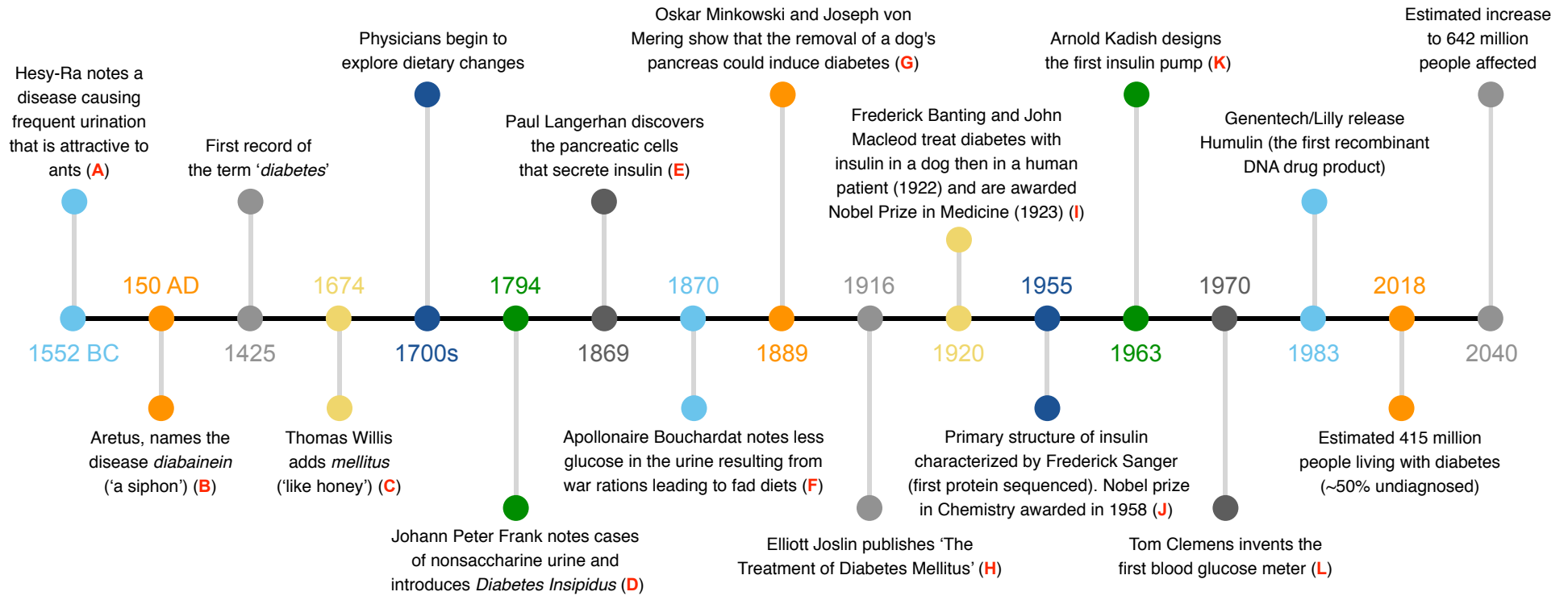
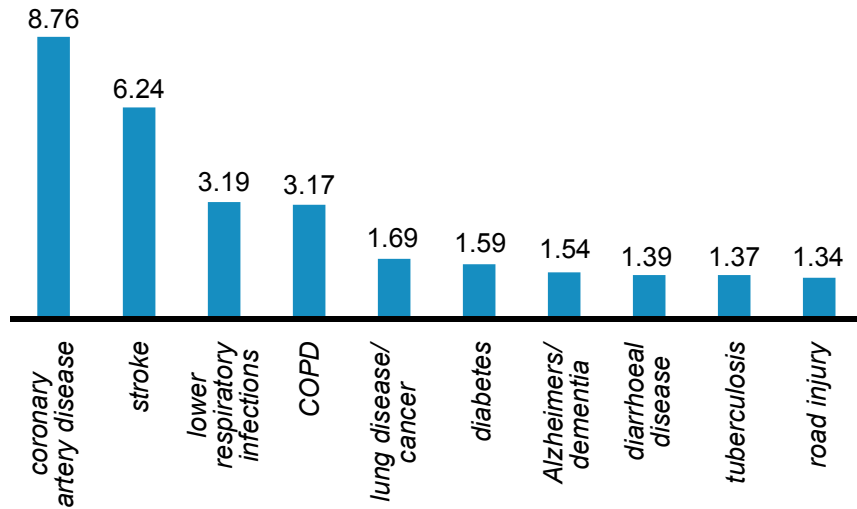


Treatment of Diabetes

Cian Kingston, 2018



Leading causes of death in 2015 (WHO global estimates in millions)



30 million cases of diabetes cost the US public more than \$245 billion annually.

