Hyperinsulinism in Infancy: From Basic Science to Clinical Disease

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I. HISTORICAL RELEVANCE AND TERMINOLOGY

The earliest description of hyperinsulinism appears to have been that provided by Laidlaw in 1938 who used the term *nesidioblastosis* to describe the severe, recurrent hypoglycemia associated with an inappropriate elevation of serum insulin, C-peptide, and proinsulin (161). While this constellation of clinical presentations remains clinically relevant, nesidioblastosis is not pathogenic for hyperinsulinism, since it describes the neodifferentiation of islets of Langerhans from pancreatic ductal epithelium and occurs in children of all ages and even adults (80, 84, 150, 245) (Fig. 1). Nesidioblastosis has generally been replaced by several synonyms that are used to identify the condition variously described as "hyperinsulinemic-hypoglycemia," including persistent hyperinsulinemic hypoglycemia of infancy (PHHI), congenital hyperinsulinism in infancy (CHI), and hyperinsulinism in infancy (HI).

For the severe, early-onset disease, two broad subtypes of the disorder are considered in this review: focal adenomatous hyperplasia associated with Ch.11p15 gene defects and diffuse β-cell abnormalities which (so far) are associated with Ch.11p15, 7p15-p13, 10q23.3, and 4q22-q26. We have described the pathological occurrences of hyperinsulinism in neonates and infants using the generic term HI. Distinction will be made between focal (Fo) and diffuse (Di) HI and the differing genetic origins of the disease by reference to the proteins they encode: HI-KATP, HI-GK, etc.

II. INTRODUCTION

Neonatal hypoglycemia was first described in newborn and older infants by Hartmann and Jaudon in 1937 (115). Interestingly, this early reference did not consider neonatal hypoglycemia as an attributable medical condition, but rather a symptom of illness or of the failure to adapt from the fetal state of continuous (transplacental) glucose consumption to the extraterine pattern of intermittent nutrient supply. This view of an immaturity of β-cell development prevailed for many years, and it was only in the 1970s and 1980s that the concept of "hyperinsulinism" was proposed and gradually accepted.

HI represents a group of clinically, genetically, morphologically, and functionally heterogeneous disorders. HI is potentially a devastating condition and one of the most difficult medical problems to face the pediatric endocrinologist. The term *hyperinsulinism* can, however, be misleading since it suggests "hypersecretion of insulin" from the β-cell, and this is only very rarely recorded in patients. Indeed, because most patients present with moderately elevated serum levels of insulin that are entirely inappropriate for the level of blood glucose, HI is best described as "inappropriate insulin release for the level of glycemia" rather than "hypersecretion" per se. Clinical diagnosis is thus based on evidence of the effects of excess insulin, which include hypoglycemia, inappropriate suppression of lipolysis and ketogenesis, and (more traditionally) positive glycemic responses after the administration of glucagon when hypoglycemic (83, 285).

Over the past 5–6 years, a combination of advances in the genetic determinants of insulin release, a greater understanding of the morphofunctional basis of hyperinsulinism, and the availability of functional data obtained from patient tissues have provided unparalleled insights into the pathogenesis of hyperinsulinism syndromes. As a consequence, the established long-term problems of HI are now being successfully confronted, and even with our current limited options of less-than-satisfactory treatments, the life-long sequelae of children with HI are being improved.

![FIG. 1. Neodifferentiation of islets of Langerhans. Nesidioblastosis in the pancreas of a normoglycemic infant. β-Cells are seen “budding off” from ducts; stained by an anti-insulin antibody (immunoperoxidase; original magnification, ×140). [From Rahier et al. (245), with permission from the BMJ Publishing Group.](http://physrev.physiology.org/)](http://physrev.physiology.org/)
III. GLUCOSE HOMEOSTASIS AND FETAL NUTRITION

Glucose, amino acids, and lactate are the principal energy substrates during fetal life, and glucose alone provides about one-half the total energy requirement necessary for growth and development. Glucose crosses the placenta by facilitated diffusion down a favorable concentration gradient between maternal and fetal plasma. The glucose concentration of the fetal circulation is close to 70–80% of that of maternal venous plasma. This provides the fetus with a readily available energy source enabling fetal glucose consumption to reach the rates of endogenous glucose production following birth. Importantly, enzyme systems involved in gluconeogenesis and glycogenolysis are present in the fetal liver but remain inactive unless provoked by extreme maternal starvation. The fetal liver contains around three times more glycogen than adult liver, and at birth this storage comprises ~1% of the neonate’s energy reserves. Fat oxidation is quantitatively thought to be less important than amino acid/glucose oxidation during fetal life, and rates of ketone body production are low (116).

The endocrinology of fetal nutrition is dominated by insulin. Insulin does not cross the placenta, and the fetal insulin axis is therefore independent of the mother’s. Fetal insulin secretion is influenced by concentrations of both glucose and amino acids, but β-cells of the fetal pancreas become progressively more responsive to glucose relatively late in gestation, with β-cell mass increasing markedly in the last trimester of pregnancy. This occurs even though mRNA for key components of the glucose-sensing apparatus of the β-cells is already present from weeks 7–10 of fetal life, i.e., SUR1, Kir6.2, GLUT2, voltage-gated Ca<sup>2+</sup> channels, etc. (M. J. Dunne, H. D. Moore, A. Naterajan, A. M. Gonzalez, L. Ruban, and P. W. Andrews, unpublished data).

As in adults, insulin promotes anabolism in the fetus by stimulating uptake of glucose into muscle and adipose tissue. Thus, in the final trimester of pregnancy, a period of rapid fetal growth occurs, particularly in the deposition of fat in adipose tissue, as the fetus stores energy reserves in preparation for birth. The induction of physiological competence during the third trimester of pregnancy is thought to be a critical period during which substrate provision “induces” or “programs” pancreatic islet development in an irreversible manner. These changes may subsequently influence the metabolic response to glucose in later life and also predispose to certain patterns of adult disease (112, 119, 134).

At birth, the newborn must switch abruptly from a state of net glucose uptake and glycogen synthesis to one of independent glucose production and homeostasis. The maintenance of normoglycemia is dependent on those conditions which determine nutrient status throughout life: the adequacy of glycogen stores, maturation of glycogenolytic and gluconeogenic pathway, and an integrated endocrine response. The endocrine events believed to trigger neonatal glucose production and the mobilization of fat from peripheral stores include increased epinephrine secretion and a rapid fall in the insulin-to-glucagon ratio as would occur during the first few hours of life. This change is accounted for by both a fall in the plasma insulin concentration and a surge in the plasma glucagon concentration that occurs at this time (157).

IV. EARLY COMPLICATIONS OF HYPERINSULINISM IN INFANCY

Congenital hyperinsulinism leads to reduced concentrations of free fatty acids and ketone bodies in association with hypoglycemia, which reflects both an increased rate of glucose uptake and a reduced rate of glucose production (138). Because a reduced postnatal glucagon surge is also thought to accompany hyperinsulinism, the combination of acute defects in nutrient management and the absence of the signals required for regulatory switching between maternal nutrient dependence and independence results in a cascade of medically related problems and is potentially fatal (330). Hyperinsulinemia promotes hepatic and skeletal muscle glycogenesis, which decreases the amount of free glucose available in the bloodstream and results in suppression of the formation of free fatty acids (FFA). Fatty acids do not cross the blood-brain barrier and cannot therefore be used by the brain as an energy substrate. However, fatty acids are utilized by the heart and muscle in the absence of readily available glucose resulting in the production of ketones. Because ketones will cross the blood-brain barrier they can be metabolized and used as fuel sources for the brain, but hyperinsulinism not only prevents glucose availability but also denies the brain of an alternative energy substrate (138). The combination of hypoglycemia, reduced FFA availability for cardiac and skeletal muscle metabolism, and reduced ketones for cerebral metabolism results in adrenergic and neuroglycopenic symptoms with severe neurological dysfunction. Seizure activity will also manifest when central nervous system (CNS) glucose levels fall from the normal range of 80–90 to below 20–30 mg/dl. If prolonged this will cause neuronal death attributable to hypoglycemia; this is not simply the result of metabolic attrition, but the outcome of an excitotoxic process. Furthermore, repeated episodes of severe, prolonged, subthalamic hypoglycemia can result in permanent neurological damage, including developmental delay, mental retardation, and/or focal CNS deficits. Complications of neonatal hyperinsulinism are found in up to 50% of survivors, and this incidence has changed little during the past 20 years.
reflecting the major problems that are faced in managing and treating this condition (5, 8, 9, 29, 166, 173, 181, 196, 201, 253, 284, 313).

In addition to genetic disorders, early-onset hyperinsulinism is also associated with the children of diabetic mothers. During gestation, glucose is transferred freely across the placenta. Prolonged hyperglycemia in poorly controlled maternal diabetes results in fetal hyperglycemia. Fetal hyperglycemia induces expansion of the fetal pancreatic β-cell mass with resultant hyperinsulinemia and macrosomia. Withdrawal of the transplacental supply of glucose after birth leads to an abrupt fall in the concentration of glucose, and in the absence of any underlying medical condition in the newborn, hyperinsulinism will typically resolve within 1–2 days after birth. Aside from diabetes, Rhesus incompatibility, perinatal stresses such as birth asphyxia, maternal toxemia, intrauterine growth retardation, or exogenous drug or insulin administration (e.g., Munchausen syndrome, Munchausen syndrome by proxy, ingestion of oral hypoglycemic agents) and insulin-secreting adenoma are also associated with hyperinsulinism in infants (34, 38, 230), but these conditions will not be featured as part of this review. Rather, we present an overview of the physiology and pathophysiology of hyperinsulinism and address the histological and genetic diversity of this condition in the context of molecular medicine.

V. IONIC AND METABOLIC DETERMINANTS OF INSULIN RELEASE

A. Depolarization-Response Coupling and Glucose-Stimulated Insulin Secretion

ATP-sensitive potassium (K\textsubscript{ATP}) channels determine the metabolic sensing of glucose in β-cells and coordinate stimulus-secretion coupling (see Ref. 233). Their function determines both “first phase” and “second phase” insulin release from the pancreas. K\textsubscript{ATP} channels are open in resting, unstimulated β-cells and, along with the Na\textsuperscript{+}-K\textsuperscript{+}-ATPase, establish a resting membrane potential of approximately −65 mV. The mechanism responsible for spontaneous channel openings has been proposed to involve the low intracellular ATP/ADP ratio that exists in resting β-cells. In support of this, ADP has been shown to be both a potent agonist of K\textsubscript{ATP} channels and to reverse the inhibitory effects of ATP even when there is a >20-fold excess in the concentration of ATP relative to ADP at the cell membrane (72, 74, 137). Consequently, despite the fact that the intracellular concentration of ATP in β-cells is in the millimolar range and K\textsubscript{ATP} channels are inhibited in vitro by <10 μM ATP, a high sensitivity to ADP ensures channel opening in resting cells. More recently, a role for phosphatidylinositol 4,5-bisphosphate (PIP\textsubscript{2}) in the endogenous activation of K\textsubscript{ATP} channels has been suggested (13, 258, 276, 280). However, because other phosphoinositides and lipids such as acyl-CoA and arachidonate also stimulate K\textsubscript{ATP} channels, the sensitivity and selectivity of these responses in the physiological context of K\textsubscript{ATP} channel activity requires further consideration (13, 81, 107, 156, 162, 250).

