Insulin & analogues

Salutes

JOURNEY FROM EXTRACTS TO ANALOGUES……

1921 : Insulin extracted by Banting & Best.

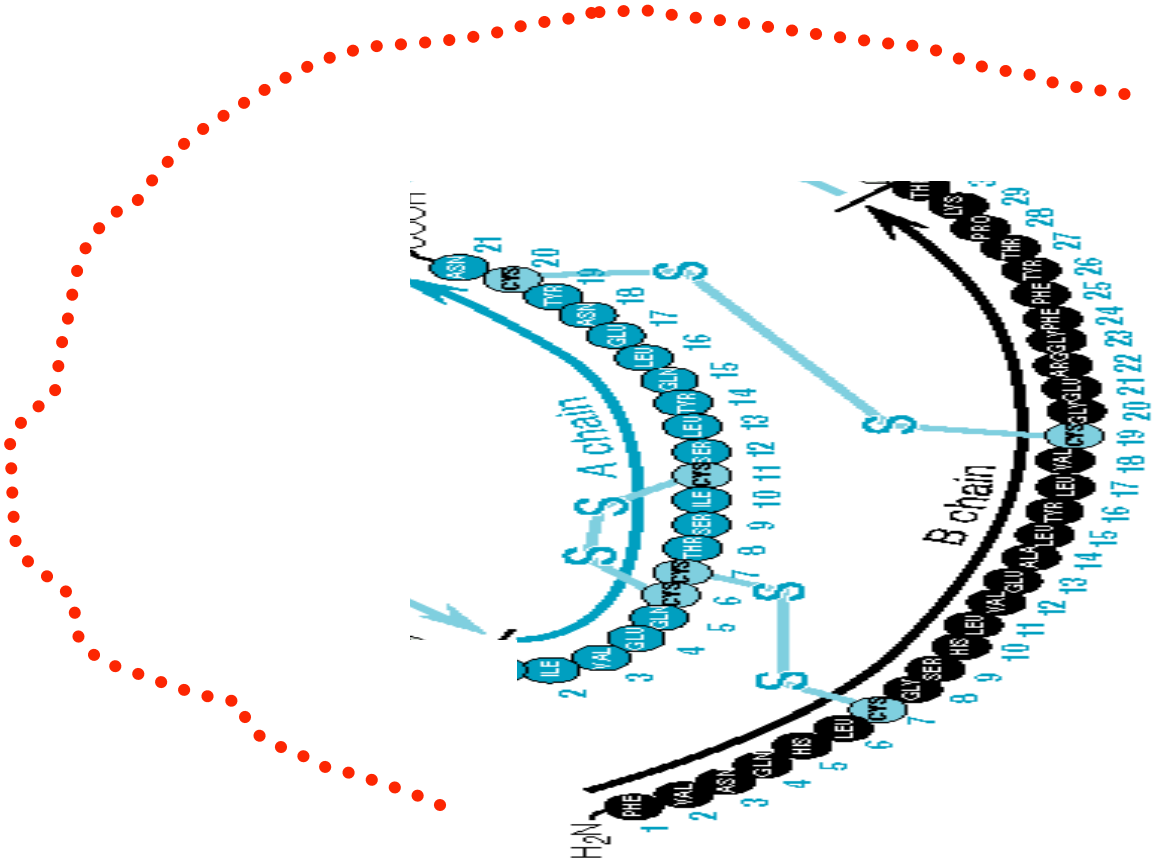
Conventional insulin preparations from beef/pork pancreas (antigenic)

1970s : Highly purified porcine insulins : Single peak insulins &
Monocompetent insulins (greater efficacy & lesser side effects)

1980s : Human insulins by recombinant DNA technology (still better)

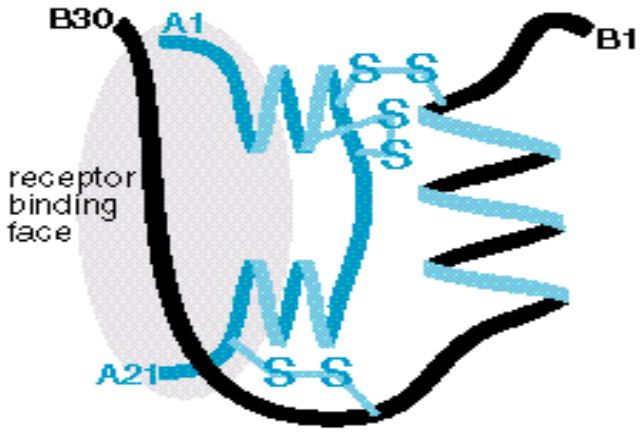
1990 : Insulin analogues with novel pharmacokinetics (*Eli Lilly& Co.)*

Human proinsulin and its conversion to insulin.



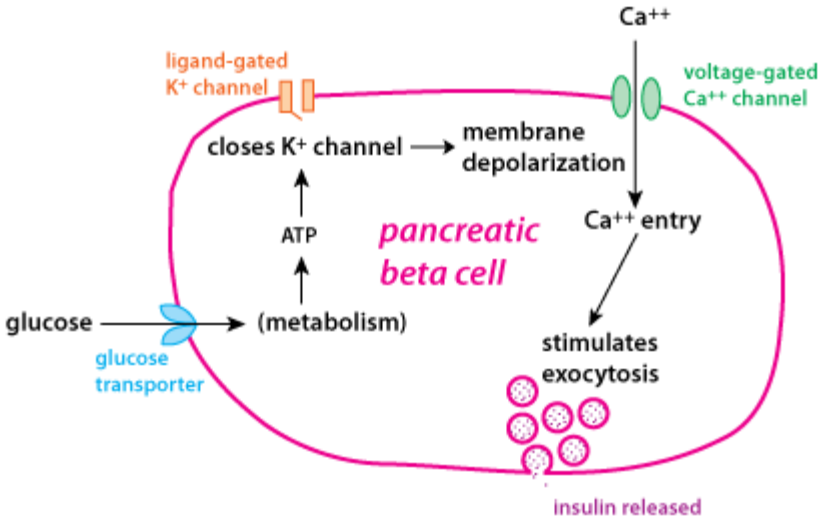
STRUCTURE OF INSULIN

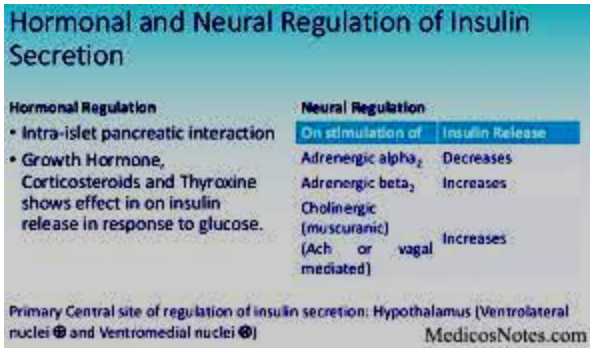
- Insulin
  - Polypeptide hormone
  - 51 amino acids
  - Two chains
    - A chain 21 a.a.
    - B chain 30 a.a.



- Held by interchange disulfide bridges

INSULIN REGULATION





Hormonal and Neural Regulation of Insulin Secretion

Hormonal Regulation

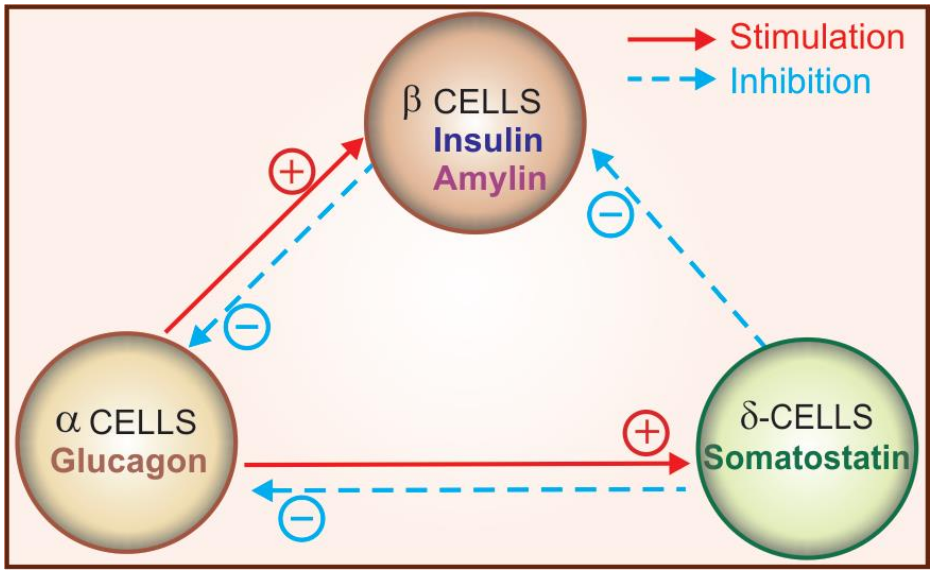
- Intra-islet pancreatic interaction
- Growth Hormone, Corticosteroids and Thyroxine shows effect in on insulin release in response to glucose.

Neural Regulation

On stimulation of	Insulin Release
Adrenergic alpha$_2$	Decreases
Adrenergic beta$_2$	Increases
Cholinergic (muscuranic) (Ach or vagal mediated)	Increases

