
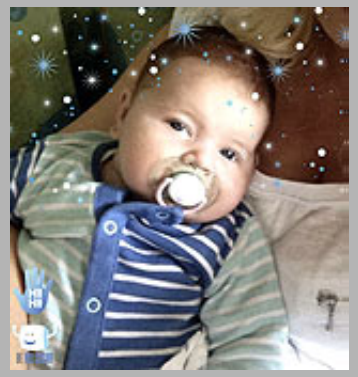
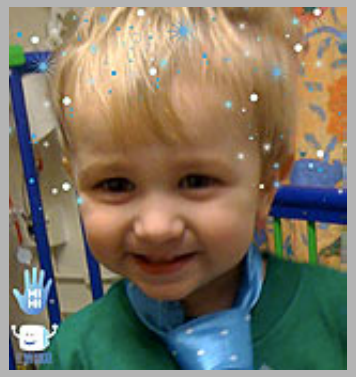

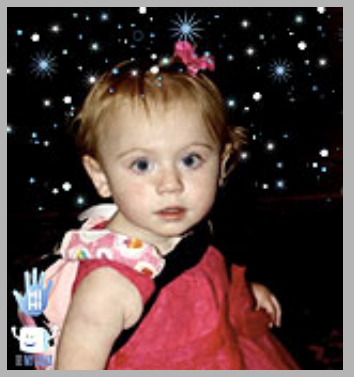

Historical perspective: How basic scientific understanding has led to improvements in hyperinsulinism treatment


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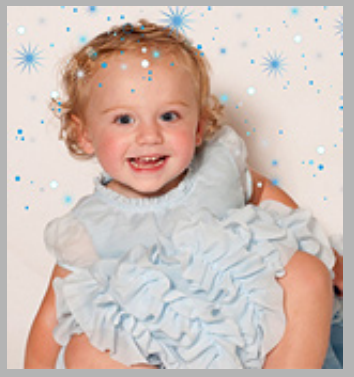
Congenital Hyperinsulinism International Family Conference
September 29-30, 2015
Hospital Sant Joan de Déu
Barcelona, Spain







pictures from CHI website (2015)

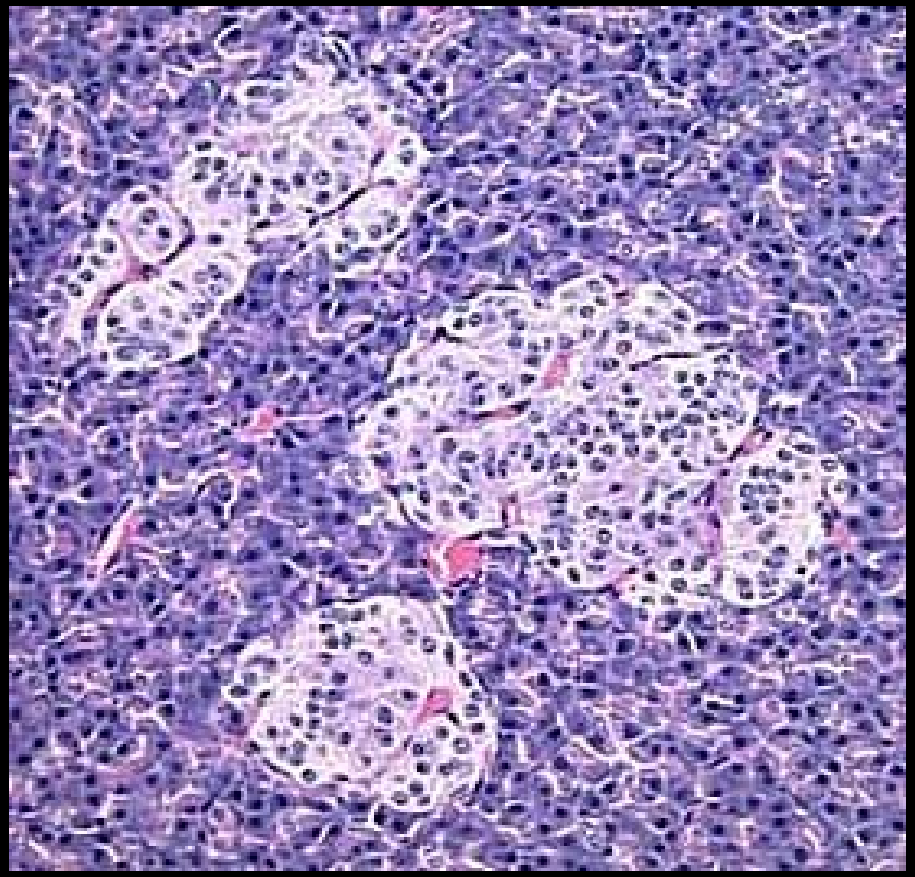
Two newborns with different ABCC8 mutations