Following both the uptake and metabolism of glucose by glucokinase and mitochondrial events, closure of K\textsubscript{ATP} channels arises when the intracellular ATP/ADP ratio increases (see Refs. 69, 94, 118, 233). Estimations of the free concentrations of ATP and ADP in the β-cell cytoplasm suggest that while ADP concentrations are in the range of 40 μM, the free ATP concentration is ~100-fold higher (94). In islets and insulin-secreting cell lines glucose induces a 30% (94) and 50% (251) decrease in the concentration of ADP, respectively, leading to an increase in the ATP/ADP ratio. Glucose-dependent closure of K\textsubscript{ATP} channels facilitates depolarization of the cell membrane and the subsequent opening of voltage-dependent Ca\textsuperscript{2+} channels, which in turn leads to an abrupt rise in the cytosolic Ca\textsuperscript{2+} concentration close to the plasma membrane. Insulin release is then initiated by the process of Ca\textsuperscript{2+}-dependent exocytosis (Fig. 2). These events describe the K\textsubscript{ATP} channel-dependent or “triggering” pathway of glucose-stimulated insulin secretion (GSIS) and are likely to account for the first phase of insulin release, i.e., the secretion of preformed insulin-containing granules located at the plasma membrane (23, 118). K\textsubscript{ATP} channels also determine second-phase insulin secretion from β-cells which is brought about by the gradual augmentation and potentiation of Ca\textsuperscript{2+}-triggered insulin release: a process that entails the preparation of previously nonreleasable granules for exocytosis. This pathway, which is termed the “amplification” or “augmentation” pathway, is also referred to as the “K\textsubscript{ATP} channel-independent pathway of GSIS,” a description that is somewhat misleading in terms of β-cell function, but an accurate description of the conditions necessary to examine those signaling events downstream of K\textsubscript{ATP} channel closure (see Refs. 4, 118).

The precise molecular mechanisms by which glucose metabolism augments distal signaling are yet to be fully resolved (see Ref. 180). Several coupling factors have been proposed including increased ATP/ADP and GTP/GDP ratio, cytosolic levels of long-chain acyl-CoA, the pyruvate-malate shuttle, and glutamate export from mitochondria. ATP is likely to have several roles as a local mediator of exocytotic mechanisms, including, for example, regulation of ATPases such as N-ethylmaleimide-sensitive fusion protein (NSF), V-type H\textsuperscript{+}-ATPases and Hrs-2, and by phosphorylation of specific proteins such as SNAP-25 (11, 15, 114, 273). The stimulation of protein kinases A (PKA) and C (PKC), and Ca\textsuperscript{2+}/calmodulin-de-
dependent kinase II (CaMKII), as would occur during exposure to hormones, neuropeptides, and neurotransmitters (some of which are collectively known as the “incretins”) or Ca$^{2+}$ following its influx is also likely to be important (4, 18, 23, 92, 153, 207, 239, 240, 292, 293, 295, 333). The involvement of G protein-coupled receptor (GPCR) events in distal signaling is supported by observations that mice lacking receptors for glucagon-like peptide 1, or gastric inhibitory polypeptide, show impaired insulin secretion and abnormal glucose tolerance without insulin resistance (206, 260). Equally, GTP can affect both small G proteins such as rab3A (223) and the larger heterotrimeric G proteins (332). Finally, although there is evidence to suggest that “amplification” of GSIS can occur independently of a rise in the cytosolic concentration of Ca$^{2+}$ in both model β-cells and human islets (293), depolarization-evoked Ca$^{2+}$ influx is sufficient by itself to cause diacylglycerol formation, PKC activation, and substrate phosphorylation (207). (For recent reviews: GSIS pathways, see Refs. 4, 23, 118, 294; mechanisms of exocytosis, see Ref. 27.)

The discrete actions of glucose on the triggering and amplification pathways of insulin secretion can be largely explained by the coordination of events that involve different pools of insulin-containing granules. Several dynamic granule pools are recognized in β-cells: reserve, docked, readily releasable, and immediately releasable pools. Activation of the triggering pathway results in exocytosis of the immediately releasable pool of granules giving rise to the first phase of GSIS. In mouse β-cells, this has been estimated to involve fewer than 50 of the 10,000 or so insulin-containing granules that are positioned for secretion by clustering within the vicinity of voltage-gated Ca$^{2+}$ channels (10). As an additional level of complexity, in neurons, defined regions of exocytosis have been described that contain cytoskeletal matrix associated active zone proteins (CAZ), which are important for the modularization of exocytosis and the mobilization of secretory vesicles (91). Although analogous zones are less well characterized in β-cells, recent reports suggest the presence of CAZ-associated proteins that are responsible for the integration of Ca$^{2+}$ sensing and PKA-independent CAMP-induced exocytosis of insulin-containing granules (90, 142, 227). A key rate-limiting step following first-phase insulin release is the conversion of readily releasable granules to the state of immediate releasability, or “priming.” This stage is known to be acutely dependent on the ATP/ADP ratio, which appears to be required in the acidification process of granules, a prerequisite to priming, and involves the granular membrane proton pump and Cl$^{-}$ uptake (11). Whilst this general model is considered relevant for all types of insulin-secreting cells, there are some important differences between species. In rat and human β-cells, for example, augmentation pathways induce a time-dependent increase in the rate of pool priming resulting in a rising second-phase response, whereas in mouse β-cells and insulin-secreting cell lines, despite biphasic insulin secretion profiles and secretory granule mobilization, the rate of this conversion does not appear to be significantly changed by glucose (see Refs. 10, 293).

In the model described above, K$_{ATP}$ channels are considered as major determinants of glucose-regulated electrical activity in β-cells, and this has important downstream consequences for GSIS, the neurohormonal regulation of insulin release and the manipulation of secretion by pharmacological agents. The central role of K$_{ATP}$ channels suggests that drugs which act as channel inhibitors such as sulfonylureas (e.g., glibenclamide, tolbutamide, etc.; Ref. 296) and glinides [e.g., repaglinide (51) and

![FIG. 2. Representation of the regulated release of insulin from normal pancreatic β-cells. Glucose metabolism causes K$_{ATP}$ channel closure and Ca$^{2+}$ influx leading to insulin release through the “triggering” pathway. Glucose also acts to "amplify" this response in a manner that is both Ca$^{2+}$ dependent and Ca$^{2+}$ independent. This involves the generation of additional signals such as diacylglycerol (DAG), cAMP, protein kinases (PK), etc., through G protein-coupled receptor (GPCR) signaling, e.g., ACh, GLP1, CCK, or Ca$^{2+}$ influx. Pharmacologically K$_{ATP}$ channels are inhibited by sulfonylureas and imidazolines and activated by diazoxide and related compounds such as BPDZ-154. In β-cells, voltage-gated Ca$^{2+}$ channels are inhibited by agents such as nifedipine, verapamil, etc.](http://physrev.physiology.org/Downloadedfromhttp://physrev.physiology.org/)

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nateglinide (123) function in vivo as antidiabetic compounds by triggering first-phase insulin release and by maintaining $K_{ATP}$ channels in a closed state in order for glucose metabolism to act distally. Conversely, $K_{ATP}$ channel agonists or “openers,” such as diazoxide and BPDZ 154, have hyperglycemia-inducing capabilities since they inhibit secretion by preventing membrane depolarization and hence reducing voltage-gated Ca$^{2+}$ channel activity (see Ref. 73; see sect. viD). In terms of pathophysiology there is now compelling evidence that defects in the genes encoding $K_{ATP}$ channels will cause both hyperinsulinism (“$K_{ATP}$ channelopathy,” see sect. vi) and type 2 diabetes mellitus (125, 259) and that defects in other proteins which control glucose metabolism (“$K_{ATP}$ channel metabolopathies,” see sect. vii) will induce inappropriate $K_{ATP}$ channel closure or activity and thereby promote either hyperinsulinism or reduce insulin release, respectively (Table 1).

### B. Glucose Metabolism, Anaplerosis, and Mitochondria

Coupling GSIS to regulated changes in the cytosolic Ca$^{2+}$ concentration ([Ca$^{2+}$]) is dependent on metabolic events (Fig. 3). Glucose is transported into $\beta$-cells by facilitative transporter(s) which allow(s) for the subsequent rapid equilibration of glucose across the $\beta$-cell membrane. In rodent insulin-secreting cells, GLUT2 is the principal transporter, but this is not the case in human $\beta$-cells. Enriched populations of human $\beta$-cells have been shown to have a 100-fold lower GLUT2 abundance than rat $\beta$-cells, while studies using isolated cells from patients with insulinomas report the expression of GLUT1/3 mRNAs but not GLUT2 (64, 264). After uptake, phosphorylation of glucose by glucokinase (GK) is the first enzymatic event in the glycolytic pathway and, since the Michaelis constant ($K_m$) for GK for glucose is $\sim10$ mM, it is this

<table>
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<tr>
<th>Condition</th>
<th>Clinical Disorder</th>
<th>Identified Defect</th>
<th>Gene</th>
<th>$\beta$-Cell Disorder</th>
<th>Reference Nos.</th>
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<td>SUR1</td>
<td>$ABCC8$</td>
<td>$K_{ATP}$ channelopathy: membrane potential</td>
<td>215, 305</td>
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<td>$KCNJ11$</td>
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<td>$GLUD1$</td>
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<td>$HADHSC$</td>
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<td>$ABCC8$</td>
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<td>$M$. tRNALeu(UUR)</td>
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<td>$HNF4A$</td>
<td>Defect in HNF4a expression</td>
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<td>$GCK$</td>
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<td>$NEURO1$</td>
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<td>$GCK$</td>
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<td>$KCNJ11$</td>
<td>$K_{ATP}$ channelopathy: membrane potential</td>
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<td>$M.GPDH$</td>
<td>Mitochondrial dysfunction</td>
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<td>$SERCA3$</td>
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<td>318</td>
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<tr>
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<td>Diabetes</td>
<td>Ca$^{2+}$-dependent exocytosis</td>
<td>$SERCA3$</td>
<td>Immune-mediated; antisulfatide antibodies</td>
<td>28</td>
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</table>

T1DM, type 1 diabetes, IDDM; T2DM, type 2 diabetes, NIDDM; MODY, maturity-onset diabetes of the young; HI, hyperinsulinism in infancy; MIDD, maternally inherited diabetes and deafness; NDM, neonatal diabetes mellitus; SCHAD, short-chain 3-hydroxyacyl-CoA dehydrogenase; HNF, hepatocyte nuclear factor; UT1C, Usher type 1C; HI-EI, exercise-induced hyperinsulinism in infancy; SERCA, sarco(endoplasmic reticulum Ca$^{2+}$-ATPase; VGGC, voltage-gated Ca$^{2+}$ channel.
constraint that determines the range of glucose concentrations that are physiologically relevant to the stimulation of insulin release (194, 195). Consequently, even small changes in GK activity can be significant and can directly affect the threshold for downstream events in GSIS. This is most clearly demonstrated by the fact that mutations in GK cause either hyperinsulinism or diabetes depending on the nature of the impairment in enzymatic activity (see sect. VII) (Table 1). Under physiological conditions the activity of GK is thought to be regulated by an endogenous factor, a precursor of the propionyl-CoA carboxylase/H9252-subunit, which raises both the affinity of GK for glucose and the enzyme’s $V_{\text{max}}$ (275). Glycolytic flux is also limited by the activity of phosphofructokinase. The predominant form of this enzyme in $\beta$-cells is an oscillatory isoform that is allosterically regulated for bursts in the production of ATP by oscillations in the ATP/ADP ratio (307). It is activated by the AMP/ADP ratio and fructose 2,6-bisphosphate and inhibited by ATP and citrate (Fig. 3). These enzymes are therefore important for determining fluctuations in the cell membrane potential via $K_{\text{ATP}}$ channels.

Glucose increases the production of cytosolic NADH by the action of glyceraldehyde-3-phosphate dehydrogenase, and the reducing equivalents are then transported into the mitochondria by the $\alpha$-glycerophosphate (\(\alpha\)-GP) and malate/aspartate shuttles for ATP synthesis (176, 177). This transport helps to maintain glycolytic flux in the direction of ATP production by preventing a decrease in the cytosolic NAD$^+/NADH$ ratio which is required for the activities of both glyceraldehyde-3-phosphate dehydrogenase and $K_{\text{ATP}}$ channels (70). Activity of the $\alpha$-GP shuttle is unusually high in $\beta$-cells, and this is thought necessary to maintain high levels of NAD$^+$ for glycolysis (265). Insulin-secreting cells have low levels of lactate dehydrogenase, and this serves to direct most of the

![Image](http://physrev.physiology.org/DownloadedFrom/10.220.33.1)
pyruvate produced from glycolysis into the mitochondria (265).

