Let’s Learn about Diabetes
GLUCOSE UPTAKE

FACILITATED DIFFUSION

Glucose

“IMPERMEABLE”

Glucose

GK = glucokinase

Glucose-6-phosphate

“TRAPPED”
Glucose Transporters

**GLUT1**
Medium affinity
(1-2 mM)
*Basal uptake*

**GLUT2**
LOW affinity
(15-20 mM)
*METABOLIC REGULATION*

**GLUT3**
HIGH affinity
(<1 mM)
*Important during HYPOGLYCEMIA*

**GLUT4**
Medium affinity
(5 mM)

**GLUT5**
Medium affinity
(1-2 mM)
*FRUCTOSE transporter*
INSULIN RELEASE

Glucose

GLUT2

GK

Glycolysis

ATP

Vesicle fusion

Insulin Release

β cell

Closing of Potassium (K_{IR}) channel

K^+

KIR

Depolarization

-70 mV

ΔΨ

-30 mV

VDCC

Insulin Release

Ca^{++}

Glucose

GLUT2

GK

Glycolysis

ATP

Vesicle fusion

Insulin Release

β cell

Closing of Potassium (K_{IR}) channel

K^+

KIR

Depolarization

-70 mV

ΔΨ

-30 mV

VDCC

Insulin Release

Ca^{++}
**INSULIN RELEASE**

Electrochemical Gradients

1. Ion concentration

<table>
<thead>
<tr>
<th>out</th>
<th>Na⁺</th>
<th>K⁺</th>
<th>Ca²⁺</th>
</tr>
</thead>
<tbody>
<tr>
<td>in</td>
<td>Na⁺</td>
<td>K⁺</td>
<td>Ca²⁺</td>
</tr>
</tbody>
</table>

2. Potential difference (voltage)

\[ \Delta V = -70 \text{ mV} \]

1 + 2 = electrochemical gradient (driving force)
**INSULIN RELEASE**

**Electrochemical Gradients**

**Step 1. Depolarization**

Voltage gated $K^+$ channel (open when depolarized)

- $-70$ mV

- $+40$ mV

**Step 2. Repolarization**

Voltage gated $K^+$ channel (open when depolarized)

- $+40$ mV

- $-70$ mV
INSULIN RELEASE
Electrochemical Gradients

Some channels are open when a cell is AT REST (-70 mV)
K⁺ATP channel (KIR) – Potassium Inward Rectifier

K⁺ IF > - 70 mV, THEN K⁺ flows OUT

K⁺ KIR keeps the cell near K⁺ eq. potential

K⁺ IF < - 70 mV, THEN K⁺ flows IN
INSULIN RELEASE
Electrochemical Gradients

1. **ATP CLOSES** the KIR POTASSIUM CHANNEL

2. $K^+$ builds up inside and membrane potential increases, **VOLTAGE CLIMBS**

3. When -30 mV is reached, $Ca^{2+}$ channels open, causing **INSULIN RELEASE**
**INSULIN RELEASE**

**Electrochemical Gradients**

**Hypokalemia (LOW blood K⁺)** INHIBITS insulin release

**Q. HOW?**

**A.** Because it “hyperpolarizes” the cell membrane

(more negative, -80 mV instead of -70 mV)

---

**Normal**

-70 mV

\[
\text{K}^+ \quad + \quad -
\]

**Hypo-K**

-80 mV

\[
\text{low K}^+ \quad + \quad -
\]

More outward flow of K⁺ ions through KIR

(more driving force)
CARBOHYDRATE METABOLISM

**METABOLIC PATHWAY:**

- **Glycolysis**: glucose breakdown
- **Glycogenesis**: glycogen synthesis
- **Gluconeogenesis**: new glucose synthesis
- **Glycogenolysis**: glycogen breakdown

**EFFECT OF INSULIN:**

- Blood Glucose
ANABOLIC HORMONE

A. REMOVES from the circulation...
B. USES or SAVES FOR LATER (stores)...
  • Fats (as Triglycerides)
  • Amino acids (as Proteins)
  • Glucose (as Glycogen or TG)
GLUCOSE UPTAKE/UTILIZATION

EFFECT OF INSULIN

- **Glycolysis**
  - Pyruvate $\rightarrow$ Acetyl-CoA
  - CO$_2$

- **Citric acid cycle**
  - CO$_2$

Glucose $\rightarrow$ Glucose-6 phosphate

- **Uptake**
  - GK
  - STIMULATES

**BLOOD**

- Glucose

= energy-producing steps in metabolism
make: NADH$+H^+$, ATP, GTP
GLUCOSE UPTAKE/STORAGE

