

## SULFONYLUREA RECEPTOR -1 (SUR1): GENETIC AND METABOLIC EVIDENCES FOR A ROLE IN THE SUSCEPTIBILITY TO TYPE 2 DIABETES MELLITUS

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**SUMMARY** - The pancreatic  $\beta$ -cell ATP-sensitive potassium channel ( $K_{ATP}$ ) is composed of two distinct subunits, an inwardly rectifying ion channel forming the pore (Kir6.2), and a regulatory subunit, namely the sulfonylurea receptor-1 (SUR1), which binds this widely used class of insulin-secreting drugs. Mutations in the genes encoding Kir6.2 and SUR1 may result in familial persistent hyperinsulinemic hypoglycaemia of infancy, demonstrating their role in the regulation of insulin secretion. Studies in various populations with different ethnic background provided evidence that various alleles of single nucleotide polymorphisms (SNPs) in the SUR1 gene, and to a less extent in the Kir6.2 gene, confer a significantly increased risk for the development of type 2 diabetes mellitus (T2DM). Allelic variations of these SNPs were shown to modulate insulin secretion and insulin sensitivity *in vivo*, thus providing a pathophysiological background to explain their contribution to the genetic susceptibility to T2DM. The aim of this review is to summarise and discuss the significant results of recent literature on the implication of  $K_{ATP}$ , and particularly of SUR1, in the genetic and pathophysiological mechanisms of T2DM.

**Key-words:** sulfonylurea receptor, insulin secretion, type 2 diabetes mellitus, genetics, ATP-sensitive potassium channel.

**RÉSUMÉ** - Récepteurs des sulfonurées -1 (SUR1) : données génétiques et métaboliques illustrant leur rôle dans la susceptibilité au diabète de type 2.

Les canaux potassiques dépendants de l'ATP des cellules  $\beta$ -pancréatiques ( $K_{ATP}$ ) sont composés de deux sous-unités. D'une part, un élément de la famille des canaux ioniques, Kir6.2, qui forme le pore. D'autre part, un élément régulateur, le récepteur des sulfamides de type 1 (SUR1) auquel se lient ces molécules insulinosécrétrices. Le rôle majeur de  $K_{ATP}$  dans la régulation de la sécrétion d'insuline a été mis en évidence par la découverte des mutations dans les gènes codant pour SUR1 ou Kir6.2 chez des individus atteints d'hypoglycémie hyperinsulinique persistante du nourrisson. Des études dans plusieurs populations suggèrent que SUR1 et Kir6.2, ou un locus proche dans le chromosome 11p15.1, jouent un rôle dans la susceptibilité au diabète de type 2 (DMT2), dans un contexte multifactoriel et polygénique. Des variations alléliques de ces gènes, fréquentes dans la population générale, semblent moduler des phénotypes intermédiaires associés au DMT2 (insulinosécrétion, sensibilité à l'insuline, obésité). Dans cette revue, nous résumons et discutons les résultats plus significatifs de la littérature sur l'implication de  $K_{ATP}$  et en particulier de SUR1, dans les mécanismes génétiques et physiopathologiques du DMT2.

**Mots-clés :** récepteurs des sulfonurées, insulino-sécrétion, diabète type 2, génétique, canaux potassiques ATP-sensibles.

