

## EDITORIALS



## ATP-Sensitive Potassium Channels — Neonatal Diabetes Mellitus and Beyond

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The revolution in molecular biology has led to widespread appreciation of a principle first described by the British physician A.E. Garrod approximately 100 years ago — that “inborn errors of metabolism” teach us much about human biology in health and disease. Neonatal diabetes mellitus is a prime example of this principle.

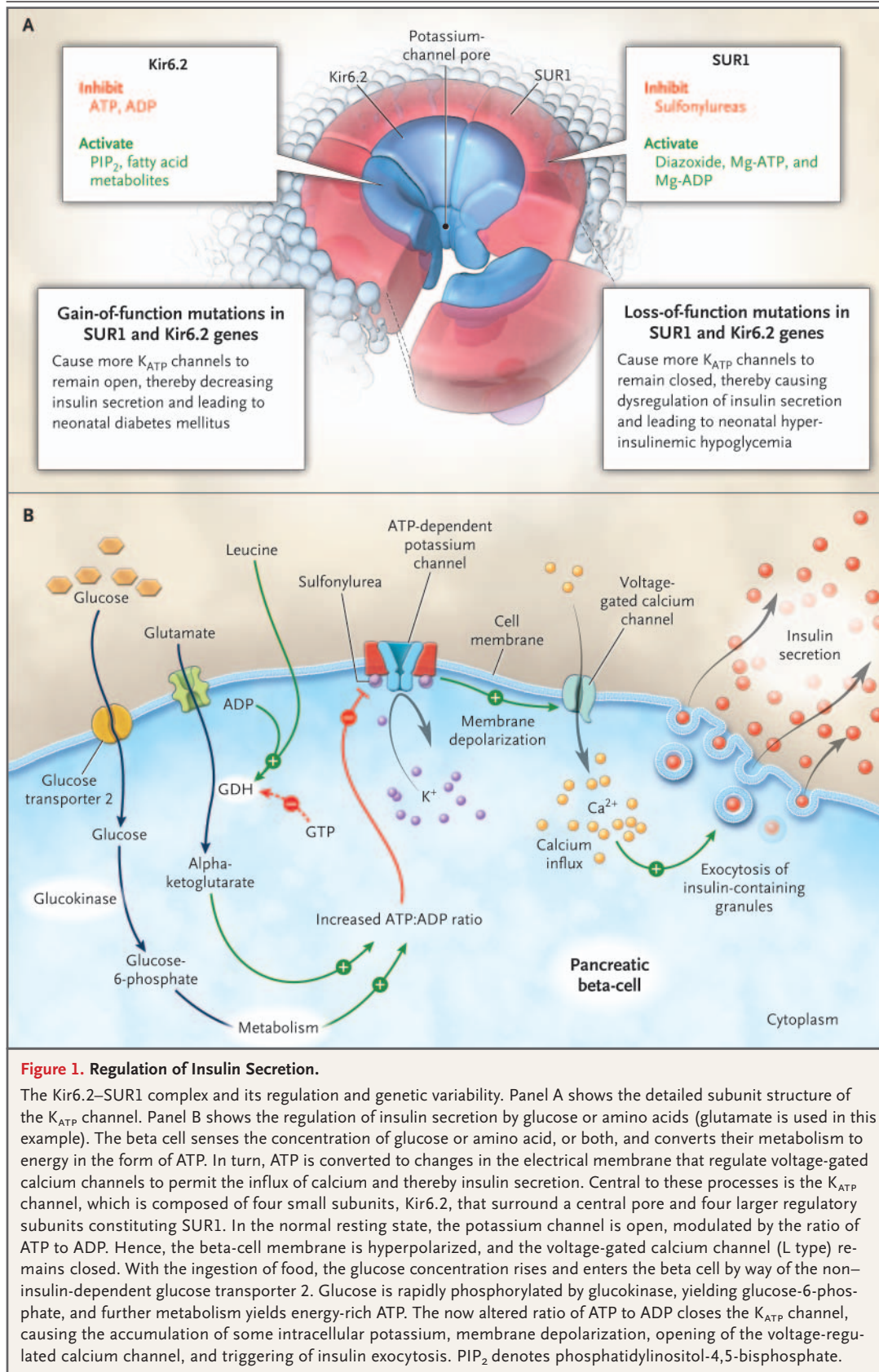
Neonatal diabetes mellitus is rare, with a reported incidence of 1 per 500,000 newborns and an estimated incidence of 1 per 100,000 newborns (Hattersley A: personal communication). Most newborns with neonatal diabetes mellitus are born with intrauterine growth restriction (IUGR). The degree of IUGR is proportional to the degree of insulin deficiency in utero; this confirms the important role of insulin as a growth factor during gestation. Clinical features of neonatal diabetes mellitus usually occur in the first three to six months of life, with glucosuria, polyuria, dehydration, failure to thrive, and frank diabetic ketoacidosis; serum levels of insulin and insulin-like growth factor I are low. Treatment with insulin results in dramatic catch-up growth; after several weeks or months, insulin may be discontinued in about half these patients, but diabetes mellitus may recur in the second to third decade of life. Most of these cases of transient neonatal diabetes mellitus are caused by a gain-of-function mutation in a zinc-finger gene. A transgenic mouse model created by insertion of the human locus reproduces most of the human features and should provide important clues to this condition.<sup>1,2</sup>