**EFFECT OF INSULIN**

- Glucose uptake
  - GK stimulantes
  - Glucose-6 phosphate
  - Glycogen synthesis
    - GS = Glycogen synthase

Blood → Cell

GLUCOSE UPTAKE/STORAGE

BLOOD GLUCOSE

GLYCOGEN → Glycogen
GLUCOSE RELEASE/SYNTHESIS

EFFECT OF INSULIN

GLUCOSE INHIBITS

Gluconeogenesis INHIBITS

Pyruvate → Glucose-6 phosphate → Glucose → Glycogen

BLOOD GLUCOSE

Glycogenolysis INHIBITS

Glycogen → Glucose-1 phosphate → GP → Glucose

GP = Glycogen phosphorylase
LIPID METABOLISM

**METABOLIC PATHWAY:**

**INSULIN STIMULATES**
- Lipogenesis
- FA Synthesis
- new FAs (from glucose)

**INSULIN INHIBITS**
- β-Oxidation
- FA breakdown
- Lipolysis
- TG breakdown (into FFA)

**EFFECT OF INSULIN:**
- TISSUE FAT STORES
FATTY ACID UTILIZATION

KETONE BODIES

- Acetone
- Acetoacetate
- β-OH-butyrate

EFFECT OF INSULIN

Citric acid cycle

β-oxidation INHIBITS

FASTING energy source

Acetyl-CoA

Citric acid cycle

CO₂
FATTY ACID STORAGE

EFFECT OF INSULIN

Fatty Acid Synthesis

STIMULATES

Lipoprotein Breakdown

STIMULATES

TRIGLYCERIDES

FAS = Fatty acid synthase

LPL = Lipoprotein lipase
TRIGLYCERIDE UTILIZATION

FREE FATTY ACIDS

Fatty acids

HSL $\downarrow$ Lipolysis $\uparrow$ INHIBITS

HSL = Hormone sensitive lipase

TRIGLYCERIDE UTILIZATION

TISSUE FAT STORES

EFFECT OF INSULIN
INSULIN SUMMARY

INSULIN

STIMULATES

GLUCOSE STORAGE

GLUCOSE AS AN ENERGY SOURCE

FAT (TG) STORAGE

INHIBITS

GLUCOSE PRODUCTION

TG, FA BREAKDOWN

KETONE BODIES

INSULIN EFFECTS:

\[\downarrow\text{BLOOD GLUCOSE}\]

\[\downarrow\text{BLOOD FFA and LIPOPROTEINS}\]

\[\uparrow\text{TISSUE FAT STORES}\]

\[\uparrow\text{LIVER/MUSCLE GLYCOGEN STORES}\]
INSULIN SIGNALING

How does this insulin receptor (when activated by insulin) change sugar and fat metabolism?

INSULIN RECEPTOR

\[ \text{cAMP} \]
\[ \text{PIP}_3 \]
\[ \text{AMP} \]

Gene expression

Intracellular second messengers

HOW DO THESE AFFECT CELL PHYSIOLOGY?
1. Insulin **ACTIVATES** PI3 kinase (PI3K)

**INSULIN SIGNALING**

EFFECT OF INSULIN

PIP$_3$ ↑

3-position

PIP$_2$  

PIP$_3$
2. Insulin **ACTIVATES** Phosphodiesterase (PDE)

EFFECT OF INSULIN

- **cAMP** $\rightarrow$ PDE $\rightarrow$ **AMP**

- **cAMP** ↓
- **AMP** ↑
INSULIN SIGNALING

3. Insulin **ACTIVATES** Gene Expression
**INSULIN SIGNALING**

**GLUCOSE UPTAKE**

- Glucose
- GLUT4
- PIP_2 → PI3K → PIP_3 → PLC → DAG → IP_3 → Vesicle fusion → Endoplasmic Reticulum → Ca^{2+} → Nucleus GLUT4 Gene
- Glucose uptake

**GLUCOSE UPTAKE**

- PI3K
- PIP_2
- PIP_3
- PLC
- DAG
- IP_3
- Vesicle fusion
- Endoplasmic Reticulum
- Ca^{2+}
- Nucleus
- GLUT4 Gene
INSULIN SIGNALING

CARB STORAGE

Akt

Akt is MORE active

GSK-3

Glycogen synthase kinase-3 is LESS active

GS

INACTIVE

GS

ACTIVE

Glycogen synthase is MORE active

Glycogenesis

G6P ➞ G1P ➞ UDP-Glucose ➞ GS ➞ Glycogen
INSULIN SIGNALING

GENE
EXPRESSION

MORE GLYCOLYSIS ENZYMES:

• Glucokinase (GK)
• Phosphofructokinase (PFK)
• Pyruvate kinase (PK)

Glucose-6 phosphate → Acetyl-CoA
INSULIN SIGNALING

MORE FA SYNTHESIS ENZYMES:

- Acetyl CoA carbonyltransferase (ACC)
- Fatty acid synthase (FAS)

\[
\text{Acetyl-CoA} \rightarrow \rightarrow \rightarrow \text{Fatty acids}
\]
Can too many carbs make you fat?