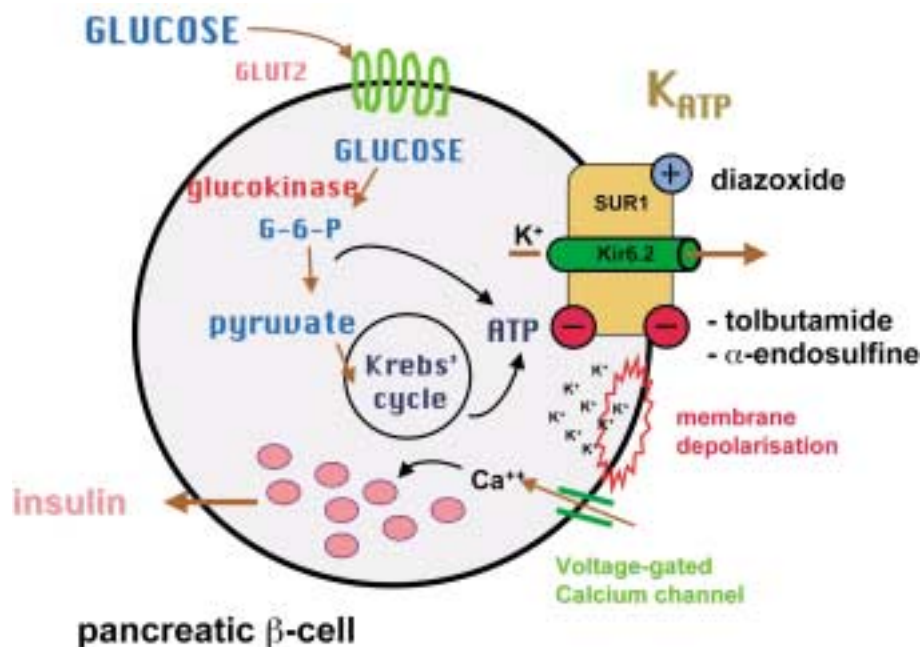


FIG. 1. Schematic representation of the role of  $K_{ATP}$  in the mechanisms of insulin secretion in response to glucose (steps 1 to 8) or sulfonylureas (steps 3 to 8) in pancreatic  $\beta$ -cells. 1) ATP generation by the glycolytic pathway and/or through the Krebs' cycle. 2) Increase in intracellular ATP/ADP ratio. 3) Closing of  $K_{ATP}$ . 4) Increase of cytoplasmic concentrations of  $K^+$ . 5) Depolarisation of the  $\beta$ -cell membrane. 6) Opening of voltage-gated  $Ca^{2+}$  channels. 7)  $Ca^{2+}$  influx and rise in cytoplasmic concentrations of  $Ca^{2+}$ . 8) Exocytosis of insulin-containing secretory granules.

The sulfonylureas promote insulin secretion by binding to a membrane receptor expressed in pancreatic  $\beta$ -cells, the sulfonylurea receptor type 1 (SUR1) [1, 2], a member of the ATP-binding cassette (ABC) superfamily. SUR1 is a functional subunit of the ATP-sensitive potassium channel ( $K_{ATP}$ ) of pancreatic  $\beta$ -cells.  $K_{ATP}$  has two distinct components, Kir6.2, an inwardly rectifying ion channel forming the pore, and SUR1, which is believed to be the regulatory subunit and ATP/ADP sensor. The genes encoding these two subunits are located 4.5 kb apart on the human chromosome 11p15.1 [1].

$K_{ATP}$  plays a key role in glucose-induced insulin secretion by linking signals derived from glucose metabolism to cell membrane depolarisation and insulin exocytosis (Fig. 1) [2]. Closure of  $K_{ATP}$  by glucose metabolism via ATP production or by sulfonylurea action increases cytoplasmic concentrations of  $K^+$  and causes depolarisation of the  $\beta$ -cell membrane. These events lead to the opening of voltage-gated  $Ca^{2+}$  channels,  $Ca^{2+}$  influx and a rise in cytoplasmic concentrations of  $Ca^{2+}$ , which in turn stimulates the exocytosis of insulin-containing secretory granules. An endogenous regulator of  $K_{ATP}$  function,  $\alpha$ -endosulfine, was recently identified [3, 4]. This peptide is encoded by the ENSA gene and is expressed in the pancreas, muscle and brain. It inhibits the binding of sulfonylureas to  $K_{ATP}$ , leads to the closing of these channels,

and enhances insulin release *in vitro* [3, 4]. These observations suggest that  $\alpha$ -endosulfine may act as an endogenous regulator of  $K_{ATP}$ , although its physiologic role remains unclear.

## ■ MOLECULAR PATHOLOGY OF $K_{ATP}$

The implication of  $K_{ATP}$  in the regulation of insulin secretion was well established in studies of patients with familial persistent hyperinsulinemic hypoglycaemia of infancy (PHHI). The loss of  $K_{ATP}$  activity in the pancreatic  $\beta$ -cells of children with PHHI, caused by functional mutations of SUR1 or Kir6.2, leads to uncontrolled oversecretion of insulin despite severe hypoglycaemia [5, 6]. In the light of these observations, SUR1 and Kir6.2 became potential candidate genes for insulin secretion defects and susceptibility to type 2 diabetes mellitus (T2DM), and were thoroughly investigated. Associations of T2DM with single nucleotide polymorphisms (SNPs) of the SUR1 gene, and particularly with those in intron 15 splice acceptor site (IVS15-3c  $\rightarrow$  t; cagGCC  $\rightarrow$  tagGCC), exon 18 (ACC  $\rightarrow$  ACT; Thr759Thr) and exon 31 (AGG  $\rightarrow$  AGA; Arg1273Arg), were observed in several populations. However, these results were not straightforward, as different SNPs or even different alleles of a given SNP were associated with T2DM in

different populations. We will summarise next the most relevant results of these studies.