Diabetes insipidus

Definition: Set of incurable hormone deficiencies

Incidence: 3 in 100,000

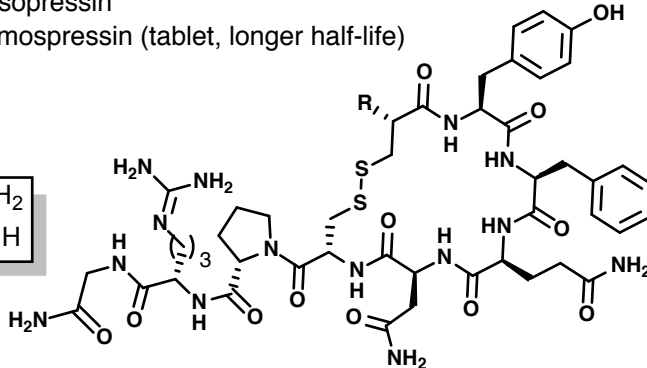
Symptoms: Excess urination (polyuria up to 20L a day) and thirst (polydipsia), no effect on the glucose levels

Complications: Dehydration, seizures etc.

Types: Four main including central DI results from insufficient production of the antidiuretic hormone vasopressin

Treatment of CDI: Desmopressin (tablet, longer half-life)

Vasopressin: R = NH₂
Desmopressin: R = H



1955 Nobel prize in Chemistry awarded to Vincent du Vigneaud for synthesis of polypeptide hormones (including vasopressin)

Diabetes mellitus

Definition: Set of incurable metabolic disorders characterized by hyperglycemia (excessive glucose in the blood)

Incidence: 770 in 100,000

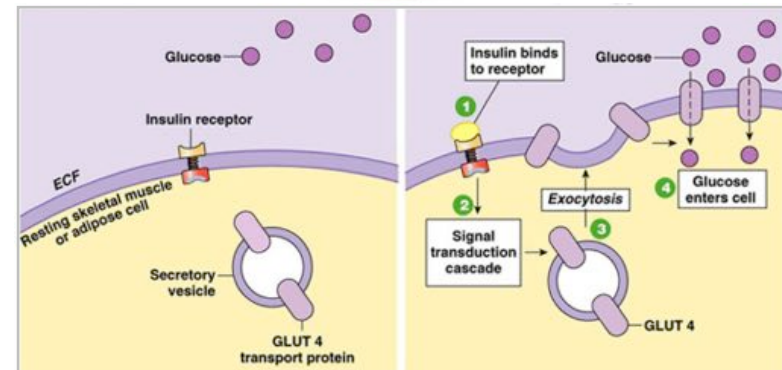
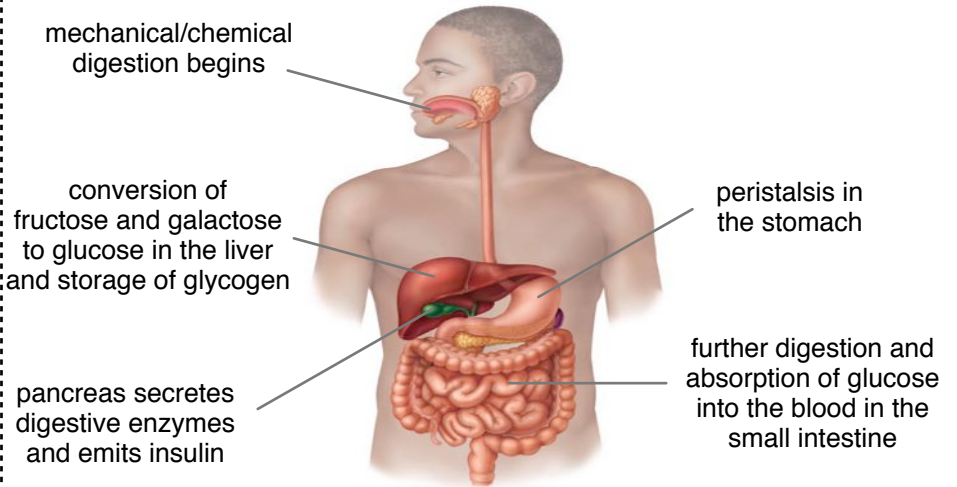
Symptoms: polyuria + polydipsia + polyphagia (the hyperglycemic triad), headache, fatigue, blurred vision, poor wound healing