Other signals generated from glucose metabolism in the \( \beta \)-cell play a major role in controlling the relative rates of glucose and FFA oxidation (FFAOx) and the shift from FFAs to glucose as a fuel source. Thus, at low levels of glucose, mitochondria fulfill the energy needs of the \( \beta \)-cell by FFAOx, but as glucose levels begin to rise, FFAOx is decreased and glucose oxidation then supplies the cellular energy requirements (183). The first step in glucose-induced inhibition of FFAOx is an increase in mitochondrial anaplerosis, resulting in citrate formation (24) (Fig. 3). Elevated mitochondrial citrate leads to an increase in the cytosolic concentration of citrate, which is then converted to malonyl-CoA by the actions of citrate lyase and acetyl-CoA carboxylase (ACC). Malonyl-CoA is a potent allosteric inhibitor of carnitine palmitoyltransferase-1 (CPT1), a mitochondrial membrane enzyme that is responsible for the transport of long-chain acyl-CoA (LC-CoA) from the cytosol into the mitochondria. The isoform of CPT1 in \( \beta \)-cells is the same as that in the liver (337). This enzyme is located in the outer mitochondrial membrane and has one inhibition site that faces the cytosol, inhibitable by dicarboxylic CoA esters (e.g., malonyl-CoA, \( \l 3 \)-hydroxybutyryl-CoA, see sect. viC), and a second site facing the intermembrane space that is inhibited by short-chain monocarboxylic CoA esters (141). Inhibition of CPT1 blocks the entry of LC-CoA into the mitochondrion, elevating the cytosolic concentration of the lipid which then acts as a signaling molecule with diverse actions that are directly related to the release of insulin, including stimulation of the insulin exocytotic machinery (55) and activation of “classic” and “novel” PKCs (182, 335). In addition, LC-CoA will inhibit mitochondrial adenine nucleotide translocase (331) and the enzyme ACC (238) and cause the activation of both sarco/endoplasmic reticulum \( \mathrm{Ca}^{2+} \)÷ATPases (57) and \( K_{\text{ATP}} \) channels (22, 107, 162). While the latter effect will tend to inhibit insulin release by lowering \([\mathrm{Ca}^{2+}]_c\) and restoring basal cytosolic \( \mathrm{Ca}^{2+} \) levels, this mechanisms may be important either for providing feedback inhibition and/or facilitating the development of glucose-induced oscillations in metabolism and \( \mathrm{Ca}^{2+} \) signaling. LC-CoA is also a modulator of ceramide- and/or nitric oxide-mediated apoptosis and the binding to nuclear transcriptional factors in insulin-secreting cells (for recent review, see Ref. 111).

In the scheme outlined above, glucose underpins the generation of two key intracellular mitochondrial signals: acetyl-CoA, which is used for ATP synthesis (see below), and citrate, which is used in the production of malonyl-CoA. The proposed role of malonyl-CoA in the inhibition of CPT1 is pivotal to GSIS and although supported by several studies (45, 61, 243) has remained controversial in the literature and much debated. More recently, it has been reported that malonyl-CoA decarboxylase over-expression in insulin-secreting cell lines lowers the levels of malonyl-CoA but has no effect on GSIS (6, 211). Even though these findings suggest that disruption of malonyl-CoA can be dissociation from GSIS, the same protocols have also been reported to cause a 50% decrease in insulin production (241).

ATP production and an elevation of the \([\mathrm{Ca}^{2+}]_c\) are important signals for GSIS, but they also have influences on \( \beta \)-cell metabolism. It has been estimated that >95% of ATP in \( \beta \)-cells is produced in the mitochondria which is regulated by substrate availability (\( \alpha \)-GP and pyruvate) and by \([\mathrm{Ca}^{2+}]_c\) (79). \( \alpha \)-GP and pyruvate concentrations are determined, in part, by ADP and the actions of the ATP/ADP ratio on phosphofructokinase (PFK) (160). In insulin-secreting cells, glucose-induced rises in the ATP/ADP ratio and mitochondrial NADH precede rises in \([\mathrm{Ca}^{2+}]_c\) (37, 176). These events increase ATP production via the activation of pyruvate dehydrogenase and mitochondrial dehydrogenases (113, 193, 253). Significantly, however, as \([\mathrm{Ca}^{2+}]_c\) continues to rise, this will act to depolarize the inner mitochondrial membrane, inhibiting ATP synthesis and resulting in a fall in the ATP/ADP ratio. This is one mechanism by which glucose metabolism results in the generation of oscillations of ATP and ADP availability which directly influence the activity of \( K_{\text{ATP}} \) channels, the cell membrane potential, and the rhythmic oscillations and closures of voltage-gated \( \mathrm{Ca}^{2+} \) channels.

C. \( K_{\text{ATP}} \) Channels

1. Structure and function

\( \beta \)-Cells express a \( K_{\text{ATP}} \) channel complex formed by subunits belonging to at least two distinct families of proteins (Fig. 4) (for reviews, see Refs. 2, 5, 263). The \( K^+ \)-selective pore is formed by the weak inward rectifier \( K^+ \) channel Kir6.2. Comprising 390 amino acids, this protein has a predicted membrane topology with two \( \alpha \)-helical transmembrane domains linked by a highly conserved sequence of amino acids that shares sequence homology with the P region or \( K^+ \) selectivity domain of voltage-gated \( K^+ \) channels. The other subunit is an ATP binding cassette protein and receptor with high affinity for sulfonylureas, designated SUR1 (3). Human SUR1 consists of 1,581 amino acids and has 17 predicted transmembrane regions that are organized into three discrete domains, designated transmembrane domains (TMD): TMD0, TMD1, and TMD2, 9 cytoplasmic loops (CL1-CL9), and 2
intracellularly disposed nucleotide-binding folds (NBF) (312). In most recombinant systems Kir6.2 will not form operational K\(_{\text{ATP}}\) channels independently of SUR1; however, when coexpressed, K\(_{\text{ATP}}\) channel currents are generated that closely resemble those of the native \(\beta\)-cell K\(_{\text{ATP}}\) channel complex (128, 129, 255). K\(_{\text{ATP}}\) channels present in other tissues are heteromultimeric complexes of different \(\text{Kir6.}x\) and \(\text{SUR}x\) proteins; e.g., cardiac K\(_{\text{ATP}}\) channels: Kir6.2 + SUR2A, smooth muscle K\(_{\text{ATP}}\) channels: Kir6.2 + SUR2B, and the smooth muscle nucleotide-activated K\(_{\text{ATP}}\) channel Kir6.1 + SUR2B (see Refs. 2, 5, 263).

K\(_{\text{ATP}}\) channels are thought to be organized as an octameric complex of four Kir6.2 subunits arranged around a central pore, coupled to four SUR1 subunits (SUR1 + Kir6.2)\(_4\) (41, 279) (Fig. 4). Each subunit is known to be differentially regulated. Kir6.2 which determines the biophysical properties of the channel complex including K\(^{+}\) selectivity, rectification, and “gating” is inhibited by ATP but activated by acyl-CoA and phosphoinositide lipids. ATP-induced channel closure appears to involve the cytoplasmic domains, but there is also evidence that actions of ATP can be almost completely abolished by individual point mutations at other sites on Kir6.2 (67, 167, 277, 309–311). SUR1 acts as a conductance regulator of Kir6.2; therefore, the sensitivity of channels to ATP, ADP, and guanosine (GTP, GDP) nucleotides involves both subunits (Fig. 4). Nucleotide hydrolysis is possible at both NBF sites of SUR1 (314). NBF1 and NBF2 are thought to form a close association leading to two binding pockets; site 1 is thought to be more selective for ATP than ADP, and this interaction is stabilized by MgATP hydrolysis at site 2. Recent data suggest that NBD1 of SUR1 has minimal (if any) ATPase activity (189, 190) and that although NBD1 plays a small but significant role in K\(_{\text{ATP}}\) channel activation by MgADP, it is not as important as NBD2 that has ATPase activity (191). It also appears that the linker regions between the Walker A and Walker B motifs of the NBDs are not required for nucleotide binding but are involved in transducing nucleotide binding into channel activation. Thus the functional regulation of K\(_{\text{ATP}}\) channels induced by changes in the ATP/ADP ratio involves cooperative

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**Fig. 4.** Schematic representations of SUR1/Kir6.2 topology. K\(_{\text{ATP}}\) channels have a predicted octameric structure of 4 SUR1 and 4 Kir6.2 subunits (A) and allow outward K\(^{+}\) currents in resting cells as a consequence of the low ATP/ADP ratio and phosphatidylinositol 4,5-bisphosphate (PIP\(_2\)). SUR1 has a characteristically high number of transmembrane spanning regions (1–17) organized into 3 predicted domains (TMDs) (B). The structure is predicted to have 9 cytoplasmic loops (CL1–9) and 2 intracellularly disposed nucleotide-binding folds (NBF). Kir6.2 is a typical inward rectifier K\(^{+}\) channel with two transmembrane domains and an inner loop that controls K\(^{+}\) influx. "P" refers to pore region. ATP and ADP binding sites are illustrated along with a number of key amino acid residues and sequence motifs that are important for correct assembly and trafficking of the channel complex.
interactions of nucleotides at both subunits with the actions of ATP-induced inhibition of Kir6.2 being countered by the activatory effects of ADP at SUR1.

2. Pharmacology of \( K_{\text{ATP}} \) channels

The SUR1 subunit plays a key role in determining the pharmacological regulation of \( K_{\text{ATP}} \) channels. \( \beta \)-Cell-selective potassium channel openers (KCOs) such as diazoxide, BPZD 154, BPZD 73, NCC 55–0118, and other less selective KCOs (e.g., levcromakalim, pinacidil, nicorandil, etc.), bind to SUR1 and activate \( K_{\text{ATP}} \) channels in a nucleotide-dependent manner (16, 21, 46, 50, 68, 163, 164, 216). The differential sensitivity of the heterogeneous family of \( K_{\text{ATP}} \) channels to these compounds is explained by the location of the binding sites for KCOs on SUR1 and SUR2. With the use of a series of chimeric SUR proteins, it has been shown that two sequences of SUR1 are critical for determining KCO binding and activation (315). These are located within the final series of transmembrane helices at amino acids 1059–1087 (KCO1) and 1218–1320 (KCO2) (SUR2B nomenclature), which correspond to part of the linking sequence between the membrane-spanning helices 13–14 and 16–17 (Fig. 4). These regions flank a putative sulfonurea binding site located in CL8 and are thought to form a binding pocket for diazoxide on the \( \beta \)-cell \( K_{\text{ATP}} \) channel (315). Sulfonylureas also interact with CL3.

3. Trafficking of \( K_{\text{ATP}} \) channels to the cell surface

Each protein subunit of the \( K_{\text{ATP}} \) channel possesses a number of signaling motifs that influence the assembly of the channel protein and its subsequent expression at the cell surface (Fig. 4). The first of these to be described was the “RKR” motif, which is composed of three amino acids: arginine-lysine-arginine, and found within the sequences of both SUR1 and Kir6.2. The RKR motifs act as endoplasmic reticulum (ER) retention signaling sequences; they must be shielded by the process of channel folding and assembly to permit the expression of \( K_{\text{ATP}} \) channels at the cell surface (338). When SUR1 and Kir6.2 fold correctly and coassemble with the correct stoichiometry (4:4) within the ER, the RKR motifs become cloaked by the other subunits, thus permitting the export of the octameric \( K_{\text{ATP}} \) channel complex from the ER. The RKR motif is located close to NBF1 of SUR1 in amino acid positions 648–650 and close to the COOH-terminal region of Kir6.2 at positions 369–371. Mutation of the RKR motif of SUR1 to AAA permits expression of SUR1 at the membrane in the absence of Kir6.2 (338). Similarly, truncation of the COOH-terminal region of Kir6.2, which removes the RKR motif, allows cell surface expression of the subunit in the absence of SUR1 (311, 338). Kir6.2 also possesses a second retrograde signaling sequence, “L355-L356,” a dileucine motif which functions in endosomal targeting in other cells. Mutation or truncation of this motif leads to an increase in membrane targeting of Kir6.2 (311, 338).