About half of patients with neonatal diabetes mellitus have permanent diabetes mellitus from the outset. For this form of neonatal diabetes, a variety of genetic causes have been identified.

They include homozygous inactivating mutations such as pancreas duodenum homeobox 1 (*PDX-1*), also known as insulin promoter factor 1, affecting proteins involved in pancreas formation, metabolic regulators such as the enzyme glucokinase, and transcription factors that regulate insulin secretion. Also implicated are genes involved in several congenital malformations.<sup>1</sup> *PDX-1* also contributes to classic type 2 diabetes mellitus in adults.<sup>1,3</sup>

The most common cause of permanent neonatal diabetes mellitus, however, is associated with activating mutations in the *KCNJ11* gene, which encodes Kir6.2 — a subunit of the ATP-sensitive potassium channel ( $K_{ATP}$ ) of the beta cell (Fig. 1). This observation was initially reported two years ago in the *Journal* by Gloyn et al.<sup>4</sup>; in this issue of the *Journal*, Pearson et al.<sup>5</sup> build on this finding. Another cause of permanent neonatal diabetes mellitus, as reported by Babenko and colleagues<sup>6</sup> in this issue of the *Journal*, is associated with activating mutations in *ABCC8*, which encodes the sulfonylurea receptor (SUR1) — the other subunit of the beta-cell  $K_{ATP}$  channel. The identification<sup>7,8</sup> of these molecules contributed to the development of a model of the regulation of insulin secretion by glucose and amino acids. In this scheme, chemical energy is transformed to electrical activity when the potassium channel is closed.  $K_{ATP}$  channels composed of Kir6.2 and SUR1 are widely expressed, regulating insulin secretion by beta cells, glucagon secretion by alpha cells, and glucagon-like peptide 1 (GLP1) secretion by intestinal L cells. They also modulate the counterregulatory response to hypoglycemia in the neurons of the ventromedial hypothalamus.<sup>9</sup>