An association of diabetes with the SNPs in intron 15 (cagGCC allele) and exon 18 was reported for a combined Utah and UK cohort [7], and associations with the intron 15 (tagGCC allele) but not with the exon 18 SNP were reported for Dutch [8] and Finnish [9] cohorts. An association with the exon 18 SNP, and a stronger association with combined intron 15 (tagGCC allele) and exon 18 genotypes were observed in Danish subjects [10], but no association was noted when only the intron 15 SNP was considered. Similarly, no association with the intron 15 SNP but an association with the exon 18 SNP was observed in a cohort of French Caucasian subjects selected for a strong family history of diabetes [11]. However, in another French cohort, an association with the intron 15 SNP (cagGCC allele) was observed [12]. Moreover, we have found an association with the A-allele of the exon 31 SNP but not with intron 15 or exon 18 SNPs in third different cohort of French Caucasian subjects, collected regardless a family history of diabetes [13]. Interestingly, an association of the G-allele of the exon 31 SNP with diabetes was reported in Finnish subjects with gestational diabetes or type 2 diabetes [9].

So, what are these results telling us about the role of SUR1 locus on the genetic susceptibility to T2DM? First of all, we should point out that studies of families and sibs with T2DM clearly suggest that SUR1 is not a major diabetogenic locus [11, 14, 15]. However, the association studies summarised above, performed in cohorts from several populations provide evidence that the SUR1 locus confers a mild but significantly increased risk for developing T2DM. For instance, in French Caucasians the odds ratio for T2DM conferred by the A-allele of the exon 31 SNP was comprised between 1.5 and 2 [13].

The genetic mechanism behind the associations of these silent or intronic SNPs with diabetes, and for that matter with other phenotypes (see below), remains unexplained. Linkage disequilibrium with a functional mutation located elsewhere in the coding regions, exon-intron boundaries or in the promoter of the SUR1 gene is a possible explanation. The variable allelic distribution of the three SNPs in diabetic and nondiabetic subjects in different Caucasian populations suggests that different risk alleles for diabetes may exist. This may be related to variable degrees of linkage disequilibrium of the SNPs with the putative functional variant. It is noteworthy that the SNP of intron 15 splice acceptor site, that could be considered potentially as a functional variant, is not in linkage disequilibrium with the other SNPs associated with diabetes [11, 13]. The entire coding region and the intron-exon boundaries of the SUR1 gene were scanned for mutations in Danish [10] and in Japanese [16] subjects. Several amino acid substitutions were

observed, but none of the variants were associated with T2DM. Several variants were also observed in the promoter region of SUR1 in British [17] and Danish [18] subjects, but no evidence for an association with T2DM was detected.

Alternatively, mutations in a nearby locus on chromosome 11p15.1 could be responsible for the associations described. One obvious candidate is the Kir6.2 gene, located 4.5 kb downstream the SUR1 gene. A glutamic acid-to-lysine substitution at codon 23 (GAG → AAG; Glu23Lys) was found to be associated with T2DM in British, Danish and French Caucasians [19], and this association has been confirmed in the UKPDS cohort [17]. Could this observation explain the results observed with the SUR1 variants? Probably not, as no linkage disequilibrium was observed between this variant and the SNPs in intron 15 and exon 18 of the SUR1 gene [19]. Moreover, the Glu23Lys variant was not associated with changes in  $K_{ATP}$  function during *in vitro* studies [20], which suggests that it is not a functional variant. As for the promoter region of Kir6.2, no variants were found in one British study [17].

## ■ SUR1 VARIANTS AND INSULIN SECRETION

The impact of the three SUR1 variants on the mechanisms of hyperglycaemia was assessed in a few *in vivo* studies of insulin secretion and insulin sensitivity in carriers of the different genotypes [9, 10, 21-24]. These studies used different methods for the assessment of  $\beta$ -cell function and yielded contrasting results (Table I). However, in most of these investigations a decrease in the insulin response to glucose or to tolbutamide was observed in carriers of at-risk alleles or of a combination of at-risk alleles at these SNPs.

