Regulation of glucose homeostasis

- Insulin production: B cells of islets of Langerhans (60-80% of cells there are B cells).
- Species differences in islet architecture
- In general, four peptides with hormonal activity are secreted by the islet cells:
  - Insulin (beta or B cells; stimulates glucose uptake)
  - Glucagon (A cells; stimulates glycogenolysis and gluconeogenesis primarily in liver, both of which increase BS)
  - Somatostatin (D cells; negatively regulates A and B cell secretions)
  - Pancreatic polypeptide (F cells)
- Insulin secretion is stimulated by glucose (alters the ATP/ADP ratio in a cell, blocks ATP-sensitive K⁺ channels [Kir6.2/SUR1], depolarizes the cell, opens voltage-gated Ca²⁺ channels causing exocytosis).

Comparison of Type 1 and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>10 %</td>
<td>90 %</td>
</tr>
<tr>
<td>Onset of Symptoms</td>
<td>Abrupt</td>
<td>Gradual</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>Usually &lt; 20</td>
<td>Usually &gt; 35</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Symptomatic</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>Insulin Dependent</td>
<td>Yes</td>
<td>Not initially</td>
</tr>
<tr>
<td>Beta Cell Destruction</td>
<td>Yes</td>
<td>Not initially</td>
</tr>
<tr>
<td>Obesity</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Insulin Resistance</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Familial</td>
<td>Unusual</td>
<td>Common</td>
</tr>
<tr>
<td>Human Lymphocyte Antigen (HLA)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Identical Twin Concordance</td>
<td>50 %</td>
<td>95 %</td>
</tr>
<tr>
<td>Islet Cell Antibodies</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Receptors</td>
<td>Normal</td>
<td>Decreased or Defective</td>
</tr>
<tr>
<td>Plasma Insulin Levels</td>
<td>Decreased</td>
<td>Elevated or Normal</td>
</tr>
<tr>
<td>Post-Receptor Defect</td>
<td>Unusual</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Type 1.5 Diabetes (Latent Autoimmune Diabetes of the Adult; LADA)

- Another name for this form of diabetes is "slowly progressing type 1 diabetes."
- Diagnosed with diabetes but it can be controlled with the oral drugs used in type 2 diabetes
- BUT, these patients also have at least one autoantibody typically seen in type 1 diabetes.
- Like type 2 diabetes, type 1.5 diabetes is "silent" lacking severe polyuria, polydipsia, weight loss or ketoacidosis.
- Half of patients with type 1.5 diabetes usually progress to insulin within four years of diagnosis.
- In contrast, 50 percent of patients with type 2 diabetes will not need insulin until about 10 years following diagnosis.
PROCESSING OF PROINSULIN

HISTORIC ACHIEVEMENTS IN INSULIN TX 1.0

- Winkler and van Beriing produced diabetes by total pancreatectomy in the dog (1886).
- Banting and Best demonstrated that pancreatic extracts were able to control hyperglycemia in diabetic dogs and humans (1921).
- 1922: Banting and Best administered 15 ml of a slightly acidic alcohol solution described as “a thick brown mush” to a diabetic patient named Leonard Thompson. The solution contained exogenous insulin, and he was the first patient to receive it. His blood glucose level dropped from 440 to 325 mg/dl, and a sterile abscess developed at the injection site.
- By 1923, the extraction process had been improved, and insulin was commercially available in North America.
- Abel crystallized insulin in 1926.

HISTORIC ACHIEVEMENTS IN INSULIN TX 2.0

- Protamine zinc insulin (PZI), a long-acting insulin, was introduced in the 1930s and remained on the market until several years ago. Neutral protamine Hagedorn (NPH) was introduced in the 1940s and the lente series of insulins in the 1950s.
- Sanger sequenced insulin in 1960.
- Mayeroff synthesized it in 1963.
- Advances in chromatography led to the production of more highly purified insulins in the 1960s and 1970s.
- In the 1980s recombinant DNA technology was used to produce human insulin.
- The most recent advance is the development of insulin analogues produced by recombinant DNA, peptide synthesis, and enzyme-catalyzed semisynthesis.
- To date, more than 300 insulin analogues have been identified, including 70 animal insulins, 80 chemically modified insulins, and 150 biosynthetic insulins. Many modified insulins have been made by genetic engineering of the insulin (proinsulin) gene.
- Most of these insulins have altered biologic properties.
- For example, replacing His position 10 of the B chain with Asp produces an insulin that resembles endogenous insulin more closely than regular insulin, which means that there is a marked delay in onset of action and shorter duration of action.

