Assessing Hyperinsulinism

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Hyperinsulinism in Infancy

- History and Definition
- Control of insulin secretion
- Pathogenesis of Hyperinsulinism
- Distinguishing focal and diffuse disease
- Diagnostic Criteria
- Treatment options
- Clinical Cases
- Future services

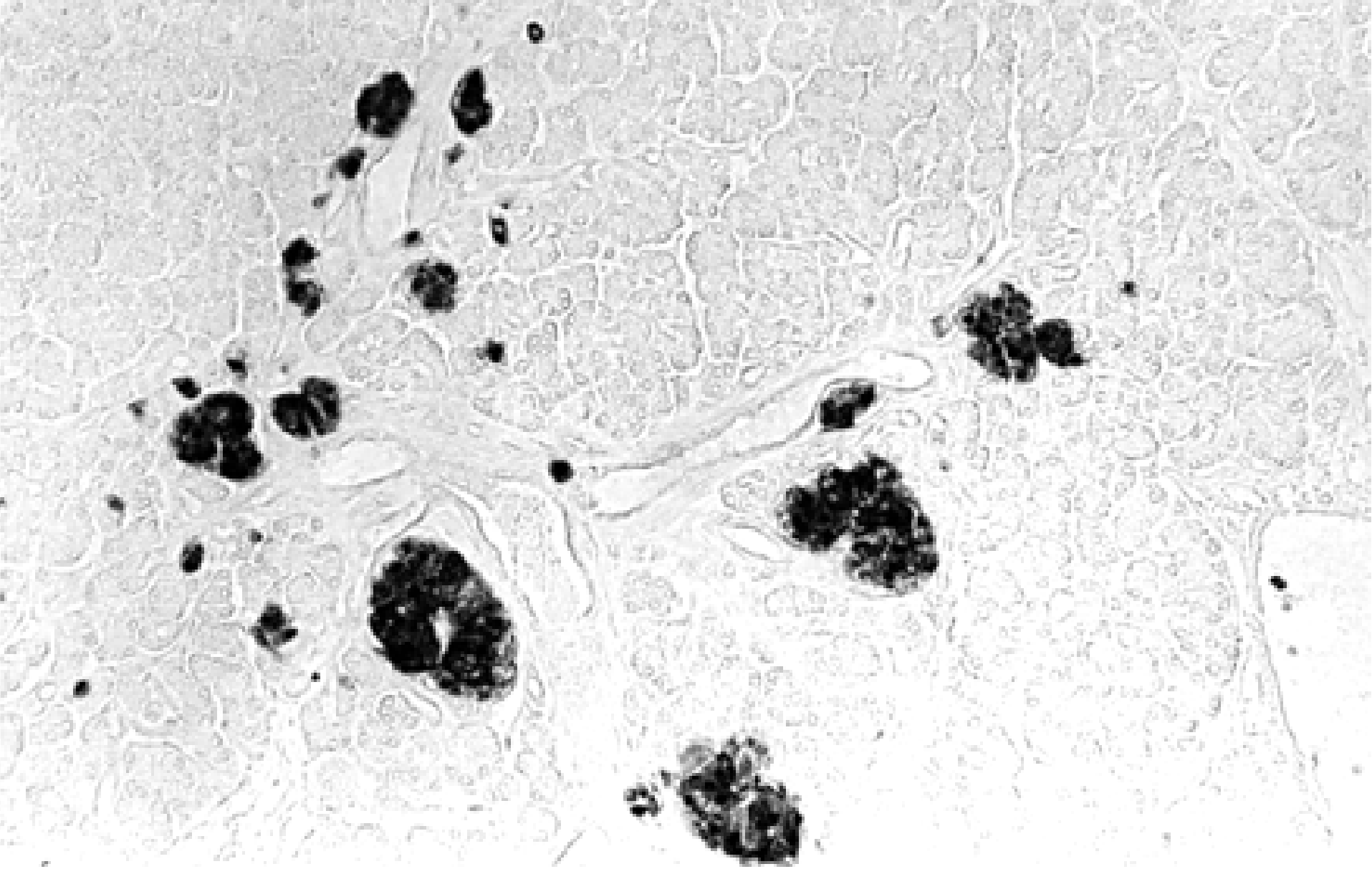
History and Definition

History

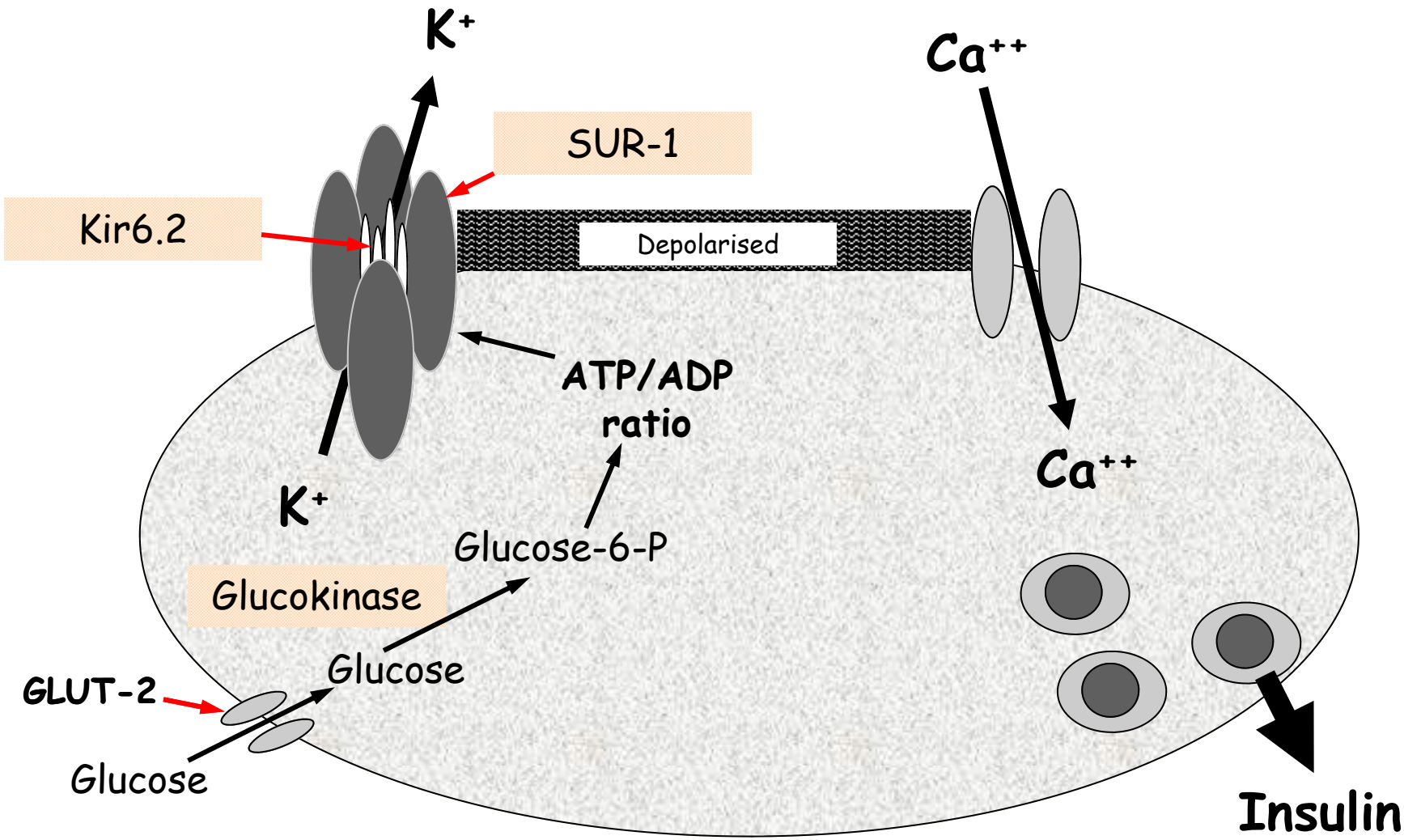
- Neonatal hypoglycaemia first described 1937 (Hartmann and Jaudon)
- Earliest description of hyperinsulinism 1938 (Laidlaw) – *nesidioblastosis*
- 1970s/80s – concept of "hyperinsulinism" finally accepted

Description and Definition

- Hyperinsulinaemic hypoglycaemia
- Persistent hypoglycaemia of infancy (PHHI)
- Congenital hyperinsulinism in infancy (CHI)
- Hyperinsulinism in infancy (HI)



