Chapter 41

Pancreatic Hormones & Antidiabetic Drugs
The Pancreas

- An organ that makes **insulin** and **enzymes for digestion**.
- Both **endocrine system** and **digestive system (exocrine)**.
Table 41–1. Pancreatic islet cells and their secretory products.

<table>
<thead>
<tr>
<th>Cell Types</th>
<th>Approximate Percent of Islet Mass</th>
<th>Secretory Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>A cell (alpha)</td>
<td>20</td>
<td>Glucagon, proglucagon</td>
</tr>
<tr>
<td>B cell (beta)</td>
<td>75</td>
<td>Insulin, C-peptide, proinsulin, amylin</td>
</tr>
<tr>
<td>D cell (delta)</td>
<td>3–5</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>F cell (PP cell)¹</td>
<td>&lt; 2</td>
<td>Pancreatic polypeptide (PP)</td>
</tr>
</tbody>
</table>
Function of the hormones

- Insulin: the storage and anabolic hormone of the body (glyco-metabolism)

- Amylin: modulates appetite, gastric emptying, and glucagon and insulin secretion

- Glucagon: the hyperglycemic factor that mobilizes glycogen stores
Disorders of the Pancreas: Diabetes Mellitus

Caused by:

- Insufficient secretion of insulin
- Resistance of body cells to the effects of insulin
Diabetes Mellitus

- **Type 1**: Insulin-dependent diabetes
- **Type 2**: Noninsulin-dependent diabetes
- **Type 3**: Gestational Diabetes Mellitus (GDM)
- **Type 4**: Other specific types

Elevated blood glucose
Type I Diabetes

--- develops suddenly, usually before age 15
- results in insulin dependence
- severe or absolute insulin deficiency
In response to high levels of glucose in the blood, the insulin-producing cells in the pancreas secrete the hormone **insulin**.

Type I diabetes occurs when **these cells** are destroyed by the body’s own **immune system**.
Treatment of Type 1 Diabetes

- Injection of insulin
- Surgery: replacing the pancreas or just the beta cells
  - pancreas-kidney transplant
  - Stem cell research

- Blood glucose monitoring
- Meal plan
- Insulin
Type II Diabetes

--- adult onset, usually occurs after age 40

- Etiology: Insulin resistance;
  relative deficiency in insulin secretion.

- blood glucose levels rise due to:
  1) Lack of insulin production
  2) Insufficient insulin action (resistant cells)
Treatment of Type II Diabetes - Drugs

- **Oral hypoglycemic agent = OHA**

- OHA + Insulin therapy

- Type 2 diabetes can be cured by one type of gastric bypass surgery in 80-100% of severely obese patients.
Oral hypoglycemic agents

- Sulfonylureas (SU)
- Biguanides
- Thiazolidinediones (TZDs)
- α-Glucosidase Inhibitors
- Insulin Secretagogues
- Insulin Sensitisers
GDM

- **Gestational diabetes mellitus (GDM)** is a condition in which women without previously diagnosed diabetes exhibit high blood glucose levels during pregnancy.

- Most patients are treated only with diet modification and moderate exercise but some take anti-diabetic drugs, including insulin therapy.
Treatment of Type III Diabetes

- Self monitoring can be accomplished using a handheld capillary glucose dosage system.

A kit with a glucose meter and diary used by a woman with gestational diabetes.
Type IV Diabetes

Other specific types

Drug-induced diabetes:
● 1992, anti-hypertensive vasodilator diazoxide, and corticosteroids in high doses could cause diabetes.
● 2006, antipsychotic drugs.
  dozens of those patients died from diabetes-related complications.
Antidiabetic Drugs

- Insulin
- Insulin Secretagogues: Sulfonylureas; Meglitinides
- Insulin Sensitisers: Biguanides; Thiazolidinediones
- Alpha-glucosidase inhibitors
- Peptide analogs:
  1. Glucagon-like peptide (GLP) analogs
  2. DPP-4 inhibitors
  3. Amylin analogues
Insulin

- **Diabetes mellitus type 1** is a disease caused by the lack of insulin.
- **Insulin** must be used in Type I, which must be injected or inhaled.
Pharmacological effects of insulin

Decrease the blood glucose concentration (BGC)
Principal types of insulin preparations

- There are several types of insulin, characterized by the rate which they are metabolized by the body.
- Duration of action
Figure 41–5. Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg; with the exception of insulin lispro, aspart, and glulisine, duration increases considerably when dosage is increased.
Insulin

- Insulin is usually given subcutaneously, either by injections or by an insulin pump.
- Research is underway of other routes of administration.
- In acute care settings, insulin may also be given intravenously.
Insulin Delivery System

- Regular injections
- Portable pen injections
- Continuous subcutaneous insulin infusion devices (CSII, insulin pumps)
- Inhaled insulin
Regular injections

Insulin Syringe

Traditional syringes are still the most common method to deliver insulin.