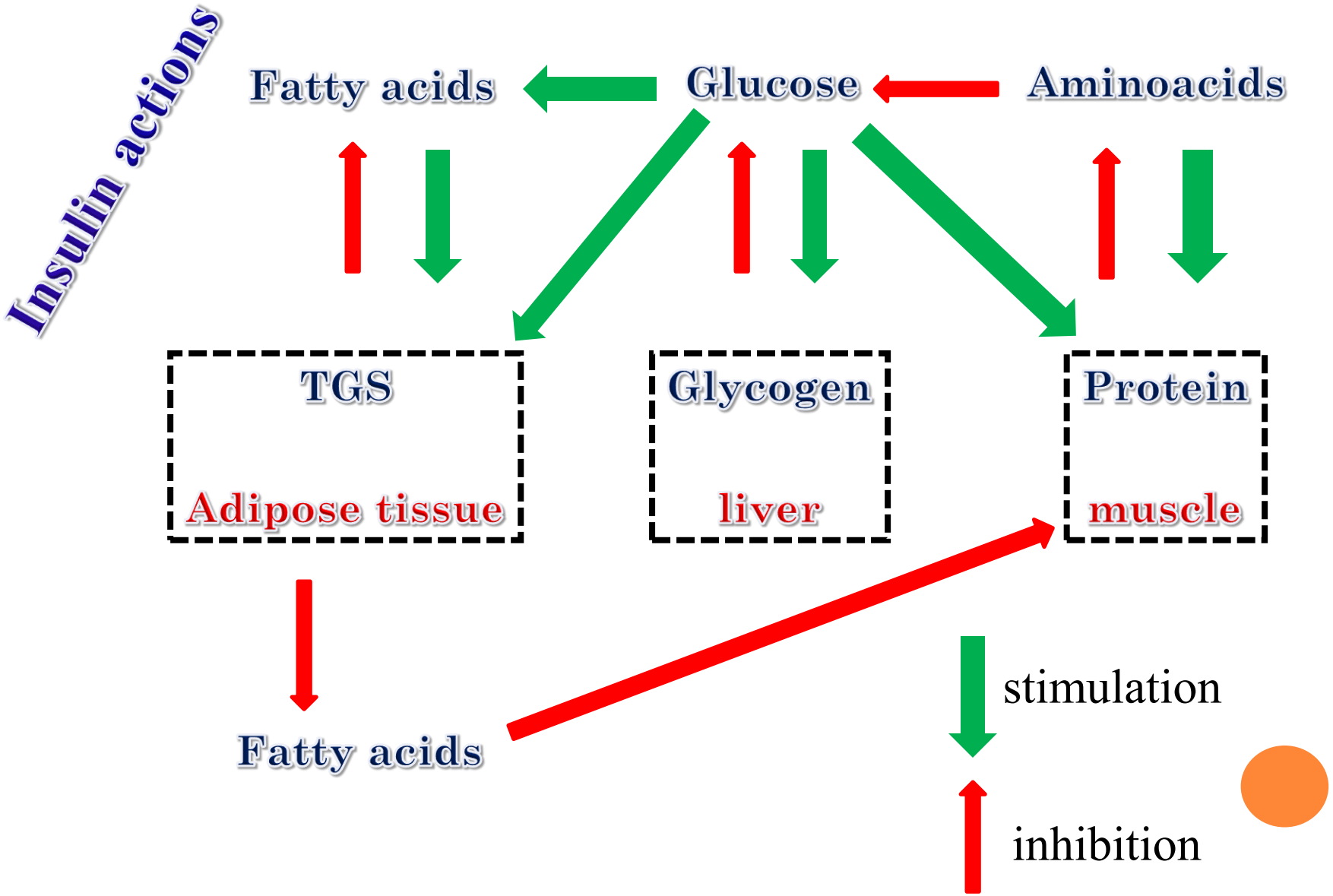
Primary Central site of regulation of insulin secretion: Hypothalamus (Ventrolateral nuclei ⊕ and Ventromedial nuclei ⊖)

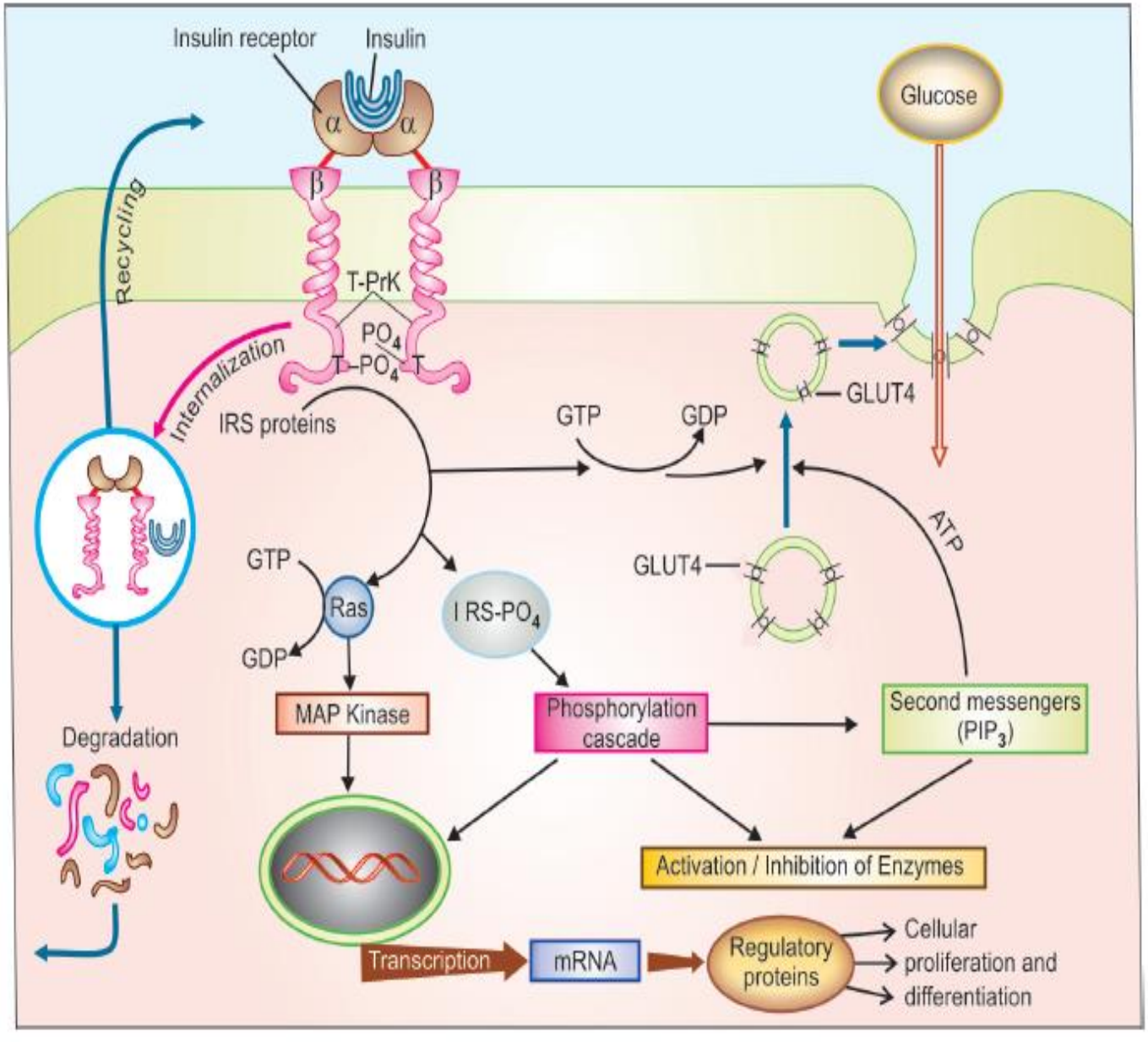
MedicosNotes.com



INCRETINS

- Glucagon like peptide(GLP)
- Glucose dependent insulinotropic polypeptide(GIP)
- Vasoactive intestinal polypeptide(VIP)


Insulin actions
Fatty acids
Glucose
Aminoacids
TGS
Adipose tissue
Glycogen
liver
Protein
muscle
Fatty acids
stimulation
inhibition


Insulin receptor
Insulin
α
α
β
β
Glucose
Recycling
T-PrK
PO4
T–PO4 T
Internalization
IRS proteins
GTP
GDP
GLUT4
GTP
Ras
GDP
I RS-PO4
GLUT4
ATP
Degradation
MAP Kinase
Phosphorylation cascade
Second messengers (PIP3)
Activation / Inhibition of Enzymes
Transcription
mRNA
Regulatory proteins
Cellular proliferation and differentiation

Sources of insulin

Species	A-chain		B-chain
	8th AA	10th AA	30th AA
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

Insulin preparations

- Regular(soluble)
- Lente(insulin-zinc suspension)
- Isophane(Neutral Protamine Hagedorn)
- Human insulins
- Insulin analogues

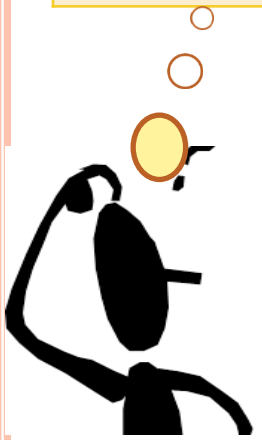
CLASSIFICATION

INSULINS

Short acting
- Regular

Intermediate acting
- lente and NPH / Isophane

Pre-mix insulins of NPH/Regular insulins



INSULIN ANALOGUES

Ultra-short acting/Rapid acting
- Lispro
- Aspart
- Glulisine

Long acting
- Glargine
- Detemir
- Degludec

** Protaminated lispro – NPL
Protaminated Aspart – NPA

Pre mix analogues of NPL with Lispro (50/50 &75/25)

Pre mix analogues of NPA with Aspart (70/30)

REGULAR INSULIN

- Buffered neutral Ph stabilized by zinc
- Insulin molecules aggregate around zinc ions
- Insulin molecules are released slowly after injection leading to slow absorption
- Peak action after 2-3hrs, lasts upto 6-8 hrs(lV- quick action)

Rapid acting and peakless long acting insulins are available
Long acting- complexing with protamine or precipitating with excess zinc

LENTE INSULIN

- Ultralente- insoluble (long-acting)
- Semilente - amorphous (short acting)
- Lente- 7:3 (intermediate acting)

ISOPHANE - protamine complexes insulin
- intermediate acting
-combined with regular insulin
(70:30 or 50:50) s.c twice daily

Human insulins

- E.coli - proinsulin recombinant bacterial(prb)
- Yeast - precursor yeast recombinant (pyr)
- Porcine – enzymatic modification of porcine insulin (emp)

- Rapid and shorter acting
- Modified isophane and lente are available

Ultra short/Rapid acting Insulin analogues

- Lispro
- Aspart
- Glulisine

LIMITATIONS OF REGULAR INSULINS

- Regular insulins form hexamers which dissociate slowly into monomers thus delaying absorption.

Delayed onset of action (1/2 to 1 hr) ——— **Post prandial hyperglycemia**

Prolonged time of peak action (2 to 3 hrs)

Duration of action (5 to 8 hrs) ——— **Late post prandial hypoglycemia**

Hence regular insulins cause a mismatch between need & availability of bolus insulin and do not ideally mimic physiological bolus secretion of insulin.

OTHER LIMITATIONS OF REGULAR INSULINS

- Regular insulin has to be administered ***30-45mins before meal*** - **dose of insulin cannot be adjusted according to size of meals.**
- Time of onset, peak action & duration of action is ***dose dependent (increases with dose)***
- Absorption ***varies with injection site & exercise*** (variability of absorption as much as 25%)

ADVANTAGES OF ULTRA SHORT ACTING ANALOGUES

- Less propensity to form hexamers. Hexamers formed dissociate rapidly into monomers & are rapidly absorbed.

Rapid onset of action - 10 to 20mins

Peak action – 1 to 2 hrs

Duration of action – 4 to 5 hrs

Better control of post prandial glucose

Decreased risk of late post prandial hypoglycemia

Mimics physiological bolus secretion.

- Can be taken <u>just before or just after meals</u> – allows adjustment of insulin dose with size of meal.