Glucose Regulation of Insulin

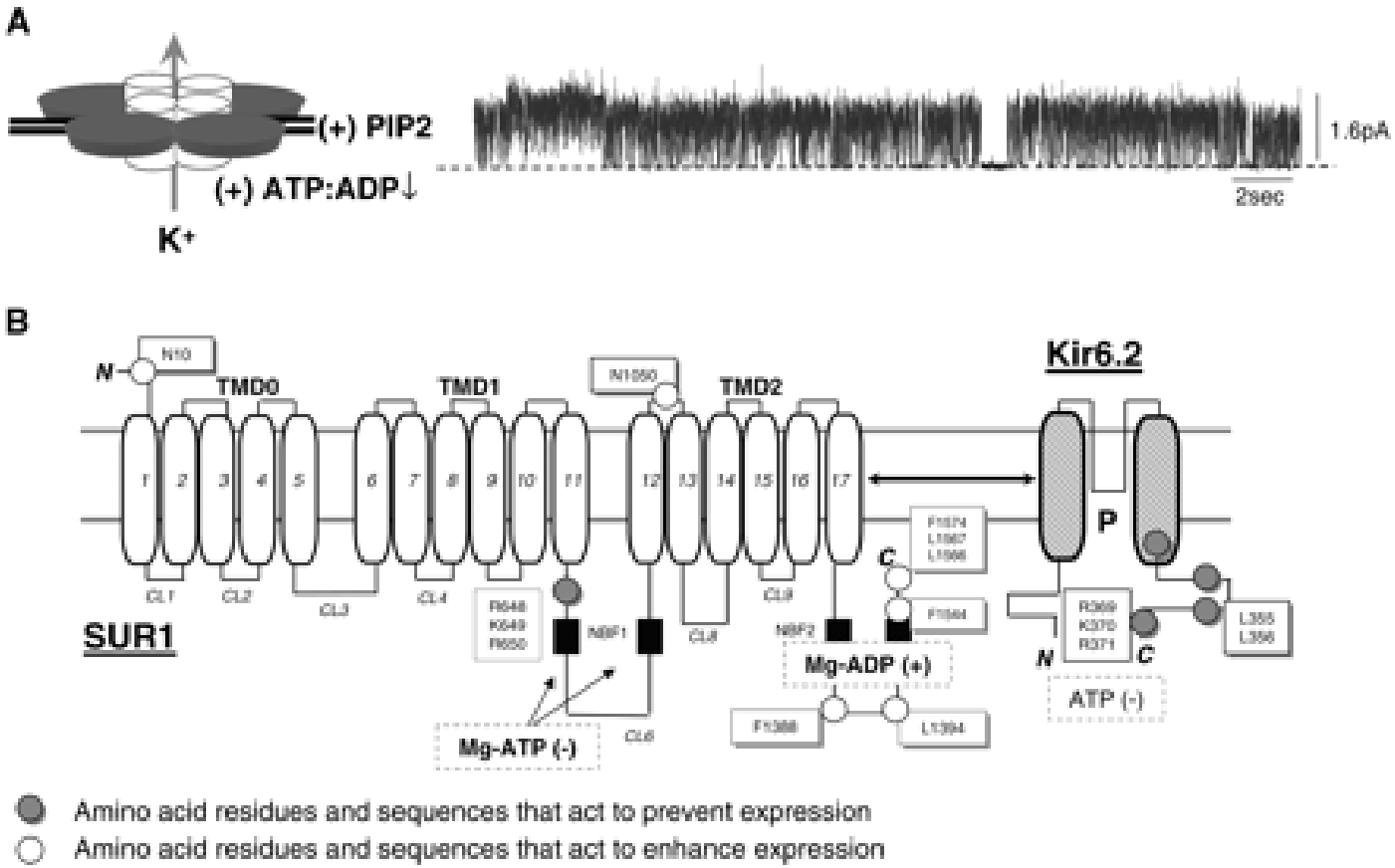


Second phase insulin secretion

- Amplification (augmentation) pathway
- Precise molecular mechanism by which glucose metabolism augments distal signalling unresolved
- Probably Ca^{2+} dependent and Ca^{2+} independent components

- Proposed coupling factors
  - Increased ATP/ADP and GTP/GDP ratio
  - Cytosolic levels of long-chain acyl co-A
  - Pyruvate-malate shuffle
  - Glutamate export from the mitochondria

Schematic representation of SUR1/Kir6.2 topology



K_{ATP} Channel and Drugs

- Antidiabetic drugs (e.g. tolbutamide, glibenclamide) cause closure of the channel, membrane depolarisation and insulin secretion.
- Diazoxide has opposite effect – keeps channel open, inhibiting insulin secretion. Is used to treat insulinomas and some types of HI.
- Mutations decreasing or destroying K_{ATP} channel activity do not normally respond to diazoxide.
- Mutations that increase nutrient metabolism and ATP/ADP ratio will normally respond.
- Nifedipine inhibits voltage-gated Ca^{2+} channels

Causes of Early-Onset Hyperinsulinism

- Infant of diabetic mother
- Hyperinsulinism associated with perinatal stress (birth asphyxia, maternal toxaemia, intrauterine growth retardation)
- Exogenous drug or insulin administration (e.g. Munchausen syndrome by proxy, ingestion of oral hypoglycaemic agents)
- Insulin-secreting adenoma

- Genetic disorders

Pathogenesis of Hyperinsulinism

- HI is the most common cause of persistent or recurrent hypoglycaemia in neonates
- HI promotes hepatic and skeletal muscle glycogenolysis which decreases free glucose in bloodstream and suppresses formation of FFA and ketones.
- Results in adrenergic and neuroglycopenic symptoms with severe neurological dysfunction
- Long term complications include developmental delay, mental retardation and/or focal CNS defects.
- Complications in 50% survivors.

Genetic Basis of Hyperinsulinism

- Unknown in >50% cases

- Known genetic causes

1. Defects in K_{ATP} channel genes (ABCC8 and KCNJ11)
2. HI-GK (Glucokinase gene defect)
3. HI-GDH (Glutamate Dehydrogenase gene defect)
4 HI-SCHAD (defect in gene coding for short chain 3-Hydroxyl-CoA Dehydrogenase)

Mutations in the β-cell K_{ATP} channel

- Most common and severest forms of HI involve defects in K_{ATP} channel genes.
- Patients are usually unresponsive to inhibitors of insulin release and require an early, near total (95% or more) resection of the pancreas.
- Leads to pancreatic insufficiency and diabetes mellitus (Incidence 75 – 85%).
- Most cases of HI are sporadic. Incidence of sporadic HI-K_{ATP} ranges from 1:27000 live births in Ireland to 1:40000 live births in Finland and 1:2500 in regions with high rates of consanguinity.

