RECENT ADVANCES IN DIABETES MELLITUS

Nihal Thomas

MD MNAMS DNB (Endo) FRACP (Endo) FRCP(Edin)

Professor,

Department of Endocrinology, Diabetes and Metabolism

Christian Medical College

Vellore

India

Newer Peroxisome Proliferator Activated Receptor Agonists

- *Balaglitazone:* partial selective agonist of PPAR.

  a partial agonist: hypothetically, the adverse effect profile may be more favourable.

  Phase 3 clinical trials are ongoing.

- *Rivoglitazone* is a complete agonist of PPAR.

  More potent in 2 mg and 3 mg doses when compared to pioglitazone with regards to glycaemic control

> peripheral oedema and weight gain associated with its usage. Lower doses of Rivoglitazone being researched upon.

- Some other PPAR agonists in phase 2 trials: include *Glitazones: Mitoglitazone* and *Netoglitazone.*

- *Glitazaars:*

  Metaglidasen, Indeglitazar, Aleglitazar.

- **Tagatose**

  It is a low calorie hexoketose (monosaccharide)

  - occurs naturally in dairy products.

Generated by isomerization of galactose

and administered orally.

Reduces postprandial peaks in plasma glucose levels.

Adverse effects:

nausea, flatulence and abdominal bloating.

In phase 2 studies.

New Hepatic Targets for Glycaemic Control in Diabetes

- *Glucagon Receptor Antagonists*

Counteracts active stimulation of glycogenolysis by glucagon

Basal gluconeogenesis not effected.

Partial down regulation of the glucagon receptor

Lowering of plasma triglycerides.

Glucagon receptor antagonists + GLP-1 agonists:

partially offset the rise in plasma glucagon.

In Phase 1 and animal studies

- *Glucose 6-phosphatase Inhibitors:*
  *(*Peroxovanadium compounds)
  Glucose 6-phosphatase catalyses the final reaction in hepatic glucose production from gluconeogenesis and glycogenolysis.
  Counteract the hyperglycaemic response to glucagon
  and have insulin mimetic properties

- Limitations:
  - acute suppression of hyperglycaemia posing a risk for hypoglycaemia
  - enzyme inhibition leading to accumulation of glucose 6-phosphate and glucagon: inducing lipogenic enzymes resulting in hepatic steatosis

In Phase 1 and animal studies

- *Fructose 1,6 bisphosphatase inhibitors*

Fructose 1, 6 bisphosphatase catalyses the penultimate reaction in Gluconeogenesis: regulated by the physiological inhibitors- AMP and Fructose 2, 6 bisphosphatase.

-AMP mimetics: inhibit gluconeogenesis and concomitantly stimulate glycogenolysis- safeguarding against hypoglycaemia.

-Advantage over Glucose 6-phosphatase Inhibitors:

even though intermediate products in gluconeogenesis are elevated, glucose 6-phosphate is not elevated-

circumventing the problem of secondary regulation of lipogenic genes.

- Glycogen Phosphorylase Inhibitors:

  Inhibition of hepatic glucose production by the phase 1 insulin secretion postprandially is mainly due to inhibition of glycogenolysis by inactivation of glycogen phosphorylase.

  -Animal Studies

- *Glucokinase Activators:*

  Glucokinase: an important role on glucose metabolism in the liver by glycogen synthesis and glycolysis.

  It has been seen that mutations that increase the enzyme's affinity for glucose had a blood glucose lowering effect.

- **Resveratrol:**

  Found in red grapes: improves glycaemic control when delivered orally to rodents.

-activates sirtuins, proteins that may mimic some of the effects of calorie restriction.

- animals have shown some evidence that when sirtuins are activated by resveratrol, that glycaemic control is improved.

- Sirtuin activators: being tested in humans as anti-diabetic compounds.

- **Renal Sodium-Glucose Transport Inhibitors**

- **Selective Sodium-Glucose Co-ransporter-2 (SGLT) Inhibitors**

Kidneys play an important role in glucose homeostasis being involved in filtration and reabsorption of blood glucose.

- Gluconeogenesis taking place in the kidney contributes to about 5-10% of the body glucose production.

- SGLT – 2: the main glucose transporter in the kidney that is located in the proximal tubule.

SGLT – 1: a smaller role in glucose reabsorption in the kidney (more in the gut).

- **Sergliflozin and Dapagliflozin:**

-in Phase 3 clinical trials and have been shown to induce glycosuria and thus lower blood glucose.

-energy loss through glycosuria:

moderate weight loss.

-Urinary glucose excretion: 85 g per week- 7 times the quantum that was seen pre-treatment.

3% weight loss : 50 mg/dl decrease in plasma glucose.

Doses from 2.5 mg to 50 mg a day.

- Adverse effects are urinary tract infections, dizziness, headache, fatigue and nasopharyngitis.

- **Colveselam:**

  Bile Acid sequestrant

  depletes intestinal bile pool- increased hepatic bile acid synthesis- depletes hepatic cholesterol

  - increased GLP-1 production?

  Approved by FDA for Rx of DM. (Monotherapy)

THE LANCET- April 20th, 2009.

Effects of a Polypill (Polycap) on risk factors in middle-aged individuals without cardiovascular disease (TIPS): a phase II, double-blind, randomized trial.

Yusuf S, Pais P, Afzal R, Xavier D, Teo K, Ekelboom J, Sigamani A, Mohan V, Gupta R, **Thomas N**

BACKGROUND: Combination of three blood-pressure-lowering drugs at low doses, with a statin, aspirin, and folic acid can reduce cardiovascular events by more than 80% in healthy individuals.

FINDINGS: Reductions in heart rate with Polycap and other groups using atenolol were similar (7.0 beats per min), and both were significantly greater than that in groups without atenolol ($p<0.0001$).

The reductions in 11-dehydrothromboxane B2 were similar with the Polycap compared with the three blood-pressure-lowering drugs plus aspirin and aspirin alone compared with groups without aspirin.

Tolerability of the Polycap was similar to that of other treatments

Components of the Polypill

- Aspirin -100mg
- Atenolol - 50mg
- Ramipril -5mg
- Simvastatin -20mg
- Hydrochlothiazide -12.5mg

Soluble Basal Insulin Analogue (SIBA)

- Metformin in Gestational Diabetes (MIG)
  NEJM 2008.

  Effective.
  Composite primary neonatal outcome satisfactory.

  50% of Metformin group needed supplemental insulin

- Sulphonylureas increase the risk of active CVD in those with diabetes

  Endocrine Practice 2008.

  >LVF, arrhythmias and death

Not with Glimeperide, Gliciazide, Nateglinide

Lack of myocardial reperfusion

GILA MONSTER

Heloderma suspectum

Produces Exendin-4 in it's saliva that has a 53% amino acid

sequence overlap with mammalian GLP-1 (Glucagon-like peptide-1),which stimulates insulin production and delays gastric emptying.

Exenatide

GLP-1 is degraded within 1-2 minutes by Dipeptidyl peptidase-IV within 1-2 minutes of entering the circulation.

Exenatide is >1000 times more potent than GLP-1 in circulation.Does not stimulate gastric acid secretion or trigger hepatic vagal efferents.

