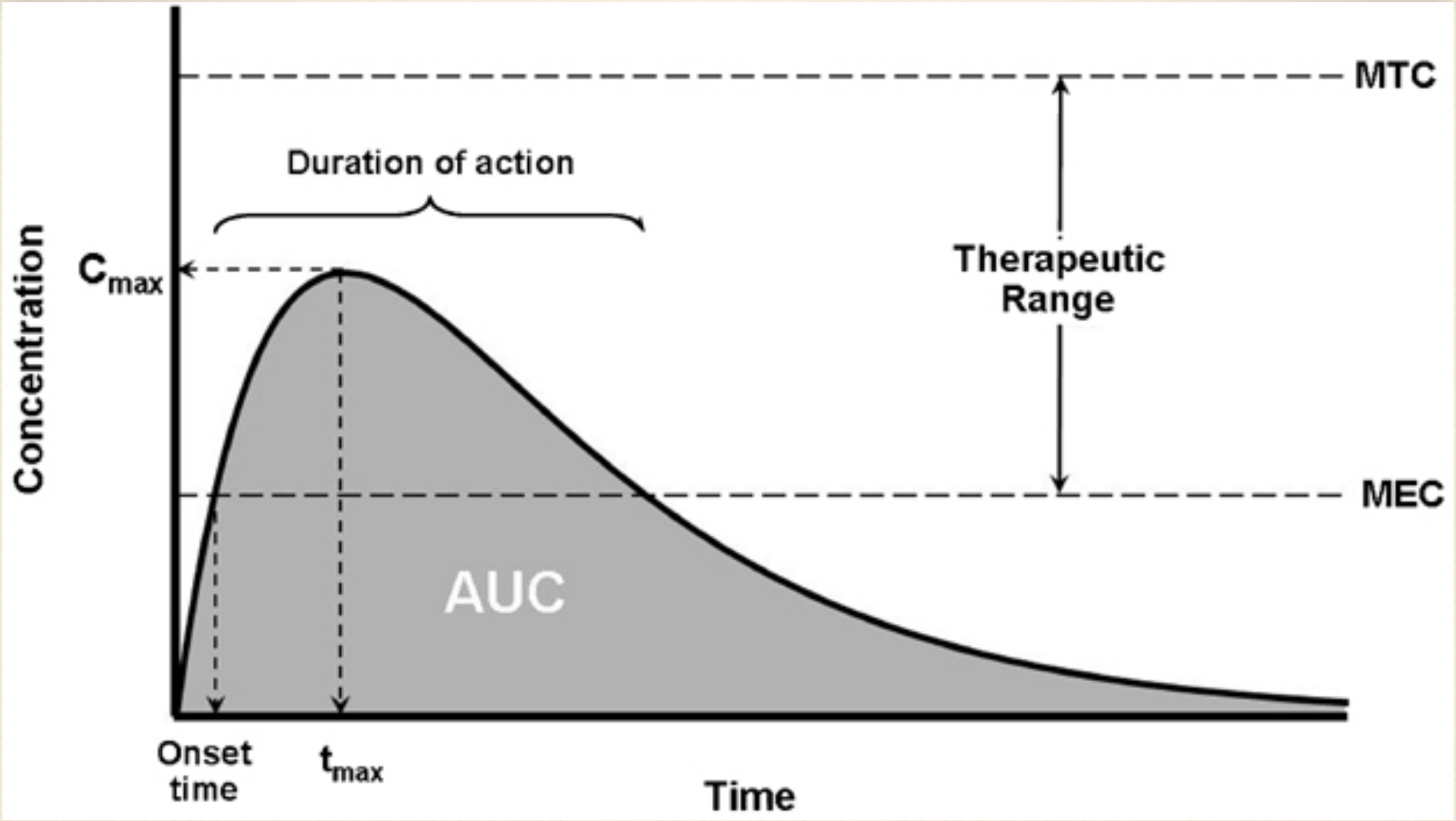
How Medications Work to Treat Diabetes

Alpha-glucosidase inhibitors.
Helps the digestive tract break down starchy foods and sugar.
Acarbose (Precose and Glucobay)
Miglitol (Glyset)
Voglibose. (Not in USA)

Alternative Treatment for Diabetes

For poorly controlled insulin dependent diabetics, please consider pancreas only transplant