Acute complications: hyperglycemic emergencies result in diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS)

Chronic complications: risk of cardiovascular disease (fatty acid deposits more build up quickly), stroke, kidney disease, nerve damage, foot ulcers, eye damage, sexual dysfunction

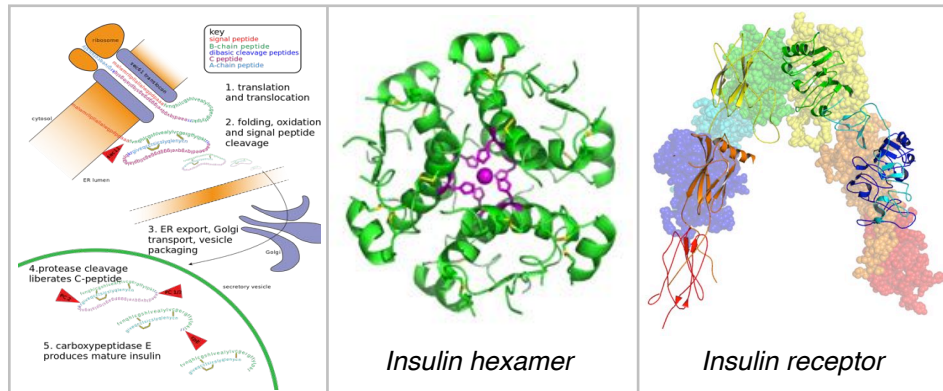
Types: Multiple

Glucose digestion and cellular uptake



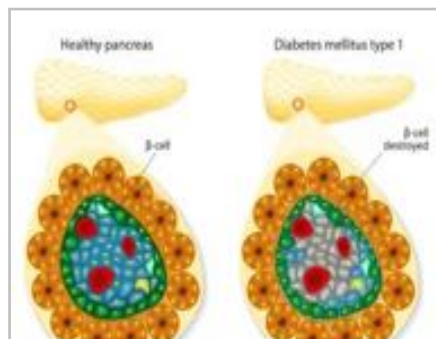
Insulin

- TFs PDX1, NeuroD1, MafA promote expression upon high glucose levels
- Stored as a hexamer in pancreatic β -cells, active as a monomer ($t_{1/2} = 5$ min)
- Increases glucose uptake + fat storage (deactivates glycogen synthase kinase)
- 51 amino acids, 5808 Da, A-chain and B-chain dimer linked by disulfide bonds
- Sequenced in 1955 by Sanger, X-ray in 1969 by Dorothy Hodgkin
- Varies between species (three AA difference in bovine, one in porcine)
- Since 2006 all insulin distributed in US is recombinant human



Type 1 DM ('insulin-dependent', 'juvenile')

- An autoimmune disease limits insulin production. (T-cell mediated attack on β -cells, cause unknown although genetic and viral factors)
- 6% of DM usually developing in children, teenagers.
- Rapid development of symptoms (DKA likely)
- Diagnose by fasting blood glucose level, monitor via HbA_{1C}
- 20 year decrease in life expectancy

