The History of Congenital Hyperinsulinism

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CHI | Congenital Hyperinsulinism International

When too little sugar hurts, we help.

KAHHA-DER

KONJENİTAL HİPERİNSÜLİNİZMİ HASTA AİLELERİ DERNEĞİ

DISCLOSURE STATEMENT

Khalid Hussain

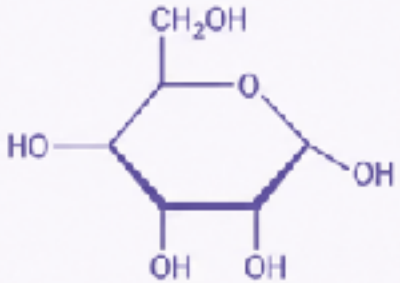
- Research Contracts
- Consulting
- Employment in the Industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

I declare that I have no potential conflict of interest.

Outline

- Acknowledgements
- Concepts of hormone, hypoglycemia and insulin discovery
- First mention of ? hyperinsulinism
- Timeline of advances: Genetics, Histology/Imaging, Treatments.

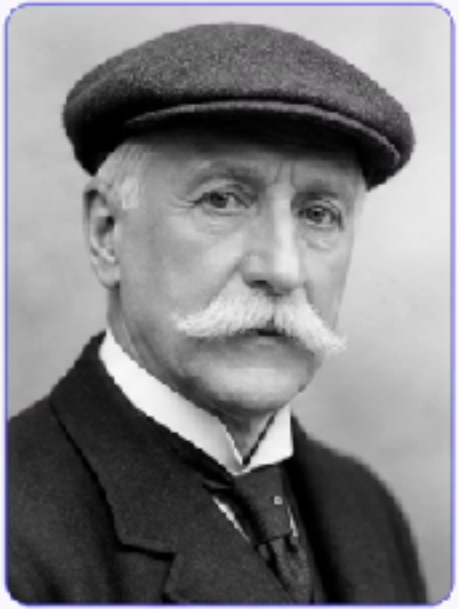
Concepts: Hormone, Hypoglycemia & Insulin Discovery.



1890 — 1900 — 1921 — 1922 — 1923+

Insulin — Hormone.

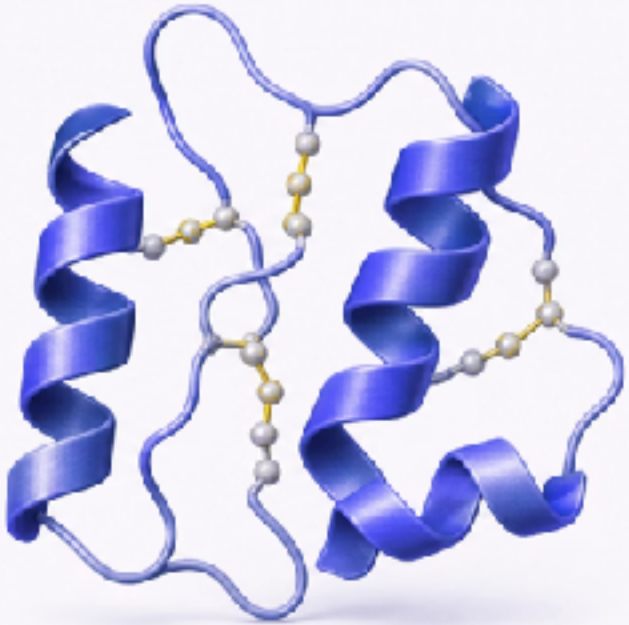
1905



SIR EDWARD ALBERT SHARPEY-SCHAFER

1850–1935

- Ernest Starling coined the term *Hormone* in 1905.
- De Meyer and Sharpey-Schafer suggested the name *insuline/insulin* for an internal secretion of the pancreas that controlled glucose metabolism.



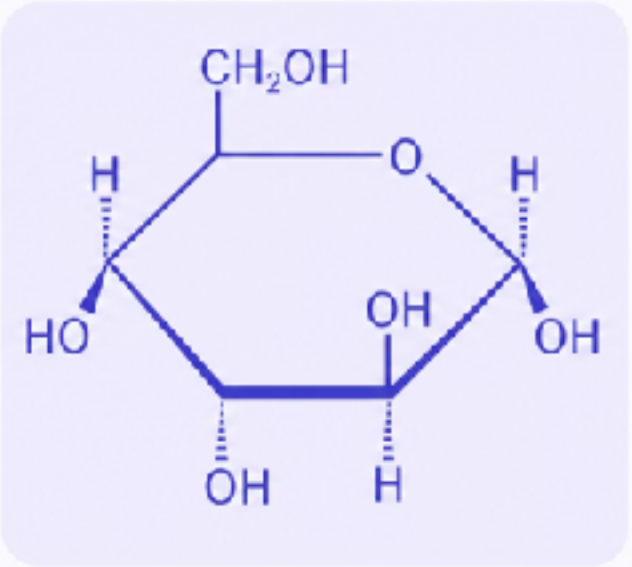
INSULIN MOLECULE

(PDB ID: 1ZNJ)

Hypoglycemia: First Reports.

1910

- Glucose first measured in the blood in the 1880s.
- In 1910, Cobliner from Germany first reported hypoglycemia in children.



Blood Glucose Measurement.

1915

- In 1915 Lewis and Benedict developed a method to measure blood glucose in small volumes of blood.

Hypoglycemia
(low blood sugar)

Normal level

Hyperglycemia
(high blood sugar)

Lewis RC, Benedict SR. A method for the estimation of sugar in small quantities of blood.
J Biol Chem. 1915;24:147–61.

The Discovery of Insulin.

In 1921, Canadian physician Frederick Banting and medical student Charles Best discovered the hormone insulin in pancreatic extracts of dogs.

They injected the hormone into a dog and found it lowered high blood glucose levels to normal.

1921

Charles Best
(27 Feb 1899 – 31 Mar 1978)

Frederick Banting
(14 Nov 1891 – 21 Feb 1941)

Nobel Prize in
Physiology or Medicine (1923)

First Patient to Receive Insulin.

1922

- On January 11, 1922, 14-year-old Leonard Thompson became the first person to receive an insulin injection as treatment for diabetes.

Leonard Thompson —
First patient to receive insulin in Toronto.

- Prior to that, people with type 1 diabetes did not survive more than a few weeks or months.

Hypoglycemia: Symptoms.

1922

Symptomatic hypoglycemia caused by insulin was first recognized in 1922 when one of the first diabetes patients treated with insulin was found climbing the walls due to hypoglycemia.

Autonomic symptoms

- Anxiety
- Sweating
- Palpitation
- Trembling
- Hunger

Neuroglycopenic symptoms

- Blurred vision
- Slurred speech
- Confusion
- Seizure
- Coma

Who First Described HI?

1800 1850 1900 1950 2000 2020

HI: ? First Description.

1937

- In 1937, Hartmann and Jaudon described several children with hypoglycemia at St. Louis Children's Hospital — possibly first description of HI.

St. Louis Children's Hospital infant ward, c. 1890s.

1879 — St. Louis Children's Hospital opens with 15 inpatient beds.

1883 — New SLCH dedicated, treats 51 kids.

Hartmann AF, Jaudon JC. Hypoglycemia. *J Pediatr*. 1937;11:1–36.

HI: ? First Description — McQuarrie 1954.

1954

- **First description** of children with HI made in 1954 by Dr. Irvin McQuarrie in his presidential address to the American Pediatric Society.
- McQuarrie termed the disorder **idiopathic hypoglycemia of infancy**; several patients required removal of most of their pancreas.
- He identified **high risk of irremediable brain injury** due to delays in diagnosis and ineffective early therapy.
- He **suggested a genetic origin** since hypoglycemia ran in families; however, he incorrectly believed insulin was not the cause.

1954

HI: McQuarrie — What He Got Wrong.

- McQuarrie named the disorder idiopathic hypoglycemia of infancy, since he thought insulin was unlikely the etiology as these infants had no insulin-producing tumors.
- It took nearly two decades to recognize these infants had genetic disorders of insulin secretion causing HI.
- One of McQuarrie's families has recently been shown to have a dominant disease-causing mutation leading to ectopic expression of HK1 in beta cells.

Amino Acids and Insulin — Leucine-Sensitive Hypoglycemia.