In general:
- The glucose uptake effects of insulin are mediated by PI3K-Akt-PDK1-GLUT4. The glucose uptake effects of insulin are mediated by PI3K-Akt-PDK1-GLUT4. The glucose uptake effects of insulin are mediated by PI3K-Akt-PDK1-GLUT4. The glucose uptake effects of insulin are mediated by PI3K-Akt-PDK1-GLUT4.

Pharmacological Management of Diabetes

Insulins:
- General considerations for insulin-replacement therapy
  - While administration of insulin has been remarkably successful in that the diabetic can now live a relatively normal life, the insulin-dependent diabetic still must be concerned about the complications of the disease.
  - The problem is one of dosing and timing:
    - The body normally releases insulin in pulses in response to elevated blood glucose levels.
    - The diabetic self-administers insulin on a regularly timed basis which usually is once or twice a day.
    - While the amount of insulin administered will be dependent on the amount of carbohydrates consumed, the timing of the injections may be less critical to when carbohydrate is consumed during the day.
    - Subcutaneous human insulin takes about two hours before reaching a maximum concentration in the SC compartment and metabolism: thus, the duration of insulin action is shorter than that of regular human insulin.
  - Complicating this timing are the variable pharmacokinetic parameters of insulin when given by the SC route can be several hours, resulting in postprandial hyperglycemia and resulting hypoglycemia.
  - The above is true even in patients who pay attention to insulin, BG, and carbo

Modified Insulins I

- Lispro (Iso-pro) (Humalog™)
  - Reversal of the amino acids at positions 28-29 (Pro) and 29-30 (Lys).
  - Lispro's structure is very close to that of the above mentioned insulin-like growth factor.
  - Results in a conformational shift in the C-terminal end of the B chain that stERICALLY hinders the ability of the insulin monomers to form dimers by a factor of 300 relative to regular insulin.
  - Also has a more rapid onset of action than regular insulin, which means that the diabetic can inject it closer to the time of eating.
  - Also appears to reduce the risk of hypoglycemic episodes caused by the diabetic injecting insulin prior to a meal and then delaying eating.
  - More convenient to the patient, but there does not appear to be a difference in outcome as measured by glycated Hb levels.
  - Presumably it can be mixed with intermediate acting insulins to obtain a longer-acting insulin preparation.

Modified Insulins II

- Insulin aspart (Humalog™)
  - P-28 D (neutral proline has been replaced with an acidic aspartate)
  - Results in a product with a faster rate of absorption than regular human insulin.
  - This insulin, like lispro, has a more rapid onset of action and shorter duration of action.

Glargine (Lantus™)
- An ultra-long-acting insulin.
  - N-Asp-D-Ala two arginines have been added to the C-terminus of the B chain.
  - Increased basicity that decreases at the physiological pH at the injection site.
  - Thus, glargine has a markedly delayed onset and prolonged activity (24-48 hours) when administered subcutaneously.
  - Rather than peaking, glargine maintains a steady prolonged activity.
  - It is claimed that this insulin more closely mimics endogenous insulin.
SUMMARY OF INSULIN NOMENCLATURE

<table>
<thead>
<tr>
<th>Insulin Amino Acids</th>
<th>Source</th>
<th>A Chain</th>
<th>B Chain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef insulin; no longer available in the United States</td>
<td>Ala</td>
<td>Thr</td>
<td>Thr</td>
</tr>
<tr>
<td>Pork insulin</td>
<td>Thr</td>
<td>Asp</td>
<td>Thr</td>
</tr>
<tr>
<td>Modified Human (glargine; Lantus™)</td>
<td>Thr</td>
<td>Gly</td>
<td>Pro</td>
</tr>
<tr>
<td>Modified Human (lispro; Humalog®)</td>
<td>Thr</td>
<td>Ile</td>
<td>Lys</td>
</tr>
<tr>
<td>Modified Human (aspart; Novorapid™)</td>
<td>Thr</td>
<td>Thr</td>
<td>Ala</td>
</tr>
</tbody>
</table>

*Pork (porcine) insulin is a closer match to human insulin relative to beef (bovine) insulin. What was called “synthetic” human insulin was produced by an enzymatic conversion of the amino acid position 29 of the B chain of porcine insulin to threonine. Most human insulins are produced by recombinant DNA technology.