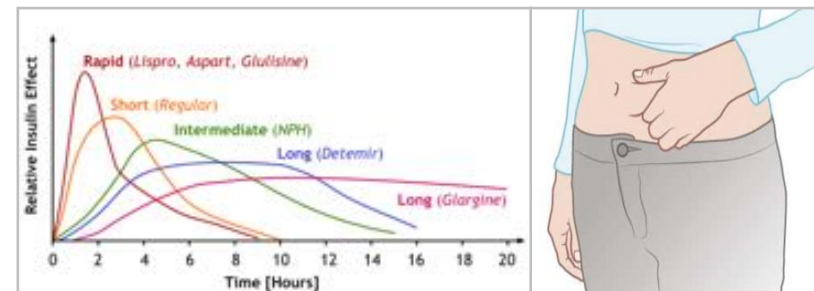


Acute complication: Diabetic ketoacidosis

- Lack of insulin promotes ketogenesis resulting in ketoacidosis (decreased pH in the blood)
- Symptoms include weakness, abdominal pain, nausea, vomiting, hyperventilation (respiratory alkalosis removes CO₂ to lower blood H₂CO₃)
- Simultaneous osmotic diuresis results in polyuria, polydipsia, cramps, vision trouble, altered level of consciousness
- Can lead to cerebral edema and death
- Treat with IV, potassium replacement and insulin therapy
- 135,000 hospital admissions annually in the US due to DKA

Insulin therapy

- Goal is tight blood-sugar control to prevent DKA
- Many dosing regimes to cover basal (background; food, exercise, health) and bolus (carbohydrate coverage) insulin replacement
- Side effect = weight gain, risk of hypo/hyperglycaemia if not managed
- Aim for 70-130 mg/dL before meals and <180 mg/dL 1-2 h after meals
- Subcutaneous injection and inhalation available, oral under massive investigation
- Analogues offer different ADME profiles (mainly single residue modifications)

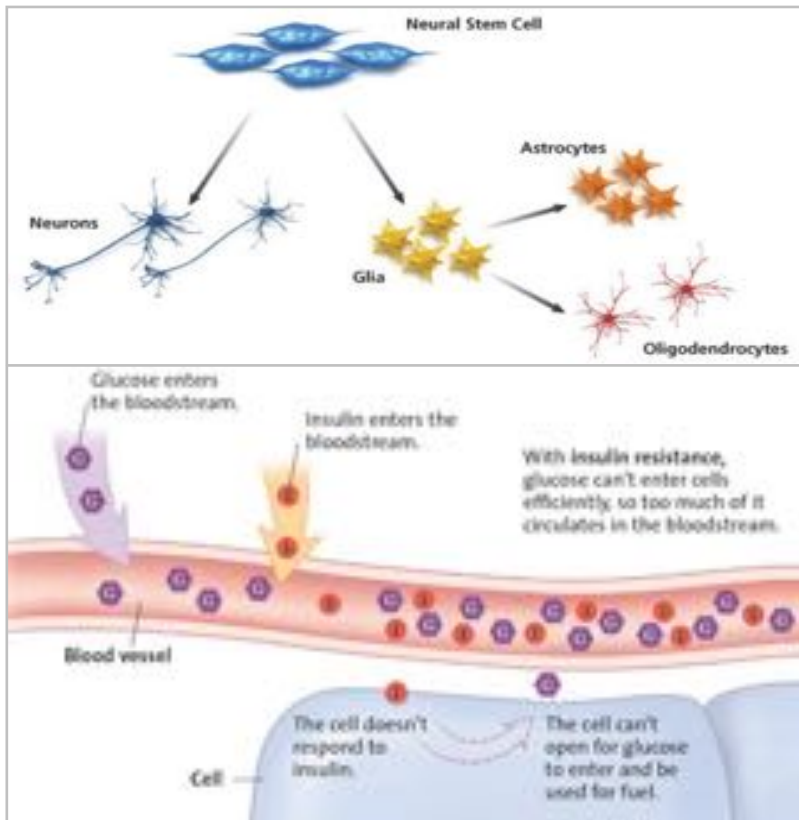


Insulin Delivery Devices



Type 2 DM ('non-insulin-dependent', 'adult-onset')

- Cells fail to respond to insulin correctly due to resistance
- Reduction in insulin production possible (pancreatic β -cell amyloid buildup)
- 90% of DM, later onset than type 1
- Risk factors incl. genetic and physiological (including overweight, inactive lifestyle, smoking, vit D deficiency)
- Type 1 symptoms observed + weight gain (insulin effect)
- Same method of diagnosis as type 1 (check blood sugar and HbA_{1c})
- Insulin/IGF1 play a role in neural stem cell differentiation via the PI3K/AKT pathway. Overloading via excessive glucose ingestion causes the body to desensitize insulin receptors (as observed in pregnancy)
- 10 year decrease in life expectancy (CV, stroke, kidney failure etc.)