1956

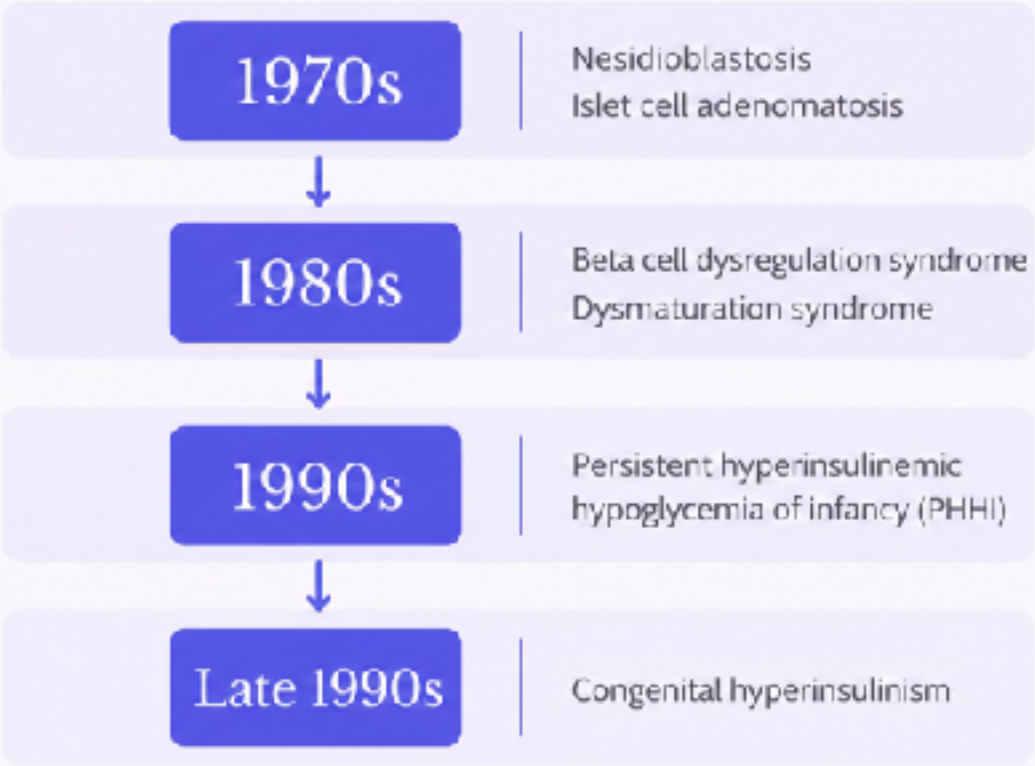
In 1956, Cochrane described a familial form of hypoglycemia aggravated by high protein feeding. The hypoglycemic effect of amino acids, especially leucine, was named leucine-sensitive hypoglycemia — the first indication that amino acids, as well as glucose, could be important insulin secretagogues.

FAMILIAL HYPOGLYCEMIA PRECIPITATED BY AMINO ACIDS

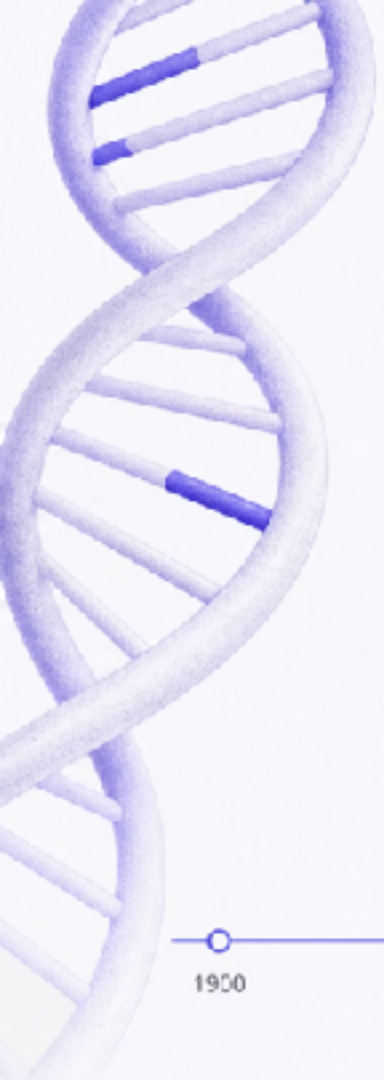
— W.A. Cochrane, W.W. Payne, M.J. Simpkiss, and L.I. Woolf
Hospital for Sick Children, Great Ormond Street, London.

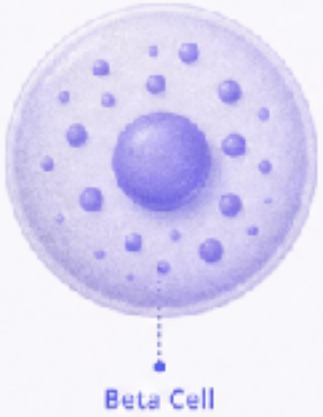
First Clue to Protein Induced HI

HI: Terminology — Names Through the Decades.



Genetics — Timeline of Key Discoveries





1900 1920 1940 1960 1980 2000 2020 Present

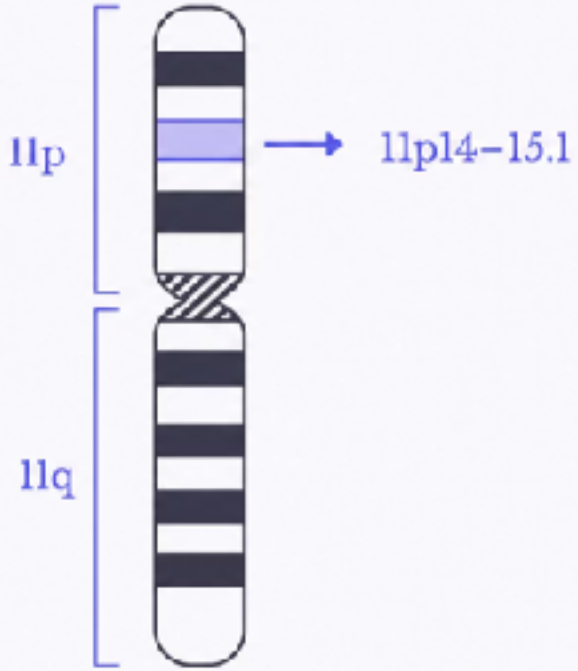
Important Region on Chromosome 11.

1994

Familial hyperinsulinism maps to chromosome 11p14–15.1, 30 cM centromeric to the insulin gene — Glaser et al., *Nature Genetics* 7, 185–188 (1994).

“

Linkage analysis in 15 families mapped HI to chromosome 11p14–15.1 (lod score = 9.5). This locus represents a candidate gene for studies of beta-cell dysfunction including NIDDM.

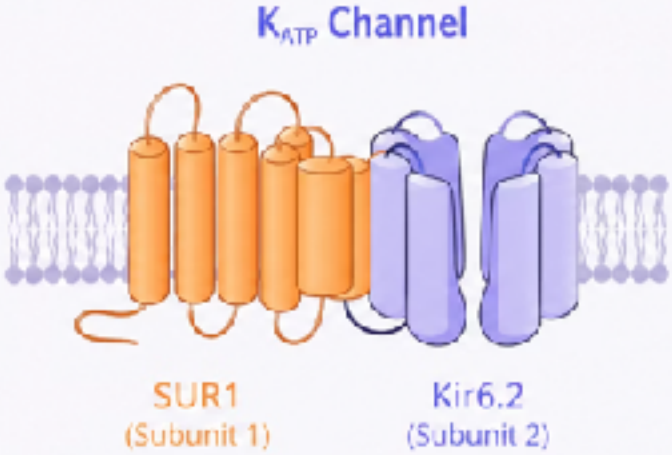


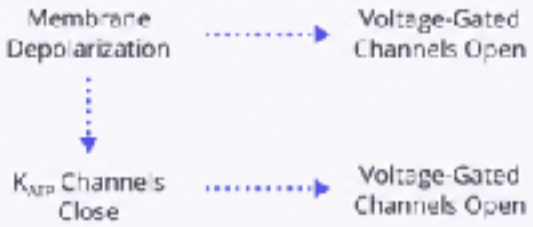
Mapping Gene to Region on Chromosome 11.

Cloning of SUR1.

1995

- Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin secretion — Aguilar-Bryan L *et al.*, Science 1995;268(5209): 423–6.





SUR1 Structure Was Worked Out.