Lispro, insulin aspart and glideine are produced by recombinant DNA methodology.

COMMERCIAL INSULIN PREPARATIONS 1.0

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset (Hours)</th>
<th>Peak (Hours)</th>
<th>Duration (Hours)</th>
<th>Compatible when mixed with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regular Insulin (Human; Novolin R; insulin + ZnCl₂ + buffer)</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>- PZI</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>- Humulin-U</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>Intermediate-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- NPH; Humulin-N; Novolin-N</td>
<td>1 - 2</td>
<td>4 - 12</td>
<td>18 - 24</td>
<td>Regular</td>
</tr>
<tr>
<td>- Humulin-U</td>
<td>1 - 2</td>
<td>4 - 12</td>
<td>18 - 24</td>
<td>Regular</td>
</tr>
</tbody>
</table>

COMMERCIAL INSULIN PREPARATIONS 2.0

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset (Hours)</th>
<th>Peak (Hours)</th>
<th>Duration (Hours)</th>
<th>Compatible when mixed with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regular Insulin (Human; Novolin R; insulin + ZnCl₂ + buffer)</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>- Humulin-U</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>Intermediate-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regular Insulin (Human; Novolin R; insulin + ZnCl₂ + buffer)</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>- Humulin-U</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
</tbody>
</table>

COMMERCIAL INSULIN PREPARATIONS 3.0

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset (Hours)</th>
<th>Peak (Hours)</th>
<th>Duration (Hours)</th>
<th>Compatible when mixed with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regular Insulin (Human; Novolin R; insulin + ZnCl₂ + buffer)</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>- Humulin-U</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>Intermediate-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Regular Insulin (Human; Novolin R; insulin + ZnCl₂ + buffer)</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>- Humulin-U</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
</tbody>
</table>

COMMERCIAL INSULIN PREPARATIONS 3.0

<table>
<thead>
<tr>
<th>Type</th>
<th>Onset (Hours)</th>
<th>Peak (Hours)</th>
<th>Duration (Hours)</th>
<th>Compatible when mixed with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>- Regular Insulin (Human; Novolin R; insulin + ZnCl₂ + buffer)</td>
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<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>- Humulin-U</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>Intermediate-Acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
<tr>
<td>- Humulin-U</td>
<td>0.5 - 1</td>
<td>2 - 3</td>
<td>5 - 7</td>
<td>All</td>
</tr>
</tbody>
</table>
Glucagon for Injection is produced by recombinant DNA technology in E. coli. The emergency kit contains a vial of sterile, lyophilized glucagon and a syringe of sterile diluent. Both may be stored at controlled room temperature. After reconstitution, the product should be used immediately. It is injected in the buttock, arm or thigh after cleaning the area with alcohol swab. In severe hypoglycemia, patients may not be able to inject themselves. Friends, family and coworkers should be familiar with guidelines and instructions for injection.

### Oral Agents for Type II Diabetes

**Sulfonylureas**

- **History**: These drugs developed from the observation that several of the sulfonamides exerted a significant hypoglycemic effect.
- **Mechanism of Action**: In the 1940’s a sulfonamide used in the treatment of typhoid caused such a severe hypoglycemic crisis that death could result.
- **Drug Interactions**: Concurrent use of drugs with hyperglycemia side effects (NSAIDs, corticosteroids, thiazide diuretics, and possibly miconazole) apparently do not increase beta cell sensitivity to glucose.
- **Studies of the past**: This was ignored for years, but finally a systematic study of the long-term effects of tolbutamide and chlorpropamide produced similar results.