Actions:

1. **Stimulation of Insulin Secretion**
2. **Suppression of Glucagon Production**
3. **Slowing of Gastric Emptying**
4. **Promote Beta Cell Proliferation**

Exenatide ……

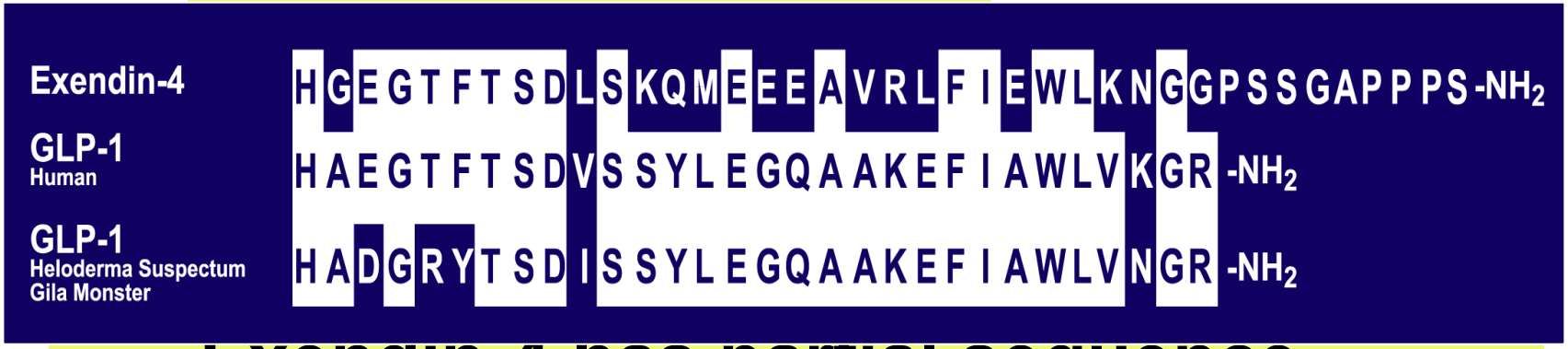
Adverse Effects

Nausea: 30%(subsides within one week of therapy)

Hypoglycaemia: Only when on Sulphonyureas

Exendin-4 and GLP-1

Amino Acid Sequences:

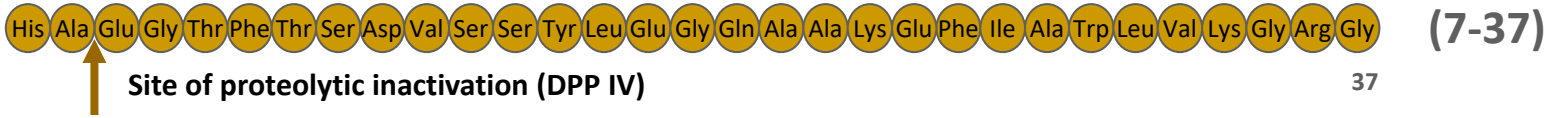


- **Exendin-4 has partial sequence identity with GLP-1**
- **Exendin-4 and GLP-1 are products from distinct genes in the Gila monster**
- **Exendin-4 and GLP-1 bind to the known pancreatic GLP-1 receptor in vitro**

Exendin-4 is Resistant to DPPIV

AC2993 (Exendin-4)