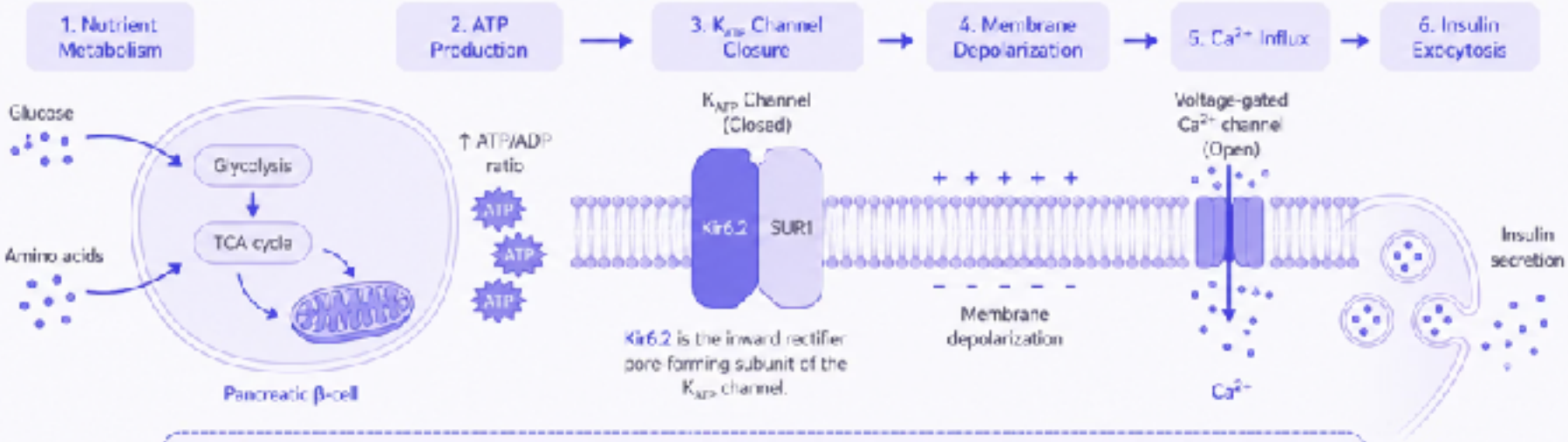
- Mutations in the sulfonylurea receptor gene in familial persistent hyperinsulinemic hypoglycemia of infancy — Thomas PM *et al.*, Science 1995;268:426–9.

First Genetic Cause of HI.

Next Genetic Cause of HI **1996**

Kir6.2 Gene and HI.

Mutation of the pancreatic islet inward rectifier Kir6.2 also leads to familial persistent hyperinsulinemic hypoglycemia of infancy — Thomas P, Ye Y, Lightner E. Hum Mol Genet. 1996;5(11):1809–12.

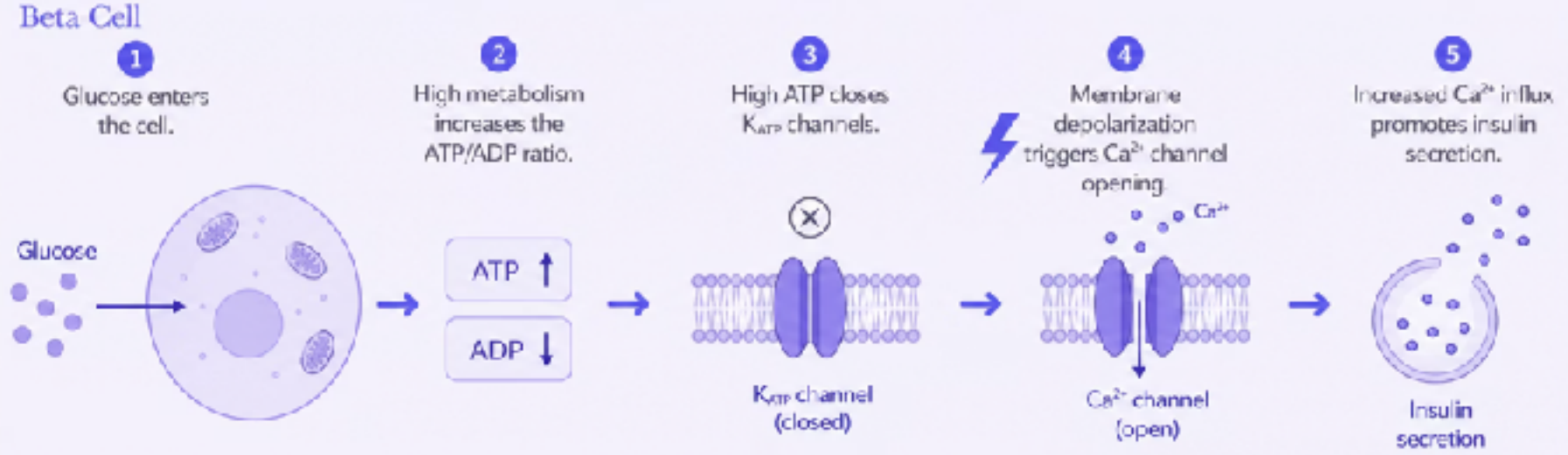


Kir6.2 (KCNJ11) encodes an essential subunit of the K_{ATP} channel in pancreatic β-cells. Loss-of-function mutations cause channel closure, leading to **increased insulin secretion** and **persistent hypoglycemia**.

Role of K_{ATP} Channels in HI.

1997

Familial persistent hyperinsulinemic hypoglycemia of infancy and mutations in the sulfonylurea receptor — Dunne MJ *et al. N Engl J Med.* 1997;336(10):703–6.

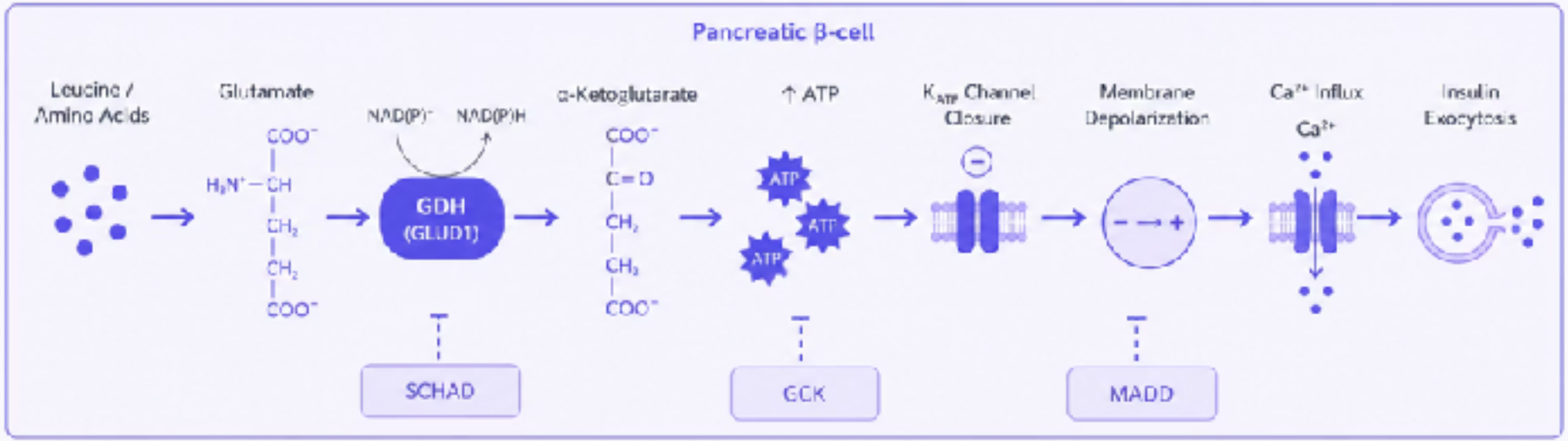


Link Between K_{ATP} Channels and Genetic Changes in Genes.

Mechanism of Leucine-Induced HI — GLUD1/GDH

1998

Hyperinsulinism and hyperammonemia in infants with regulatory mutations of the glutamate dehydrogenase gene — Stanley CA et al. N Engl J Med. 1998;338(19):1352–7.