Places on the body where insulin is usually injected.
Portable pen injections

- It is an insulin injection tool that resembles a pen.
- This is great for people who need to give themselves an insulin injection when out in public but do not like it to be noticeable.
- The Insulin Pen also contains memory of your last 16 injections.
Continuous Subcutaneous Insulin Infusion - CSII

Continuous infusion of a short-acting insulin driven by mechanical force and delivered via a needle or soft cannula under the skin.
Inhaled insulin

- Inhaled insulin is a powdered form of insulin absorbed by the lungs through use of a hand-held inhaler.
- Inhaled insulin is the first noninjectable option.
Complications of Insulin Therapy

- **Hypoglycemia**
- Immunopathology: Insulin allergy; Immune insulin resistance
- Lipodystrophy at injection sites
Normal and target blood glucose ranges (mg/dL)

**Normal blood glucose levels in people who do not have diabetes:**
- Upon waking (fasting): 70 to 110
- After meals: 70 to 140

**Target blood glucose levels in people who have diabetes:**
- Before meals: 90 to 130
- 1 to 2 hours after the start of a meal: less than 180

**Hypoglycemia (low blood glucose):** 70 or below
Treatment of Hypoglycemia

**Glucagon**

- A hormone produced by the alpha cells in the pancreas.
- It raises blood glucose.
- An injectable form of glucagon.
Contents

- Insulin
- Insulin Secretagogues
- Insulin Sensitisers
- Alpha-glucosidase inhibitors
- Peptide analogs
Overview

- **Diabetes mellitus type 2** is a disease of insulin resistance by cells.

- Treatments include:
  1. agents which increase the amount of insulin secreted by the pancreas--- **Insulin Secretagogues**
  2. agents which increase the sensitivity of target organs to insulin--- **Insulin Sensitisers**
  3. agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract.
Insulin Secretagogues:
(1) Sulfonylureas (SU)
(2) Meglitinides

Insulin Sensitisers:
(1) Biguanides
(2) Thiazolidinediones (TZDs)

Alpha-glucosidase inhibitors

Peptide analogs:
(1) Glucagon-like peptide (GLP) analogs
(2) DPP-4 inhibitors
(3) Amylin analogues
Sulfonylureas (SU)

- Sulfonylureas were the first widely used oral hypoglycemic medications.

**Mechanism of Action:**
- trigger insulin release by direct action on the K channel of the pancreatic beta cells.
Sulfonylureas

- 1st generation
  - Tolbutamide
  - Tolazamide
  - Chlorpropamide

- 2nd generation
  - Glyburide
  - Glipizide
  - Glimepiride

- 3rd generation
  - gliclazide

More efficacious than the 1st generation, have fewer adverse effects.
Therapeutic uses

- Only useful in Type II diabetes
  
  They work best with patients over 40 years old, who have had diabetes mellitus for under ten years.

- **Diabetes insipidus**
  
  *Chlorpropamide* has also an antidiuretic effect and may be used to treat diabetes insipidus.
Adverse reactions

- **Serious adverse reaction is hypoglycemia**
- Common adverse effects: gastrointestinal reactions such as nausea and vomiting
- Occasional adverse reaction: hematologic reaction such as leukopenia
- **Meglitinides** help the pancreas produce insulin and are often called "short-acting secretagogues."
- Their mode of action is original, affecting potassium channels.
- By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, hence enhancing insulin secretion.
- They are taken with meals to boost the insulin response to each meal.
Meglitinides

<table>
<thead>
<tr>
<th>Drug</th>
<th>Chemical Structure</th>
<th>Oral Dose</th>
<th>$t_{1/2}$</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repaglinide</td>
<td><img src="repaglinide.png" alt="Chemical Structure" /></td>
<td>0.25–4 mg before meals</td>
<td>1 hour</td>
<td>4–5</td>
</tr>
<tr>
<td>(Prandin)</td>
<td><img src="repaglinide.png" alt="Chemical Structure" /></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nateglinide</td>
<td><img src="nateglinide.png" alt="Chemical Structure" /></td>
<td>60–120 mg before meals</td>
<td>1 hour</td>
<td>4</td>
</tr>
<tr>
<td>(Starlix)</td>
<td><img src="nateglinide.png" alt="Chemical Structure" /></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
- **repaglinide** (Prandin) - The maximum dosage is 16 mg/day, taken 0 to 30 minutes before meals. If a meal is skipped, the medication is also skipped.