GLP-1 **Glycine-extended form**



Exenatide ……

Benefits

Can be combined with Most oral hypoglycaemic agents & Insulins

Weight Reduction

Favourable impact on Lipid Profile

Exenatide ……

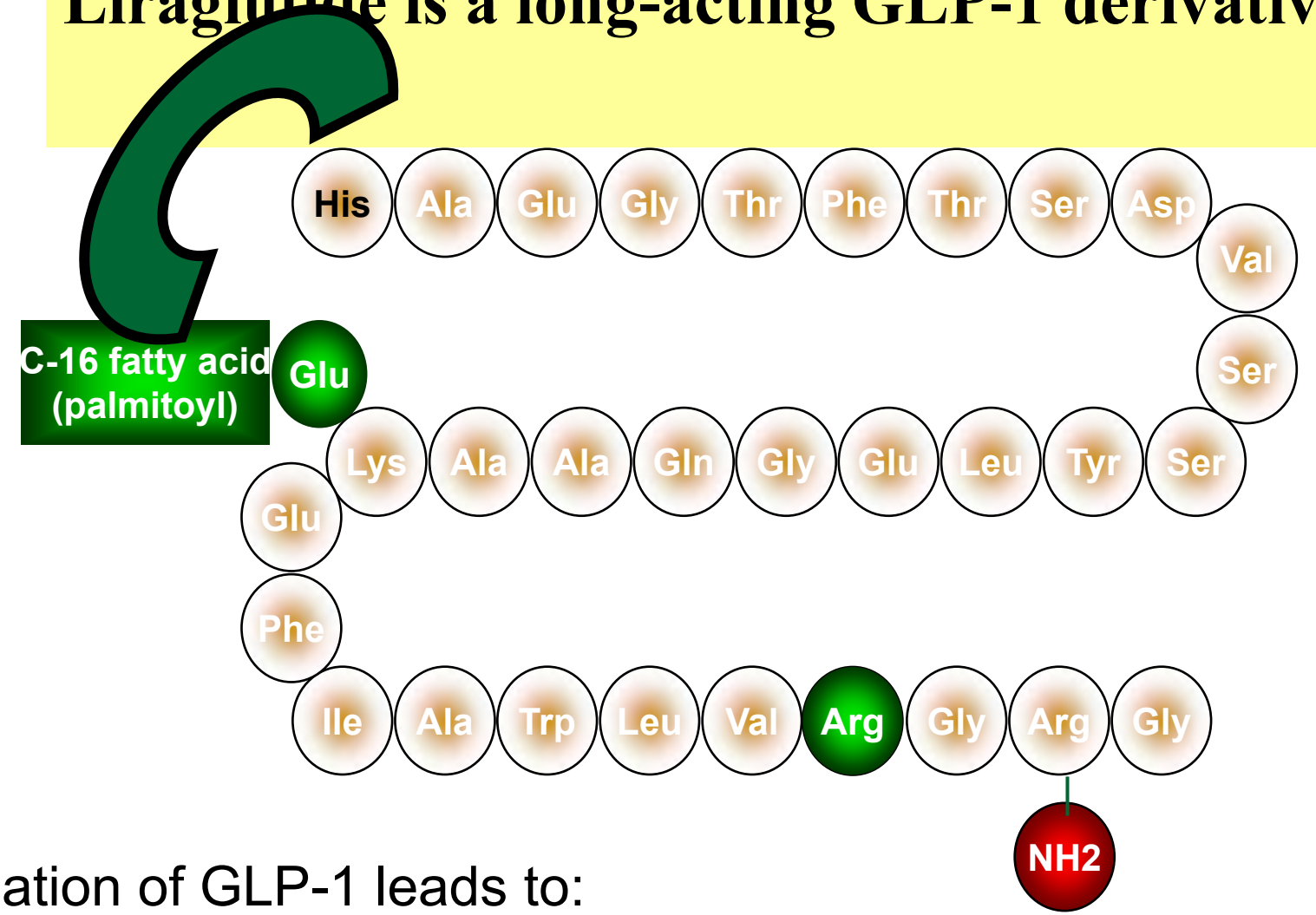
Therapeutic Use

Subcutaneously

0.08 units/kg body weight per day twice a day

Major Adverse Effect: Acute Pancreatitis

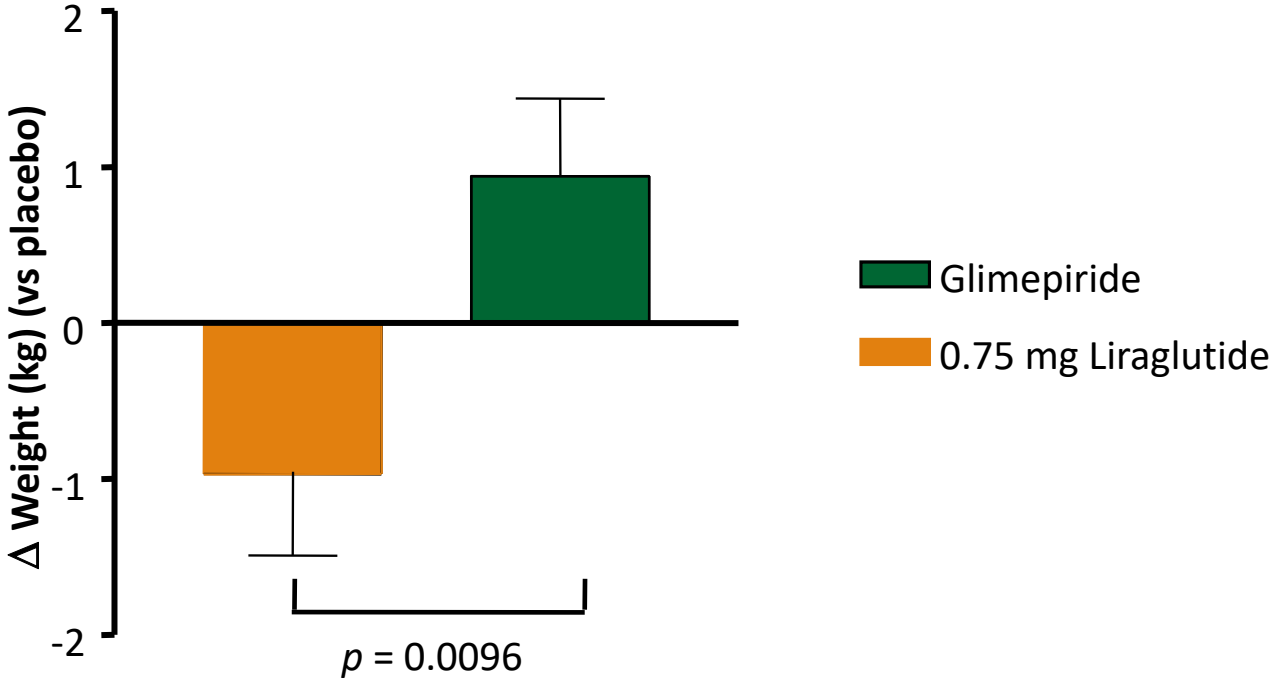
Liraglutide is a long-acting GLP-1 derivative



Acylation of GLP-1 leads to:

- Slow absorption
- Albumin binding
- Reduced renal clearance

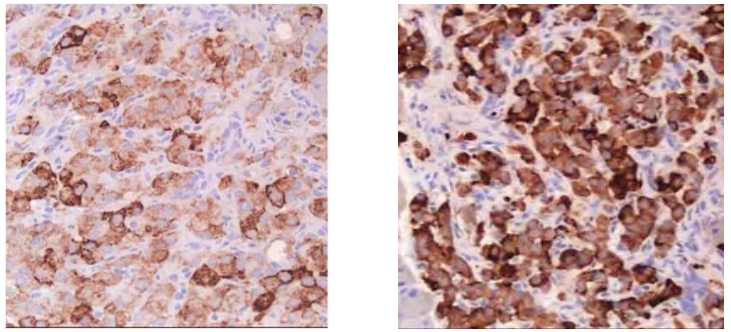
Liraglutide reduces weight……



Matthews et al. Diabetes 2002; 51 (Suppl 1)

Liraglutide induced β-cell proliferation is glucose-dependent

- Dosed for 2 weeks, liraglutide completely prevents the progression of diabetes in 8-weeks old ZDF rats
- Proliferation and volume of β-cells is normalized



Increased insulin staining intensity after treatment

Liraglutide .....

- Has Gone through Phase 3 trials

- 2 mg preparation of Exenatide-LAR: administered on a once weekly basis:

  compared with conventional Exenatide 10 mcg on a twice daily basis: greater reduction in HbA1c levels.

- *Taspoglutide*

  Another extended release molecule works on a once weekly basis

  - promising results in phase 2 studies.

- *Albiglutide* undergoing phase 2 studies

GLP-1 Formulations and Analogues

Native GLP –1	
Various	Sublingual, SC depot
GLP-1 Analogues	
Exendin-4 (Exenatide)	More stable GLP-1 analogue
NN2211 (Liraglutide)*	GLP-1-fatty acid,[1] $t_{½}$ 12.6h
LY307161	Long-acting GLP-1 analogue
BIM-51077 (acquired by Roche)	Long-acting GLP-1 analogue
CJC-1131	GLP-1 (drug affinity complex)
Oral GLP-1	D-ala2-GLP-1 in microspheres
Ulster-GLP-1	Modified-GLP-1

- **IMMUNOTHERAPY FOR TYPE 1 DIABETES**

Humanized anti-CD3 Monoclonal Antibodies

Otelixizumab **and** ***Teplizumab*** **bind to CD3/TCR complex and block full T cell activation, proliferation and cytokine release.**

- **Down regulation of T-effector cells, may lead to a reduced autoimmune attack on the beta cells.**

- **Otelixizumab: administered for 8 consecutive day- subjects have been followed up to observe remission of new onset Type 1 diabetes mellitus.**

- **Teplizumab has been used in new onset Type 1 diabetes mellitus, with the administration of 14 consecutive day injections.**

  An annual follow up: glycaemic remission and maintenance of C-peptide levels appear to be promising.

- **Longer follow up is required to assess whether remission of diabetes may be prolonged.**

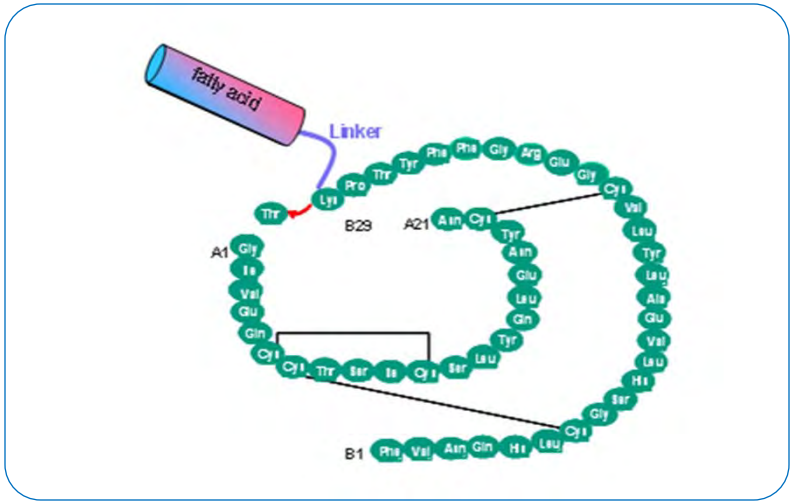
- **Recombinant Human Glutamic Acid Decarboxylase (rhGAD65)**

- Vaccine that induces immunotolerization and may slow or prevent autoimmune beta cell destruction.