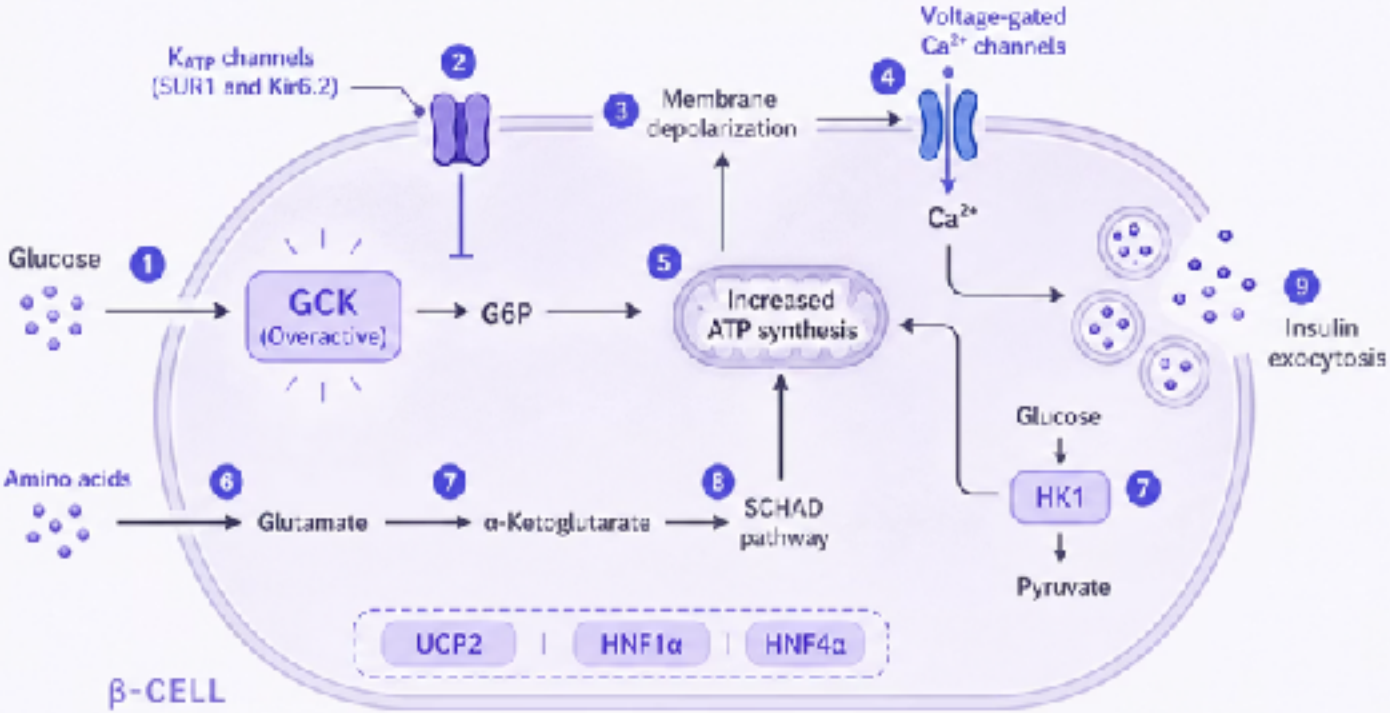


Key role of enzyme **GLUD1** in leucine metabolism and insulin secretion: **HI/HA syndrome**.

GCK and HI — Activating Glucokinase Mutation

1998

Familial hyperinsulinism caused by an activating glucokinase mutation — Glaser B et al. N Engl J Med. 1998;338(4):226–30.



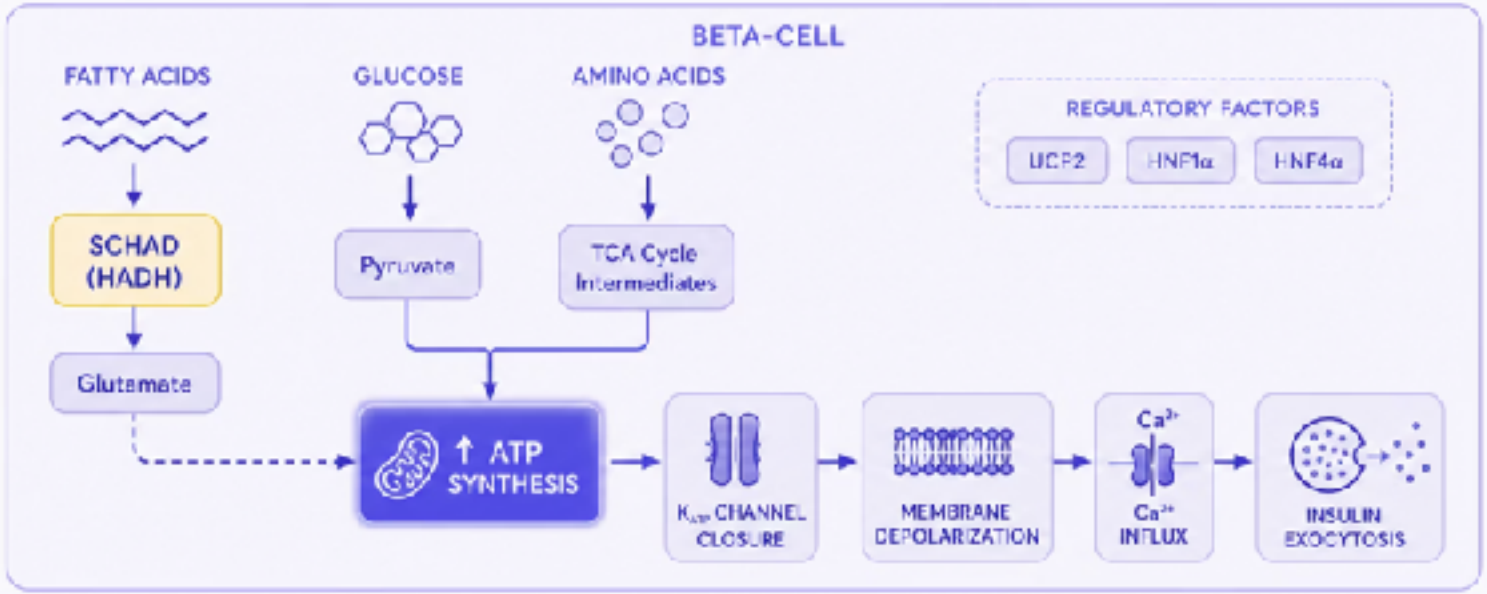
Key Role of the Enzyme Glucokinase

due to Overactivity.

HADH and HI — Fatty Acid Oxidation Link.

2001

Hyperinsulinism in short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency reveals the importance of beta-oxidation in insulin secretion —
Clayton PT et al. *J Clin Invest.* 2001;108(3):457–65.



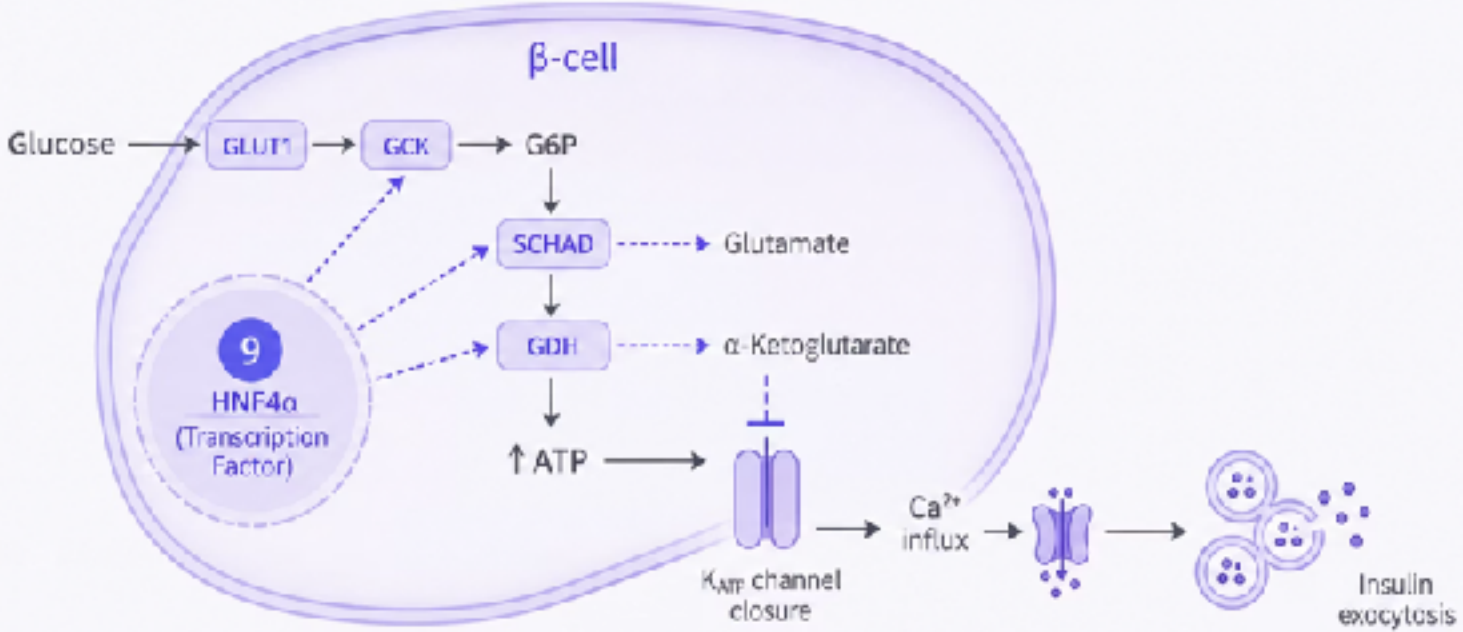
First Study to Link Defect in Fatty Acid Oxidation and HI.