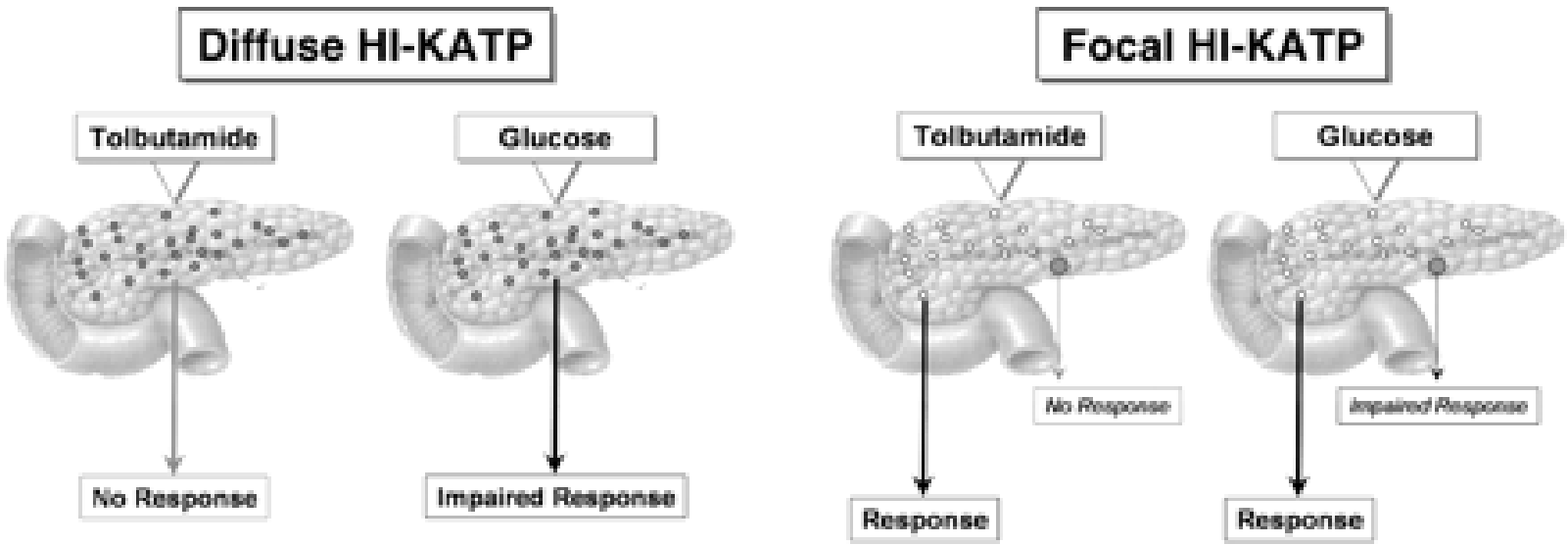
Focal (Fo-HI) versus Diffuse (Di-HI) Disease

- Di-HI predominantly arises from autosomal recessive inheritance of K_{ATP} channel gene mutations.
- Affects all islets of Langerhans and usually requires near total pancreatectomy.
- Fo-HI has non-Mendelian mode of inheritance. Results from somatic loss of maternal allele of chromosome 11p in a patient carrying a SUR1 mutation on the paternal allele.
- Focal lesions small regions (2-5mm) islet adenomatosis.
- Recent studies suggest 40-65% all patients with HI have the focal form of HI-KATP.

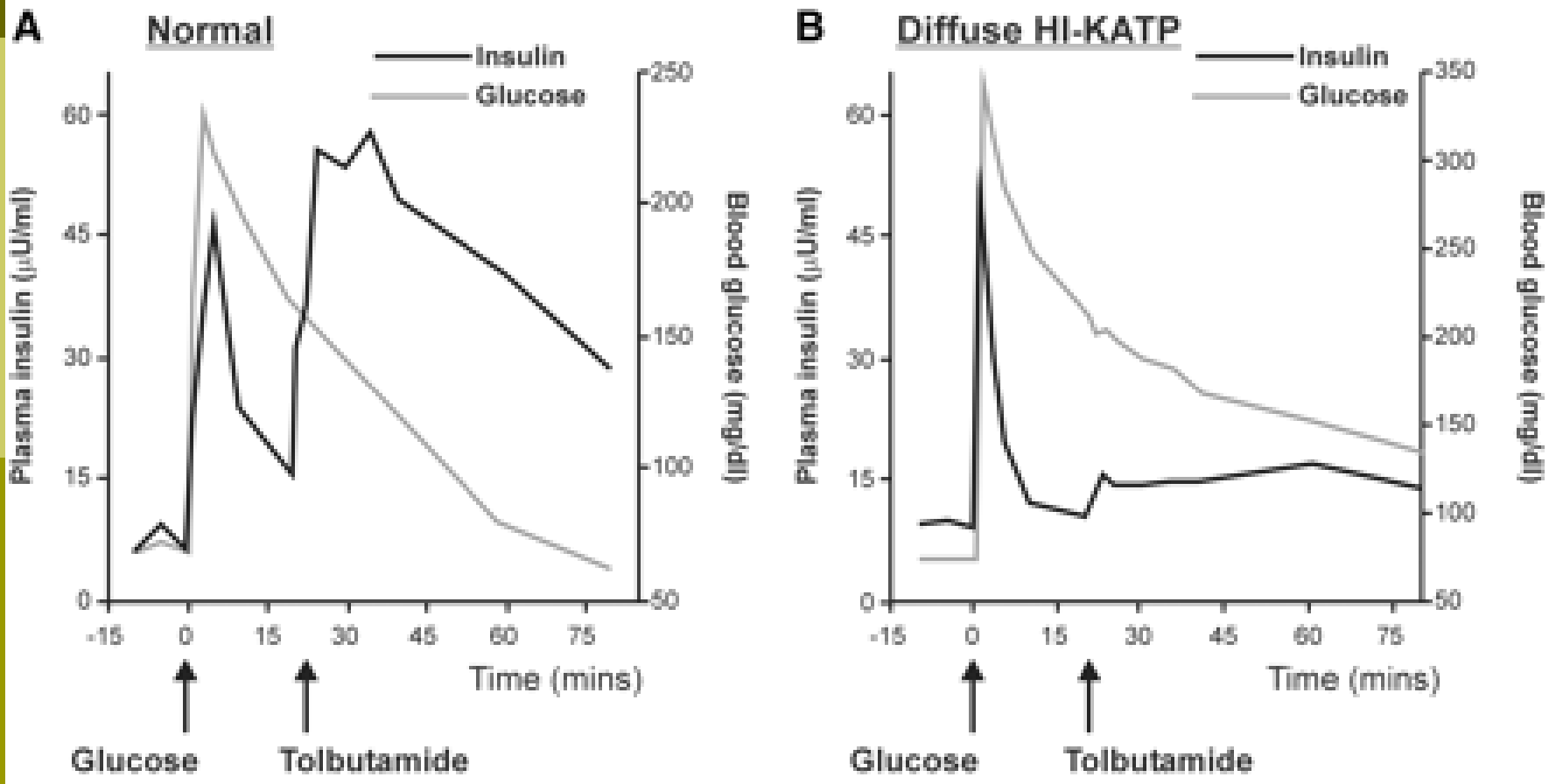
Procedures for Differentiating Fo-HI and Di-HI

