HYPOGLYCEMIC AGENTS

Westmead Primary Exam Course

Insulin

- Secretions - released from pancreatic B cells at a low basal rate and a much higher stimulated response to a variety of stimuli - especially glucose.
- Other stimulants include
    - Mannose
    - Certain amino acids
    - Vagal activity
- Hyperglycemia —> increased intracellular ATP levels —> close the ATP dependent K channel —> decreased outward efflux causes depolarisation of the B cells —> opens voltage gated Ca channel —> increased intracellular calcium tigers secretion of insulin

Insulin

- Metabolism
  - Liver and kidneys are two main organs
    - Liver = 60%
    - Kidney 30 - 40% of endogenous hormone
    - This ratio is reversed with the administration of exogenous hormone
    - The half life of circulating insulin is 3 - 5 minutes

Insulin

- The insulin receptor -
    - Insulin diffuses into tissues and binds to specialised tissue
    - Receptors consist of
        - Alpha - extracellular - subunit and is the recognition site
        - Beta subunit - spans the membrane
            - Contains a tyrosine kinase unit
- The binding to the alpha subunit activates the receptor and facilitates mutual phosphorylation of the beta subunit
- Activation of receptor causes
    - GLUT 4 insertion into cell membrane and increased glucose uptake
    - Increase glycogen formation
    - Effects of portein and fat synthesis
    - Cell growth and division

Insulin

- Effects of insulin - supports storage of fat and glucose inside specialised cells
- Liver
    - Reverses catabolic effects of insulin deficiency
        - inhibits glyogenolysis
        - inhibits formation of ketoacids
        - inhibits conversion of amino acids to glucose
    - Anabolic action
        - Promotes glucose storgage
        - Increased triglyceride secretion
- Muscle
    - Increase protein synthesis
    - Increase glycogen synthesis
- Adipose tissue
    - Increase triglyceride storage —> lipoprotein lipase induction

Insulin

- Rapid acting vs Short acting vs Intermediate acting vs Long acting
    - Rapid - clear in appearance, action in one hour
        - e.g. Lispro, aspart, glulisine
    - Short acting - clear in appearance, peak in 3 - 4 hours
        - e.g. Novolin
    - Intermediate - turbid with protamine, peak action is 4 - 8 hours
        - e.g. Humulin N
    - Long acting - clear, has a low level of effect for a long period of time - up to 6 - 23 hours
        - e.g. Levemir

Insulin

- 3 modalities
  - Portable pen injector
  - SC pumps
  - Inhaled insulin ? dubuious efficacy and risks associated with administration

Insulin therapy

- Complications of insulin therapy
  - Hypoglycaemia - most common complication - tachycardia, palpitations, sweating, nausea
  - Immunopathology of insulin therapy - insulin allergy and resistance
  - Lipodystrophy at injection sites

Oral Hypo glycemic Therapy

- Sulphonylureas
    - Increase insulin release from pancreas - binds K channels in B cells —> causes cellular depolarisation —> Ca influx —> insulin release
    - Reduce serum glucagon - occurs over long term
    - First generation agents - more adverse effects and drug interactions
    - Second generation agents - Glipizide - much better tolerated
    - Tachyphylaxis and secondary failure can occur

- Biguanides - Metformin is the prototype
    - MOA: remains elusive - does not depend on functioning B cells
        - Hypoglycemia does not happen - a euglycemic agent
    - Pharmacokinetics
        - A: Well absorbed
        - D: Not bound to plasma protiens, widely distributed
        - M: Not metabolised - can impair the metabolism of lactic acid, therefore in renal failure they accumulate and further inhibit the hepatic metabolism of lactic acid, causing a lactic acidosis
        - E: Excreted via kidney as active compound

- Metformin
    - Clinical use: Hyperglycemia due to insulin resistance
        - Can also prevent new onset of T2DM in middle aged obese people with IGT or fasting hyperglycaemia
    - Toxicity -
        - GIT
        - Can have mal absorption of vitamin B 12
        - Contraindicated in patients with alcoholism, renal failure, hepatic disease

Other OHG

- Acarbose - Reduce GIT conversion of starch disaccharides to monosaccharides and therefore reduce post prandial hyperglycaemia
- Rosiglitazone - Reduce peripheral insulin resistance via the regulation of gene expression
    - Can cause weight gain, fluid retention,
    - Contrainidcated in CCF and hepatic disease
- Sitagliptin - blocks degradation of GLP 1

Glucagon

- Chemistry and metabolism - synthesised by the A cells of the pancreas
- Extensively degraded in the liver and kidney as well as in plasma
- Because of its rapid inactivation in plasma - special storage methods are required to prolong activity

Glucagon

- Pharmacological effects
    - Metabolic effects - binds to specific receptors on liver cells and facilitates catabolism of stored glycogen and increases gluconeogenesis and ketogenesis
    - Cardiac effects - potent chronotropic and inotropic effects - very similar effects to beta adrenoreceptors without requiring functioning beta receptors
- Clinical use - hypoglycaemia