__/__/____

ANTI DIABETIC:

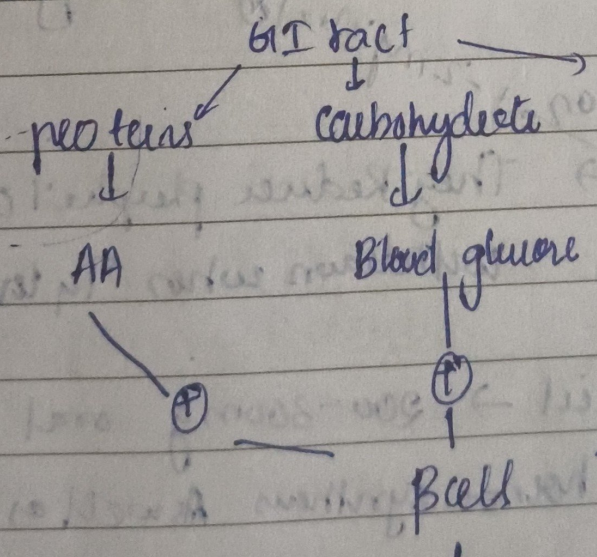
Type I DM → immunological, Beta cells of pancreas are destroyed by An Autoimmune process.

Type II DM → mainly genetic influence.
Non-insulin dependent.
Due - Abnormality in gluco-Receptor of B cell
- Reduce sensitivity of phospholipase to insulin
- Obesity.

→ Anabolic hormone.

INSULIN: two peptide chain called A & B.
↓
51 AA
21A, 30B
connected by two disulphide Bridge (2 chain)
Stabilized by 2 intrachain & 1 interchain disulphide bonds.

REGULATION: - chemical, hormone, neural



Chemical: Glucose entry → Activation of glucokinase in B cell
↓
Inhibit ATP → Insulin Release

Insulin - 3 form : hexamer, dimer, monomer
↓
Rapid diffusion.

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Neural: Both parasympathetic And sympathetic fibres supply the islet cells.

Para → ↑ Insulin = ↓ BSL.

Beta cell have both α & β Receptors

⇒ β_2 stimulation = ↑ Insulin = ↓ BSL

⇒ α_2 stimulation = ↓ Insulin - ↑ BSL.

promotes drug Absorption.

Hormonal - Glucagon, corticosteroids, Growth hormone

ACTION OF INSULIN:

- Insulin Inhibit hepatic glycogenolysis & gluconeogenesis
- Insulin enchances entry of AA.
- Insulin Also promote pheripheral utilization.

MOA - Transmembrane tyrosine kinase Receptor

⇒ Insulin bind to specific Receptors (tyrosine kinase Receptor) present on cell membrane

↓

The Receptor consist of two α & two β subunit (α - extracellular, β - transmembrane)

↓

Binding to α subunit Activate tyrosine kinase

Resulting β subunit - Phosphorylation

↓

Phosphorylated - dephosphorylate K^+ promote entry of glucose into the cell.

Molecules produced by genetic engineering where is AA sequence in human Insulin is changed to alter its PK/PD However they bind to insulin Receptor is same way as human Insulin & produce

PK:

not effective orally (case, peptide → degraded in GIT ↓ Never oral)

s/c given

metabolized by the liver

t½ - 5 - 9 min

After meal Insulin peak at 30-40 min And Return to normal basal level 2-3 hrs

INSULIN ANALOGUES:

They are produced by DNA Recombinant technology is Costly

★ RAPIDLY ACTING INSULIN ANALOGUES:

→ Eg. insulin lispro, insulin aspart, insulin glulisine

Ad ⇒ They have less tendency to form hexamers (unlike Regular Insulin)

⇒ MOA: → They quickly dissociate into monomers.

↓

Rapidly Absorbed

↓

Rapid onset of Action within 5-15 min

↓

Ad just before meals (20-30 min)

⇒ Duration of Action is 4 hours, ↓ post prandial hypoglycemic.

⇒ Defined peak.

★ LONG ACTING INSULIN ANALOGUES:

Eg: Insulin glargine And Insulin detemir.