Inactivating mutations of the SUR1 gene,



**Figure 1. Regulation of Insulin Secretion.**

The Kir6.2–SUR1 complex and its regulation and genetic variability. Panel A shows the detailed subunit structure of the K<sub>ATP</sub> channel. Panel B shows the regulation of insulin secretion by glucose or amino acids (glutamate is used in this example). The beta cell senses the concentration of glucose or amino acid, or both, and converts their metabolism to energy in the form of ATP. In turn, ATP is converted to changes in the electrical membrane that regulate voltage-gated calcium channels to permit the influx of calcium and thereby insulin secretion. Central to these processes is the K<sub>ATP</sub> channel, which is composed of four small subunits, Kir6.2, that surround a central pore and four larger regulatory subunits constituting SUR1. In the normal resting state, the potassium channel is open, modulated by the ratio of ATP to ADP. Hence, the beta-cell membrane is hyperpolarized, and the voltage-gated calcium channel (L type) remains closed. With the ingestion of food, the glucose concentration rises and enters the beta cell by way of the non-insulin-dependent glucose transporter 2. Glucose is rapidly phosphorylated by glucokinase, yielding glucose-6-phosphate, and further metabolism yields energy-rich ATP. The now altered ratio of ATP to ADP closes the K<sub>ATP</sub> channel, causing the accumulation of some intracellular potassium, membrane depolarization, opening of the voltage-regulated calcium channel, and triggering of insulin exocytosis. PIP<sub>2</sub> denotes phosphatidylinositol-4,5-bisphosphate.

which keep the channel constitutively closed and thereby cause dysregulated secretion of insulin, result in familial hyperinsulinemic hypoglycemia of infancy.<sup>9,10</sup> Most cases of this condition are caused by mutations in SUR1, and only a minority of cases result from inactivating mutations in the Kir6.2 gene.<sup>9,11</sup>

Whereas inactivating mutations cause hyperinsulemic hypoglycemia of infancy, it was reasoned that activating mutations in the  $K_{ATP}$  channel would cause permanent neonatal diabetes mellitus because keeping the channel open in the face of an increased ratio of ATP to ADP would prevent depolarization and thereby limit insulin secretion. The findings of Pearson et al. and of Babenko et al. show that this is the case, and they reveal a mirror image of the situation relative to hyperinsulinemic hypoglycemia of infancy; in neonatal diabetes mellitus, most of the disease-causing mutations so far observed affect Kir6.2, and a minority of mutations affect SUR1.<sup>4-6</sup> Severe developmental delay, epilepsy, and dysmorphic features associated with neonatal diabetes mellitus (known as the DEND syndrome) are present in some patients with permanent neonatal diabetes mellitus.<sup>4,5,9,12</sup> As revealed by in vitro assays, the severity of these and other clinical characteristics is directly related to the ATP sensitivity of the mutant channels: the greater the degree of insensitivity, the more severe the phenotype.<sup>4,5,9,12</sup> The response of patients with permanent neonatal diabetes mellitus and mutations affecting Kir6.2 to tolbutamide (a sulfonylurea that binds SUR1 and brings about closure of the  $K_{ATP}$  channel)<sup>4</sup> suggests that the treatment of some other patients with permanent neonatal diabetes mellitus might be successfully switched to oral sulfonylurea medication.

Pearson et al. report the successful switching of the treatment of 44 of 49 consecutive patients with permanent neonatal diabetes mellitus (90 percent) from subcutaneous insulin injections to oral glyburide. In vivo responses to this sulfonylurea were extended in subgroups to investigate insulin responses to intravenous and oral glucose, a mixed meal, and intravenous glucagon, before and after treatment with the drug. Remarkably, the use of glyburide restored insulin secretion, and the effect was much stronger when patients received oral glucose or a mixed meal than when they received intravenous glucose; a response to glucagon was observed only when the treatment

of patients was successfully switched to sulfonylurea. Metabolic control of diabetes, as reflected by glycated hemoglobin concentrations, markedly improved with the use of a sulfonylurea in all successfully treated patients, with values falling from 8.1 percent before treatment to 6.4 percent after 12 weeks of treatment. The extent to which tolbutamide was able to close mutant ATP channels (as determined by an in vitro assay) was proportionate to the patient's response. Hence, the authors propose that the pharmacogenetic response results from the closure of mutant  $K_{ATP}$  channels by the binding of sulfonylurea to the SUR1 regulatory subunit; this restores insulin secretion consequent to glucose metabolism with amplified effects through incretins such as GLP1, the levels of which increase after ingestion of nutrients.