- Onset of action & peak action <u>independent of dose/site of injection / exercise.</u>

LONG ACTING INSULIN ANALOGUES

- Glargine
- Detemir
- Degludec

LIMITATIONS OF NPH INSULINS

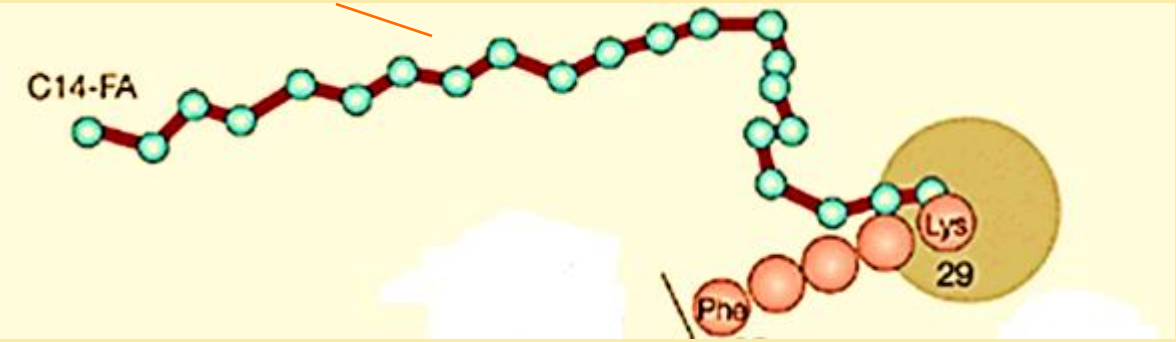
- Doesn't mimic physiological basal insulin secretion
  - Peak action 5 to 7hrs after administration (risk of **nocturnal hypoglycemia** (if administered at bedtime)
  - Duration of action not long(≈20hours) enough to cover insulin requirements of the whole day with a single injection .
- Action profile depends on dose.
- Variability of absorption with site/exercise/variation in mixing of suspension (50%variability). Highly unpredictable action profile.

ADVANTAGES OF GLARGINE OVER NPH

- Low insulin levels maintained uniformly for 24hrs with **no peak**(**mimics physiological basal insulin secretion**)
  - Decreased risk of nocturnal hypoglycemia
  - Fasting & interdigestive blood glucose levels effectively controlled throughout the day irrespective of the time of injection
  - Suitable for once daily dosing.
  - Predictable absorption independent of dose/site of inj/exercise/mixing
- Wt gain reported less with glargine.

DETEMIR

Myristic acid

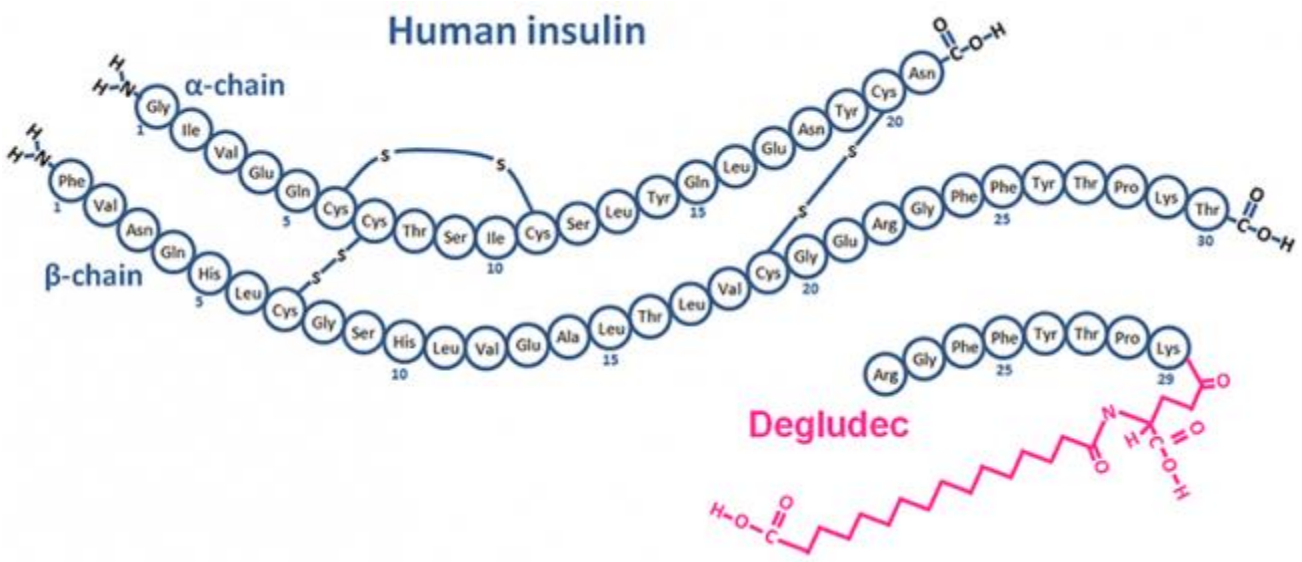


Smooth time action profile with no peak.

Glycemic control similar to NPH but produces less hypoglycemia than NPH

Onset of action is dose dependent

Duration of action slightly less than 24 hrs & may require twice daily dosing.

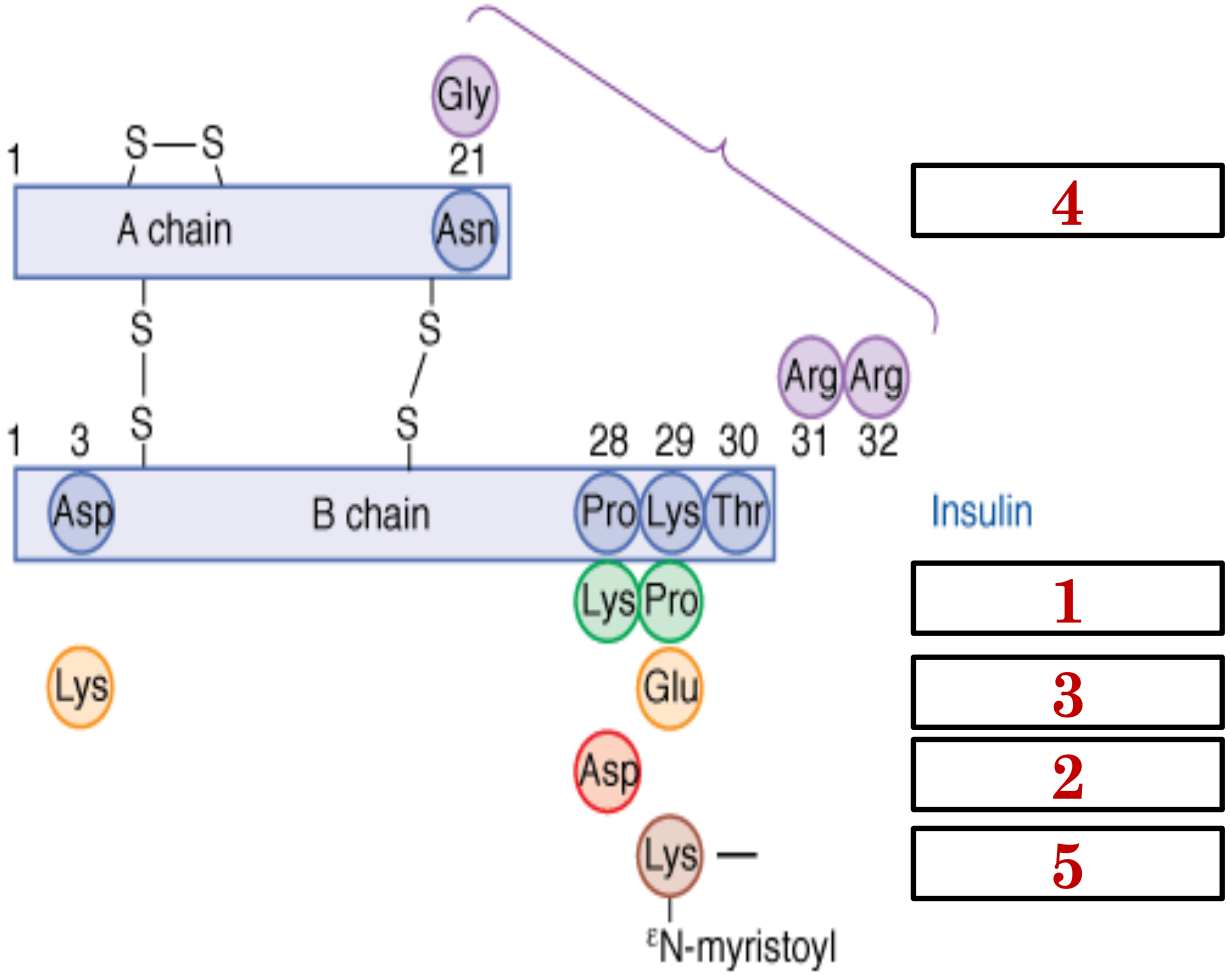


Hexadecanedioic acid

DEGLUDEC

- Ultralong acting insulin analogue in the process of development.
- Suitable for thrice weekly administration

Pharmacology of Insulin: Insulin Analogues



INSULIN REACTIONS

- Hypoglycemia(glucose or glucagon)
- Local reactions
- Allergy
- Edema

INTERACTONS

- ß blockers (non-selective) prolong hypoglycaemia
- Diuretics, corticosteroids, OCs, salbutamol…
- Alcohol
- Li, aspirin

