The History and Future of Insulin Formulations

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Presentation Objectives

To share the history of development of insulin products as a possible basis for predicting the future directions with protein therapeutics

Outline

- History of insulin
- Formulations and products
- The birth of the recombinant era
- Future possibilities
- Summary

Early History of Diabetes

- 1552 BC – earliest known record of diabetes
- 1st century AD – diabetes described as “melting down of the flesh and limbs into urine”
- 16th century – Paracelsus identified diabetes as a serious general disorder
- 1870s – Bouchardat noted disappearance of glycosuria in diabetes patients during rationing of food in Paris
- 1869 – Langerhans announces that pancreas has two systems of cells
- 1889 – Minkowski and von Mering first study effect of removal of pancreas in dogs
- 1908 – Zuelzer develops first injectable pancreatic extract but severe side effects
- 1919-20 Frederick Allen establishes first treatment center in the US

History of Insulin

- Frederick Banting's initial idea: "Ligate pancreatic ducts of dogs. Wait 6-8 weeks for degeneration. Remove the residue and extract."
- Requested access to dogs from J.J.R.Macleod in Toronto and worked with the assistance of Charles Best
- Announced results from early experiments on December 26, 1921 at American Physiological Society meeting at Yale, along with intent to conduct human studies with extract
- First human study on January 11, 1922 with a critically ill 14 year old

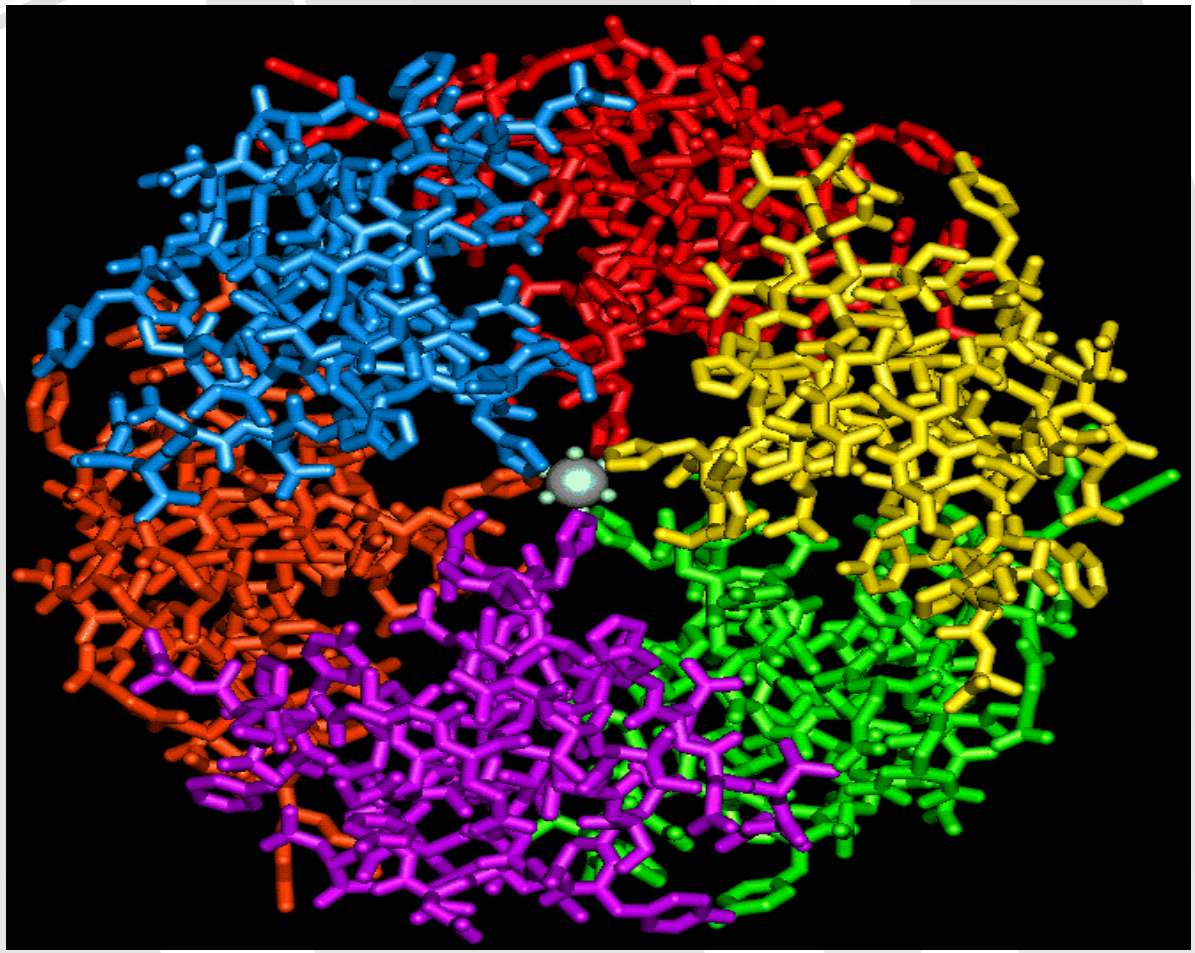
History of Insulin

- George Clowes, Eli Lilly and Company, attended the Yale meeting and suggested Lilly could provide resources to produce the extract in quantity
- May 1922 an agreement was signed between the University of Toronto and Lilly
- Lilly committed $250,000 to the joint effort