- Interventional radiological procedures
  - arterial calcium stimulation
  - venous insulin sampling
  - transhepatic portal venous insulin sampling
  - positron emission tomography
- Examination of multiple biopsies
- Glucose/tolbutamide acute insulin response (AIR)

Predicted Outcomes of Acute Insulin Response in Fo-HI and Di-HI



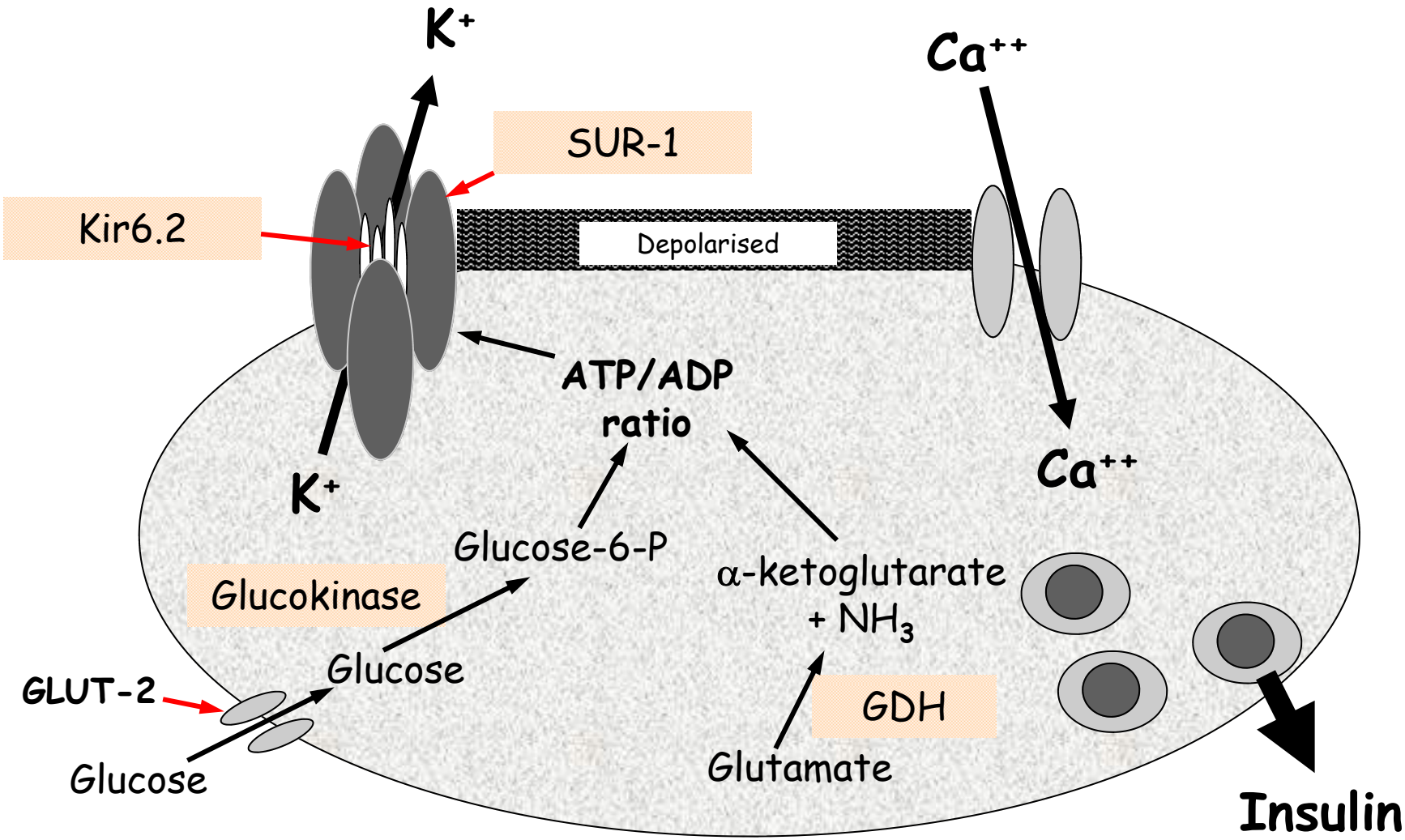
AIRs to glucose and tolbutamide in children with diffuse HI-KATP (Grimberg et al, 2001)