  In some subjects with LADA, there has been an associated improvement in glycaemic control and rise in stimulated C-peptide levels.

  (Phase 2 and 3 studies)

Insulin degludec is a new generation, ultra-long acting basal insulin



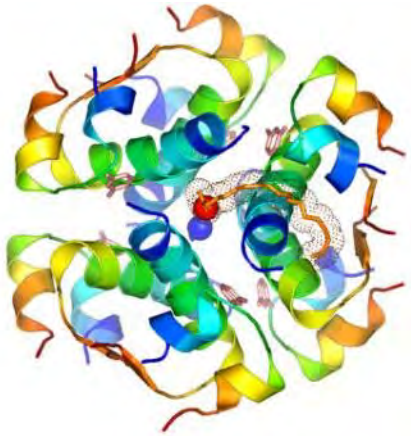
De

glu

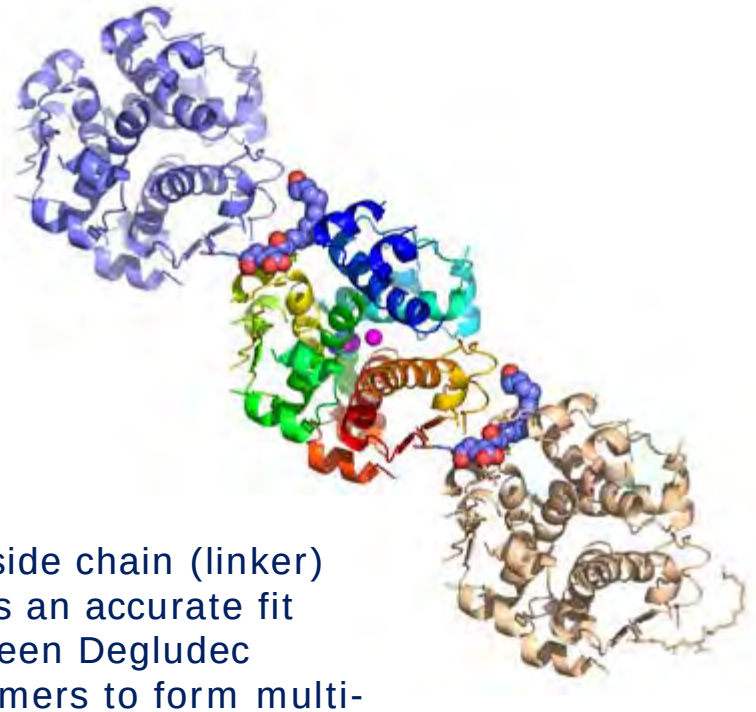
dec

- Degludec
  - Insulin backbone
  - Side chain: fatty acid + linker
    - Allows formation of multi-hexamers
    - Confers albumin binding