**INSULIN SIGNALING**

YES, and insulin is partly to blame
WHAT HAPPENS IN DIABETES:
• HIGH SERUM LIPIDS, FATTY LIVER
• KETONE BODIES (TYPE 1)
INSULIN SIGNALING

MORE LDL UPTAKE

PI3K → PIP₃ → PLC → DAG → IP₃ → 

Endoplasmic Reticulum → Ca²⁺

CD36 (oxLDL receptor) → LDL-R (LDL receptor)

Vesicle fusion
**INSULIN SIGNALING**

MORE CHOLESTEROL SYNTHESIS

**cAMP** → **PDE** → **AMP**

MORE AMP

**AMPK** → **HMG-CoAR**

HMG-CoA Reductase MORE active

Mevalonate → Cholesterol

INSULIN SIGNALING

PROTEIN SYNTHESIS

Akt

Akt MORE active

PI3K

PIP$_2$ → PIP$_3$

PIP$_2$ → PIP$_3$

Akt

Akt MORE active

PIP$_3$

Akt

Akt MORE active

mTOR

eIF2α

eIF2α

eIF2α

eIF2α

GTP

GTP

GDP

GDP

INACTIVE

ACTIVE

eIF2α = eukaryotic initiation factor 2 alpha

mTOR = mammalian target of rapamycin

MORE PROTEIN SYNTHESIS (insulin is anabolic)
DIABETES ETIOLOGY AND SYMPTOMS

**TYPE 1** – Insulin **DEFICIENCY** (β-cell death)
**TYPE 2** – Insulin **RESISTANCE** (i.e. insensitivity)

YOU CAN NOW EXPLAIN HOW THESE HAPPEN:

1. High blood glucose (urinary glucose)
2. High serum triglycerides and FFA
3. High LDL/Low HDL (NOT hypercholesterolemia)

Also (Type 1 DM):

4. Ketone bodies (acetone breath)
5. Weight loss (muscle mass)
6. Reduced cholesterol synthesis* (but higher absorption of dietary cholesterol to compensate)

Type 1: ONLY pharmaceutical option
Type 2: If drugs, diet changes fail

Insulin is a PROTEIN

Proteins are digested in the GI tract
Insulin is NOT an effective oral drug
Insulin is TYPICALLY injected

RAPID, SHORT, INTERMEDIATE, LONG, ULTRA-LONG
RAPID-Acting
Recombinant, small mutations from human sequence disrupt interactions between proteins, make crystals less stable – allow for FASTER dissolution

COMPOSITION:

**Aspart** (Novolog® – Novo Nordisk) – SQ, IV, PUMP
Mutation P28D in B chain

**Lispro** (Humalog® – Eli Lilly) – SQ, IV, PUMP
2 amino acids (Lys, Pro) transposed in B chain

**Glulisine** (Apidra® – Sanofi-Aventis) – SQ, IV, PUMP
2 Mutations N3K and K29E in B chain
DIABETES PHARMACOTHERAPY
EXOGENOUS INSULIN

RAPID-Acting

USE: POSTPRANDIAL or ACUTE Hyperglycemia
ONSET: 5-15 min*
PEAK: 30-90 min
DURATION: 3-5 h

* values for onset, peak, duration come from the NIDDK publication “What I need to know about Diabetes Medicines”
EXOGENOUS INSULIN

SHORT-Acting

Insulin Regular

(Humulin® R – Eli Lilly) – IV, SQ
(Novolin® R – Novo Nordisk) – IV

COMPOSITION: Unmodified zinc insulin crystals
USE: BASAL insulin maintenance and/or
OVERNIGHT coverage
ONSET: 30-60 min
PEAK: 2-4 h
DURATION: 5-8 h
DIABETES PHARMACOTHERAPY

EXOGENOUS INSULIN

INTERMEDIATE-Acting

Isophane Insulin

a.k.a. NPH (Neutral Protamine Hagedorn)