HNF4 and HI — Link Between HI and MODY.

2007

Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene —

Pearson ER et al. *PLoS Med.* 2007;4(4):e118.

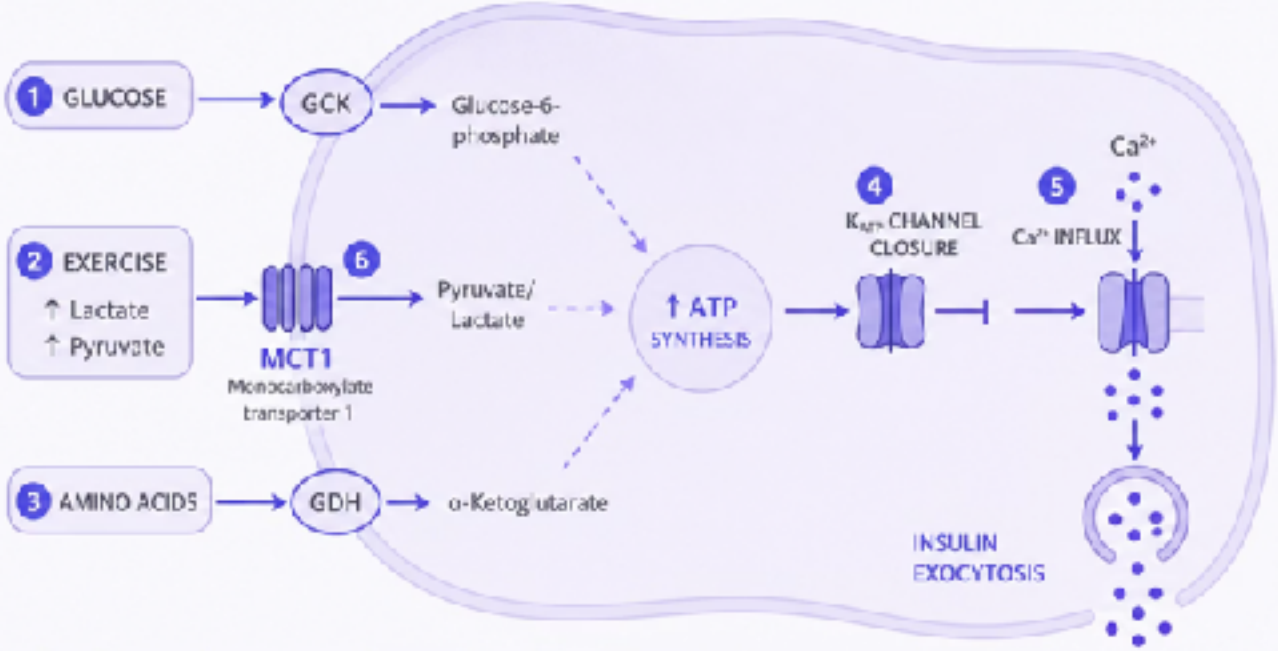


Link Between HI and MODY.

Exercise-Induced HI — MCT1

2007

Physical exercise-induced hypoglycemia caused by failed silencing of monocarboxylate transporter 1 in pancreatic beta cells — Otonkoski T et al. *Am J Hum Genet.* 2007;81(3):467–74.



Abbreviations: MCT1, monocarboxylate transporter 1; GCK, glucokinase; GDH, glutamate dehydrogenase; K_{ATP}, ATP-sensitive potassium channel.

Link Between Exercise and HI

1. Glucose enters via GCK (pathway 1).
2. During exercise, lactate/pyruvate enter β cells via MCT1 (pathway 6).
3. Amino acids fuel metabolism via GDH (pathway 3).
4. Increased ATP synthesis leads to K_{ATP} channel closure.
5. Membrane depolarization opens Ca^{2+} channels → Ca^{2+} influx.
6. Calcium triggers insulin exocytosis → hypoglycemia.

2024–2025

New Causes of HI.

Non-coding cis-regulatory variants in *HK1* cause congenital hyperinsulinism with variable disease severity

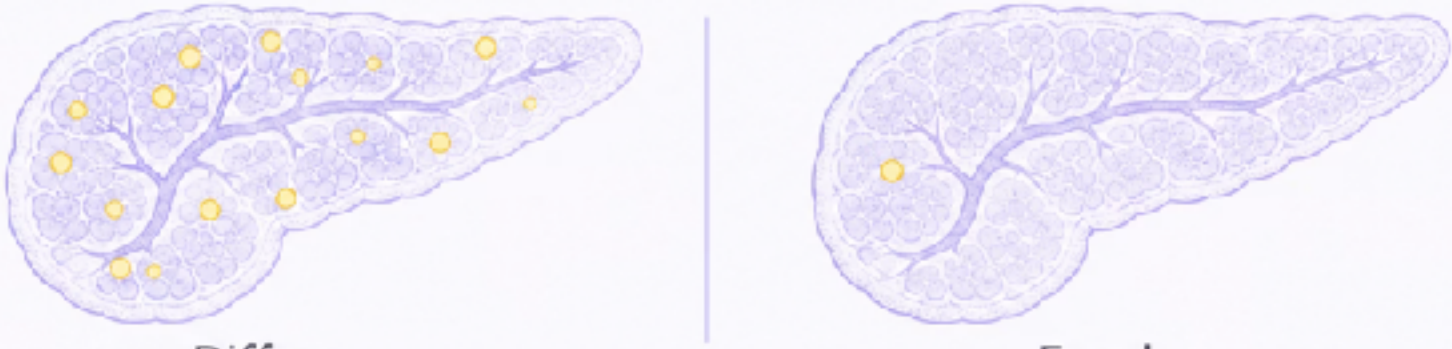
Bennett JJ et al., Genome Medicine, March 2025. International Congenital Hyperinsulinism Consortium.

Chromosome 20p11.2 deletions cause congenital hyperinsulinism via the loss of *FOXA2* or its regulatory elements

Laver TW et al., European Journal of Human Genetics 32, 813–818 (2024).

New Causes of HI.

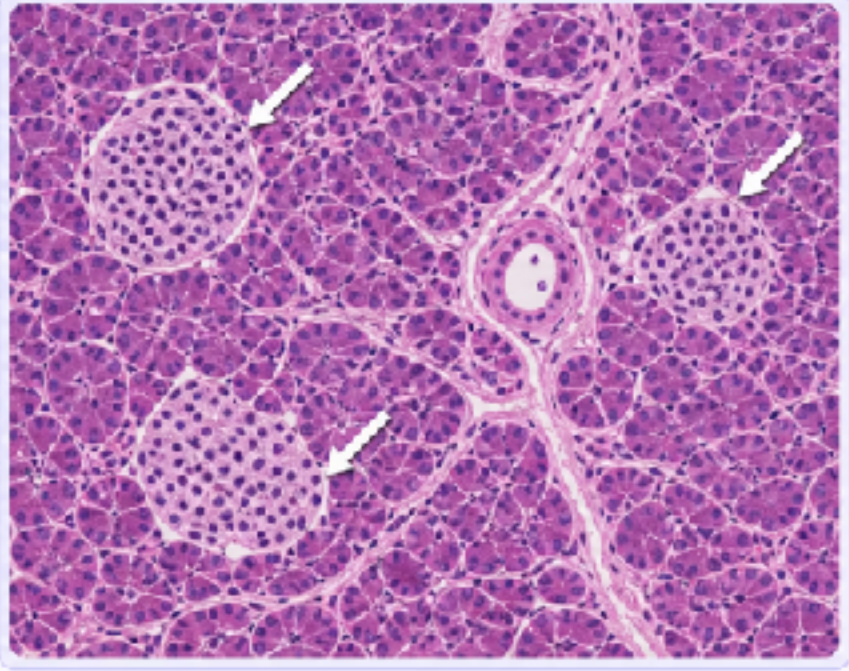
Histology — Timeline of Key Discoveries



Nesidioblastosis — First Description.