Degludec – Multi-hexamer formation key to protraction mechanism

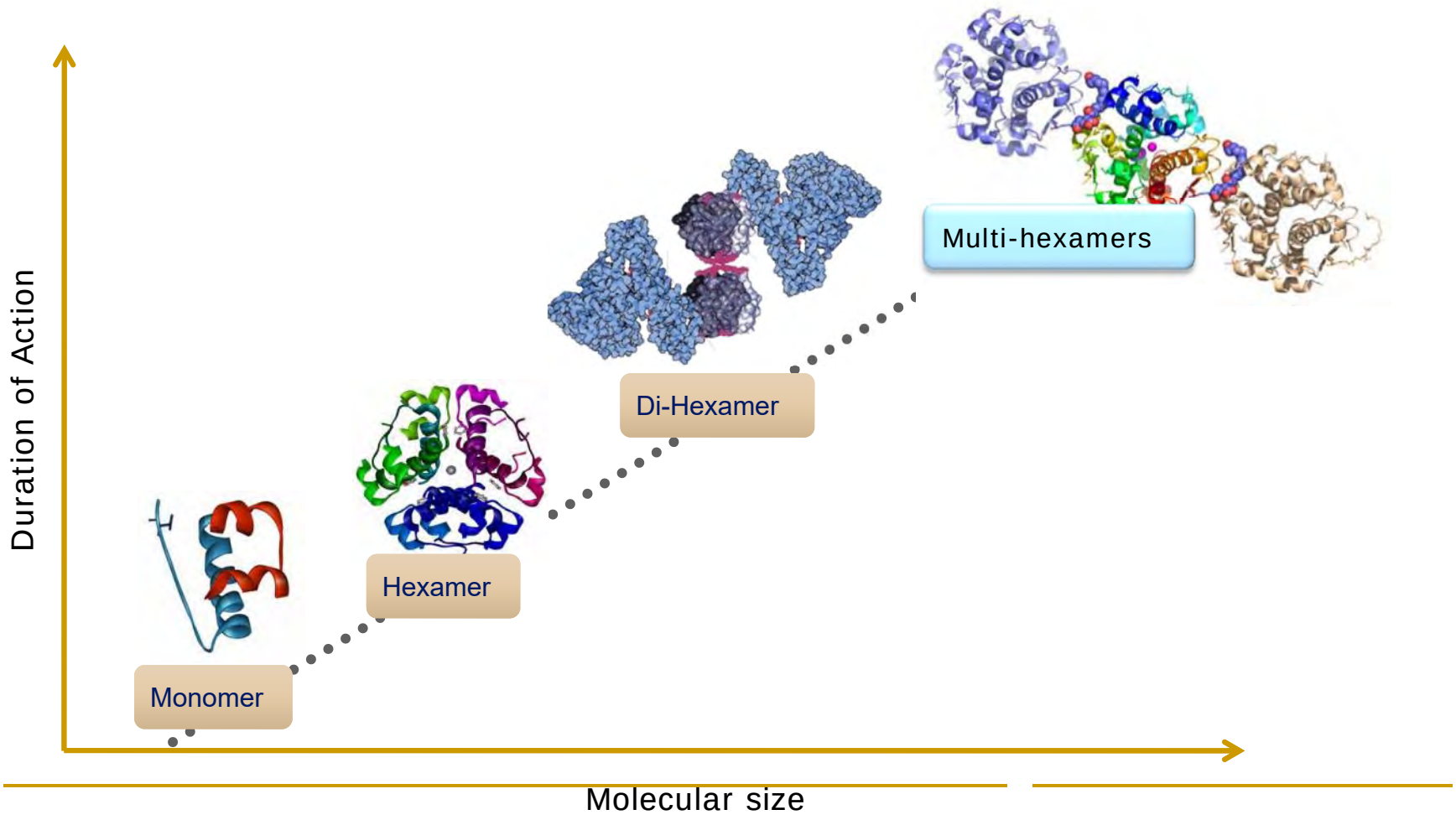


Degludec ligand carboxy group binds to Zn in hexamer

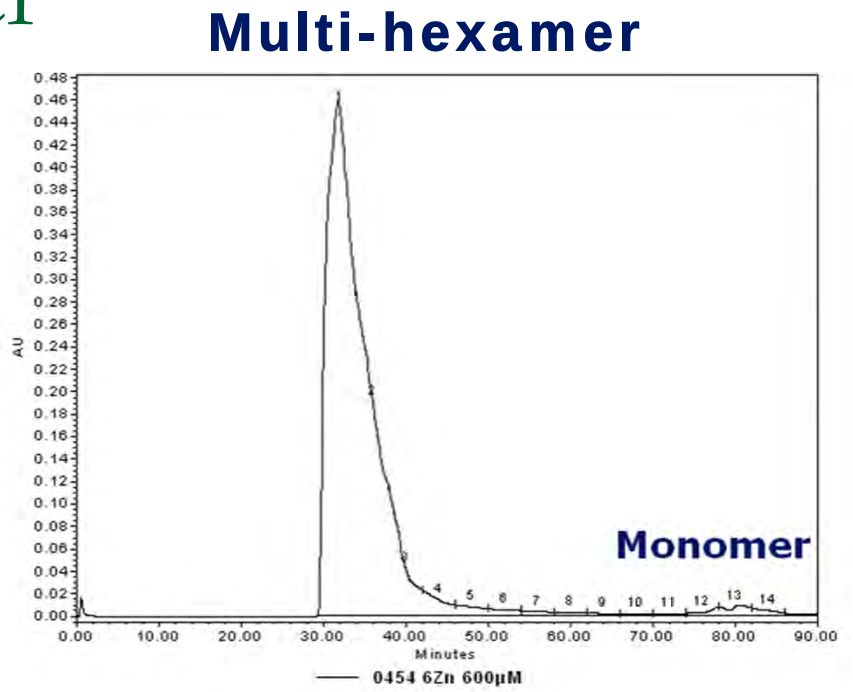


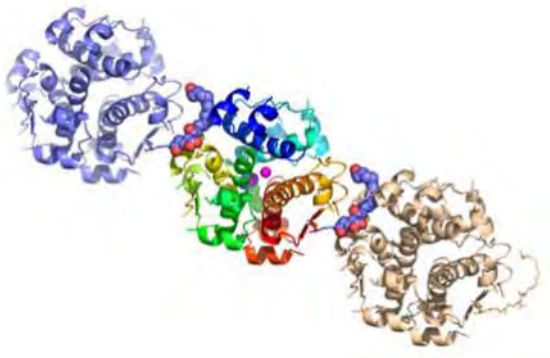
The side chain (linker) forms an accurate fit between Degludec hexamers to form multi-hexamers

Molecular size correlates with rate of absorption



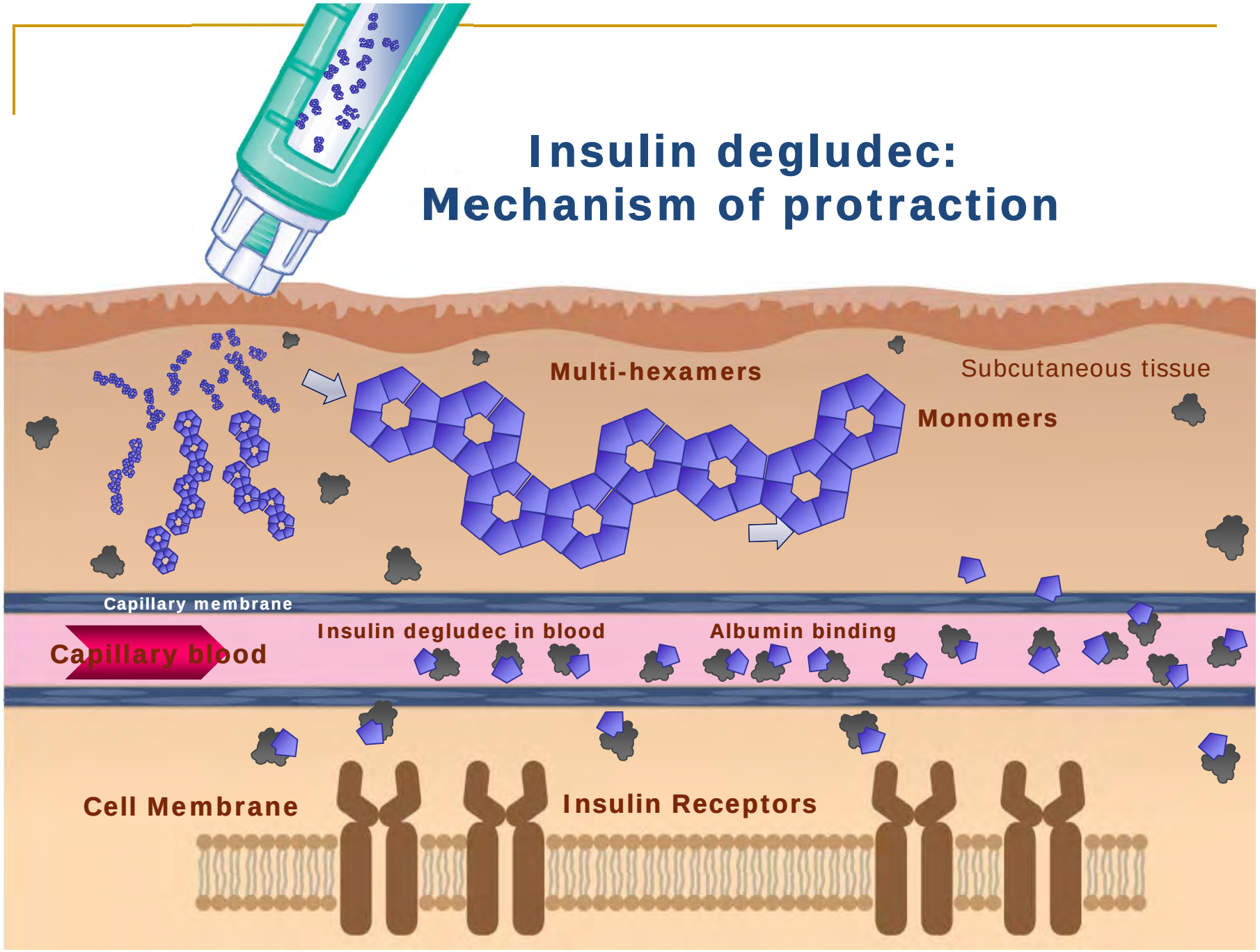
Size exclusion chromatography of Degludec in a subcutaneous model