(Humulin® N – Eli Lilly) – SQ
(Novolin® N – Novo Nordisk) – SQ

COMPOSITION: Protamine zinc insulin + PO$_4^{3-}$ buffer

USE: BASAL insulin maintenance and/or

OVERNIGHT coverage

ONSET: 1-3 h

PEAK: 8 h

DURATION: 12-16 h
LONG-Acting

Recombinant, small mutations from human sequence change pharmacokinetics to prolong half-life

COMPOSITION:

Detemir (Levemir® – Novo Nordisk)
  ▪ L (Lys) 29 in B chain is myristoylated (lipid)
    (BINDS strongly to albumin)

Glargine (Lantus® – Sanofi-Aventis)
  ▪ G21N in A chain; Two additional R (Arg) in B chain
  Enhances crystal stability, change pKa of insulin
  low pH (4) = soluble, pH (7) = insoluble
  (Slows dissolution)
LONG-Acting

USE: BASAL insulin maintenance (1-2 INJ daily)

ONSET: 1 h

PEAK:
  - Detemir (Peakless)
  - Glargine (Peakless)

DURATION: 20-26 h
ULTRA-LONG-Acting
Recombinant, small mutations from human sequence change pharmacokinetics (binding to albumin, or slower dissolution) to prolong half-life

COMPOSITION:
Degludec (Tresiba® – Novo Nordisk)
- L (Lys) 29 in B chain is conjugated to hexadecadienoic acid (16-carbon lipid) (BINDS strongly to albumin)
- R (Thr) 30 in B chain is deleted.
DIABETES PHARMACOTHERAPY

EXOGENOUS INSULIN

ULTRA-LONG-Acting

USE: BASAL insulin maintenance (1 INJ daily)

ONSET: 1 h

PEAK:

Degludec (Peakless)

DURATION: up to 42 h
“Peakless” = Detemir, Glargine, Degludec

Katzung, 2009
EXOGENOUS INSULIN

INSULIN MIXES

PROPERTIES: SQ INJ

Quick onset of rapid-acting insulin (5-15 min)
+ Longer duration of isophane (10-12 h)

RAPID + INTERMEDIATE:

Isophane (Humulin N) + Lispro
  = Humalog® 50/50 or 75/25

Isophane (Novolin N) + Aspart
  = Novalog® 70/30
EXOGENOUS INSULIN

INSULIN MIXES

PROPERTIES: SQ INJ

Short onset of regular insulin (30-60 min)
+ Longer duration of isophane (10-12 h)

SHORT + INTERMEDIATE:

Isophane (Humulin N) + Insulin Regular
= Humulin® 70/30

Isophane (Novolin N) + Insulin Regular
= Novolin® 70/30
INHALED Insulin

FIRST ATTEMPT

Exubera – DISCONTINUED (Pfizer)
- Dry 1-5 μm insulin particles
- Discontinued 1 year after release (in 2007)
- Poor sales + Lung cancer risk?
INHALED Insulin

2014 APPROVAL
Afrezza – Sanofi/Afrezza
“technosphere” crystals

ONSET: 5-15 min
DURATION: 2.5 – 3 hours
PEAK: 15 min

BLACK BOX WARNING:
Risk of acute bronchospasm in patients with chronic lung disease (COPD, Asthma)
MAJOR adverse effect: HYPOGLYCEMIA!

OTHER ADVERSE EFFECTS:

• Lipodystrophy: SQ Injection site reactions (fat dimples)
• Insulin resistance: IgG antibodies, can neutralize the action of insulin (usually only a small effect)
• Allergic reactions: Immediate type hypersensitivity, rare, local or systemic urticaria (hives) due to histamine release from mast cells sensitized by anti-insulin IgE antibodies. Anaphylaxis may result!
• Hypokaleemia (next slide)
Why? Insulin stimulates $\text{Na}^+/\text{K}^+$ ATP Pump
Emergency Insulin Administration can cause HYPOKALEMIA (and EKG abnormalities)

BUT, IT IS USEFUL TOO: EMERGENCY HYPERKALEMIA TREATMENT:
Insulin + furosemide + glucose
(glucose given to prevent hypoglycemic shock)
Amylin

Pancreatic hormone synthesized by \( \beta \)-cells
Secreted along with insulin (about 1%)

- **ENHANCES INSULIN SENSITIVITY**
- **INHIBITS GLUCAGON SECRETION**

Amyloid protein – toxic actions (similar to A\( \beta \))?
Major component of diabetes-associated \( \beta \)-cell amyloid deposits!