Insulin Glargine

__/__/__

→ This Analogue Remain soluble at PH4 of the formulation but precipitates at ~~PH4 of the~~ Alkalin PH of the formulations. ∞ S.C inj.
→ Ad once daily at bed time
→ ↓ Risk of nocturnal Hypoglycemia
→ cannot be mixed with other insulin because of Acidic PH
→ smooth peakless plasma concentration.
→ C/I in pregnancy.

Insulin Detemir

→ bind to Albumin blood → prolonged duration of Action.
– twice daily

INTERMEDIATE ACTING INSULIN:

NPH (Neutral Protamine Hagedorn) / Isophane Insulin

→ Insulin is complexed with protamine And zinc
→ onset of Action is delayed
– Given S.C once or twice daily.

SHORT ACTING INSULIN:

① ## Regular (Soluble Insulin)
A → from hexamers after S.C inj → Slowly Absorbed → ~~onset of Action is within 30min~~.
→ Available as 40U/ml, 100 U/ml, 500 U/ml
→ Ad S.C, im, IV Route

MAIN NOTE

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~~DIABETIC KETOACIDOSIS~~

⇒ Buffered neutral PH solution of unmodified Insulin
⇒ Peak Action after 2-3 hrs. DOA → 6-8 hrs
⇒ Injected S.C befor meal → !
⇒ Easy postprandial hyperglycemia
⇒ Late postprandial hypoglycemia