This proposition is reasonable, although not all of the beneficial effects depend on the beta-cell response; as Pearson et al. note,  $K_{ATP}$  channels also modulate the GLP1 response in gastrointestinal L cells and glucagon secretion by alpha cells. Counterregulatory hormone responses to hypoglycemia mediated by  $K_{ATP}$  channels in the ventromedial hypothalamus before and after treatment with a sulfonylurea may be the subject of future investigations.

Babenko et al. report the successful switch from insulin injection to oral sulfonylurea therapy by five of nine patients with permanent neonatal diabetes mellitus caused by mutations in the SUR1 regulatory subunit of  $K_{ATP}$ . Four of these mutations, which were found in patients with familial diabetes mellitus, showed vertical transmission with neonatal and adult-onset diabetes.

The response of patients with permanent neonatal diabetes mellitus with mutant Kir6.2 or mutant SUR1 to sulfonylureas illustrates the power of genetics to identify patients who may benefit from a treatment. It is ironic that a drug initially developed to treat millions of patients affected by type 2 diabetes mellitus, generally considered a disease of middle to older age, should find its most physiologic application in newborns. Clearly, all newborns in whom clinical diabetes mellitus — transient or permanent — develops within six months after birth should be tested for mutations in the gene encoding Kir6.2 and, in the absence of a positive result, SUR1. (Because the *KCNJ11* gene, which encodes Kir6.2, has 1 exon and the *ABCC8* gene, which encodes

SUR1, has 39 exons, and because, as compared with mutant SUR1, mutant Kir6.2 is a more common cause of permanent neonatal diabetes, a sensible approach would be to analyze Kir6.2 first.) On a related note, since neonatal diabetes mellitus is a congenital disease with an incidence of approximately 1 per 100,000 newborns, has severe consequences if left untreated, and in many cases can be treated by a pill, a test for it should be included as part of routine newborn screening programs.

It is also intriguing to consider the role of these mutations in adults with diabetes mellitus. One mutation affecting Kir6.2 has been identified as a cause of transient neonatal diabetes mellitus, childhood diabetes, and the later onset of classic type 2 diabetes mellitus.<sup>1</sup> Mutations affecting Kir6.2 and SUR1 have been identified in familial forms of diabetes mellitus; milder mutations may contribute to the clinical appearance of type 2 diabetes mellitus when insulin resistance develops. Hence, genotyping of a large number of patients with type 2 diabetes mellitus may prove rewarding by determining the extent to which patients with Kir6.2 mutations or polymorphisms might benefit from sulfonylurea therapy.

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## Cardiac Resuscitation — When Is Enough Enough?

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Cardiac arrest is a leading cause of death in the United States.<sup>1</sup> In spite of periodic updates of the Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care of the American Heart Association (AHA) (hereafter referred to as the AHA guidelines), survival rates are dismal in the absence of early defibrillation and have remained essentially unchanged for decades.<sup>1,2</sup> In large cities in the United States, overall survival of out-of-hospital arrest of presumed cardiac cause is about 1 percent — approximately the rate that has been suggested to define medical futility.<sup>2,3</sup> The cost of providing emergency medical services (EMS) to persons with out-of-hospital arrest of presumed cardiac cause is considerable. Given these facts, the cost-benefit ratio might be questioned.

At one end of the spectrum of patients with out-of-hospital arrest of presumed cardiac cause are those in whom the arrest was not witnessed, those in whom the arrest was witnessed but no resuscitative efforts were made by a bystander, and those for whom the arrival of EMS personnel was late. This subgroup of patients have little chance of survival. If, in addition, a shock is not delivered or advised and there is no return of spontaneous circulation, almost none survive. Transportation of such patients to the emergency department consumes resources, puts the public (because of road hazards) and the providers at risk, increases costs, and may decrease the availability to other patients of the resources of the EMS system and the emergency department.<sup>4</sup>

It has therefore been acknowledged by expert