HI-GK (Glucokinase gene defect)

- Glucokinase is the rate limiting step in the metabolism glucose and acts as the cellular sensor of glucose concentrations.
- Gene mutations that decrease the sensitivity of the enzyme for glucose lead to Maturity Onset Diabetes of the Young (MODY).
- HI-GK mutations result in generation of an "activated" gene product with markedly increased sensitivity to glucose.
- Excessive ATP production in β-cells leads to inappropriate closure of K_{ATP} channels, unregulated Ca influx and insulin release.
- This form of HI only reported twice in the literature.
- Patients are clinically responsive to diazoxide.

HI-GDH (Glutamate Dehydrogenase gene defect)



HI-GDH (Glutamate Dehydrogenase gene defect)

- Increased insulin secretion occurs without any correlation with glucose concentration but is triggered by high protein diets.
- Many of these patients would have been previously described as having leucine sensitive hypoglycaemia.
- Plasma ammonia concentrations are 3 -5 x normal.
- Diazoxide therapy is effective in most cases.

Clinical Presentation of Hyperinsulinism

- Classically babies are macrosomic, resembling the infant of a diabetic mother but they may also be appropriate, or small for gestational age, or premature.
- Typically present in first post-natal hours or days but others may present during first year.
- Hypoglycaemia is persistent and usually severe.
- May be non-specific symptoms – e.g. floppiness, jitteriness, poor feeding and lethargy.

Diagnostic Criteria for Hyperinsulinism

- Glucose requirement >6-8 mg/kg/min to maintain blood glucose above 2.6 – 3 mmol/L.
- Laboratory blood glucose <2.6 mmol/L
- Detectable insulin at the point of hypoglycaemia with raised C-peptide.
- Inappropriately low free fatty acid and ketone body concentrations in the blood at the time of hypoglycaemia.
- Glycaemic response to administration of glucagon when hypoglycaemic.
- Absence of ketonuria.