Acute complication: Hyperosmolar hyperglycemic state

- Osmotic diuresis without significant ketogenesis (due to sufficient insulin in the blood)
- Complications may include seizures, blod clots, mesenteric ischemia and rhabdomyolysis
- Usually preceded by infection
- Treat with IV, low mw heparin, potassium replacement, antibiotics
- Common especially in elderly (exact frequency unknown)

Treatment: Diet and exercise

- Excess body fat associated with 30% (Chinese), 60-80% (European/African) and 100% (Pacific Islanders) of cases
- Vigorous exercise once per week found to reduce risk of type 2 by 30%
- Glycemic index rates foods by how much and how quickly they raise blood glucose
- Weight loss surgery is effective for patients unable to control blood sugar

Low GI (<55), Medium GI (56-69) and High GI (70>)

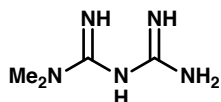
Grains / Starchs	Vegetables	Fruits	Dairy	Proteins
Rice Bran 27	Asparagus 15	Grapefruit 25	Low-Fat Yogurt 14	Peanuts 21
Bran Cereal 42	Broccoli 15	Apple 38	Plain Yogurt 14	Beans, Dried 40
Spaghetti 42	Celery 15	Peach 42	Whole Milk 27	Lentils 41
Corn, sweet 54	Cucumber 15	Orange 44	Soy Milk 30	Kidney Beans 41
Wild Rice 57	Lettuce 15	Grape 46	Fat-Free Milk 32	Split Peas 45
Sweet Potatoes 61	Peppers 15	Banana 54	Skim Milk 32	Lima Beans 46
White Rice 64	Spinach 15	Mango 56	Chocolate Milk 35	Chickpeas 47
Cous Cous 65	Tomatoes 15	Pineapple 66	Fruit Yogurt 36	Pinto Beans 55
Whole Wheat Bread 71	Chickpeas 33	Watermelon 72	Ice Cream 61	Black-Eyed Beans 59
Muesli 80	Cooked Carrots 39			
Baked Potatoes 85				
Oatmeal 87				
Taco Shells 97				
White Bread 100				
Bagel, White 103				

Treatment of Diabetes

Cian Kingston, 2018

Treatment: Medications

Metformin



Overview: First-line, oral delivery, generic: \$5-\$25 per month, $t_{1/2}$ = 6h in plasma

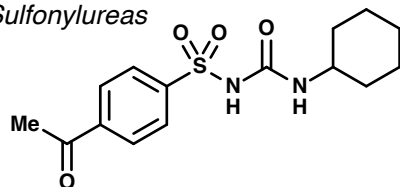
History: Introduced 1957 France, 1995 US, WHO LEM

Action: suppress gluconeogenesis in liver (not well understood) and increases insulin sensitivity (stimulates GLUT4)

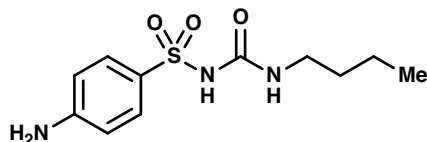
Possible side effects: Diarrhea, nausea, abdominal pain, lactic acidosis

Contraindications: Any risk of LA (kidney disorder, liver/lung disease)

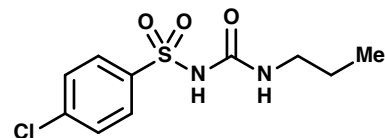
Sulfonylureas



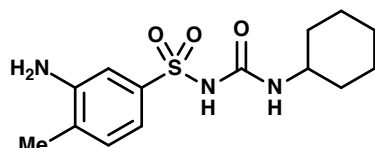
Acetohexamamide (1st gen)



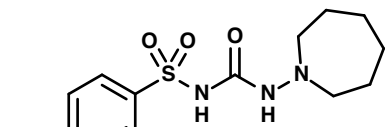
Carbutamide (1st)



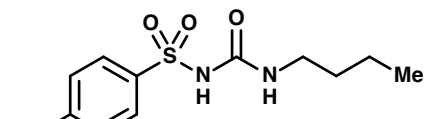
Chlorpropamide (1st)