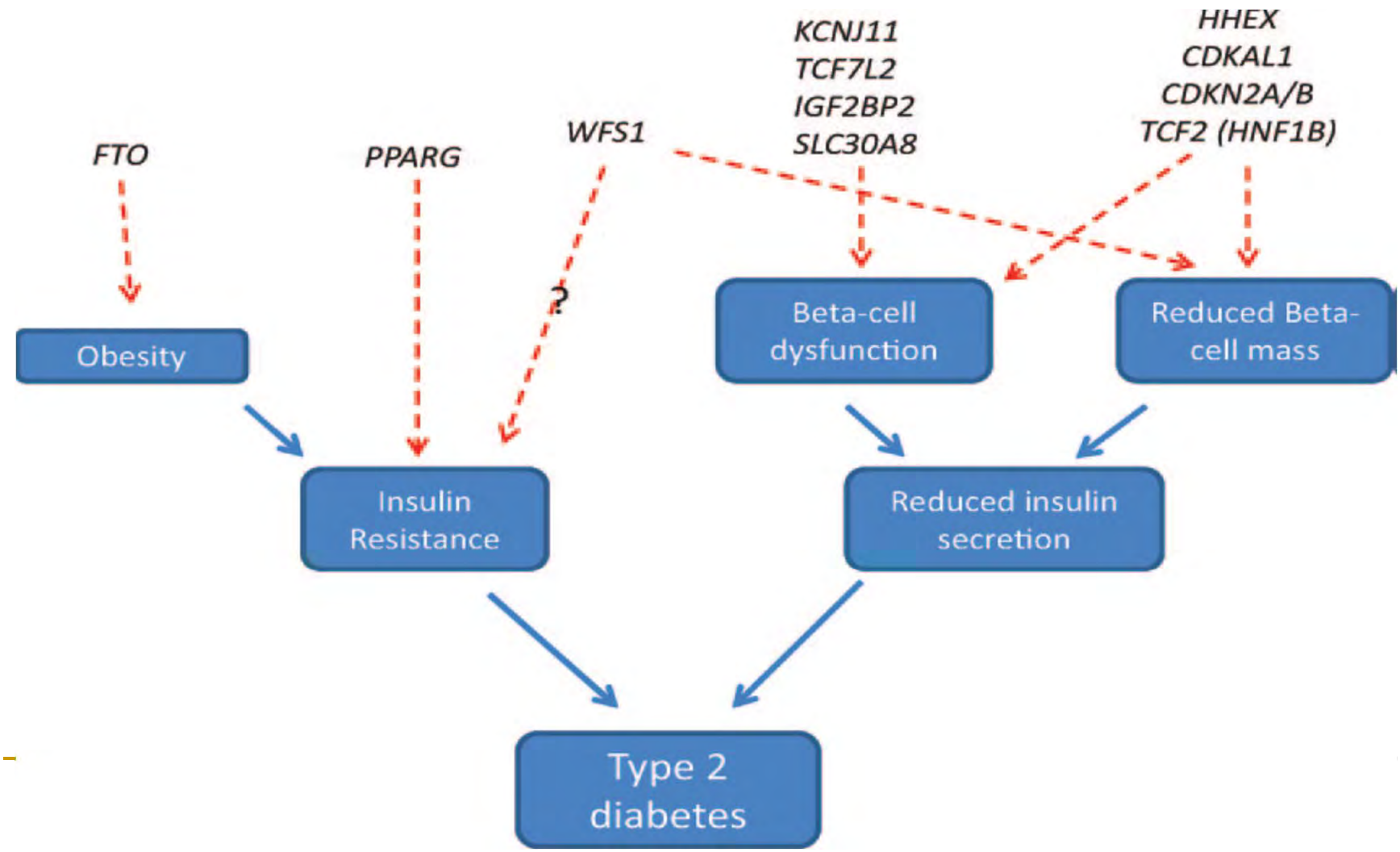


- After injection, Degludec exists only in the multi-hexamer state

Insulin degludec: Mechanism of protraction



Processes involved in genetic predisposition to type 2 diabetes, based on the best candidates within each signal and human physiological studies. Most genes implicated in diabetes susceptibility act through effects on beta-cell function or mass. [McCarthy and Hattersly, 2008]



Monogenic Diabetes……..

Gene	Disease	Polygenic variant
KCNJ11	PNDM	E23 (OR 1.2)
ABCC8	CHI	L270V(OR 1.15)
HNF4alfa	MODY1	5'SNPs (OR 1.4)
Glucokinase	MODY2	Variant-30G/A
HNF1alfa	MODY3	GS19S
IPF1	MODY4	5'SNP(OR 1.8)
INSR	Type A ins resistance	V985(OR1.87)

Monogenic Diabetes……..

- **Classical MODYs**

3. HNF1alpha (MODY 3)

accelerates the onset of type 2 DM by 7 years

40% prevalence in some populations

mechanism: ? Insulin deficiency

? Hepatic gluconeogenesis

Monogenic Diabetes……..

- **Classical MODYs**

  4. HNF 4alpha (MODY 1)

  accelerates the onset of type 2 DM

- **TCF2L7: Transcription Factor 2 Like-7**
- **CDKALI1: CDK5 regulatory subunit associated protein 1-like 1**
- **CDKN2A/B: Cyclin-dependent kinase inhibitors 2A/2B**
- **SLC30A8: Solute carrier family 30 (zinc transporter), member 8**

- **HHEX: Hematopoietically-expressed homeobox protein**
- **WFS1: Wolfram syndrome 1 (wolframin)**
- **Cathepsinase**
- **FTO : Fused-toes obese (mouse)**

Monogenic Diabetes……..