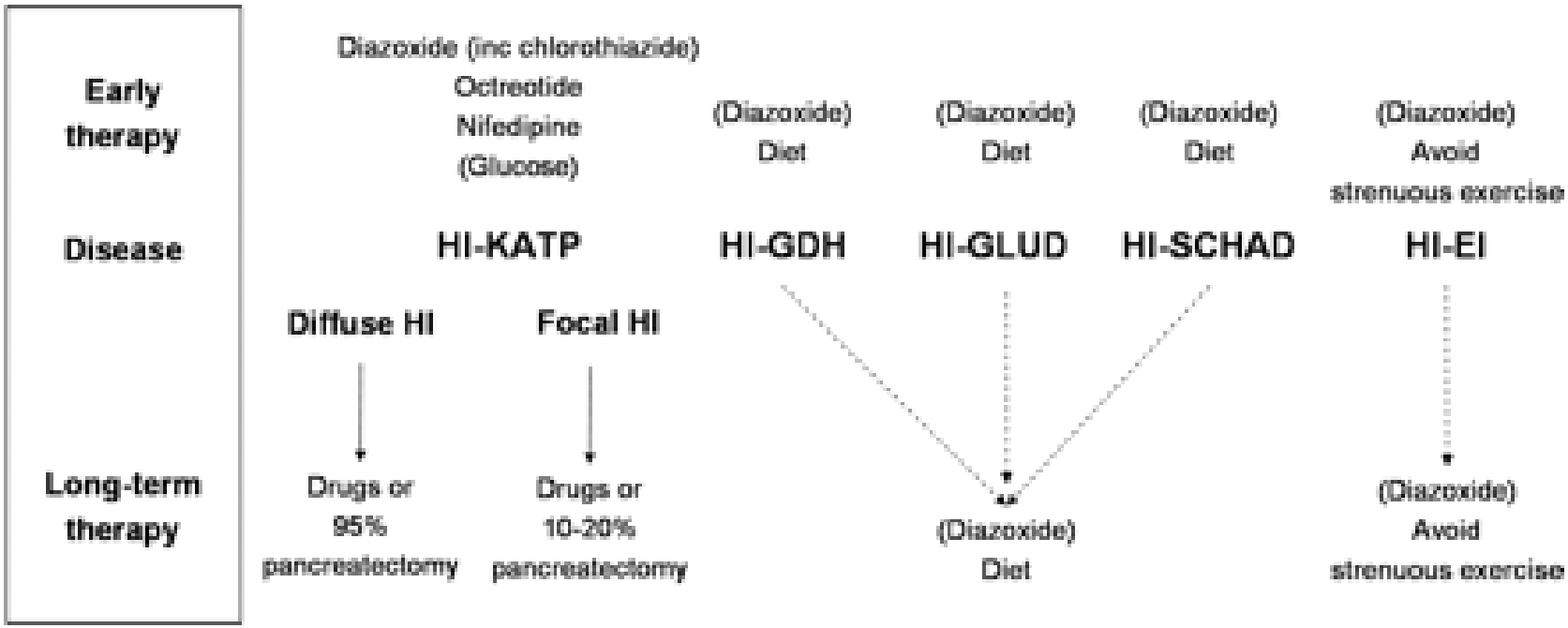
Practical Considerations

- Is a laboratory glucose measurement mandatory for the diagnosis of HI?
- Is it feasible to obtain 2-hourly laboratory glucose measurements on neonates in order to establish the infusion rate necessary to maintain glucose above 2.6 – 3 mmol/L?
- What level of insulin is diagnostic of HI?
- What constitutes inappropriately low ffa/ketone levels in presence of hypoglycaemia?

Management Cascade

- Initial stabilisation of the infant
- Pharmacological therapy
- Surgical management

Pharmacological Therapy



Clinical Case

- MR , a baby boy, was born at 35 weeks gestation by emergency caesarian section but with a birthweight of 4.73kg.
- Both parents were Ashkenazi Jews. Mother 23 years old, one previous delivery of normal, healthy child.
- MR was found to be hypoglycaemic aged 12 hours although asymptomatic. By day 2 he was requiring 120ml/kg/day of 12.5% dextrose to maintain normoglycaemia. Later that day his sugars became low again and he was given further carbohydrate in the form of bottle feeds.

Laboratory Investigations

- Insulin 37 mU/l with a glucose of 1.5 mmol/l.
- Growth hormone 78.4 mU/l.
- Cortisol 599 nmol/l.
- T4 142 nmol/l, TSH 7.12 mU/l
- Ammonia and liver function tests normal.
- Urine amino and organic acids normal.
- No ketonuria.

- PCR analysis of DNA - both parents were found to be heterozygous for the SUR 1 Intron 32 3992-9g to a mutation and the baby homozygous.

Progress (1)

- At 4 weeks old, a glucose infusion of 14.7 mg/kg/min was failing to maintain blood glucose above 2.6 mmol/l.
- MR was commenced on chlorthiazide (10 mg/kg/day) and diazoxide (15 mg/kg/day). Polycal was added to his feeds, giving total glucose intake of 18.2 mg/kg/min.
- The above therapy still failed to maintain euglycaemia and Nifedipine (0.5 mg/kg/day) was commenced.
- Blood glucose levels appeared to stabilise and iv glucose was stopped but oral feeds continued 2 hourly with plan to eventually decrease to 3 hourly, then 4 hourly.

Progress (2)

- Unfortunately, hypoglycaemia returned and it proved impossible to establish a normal feeding pattern whilst preventing hypoglycaemia.
- An echo showed MR to have mild to moderate left ventricular hypertrophy. It was felt unwise to further increase diazoxide because of the risk of cardiotoxicity.
- Age 2.5 months, MR underwent 95% pancreatectomy. Histological examination of frozen section of the pancreas, taken at the time of operation showed enlarged, hypertrophic nuclei in the islets dispersed throughout the biopsy, consistent with diffuse change.
- Post operatively MR developed insulin dependent diabetes mellitus requiring Humulin I: 2 units b.d.

Summary and conclusions

- Clinical presentation was typical. MR was macrosomic and presented 12 hours after delivery with persistent, severe hypoglycaemia.
- The majority of diagnostic criteria for HI were met (glucose requirement >6-8 mg/kg/min, laboratory glucose <2.6 mmol/l, detectable insulin at point of hypoglycaemia, absence of ketonuria).
- The baby was found to be homozygous for the SUR1 mutation 3992-9 g-a mutation which is found in 70% of Ashkenazi Jewish HI associated chromosomes.
- The disease was found to be resistant to medical treatment which is consistent with the mutation described.

Footnote

- MR is now 4yrs 10 months
- C-peptide analysis confirmed that he is producing some endogenous insulin.
- Neverthless his insulin requirements have increased over the years and he is now on:
  - Humulin I: 5 units in the morning, 1-2 units occasionally at night
  - Humulin S: 2units at tea –time
- He is also on exocrine pancreatic replacement therapy.
- His blood sugars are fluctuate between 2.7 and 14 mmol/L his last HbA1c was 8.1%.
- He has had rather poor weight gain over the last 12 months but this appears to be improving.
- He is energetic and active but will need help with speech and language.