In addition to the retrograde signaling sequences outlined above, SUR1 possesses a number of anterograde signaling sequences. The COOH-terminal region of SUR1 possesses a dileucine motif (L1566-L1567) and downstream phenylalanine (F1574), which are required for \( K_{\text{ATP}} \) channels to exit the ER (270). Mutation of these amino acids (or COOH-terminal truncations, as observed in some HI-related mutations, see below) leads to reduced surface expression of functional \( K_{\text{ATP}} \) channels, although the downstream receptors for these signaling motifs have not yet been identified. However, a third leucine residue located close to the COOH-terminal region of SUR1 (L1544) has been implicated in the formation of the RKR shield which allows the protein to exit the ER, thus forming another anterograde signal for forward trafficking (303). N-linked glycosylation sites of SUR1 (N10, N1050) may also be important sites for forward trafficking of \( K_{\text{ATP}} \) channels, since in vitro mutations of these residues result in entrapment of the protein within the ER (45).

D. PDX1, HNF-3\( \beta \), and GSIS

Concurrent with the mechanisms of insulin release, glucose metabolism is also coupled to increases in the levels of insulin mRNA through increased transcription of the insulin gene. Although the first description of the actions of glucose on the insulin gene was described some 30 years ago, it was not until recently that the mechanisms were elucidated (132). A key determinant of this is the homeodomain transcription factor PDX1, which becomes phosphorylated during glucose metabolism and is translocated from the cytoplasm to the nucleus (186, 199, 222, 232). Additionally, PDX1 is a transcriptional modulator of a number of other genes preferentially expressed in \( \beta \)-cells including the glucose transporter GLUT2 (324), SUR1 (7), Kir6.2 (7), glucokinase (327), islet amyloid polypeptide (32), and the proinsulin processing enzymes PC1/3 and PC2 (for detailed reviews, see Ref. 200). PDX1 also determines \( \beta \)-cell lineage and development (133, 290); hence, defects in PDX1 not only alter the identity of \( \beta \)-cells causing maturity-onset diabetes in the young type 4 and neonatal diabetes mellitus, but also exacerbate insufficiency and pancreatic agenesis (133, 200, 290). At this stage the role of PDX1, or indeed other transcription factors, in determining the pathogenesis of hyperinsulinism in humans has not been critically examined. However, it is of note that impaired PDX1 activity is a phenotypic feature of a hyperinsulinism-derived human \( \beta \)-cell line NES2Y (178) and that in mouse \( \beta \)-cells ablation of HNF-3\( \beta \) (Foxa2), an upstream transactivator of PDX-1, resulted in hyperinsulinemic hypoglycemia (297). As in both trans-
genic mice and insulin-secreting cell lines HNF-3β defects led to a marked decrease in the mRNA expression levels of the K<sub>ATP</sub> channel subunits SUR1 and Kir6.2 (297, 3326), an examination of gene defects in the transcriptional regulation of K<sub>ATP</sub> channels and/or other elements of the GSIS pathway is likely to produce new candidate genes and causes of HI.

VI. ATP-SENSITIVE POTASSIUM CHANNEL CHANNELOPATHIES AND HYPERINSULINISM

In more than 50% of patients, the genetic basis of HI has yet to be determined (85, 95). So far, there are five known genetic causes of the disease that involve either defects in K<sub>ATP</sub> channel genes (channelopathies) or defects in K<sub>ATP</sub> channel function (metabolopathies) (see sect. vii). The most severe type of HI involves defects in K<sub>ATP</sub> channel genes, termed HI-KATP.

A. Clinical Features and Diagnosis of HI-KATP

HI per se cannot be detected in utero, and there are no characteristic visual, auscultatory, or tactile findings to suggest hyperinsulinism. Infants with prenatal hyperinsulinism may have a characteristic appearance of macrosomia which reflects the anabolic effects of prolonged hyperinsulinemia in utero resulting in increased muscle, fat, and liver mass. However, many are born with appropriate or even low birth weights, yet others are preterm children (8). It has also been reported that many patients with hyperinsulinism have a distinct facial appearance that could be the consequence of fetal intoxication by insulin (59). The first clinical manifestations of hyperinsulinism-induced hypoglycemia are mainly experienced shortly after birth. These may include cyanosis, respiratory distress, sweating, hypothermia, irritability, poor feeding, hunger, jitteriness, lethargy, apnea, which can progress to vomiting, seizures, tachycardia, and averted neonatal death. In older children and adults symptoms tend to be typical of those of hypoglycemia including confusion, headaches, dizziness, syncope, and when severe, loss of consciousness.

The definition of a glucose requirement to maintain normoglycemia is a key indicator as well as therapeutic step in HI, and the demonstration of an increased glucose requirement is the sign of underlying hyperinsulinism. For patients with severe early-onset HI, there is now general agreement that the diagnostic criteria are: 1) a glucose requirement of >6–8 mg·kg<sup>-1</sup>·min<sup>-1</sup>, which is needed to maintain blood glucose above 2.6–3 mM; 2) laboratory blood glucose values <2.6 mM; 3) detectable insulin at the point of hypoglycemia with raised C-peptide; 4) inappropriately low blood FFA and ketone body concentrations at the time of hypoglycemia; 5) a glycemic response after the administration of glucagon when hypoglycemic; and 6) the absence of ketonuria (8).

Most infants with hyperinsulinism present during the first postnatal days, with others during the first year. Rarely, older children present de novo with symptoms of hyperinsulinism-induced hypoglycemia. Failure to recognize and to promptly treat hypoglycemia carries a substantial risk of severe brain damage and mental retardation because of a lack of fuels to sustain normal brain metabolism (for review, see Ref. 100). Medical therapy for the disorder involves an increased carbohydrate intake to meet the elevated requirement, and usually one or more drugs that inhibit insulin secretion (see sect. ix). Unfortunately, the responsiveness of children with HI to these agents is inconsistent and variable as a result of the heterogeneous defects in the mechanisms that control insulin release, and patients who do not show an adequate and immediate response require surgery in the form of a pancreatectomy to prevent recurrent neuroglycopenia (1, 9, 19, 46, 71, 136, 139, 140, 171, 224, 225, 228, 291). Surgical interventions can vary from a sub-total to near-total pancreatectomy and, although these procedures may prevent subsequent hypoglycemic episodes, they also lead to pancreatic insufficiency and iatrogenic diabetes mellitus. The extent of a pancreatic resection necessary to achieve a cure for HI has been the subject of several studies. In a recent review of the literature, Shilyansky et al. (272) recorded resolved hypoglycemia in only 54% of 220 patients undergoing a subtotal pancreatectomy (<95% resection), compared with 64% of 83 patients undergoing a 95% pancreatectomy, and 97% of 74 after a 98% pancreatectomy. To achieve euglycemia, most patients therefore undergo a 95% (or more) resection, but this is associated with complications, since a high incidence of diabetes, from 75 to 85%, has been reported (166, 272).

Most cases of HI are sporadic, and familial forms, although rare, are well documented. Sporadic HI has an estimated incidence of 1 in 27,000 live births in Ireland and 1 in 50,000 live births in Finland (103), compared with 1 in 20,000 in Kuwait (247). However, in some isolated communities the disease incidence is much higher, e.g., 1 in 3,200 in the central area of Finland and 1 in 2,500 in the Arabian peninsula (103). The diffuse form of HI (see below) has a male-to-female incidence ratio of 1.2:1 and the focal form 1.8:1.

B. Genetic and Histopathophysiological Diversity of HI-KATP: Fo-HI Versus Di-HI

The SUR1 gene ABCC8 comprises 39 exon boundaries and is clustered with the Kir6.2 gene KCNJ11, a
single open reading frame lying immediately 3’ of ABCC8, on the short arm of chromosome 11, Ch.11p15 (96, 305). This is a genetic locus linked to both Di-HI and Fo-HI (reviewed by Refs. 100, 103).

Although autosomal dominant mutations have been described (126), Di-HI predominantly arises from the autosomal recessive inheritance of K<sub>ATP</sub> channel gene mutations (103). This condition affects all of the islets of Langerhans of the affected pancreas (Fig. 5), and surgical treatment usually requires the removal of a minimum of 95% of the pancreas (Di-HI can also be treated by long-term conservative therapeutic regimes, see below). Until 1997 Di-HI was widely believed to be the main cause of congenital hyperinsulinism, despite the fact that cases of “focal hyperinsulinism” were first described more than 25 years ago (105, 117, 131, 152, 244, 298). Fo-HI has a non-Mendelian mode of inheritance of K<sub>ATP</sub> channel dysfunction and β-cell hyperplasia leading to HI (60–62, 86, 102, 322). Fo-HI has a non-Mendelian mode of inheritance of K<sub>ATP</sub> channel dysfunction and β-cell hyperplasia leading to HI (60–62, 86, 102, 322). In this condition, epigenetic phenomena involving gene silencing lead to a loss of heterozygosity of a region of the maternal chromosome 11p15 and a reduction to homozygosity of paternally derived genes, and this results in a somatic lesion of defective β-cells within the pancreas. Focal lesions appear histologically as small regions of islet adenomatosis measuring 2–5 mm in size (Fig. 5) and appear to develop through imbalanced expression of maternally imprinted tumor suppressor genes H19 and p57<sup>kip2</sup>, and the paternally derived insulin-like growth factor II gene (Fig. 6). Also encoded by chromosome 11p15.5 is Pidd, a p53-induced protein with a death domain (170). Pidd is thought to promote apoptosis by acting as a downstream regulator of the tumor suppressor p53 (170). It is not known whether Pidd is subject to imprinting, but since antisense inhibition of Pidd expression attenuates apoptosis in response to p53 activation and DNA damage (170), loss of Pidd through gene silencing may contribute to the development of focal lesions. Importantly, away from the lesion, the remainder of the pancreas retains a relatively normal histological appearance (see Ref. 267).

Recent estimates from France, Israel, and the United States now suggest that 40–65% of all patients with HI have the focal form of HI-KATP (62, 102, 284). Because this represents a significant number of patients that are potentially curable through a limited surgical intervention to remove just the focal lesion, much effort is now being placed on attempts to diagnose Fo-HI to avoid the obvious long-term complications of radical pancreatic surgery (49, 173, 192, 201, 299). Suggested diagnostic procedures include preoperative interventional radiography such as intra-arterial calcium stimulation tests, pancreatic venous sampling or transhepatic portal venous insulin sampling, positron emission tomography, laparoscopy, and intraoperative histological examination of biopsies of the resected pancreas (14, 20, 25, 33, 62, 82, 220, 245, 246). A greater understanding of the pathophysiology of β-cells in HI has also led to the introduction of a noninvasive procedure to monitor acute insulin-response profiles to glucose and tolbutamide in patients to distinguish focal forms of HI from diffuse disease (108, see sect. VI D).
C. K<sup>ATP</sup> Channel Gene Defects and HI-KATP

More than 100 mutations in the \textit{ABCC8} and \textit{KCNJ11} genes have so far been described (85). For a number of these mutations it has been possible to demonstrate that they result in differing abnormalities of recombinant KATP channels including protein folding defects, assembly and trafficking defects, and alterations in both nucleotide regulation and open-state frequency (Fig. 7). However, since in \textit{>50}\% of Di-HI and \textit{<30}\% of Fo-HI patients, screening has failed to define the genetic basis of disease (85, 86, 213) and in Japan SUR1 mutations account for only \textit{<20}\% of HI cases, our overall understanding of the pathogenesis of HI is far from complete (103, 282, 284). To address this and to define the causal relationship between \textit{ABCC8}, \textit{KCNJ11}, K<sup>ATP</sup> channel dysfunction, and inappropriate insulin release, we undertook studies on \textit{β}-cells from more than 110 patients with early-onset hyperinsulinism who required pancreatectomy. In this group \textit{85}\% of all patients carried functional defects in channels, which confirms that HI-KATP is the principal cause of early-onset, aggressive HI, but also reveals that in nearly \textit{15}\% of HI cases, our overall understanding of the pathogenesis of HI is far from complete (103, 282, 284). To address this and to define the causal relationship between \textit{ABCC8}, \textit{KCNJ11}, K<sup>ATP</sup> channel dysfunction, and inappropriate insulin release, we undertook studies on \textit{β}-cells from more than 110 patients with early-onset hyperinsulinism who required pancreatectomy. In this group \textit{85}\% of all patients carried functional defects in channels, which confirms that HI-KATP is the principal cause of early-onset, aggressive HI, but also reveals that in nearly \textit{15}\% of patients with this clinical phenotype, hyperinsulinism is unrelated to loss of channel function per se (1, 19, 46, 71, 139, 140, 171, 224, 228, 291). These patients therefore represent a group likely to yield novel HI disease-causing mutations unrelated to the known K<sup>ATP</sup> channel genes.