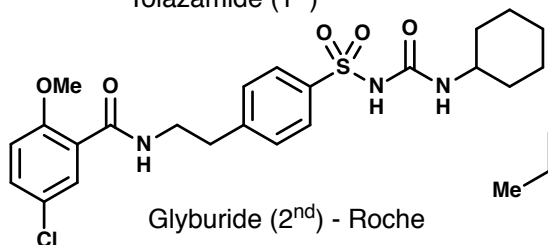
Metahexamamide (1st)



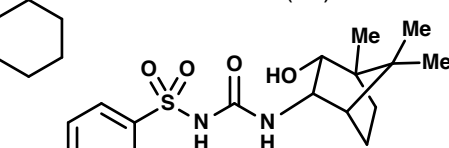
Tolazamide (1st)



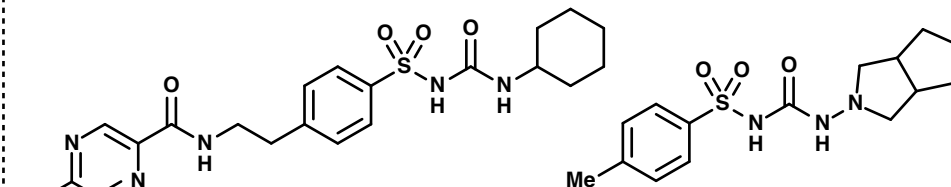
Tolbutamide (1st)



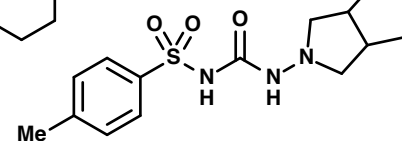
Glyburide (2nd) - Roche



Glibornuride (2nd) - MEDA

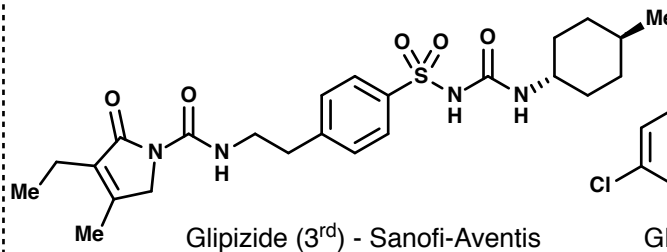


Glipizide (2nd) - Pfizer

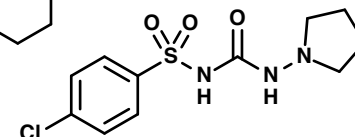


Gliclazide (2nd)

WHO LEM, \$4 per month,



Glipizide (3rd) - Sanofi-Aventis



Glicopyramide (2nd)

Overview: Oral delivery, generally disfavored due to weight gain

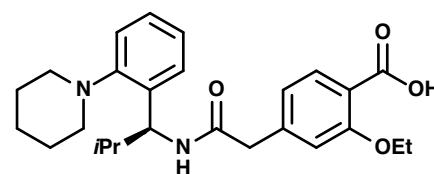
History: Discovered 1942

Action: stimulates insulin secretion, evidence of increased sensitivity and decreased lipolysis

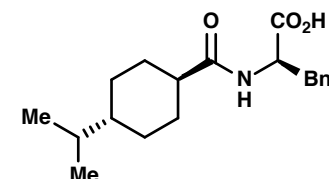
Possible side effects: Risk of hypoglycemia, weight gain, gastrointestinal, headache, CV

Contraindications: Liver/kidney impairment (hypoglycemia risk)

Meglitinides



Repaglinide - Novo Nordisk

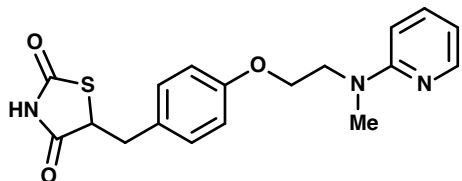


Nateglinide - Novartis

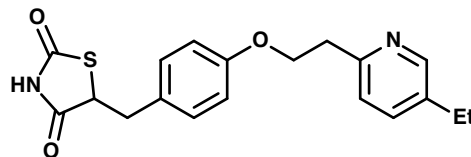
Overview: Similar to sulfonylureas but milder