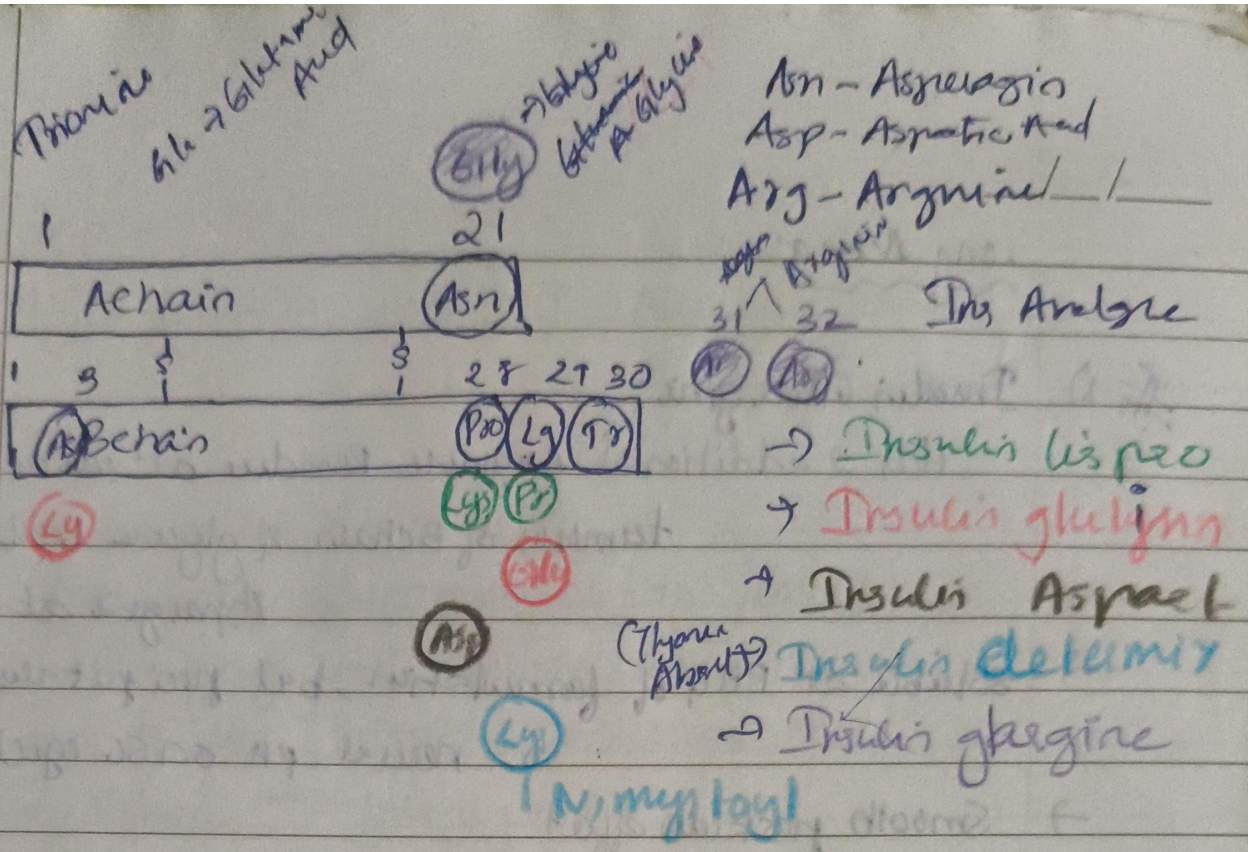
Dis

mismatch b/w need And Availibity of Insulin
⇒ Recommended to Administer - 1 hour befor meal
⇒ Long Acting Retard preparation → Insulin complexed with protamine & zinc

② ISOPHANE INSULIN (NPH)
- Neutral Protamine Hagedorn.
- Protamine complexing all Insulin molecules
- PH neutral
- S.C injection → complex dissociate slowly → intermediate duration of Act

Newer Insulin
→ Designer Insulin / Democratic Insulin
⇒ They made f/t flexible, safer, simpler
→ Faster Acting prepprandial insulin
→ Less hypoglycemia

⇒ B26-30 AA Region (critical for Insulin Receptor Recognition) it is site prefer for smaller Alter of Insulin molecules



Ultrashort / Rapid Acting Insulin

→ Form very weak hexamer, dissociate in S.C inj

→ Quick defined peaks

→ Shorter DOA

1) Insulin Lispro.

- Reverse proline of lysine at carboxy terminal B28 & B29.

2) Insulin Aspart:

- Proline at B28 Replaced by Aspartic Acid.

BIPHASIC INSULIN ASPART:

70:30 of isophane complex of Insulin Aspart with unmodified Insulin Aspart

- Rapid onset & Intermediate DOA

3) Insulin Glulisine

Lysine Replacing Asparagine at B3 & glutamic Acid Replacing lysine at B29

- For continuous subcutaneous Insulin Infusion. (CSII)

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Long Acting:

1) Insulin Glargine:
Has 2 additional Arginine Residue at carboxy terminus of B chain & glycine Replace Asparagine at A21

→ soluble at PH4 of formulation, but precipitates at neural PH on SC injection
→ Smooth peakless effect
→ mostly given at bedtime.

2) Insulin Determir:
Myristoyl Radical attached to Amino group of lysine at B29 & threonine at B30 is Removed
→ Bind to Albumin after SC. inj free form slowly Released

3) Insulin Degludec;
Ultra long Acting Insulin
→ A 16-C long fatty Acid conjugated to lysine at B-29 & Removal of threonine from B30

CLASSIFICATION OF INSULIN:
1) Rapid Acting → Insulin lispro, Aspart, glulisine
2) SHORT ACTING → Regular / soluble insulin
3) INTERMEDIATE → NPH
4) LONG ACTING → Insulin glargine, determir, degludec

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ADR

→ Hypoglycemia, local Rx, Allergy, Edema.

DI

- Non-selective β Blocker.
- Mask warning sign of hypoglycemia.
  ↑ hypoglycemic episodes, delay Recovery
- Loop diuretics, thiazide, corticosteroid, OCP.
- Alcohol → hypoglycemia.
- Acute ingestion of Alcohol → Hypoglycemia.

Insulin Resistance:

→ suboptimal Response of body tissue to insulin
Age, Obesity, sedentary, lifestyle, PCOD, OCP.

Acute Insulin Resistance:

Infection, trauma, surgery, stress → Release corticoids → hyperglycemia.

- DKA. → Rx → High dose Regular Insulin

Uses of Insulin: DM, DKA, Hyperosmolar coma.

⇒ Split mixed Regimen: NPH combined with Regular Insulin (70:30 or 50:50) ℞ injected S.C B.D before breakfast & before dinner.

⇒ Basal Bolus Regimen: Long Acting Insulin injected OD before breakfast or before bedtime
Rapid Acting Insulin give 2-3 time covering meals.