1938

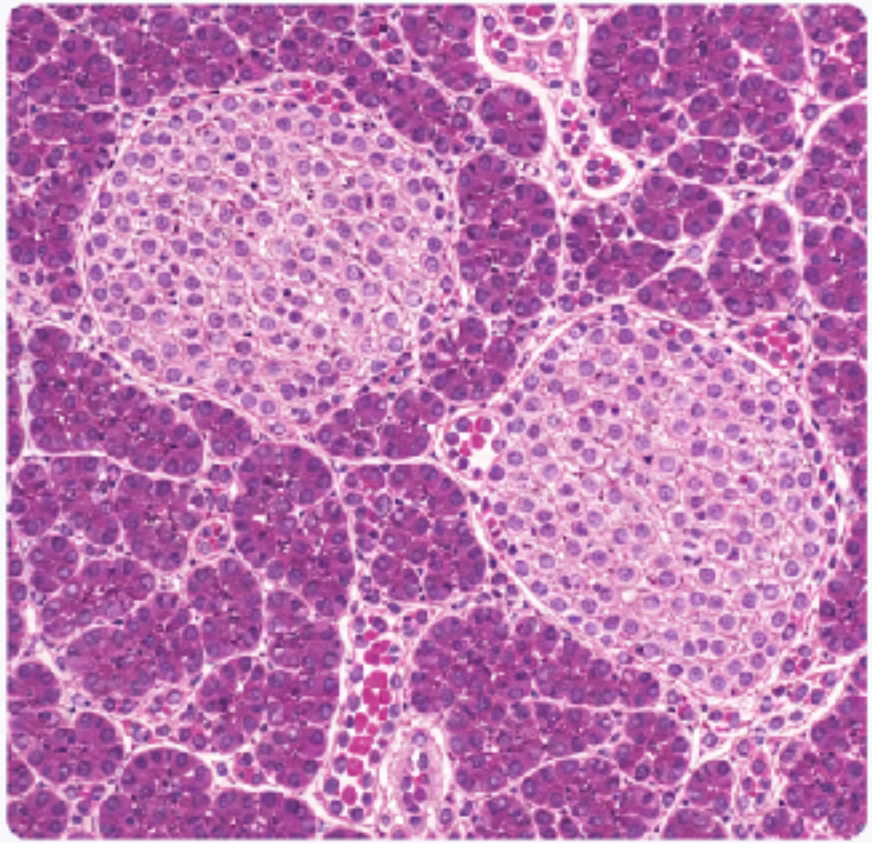
- Laidlaw GF (1938). Nesidioblastoma: The Islet Tumor of the Pancreas. Am J Pathol. 14(2):125–134.
- Laidlaw first introduced the term nesidioblastosis to describe abnormal islet formation and associated hypoglycemia.
- The term referred to new islet formation (from the Greek nesidion = small island), primarily in the context of pancreatic ductal epithelium giving rise to endocrine cells.



1971

Early Histological Aspects — Nesidioblastosis in HI

- Pancreatectomy samples from HI patients enabled examination of histological features of HI.
- In 1971, Lester Baker and Yakovac described nesidioblastosis in infants with idiopathic hypoglycemia of infancy.



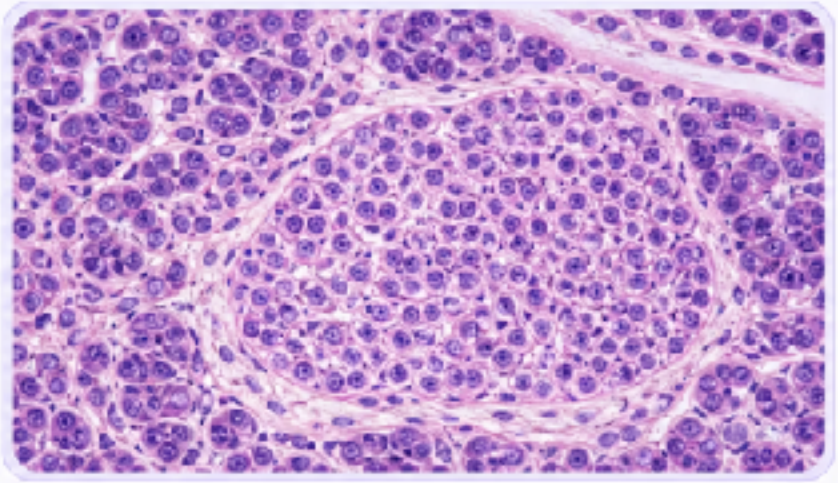
> Beta cell nesidioblastosis in idiopathic hypoglycemia of infancy —
> Yakovac WC, Baker L, Hummeler K.
> *J Pediatr*. 1971;79(2):226–31.

Nesidioblastosis — A Normal Fetal Appearance.

1980–1984

Pancreatic pathology in hyperinsulinemic hypoglycemia of infancy —
Jaffe R, Hashida Y, Yunis EJ.
Lab Invest. 1980;42(3):356–65.

The basic structural lesion of persistent neonatal hypoglycaemia with hyperinsulinism —
Rahier J et al.
Diabetologia. 1984;26(4):282–9.



Nesidioblastosis is not a specific entity but is rather the normal appearance of the pancreas during fetal development and in early infancy when islet development is still ongoing.

Nesidioblastosis ≠ HI.

2000

Persistent hyperinsulinaemic hypoglycaemia of infancy: a heterogeneous syndrome unrelated to nesidioblastosis

Rahier J, Guiot Y, Sempoux C.
Arch Dis Child Fetal Neonatal Ed. 2000;82(2):F108–12.

Nesidioblastosis Not The Same as HI.

2011

Nesidioblastosis no longer! It's all about genetics

Palladino AA, Stanley CA.
J Clin Endocrinol Metab. 2011;96(3):617–9.

Nesidioblastosis Not The Same as HI.

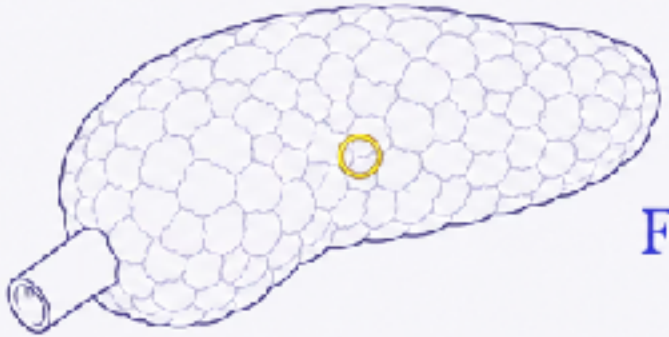
Multiple studies confirm that nesidioblastosis is not the same as HI.

Focal Lesions — First Description.

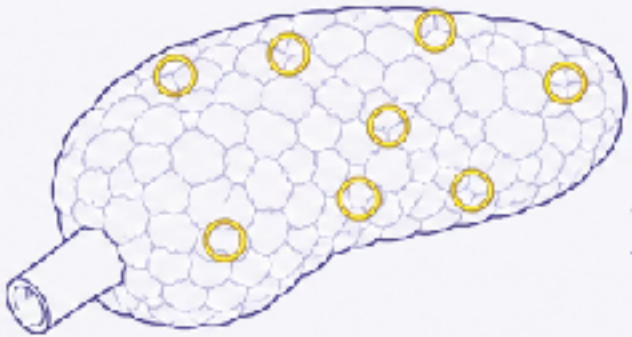
1980–1984

1. Pancreatic pathology in hyperinsulinemic hypoglycemia of infancy — Jaffe R, Hashida Y, Yunis EJ. *Lab Invest.* 1980;42(3):356–65.
2. The basic structural lesion of persistent neonatal hypoglycaemia with hyperinsulinism — Rahier J et al. *Diabetologia.* 1984;26(4):282–9.

> “In three cases, a focal lesion was detected by gross examination.