Does not sound like good drug.
How to get around this problem?
DIABETES PHARMACOTHERAPY

AMYLIN ANALOGS

Pramlintide (Symlin®)

Human Amylin: (amyloidogenic)
KCNTATCATQRLANFLVHSSNNFGAILSTNVGSNTY

Rat Amylin: (NON-amyloidogenic)
KCNTATCATQRLANFLVRSNNFGPVLPPTNVGSNTY

Pramlintide: (NON-amyloidogenic)
KCNTATCATQRLANFLVHSSNNFGPILPPTNVGSNTY
AMYLIN ANALOGS

Pramlintide (Symlin®)

ONSET: Rapid
PEAK: 20 min
DURATION: 3 h

ADMIN: Taken BEFORE meals (INJ)
DANGER: Co-administration w/insulin may cause SEVERE HYPOGLYCEMIA!
DIABETES PHARMACOTHERAPY

AMYLIN ANALOGS

Pramlintide (Symlin®)

ADVERSE EFFECTS:
• GI: nausea, vomiting, diarrhea, anorexia
• Severe hypoglycemia (BLACK BOX WARNING)
  (especially if used together with insulin in type 1 diabetes patients)

DRUG INTERACTIONS: enhances effects of anticholinergic drugs in GI tract (i.e. CONSTIPATION)
INCRETINS = Gastric inhibitory peptide (GIP) and Glucagon-like peptide-1 (GLP-1) (both are intestinal hormones)

PROMOTE:
- \( \beta \)-cell proliferation
- INSULIN SYNTHESIS
- GLUCOSE-DEPENDENT insulin secretion
  (does NOT cause insulin secretion alone)

INHIBIT:
- Glucagon secretion

GLP-1 half-life = 2 min, GIP half-life = 7 min
(TOO SHORT to use as drugs!)
GLP-1 RECEPTOR AGONISTS:
Exenatide, Liraglutide, Albiglutide, Dulaglutide

MAIN ACTIONS:
• Enhance pancreatic insulin synthesis
• “Glucose-dependent insulinotropism”
  Glucose-dependent insulin secretion
  (do NOT cause insulin secretion alone)
Exenatide (Byetta®) Recombinant form of exendin-4 Protein from Gila monster saliva Only 53% homology to GLP-1, but still has GLP-1-like actions.

Exendin-4 is NOT GLP-1, but IS A RECEPTOR AGONIST

Half-life = 2.4 hr in circulation (Taken TWICE DAILY)

Exenatide (Byetta®)

ADMIN: Taken BEFORE meals (INJ)

ADVERSE EFFECTS:
- GI: nausea, vomiting, diarrhea, anorexia
- Neutralizing antibodies (IgG) – 6% of patients (causes attenuated drug response)

POTENTIAL SERIOUS EFFECTS:
- Some cases of acute pancreatitis
- Possible link to thyroid cancer
Exenatide (Byetta®)

LOWER RISK of hypoglycemia than Pramlintide

Why? **Glucose-dependent insulinotropism**

The ability of an agent to enhance insulin secretion from the pancreas only during euglycemia (normal blood sugar) or during hyperglycemia, but **NOT** during hypoglycemia
Liraglutide (Victoza®)

Lipid-modified GLP-1 (recombinant)
- Rapidly absorbed, but lipid group binds to albumin (similar idea as Insulin Detemir – also Novo Nordisk)
- Half-life = 11-15 hr in circulation (Taken DAILY)

BLACK BOX: (ALL GLP-1 AGONISTS)
Possible link to medullary thyroid cancer = Calcitonin-secreting tumors of the Parafollicular C-cells
Albiglutide (Tanzeum®) 

Albumin-conjugated GLP-1 (recombinant) 

TWO GLP-1 MOLECULES (amino acids 1-30) 
• Covalently attached to albumin 
• Mutated to make it resistant to DPP-4 
• Half-life = 4-7 DAYS in circulation!
Dulaglutide (Trulicity®)  

IgG4-conjugated GLP-1 (recombinant)  
TWO GLP-1 MOLECULES (amino acids 7-37)  
• Covalently attached to Fc domain of IgG4  
• Also resistant to DPP-4  
• **Half-life** = 4-7 DAYS in circulation!
ORAL ANTIDIABETICS

α-Glucosidase Inhibitors
- Acarbose
- Miglitol

Sulfonylureas
- Chlorpropamide
- Glimepiride
- Glipizide
- Glyburide
- Tolazamide
- Tolbutamide