Insulin resistance

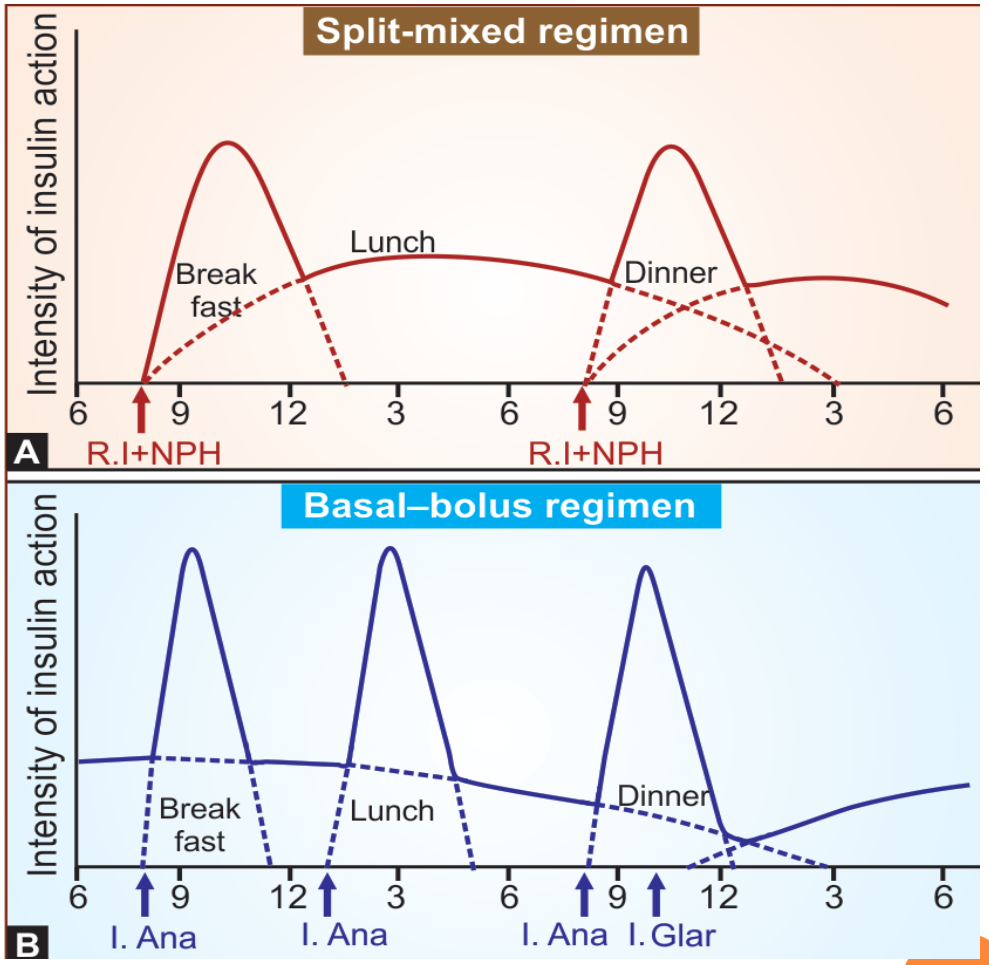
- Chronic- age, obesity and sedentry life
- Acute- infection, stress, trauma, surgery….
- Ketoacidosis
- Treat the precipitating cause and high doses of insulin

Insulin uses

- T_1DM
- Post pancreatectomy
- GDM
- T_2DM –Inadequately controlled by OHA
- Infections, trauma, surgery, DKA and hyperosmolar coma

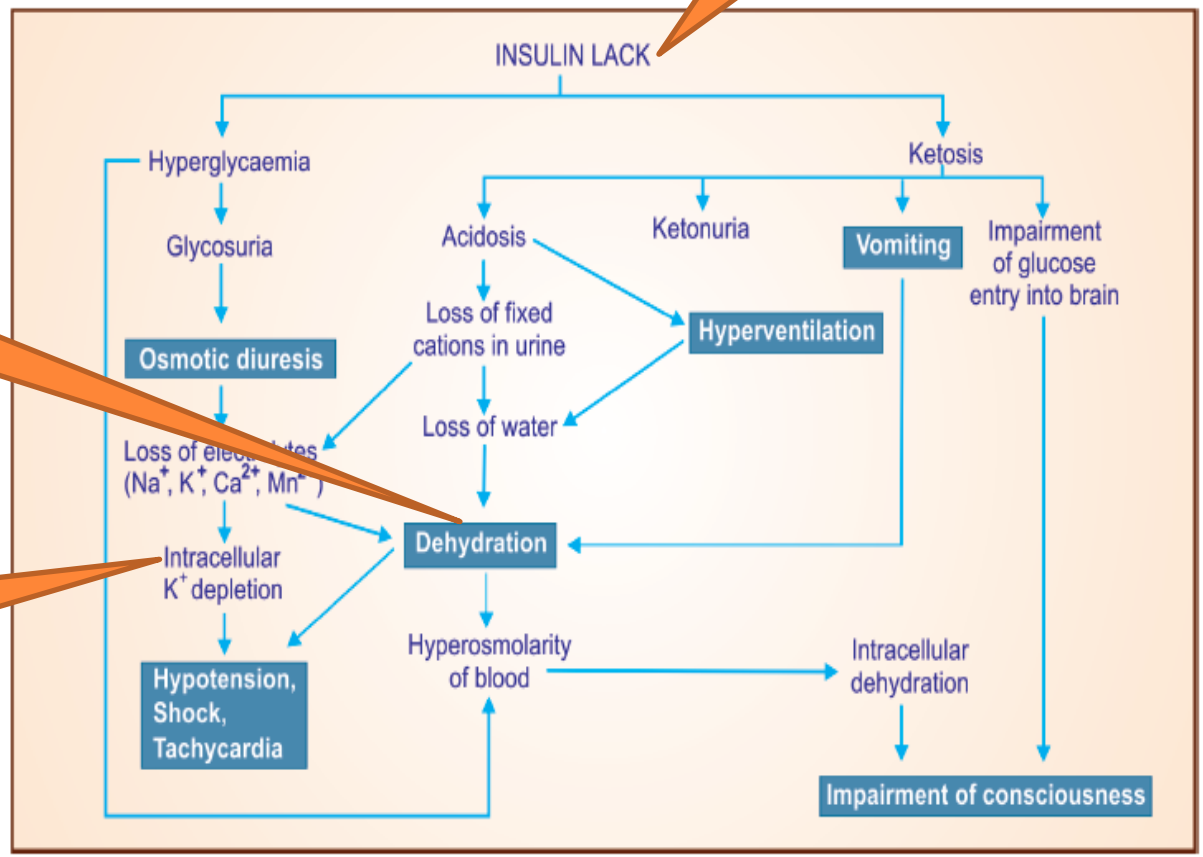
T1DM 0.4-0.8 U/Kg/Day

T2DM 0.2-1.6 U/Kg/Day



Insulin in DKA

insulin
0.1-0.2 IU/Kg →
0.1 IU/Kg/Hr



NS →
5%

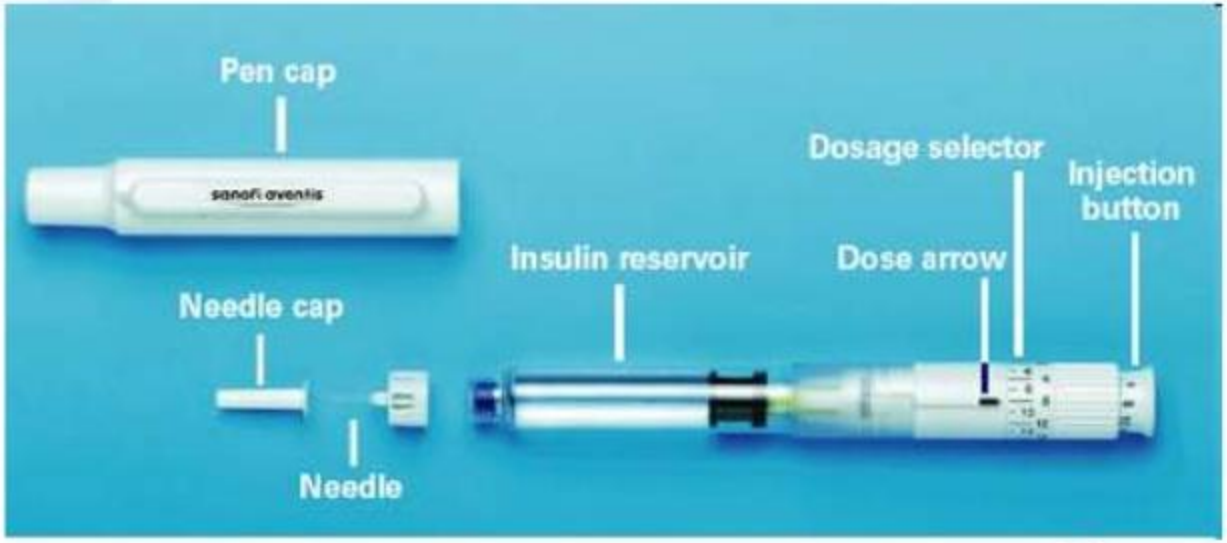
added
to IV

- IV sodium bicarbonate
- IV sodium/ potassium phosphate
- Antibiotics
- Other supportive measures

Newer insulin devices

PREFILLED SYRINGES

Portable Pen Injector



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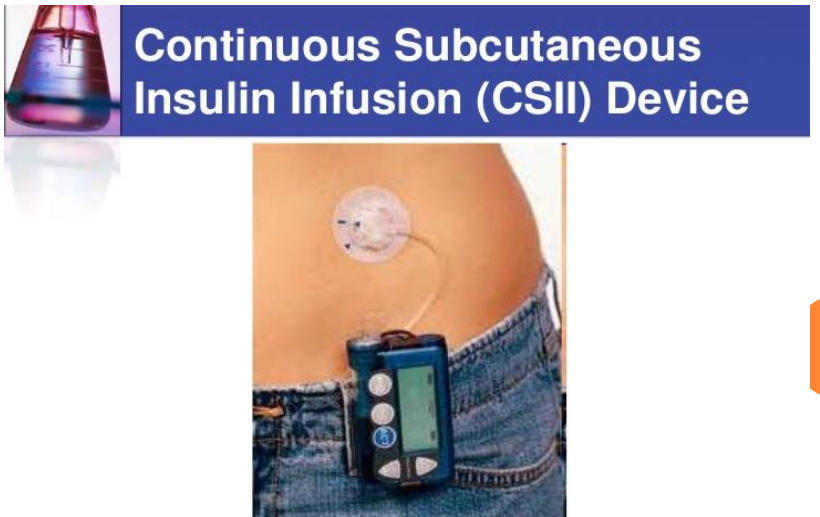
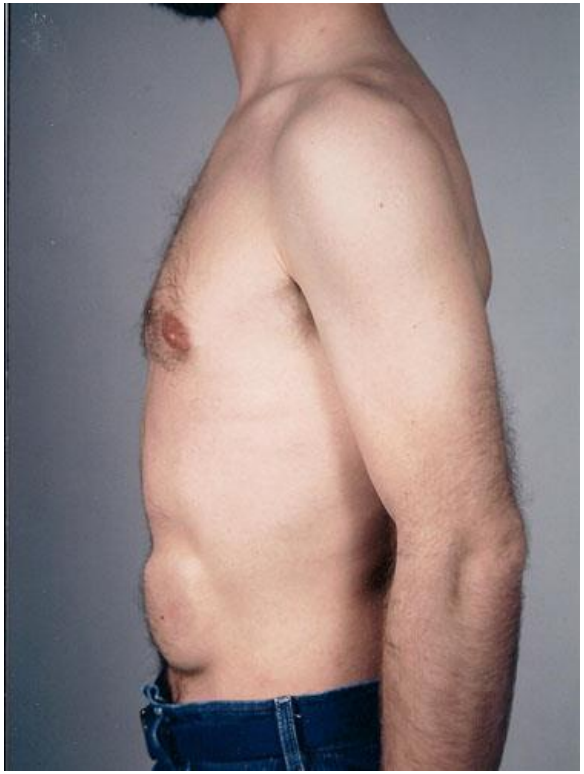
BIDNESS ETC
SANOFI
SANOFI
Insulin

Continuous subcutaneous insulin infusion (CSII) through pumps

- Most physiological method of insulin delivery
- Preferred in patients uncontrolled on multiple injections & those needing excellent control(pregnancy)
- Specially suitable for patients with risk of hypoglycemia, uncertain lifestyles,meal times.