#### Table: Sulfonylureas

<table>
<thead>
<tr>
<th>Name</th>
<th>Dose (effective)</th>
<th>Serum Glucose</th>
<th>Onset</th>
<th>Duration</th>
<th>Active Metabolites</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolbutamide Orinase®</td>
<td>250-2000 mg</td>
<td>1-4 mg qd</td>
<td>2-3</td>
<td>2-3</td>
<td>The first metabolite formed has activity, but further metabolism causes a loss of activity.</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>1-6.25 mg qd</td>
<td>1-4 mg qd</td>
<td>2-4</td>
<td>10-24</td>
<td>Inactive metabolites.</td>
</tr>
<tr>
<td>Acetohexamide Dymelor®</td>
<td>0.75-12 mg qd</td>
<td>2-3</td>
<td>1-3</td>
<td>10-24</td>
<td>Weakly active metabolites.</td>
</tr>
<tr>
<td>Glipizide Glucotrol®</td>
<td>5-20 mg qd</td>
<td>2-3</td>
<td>1-3</td>
<td>10-24</td>
<td>Inactive metabolites.</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>0.5-20 mg qd</td>
<td>3-8</td>
<td>2-4</td>
<td>12-18</td>
<td>Weakly active metabolites.</td>
</tr>
<tr>
<td>Glyburide</td>
<td>1.25-100 mg</td>
<td>1-4</td>
<td>2-4</td>
<td>10-24</td>
<td>Inactive metabolites.</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>30-120 mg</td>
<td>1-3</td>
<td>2-4</td>
<td>10-24</td>
<td>Inactive metabolites.</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>0.5 mg with meals</td>
<td>1-3</td>
<td>2-4</td>
<td>1-3</td>
<td>Inactive metabolites.</td>
</tr>
</tbody>
</table>

**Meglitinides**

- **Rapid release rather than the sustained insulin release seen with sulfonylureas.**
- **Rapaglinide differs from the sulfonylureas with its very rapid onset and offset of action.**
- **This action is dependent on functioning beta cells in the pancreatic islets (insulin release is glucose-dependent and diminishes at low glucose concentrations).**
- **Nordisk claim it may have a lower incidence of hypoglycemia relative to sulfonylureas drugs (4% versus 2.8%), but FDA states this claim remains to be proven.**
- **Other brand names: NovoNorm® (Europe); ActoNorm® (Canada)**

**Thiazolidinediones**: The sulfonylureas apparently do not increase beta cell sensitivity to glucose. Insulin resistance appears to represent a more fundamental alteration in the function of the pancreatic islets. These drugs develop from the observation that several of the sulfonylureas (such as tolbutamide) exerted a significant hypoglycemic effect.

**Metformin**

- **Incretin mimetics**: Incretin mimetics such as exenatide, a metabolically stable version of glucagon-like peptide-1 (GLP1), which slows GI emptying and also stimulates glucogen-dependent insulin secretion.

**Pramlintide**

- **Activation of pancreatic beta cells**: This action is independent of glucose concentration, e.g., sulfonylureas apparently do not increase beta cell sensitivity to glucose.
- **There seems to be a lack of effectiveness over time. Some clinicians have promoted intermittent cessation of sulfonylurea therapy.**

**Meglitinides (Rapaglinide, Prandil™)**

- **The meglitinides lower blood glucose levels by stimulating the release of insulin from the pancreas in a manner similar to that of the sulfonylureas.**
- **Rapaglinide differs from the sulfonylureas with its very rapid onset and offset of action.**
- **Thus, the claim is made that rapaglinide produces a more physiologic (episodic) insulin release rather than the sustained insulin release seen with sulfonylurea therapy.**
- **This action is dependent on functioning beta cells in the pancreatic islets (insulin release is glucose-dependent and diminishes at low glucose concentrations).**
- **Nordisk claim it may have a lower incidence of hypoglycemia relative to sulfonylureas drugs (4% versus 2.8%), but FDA states this claim remains to be proven.**
- **Other brand names: NovoNorm® (Europe); ActoNorm® (Canada)**

**Indication**: “An adjunct to diet and exercise to lower the blood glucose in patients with Type 2 Diabetes Mellitus whose hyperglycemia cannot be controlled satisfactorily by diet and exercise alone.”

**Pharmacokinetics**: Elimination half-life: 1 hour; liver metabolism, bile elimination)

**Dosing**: 0.5 mg with meals rather than a set daily dose.
Oral Agents for Type II Diabetes—Biguanides 1.0

3. Biguanides (Metformin: Glucophage™)

- **History**
  - The biguanides are an "old" class of hypoglycemics having been first used in the early 20th century.
  - The biguanide structure is based on the hypoglycemic component, gaulthie, of Galega officinalis (French lilac).
  - Metformin and phenformin were first synthesized in the 1950s.