There are numerous mechanisms that could result in defects in K<sup>ATP</sup> channel function, and in most cases the relationship of molecular mechanisms, cellular defect, and clinical hyperinsulinism has yet to be established. Figure 7 attempts to summarize these with reference to SUR1/Kir6.2 gene transcription, translation, protein formation (synthesis, folding, and assembly), exit from the ER, and the function of SUR1/Kir6.2 at the membrane. Potentially, gene defects in K<sup>ATP</sup> channel subunits could influence any of the steps that ultimately result in protein expression at the plasma membrane. From functional studies of HI-KATP, patients have been classified into two groupings.

In type 1 disease, functional K<sup>ATP</sup> channel currents were ablated in \textit{β}-cells. Accounting for \textit{<10}\% of all Di-HI patients and \textit{<55}\% of Fo-HI patients, this condition is typified by abnormalities in gene expression, protein synthesis, maturation, assembly, or trafficking (Fig. 7, \textit{D–H}). Type 1 HI-KATP was originally described in two patients from interrelated Saudi Arabian families who carried the autosomal recessive R1437Q(23)X mutation in exon 35 of \textit{ABCC8} (71). Probands presented with severe, early-onset, and drug-resistant Di-HI and no functional K<sup>ATP</sup> channels in \textit{β}-cells. In this case, the SUR1 mutation truncates 200 amino acids from the COOH-terminal region of the protein, an area that contains the L1566, L1567, F1574 anterograde signaling sequence and residue L1544 which is part of the cloaking region for the RKR sequence. Because this defect will affect the exit of channel subunits from the ER compartment, the functional loss of K<sup>ATP</sup> channels in these patients appears to arise from a trafficking abnormality, which was confirmed when a parallel mutation was engineered and then coexpressed with wild-type...
Kir6.2 in COS cells (71). In addition to SUR1 gene defects that cause major protein truncations, trafficking abnormalities have been reported in recombinant cells for the ΔF1388 and R1394H disease-causing SUR mutations (30, 229, 302).

More than 60% of Di-HI and ~45% of Fo-Hi patients have a type 2 K<sub>ATP</sub> channelopathy. This reflects a diverse group of patients in which K<sub>ATP</sub> channel currents were recordable in β-cells but were found either to express defects in function or were present in limited numbers (Fig. 7, B–D). The V1479R SUR1 mutation located in NBF2 is a typical example of a gene defect leading to a regulatory abnormality in K<sub>ATP</sub> channels (217). In recombinant cells this mutation leads to loss of ADP-dependent K<sub>ATP</sub> channel gating and sensitivity to diazoxide. A number of other HI-associated mutations have similar actions (F591L, T1139M, R1215Q, G1382S, E1506K, I446T, R1420C, and R1436Q) and are linked to the clinical phenotype, since the loss of ADP-dependent gating results in the constitutive inhibition of K<sub>ATP</sub> channels by ATP (126, 191, 278, 301).

In the first study of nonconsanguineous familial disease in the United Kingdom cohort of HI patients, we recently described three caucasian neonates from two separate families with early-onset, drug-resistant HI (291). Genotyping revealed a novel defect in intron 16 of ABCC8 -2154+3a->g in all probands which was paternally inherited in one family and located on the maternal allele in the other. The intronic mutation is approximate to the NBF1 coding region, and functional studies were used to describe a >95% loss of K<sub>ATP</sub> channel function (Fig. 8), with no responses to ADP and diazoxide. It is not entirely clear how the intronic defect alters the amino acid sequence of SUR1, but one suggestion is that the abnormality is able to
introduce a cryptic splice site in the \textit{ABCC8} reading frame. Because the defect is proximal to the RKR retention sequence R648-K649-R650, it is tempting to speculate that the folding of the mutated SUR1 fails to effectively cloak the RKR motifs, leading to a cell surface trafficking abnormality in the \(\beta\)-cell. In insulin-secreting cells from patients, we were also able to demonstrate that the effects of the SUR1 mutation were selective for K\(_{ATP}\) channels, as there were no defects in the expression or function of voltage-gated K\(^+\) channels, nor the actions of sulfonylureas on Ca\(^{2+}\)-dependent exocytosis (291). The V187D SUR1 mutation, located in TMD0 of SUR1, leads to early-onset HI and is one of the two founder mutations associated with \(\sim 50\%\) of HI in the Finnish population (224). In \(\beta\)-cells from patients, \(>95\%\) of the normal current magnitude was lost, and residual channels were unresponsive to ADP and diazoxide (224). These types of experiments indicate that the outcome of mutations located towards NBF1 and the NH\(_2\)-terminal sequence of SUR1 can be equally as severe as COOH-terminal truncations and mutations located within the regions of \textit{ABCC8} that encode for the NBFs. Interestingly, HI resulting from the V187D mutation is equally as severe in patients who are homozygous or heterozygous for the mutation, yet carriers can also be asymptomatic with normal insulin secretion profiles, tissue sensitivity to insulin, and appropriate insulin release profiles during hypoglycemia (127).

In Ashkenazi Jewish patients, two \textit{ABCC8} mutations, \(\Delta F1388\) and 3092-9g>a, appear to account for \(>90\%\) of all cases (58, 215, 305). The \(\Delta F1388\) mutation causes defective channel trafficking since in recombinant cells \(\Delta F1388\)-SUR1 mutant channels were retained in the ER and were thereby unable to reach the cell surface (30, 31). The intron 32 3992–9g>a defect is associated with \(\sim 70\%\) of Ashkenazi Jewish HI patients and is particularly interesting since homozygous patients present with markedly

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig8.png}
\caption{Type 2 HI-KATP, reduced K\(_{ATP}\) channel function in \(\beta\)-cells. Macroscopic K\(_{ATP}\) channel currents in human control and HI \(\beta\)-cells obtained using the whole cell configuration of the patch-clamp technique. The data show that when the pipette was filled with a solution containing 0.3 mM ATP, there was a marked time-dependent increase in the amplitude of K\(_{ATP}\) channel currents in control but only a modest increase in HI-KATP (SUR1 2154+3a>g) cells (A, bottom). B: summary data from several experiments showing that current amplitudes were \(\sim 7\%\) of control value in HI cells. C: model of HI-KATP in \(\beta\)-cells. See Fig. 2 for abbreviations. [A and B from Straub et al. (291), copyright 2001 The American Diabetes Association.]}\end{figure}
different phenotypic expressions of the disease. These can range from a severe drug-resistant HI to mild disease and clinically unaffected individuals (58, 215). Numerous explanations have been proposed to account for the heterogeneous outcome including the actions of modulator genes, exogenous factors that modify the phenotype, and a variable degree of penetrance of the mutation (215). Unpublished data from our experiments suggest that this mutation is able to produce a number of variable gene products as in β-cells isolated from three unrelated patients, some cells manifested a type 1 channelopathy, others a type 2, and yet other cells had no defects in K<sub>ATP</sub> channels and were fully responsive to intracellular ADP and diazoxide.

Finally, mutations in KCNJ11 are relatively rare causes of HI. Several mutations have been described to date, e.g., Y12X, L147P, and W91R, which when coexpressed with recombinant SUR1 did not generate active K<sub>ATP</sub> channels (191, 214, 304).

D. Depolarization-Response Coupling in HI-KATP β-Cells

By studying tissues isolated from patients with HI, we were able to characterize the relationship between K<sub>ATP</sub> channelopathies and inappropriate insulin release (271). In normal β-cells, open K<sub>ATP</sub> channels stabilize the cell membrane potential under resting conditions and, as a consequence of either decreased numbers of channels or altered biophysical or biochemical regulation (particularly in terms of ADP sensitivity), HI β-cells are depolarized in the absence of glucose metabolism. The "resting" membrane potential in HI β-cells is therefore close to the threshold for the activation of voltage-dependent Ca<sup>2+</sup> channels (VGCC), leading to inappropriate VGCC activity, the generation of action potentials, and elevated [Ca<sup>2+</sup>]<sub>i</sub> under basal conditions (1, 140, 291). Because Ca<sup>2+</sup> influx regulates the dynamics of the immediately releasable granules, defects in the triggering pathway caused by the loss of K<sub>ATP</sub> channel activity largely account for inappropriate insulin release under hypoglycemic conditions. The loss of K<sub>ATP</sub> channels linked to Ca<sup>2+</sup> influx in HI β-cells also accounts for the insensitivity of many patients to medical treatment since, in the absence of operational K<sub>ATP</sub> channels, diazoxide is unable to effectively repolarize the cell membrane potential and thereby terminate Ca<sup>2+</sup> influx through VGCC.

In vitro, the activity of VGCCs can be reduced by either hyperpolarizing the cell membrane under voltage-clamp conditions or by directly inhibiting Ca<sup>2+</sup> channels with dihydropyridines such as nifedipine or phenylalkylamines such as verapamil (140). The important role of VGCCs in the pathophysiology of HI is also supported by the positive benefits of therapeutic intervention with VGCC blockers (see sect. IX). In patients with HI-KATP as a result of SUR1 gene defects, VGCC channel activity was directly coupled to compound exocytosis (Fig. 9), which was found to be Ca<sup>2+</sup>-dependent and enhanced by agonists of PKC and PKA (291). The overall rates of Ca<sup>2+</sup>-dependent increases in membrane capacitance were found to be moderately reduced compared with control human β-cells, which may reflect a dynamics decrease in the rate of exocytosis or an increase in the rate of endocytosis in these β-cells following loss of K<sub>ATP</sub> channels (291) (Fig. 10, A and B).

There is also evidence from in vivo and in vitro

![Figure 9](http://physrev.physiology.org/...)

**Fig. 9.** Voltage-dependent Ca<sup>2+</sup> influx and exocytosis in HI-KATP β-cells. With the use of the perforated patch configuration of the patch-clamp technique, voltage-gated Ca<sup>2+</sup> influx was initiated by depolarizing the cell under voltage-clamp conditions from −70 to 0 mV (A, i). Under control conditions, this led to a modest increase in the rate of exocytosis (A, ii, and B). Challenging the cells with 2 μM forskolin to activate protein kinase A and 10 nM phorbol 12-myristate 13-acetate (PMA) to activate protein kinase C led to more marked increases in the rate of exocytosis in HI-SUR1 β-cells. [From Straub et al. (291), copyright 2001 The American Diabetes Association.]
studies that VGCC activity is attenuated in HI β-cells. In the paradigm outlined, blockers of VGCCs should be therapeutically efficacious in all cases of HI. A review of the literature suggests, however, that this is not the case, and whilst some patients are clearly responsive (12, 76, 171, 256, 269), in others, nifedipine is ineffective in the control of hypoglycemia (71, 291). This may, in part, be related to the dose of nifedipine that can be safely administered to neonates, but there is also evidence that the activity of voltage-gated Ca\(^{2+}\)-channels in HI β-cells is functionally heterogeneous (48). In a study of β-cells isolated from 11 patients undergoing surgery for HI, VGCCs were detected in 50% of all experiments and, where present, were found to be inhibited by in vitro conditions that mimic hyperinsulinism (71, 291). This may, in part, be related to the dose of nifedipine that can be safely administered to neonates, but there is also evidence that the activity of voltage-gated Ca\(^{2+}\)-channels in HI β-cells is functionally heterogeneous (48).

