DIABETES

Describe the potential drug targets in Diabetes.

1. Ion channels (K+ channel)
2. Receptors (nuclear receptor – PPARγ agonist; tyrosine kinase receptor - insulin receptor, GLP-1)
3. Enzymes (α-glycosidase, DPP-IV)
4. Transporters (SGLT2 inhibitor)

DRUGS FOR T1DM – i.e. insulin

- Target organ: liver and skeletal muscle
- Mechanism of action: decrease hepatic glucose output, increase glucose utilisation in skeletal muscle
- Monomeric form is the biologically active form; hexamer (trimer of dimer) is more stable and inactive which provides chemical stability in storage and possibly in vivo

Describe the SAR of insulin.

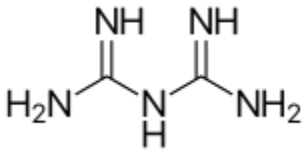
- Disulfide bond is important for activity
- His^{B10} replaced by Asp^{B10} increases potency and absorption, but decreases stability and slows dissociation from receptor and lead to cancer

Describe the different formulations of insulin used for subcutaneous injection.

USP name	Trade name	Formulation
Aspart	Novolog / Novorapid	Pro^{B28} replaced by Asp^{B28}
Glulisine	Apidra	$Asp^{B3}Lys^{B29}$ replaced by $Lys^{B3}Glu^{B29}$
Lispro	Humalog	Pro^{B28} & Lys^{B29} swapped in original insulin molecule to make dimer more readily to form monomer = rapid onset of action
Human insulin	Humulin	Regular • Clear solution of zinc insulin
	Novolin	NPH or isophane
		Lente • Mixed amorphous and crystalline zinc insulin
		Ultralente • Suspension of crystalline insulin with high zinc content
Glargine	Lantus	Addition of two Arg^{B31} and Arg^{B32} (basic residues) to change pI of insulin; microprecipitate formation at pH 7.4 for slow-release
Detemir	Levemir	Increase albumin binding to protect from hydrolysis

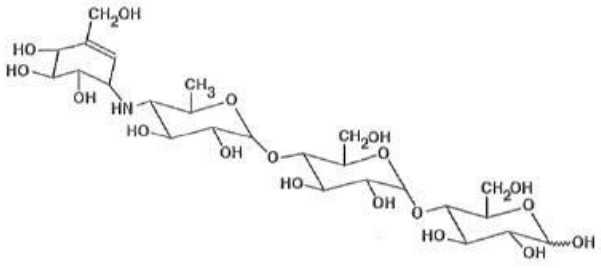
DRUGS FOR T2DM

Biguanide



- Biguanide: two guanidine molecules
- Target organs: skeletal muscles and liver
- Mechanism of action:
  - inhibits mitochondrial complex I, causes increase in the AMP/ATP ratio, results in activation of AMPK
- Principal effect:
  - **Skeletal muscles:** Increasing glucose uptake via GLUT4 by skeletal muscles
  - **Liver:** Reducing gluconeogenesis (via reduction in gluconeogenic gene expression) and glycogenolysis, hence reducing hepatic glucose output; also improve lipid profile (i.e. significant cardiovascular benefit)
- Not associated with weight gain (and may cause some weight loss instead)
- Not associated with hypoglycaemia
- Drug story:
  - Phenformin (has phenyl group) has active metabolites to give long duration of action; however discontinued due to lactic acidosis
  - Metformin (has methyl group) has rapid clearance as it is a low molecular weight drug

α-glucosidase inhibitor



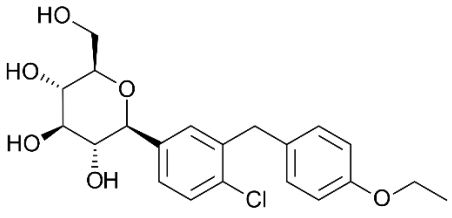
- Target organ: Gut (villi of small intestine)
- Mechanism of action:
  - Inhibits α-glucosidase (e.g. sucrase-isomaltase; maltase-glucoamylase; lactase) present in intestinal brush border that digest sucrose and starch-derived oligosaccharides
- Principal effect:
  - **Gut:** delay digestion of dietary carbohydrate (i.e. starch and sucrose), hence lowering post-prandial glucose levels

- Not associated with weight gain

- Associated with hypoglycaemia

- Drug story:
    - Drug should be poorly absorbed
    - Drug should mimic transition state of substrate (charged & flattened ring) to increase potency (because an enzyme will bind more strongly to the transition state of a substrate)
    - Leads to side effects such as flatulence and diarrhoea due to undigested carbohydrate
    - E.g. Acarbose – potent inhibitor of glucoamylase and α-amylase only
    - E.g. Miglitol – potent inhibitor of sucrase only

<u>SGLT2 (sodium glucose co-transporter 2) inhibitor</u>



- Target organ: Kidney

- Mechanism of action:
    - Inhibits SGLT2 to inhibit 90% glucose reuptake *(EXTRA: another 10% via SGLT1)* from renal tubule into bloodstream, leading to increased excretion of glucose in urine

- Principal effect:
    - **Kidney:** reduces plasma glucose and associate calories intake
    - **Skeletal muscle, liver, pancreas, kidney:** reversing glucotoxicity
        - Increasing insulin sensitivity in skeletal muscle
        - Reducing glucose-6-phosphatase activity in liver
        - Increasing beta cell function in pancreas
        - Reducing gluconeogenesis in liver and kidney

- Not associated with weight gain (and may cause some weight loss instead)

- Associated with hypoglycaemia (when used with a sulfonylurea or insulin)

- Drug story:
    - <u>Incorporation of big lipophilic tail</u> + <u>ether bond is replaced by direct C-C bond</u> to enhance selectivity for SGLT2 and decrease affinity for SGLT1. Beneficial because inhibition of SGLT1 will lead to malabsorption due to its expression in the gut
    - Increased glucose in urine → increased risk of UTI
    - Need to have good kidney function for drug to be useful → but older or long-term diabetics have impaired kidney function
    - E.g. dapagliflozin, canagliflozin