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Perspective



# Congenital Hyperinsulinism: An Unfortunate Therapeutical Situation

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## Abstract

Congenital hyperinsulinism in newborns occurs in approximately 1 in 28,000 to 50,000 births. It can manifest as syndromic or non-syndromic, nonketotic, or ketotic cases, with focal, diffuse, or atypical histological forms. The primary diagnostic criteria include detectable insulin levels and hypoglycemia in the blood. Both early and late onset forms of the condition exist, leading to a wide range of patient phenotypes and significant care burdens for families. The disease is primarily genetic, with mutations in multiple genes, particularly in the 11p15 chromosomal region, including the K+ ATP channel on region 11p15.1. Finding a cure involves repairing the genetic mutation, but the complexity of the genetic origins poses challenges in developing curative treatments for affected children.

**Keywords:** Congenital hyperinsulinism, Newborn, Insulin, Child treatment

## Perspective

Hyperinsulinism is a condition marked by high insulin levels in the blood, leading to low blood sugar levels and health risks [1-4]. Causes include increased insulin secretion or impaired insulin breakdown, possibly due to insulin resistance or tumors like insulinomas [5,6]. Excessive insulin production lowers blood sugar levels, causing hypoglycemia. Diagnostic tests include fasting insulin levels above 17mU/l, low blood sugar levels, elevated C-peptide levels, and abnormal glucose tolerance tests. Mutations in genes like ABCC8 and KCNJ11 are associated with hyperinsulinism [7-9]. Syndromes like Wiedemann-Beckwith and Turner syndrome can also be linked to congenital hyperinsulinism [10]. Diagnostic parameters include glucose, insulin, C-peptide, ketone bodies, and genetic testing [11]. Therapy typically begins with diazoxide, a K+ ATP channel agonist [12]. Some cases may not respond to diazoxide treatment due to mutations in the ABCC8, KCNJ11, and GCK genes [13]. Long-term use of diazoxide can lead to side effects such as bone marrow suppression, hypertrichosis, hair loss, and pulmonary hypertension. Diazoxide is an effective potassium channel opener used to treat hypoglycemia by inhibiting insulin secretion. It binds to the sulfonylurea receptor 1 (SUR1) and keeps the potassium channel open, reducing insulin secretion. Diazoxide is contraindicated in cases of hypersensitivity, heart disease, diabetes, and other conditions. Adverse effects may include sodium retention, hyperuricemia, hypertrichosis, leukopenia, thrombocytopenia, headaches, and dizziness. It is important to avoid diazoxide during pregnancy and breastfeeding due to potential risks to the fetus and infant.

Therapy is primarily started with diazoxide, a K+ ATP channel agonist. Unresponsive and responsive cases to diazoxide treatment do exist [14]. Unresponsive cases are related to ABCC8, KCNJ11 and GCK gene mutations [15]. Unresponsive cases are related to ABCC8, KCNJ11 and GCK gene mutations. Long treatment is negative influenced by bone marrow suppression, hypertrichosis, hair loss and pulmonary hypertension. Diazoxide is a benzothiadiazide derivative that does not have diuretic effects. It is lipophilic and at physiological pH, only about 10% exists as an anion. It is an orally effective selective potassium channel opener used as a therapeutic agent for

hypoglycemia. It causes a rapid and temporary dose-dependent increase in blood sugar levels by inhibiting insulin secretion from the pancreatic islets of Langerhans, generally lasting less than eight hours. Diazoxide is a sulfonylurea receptor 1 (SUR1) agonist. SUR1 and Kir6.2, for example, form the functional ATP-dependent potassium channel K(ATP) in the pancreas. Activation of this channel leads to potassium efflux, which stabilizes the membrane potential. In the pancreas, this inhibits or reduces insulin secretion. Diazoxide binds to SUR1, which acts as a regulatory subunit and likely alters the spatial structure of the receptor, keeping the channel pore, composed of Kir6.2 subunits, open for longer. As more potassium leaves the cell, the resting membrane potential becomes more negative, reducing the likelihood of insulin secretion. The drug diazoxide is orally administered for hypoglycemia of various origins, such as congenital leucine hypersensitivity, some congenital defects of the KATP channel, nesidioblastosis, pancreatic and extra pancreatic insulin-producing tumors, refractory malignant hypertension in renal insufficiency, and glycogen storage disease. Treatment with diazoxide is contraindicated in cases of hypersensitivity to the active ingredient, allergy to benzothiadiazides, coronary heart disease and heart failure, diabetes mellitus, pheochromocytoma, azo dye and analgesic intolerance. Embryotoxicity was found in animal studies. The drug should not be used during pregnancy unless absolutely necessary. Since it is unknown if diazoxide passes into breast milk and poses a risk of potentially severe side effects for the infant, women who need treatment during breastfeeding should stop breastfeeding. The main adverse effects of diazoxide are sodium and water retention, hyperuricemia, hypertrichosis especially in children, leukopenia and thrombocytopenia, headaches, dizziness. Extrapyramidal symptoms may occur with long-term treatment. Orally administered diazoxide has only a minor effect on blood pressure.