❑ Consists of insulin reservoir, program chip, keypad& screen. Insulin infused through plastic tubings connected to s/c inserted infusion set .






pharmacy
Rx
DIN: 0123456789
Remain: 0 TAB

????

- The incretins for insulin release are?
- Species insulin which is more homologues with human is?
- The subunit of insulin receptor which carries the bindind site is?
- Insulin receptor is _____ type of receptor?

????

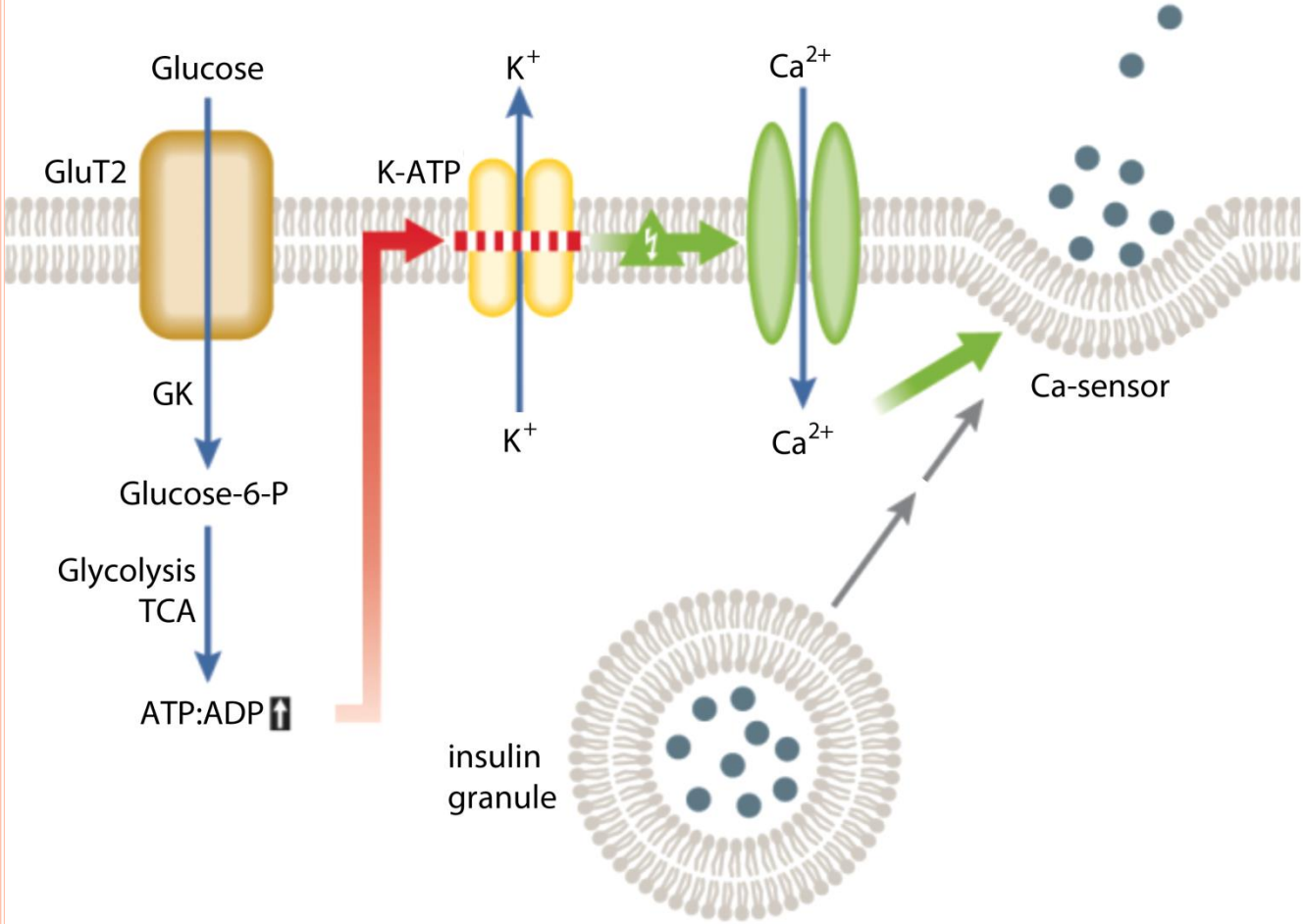
- Various types of insulin preparations are….?
- Human insulins are developed using this technology

Thank You

BIOSYNTHESIS OF INSULIN

- Synthesis of Preproinsulin-110AA
- Conversion of preproinsulin to proinsulin-86AA
- Conversion of proinsulin to insulin-51AA
- 1U reduces FBS 45mg/dl
- 1mg of insulin=28U

INSULIN REGULATION



Guess?????

Which is the principal regulator of insulin?

Which is the immediate precursor of insulin?

CATABOLISM OF INSULIN

- Half life: 5-9 minutes
- Major organs of degradation
  - > Liver.(proteinase)
  - >Kidney.
  - >Muscles.
- 50% of insulin removed in a single pass through liver.

SO……WHAT ARE INSULIN ANALOGUES??

Molecules produced by genetic engineering wherein the amino acid sequence in human insulin is changed to alter its pharmacokinetics. However, they bind to insulin receptors in the same way as human insulin and produce similar effects

Also termed as:

Designer Insulins

Democratic insulins

Diabetic coma

- Regular insulin(bolus 0.1U/Kg IV followed by 0.1U/kg/hr)- 10% / hr should be a adequate response
- After 6 hrs 2-3U/hr
- IV fluids for dehydration(NS, ½NS,5%D in ½NS)
- KCl infusion to counter hypokalemia
- Sod.bicarbonate to correct acidosis
- Antibiotics
- Phosphate infusion

Insulin preparations

- Regular(soluble)
- Lente(insulin-zinc suspension)
- Isophane(Neutral Protamine Hagedorn)
- Human insulins
- Insulin analogues

What was the need for insulin analogues when we had improved insulins???

Insulin therapy aims to ***mimic physiological insulin secretion*** *(Basal & Bolus)*

Preparations providing bolus insulin requirements should have ***rapid onset, rapid peak & short duration*** *& those providing basal requirements should have* ***low basal conc(without a peak) for a long duration.***

Std. insulins don't mimic ***physiological insulin secretion,***

often result in ***mismatch between requirement & availability***

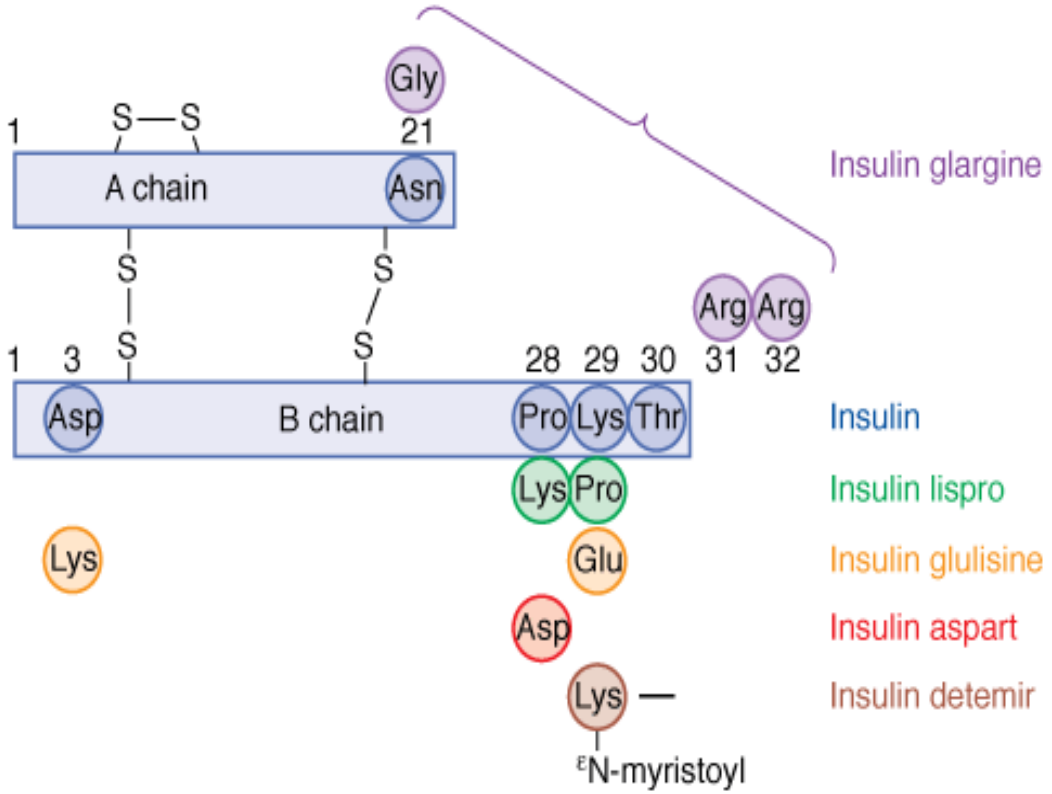
& result ***in inadequate glycemic control*** *&* ***late hypoglycemia***

So……

Insulin analogues were developed to overcome the limitations of available insulins:-

- ***Ultrashort acting analogues to overcome limitations of short acting insulins(regular)***
- ***Long acting analogues to overcome limitations of long/intermediate acting insulins(NPH)***