Drug Metabolism and Duration of Effect



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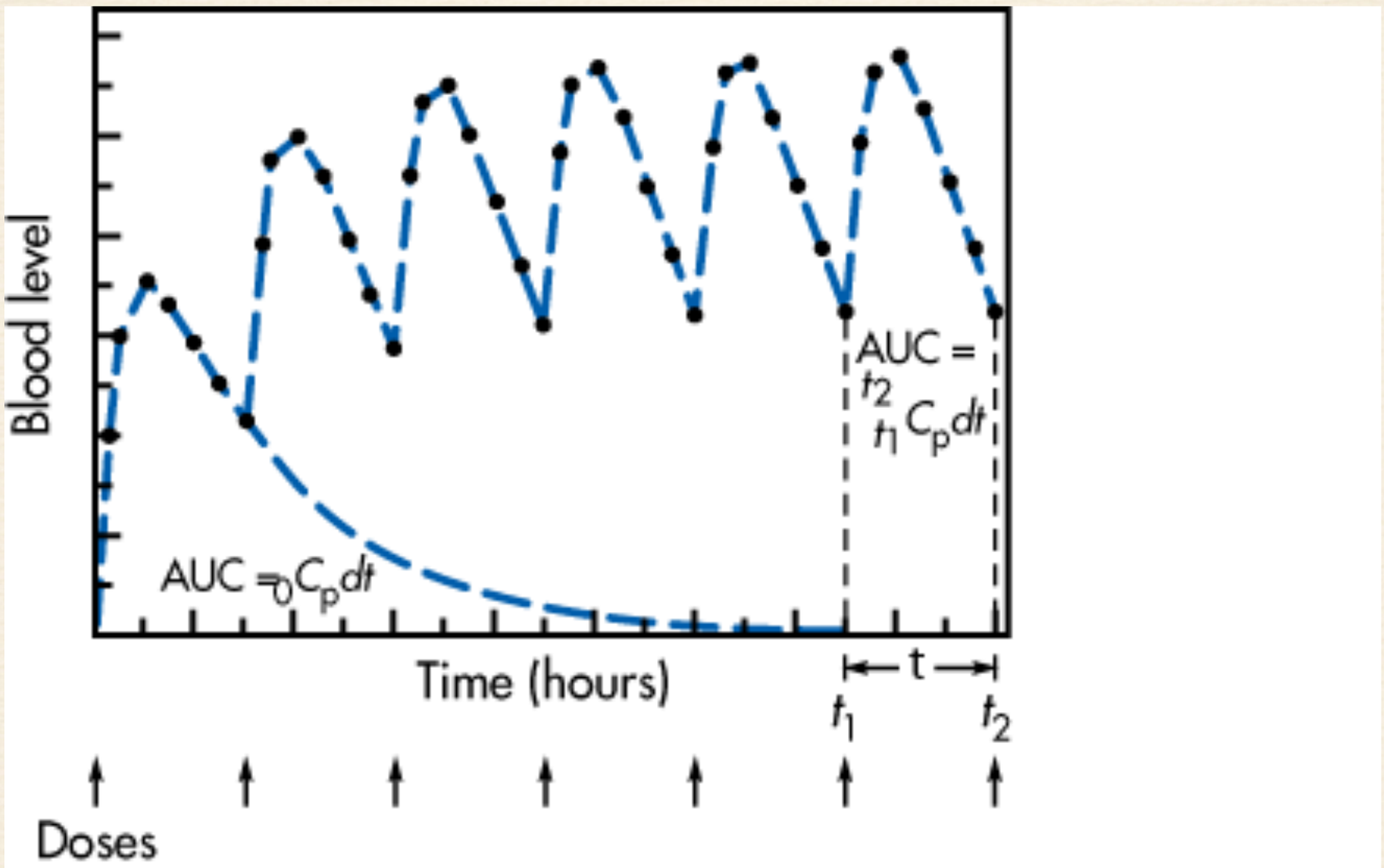

Source: Shargel L, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics, 6th Edition*: www.accesspharmacy.com

Bibliography

JAMA. 2014; 311(22): 2288-2296
The Journal of Cell Biology, 2018; jcb 201711047 DOI: 1083/jcb.201711047
Diabetes care 2016;39(Suppl. 2):S165-S171
Lancet 1964 July 4;2:20-1
J Clin Endocrinol Metab. 1973 Nov;37(5):826-8
CNS Drugs 2003; 17(1):27-45.
Diabetes care 2011 May; 34 (suppl 2):S251-S257
Diabetologia 2012 Jul;55(7):1865-8.
Regul Pept. 2005 Jun 15;128(2):93-6
J Clin Invest. 2017; 127(12):4217-4227
JASN November 2004, 15(11) 2816-2827
Nature Medicine, 2015; DOI: 10.1038
Diabetes 2014 Jul; 63(7): 2262-2272l
Hepatobiliary surg nutr. 2015 Apr; 4(2); 109-116
Vasc Health Risk Manag. 2008;4(6):1349-60

The Benefits of Apples

It has been scientifically proven that an apple a day keeps the doctor away.

You just have to make sure that you aim it real well!