E. Amplification Pathways of Regulated Insulin Release From HI-KATP β-Cells

In HI-KATP β-cells, loss of K\(_{ATP}\) channel function leads to raised levels of cytosolic Ca\(^{2+}\) and the stimulation of Ca\(^{2+}\)-dependent exocytosis. This is analogous to those conditions in vitro that are required for studying the K\(_{ATP}\) channel-independent pathways of GSIS, and we were therefore able to show in HI β-cells that glucose, but not tolbutamide, enhanced insulin release (291). The effects of glucose under these conditions were Ca\(^{2+}\) dependent, but GSIS could also be facilitated by stimulation of PKC and PKA in the absence of extracellular Ca\(^{2+}\) (Fig. 10).
10, C and D). Consistent with persistently depolarized cells, challenging HI-KATP islets of Langerhans with high extracellular KCl failed to evoke insulin release, but agonists that act independently of the cell membrane potential elevated \([\text{Ca}^{2+}]_{c}\) and elicited insulin secretion (291).

F. Clinical Implications of an Advanced Understanding of the HI \(\beta\)-Cell

The results of investigations of the molecular pathophysiology of HI-KATP \(\beta\)-cells have several clinical implications. First, the heterogeneity of K\(_{ATP}\) channel defects and uncontrolled influx of \(\text{Ca}^{2+}\) provides for a rational understanding of the variability of patient responsiveness to diazoxide treatment (139), the intra-arterial calcium stimulation test (1), and nifedipine in the treatment regimen for HI (171). Second, the differential responsiveness of HI-KATP \(\beta\)-cells to tolbutamide and glucose has proven useful in the development of acute insulin response (AIR) profiling as a novel preoperative procedure for the assessment of Fo- or Di-HI (108, 291). The basis of glucose/tolbutamide AIR tests is that patients with HI-KATP will have impaired responses to intravenous tolbutamide in affected parts of the pancreas and varying responses to glucose as a result of the contributing pathways of GSIS (Fig. 11). As demonstrated by Grimberg et al. (108), in patients with diffuse HI-KATP, \(\beta\)-cells will not respond to tolbutamide stimulation, whereas they will release insulin, in a relatively blunted manner through the “glucose amplification” pathway (Fig. 12). In contrast, in patients

**Fig. 11.** The predicted outcomes of acute insulin response (AIR) profiles to glucose and tolbutamide in the diffuse and focal HI pancreas. In Di-HI, K\(_{ATP}\) channel defects prevent tolbutamide-induced insulin release and impair glucose-induced insulin release that can operate only through the amplification pathways. In contrast, in Fo-HI \(\beta\)-cells both glucose and tolbutamide AIRs will appear “as normal,” since islets outside of the focal lesion do not express K\(_{ATP}\) channel defects.

**Fig. 12.** AIRs to glucose and tolbutamide in children with diffuse HI-KATP. A: normal adult control. B: patient with diffuse HI-KATP. [From Grimberg et al. (108), copyright 2001 The American Diabetes Association.]
with Fo-HI, since the region of the pancreas outside of the lesion is normal, AIR tests to both tolbutamide and glucose are positive. However, in the only other published evaluation of AIR profiles, some patients with diffuse HI-KATP (due to Kir6.2 gene defects) were found to be tolbutamide sensitive, thereby suggesting that a more widespread evaluation of these approaches must be undertaken (124). AIR testing may prevent as many as two-thirds of HI patients undergoing a radical 95% pancreatectomy, which inevitably leads to pancreatic insufficiency and diabetes, to achieve euglycemia. Investigative AIR to glucose and tolbutamide could be carried out in parallel with a calcium stimulation test, which has been useful in the detection of focal lesions for several years (1, 33, 82, 124). The intra-arterial calcium stimulation test, which is also used for the diagnosis of insulinomas, relies on a rapid bolus of calcium gluconate being administered via a catheter in the celiac axis and splenic, superior mesenteric, and gastroduodenal arteries. Blood samples are then collected and tested for glucose and insulin levels. An excessive insulin response from calcium stimulation in a single artery suggests a Fo-HI (Fig. 13), while excessive poststimulation insulin secretion associated with all arteries suggests a Di-HI (1). The pancreatic arterial calcium stimulation (PACS) test is therefore able to detect hyperactive \( \beta \)-cells via external \( Ca^{2+} \)-stimulated insulin release. The molecular basis for this is likely to be inappropriate \( Ca^{2+} \) influx via VGCCs. Finally, because HI-KATP \( \beta \)-cells were shown to be glucose responsive both in vivo and in vitro, care must be taken when high rates of glucose infusion are used in critical care to maintain normoglycemia, as exogenous glucose may also act to further augment insulin release and bring about inappropriate hypoglycemic episodes. Similarly, because HI-KATP \( \beta \)-cells respond to PKC- and PKA-dependent agonists, incretins and other mediators of the entero-insular axis will facilitate enhanced insulin release in vivo, suggesting that patients who are administered oral glucose/enteral feeds are more likely to experience the deleterious effects of enhanced insulin release than patients provided with intravenous infusions of glucose (291).

VII. METABOLOPATHIES OF ATP-SENSITIVE POTASSIUM CHANNELS AND HYPERINSULINISM

Some children with congenital hyperinsulinism present with milder symptoms of hyperinsulinemic-induced hypoglycemia than described for HI-KATP, often with episodes of hypoglycemia that are sporadic and occur postprandially (98, 287). In addition, patients can also present later in life, even in adulthood (268). In these cases, hyperinsulinism is sometimes diazoxide responsive, inherited in an autosomal dominant fashion, and not linked to defects in the \( ABCCS8 \) or \( KCNJ11 \) genes. So far, mutations in three other genes, each associated with glucose homeostasis and acquired \( K_{ATP} \) channel abnormalities in \( \beta \)-cells, have been described. Each of these metabolopathies gives rise to a clinically distinct form of congenital/infantile hyperinsulinism: HI-GK, HI-GDH, and HI-SCHAD (see Table 1). In addition, hyperinsulinism induced by exercise has recently been described, HI-EI (197, 226), and there are also reports in the literature of patients with hyperinsulinism not linked to any known HI-causing loci (158, 208).

A. Glutamate Dehydrogenase and Hyperinsulinism

Instances of congenital hyperinsulinism where patients present with plasma ammonia concentrations that are persistently elevated to three to five times normal values are caused by dominantly expressed gain-of-function mutations of the mitochondrial enzyme glutamate dehydrogenase (GDH), HI-GDH (287). This form of hyperinsulinism is also known as the hyperinsulinism-hyperammonemia syndrome (151, 336; see Ref. 147 for recent review). GDH acts to link glutamate metabolism with the tricarboxylic acid cycle and catalyzes the conversion of glutamate to \( \alpha \)-ketoglutarate in islets and the liver. Encoded by the \( GLUD1 \) gene, GDH is normally activated by leucine and ADP, with GTP acting as an allosteric inhibitor of the enzyme. Defects in the region of \( GLUD1 \) re-
lated to the GTP-binding domain of the enzyme have been identified in many HI-GDH patients and lead to a decrease in the sensitivity of GDH to GTP (81, 179, 286, 287). This results in an “activated enzyme” complex. Other GLUD1 gene defects, found outside the GTP binding domain of the enzyme, are thought to be associated with a constitutively high level of GDH activity (204, 336). In the liver, enhanced activity of GDH leads to increased α-ketoglutarate and ammonia production and a fall in glutamate concentrations. Because glutamate is an essential substrate for the formation of N-acetylglutamate (NAG), an allosteric stimulator of carbamoyl phosphate synthetase, decreased concentrations of NAG reduce carbamoyl phosphate synthetase activity and ammonia levels rise owing to inhibition of the urea cycle. The effects of such GDH defects on β-cells are that patients experience fasting hypoglycemia, leucine hypersensitivity, and protein-induced hypoglycemia. Precisely how GDH mutations cause hyperinsulinism currently remains to be determined. Studies involving both cells lines and transgenic animals expressing disease-causing GDH mutations have shown recently that GDH substrates such as glutamine and leucine do not affect control cells, yet cause marked increases in insulin release only in HI-GDH cells (145, 302). This may be explained by GDH providing NADH and α-ketoglutarate to fuel the tricarboxylic acid cycle, leading to an increase in the ATP/ADP ratio, hence, KATP channel closure and inappropriate stimulation of the triggering pathway (Fig. 14). Diazoxide therapy is effective in most cases, since KATP channels are operational in HI-GDH patients. However, there are unpublished reports of patients with HI-GDH who remain unresponsive to diazoxide, which suggests that, in some patients, there may be KATP channel-independent modes of insulin release that may also be dysregulated (see Ref. 103).

Leucine hyperresponsiveness of children with HI-GDH suggests that some patients described previously as having “leucine-sensitive hypoglycemia of infancy” may have carried regulatory mutations of GDH. Numerous cases were reported in infants and children since the first description of this condition in 1955 (42, 66, 106, 175). However, it is also clear that there are patients with leucine-sensitive hyperinsulinism in whom elevated plasma ammonium concentrations are not found, which suggests that sites other than GDH should, therefore, also be considered as new candidates for β-cell metabolopathies. Finally, because HI-GDH can be detected biochemically from serum ammonia concentrations, or by AIR

![Image](http://physrev.physiology.org/)

**FIG. 14.** The proposed mechanism of inappropriate insulin release from HI-GDH β-cells. The GDH reaction is freely reversible, but is considered to progress in the oxidative direction towards α-KG and NH₃ formation, since internal glutamate concentrations are high. Defects in GDH occur in the catalytic or regulatory domains and lead to the generation of signals from enhanced metabolic events, illustrated by asterisks, that are inappropriate for the level of glycemia. Inappropriately raised levels of the ATP/ADP ratio close KATP channels and depolarize the membrane potential. However, as KATP channels are intact, patients are responsive to diazoxide treatment in vivo. Inset: representation of the GLUD1 gene, exons, and common HI-GDH mutations.
profiles to leucine, the disease can be both easily identified and treated with dietary manipulation and diazoxide (146).

B. Glucokinase and Hyperinsulinism

In β-cells, glucokinase (GK) catalyzes the initial reaction of glycolysis, the conversion of glucose to glucose-6-phosphate. Numerous different mutations (>100 to date) have been described and shown to cause hyperglycemia and diabetes (88, 236, 321). Among the different effects that these mutations have are reduced catalytic activities, increased glucose Km values, a shortening of the half-life and stability of the protein, a decrease in the ATP-binding affinity, impaired gene expression, and premature termination of protein translation (109, 155, 169, 205). The outcome of these mutations is, therefore, a reduction in GK activity, which reduces glycolytic flux, lowers the [ATP]/[ADP] ratio, and increases KATP channel activity. Regulated insulin secretion is therefore suppressed, and this largely explains the mechanism of impaired insulin release in patients with maturity-onset diabetes of the young type 2 (see Refs. 87, 89). HI-GK, on the other hand, results from the inheritance of autosomal dominantly expressed gain-of-function mutations that enhance the activity of GK (304). Patients with this rare condition typically have low fasting and postprandial glucose concentrations that are below the threshold of symptomatic neuroglycopenia, resulting in both fasting and reactive hypoglycemia. This form of HI has only been reported twice in the literature: a missense mutation V455M and A456V in exon 10, both of which cause metabolopathies. HI-GK is treatable by diazoxide, which suggests that the drug can overcome the downstream action of L-3-hydroxybutyryl-CoA and reverse inappropriate insulin release (39).

To date there are only two reports in the literature of families harboring SCHAD defects, suggesting that this is likely to be a rare cause of HI (39, 283). Nevertheless, HI-SCHAD is the first description of a fatty acid oxidation disorder linked to hyperinsulinism and raises the possibility that other enzymes associated with mitochondrial metabolism should be examined as candidates for HI-causing metabolopathies. HI-SCHAD can be detected either by the analysis of L-3-hydroxybutyrylcarnitine in the blood or excess L-3-hydroxybutyrate in the urine and by measurement of the activity of L-3-hydroxyacyl-CoA dehydrogenase in cultured skin fibroblasts (39).

D. Exercise-Induced Hyperinsulinism

Strenuous physical exercise has been shown to cause hyperinsulinemia and hypoglycemia in some patients who do not normally experience fasting hypoglycemia; this condition has been termed exercise-induced hyperinsulinism, HI-EI (197). Since exogenous lactate and pyruvate do not trigger insulin secretion in vitro due to insufficient uptake into the β-cell, it was suggested that HI-EI may be caused by abnormal responses to these muscle metabolites during exercise (130). Recently, an autosomal dominant form of HI-EI found in 10 additional cases from 2 families was linked to abnormal transport or metabolism of pyruvate in the insulin-producing cells; however, it was not associated with defects in the monocarboxylate transporter genes, MCT1-MCT8 (226).