It is noteworthy that insulin sensitivity, when tested in these investigations, was comparable in carriers of the different SUR1 genotypes. However, one study of insulin sensitivity by the minimal model as a function of Kir6.2 genotypes in Danish subjects yielded unexpected results. Carriers of a combined genotype for three SNPs (Lys-homozygous at Glu23Lys, Val-homozygous at Ile337Val and Leu270Val heterozygous) presented increased insulin sensitivity (62%) as compared to non-carriers [25]. In that study, insulin secretion in response to intravenous injections of glucose or tolbutamide was similar in carriers of different genotypes. Interestingly, increased insulin sensitivity was also observed in Kir6.2 knockout mice [26].

TABLE I. *Insulin secretion and SUR1 genotypes.*

Reference	Population	Methods	SNP <sup>a</sup>	Insulin Secretion
t Hart <i>et al.</i> [21]	Dutch subjects with NGT or IGT	Hyperglycemic clamp	15	25 % reduction in second phase insulin secretion in tt or tc carriers.
			18	Similar profiles between genotypes.
			15/18 <sup>b</sup>	Similar profiles between genotypes.
Elbein <i>et al.</i> [22]	American subjects with NGT or IGT having at least two siblings with T2DM	tolbutamide-modified IVGTT	15	Reduced insulin secretion in response to glucose or tolbutamide and reduction in beta-cell compensation to decreased insulin sensitivity in tt carriers.
			18	Similar profiles between genotypes.
Hansen <i>et al.</i> [10]	Danish subjects with NGT	tolbutamide-modified IVGTT	15	Similar responses to glucose or tolbutamide between genotypes.
			18	Similar responses to glucose or tolbutamide between genotypes.
			15/18 <sup>b</sup>	50 % reduction in response to tolbutamide in tt/CT or tc/CT carriers, but similar responses to glucose.
Weisnagel <i>et al.</i> [23]	French-Canadian subjects with NGT	OGTT	18	13 % reduction in C-peptide levels in CT carriers.
			15/18 <sup>b</sup>	20 % reduction in C-peptide levels in tt/CT or tc/CT carriers.
Reis <i>et al.</i> (unpublished data)	French subjects with NGT having first-degree relatives with T2DM who carry the at-risk T-allele	Graded infusions of glucose	18	19 % reduction of insulin secretion rates in CT carriers.
Goskel <i>et al.</i> [24]	Mexican-American subjects with NGT	OGTT	31	Fasting hyperinsulinemia and 70 % increase in 2 h insulin levels in AA carriers.
Rissanen <i>et al.</i> [9]	Finish subjects with NGT	OGTT and IVGTT	15	Similar profiles between genotypes.
			18	Similar profiles between genotypes.
			31	Similar profiles between genotypes.

NGT and IGT stand for normal or impaired glucose tolerance, respectively.

<sup>a</sup>intron 15 splice acceptor site (IVS15-3c → t; cagGCC → tagGCC), exon 18 (ACC → ACT; Thr759Thr) and exon 31 (AGG → AGA; Arg1273Arg).

tt, tc and cc stand for homozygous tagGCC, heterozygous tagGCC-cagGCC and homozygous cagGCC alleles of intron 15 SNP, respectively.

<sup>b</sup>combined at-risk genotypes of intron 15 and exon 18 SNPs.

## ■ SUR1 VARIANTS AND OTHER PHENOTYPES

Associations of SUR1 variants with other phenotypes have been reported in a few studies. Homozygosity for the tagGCC allele of the exon 16 SNP was found to be associated with a more severe form of obesity in a group of French Caucasians subjects with morbid obesity [11]. In that study, this association was

stronger for subjects who were both morbidly obese and hyperglycaemic. We have observed an association of the homozygosity for the G-allele of exon 31 SNP with arterial hypertension in obese diabetic subjects [13]. This association was independent from sex, age and BMI. It is noteworthy that an association of the cagGCC allele of exon 16 SNP with blood pressure and with arterial hypertension has also been reported in Dutch subjects with impaired glucose tolerance

[27]. In that study, as in ours, the allele found to be associated with increased prevalence of arterial hypertension was not the same one found to be associated with hyperglycaemia.

An association of intron 15 SNP with the efficiency of sulfonylurea therapy to decrease diabetes-related hypertriglyceridemia was recently reported in French subjects with T2DM [12]. Homozygous or heterozygous carriers of the cagGCC allele treated with sulfonylureas had fasting plasma triglyceride levels 35% lower than those of homozygous carriers of the tagGCC allele, whereas no differences could be detected between genotypes for subjects treated otherwise. In contrast, in the UKPDS cohort, the intron 15 and exon 18 variants of SUR1, as well as the Glu23Lys variant of Kir6.2, were not associated with any particular clinical characteristics nor did they affect response to sulfonylurea therapy [17].