Alice

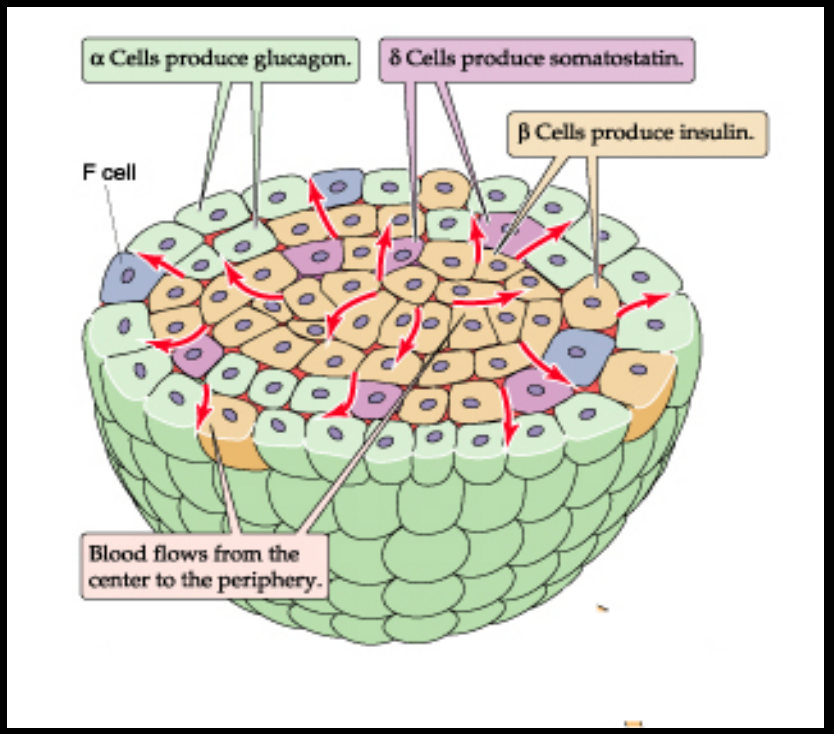
- Alice was born to 1st. cousin parents after a normal 40 week pregnancy.
- At birth she weighed 5 kilos (11 lbs).
- Two hours after birth Alice was unresponsive with shallow and irregular breathing.
- Severe hypoglycemia was documented and a diagnosis of congenital hyperinsulinism was confirmed biochemically 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.



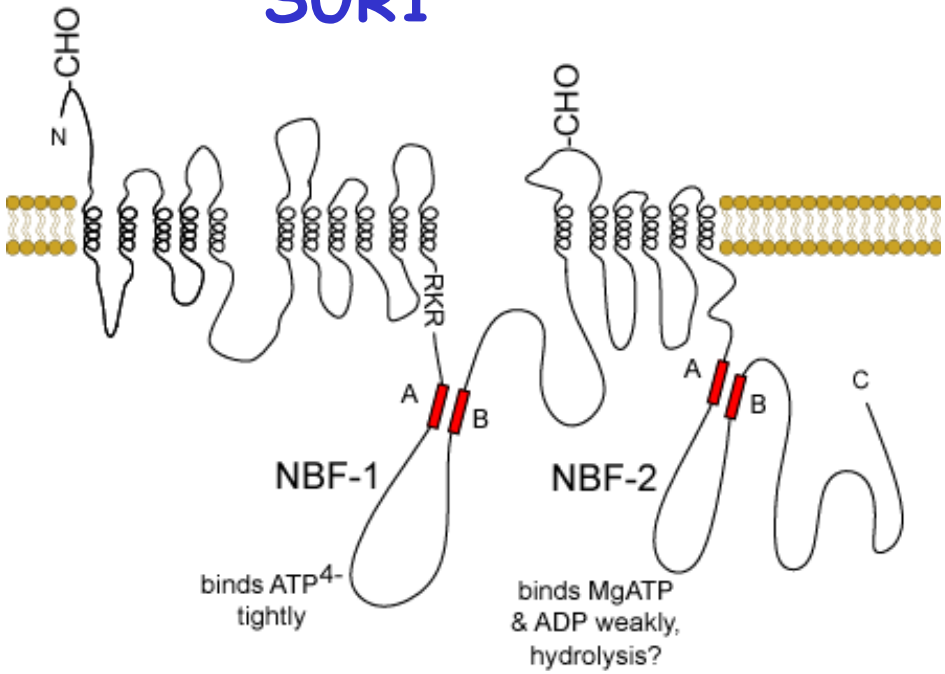
- α cells ~15-20% produce glucagon
- δ cells ~3-10% produce somatostatin
- β cells 65-80% produce c-peptide, insulin and pro-insulin