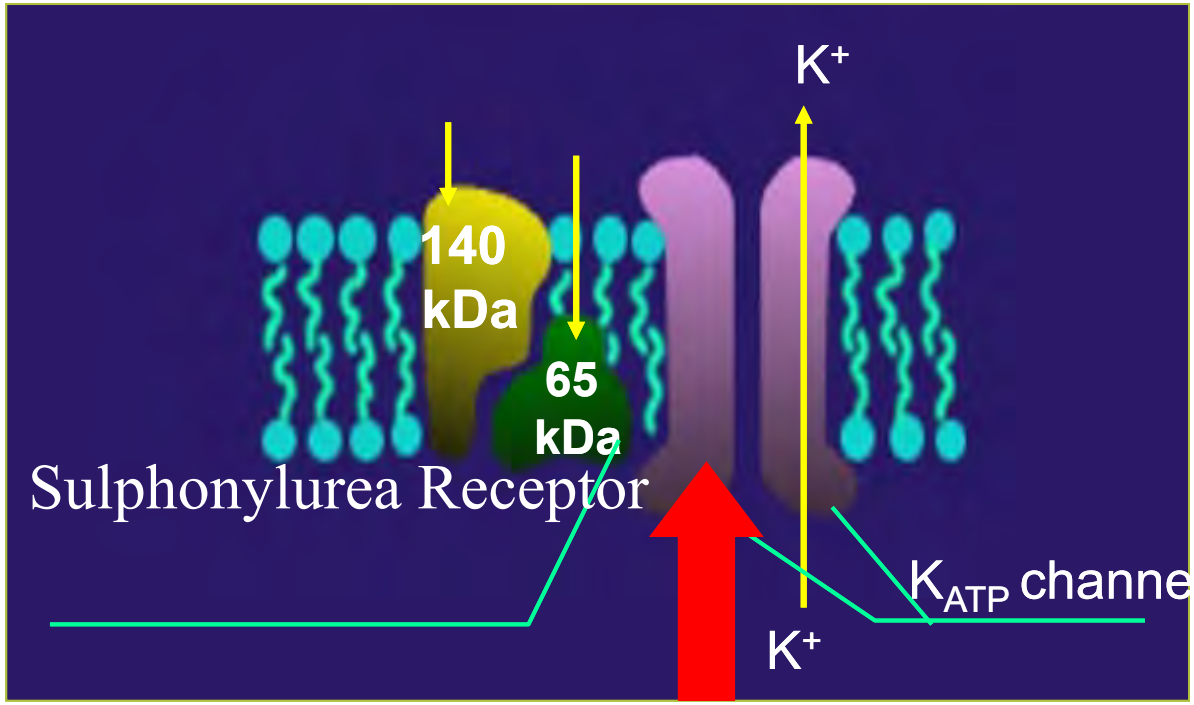
- **1.KCNJ11:**

Potassium channel, inwardly rectifying subfamily J member

Phenotype: Persistent neonatal diabetes
Relapsing Diabetes
Developmental delay, muscle weakness, epilepsy

Genetic anomaly: defective Kir6.2 (inward rectifying K+ATP channel)

KCNJ11……mechanism



Monogenic Diabetes……..

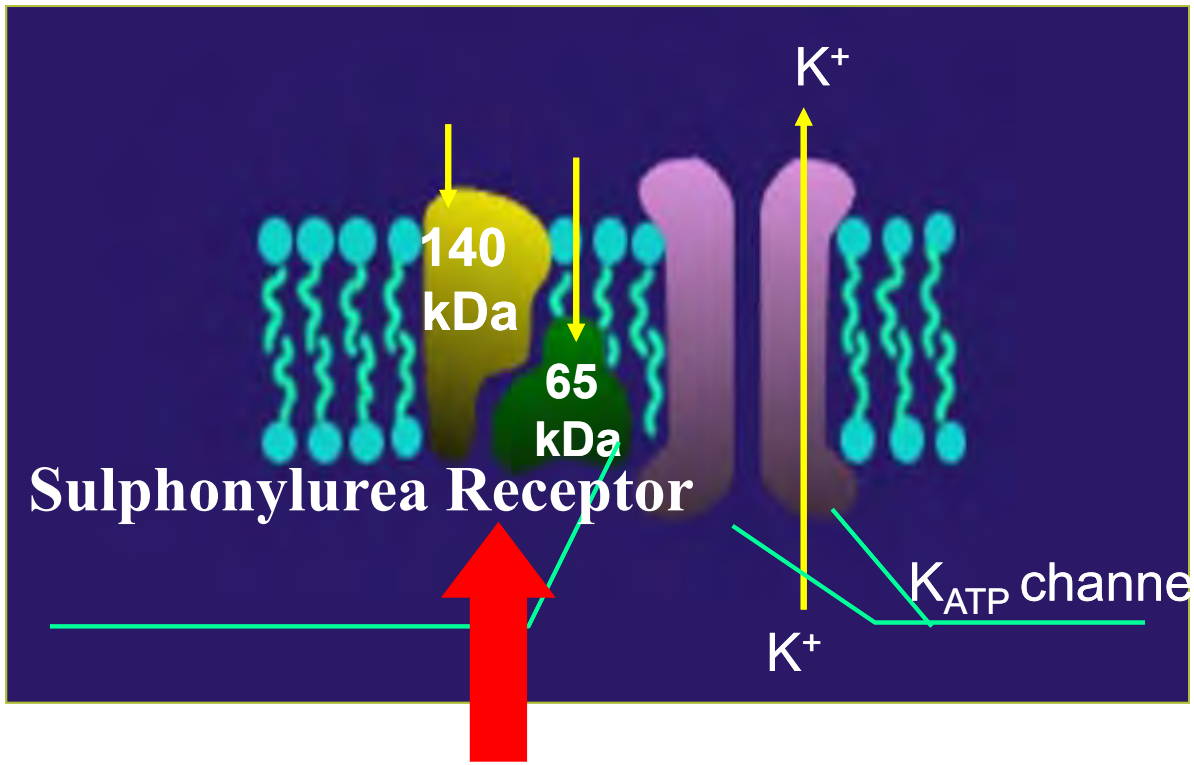
- **2. ABCC8**

ATP-binding cassette transporter sub-family C member 8

Phenotype: Childhood congenital hyperinsulinism, adult diabetes

Genetic anomaly: defective Sulphonylurea (SUR receptor)

ABCC8…..mechanism



FTO Gene

- Fused-toed obese Mouse gene
- Found on Chromosome 16 in humans
- Mutation associated with obesity, impaired glucose tolerance, hyperinsulinemia
- FTO normally up regulates the hypothalamus

Inhaled Insulin……..

THE TECHNOLOGY

Concentrated Insulin in aerosolized form

OR

Dry Powder

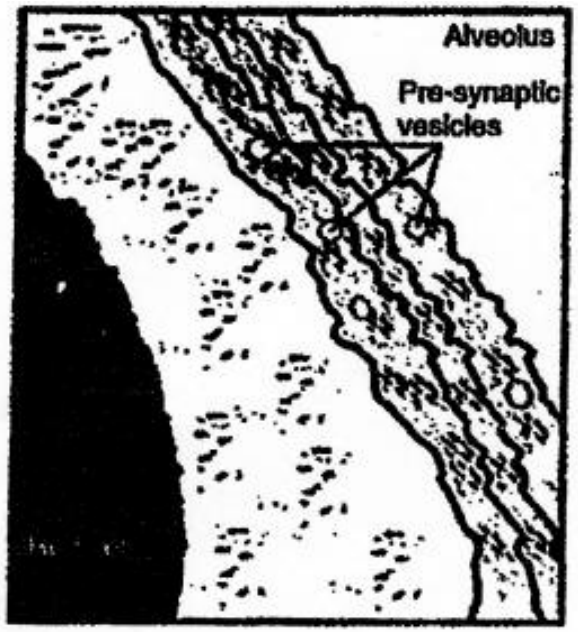
Can be administered as an orally inhaled dosage