Insulin analogues



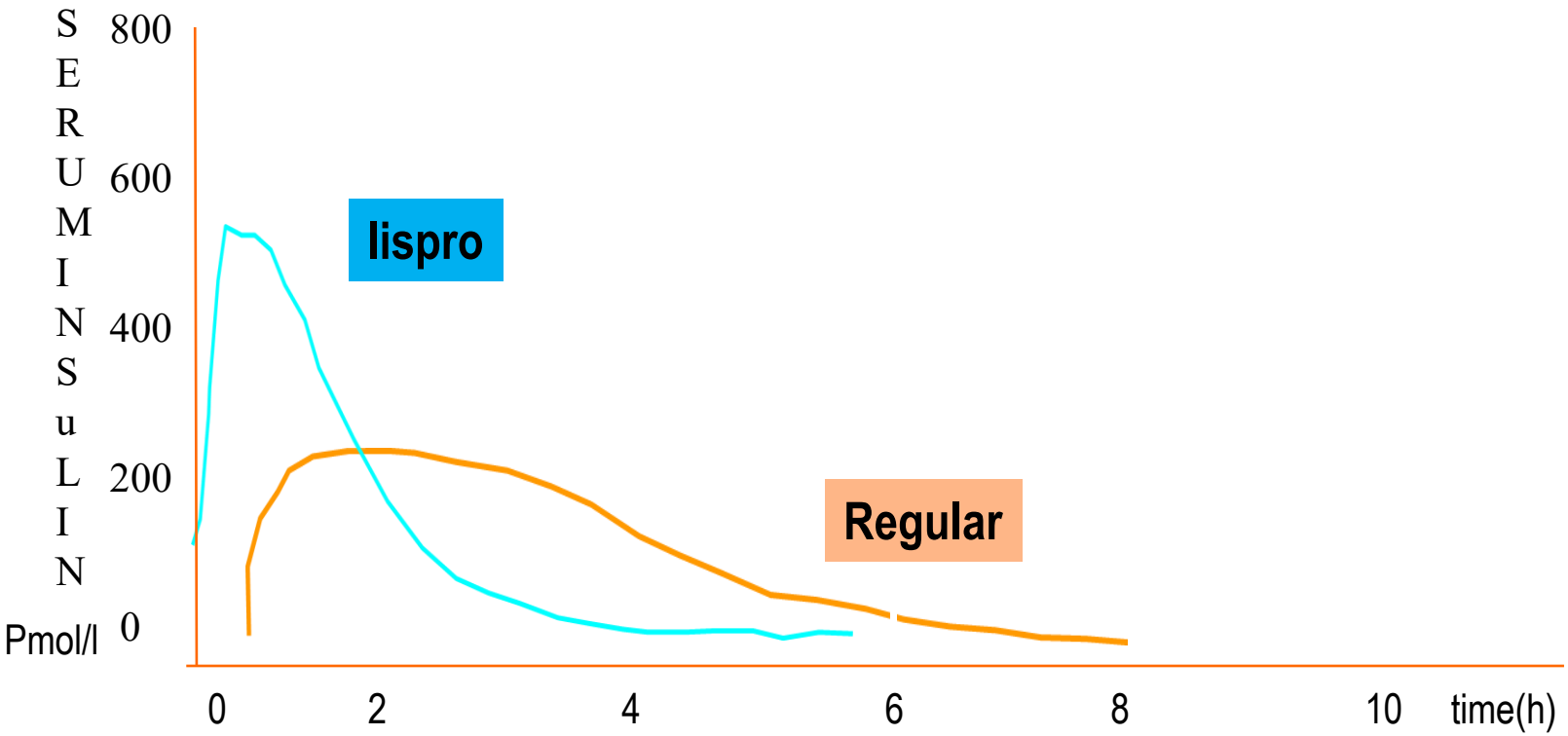
What is a satisfactory insulin regimen?

Provide insulin for basal control

Supply extra insulin to meet Postprandial needs

Multiple injections of long and short Acting insulins/single long acting insulin supplemented with OHA

LISPRO VS REGULAR



GLARGINE

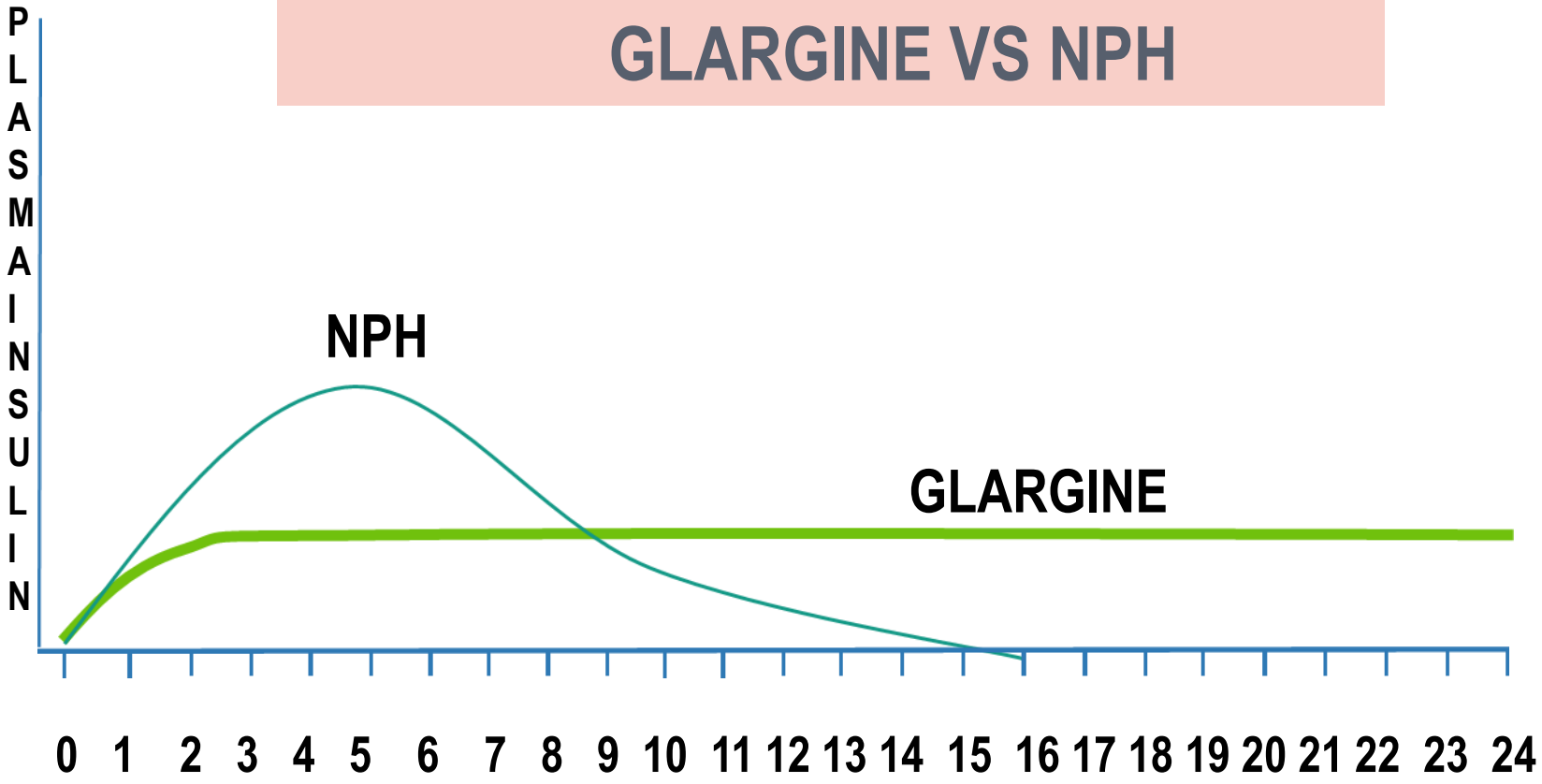
- Action prolonged by changing isoelectric point in glargine.

  Glargine available as a clear solution at pH 4 but precipitates at neutral pH in subcutaneous tissue.

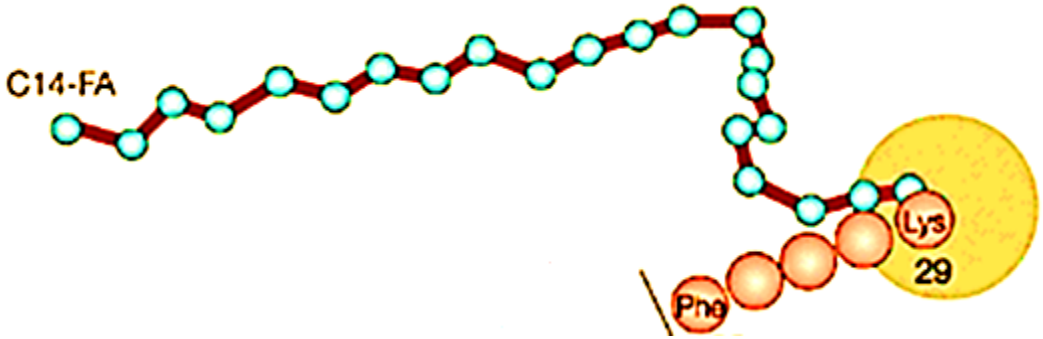
  ↓

  Precipitate slowly dissociates to release monomers which are absorbed slowly providing prolonged, uniform action.