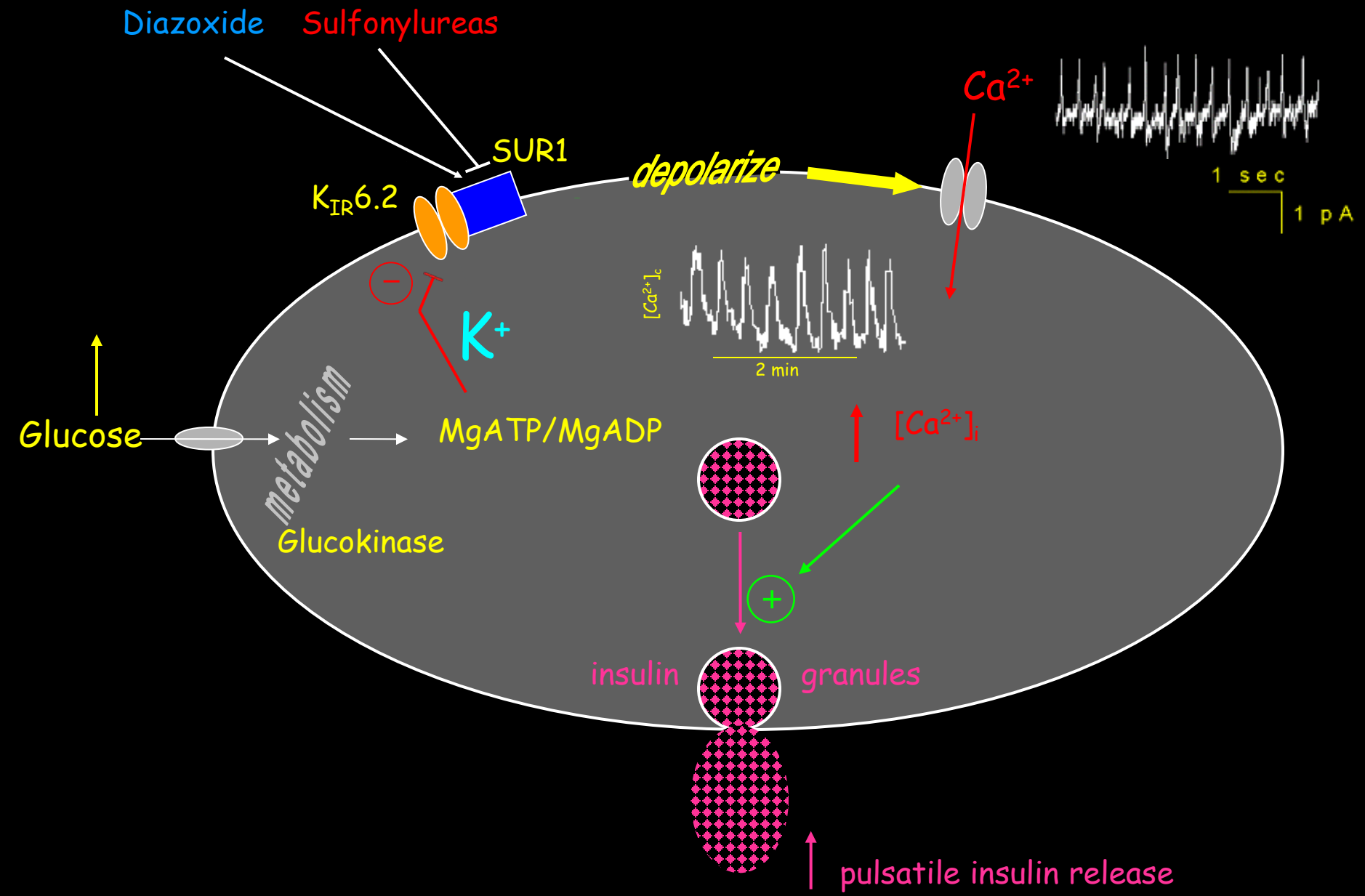
- F or PPI cells ~3-5% produce pancreatic polypeptide
- ε cells <1% produce ghrelin

K_{ATP} channels

SUR1



K_{ATP} channels and the regulation of insulin release



Understanding Alice's CHI

K_{ATP} channels are made and put together here

The protein "factory"