- **nateglinide** (Starlix) - The maximum dosage is 360 mg/day, usually 120 mg **three times a day (TID)**.
Adverse reactions include:

- weight gain
- hypoglycemia
There are two currently available biguanides:

- Metformin
- Phenformine
Biguanides

Mechanism of action

- Direct stimulation of glycolysis in tissues, with increased glucose removal from blood
- Inhibiting gluconeogenesis
- Reducing the absorption of glucose from the intestine
Therapeutic uses:

- Metformin is usually the first-line medication used for treatment of type-2 diabetes.
- Initial dosing is 500 mg twice daily, but can be increased up to 1000 mg twice daily. It is also available in combination with other oral diabetic medications.
Adverse reactions

1. The main adverse reactions of Phenformin are lactic acidosis, and because of this complication these agents were withdrawn in many countries.

2. The most frequent toxic effects of Metformin are gastrointestinal symptoms including nausea, vomiting, and diarrhea.
Thiazolidinediones (TZDs)

- Pioglitazone
- Rosiglitazone
- Ciglitazone
- Englitazone
- Troglitazone

Mechanism of action:

Enhance the target tissue's sensitivity to insulin through PPAR-γ pathway.

- PPAR-γ is a type of nuclear regulatory proteins involved in transcription of genes regulating glucose and fat metabolism. These PPARs act on Peroxysome Proliferator Responsive Elements (PPRE). The PPREs influence insulin sensitive genes, which enhance production of mRNAs of insulin dependent enzymes. The final result is better use of glucose by the cells.
Adverse effects

Adverse effects are mild, including:
- edema
- anemia headache
- gastrointestinal symptoms
α-Glucosidase Inhibitors

Acarbose
Miglitol
Voglibose

Mechanism of action:
Reduces intestinal absorption of starch and dextrin by inhibiting the action of α-glucosidase in intestinal brush border.
Clinical use:

- The agents are effective by themselves only in the earliest stages of impaired glucose tolerance, but can be helpful in combination with other agents in type 2 diabetes.
These medications are rarely used in the United States because of the severity of their side effects (flatulence and bloating). They are more commonly prescribed in Europe.

They do have the potential to cause weight loss by lowering the amount of sugar metabolized.
Overview of insulin secretion

Incretin mimetics

- **Incretins** are insulin *secretagogues*.
- The main candidate molecules that fulfill criteria for being an incretin are *Glucagon-like peptide-1* (GLP-1).
- GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4).
Glucagon-like peptide (GLP) analogs

- GLP agonists bind to a membrane GLP receptor.

- As a consequence of this, insulin release from the pancreatic beta cells is increased.

Injectable medication: Exenatide
Glucagon-like peptide (GLP) analogs

- **Exenatide** (also Exendin-4, marketed as Byetta) is the first GLP agonist approved for the treatment of type 2 diabetes.

- Exenatide is not an analogue of GLP, but rather a GLP agonist.

- It is an **injectable** medication.
Glucagon-like peptide (GLP) analogs

- These agents may also cause a decrease in gastric motility, responsible for the common side effect of nausea, and is probably the mechanism by which weight loss occurs.
DPP-4 inhibitors

Sitagliptin:

- an inhibitor of dipeptidyl peptidase-4 (DPP-4), the enzyme that degrades incretin and other GLP-1-like molecules.
- increase blood concentration of the incretin GLP-1
- This drug appears likely to be approved for use in type 2 diabetes.
Amylin analogues

- Amylin agonist analogues slow gastric emptying and suppress glucagon.
- As of 2007, pramlintide is the only clinically available amylin analogue.
- Like insulin, it is administered by subcutaneous injection.
- The most frequent and severe adverse effect of pramlintide is nausea, which occurs mostly at the beginning of treatment and gradually reduces.

Pramlintide
Injectable medication