Focal



Diffuse

First Description of Focal Lesions

Mechanism of Focal Disease — Genetics.

1997–1998

Genetic Mechanism of Focal Lesions

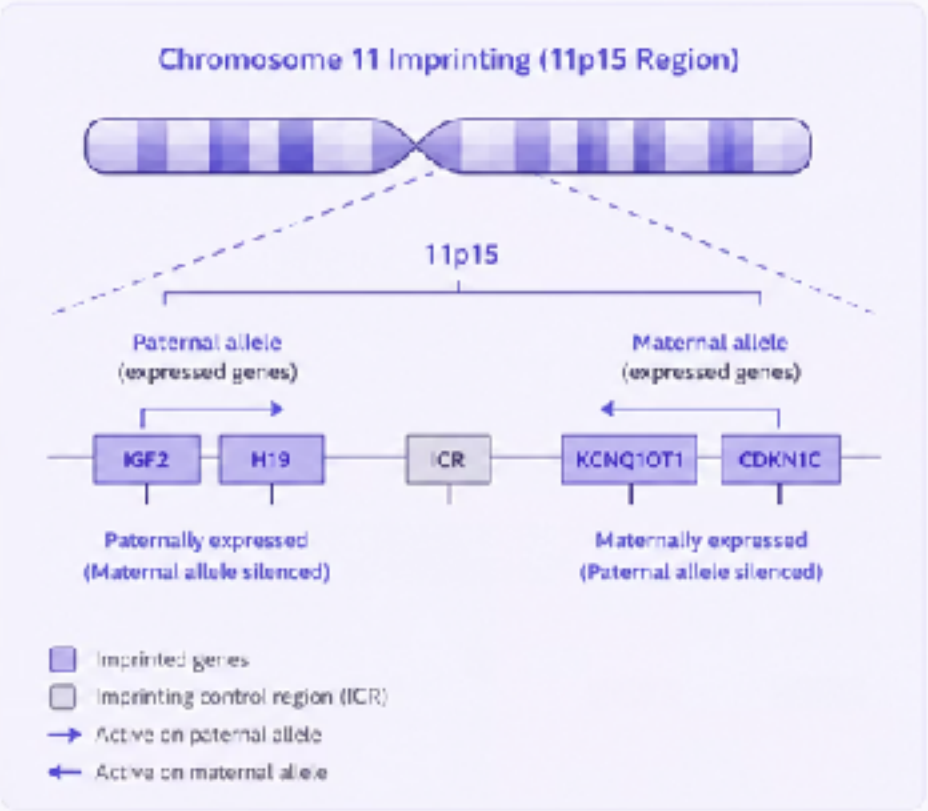
Paternal mutation of the sulfonylurea receptor (SUR1) gene and maternal loss of 11p15 imprinted genes lead to persistent hyperinsulinism in focal adenomatous hyperplasia — Verkarre V et al.

J Clin Invest. 1998;102(7):1286–91.

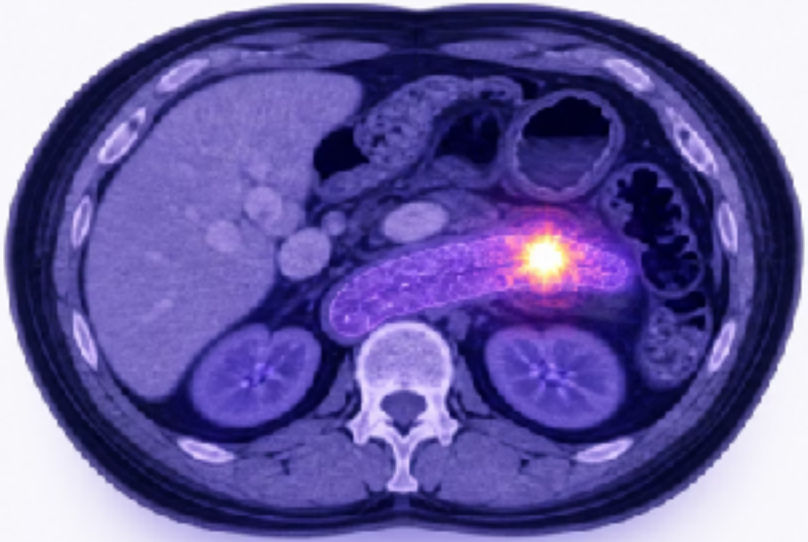
Partial Pancreatectomy for Focal Lesions

Somatic deletion of the imprinted 11p15 region in sporadic persistent hyperinsulinemic hypoglycemia of infancy is specific of focal adenomatous hyperplasia and endorses partial pancreatectomy — de Lonlay P et al.

J Clin Invest. 1997;100(4):802–7.



Imaging — Timeline of Key Discoveries



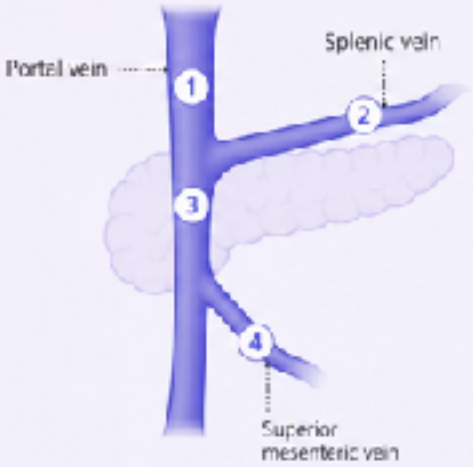
Pancreatic Venous Sampling (PVS).

1999

Clinical features of 52 neonates with hyperinsulinism —
de Lonlay-Debeney P et al. *N Engl J Med*. 1999;340(15):1169–75.

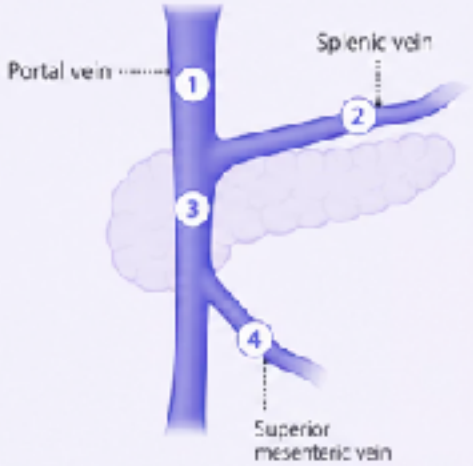
First Description of PVS.

A.



Site	Insulin (µU/mL)	Glucose (mg/dL)
1	220	10
2	190	9
3	81	8
4	10	8

B.



Site	Insulin (µU/mL)	Glucose (mg/dL)
1	50	111
2	41	450
3	45	72
4	111	72

2000

Calcium Stimulation Test.

Calcium-stimulated insulin secretion in diffuse and focal forms of congenital hyperinsulinism — Ferry RJ Jr et al. The Journal of Pediatrics, Volume 137, Issue 2, August 2000, Pages 239–246.

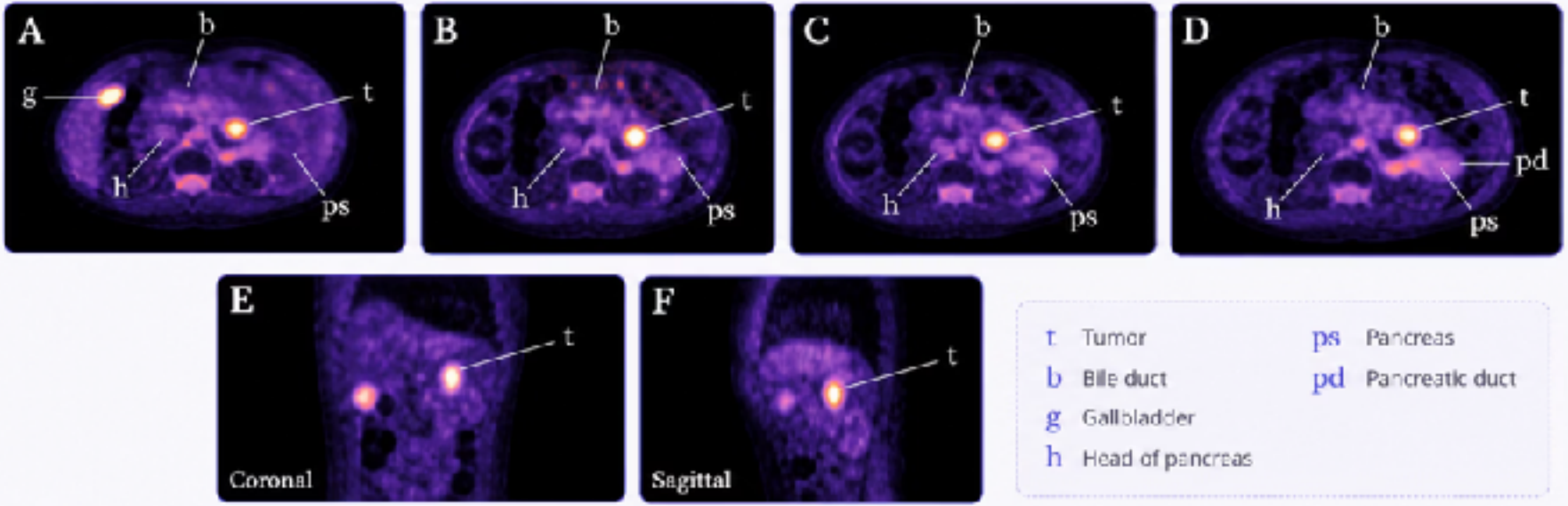
Presented at the Eighty-first Annual Endocrine Society Meeting, San Diego, June 1999.