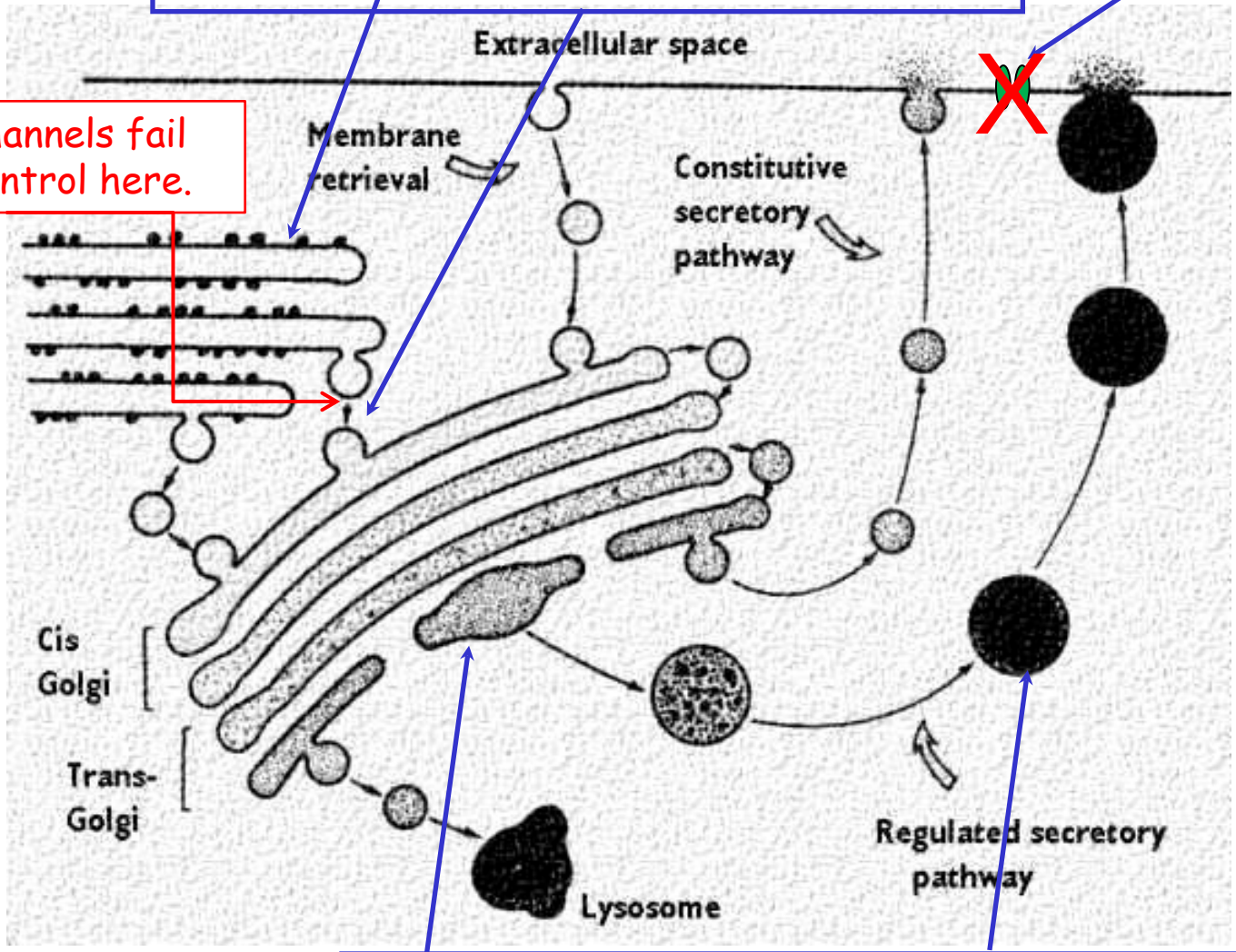
Quality control is done here. Normal, and some mutant, K_{ATP} channels are sent back to the ER

Some mutant K_{ATP} channels are destroyed

Making K_{ATP} channels in β-cells

K_{ATP} channels are at cell surface

Alice's channels fail quality control here.