History of Insulin

- Potency of extract diminished as process was scaled up
- Walden, at Lilly, recognized that a precipitate that was discarded was where the potent material was
- Led to process of isoelectric precipitation with standardized purity and potency
- First US physician to use Lilly insulin was Elliot Joslin
- Lilly's Iletin® marketed in October 1923 after being tested with 7000 doctors and their patients
- By 1975 Lilly was processing 1 ton of pancreas per hour to keep up with demand

Insulin Hexamer



Recombinant Insulin

- Genentech rDNA human insulin obtained on 24 August, 1978 from combination of A and B chains individually expressed in E. coli
- Key technologies included
  - Rapid chemical synthesis of DNA
  - Use of RP-HPLC for purification of DNA fragments and detection and characterization of expressed proteins

Recombinant Insulin timeline

- 24 August 1978: first rDNA insulin (approx. 20 ng.)
- 25 August 1978: Lilly and Genentech sign development agreement (announced September 6)
- 5 October 1979: Lilly gets permission for 150L fermentation
- 7 October 1979: Zinc insulin crystals from first significant batch
- 15 July 1980: first human studies with BHI at Guy's Hospital in London
- 9 July 1981: first 40,000L fermentation
- 26 August 1982: Approval to market BHI in UK
- 10 April 1986: Approval to market BHI derived from human proinsulin

DiabetesphotoBHI volunteers (2).lnk

Rationale for recombinant human insulin

- Limited supply of animal pancreas to support increasing incidence of diabetes
- Continuing possibility of allergic reactions to animal insulin
- Logic of use of human protein if available
- Because it was possible!

Tests Used to Evaluate BHI

- Rabbit hypoglycemia assay
- Insulin radioreceptor assay
- Amino acid composition
- Amino acid sequence
- Gel electrophoresis
- FAB mass spectrometry
- Disulfide bond verification
- HPLC
- Peptide mapping
- Zinc crystallization
- X-ray structure
- 2D NMR
- Limulus assay for endotoxins
- Insulin receptor assay
- USP rabbit pyrogen test
- BP proteolytic activity assay
- Proinsulin RIA
- C-Peptide RIA
- E. coli peptide RIA