- **Mechanism**
  - Reduces hepatic glucose production possibly by inhibiting hepatic gluconeogenesis.
  - In addition there is evidence that metformin increases insulin-mediated glucose uptake leading to increased glycogen formation and possibly enhanced tissue sensitivity to insulin.
  - Metformin is claimed to be superior to the sulfonureas because it does not cause hyperglycemia at therapeutic doses and apparently lowers serum lipids/serum triglycerides, which are a serious complication of diabetes.
  - There have been some suggestions that metformin might decrease the risk that Type 2 patients will progress to Type 1, but further studies are needed. One study showed a 31% reduction in prediabetic patients developing diabetes.

- **Lactic Acidosis**
  - Phenformin was removed from market in 1977 because fatal lactic acidosis developed in some Type 2 patients.
  - In general, the biguanide family of hypoglycemic agents have shown a tendency to cause lactic acidosis, probably due to an inhibition of oxidative phosphorylation causing a shift to anaerobic glycolysis.

- **Complications:** Flatulence (41.5%); diarrhea (28.7%).

- **Dosage**
  - Metformin is absorbed into systemic circulation and distributed to all body tissues, with highest concentrations in liver, adipose tissue, and skeletal muscle (100 to 200 mg/L). Metformin is also distributed to breast milk.
  - Extended release tablet dosing: 500 mg qd.
  - 1000 mg bid or 850 mg bid-tid.

Oral Agents for Type II Diabetes—Biguanides 2.0

4. Thiazolidinediones (TZDs, Glitazones)

- **Combination Therapy:** The thiazolidinediones are approved for combination therapies with sulfonylureas, metformin, and insulin.

- **Warnings**
  - TZDs are not to be used in patients with renal impairment (a potential problem in diabetes) because these agents may cause fluid retention leading to possible cardiac failure.
  - Because liver failure was the principal adverse reaction seen with troglitazone, the currently marketed TZDs carry warnings that liver function should be monitored.

- **Agents in this class**
  - Rosiglitazone (Avandia™): 4 - 8 mg daily either as monotherapy or divided doses, with or without food.
  - Pioglitazone (Actos™): 15 - 45 mg once daily with or without food.

- **Mechanism**
  - Rosiglitazone and pioglitazone are highly selective and potent agonists for the peroxisome proliferator-activated receptor gamma (PPAR-γ).
  - Thiazolidinediones improve glycemic control while reducing circulating insulin levels.
  - These agents are considered part of another chemical class.

- **History**
  - Although the TZDs share chemical features with the sulfonylureas, TZDs are considered part of another chemical class.
  - Rosiglitazone (Ro-44-5250) was the first of this chemical class to be approved in the United States. Reports of death from liver complications, troglitazone was removed from the U.S. and many foreign markets.

- **Complications:** Flatulence (41.5%); diarrhea (28.7%).

Oral Agents for Type II Diabetes—$$\alpha$$-glucosidase inhibitors

5. Inhibitors of Glucose Absorption

- **Acarbose (Precose™)**
  - First isolated from an actinomycete as part of a screen for $$\alpha$$-glucosidase inhibitors which competitively inhibits $$\alpha$$-glucosidase (a maltase) and pancreatic amylose preventing final digestion of starch followed by glucose absorption.
  - Only useful for type 2 Diabetes.
  - Dosing: Initial: 25 mg tid with the first bite of each meal.
  - Maintenance: 50 - 100 mg tid (takes 8 - 12 weeks before reaching the maximum dose).
  - Complications: Flatulence (77%); diarrhea (33%).

- **Miglitol (Glyset™)**
  - In contrast to acarbose, miglitol is absorbed into systemic circulation and excreted through the kidney with little metabolic change.
  - Dosing: Initial: 25 mg tid with the first bite of each meal.
  - Maintenance: 50 - 100 mg tid (takes 12 weeks before reaching the maximum dose).
  - Complications: Flatulence (41.5%); diarrhea (28.7%).
Other Agents for T2DM

6. New Drugs
• Pancreatic Amylase (Symlin™)
  - This is a 37 residue peptide based on the hormone amylin which is co-secreted with insulin from beta cells; activates a GLP1R in gut.
  - Activation of amylase receptors increases gastric emptying time closing release of stomach contents to the intestines. The result is a slowing of carbohydrates digestion and glucose absorption; a CNS-mediated reduction in appetite has also been proposed based on the appetite-stimulating effects of amylin receptor antagonists.
• Administration is subcutaneous.
• GLP1 agents (exendin-4 [Byetta, Exenatide]—see next page)
• Dipeptidyl peptides IV (DPP-IV) inhibitors (Vildaglifln)—see next page