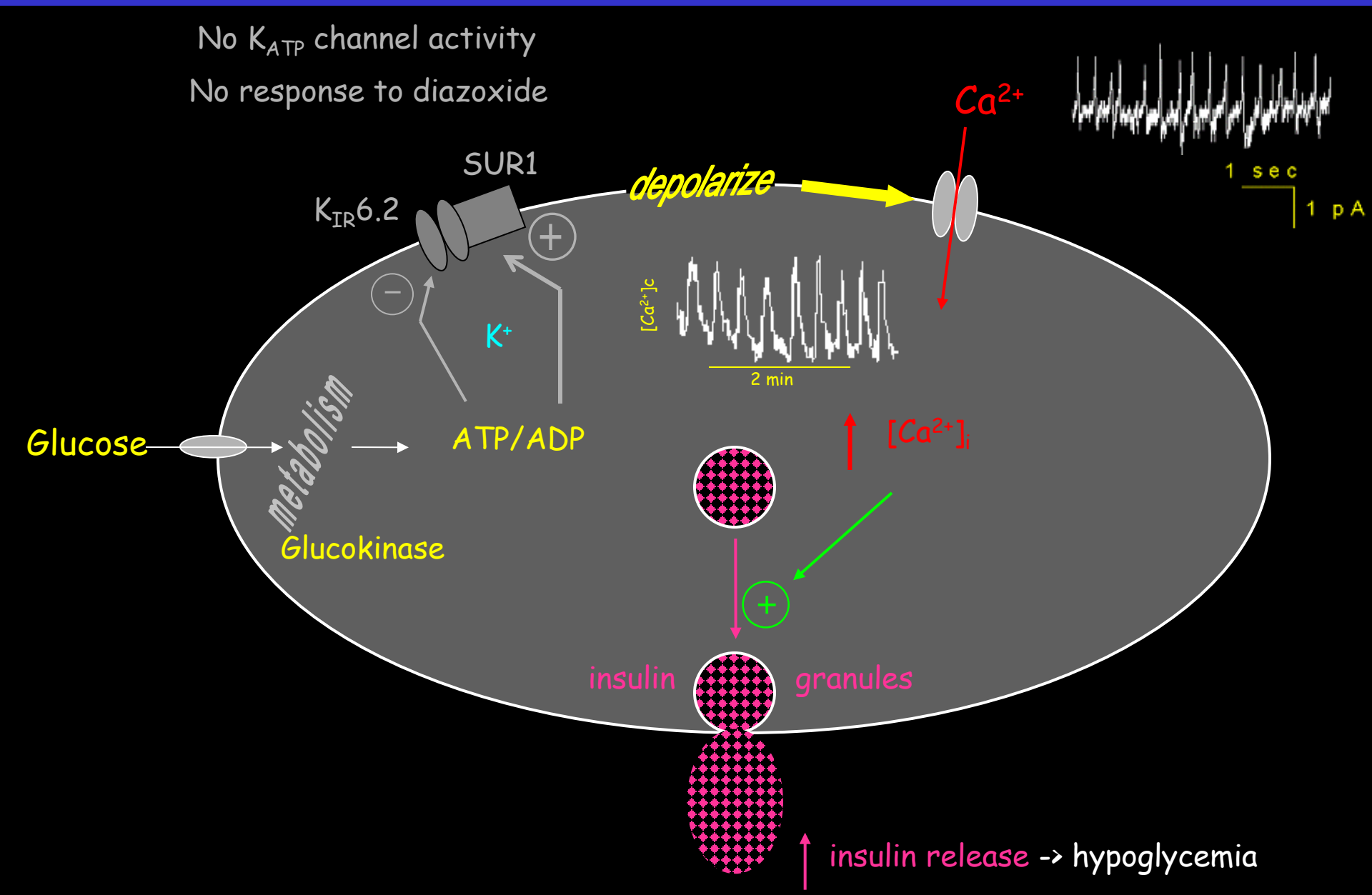


K_{ATP} channels move to the cell surface with insulin

Channels are modified and packaged in transport vesicles here