History: Main branded drug is repaglinide which gained FDA approval in 1997

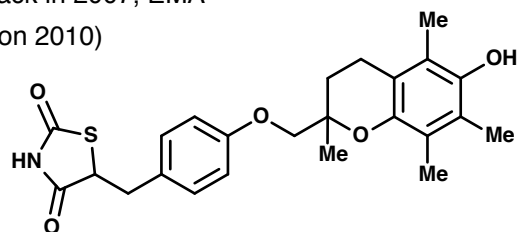
Thiazolidinediones



Rosiglitazone - GSK
(released 1999, \$2.5 bn in 2006,
linked to heart attack in 2007, EMA
suspension 2010)



Pioglitazone - Takeda
(\$2.4 bn in US in 2008)



Troglitazone - Parke-Davis then Pfizer
(FDA approval against recommendation in 1997, hepatotoxicity
discovered, Pfizer have resolved claims to cost of \$750 million)

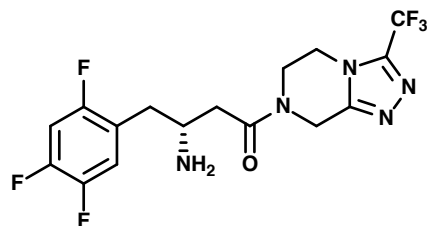
Overview: Disfavored due to numerous side effects

History: Multiple controversies, withdrawals

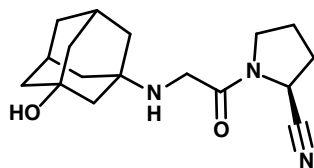
Action: increase storage of fatty acids in the liver

Possible side effects: Various including bladder cancer, CV

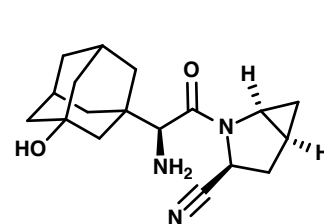
Dipeptidyl peptidase-4 inhibitors



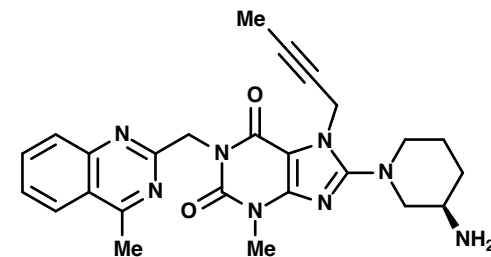
Sitagliptin - Merck



Vildagliptin - Novartis



Saxagliptin - BMS/AstraZeneca



Linagliptin - Boehringer Ingelheim/Lilly

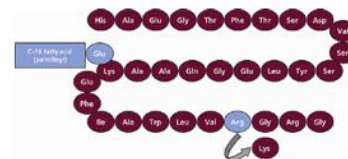
Overview: Relatively new class of drugs, oral delivery

History: First agent - sitagliptin - approved by FDA in 2006

Action: The DPP-4 enzyme inactivates incretins which inhibit glucagon release

Possible side effects: Heart failure, severe joint pain, headache, nausea, rash

Glucagon-like peptide-1 receptor agonists



Liraglutide - Novo Nordisk



Albiglutide - GSK

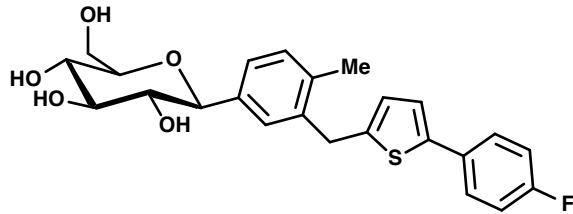
Overview: Lower risk of hypoglycemia, subcutaneous delivery

History: New class, four drugs FDA approved since 2014

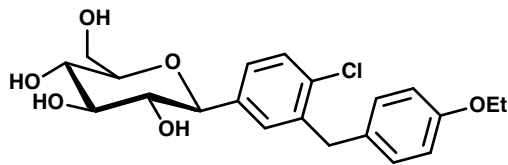
Action: increase insulin secretion

Possible side effects: weight loss, unclear risk of pancreatic cancer

Sodium-glucose transport protein 2 inhibitors/gliflozin drugs



Canagliflozin - Janssen



Dapagliflozin - BMS/AstraZeneca

Overview: Low chance of DDI, oral delivery, administered w/o regard for meals

History: Newest class of drugs on the market

Action: Blocks renal glucose reabsorption thereby dramatically lowering blood sugar levels independent of insulin secretion (state of β -cells has no effect)