C. Short-Chain L-3-Hydroxyacyl-CoA Dehydrogenase and Hyperinsulinism

Recently, the first defect in fatty acid β-oxidation associated with hyperinsulinism was described in the enzyme short-chain L-3-hydroxyacyl-CoA dehydrogenase, HI-SCHAD. SCHAD is expressed most abundantly in skeletal and cardiac muscle, the liver, and the pancreas. A homozygous mutation (C773T) in the gene encoding SCHAD, HADHSC on ch4q24-4q25, was described and found to elicit symptoms of hyperinsulinism with nonketotic hypoglycemia (39).
VIII. BECKWITH-WIEDEMANN SYNDROME AND HYPERINSULINISM

Beckwith-Wiedemann Syndrome (BWS) is a congenital overgrowth syndrome associated with a constellation of pathogenomonic physical features including macroglossia, anterior abdominal wall defects, exomphalos, transverse creases of the ear lobes, facial nevus, hyperinsulinism, renal abnormalities, hemihypertrophy, genitourinary abnormalities and, in up to 20% of patients, embryonal tumors (most frequently Wilms’ tumor) and adrenal tumors such as adrenocortical neoplasias (43, 328). Less commonly (<10% of cases), cardiac malformation, intestinal malrotation, neoplasia, and mental retardation are also found. The term BWS was first coined following the publications in 1964 by Wiedemann and in 1969 by Beckwith and has an estimated frequency of 1:15,000 live births in the United States and 1:13,700 live births in other developed countries (17, 329). However, because milder forms of the syndrome also exist and the condition is clinically and genetically heterogeneous, these figures most likely underestimate the true incidence. A recent report has also indicated that the prevalence of BWS may be positively associated with in vitro fertilization, since cell culture conditions may adversely alter DNA methylation (54).

The underlying causes of BWS remain largely unclear. In 80% of BWS patients, genotypic abnormalities of an imprinting region in the distal location of chromosome 11 are demonstrated. As discussed, several 11p genes are imprinted within this domain including p57kip2 (CDKN1C gene), IGF2 (IGF2 gene), the gene for insulin (INS), H19 (H19 gene), and the voltage-gated K+ channel KvLQT1 (KCNJ1 gene). BWS is inherited in a complex manner; reported patterns include spontaneous origins of the disease in ~85% of cases, autosomal dominance with variable expression, contiguous gene duplication at band 11p15.5 (usually paternally inherited), and aberrant genomic imprinting (resulting from a defective or absent copy of the maternally derived gene) (168). Whilst the “overgrowth” phenotype of BWS can be correlated with an imbalance in the expression of p57kip2, H19, and IGF2, 20% of patients with BWS have no identified genotypic disorder and only ~30% of the sporadic cases appear to result from p57kip2 abnormalities, suggesting that the genetic basis of most cases of BWS has yet to be completely evaluated (168). This is in part related to an incomplete understanding of the epigenetic process of imprinting and loss of heterogeneity, a process that can involve hypomethylation or hypermethylation of genes. Thus, for H19, patients with BWS who have imprinting defects show hypermethylation, which leads to the aberrant activation of IGF2 (210, 288), whilst p57kip2 defects appear to involve hypomethylation of the gene (40, 120). In more severe forms of BWS, it therefore seems probable that there may be more widespread loss of maternal tumor suppressor genes in combination with either enhanced upregulation of paternal growth promoter genes, IGF2, and/or defects in genes that determine the physiological competence of β-cells which may include ABCG8, KCNJ11, etc.

Inappropriate and sustained insulin release and/or reactive hypoglycemia have been reported in ~50% of all patients with BWS (43, 104, 187, 209, 249, 257). In some, hyperinsulinemia-induced hypoglycemia is mild and asymptomatic, whereas in others, hypoglycemia can be prolonged and difficult to manage (77). Owing to an absence of functional data, the mechanisms of β-cell pathology in BWS are unresolved. Many BWS patients generally
show good responses to diazoxide treatment, and the actions of arginine and leucine on insulin secretion are normal (43, 249, 257). This may suggest either that $K_{ATP}$ channel dysfunction is unrelated to hyperinsulinism in BWS, or that defects in channel expression levels, rather than their regulation, are a common cause of hypoglycemia in BWS cases. In addition, there are reports of severe, diazoxide-resistant, hyperinsulinemic hypoglycemia in BWS, and this clearly suggests that the pathogenesis of hyperinsulinism is multifactorial (93, 198, 209, 249). At this stage the underlying histopathology of BWS is incompletely understood, since data are limited to those severe cases in which the patient has died or undergone a pancreactectomy, and this is unrepresentative of the majority of BWS patients in which hyperinsulinism has been recorded (43, 131, 249). Where available, data suggest that a diffuse pathology and $\beta$-cell hyperplasia/hyper trophy are associated with BWS (43, 165, 174, 249).

IX. THE THERAPEUTIC ARMAMENTARIUM FOR HYPERINSULINISM IN INFANCY

Acute treatment regimens for HI are targeted at either the inhibition of insulin release or glucagon to promote mobilization of hepatic glucose. For early-onset HI as a result of $K_{ATP}$ channel defects, all compounds are delivered under the cover of a constant glucose infusion to protect against hypoglycemia-induced neurological damage. The drugs of preference are those that can be administered orally, followed by agents that are delivered intravenously or subcutaneously. However, none of the agents that are currently used is specific for the inhibition of insulin release, and glucagon, which has a powerful effect on mobilizing glucose, is also an insulin secretagogue. Because hyperglycemia-inducing reagents modulate $K_{ATP}$ channels in $\beta$-cells, many patients fail to respond appropriately to treatment and must undergo surgery to alleviate hypoglycemia.

Alternative treatment strategies to acute drug regimens and surgery have been advocated in a number of centers. Logistically, the conservative management of hyperinsulinism with agents such as diazoxide or somatostatin are laborsome for both the family and the physician and can be protracted over several years (52, 97, 99, 101). Nevertheless, as long as euglycemia is accomplished and maintained, the benefits to patients who then avoid surgery are clear. More recently, suggestions have been made that intensive combinational/polymedical therapies of available agents might also be of value in the treatment of HI. Preliminary data from two groups now suggest that although problematic, this approach may be of value and eliminate/delay the need for pancreatectomy (53, 256).

Patients with hyperinsulinism as a result of metabolicopathies retain functional $K_{ATP}$ channels, and hypoglycemia is generally responsive to diazoxide, somatostatin analogs, or by dietary manipulation.

A. Glucagon

Glucagon has a powerful effect on mobilizing glucose from hepatic glycogen by increasing the rates of glycolysis and gluconeogenesis. Administration of glucagon, usually a continuous intravenous infusion at rates of between 5 and 10 $\mu$g·kg$^{-1}$·h$^{-1}$, can therefore help to reduce the infusion rate of glucose needed to maintain normoglycemia. However, one of the major arguments against the use of glucagon is the fact that in addition to glucose mobilization, the hormone will also act as a potent insulin secretagogue, and its administration will therefore maintain a drive toward insulin hypersecretion. For this reason, glucagon tends to be used in conjunction with other inhibitors of insulin release. Because glucagon has actions on a number of other tissues, side effects of therapy include nausea, vomiting, increased growth hormone concentrations, increased myocardial contractility, and decreased gastric acid/pancreatic enzyme secretions. In high doses glucagon causes tachyphylaxis and erythema necrolyticum migrans (8, 325).

B. Somatostatin

The somatostatin analogs Octeotride and Sandostatin are important clinical agents that are widely used in the short and long term, in some cases over several years, e.g., treatment of HI-KATP. These agents are administered as either an intramuscular or intravenous bolus, or more effectively as a continuous subcutaneous infusion (dose 1–10 $\mu$g·kg$^{-1}$·day$^{-1}$). Somatostatin is a potent inhibitor of insulin release with multifactorial modulation of $\beta$-cell function. It induces a pertussis toxin-sensitive hyperpolarization of the $\beta$-cell membrane potential, which therefore acts to prevent Ca$^{2+}$ influx (218). The ionic mechanisms that underlie these electrophysiological events are incompletely understood in rodent $\beta$-cells and $\beta$-cell lines and have not been investigated in detail in human insulin-secreting cells. Somatostatin-induced hyperpolarization of the membrane potential involves the activation of different K$^+$ channels including $K_{ATP}$ channels, G protein-coupled inward rectifier K$^+$ channels, delayed rectifier K$^+$ channels, Ca$^{2+}$- and voltage-gated K$^+$ channels, etc. (65, 248, 281). Somatostatin will also inhibit voltage-gated Ca$^{2+}$ channels independently of the membrane potential (122) and inhibit insulin release by mechanisms distal to Ca$^{2+}$ influx, e.g., by reducing cytoplasmic levels of cAMP (121, 185) and by direct interactions with the exocytotic machinery (316). The multiplicity of target sites is in part related to the fact...
that five distinct somatostatin receptor subtypes have been characterized and designated as SSTR1–5, as well as two splice variants of SSTR2, SSTR2a and SSTR2b (27, 231). The expression profiles of the identified and cloned SSTRs appear to differ in different species and sources of insulin-secreting cells. For example, the β-cell line MIN6 expresses all receptor subtypes, whereas only SSTR1 and SSTR5 appear to be expressed in human islets (159, 231, 281). Because SSTRs are found in numerous tissues, the therapeutic application of somatostatin analogs such as Octeotride or Sandostatin is problematic because of adverse side effects. These include a diverse number of endocrine effects, including suppression of LH response to gonadotropin releasing hormone, decreased splanchnic blood flow, and the inhibition of the release of several hormones including growth hormone, serotonin, gastrin, vasoactive intestinal polypeptide (VIP), secretin, motilin, pancreatic polypeptide, ACTH, and thyroid-stimulating hormone (TSH). Somatostatin analogs decrease gallbladder contractility and bile secretion and cause steatorrhea, cholelithiasis, abdominal distension, and a decrease in growth rate. Long-acting Octeotride and more potent and selective analogs are currently available as experimental agents, but they are, as yet, unavailable for clinical use.

C. Corticosteroids

Agents such as prednisone, prednisolone, and methylprednisolone are valuable in HI treatment since they increase gluconeogenesis. Although their action is not immediate, corticosteroids may be useful in the short term to maintain adequate blood glucose levels. However, there are adverse effects of prolonged corticosteroid use, and this severely limits their long-term application; adverse actions include a reduced immune responsiveness, and in the long term that may cause obesity, cataracts, and decreased bone density.