Meglitinides
- Nateglinide
- Repaglinide

Biguanides
- Metformin

Thiazolidinediones
- Pioglitazone
- Rosiglitazone

DPP-4 Inhibitors
- Alogliptin
- Linagliptin
- Saxagliptin
- Sitagliptin

SGLT2 Inhibitors
- Canagliflozin
- Dapagliflozin
- Empagliflozin
DIABETES PHARMACOTHERAPY

$\alpha$-GLUCOSIDASE INHIBITORS

Acarbose (Precose®)
Miglitol (Glyset®)

$\alpha$-Glucosidases:
Pancreatic amylase
Maltase
Isomaltase
Sucrase
Glucoamylase

STARCHES (disaccharides)

SIMPLE SUGARS (glucose)

small intestine
### DIABETES PHARMACOTHERAPY

**α-GLUCOSIDASE INHIBITORS**

<table>
<thead>
<tr>
<th>P-KINETICS</th>
<th>Acarbose</th>
<th>Miglitol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Active drug <strong>NOT ABSORBED</strong> but some inactive metabolites made in gut are absorbed</td>
<td><strong>COMPLETE ABSORPTION</strong></td>
</tr>
<tr>
<td>Metabolism</td>
<td>GI TRACT metabolism by gut bacteria, digestive enzymes</td>
<td><strong>NO metabolism</strong></td>
</tr>
<tr>
<td>Elimination</td>
<td>2 hr</td>
<td>2 hr</td>
</tr>
<tr>
<td>Excretion</td>
<td>Urine + Feces</td>
<td>Urine (unchanged)</td>
</tr>
</tbody>
</table>
ADVERSE EFFECTS
Flatulence, bloating, abdominal cramps, diarrhea
(GAS released by bacteria fermenting undigested carbohydrates that reach the colon)
Lessens with continued use
Contraindicated in IBD
# DIABETES PHARMACOTHERAPY

## SULFONYLUREAS

<table>
<thead>
<tr>
<th>LOWER POTENCY</th>
<th>HIGHER POTENCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>(high mg – gram doses)</td>
<td>(low – mid mg doses)</td>
</tr>
<tr>
<td>(1950’s-80’s)</td>
<td>(1980’s-90’s)</td>
</tr>
</tbody>
</table>

### 1st GENERATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpropamide</td>
<td>Diabinese®</td>
</tr>
<tr>
<td>Tolazamide</td>
<td>Tolinase®</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Orinase®</td>
</tr>
</tbody>
</table>

### 2nd GENERATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide</td>
<td>Dibeta®, Micronase®, etc.</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Glucotrol®</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Amaryl®</td>
</tr>
</tbody>
</table>
MECHANISMS

Sulfonylurea receptor (SUR) + Inwardly rectifying potassium channel (Kir 6.2)

Sulfonylurea binding site

SULFONYLUREAS

MECHANISMS

**PRIMARY** – Cause pancreatic INSULIN RELEASE by inhibiting the *sulfonylurea receptor* (KIR inhibition)

**SECONDARY**

*Other mechanisms include:*

↑ Peripheral insulin receptors  
(INCREASE INSULIN SENSITIVITY)

↓ INHIBIT GLUCOSE RELEASE from liver

↓ INHIBIT GLUCAGON SECRETION
DIABETES PHARMACOTHERAPY
SULFONYLUREAS

P-KINETICS

ABSORPTION: GOOD, but...
- SLOWED BY FOOD
- SLOWED BY HYPERGLYCEMIA
  (both slow gastric and intestinal motility)

PROTEIN BINDING: HIGH (90-99%),
mainly to albumin (e.g. Glyburide > 99% bound)

Similar LOW VOLUME of DISTRIBUTION 10-20 liters
(due mainly to high serum protein binding)
P-KINETICS

METABOLISM: HEPATIC by CYP2C9
(except Tolazamide)

HALF-LIVES

Glipizide: 3-5 hr
Tolazamide, Tolbutamide: 4-7 hr
Glyburide, Glimerpiride: 5-10 hr
Chlorpropamamide: 24-48 hr
ADVERSE EFFECTS

Sulfonylureas are usually WELL TOLERATED (older drugs cause GI upset and fatigue)

• HYPOGLYCEMIA
  
  does **NOT** seem to relate to drug half-life:
  
  Glyburide (5-10 hr): 20-30% incidence
  Glimepiride (5-10 hr): 4% incidence

• WEIGHT GAIN (increased insulin secretion, sensitivity)
ADVERSE EFFECTS

CROSS-SENSITIVITY to other sulfur-containing drugs:

• Sulfonamides
• Carbonic anhydrase inhibitors
• Thiazide diuretics
• Loop diuretics (some, incl. Furosemide)
DRUG INTERACTIONS

STRONG CYP2C9 Inhibitors – Less sulfonylurea metabolism
Combination may increase risk of hypoglycemia
(Except tolazamide)

Disulfiram-like reaction
Avoid excessive ALCOHOL
(worst offender is chlorpropamide)

LASTLY...they are cheap
# DIABETES PHARMACOTHERAPY

## MEGLITINIDES

### MECHANISM
- Inhibit the **sulfonylurea receptor** (KIR inhibition)

<table>
<thead>
<tr>
<th></th>
<th>Nateglinide (Starlix®)</th>
<th>Repaglinide (Prandin®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption:</strong></td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td><strong>Bioavailability:</strong></td>
<td>73%</td>
<td>56%</td>
</tr>
<tr>
<td><strong>Protein binding:</strong></td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td><strong>Duration:</strong></td>
<td>4 hr</td>
<td>4-6 hr</td>
</tr>
<tr>
<td><strong>Metabolism:</strong></td>
<td>CYP&lt;sub&gt;2C9&lt;/sub&gt; + 3A4</td>
<td>CYP&lt;sub&gt;2C8&lt;/sub&gt; + 3A4</td>
</tr>
<tr>
<td><strong>Half-life:</strong></td>
<td>1.5 hr</td>
<td>1 hr</td>
</tr>
<tr>
<td><strong>Excretion:</strong></td>
<td>URINE (83%)</td>
<td>FECES (90%)</td>
</tr>
</tbody>
</table>

---

**Diagram:**
- ATP
- Meglitinides

**Legend:**
- ATP
- Meglitinides
ADVERSE EFFECTS

Hypoglycemia
Weight gain

DRUG INTERACTIONS

STRONG CYP 2C8 Inhibitors – ↑ Repaglinide levels
STRONG CYP 2C9 Inhibitors – ↑ Nateglinide levels
STRONG CYP 3A4 Inhibitors – ↑ EITHER DRUG
Metformin (Glucophage®, etc.) – introduced 1957!

“EUGLYCEMIC” Effect:

• Promotes glucose and lipid homeostasis
  - INHIBITS gluconeogenesis in the liver
  - INCREASES glycogen synthesis
  - INHIBITS lipolysis (TG breakdown)
  - INHIBITS fatty acid biosynthesis in the liver
    \[\text{(OPPOSITE to insulin!)}\] – less fatty liver
    \[\text{in T2DM} = \text{“healthier” liver}\]

• Does \underline{NOT} cause insulin secretion
  - LOW risk of hypoglycemia
DIABETES PHARMACOTHERAPY

BIGUANIDES

Metformin (Glucophage®, etc.)

PROPOSED MECHANISM:

Activates AMPK (like insulin)

```
cAMP → PDE → AMP
   ↓
Insulin
   ↓
Metformin
   ↓
AMPK

"Glucose and Lipid Homeostasis"
```
Metformin

**P-KINETICS**

**ADMIN:** ORAL
**BIOAvailability:** 50%
**DISTRIBUTion:** HIGH ~1000 L (accumulates in RBC)
**PROTEIN BINDING:** NONE
**METABOLISM:** NONE
**HALF-LIFE:** 1.5-3 hours
**EXCRETION:** URINE (unchanged)
Metformin

ADVERSE EFFECTS

COMMON: Diarrhea, nausea, fatigue

RARE, SERIOUS:
- Megaloblastic anemia  
  (Inhibits B$_{12}$ absorption)
- Lactic Acidosis (Avoid use in alcoholics)

OTHER NOTABLE PROPERTIES

- Does **NOT** tend to cause hypoglycemia
- Does **NOT** tend to cause weight gain
WHY does Metformin cause LA?
Blame it on the CORI CYCLE

LACTIC ACIDOSIS

\[
\text{NAD}^+ \rightarrow \text{NADH} + H^+ \\
\text{NADH} + H^+ \rightarrow \text{pyruvate} \\
\text{pyruvate} \rightarrow \text{lactate} \\
\text{lactate} \rightarrow \text{NAD}^+ + 2\text{NADH} + 2H^+ \\
\text{NADH} + H^+ \rightarrow \text{NAD}^+ \\
\text{NAD}^+ \rightarrow \text{Glycolysis} \\
\text{Glycolysis} \rightarrow \text{Glucose} \\
\text{Gluconeogenesis} \\
\]

Metformin

\[
\text{citric acid cycle} \quad \text{low O}_2 \text{ (anaerobic)}
\]


**DIABETES PHARMACOTHERAPY**

**THIAZOLIDINEDIONES**

PPAR-gamma

Target Tissues

Promotes

**GLUCOSE homeostasis:**

**INSULIN RECEPTOR**

**ALSO promotes**

**FAT sequestration:**

**CD36 ‘SCAVENGER’ RECEPTOR**

**LIPOPROTEIN LIPASE (LPL)**
DIABETES PHARMACOTHERAPY

THIAZOLIDINEDIONES

ENDOGENOUS PPAR-γ Ligands???