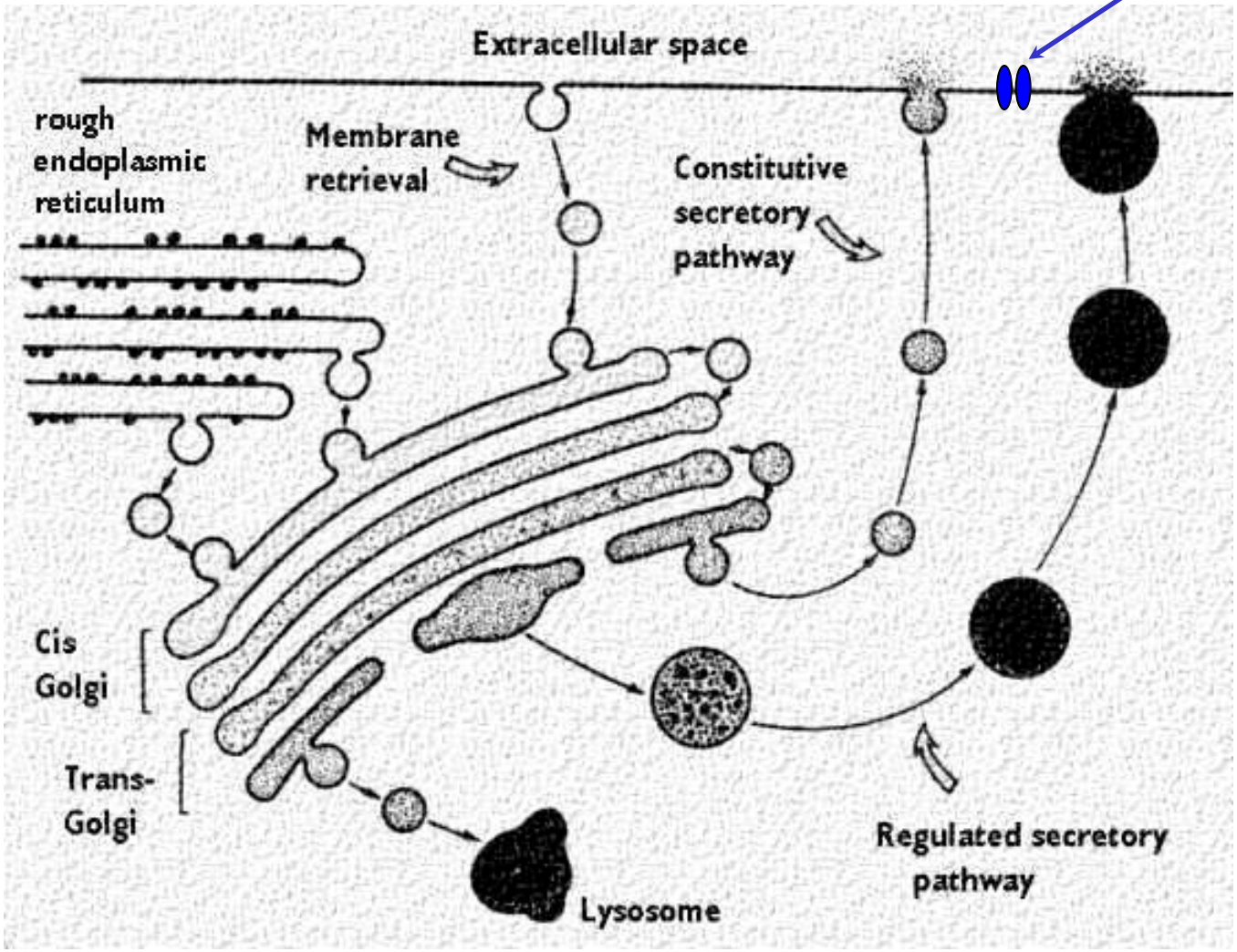
The protein Assembly Line

Alice's lack of K_{ATP} channels cause her hyperinsulinism



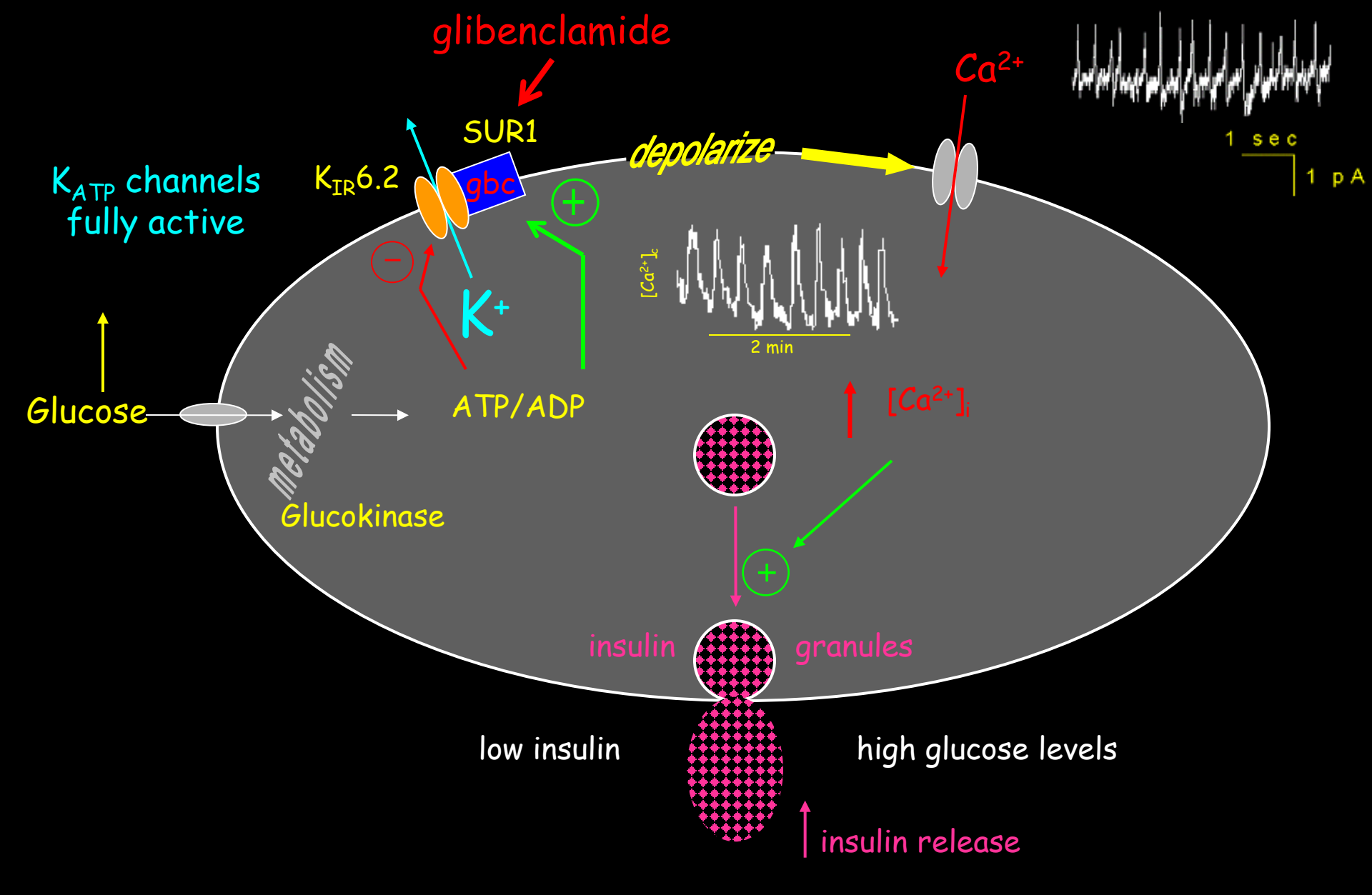
Understanding Bob's ND.