<table>
<thead>
<tr>
<th>Amylin agonists</th>
<th>GLP-1R agonists</th>
<th>DPP-IV inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ancestral function</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Insulin secretion</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Slows gastric emptying</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Increases satiety and weight loss</td>
<td>2</td>
<td>3</td>
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<td>Improves B-cell function</td>
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INCRETIN EFFECT

- When glucose is taken orally, insulin secretion is stimulated much more than it is when glucose is infused intravenously.
- This effect, which is called the incretin effect and is estimated to be responsible for 50 to 70% of the insulin response to glucose, is caused mainly by the two intestinal insulin-stimulating hormones.
  - GLP-1-like peptide-1 (GLP1)
    - Alternatively splice product of the glucagon gene
    - Pancreatic A cells: Proglucagon — Glucagon (preproglucagon)
    - Intestinal L cells: Proglucagon — GLP1, GLP2 (stimulated by both in gut)
  - GLP1 receptors on pancreatic B cells stimulate glucose-dependent, insulin exocytosis, and beta cell proliferation.
  - Glucose-dependent insulinotropic polypeptide (GIP)
    - Secreted from duodenal K cells in response to carb- and lipoprotein meals.
    - Activates a GPCR on pancreatic B cells, promotes insulin exocytosis.
  - Probably less important than GLP1 in the context of the incretin response.

INCRETIN EFFECT

- Lizards have separate exendin and GLP1 genes: humans?

Pharmacological Px/TxDiabetic Complications

- At diagnosis of type 2 diabetes, beta cell function is reduced to approximately 50% of normal and continues to decrease in spite of therapies that effectively reduce hyperglycemia.

There are four hypotheses for how hyperglycemia causes the vascular complications of diabetes:
- Increased polyol pathway flux.
- Increased advanced glycation end-product (AGE) formation.
- Activation of protein kinase C (PKC) isoforms.
- Increased hexosamine pathway flux.
A unifying hypothesis linking these four mechanisms, in which vascular damage is caused by the activation of these pathways by hyperglycemia, is shown.

INCRETIN EFFECT

- A truncated version of exendin-4, exendin (9-39) binds to but does not activate the GLP-1 receptor and functions as a GLP-1 receptor antagonist. Exendin (9-39) has been employed as a GLP1R antagonist in multiple preclinical studies and in human experiments to probe the consequences of disrupting GLP1R activation.
- GLP1 is rapidly degraded in vivo by dipeptidyl peptidase IV (DPP-IV). So both modified GLP1 peptide agonists, such as exendin, that are resistant to this degradation and DPP-IV inhibitors have been investigated in an attempt to address this issue.
- Importantly, exendin-mediated stimulation of insulin secretion occurs only in the presence of elevated blood-glucone concentrations, the risk of hypoglycemia, which is a problem with some other anti-diabetic agents, such as sulfonylureas, should be reduced with exendin.
- In animal studies exendin administration resulted in preservation and formation of new beta cells, the insulin-producing cells in the pancreas, which fail as type 2 diabetes progresses.
- Exendin is approved by the FDA as an adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea, or a combination of metformin and a thiazolidinedione but who have not achieved adequate glycemic control.
- A major off-label use of exendin is for the T x of obesity as this agent reduces appetite (hypothalamic receptors) and gastric emptying.
The protein kinase C beta inhibitor ruboxistaurin has recently been reported to reduce visual loss and preserve kidney function in patients with diabetes, and could soon be submitted for regulatory approval.

Studies on the hexosamine pathway are still confined to animals, but a thiamine derivative (benfotiamine) that decreased levels of glyceraldehyde-3-phosphate in vitro prevented the early changes of retinopathy in diabetic rats.

Exenatide has the potential to combat two characteristics of type 2 diabetes: obesity and deterioration of insulin secretion.

In addition to DPP-IV inhibitors, several other drugs are in the later stages of development.

Inhaled insulin is in use (Exubera), and insulin sprayed onto the buccal membranes in the mouth is being studied.

Drugs that target both PPARgamma and PPARalpha are also being evaluated.

Fibretics, which target PPARalpha, are used to reduce triglyceride levels, which are usually elevated in people with type 2 diabetes and which are associated with cardiovascular disease. So, dual PPARalpha/gamma modulators might combine the therapeutic activities of both thiazolidinediones and fibretics.