Congenital hyperinsulinism: from bench to bedside .... and back?

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Congenital Hyperinsulinism in Infancy (HI) is a potentially-lethal condition of neonates and early childhood. Recent advances in genetics, histopathology and the molecular physiology of insulin release have now revealed the causes of HI in a large cohort of patients. From defects in the genes that encode ion channel subunits, β-cell metabolism and anaplerosis, the causes of HI are both varied and numerous. However, the consequences of these mutations appear to converge in their action upon a common target protein – the ATP-sensitive K-channel. The function of these channels is not only critical to the control of healthy normal insulin-secreting cell function, but "activating" defects in these channels lead to permanent neonatal diabetes and type 2 diabetes. HI can arise through 'channelopathies' by way of defects in the sulfonylurea receptor (encoded by ABCC8, Ch11.p15)[1] or the inwardly-rectifying potassium channel subunit Kir6.2 (encoded by KCNJ11, Ch11.p15).[2] It can also arise as a result of 'metabolopathies' through defects in the genes encoding glucokinase HI-GK (GCK, Ch.7p15-p13),[3] glutamate dehydrogenase HI-GDH (GLUD1, Ch.10q23.3)[4] and Short-chain L-3-hydroxyacyl-CoA dehydrogenase HI-SCHAD (HADHSC, Ch.4q22-q26).[5] Despite advances, medical therapy for HI remains largely unchanged due to the availability of limited agents that are selective and specific for the termination of insulin release from ß-cells. Congenital Hyperinsulinism can be a devastating disease, and interest focuses upon the relationship between the causes of HI and current / future therapies, including stem cells.

1. Online Mendelian Inheritance in Man. http://www.ncbi.nlm.nih.gov/Omim/getmap.cgi?l600509
2. Online Mendelian Inheritance in Man. http://www.ncbi.nlm.nih.gov/Omim/getmap.cgi?l600937
3. Online Mendelian Inheritance in Man. http://www.ncbi.nlm.nih.gov/Omim/getmap.cgi?l138079
4. Online Mendelian Inheritance in Man. http://www.ncbi.nlm.nih.gov/Omim/getmap.cgi?l138130
5. Online Mendelian Inheritance in Man. http://www.ncbi.nlm.nih.gov/Omim/getmap.cgi?l601609