K\textsubscript{ATP} channels and glucose-induced insulin release: lessons from persistent hyperinsulinemic hypoglycemia of infancy

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Persistent hyperinsulinemic hypoglycemia of infancy (PHHI) is a disorder characterized by severe, recurrent hypoglycemia with inappropriately elevated circulating insulin levels. It usually becomes manifest rapidly after birth and, if unrecognized, may lead to severe brain damage. Although the symptoms can be transiently alleviated by fractionated carbohydrate intake, diazoxide or somatostatin, treatment may require total or subtotal pancreatectomy. The disease occurs either in a familial or in a sporadic form. PHHI, a dramatic but rare condition, has recently attracted considerable attention as a model disease of defective glucose-induced insulin secretion.

The role of ion channels in the control of insulin release is increasingly recognized. In pancreatic β-cells, the normal resting membrane potential is maintained by potassium (K\textsuperscript{+}) efflux, via ATP-sensitive K\textsuperscript{+} channels (K\textsubscript{ATP} channels). The main stimulus for insulin secretion is a rise in blood glucose concentration. Glucose enters the β-cell where it is metabolized, resulting in increased intracellular ATP and decreased ADP concentrations. The increased ATP concentration (or rather the increased ATP/ADP ratio) induces the closure of K\textsubscript{ATP} channels, resulting in membrane depolarization. Depolarization, in turn, induces the opening of voltage-sensitive L-type calcium channels, resulting in calcium influx and a rise in intracellular free calcium concentration ([Ca\textsuperscript{2+}]) which triggers insulin exocytosis (reviewed in 1). K\textsubscript{ATP} channels are closed by sulfonylureas (SU), a class of drugs widely used in the treatment of non-insulin-dependent diabetes (NIDDM) to stimulate insulin release. Conversely, K\textsubscript{ATP} channels are opened by diazoxide, a drug used to inhibit insulin release. These observations imply that K\textsubscript{ATP} channels are identical with, or closely related to, the SU receptor.

Aguilar-Bryan et al. have recently reported the cloning of the SU receptor (SUR) (2). These authors identified a β-cell-specific membrane protein that binds the sulfonylurea glyburide (glibenclamide). Using a classical approach based on the microsequencing of the purified protein and the deduced nucleotide sequence, they identified a cDNA encoding for a 177 kDa protein in both hamster and mouse β-cell lines. The protein contains 13 membrane-spanning domains and 2 intracellular ATP-binding sites (so-called nucleotide binding folds, NBFs). It is a member of the family of ATP-binding cassette (ABP) proteins that include the cystic fibrosis (CFTR) and the multidrug resistance (MDR) proteins. The protein expressed in heterologous cells by transfection of the cDNA conferred SU binding. However, in a Xenopus oocyte system used for electrophysiological studies, expression of the protein failed to induce K\textsubscript{ATP} channel activity. The most likely explanation for this lack of activity was that the SU-sensitive potassium (K\textsuperscript{+}) currents may be mediated by a dimer of a K\textsuperscript{+} channel and the SUR, the latter functioning as a regulatory subunit.

This hypothesis was confirmed by Inagaki et al. (3) who identified and cloned Kir 6.2, a new member of the two-membrane-spanning domain, inwardly rectifying K\textsuperscript{+} channel family. In contrast to Kir 6.1, a previously identified isoform, Kir 6.2 is highly expressed in pancreatic islets and insulin-producing cell lines. Transfection of heterologous cells with either Kir 6.2 or the SUR failed to increase potassium efflux. However, coexpression of Kir 6.2 and the SUR reconstituted K\textsuperscript{+} channel activity which, on the one hand, was inhibited by ATP and glibenclamide and, on the other hand, was stimulated by diazoxide. Gene mapping showed that the two subunits genes are clustered on human chromosome 11, at position 11p15.1. These experiments provide decisive evidence that functional K\textsubscript{ATP} channels are a complex of (at least) two components, with Kir 6.2 as the actual ion permeation subunit and the SUR as a regulatory subunit.

So how does PHHI enter the picture? The occurrence of hyperinsulinemia in the face of severe hypoglycemia has long suggested that the disease results from a signaling defect in the pancreatic β-cell that causes continued, unregulated insulin secretion, for which K\textsubscript{ATP} channels are attractive candidates. This hypothesis was strengthened by the mapping of the gene defect in familial PHHI to position 11p15.1 on chromosome 11, the same position as the two subunits of the K\textsubscript{ATP} channel. Thomas et al. (4) have identified two different mutations in nine families with PHHI which result in disruption of the second NBF of the SU receptor. The homozygous mutations were found in all affected individuals, compatible with the recessive inheritance of the disease. The mRNA of the mutated gene appears to be unstable, which could account for decreased expression of the SU receptor protein and loss of K\textsubscript{ATP} channel activity.
Kane et al. (5) have recently reported electrophysiological studies on β-cells from five individuals with sporadic PHHI. The technical merit of performing patch-clamp studies on single β-cells obtained from pancreatectomy samples deserves to be emphasized. In cells from control individuals, whole-cell recordings performed at low glucose concentrations (2.5 mM) display only outward K+ current events. However, cells from affected patients display spontaneous voltage-regulated Ca2+-dependent action potentials. These action potentials are inhibited by the L-type calcium channel blocker, verapamil. Thus, the study demonstrates that a defect in KATP channel activity leads to membrane depolarization and the opening of voltage-gated calcium channels. As a consequence, calcium influx evokes sustained increases in cytosolic free calcium concentrations (measured with the fluorescent calcium indicator fura-2) and stimulation of insulin secretion. The mutations involved in these sporadic cases have not yet been identified. The familial PHHI mutations just described have been ruled out, suggesting that additional mutations in either SU receptors or Kir 6.2 remain to be discovered.

These studies provide compelling evidence that KATP channels are involved in the physiological regulation of insulin secretion. Further, they identify the molecular basis for the action of the sulfonylurea and diazoxide drugs. They also suggest that L-type calcium channel blockers such as verapamil or nifedipine could be useful in the treatment of PHHI. Finally, additional gain-of-function mutations either in the SU receptor or in Kir 6.2 may be involved in NIDDM. Inoue et al. (6) have reported two mutations in the SU receptor that are associated with NIDDM. Although these are silent mutations, they may be in linkage disequilibrium with other functional mutations in the SU receptor or a nearby related gene. More studies are needed to determine whether KATP channels contribute to the pathogenesis of NIDDM as well as PHHI.

References