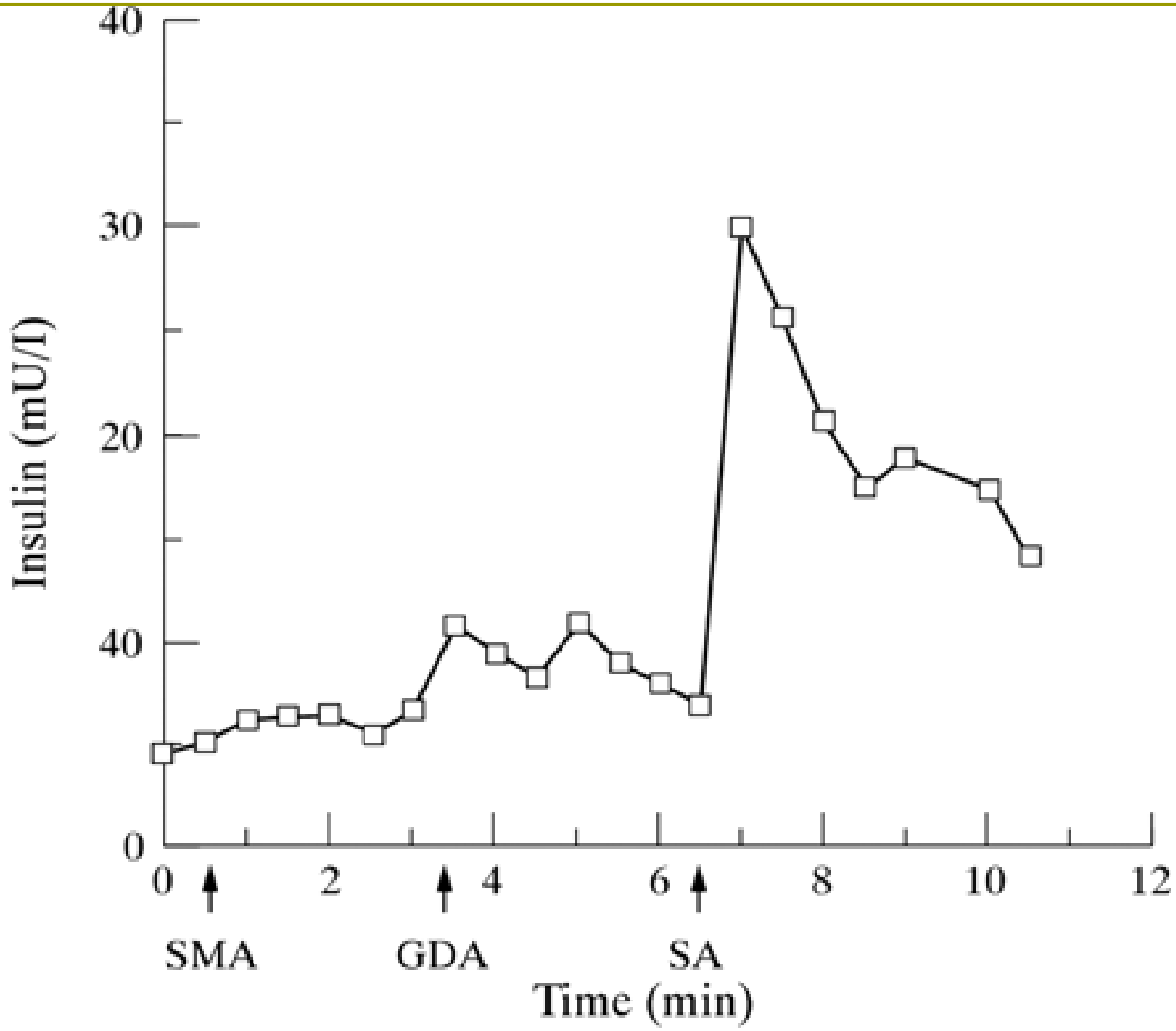
Development of a National Specialised service for Hyperinsulinism

- HI is the most common cause of persistent and recurrent hypoglycaemia in infancy and childhood.
- It is extremely complicated and heterogeneous and is difficult to both diagnose and manage.
- ENRHI site late referral to a specialist centre as one of the main reasons for continuing high neurological morbidity.
- Management requires a multi-disciplinary team approach.
- Differentiation of focal from diffuse disease is crucial.
- An estimated 55 cases/annum will present in the U.K. with ?HI.
- Numbers not appropriate for management at PCT or even regional level
- 2 specialist centres are required and funding has been sought for this.

Acknowledgements

- Prof Peter Clayton
- Dr Tony Price
- Dr Catherine Hall
- Colin Cusick
- Many other laboratory staff at Manchester Children's Hospital

Intra-arterial calcium stimulation test in a patient with fo-HI (Abernethy et al)



Diagnosis of HI – Intermediary Metabolites and Hormones to be Measured at Point of Hypoglycaemia

Blood	Urine
Glucose Lactate/pyruvate Ketone bodies Free fatty acids Amino acids Ammonia Total/ free carnitine Acyl-carnitine profile Insulin/ C-peptide Cortisol/ growth hormone	Ketones Reducing substances Organic acids

Treatment of Hyperinsulinism - Objectives

- Prevent hypoglycaemic brain damage and allow normal psychomotor development.
- Establish normal feed volume, content and frequency for age of child.
- Ensure normal tolerance to fasting for age without developing hypoglycaemia.
- Maintain family integrity

Summary and conclusions (2)

- Pre-operative percutaneous trans-hepatic venous sampling has been advocated (1) to differentiate focal and diffuse HI but is restricted to one or two centres nationally and could not be arranged in this case.
- MR underwent 95% pancreatectomy, the recommended treatment for diffuse HI which is unresponsive to medical treatment.
- Post-operatively histological examination confirmed diffuse HI which was also consistent with the specific mutation.
- MR developed post-operative diabetes mellitus which is common following 95% pancreatectomy.