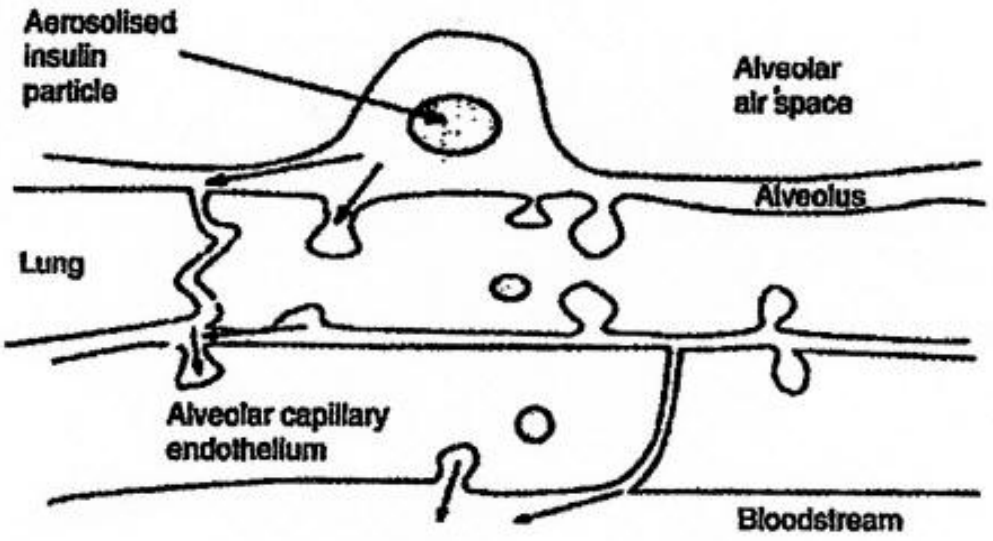
Mode of delivery

- Lungs
- The large absorptive area.
- relatively high permeability of the alveoli
- vast vascularization

- provide a natural and efficient portal of entry into the bloodstream.

Transcytosis of inhaled insulin……





Inhaled Insulin…….

AVAILABLE DEVICES

Exubera

AER

Alkermes

EXUBERA®
(insulin human [rDNA origin])
Inhalation Powder

formulation will be available in blisters of 1mg/ 3mg of dry powder.

1mg approximately = 3IU sc Insulin
3mg approximately=8 IU sc Insulin.
For each inhalation, a single-dose blister is filled with powdered insulin

The blister is punctured, and the powder is dispersed into a visible forming cloud aerosol inside a holding chamber.

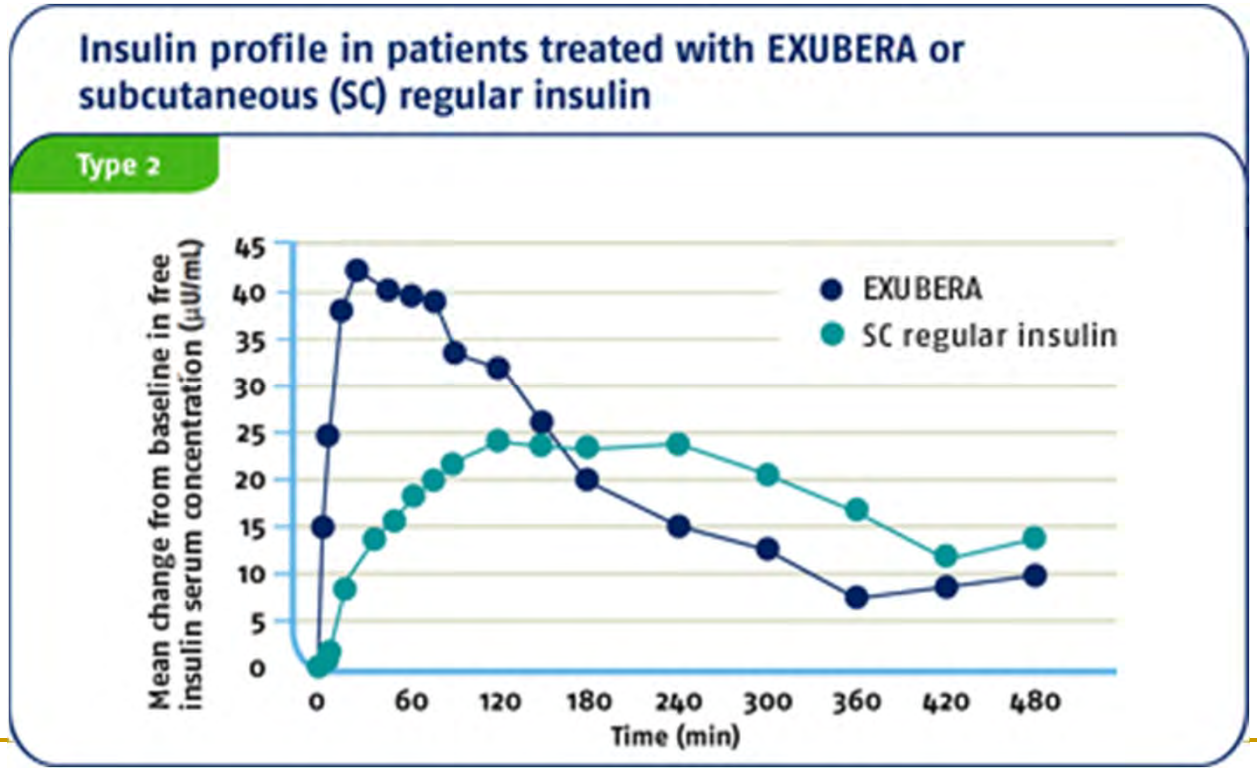
- **The absorption of inhaled insulin is as rapid as**

  subcutaneously injected (SC) rapid-acting insulin

  analog lispro and more rapid than regular human

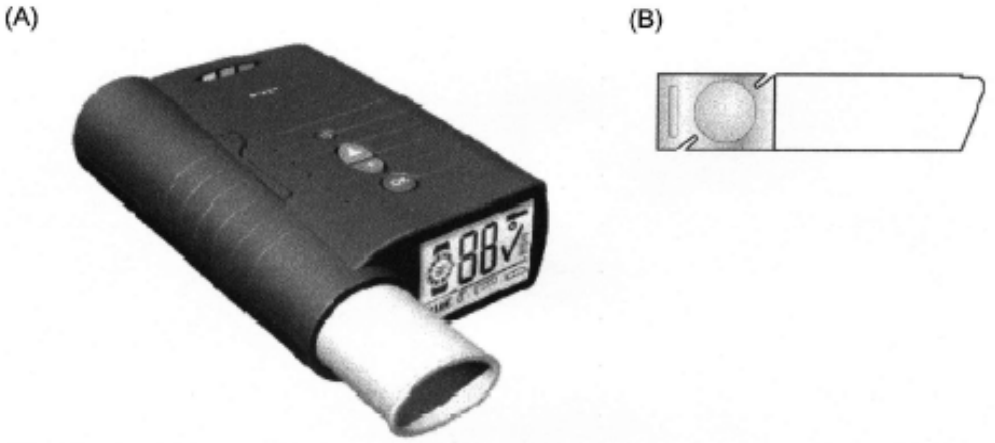
  insulin.

Mean changes in free insulin serum concentrations following inhaled insulin of (6 mg)
or SC regular insulin (18 IU).



Inhaled Insulin…….

THE DEVICE



Inhaled Insulin……..

POINTS OF IMPORTANCE

Can Be used in chronic respiratory disease

More Rapid absorption in Smokers

Decreased absorption in Obstructive Lung disease (Asthma and COPD)

Less weight gain

Slightly less optimal control

****

2008: FDA issues a lung cancer warning on inhaled insulin

NOT TO BE MINISTERED UNTO BUT TO MINISTER

CHRISTIAN MEDICAL COLLEGE

VELLORE

INDIA