As a second line treatment, octreotide is a synthetic analog of the peptide hormone somatostatin, used as a medication. Octreotide consists of eight amino acids (D-Phe-cyclo[Cys-Phe-D-Trp-Lys-Thr-Cys]-Thr(ol)). In Germany, Octreotide is approved for the treatment of acromegaly and certain gastrointestinal tumors (GEP-NET, carcinoids). When coupled to DOTA with 111-Indium or 68-Gallium (Edotreotide, DOTATOC), it is used in somatostatin receptor scintigraphy or positron emission tomography for the detection of these tumors. For therapeutic purposes as a radionuclide, beta emitter such as 90-Yttrium or 177-Lutetium can be used. Octreotide can be used for the treatment of cluster headache attacks and secretory diarrhea in children when other medications are ineffective or contraindicated. In newborns, it will be used as second line treatment for congenital hyperinsulinism. A cAMP-mediated reduction in insulin secretion in the pancreatic beta cell is found, Octreotide is applicated newborns for CHI subcutaneously 15-30micro/kg/day in three doses. Tachyphylaxis, growth restriction, NEC and gallstones are well known side effects in newborns and older children treated with octreotide. Octreotide is a synthetic analog of somatostatin used as a medication for acromegaly and certain gastrointestinal tumors. It can be coupled with radionuclides for tumor detection and used for cluster headaches and diarrhea in children. In newborns, it is a second-line treatment for congenital hyperinsulinism. Side effects include tachyphylaxis, growth restriction, NEC, and gallstones. Recent studies have analyzed Dasiglucagon for nonfocal congenital hyperinsulinism.

Sirolimus, an mTOR inhibitor, is used to treat congenital hyperinsulinism and prevent organ rejection after kidney transplants [16-19]. It has anti-proliferative effects and is used in cardiology to prevent restenosis after stent implantation. Sirolimus is also explored in anticancer therapy and approved for various conditions, including lymphangioleiomyomatosis and facial angiofibromas. It inhibits the mTOR signaling pathway and has shown efficacy in autoimmune lymphoproliferative syndrome. Sirolimus extends lifespan in mice by inhibiting mTOR activity, suppressing cytokine-mediated signaling pathways, and inhibiting T cell proliferation. Sirolimus, also known as Rapamycin, is an immunosuppressant used to treat congenital hyperinsulinism. It is derived from Streptomyces hygroscopicus and is commonly used post-kidney transplant to prevent rejection. Sirolimus is non-nephrotoxic and is often combined with Cyclosporine and corticosteroids. In cardiology, it is used to prevent restenosis after stent implantation in coronary arteries. Sirolimus has anti-proliferative effects and is being explored for anticancer therapy. It is also approved for rare lung diseases and facial angiofibromas. In autoimmune lymphoproliferative syndrome, it inhibits the mTOR signaling pathway. Sirolimus extends lifespan in mice but results may not directly apply to humans. Its mechanism of action involves inhibiting mTOR activity, suppressing cytokine-mediated signaling pathways, and preventing T cell proliferation.

Exendin (9-39) amide, also known as Avexitide, is a glucagon-like peptide-1 (GLP-1) antagonist that blocks the effects of excess GLP-1 secretion by competing with endogenous GLP-1 for binding to GLP-1 receptors [20-23]. It has shown potential in managing postoperative hypoglycemia and congenital hyperinsulinemia. Surgical interventions, such as focal lesionectomy or subtotal pancreatectomy, are considered when drug treatments are ineffective, especially for diffuse forms of congenital hyperinsulinism [24]. However, surgical treatment may lead to relapses and exocrine pancreas insufficiency, necessitating pancreas enzyme supplementation. Research is ongoing on insulin receptor antibodies, chaperones, carbamazepine and gene therapy for congenital hyperinsulinism [25-28,21,29]. Further studies are needed to explore new treatment options for this rare pediatric condition [30].

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## Conflict of Interest

None.

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