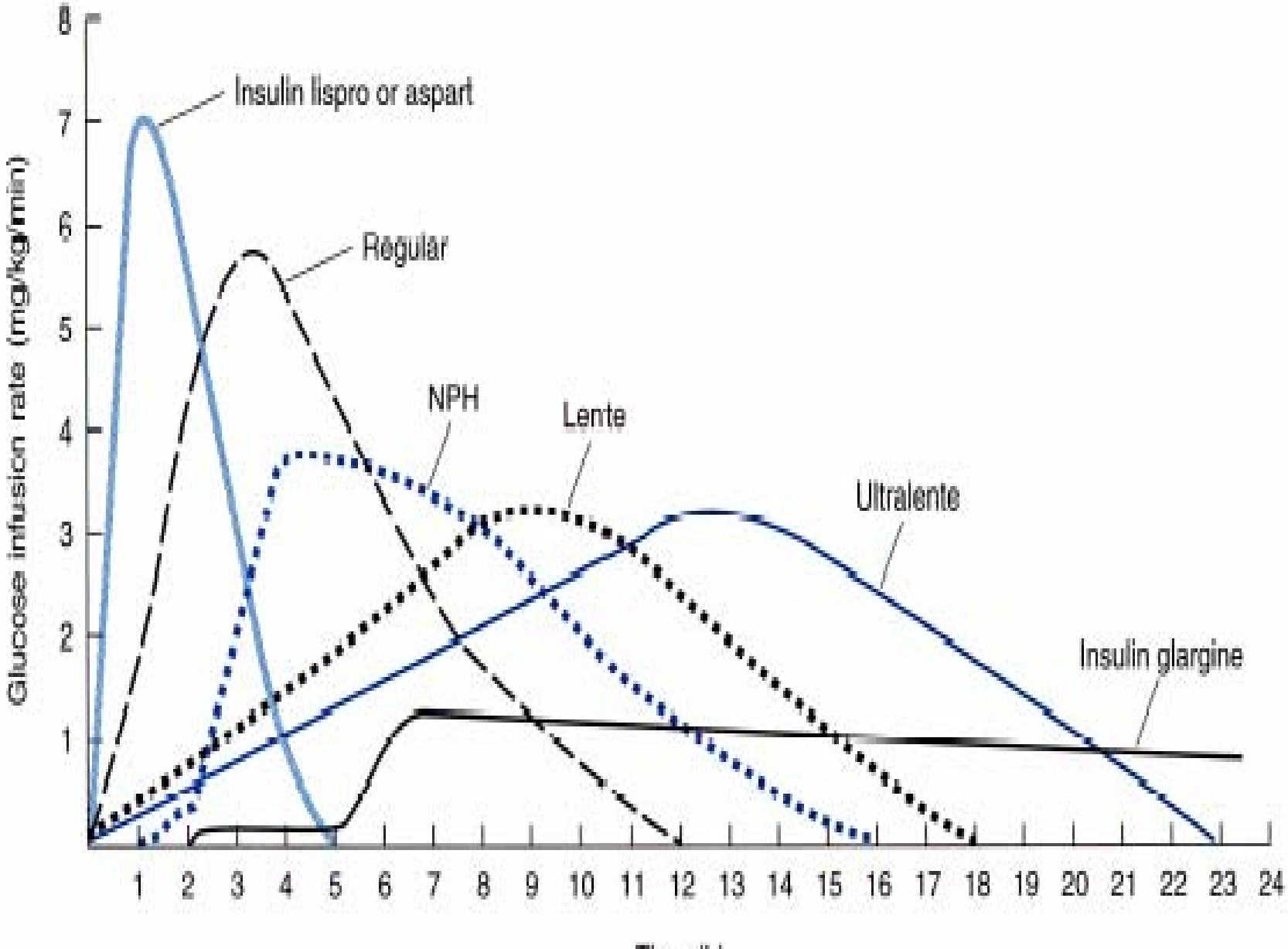
Insulin Physiology

- Normal physiology of basal concentrations supplemented by large prandial insulin spikes
- Target for therapy is to provide formulations or systems that mimic normal physiology
- Goal to maintain hA1Cs in patients with diabetes at less than 7.0

History of insulin formulations

- **Regular animal sourced insulin 1920’s**
- **NPH insulin 1940’s**
- **Lente and Ultralente insulins – longer acting formulations – 1953**
- **Human rDNA insulin 1980’s**
- **Insulin lispro – gentically modified short acting insulin 1990’s**
- **Insulin glargine – gentically modified long acting insulin 2000’s**
- **Non-injectable insulin formulations**

Insulin product profiles



NPH Insulin

- 1936 protamine zinc insulin described
- 1946 Neutral Protamine Hagedorn (NPH) introduced by Nordisk
- Neutral insulin with prolonged action
- Could be mixed with regular insulin

Lente Insulins

- 1953 Ultralente, Lente, and Semilente formulations made available
- Zinc used as delaying agent

Modified Insulins

- **Lispro insulin (Humalog® - Lilly)**
  - Onset in 10-15 minutes
  - Avoids need to carefully plan time of injection prior to meal
  - Peak at 30-90 minutes with duration of 3-5 hours
- **Insulin glargine (Lantus® - Aventis)**
  - Acidic solution
  - Microprecipitates after s.c. injection
  - Crystals dissolve slowly to release insulin glargine with full activity after 4-5 hours and sustained to 24 hours
  - No significant peak

Modified Insulins

- Insulin detemir (Levemir® - Novo Nordisk)
  - Basal insulin analog
  - Covalent link to a fatty acid that enhances binding to albumin
  - Detemir released at a constant rate over 24 hours
  - Data suggests improved and more predictable control

History of pump development – exemplified by MiniMed story

- 1979 - Al Mann CEO of PaceSetter Systems became interested in insulin pumps
- 1983 - MiniMed 502 introduced
- 1985 - MiniMed spun out
- 1986 - MiniMed introduced “insulin friendly tubing”
- 1992 - Launch of the MiniMed 506
- 1996 - Launch of 507C
- 1999 - Model 508
- 2001 - MiniMed acquired by Medtronic

Pump Insulins

- Limitation of aggregation of insulin in lines
  - Buffered insulin formulations
  - New tubing materials
  - Less aggregating insulin (e.g. lispro)

Alternatives to injection of insulin

- Inhaled insulin
  - Insulin is absorbed through the lung alveoli
  - Extensive studies have shown a similar kinetic profile to fast acting injected insulin
  - Exubera ® - Pfizer, expected to be available shortly
- Buccal insulin (Oralin®- Generex)
  - Uses RapidMist™ technology to deliver insulin to buccal mucosa
  - Mixture of insulin, surfactants and lipids
  - Approved in 2005 in Ecuador

Alternatives to insulin injections

- Oral insulin
  - Emisphere Technologies
    - Eligen® technology
    - Carrier facilitates transport across membranes
    - Suggests modification of parent molecule conformation
    - Insulin dissociates from complex after transport
  - Nobex
    - Hexyl insulin monoconjugate 2 (HIM2)
    - Covalent modification of insulin with oligomers at select sites
    - Facilitates transport across membranes

Future projections

- Islet replacement for Type I disease
- Gene replacement for Type I disease
- Closed loop feedback pumps
- Improved delivery devices to improve compliance
- Better control of obesity in the developed world beginning to lessen incidence of Type II disease