Possible side effects: weight loss, CV benefit, ketoacidosis, UTI, hypoglycemia

Other types of diabetes mellitus

Prediabetes: leads to type 2

Gestational: 2-5% of pregnant women affected, hormones interfere with insulin. Usually disappears but greater risk of type 2 in future

Type 3c (pancreatogenic): Possibly 5-10% of all diabetic cases. 80% of cases result from chronic pancreatitis

CF-related: Mucus causes scarring of the pancreas

Mitochondrial: Gradual pancreatic beta-cell dysfunction upon aging

LADA: Latent version of type 1

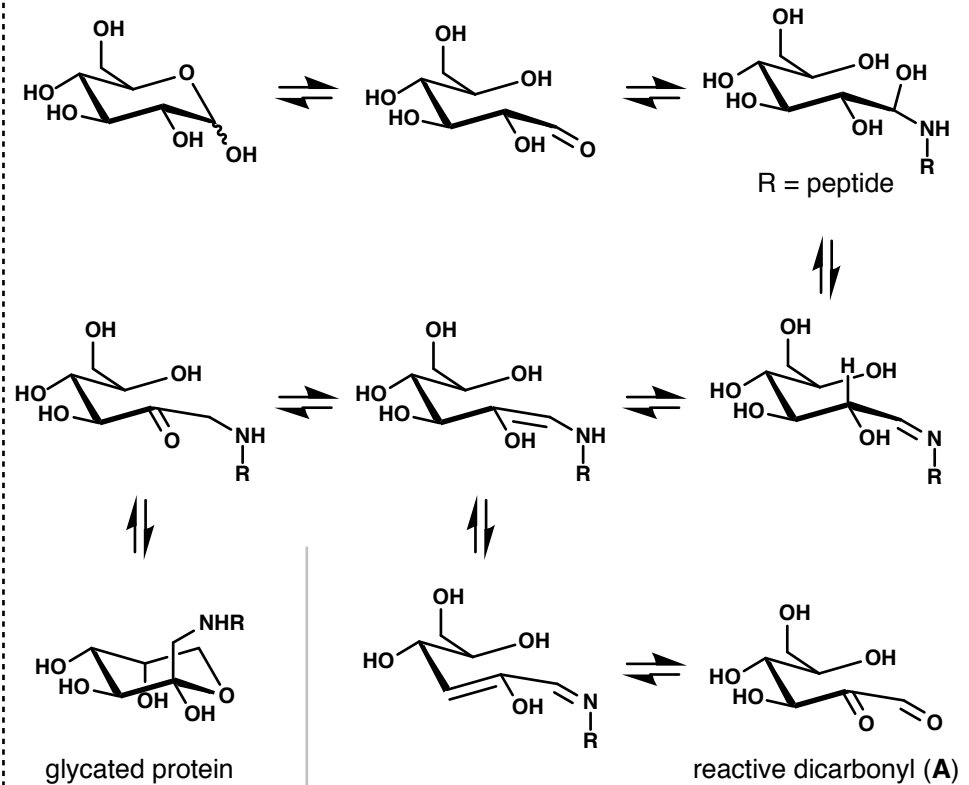
MODY: hereditary, 11 types

Neonatal DM: Monogenic, occurs in first 6 months

'Type 3': Alzheimer's

Future therapeutics: Advanced glycation end-products (AGE)

- Glycation (non-enzymatic glycosylation) is the addition of a sugar to a protein (usually via lysine) or lipid
- Implicated in age-related diseases e.g. Alzheimers, CV, cancer, blindness, stroke, kidney failure etc
- Particularly bad in long lived cells incl. pancreatic β -cells
- Glucose usually has a low rate of glycation (10 times less than fructose), but accelerated due to higher concentration with DM
- Multiple (unknown) deleterious pathways and potential therapies



Degradation of asparagine