Calcium Stimulation Test.

18F DOPA-PET — Noninvasive Diagnosis of Focal HI.

2006

Noninvasive diagnosis of focal hyperinsulinism of infancy with [^{18}F]-DOPA positron emission tomography — Otonkoski T et al. Diabetes. 2006;55(1):13–8.



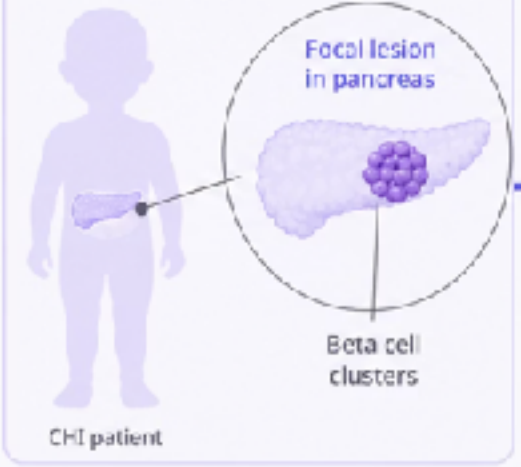
First Report of ^{18}F DOPA-PET Scan

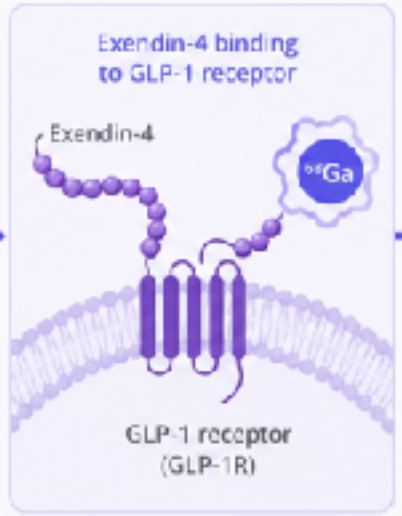
^{68}Ga-NODAGA-Exendin-4 PET/CT — Improved Detection of Focal CHI.

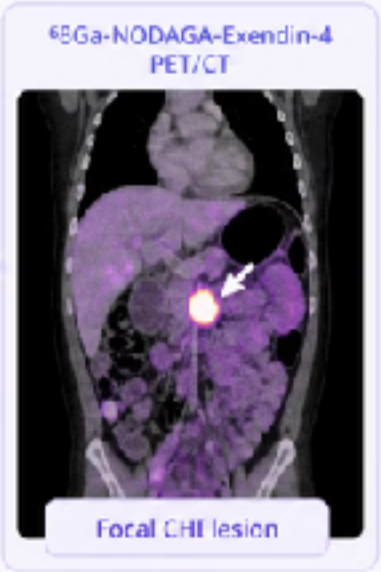
2022

68Ga-NODAGA-Exendin-4 PET/CT Improves the Detection of Focal Congenital Hyperinsulinism — Boss M et al. *Journal of Nuclear Medicine*, February 2022. 63(2):310–315.

VISUAL ABSTRACT



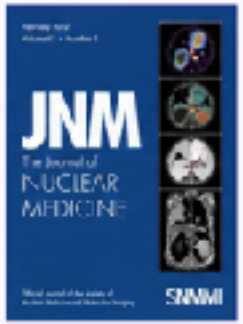




Superior to ^{18}F-DOPA PET

- ✓ Higher sensitivity
- ✓ Better contrast and image quality

Journal of Nuclear Medicine
Feb 2022



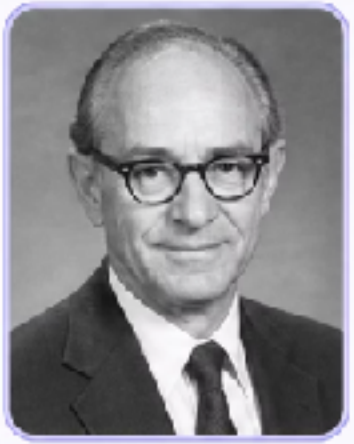
Treatment — Timeline of Key Discoveries

1964 1980 1995 2010 2025

Diazoxide — First Medical Treatment.

1964

- In 1964, Allan L. Drash reported that diazoxide could control blood glucose levels in some infants with leucine-sensitive hypoglycemia, providing further evidence that the disorder was due to HI.



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First Report on The Use of Diazoxide for HI.

Octreotide — Short and Long Acting

1993

Persistent hyperinsulinemic hypoglycemia of infancy: long-term octreotide treatment without pancreatectomy

Glaser B, Hirsch HJ, Landau H. *J Pediatr.* 1993;123(4):644–50.

Short- and long-term use of octreotide in the treatment of congenital hyperinsulinism

Thornton PS et al. *J Pediatr.* 1993;123(4):637–43.

First Description of Short-Acting Octreotide in HI

2012

Successful treatment of congenital hyperinsulinism with long-acting release octreotide

Le Quan Sang KH et al. *Eur J Endocrinol.* 2012;166(2):333–9.

First Description of Long-Acting Octreotide in HI

Nifedipine and Sirolimus — Additional Therapies

1999

- Treatment of hyperinsulinaemic hypoglycaemia with nifedipine — European Journal of Pediatrics, Volume 158, February 1999.
- Treatment of persistent neonatal hyperinsulinemic hypoglycemia with nifedipine — Journal of Pediatric Endocrinology & Metabolism 1999;12(4):511–514.

First Description of Nifedipine Use in HI

2014

- Sirolimus therapy in infants with severe hyperinsulinemic hypoglycemia — Senniappan S, Alexandrescu S, Shah P, Hussain K et al. N Engl J Med. 2014;370(12);1131–7.

First Description of Sirolimus Therapy for HI

Glucagon & Emerging Therapies.

1923
Discovery of glucagon by Kimball and Murlin

1950s
First clinical use for severe hypoglycemia

1980s–1990s
Used in CHI for acute hypoglycemia

2000s–present
Wider acceptance in CHI protocols

New Glucagon Formulation

Dasiglucagon for the treatment of congenital hyperinsulinism: randomised phase 3 trial — Thornton PS, De Leon DD et al. *J Clin Endocrinol Metab*. 2023.

RIZE RZ358-606 (Ersodetug)

- Significantly reduced hypoglycemia time and events in CHI patients
- Safe and well tolerated
- Potential treatment for all forms of hyperinsulinism

Demirbilek et al. *Med* (2025).

- **Adjuvant Alpelisib Therapy for Congenital Hyperinsulinism** — Dauleh H, Hussain K et al. *N Engl J Med*. 2024;390(4):379–380.
- **Alpelisib Therapy in 2 Patients With Congenital Hyperinsulinism** — Alburshad K, Amin R, Hussain K et al. *JCEM Case Reports* 2025.

First Description of Re-purposing Alpelisib for HI

A Global Community Fighting Back

From diagnosis to discovery — families and scientists united across six continents.

CHI
INTERNATIONAL

Summary

From McQuarrie to Today

Come a long way from the first description of HI

New Genetic Frontiers

New genetic mechanisms discovered

Expanding Treatment Options

Many new treatment options on the way

A Bright Future for HI

The future for HI is bright

Hope Has a Name

Together, funding research. Supporting families. Demanding better.

Pancreatic Beta-Cell: Metabolic Regulation of Insulin Secretion.