D. Diazoxide and Diazoxide Analogs

Diazoxide (given within the range 10–20 mg·kg⁻¹·day⁻¹) is the cornerstone of medical treatment for hyperinsulinism, since the drug is an effective inhibitor of insulin secretion and can be administered orally. However, despite the widespread use of diazoxide, the agent is poorly tolerated by a number of patients due mainly to adverse side effects. Treatment with diazoxide is generally combined with chlorothiazide (7–10 mg·kg⁻¹·day⁻¹), a diuretic that has the ability to both overcome the fluid-retaining actions of diazoxide and to inhibit insulin release. Patients in whom the origins of hyperinsulinism are metabolic generally respond well to long-term diazoxide treatment, but since diazoxide is an agonist of K_{ATP} channels, the responsiveness of patients with HI-KATP is highly variable. Some reports suggest success rates of diazoxide treatment as low as 15%, others 60% or greater (8). This difference in responsiveness may reflect the selection of cases being referred for treatment, the relative effectiveness of different doses in vivo, and the known heterogeneity in molecular, genetic, and histological pathology associated with HI. Thus children who fail to respond to diazoxide at a dose of 15–20 mg·kg⁻¹·day⁻¹ might have β-cells that will respond in vitro to higher concentrations (139). Even though diazoxide is widely used in practice, numerous side effects are known for the compound. One of the reasons for side effects is that diazoxide is highly bound to serum protein and will displace other protein-bound substances such as bilirubin or coumarin, increasing their serum levels. Of particular note are those complications related to nausea and vomiting or sodium and water retention, which can lead to further problems in patients with congestive heart defects or poor cardiac reserve, hyperuricemia, hypotension, hypertrichosis and on occasions blood dyscrasias, leucopenia, and thrombocytopenia. In addition, diazoxide therapy is associated with decreased serum immunoglobulin G levels, and this can lead to problems associated with infection, and with long-term use there are also reports of hyperosmolar nonketotic comas (8, 59, 254, 308). Because not all patients with HI have channelopathies and not all HI-KATP patients have ablated ion channel function, the availability of more potent and more selective diazoxide analogs for the inhibition of insulin release would seem to be a logical progression of the K_{ATP} channel-based treatment option. Several agents are currently available for experimental purposes, and these have produced significant advances in identifying the structural elements of SUR1/Kir6.2 homologs that allow selectivity for the β-cell (163). Such compounds include quinolinonic compounds such as HEI 713 (16) and the benzothiadiazine 1,1-dioxides 3-alkylamino-4H-1,2,4-benzothiadiazine 1,1-dioxide (BPDZ 73) (21), 3-alkylamino-4H-pyrido[4,3-e]-1,2,4-thiadiazine 1,1-dioxide (BPDZ 44) (149), and 6,7-dichloro-3-isopropylamino-4H-1,2,4-benzothiadiazine 1,1-dioxide (BPDZ 154) (46) (Fig. 16). BPDZ 154 is of particular interest since it is one of the most potent K_{ATP} channel agonists developed. The agent has an EC₅₀ of 0.28 μM for the inhibition of GSIS, which is ~100-fold more potent than diazoxide (16). Additionally, BPDZ 154 reverses sulfonylurea- and efaroxan-induced inhibition of K_{ATP} channels and reverses the actions of glibenclamide on insulin release (46). In patients with type 1 or type 2 HI-KATP, BPDZ 154 failed to activate K_{ATP} channels at the cell surface (46). However, when the compound was added to the cell culture medium to
preexpose HI β-cells to BPDZ 154 for up to 60 h, this led to the recovery of functional channels (47). BPDZ 154 was also found to be a potent agonist of K<sub>ATP</sub> channels in insulinoma β-cells and in β-cells from patients with HI where hyperinsulinism is unrelated to K<sub>ATP</sub> channel function (46) (Fig. 17). Thus the potential application of these types of compounds to the clinical management of HI could bring about more effective treatment without the adverse side effects of diazoxide.

E. Nifedipine

When the link between loss of K<sub>ATP</sub> channel dysfunction and uncontrolled insulin release was established, this led to the suggestion that clinically relevant inhibitors of VGCCs may be of therapeutic value in the management of HI. In 1996 we first suggested this as an option based on an index case in which nifedipine was administered for recurrent postoperative hypoglycemia. Nifedipine brought about a stabilization of blood glucose levels and a significant increase in the patient’s tolerance to fasting (171). The use of nifedipine in HI therapy is therefore relatively new, and the drug has advantages over diazoxide in that it will directly modulate the molecular events that determine inappropriate insulin release, it can be delivered orally, and at doses of 0.25 to 2.5 mg·kg<sup>-1</sup>·day<sup>-1</sup>, it appears to be remarkably safe and well tolerated. Most information on adverse effects of nifedipine has been obtained from studies of adults using the drug for angina pectoris at proportionately higher doses than those used in children. No adverse effects have so far been reported in patients with HI. However, the response rates of patients are variable, blood pressure monitoring is mandatory, and because only a limited number of centers have reported clinical experiences of nifedipine, there is no data on long-term use in the treatment of hyperinsulinism (12, 71, 76, 256, 269, 291).

Figure 18 summarizes the key therapeutic options and long-term strategies for patients with the different hyperinsulinism syndromes.

X. ANIMAL MODELS OF HYPERINSULINISM IN INFANCY

Transgenic mice expressing overactive β-cell K<sub>ATP</sub> channels have been shown to exhibit profound neonatal...
diabetes due to permanent suppression of insulin release (154). However, attempts to produce murine models of HI-KATP through manipulation of the SUR1 or Kir6.2 genes have met with variable and incomplete results. Miki et al. (203) generated the first transgenic mouse model by expressing a dominant-negative mutant of Kir6.2 (G132S) in the β-cell and other tissues. This mutation altered the ability of Kir6.2 to conduct potassium ions rendering these channels either nonfunctional or with a modest permeability to Na⁺ (212). K ATP currents were significantly reduced in β-cells with downstream consequences of a depolarized resting cell membrane potential and elevated basal [Ca²⁺]i levels, typical of those described in human HI β-cells, suggesting that these mice had a phenotype that was also similar to humans with HI-KATP (140). During the neonatal period the mice exhibited hyperinsulinemia alongside hypoglycemia, but they later developed hyperglycemia coupled with reduced glucose-induced insulin secretion, which resulted from β-cell apoptosis. This may have a correlation with HI-KATP in humans, since in some patients that have been treated over long periods, intensive somatostatin therapy will obviate the requirement for surgery (97, 99, 101). In these patients, despite the clinical remission of symptoms, impaired insulin responses to glucose persists, suggesting a decline in the mass of β-cells is the likely cause of the amelioration of symptoms (166). In support of a role for apoptosis under these conditions, Kassem et al. (143)
have shown increased β-cell apoptosis in histological samples of HI-KATP tissues (143). Miki et al. (202) later developed a Kir6.2 knock-out mouse model by homologous recombination. These animals showed only a transient hypoglycemia, since neonates and older animals were normal with no subsequent hyperglycemia despite their β-cells being depolarized and [Ca^{2+}] levels elevated. This surprisingly “normal” phenotype would appear to result from enhanced glucose utilization in skeletal muscle cells as a consequence of the loss of Kir6.2. A similar phenotype was also found in a SUR1 knock-out mouse (SUR1⁻/⁻), which also completely lacked K\(_{ATP}\) channels in β-cells and other tissues (261). On the first day of life, these mice had an inappropriately high insulin secretion for the observed serum glucose level. However, by day 5 all animals were reported to have a hyperglycemic phenotype. It is interesting to note that certain incretins that bypass the triggering pathway of glucose-induced secretion were able to produce enhanced insulin secretion in these animals (261). In summary, in mice with SUR1⁻/⁻ or Kir6.2⁻/⁻ genotypes, glucose tolerance is little perturbed and blood glucose levels are normal. Although the ablation of K\(_{ATP}\) channels and elevated [Ca^{2+}] in animal models do appear to parallel the β-cell phenotypes of human HI-KATP, the human disease is not fully reproduced (see Ref. 262 for review).

More recently, a second transgenic mouse with an altered selectivity filter in the K\(_{ATP}\) channel has been generated in which residues 132–134 (Gly-Tyr-Gly) were replaced by Ala-Ala-Ala (155). In these animals the manipulation was placed under the insulin gene promoter to produce a conditional ablation of K\(_{ATP}\) channel activity in β-cells. In contrast to the study of Miki et al. (203), AAA-TG mice developed normally; there was no increased mortality, and body weight, blood glucose levels, and islet architecture were normal. However, in adult mice, hyperinsulinism was evident and isolated islets showed enhanced GSIS due to increased glucose sensitivity. In these animals, it was found that rather than a complete knock-out of K\(_{ATP}\) channels in β-cells, AAA-TG mice express a partial phenotype with ~70% of β-cell expressing no measurable channel activity, whereas in the remaining 30% activity is apparently normal. A leftward shift in the glucose-secretion curve is the likely outcome of this, thereby explaining increased glucose sensitivity (154). As with other animal models of HI-KATP, AAA-TG mice also fail to mirror the human condition, but they do have a parallel with a rare form of HI-KATP in which the onset of hyperinsulinism occurs outside of the neonatal or infancy period. In these patients, late-onset hyperinsulinism is partly responsive to diazoxide, and in β-cells, K\(_{ATP}\) channels are present with decreased levels of activity but normal regulation, thereby providing an explanation for both the clinical symptoms and sensitivity to diazoxide (266).

Transgenic animals for studies of other types of hyperinsulinism are limited. SCHAD knock-out mice have been developed, but these die when subjected to a 10-h fast (221). Although the mechanisms responsible for this have not been determined, because of our understanding of HI-SCHAD it seems likely that this could be due to hyperinsulinemic hypoglycemia. There is no animal model of HI-GK, but recent work with a transgenic mouse engineered to express a GDH HI-causing mutation suggests that this may be a valuable model system to replicate the human disorder (145).

Several other animal models have been engineered with either β-cell selective, unconditional knock-outs or overexpression of proteins directly associated with metabolic processes. In several of these, hyperinsulinemia-induced hypoglycemia was seen with breakthrough diabetes; these include hexokinase (78), tumor necrosis factor-α (234, 235), VIP (144), calcitonin gene-related peptide (148), parathyroid hormone-related peptide (237), placental lactogen (319), GLUT2 (110, 306), and insulin-like growth factor II (63).

XI. PROSPECTS AND CONCLUDING REMARKS

The term hyperinsulinism is somewhat disingenuous, but it embraces those conditions related to “oversecretion” of insulin and, more commonly, inappropriate insulin release. Until relatively recently, hyperinsulinism was considered an enigmatic condition. But since 1996 there has been an outpouring of knowledge and information concerning the molecular genetics, cell biology, histology, and physiology of hyperinsulinism syndromes. This has provided new insights into the causes and development of the disease and provided exciting opportunities for the diagnosis, management, and treatment. A marked heterogeneity in genes leading to hyperinsulinism is already apparent, and because many patients with HI have yet to have the genetic basis of their condition defined, there will be more genetic causes of HI.

The genetics of HI-KATP have so far revealed that defects in either ABCC8 or KCNJ11 will cause disease, and more importantly, mutations across all regions of SUR1 are pathogenic. In the same way that genotype-phenotype information has provided insights into the structural components of K\(_{ATP}\) channels, HI-metabolopathies are providing new information for the biology of insulin-secreting cells. For example, recent work on HI-GDH has raised contrasting opinions on the fundamental role of glutamine as a signaling molecule in β-cells and the relationship between glutaminolysis and basal insulin secretion (145). Lastly, a new area of activity is emerging based on the relationship between exercise and hyperinsulinism which will have far-reaching implications for the control of intermediary metabolism and glucose homeostasis (226).
Gene defects in K\textsubscript{ATP} channels remain the major cause of severe early-onset HI, but studies related to the pathogenesis of HI-KATP and the genomics of K\textsubscript{ATP} channels are important in the wider fields of \(\beta\)-cell physiology and diabetes. Understanding the signature motifs and crucial amino acid residues contained within the coding and noncoding regions of \(ABCC8\) and \(KCNJ11\) is of generic importance to ion channel physiology, pharmacology, and the trafficking of membrane proteins. The genetics of \(KCNJ11\) and \(ABCC8\) are also proving relevant to type 2 diabetes. First, carriers of the HI-causing E1506K-SUR1 mutation were found to be asymptomatic for HI but presented with insulin deficiency later in life and developed diabetes mellitus (125, 126). Since this autosomal dominant SUR1 mutation causes HI and familial diabetes in the same subject groups, it raises the possibility that altered \(\beta\)-cell function per se is pleiotropic for the control of intermediary metabolism and insulin signaling (125). Second, in certain type 2 diabetic cohorts, as many as 1 in 10 patients are thought to carry an E23K mutation in Kir6.2, which acts to increase the opening frequency of channels and thereby lower the ATP sensitivity of the channel (259). The outcome of this will be defective depolarization-response coupling and impaired insulin release, consistent with the clinical feature of diabetes. Because similar parallel relationships exist between HI and diabetes for defects in glucokinase, the value of these types of studies related to rare disorders for more common diseases of glucose homeostasis is self-evident. Within the European community, a concerted action group, ENRHI, has been set up to define HI and to work towards a cure for the disease. In addition to recently published collaborative work, we are now at the point of defining new syndromes of HI, new genes, new pathologies at the level of the \(\beta\)-cell, novel histopathological forms and features of the HI pancreas, new mechanisms of genetic inheritance of HI genes, and a detailed evaluation of the outcomes and courses of HI.

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