## ■ LESSONS OF SUR-1 KNOCKOUT MICE

Knockout animals are useful tools for understanding the physiological repercussions of the loss of function of the knocked-out gene. Mice with homozygous deletion of the SUR1 gene (*Sur1*<sup>-/-</sup>) were recently studied [28]. They were viable and fertile, but presented abnormal profiles of insulin secretion. At birth, *Sur1*<sup>-/-</sup> pups were hypoglycaemic, with the insulin/glucose ratio abnormally increased. However, they became hyperglycaemic in the fifth day of life, with the insulin/glucose ratio reduced by half as compared with values in control animals. Adult *Sur1*<sup>-/-</sup> animals were hypoglycaemic after a prolonged fast (16 hours) as compared with controls. On the other hand, they presented impaired glucose tolerance following intraperitoneal glucose load. Insulin secretion was decreased in *Sur1*<sup>-/-</sup> mice throughout an 8-hour glucose infusion. However, at the end of the glucose stimulation, they presented marked residual hyperinsulinemia, which decreased more slowly than in control animals. Insulin sensitivity was normal in *Sur1*<sup>-/-</sup> mice. Islands of Langerhans isolated from *Sur1*<sup>-/-</sup> mice were histologically normal, with a rate of apoptosis that was similar to that of controls. Upon stimulation by perfused glucose, they presented an abolition of the first phase insulin secretion followed by a decreased second phase as compared to control islands. Following the end of glucose perfusion, residual secretion of insulin was higher than in control islands. Insulin secretion in response to tolbutamide was abolished.

Transgenic mice expressing a dominant-negative form of Kir6.2 in pancreatic  $\beta$ -cells were also generated [29]. Neonates developed hypoglycaemia with hyperinsulinemia, but this clinical picture evolved in adult animals to that of hyperglycaemia with hypoinsulinemia, associated with a decrease in  $\beta$ -cell mass. A

high frequency of apoptotic  $\beta$ -cells was observed in these animals before the appearance of hyperglycaemia. In another study, *Kir6.2*<sup>(-/-)</sup> knock-out mice were generated [26]. No significant insulin secretion in response to either glucose or tolbutamide was observed in isolated pancreatic islets of these animals. However, *Kir6.2*<sup>(-/-)</sup> animals showed only a mild impairment in glucose tolerance as the defect in glucose-induced insulin secretion was largely compensated by increased insulin sensitivity.

Taken together, these results underline the role of  $K_{ATP}$  in the physiological mechanisms of insulin secretion. They allow reconciling the data regarding SUR1 and Kir6.2 roles in PHHI and hyperglycaemia in man, and strengthen the hypothesis of an implication of the SUR1/Kir6.2 locus in the pathophysiology of T2DM.

## ■ CONCLUSIONS

The central role of  $K_{ATP}$  in glucose-induced insulin secretion is now well recognised. Mutations in the two functional sub-units of  $K_{ATP}$ , SUR1 and Kir6.2, are responsible for most cases of PHHI. On the other hand, it seems certain that the genes coding for SUR1 and Kir6.2 are not major susceptibility determinants for T2DM. Nevertheless, the allelic variations of these genes frequently found in the general population could modulate intermediate phenotypes such as insulin secretion, insulin sensitivity, or obesity, and contribute to the genetic susceptibility to T2DM in a multifactorial and polygenic context. T2DM, obesity and arterial hypertension are frequently associated and share metabolic abnormalities. Studies in large populations with detailed phenotypes regarding the intermediate traits associated with these conditions are now required to properly investigate their interactions with SUR1 and Kir6.2 variants. Additional efforts are also needed to understand the genetic basis of the associations of SUR1 and Kir6.2 loci with these phenotypes. The identification of the functional variants responsible for these associations would permit pharmacogenetic characterisations of patients, and possibly, a better targeting of sulfonylurea treatment. The identification of  $K_{ATP}$  endogenous ligands and the understanding of their physiology could open new therapeutic perspectives for T2DM, leading to the development of novel compounds to modulate insulin secretion. In the immediate meantime, it is clear that the ENSA gene coding for  $\alpha$ -endosulfine is an interesting candidate for PHHI, T2DM and also for obesity.

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