Bob's K_{ATP} channels reach the cell surface, but are defective.

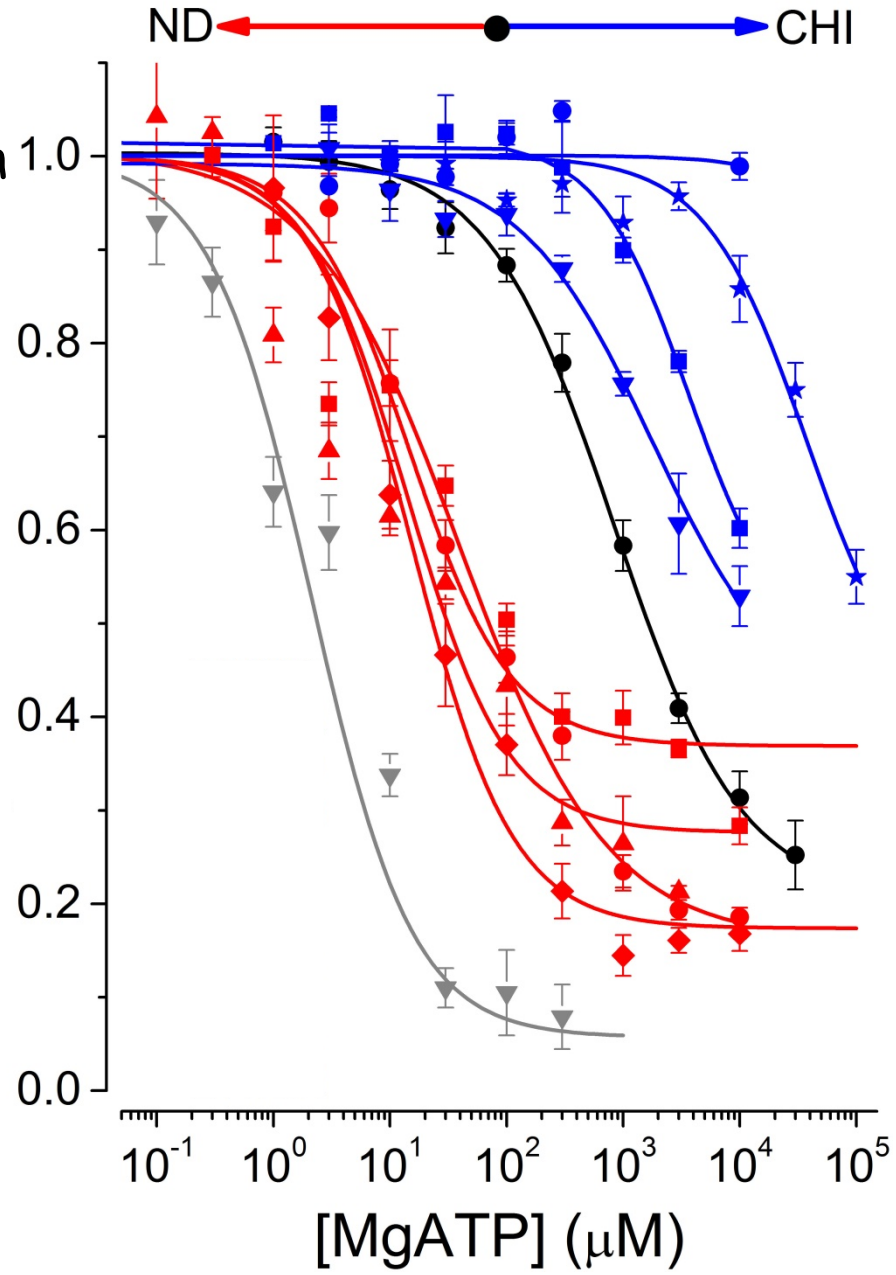


The Protein Assembly Line

Bob's K_{ATP} channels are too active -> insulin levels low



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

Modified from Ortiz & Bryan, Frontiers in Endocrinology (2015)