GLARGINE VS NPH

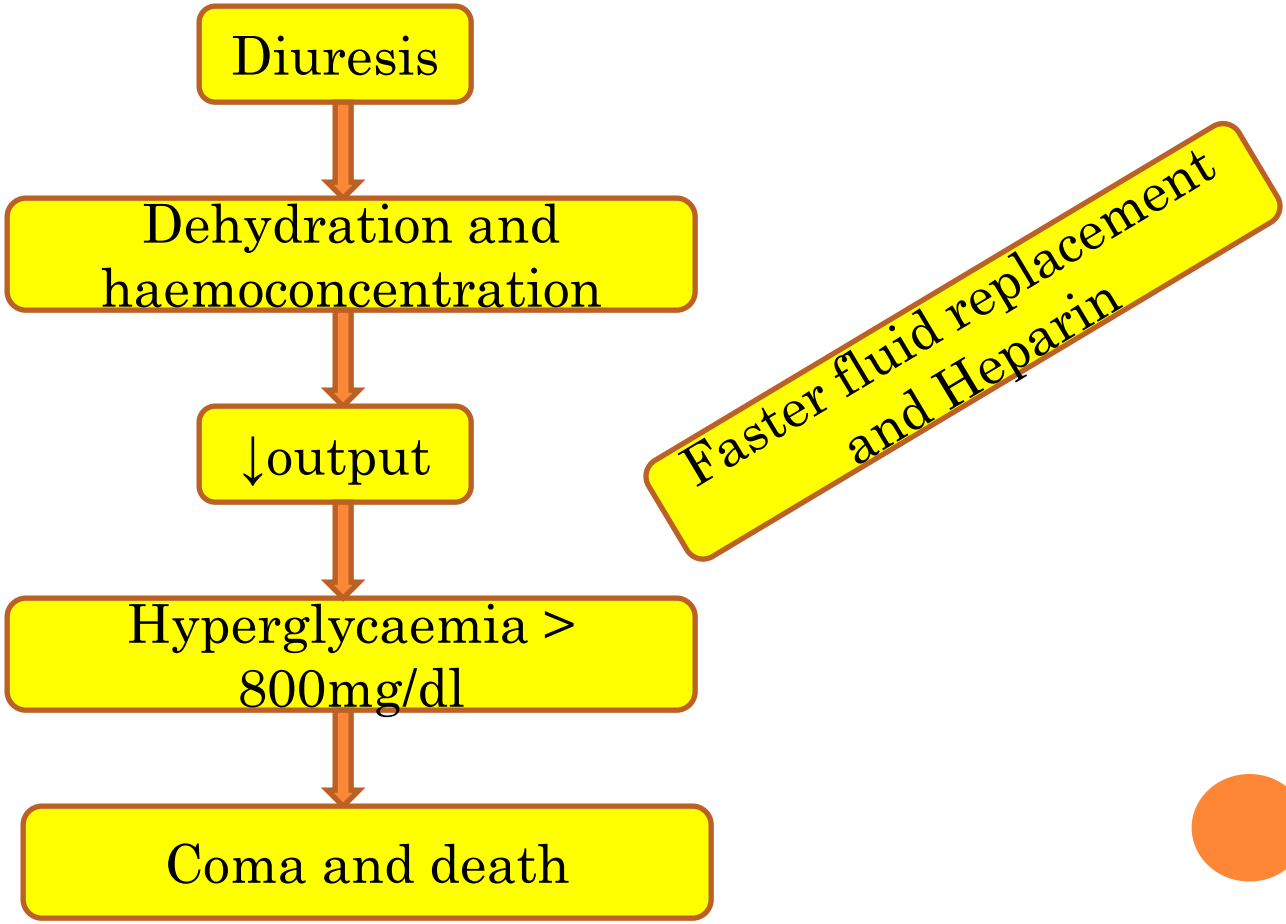


Detemir



NONKETOTIC HYPEROGLYCAEMIC COMA

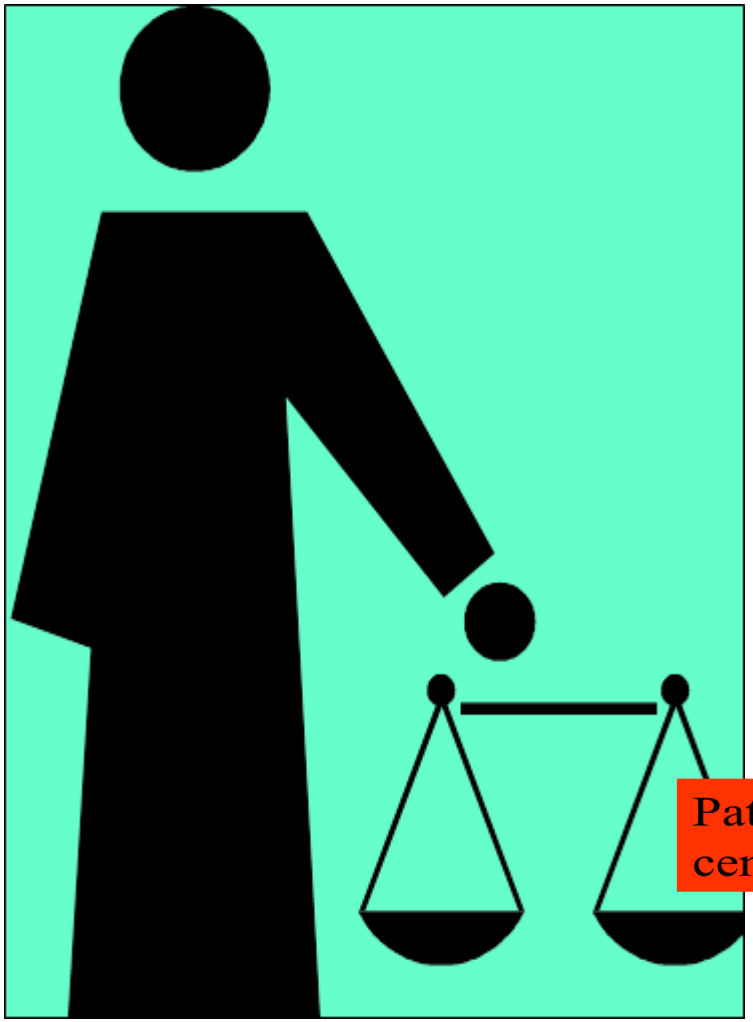
- Elderly T2 patients due to uncontrolled glycosuria



SUMMARY

- Insulin analogues have modified chemical structure with novel pharmacokinetics
- Classified into short acting(Lispro,Aspart,Glulisine)& long acting(Glargine, Detemir,)
- Mimic physiological insulin secretion closely with less risks of hypoglycemia.
- High cost is one main drawback. Also possibilities of unforeseen risks cant be ruled out . Hence prescribed if benefits in the patient outweigh demerits.

WEIGH COST & BENEFITS BEFORE PRESCRIBING…….



INSULIN DELIVERY – short acting insulin analogues like Aspart(lispro) used.

- Provides constant basal infusion of insulin & patient can activate pre-meal boluses.
- Pumps can be discontinued for short periods for activities like exercise
- Pump can be pre-programmed to compensate for nocturnal & early morning glucose fluctuation.

Advantages

- Rate of insulin absorption more predictable than multiple injections
- Risk of hypoglycemia less

Drawbacks

- Pump failure -→ketoacidosis
- Injection site abscess
- Only motivated & commited patients can use it.

INSULIN ANALOGUES IN SPECIAL SITUATIONS

- Diabetic ketoacidosis – Lispro (i.v)
- Pregnancy

  Lispro & Aspart demonstrated efficacy&safety (Cat B)

  Long acting analogues not studied.
- Children

  Data on insulin analogues is limited.
- Elderly (at risk of hypoglycemia)

  Insulin analogues preferred.

NEW DELIVERY SYSTEMS USING ANALOGUES

- Insulin pens (ultra short acting/long acting/pre-mix analogues)

- CSII pumps (Aspart>Lispro)

SUMMING UP THE MERITS OF INSULIN ANALOGUES…….

- Better mimicking of physiological insulin secretion.
- Better control of post prandial blood glucose levels
- Better control of glucose levels in the fasting, interdigestive period.
- Lesser risk of hypoglycemia.
- Action profile independent of dose/site of inj/exercise- more predictable action.
- Greater flexibility with short acting analogues as they can be given at meal times.

DEMERITS

- No significantly different adverse effects when compared to std insulins.
- Worsening Retinopathy with Lispro (homologous to IGF-1)
- ???Carcinogenicity: Concerns over Glargine carcinogenicity (FDA considers Glargine as a Black triangle drug)

- **COST**

Analogue (1000 u/vial)	Insulin (1000u/vial)
Lispro - $ 105 **Aspart - $ 105** **Glulisine - $ 95**	**Regular - $45**
Glargine - $95 **Detemir - $95**	**NPH - $45**

SO……INSULIN ANALOGUES ARE PREFERRED IN :

- Persons with uncertain lifestyle/qty of meals/time of meals (busy persons) not controlled by std.insulins
- High unpredictable FBS/PPBS
- Risk of hypoglycemia esp. nocturnal (elderly)
- Unexpected exercise (sportsmen/policemen)
- Critical patients (hepatic & renal disease, ICU patients shifted from iv to s/c, periop patients)
- Wt gain with std. insulins(?)

CONCLUSION

INSULIN ANALOGUES

So far seem to be fulfilling the promise of Recombinant DNA technology

with

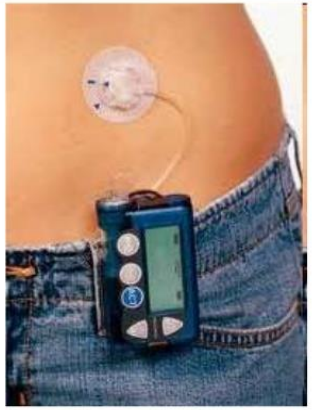
Better Bolus insulin

Better Basal insulin

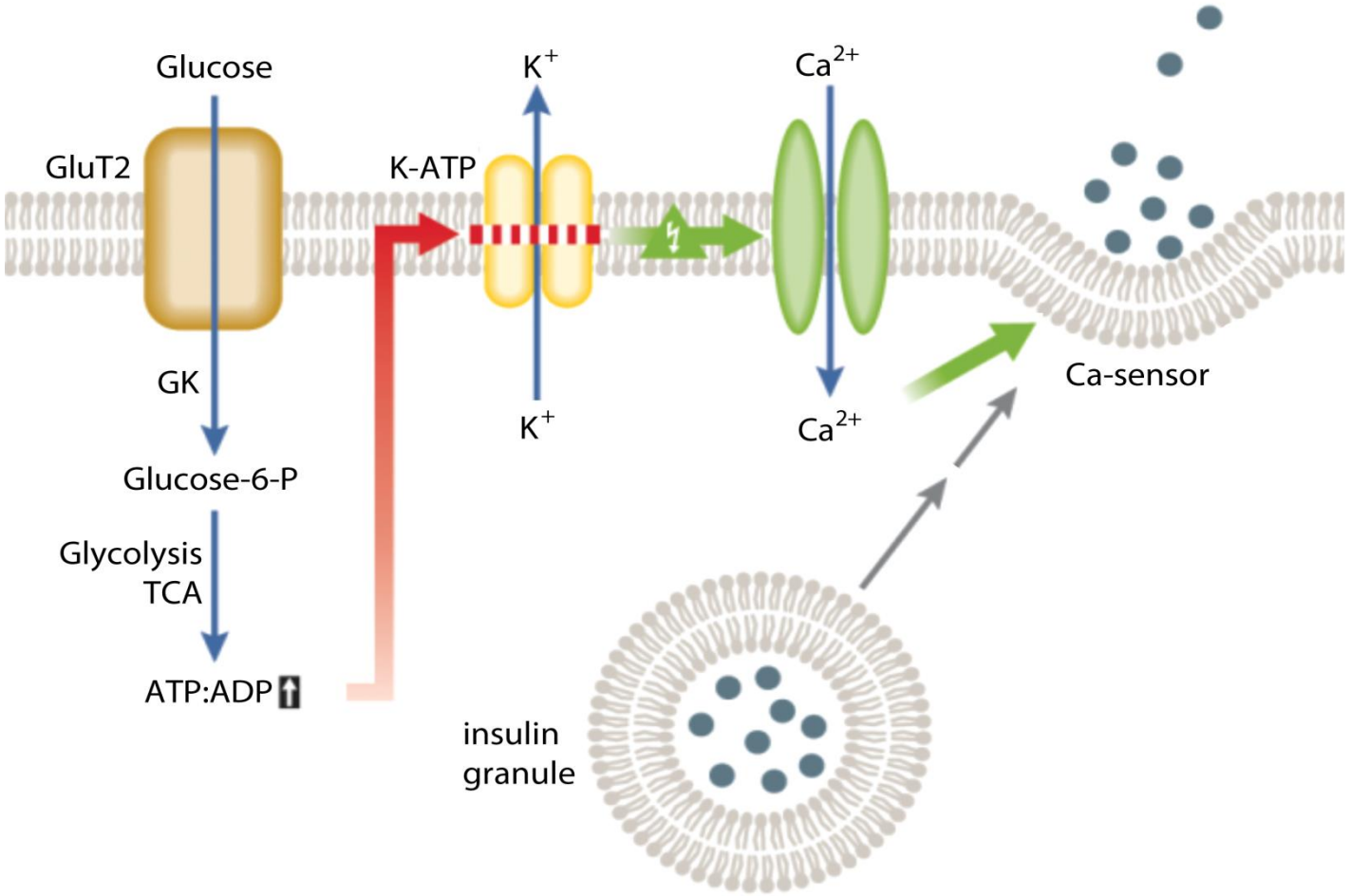
Better Blood glucose

However, more years of experience needed before we can fully trust them for our patients !!!