• 15-deoxy-Δ^{12,14}-Prostaglandin J_{2}
• Prostacyclin (PGI_{2})
• 9-HODE, 13-HODE
• 9-Nitrolinoleic acid

PHARMACEUTICAL PPAR-γ Ligands

Pioglitazone (Actos®) - Takeda
Rosiglitazone (Avandia®) - GSK (restricted use)

Pharmaceutical ligands have MUCH higher affinity
THIAZOLIDINEDIONES

Pioglitazone, Rosiglitazone

P-KINETICS

ADMIN: ORAL

BIOAVAILABILITY: Pioglitazone (80%) Rosiglitazone (99%)
TIME TO PEAK LEVEL: 1-2 hr (slowed by food)
DISTRIBUTION: LOW about 15L (HIGH protein binding)
METABOLISM: hepatic (CYP2C8)
HALF-LIFE: 3-5 hr
DURATION: LONGER – Gene expression
EXCRETION: BOTH urine and feces
DIABETES PHARMACOTHERAPY

THIAZOLIDINEDIONES

ADVERSE EFFECTS

1. WEIGHT GAIN
2. BONE FRACTURE

ADVERSE EFFECTS

3. Congestive Heart Failure (CHF)

More Vascular Permeability

Renal Perfusion Pressure (Less sodium loss)

→ EDEMA

May add diuretics to prevent edema (i.e. spironolactone)

4. HEART ATTACK and STROKE
DPP-4 INHIBITORS

Dipeptidyl Peptidase-4

Integral membrane glycoprotein PROTEASE found on the surface of many cells

Large variety of substrates DEGRADES INCRETINS (GLP-1, GIP)
Normal incretin \( t_{1/2} = 2 \text{ min in circulation} \)

INHIBITING DPP-4 means:

\[ \uparrow \text{ LEVELS of ENDOGENOUS INCRETINS} \]
### DIABETES PHARMACOTHERAPY

#### DPP-4 INHIBITORS

<table>
<thead>
<tr>
<th>Year</th>
<th>Company</th>
<th>Drug Name</th>
<th>2006</th>
<th>2009</th>
<th>2011</th>
<th>2013</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MSD</td>
<td>Sitagliptin (Januvia®)</td>
<td>87%</td>
<td>75%</td>
<td>30%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>200 L</td>
<td>200 L</td>
<td>1,100 L</td>
<td>420 L</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PB</td>
<td>40%</td>
<td>0%</td>
<td>80-99%</td>
<td>20%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MINOR</td>
<td>CYP3A4</td>
<td>MINOR</td>
<td>MINOR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HL</td>
<td>8-12 h</td>
<td>2-3 h</td>
<td>&gt;100 h</td>
<td>12-24 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E</td>
<td>URINE</td>
<td>URINE</td>
<td>HEPATIC</td>
<td>URINE</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>unchanged</td>
<td>metabolite</td>
<td>unchanged</td>
<td>most unchanged</td>
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</tbody>
</table>

(1/2 as active)

(unique differences in **RED**)

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DIABETES PHARMACOTHERAPY

DPP-4 INHIBITORS

NATURAL DPP-4 Inhibitors

**Berberine**

*Hydrastis canadensis* (Goldenseal*)

*Berberis vulgaris* (European barberry)

*CYP3A4 inhibitor!*
SGLT2 INHIBITORS

Canagliflozin (Invokana®) – 2013
Dapagliflozin (Farxiga®) – 2014
Empagliflozin (Jardiance®) – 2014

MOA: ↑ Glucose excretion in urine
SGLT2 INHIBITORS

P-KINETICS

ADMIN: ORAL
BIOAVAILABILITY: for Canagliflozin = 65%
METABOLISM: hepatic glucuronidation
HALF-LIFE: 10-13 hr
EXCRETION: BOTH urine and feces

ADVERSE EFFECTS

- Increased urination
- Ketoacidosis