Non-stimulatory SUR1 configuration
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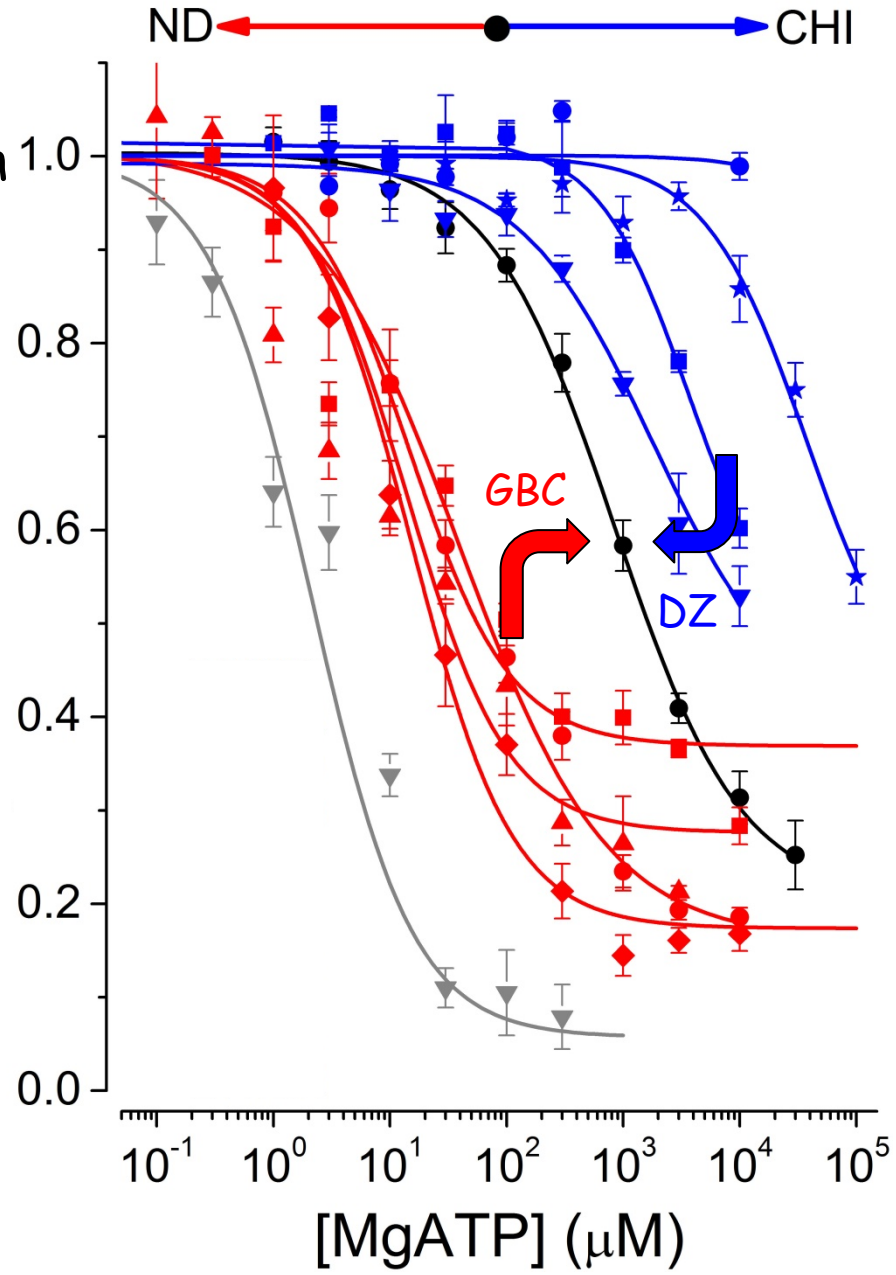

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GBC = glibenclamide

Modified from Ortiz & Bryan, Frontiers in Endocrinology (2015)


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