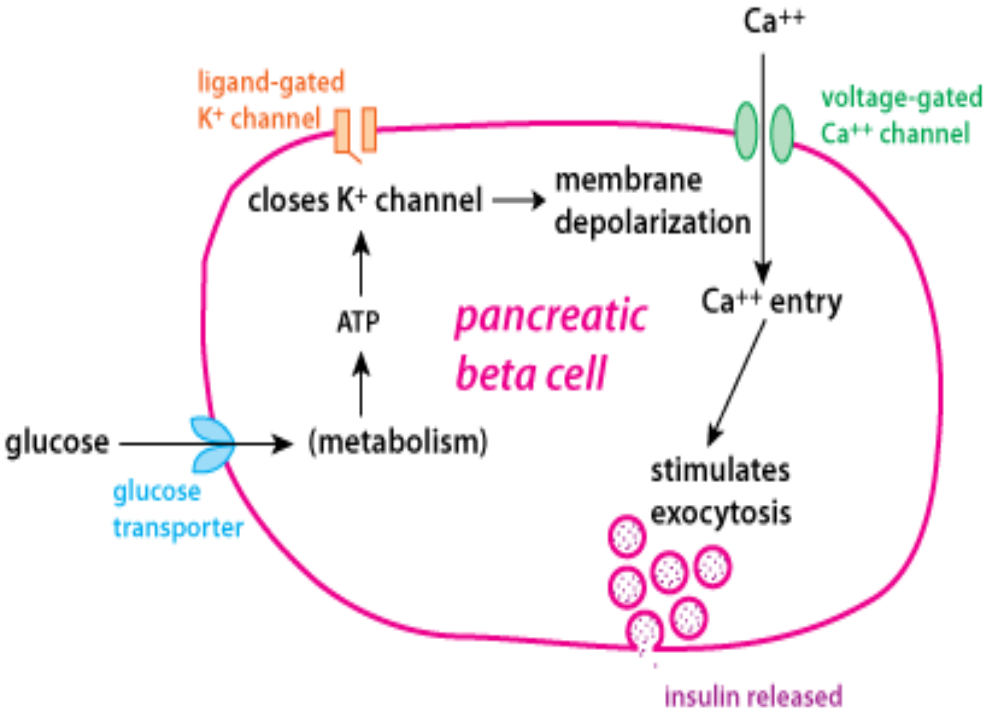
Continuous Subcutaneous Insulin Infusion (CSII) Device



INSULIN REGULATION

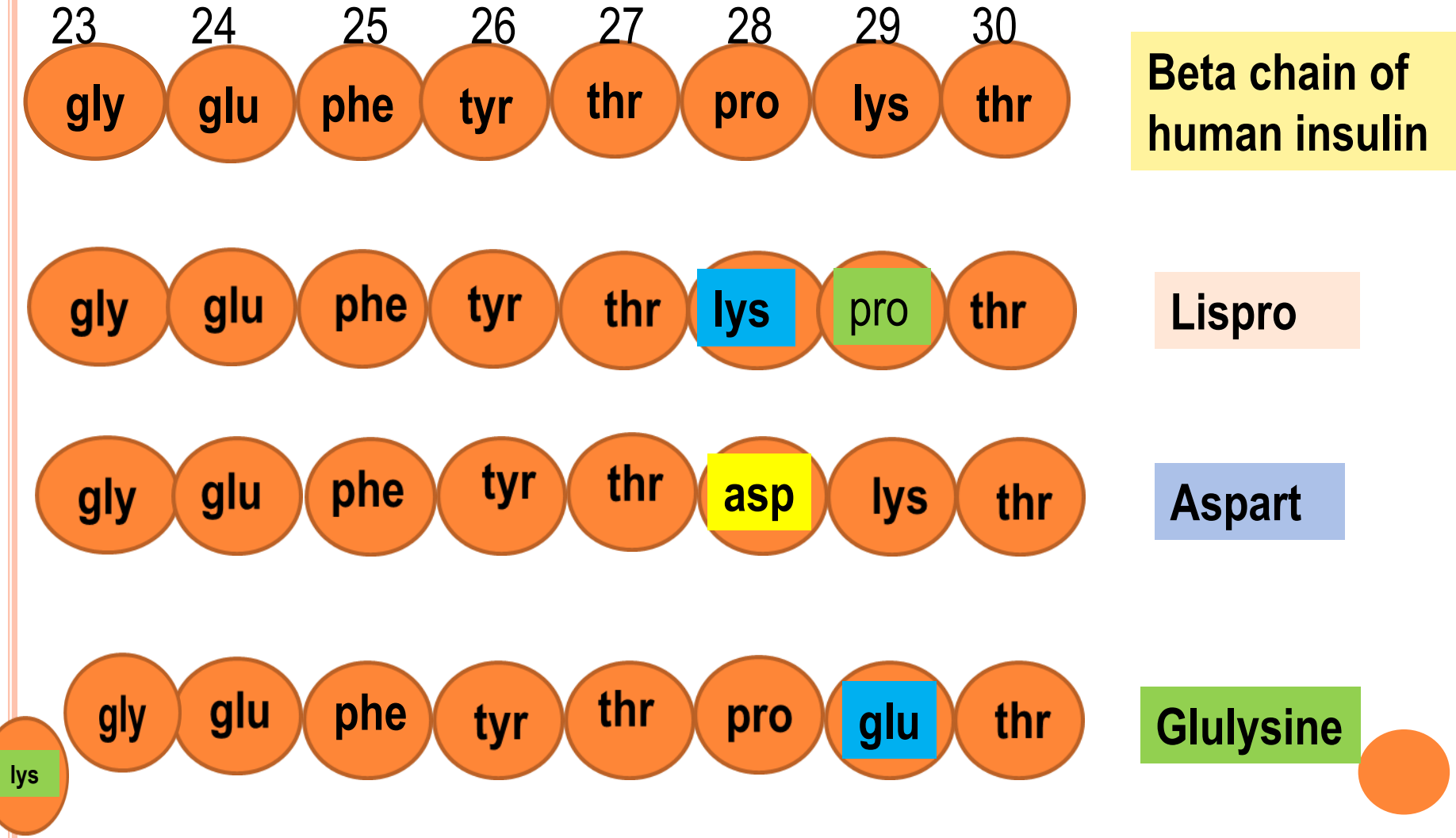


Insulin regulation



Species	*A-chain*		*B-chain*
	8th AA	*10th AA*	*30th AA*
Human	THR	ILEU	THR
Pork	THR	ILEU	ALA
Beef	ALA	VAL	ALA

LISPRO , ASPART & GLULISINE

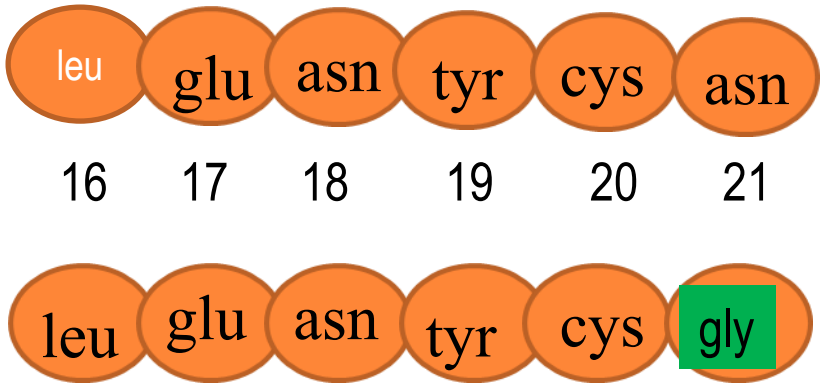


CLASSIFICATION

Insulin and analogue preparations

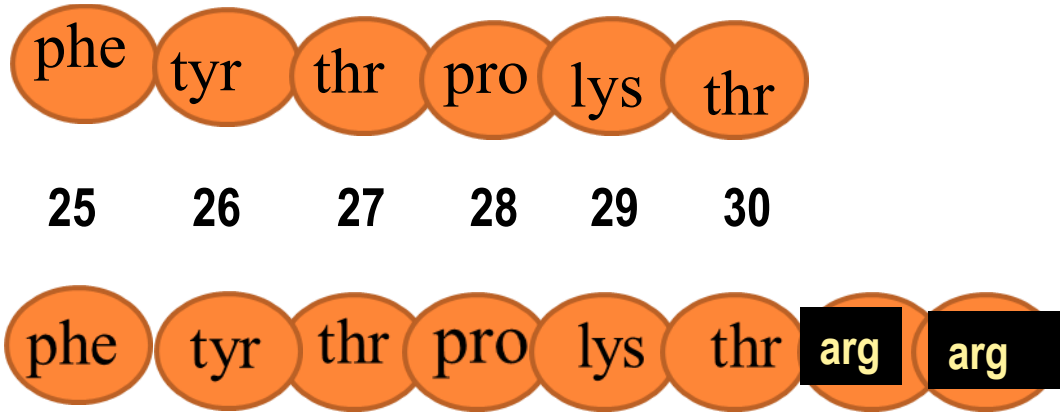
Short acting	Long acting
- Regular	- NPH, lente
- Lispro	- Glargine
- Aspart	- Detemir
- Glulisine	- Degludec

GLARGINE – CHEMICAL MODIFICATION



Alpha chain of insulin

Alpha chain of glargine



Beta chain of insulin

Beta chain of glargine

INSULIN REGIMES WITH INSULIN ANALOGUES

- **Basal regime** : Glargine once daily at bedtime or Detemir twice daily .
  - *May be used when starting insulin in type 2 DM (along with OHA)*
  - *Used when there is dependence on others for injection*.
- **Conventional split dose regimes** : Pre-mix analogues injected twice a day (pre-breakfast & pre-evening meal).
  - *Type 1 & 2 diabetes*
  - *Simplify dosing & decreases no. of injections*.
- **Basal bolus regimen (intensive regimes):** Glargine at bedtime to cover basal insulin secretion + short acting analogue to cover mealtime
  - *Type 1 usually (Type 2 at times)*

  Analogues preferred in intensive regimes due to decreased risk of hypoglycemia with their use.