Historical perspective: How basic scientific understanding has led to improvements in hyperinsulinism treatment

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pictures from CHI website (2015)
Two newborns with different ABCC8 mutations

Alice
- Alice was born to 1st. cousin parents after a normal 40 week pregnancy.
- At birth she weighed 5 kilos (11 lbs).
- Two hours after birth Alice was unresponsive with shallow and irregular breathing.
- Severe hypoglycemia was documented and a diagnosis of congenital hyperinsulinism was confirmed biochemically and genetically. Alice’s ABCC8 mutation led to premature truncation of SUR1, an incomplete protein unable to make a functional channel.
- Alice did not respond to diazoxide or octreotide, inhibitors of insulin secretion; a partial pancreatectomy was done at 17 days of age followed by a total one at 32 days to reduce her insulin levels.

Bob
- Bob was born to unrelated parents after a normal 39 week pregnancy.
- Bob weighed 2 kilos (4.5 lbs) at birth.
- After a week he was dehydrated due to very high blood glucose levels.
- Bob was diagnosed with neonatal diabetes and given insulin to lower his blood sugar levels.
- Bob’s ABCC8 mutation produced a protein which was too active. His $K_{ATP}$ channels were always open preventing insulin secretion.
- Fortunately, his mutation was responsive to the oral sulfonylurea, glibenclamide, a $K_{ATP}$ channel inhibitor, and he was eventually weaned off insulin and is in excellent control.
• δ cells ~3-10% produce somatostatin
• α cells ~15-20% produce glucagon
• β cells 65-80% produce c-peptide, insulin and pro-insulin
• F or PPI cells ~3-5% produce pancreatic polypeptide
• ε cells <1% produce ghrelin
\( \kappa_{\text{ATP}} \) channels

SUR1

NBF-1

binds ATP\(^4-\) tightly

NBF-2

binds MgATP & ADP weakly, hydrolysis?
$K_{ATP}$ channels and the regulation of insulin release

- Glucose metabolism
- MgATP/MgADP
- Glucokinase
- $K_{IR6.2}$ channel activity
- [Ca$^{2+}$]$_i$
- Pulsatile insulin release

Drugs:
- Diazoxide
- Sulfonylureas

Factors:
- [Ca$^{2+}$]$_c$
- 2 min
- 1 sec
- 1 pA
The protein "factory" Quality control is done here. Normal, and some mutant, $K_{ATP}$ channels are made and put together here. Some mutant SUR1/KIR channels are returned to the factory and destroyed.

Channels are modified and packaged into insulin granules here.

$K_{ATP}$ channels move to the cell surface with insulin.

Alice's channels fail quality control here.
Alice’s lack of $K_{ATP}$ channels cause her hyperinsulinism

No $K_{ATP}$ channel activity
No response to diazoxide

Glucose $\rightarrow$ ATP/ADP $\rightarrow$ Glucokinase

$\uparrow$ [Ca$^{2+}$]$_i$

insulin granules $\rightarrow$ insulin release $\rightarrow$ hypoglycemia
Understanding Bob's ND.

Bob's $K_{ATP}$ channels reach the cell surface, but are defective.
Bob's $K_{\text{ATP}}$ channels are too active $\rightarrow$ insulin levels low

- $K_{\text{IR}6.2}$
- $K_{\text{ATP}}$ channels fully active
- Glucose ATP/ADP
- Ca$^{2+}$
- Glibenclamide
- Depolarize
- Glucokinase
- ATP/ADP
- Insulin release
- Insulin granules
- Low insulin $\rightarrow$ high glucose levels
- Insulin release
Non-stimulatory SUR1 configuration (channels closed)

Stimulatory SUR1 configuration (channels open)

Amino acids changed in SUR1
- E1506Q
- Q1178R
- E1506D
- R1182Q
- I1424V
- WT
- S1185A
- C1174F
- E1506K
- G1479R

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GBC = glibenclamide

Thank you Parents and Children! Our Science absolutely cannot progress without your participation.