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REVIEW ARTICLE

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Current status of the E23K Kir6.2 polymorphism: implications for type-2 diabetes

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Abstract The ATP-sensitive potassium (K_{ATP}) channel couples membrane excitability to cellular metabolism and is a critical mediator in the process of glucose-stimulated insulin secretion. Increasing numbers of K_{ATP} channel polymorphisms are being described and linked to altered insulin secretion indicating that genes encoding this ion channel could be susceptibility markers for type-2 diabetes. Genetic variation of K_{ATP} channels may result in altered β-cell electrical activity, glucose homeostasis, and increased susceptibility to type-2 diabetes. Of particular interest is the Kir6.2 E23K polymorphism, which is linked to increased susceptibility to type-2 diabetes in Caucasian populations and may also be associated with weight gain and obesity, both of which are major diabetes risk factors. This association highlights the potential contribution of both genetic and environmental factors to the development and progression of type-2 diabetes. In addition, the common occurrence of the E23K polymorphism in Caucasian populations may have conferred an evolutionary advantage to our ancestors. This review will summarize the current status of the association of K_{ATP} channel polymorphisms with type-2 diabetes, focusing on the possible mechanisms by which these polymorphisms alter glucose homeostasis and offering insights into possible evolutionary pressures that may have contributed to the high prevalence of K_{ATP} channel polymorphisms in the Caucasian population.

Keywords K_{ATP} channel · Type-2 diabetes · Glucose homeostasis · E23K polymorphism · Evolution · Caucasian population

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Introduction

The prevalence of type-2 diabetes is reaching epidemic proportions throughout the world. In excess of 170 million individuals are currently affected worldwide, with that number projected to double by 2030 (Wild et al. 2004). In addition to environmental and lifestyle factors, a significant, albeit poorly characterized, genetic component is associated with common type-2 diabetes and probably involves multiple genes and polymorphisms spread throughout the genome (Beck-Nielsen et al. 2003; Elbein 2002; Kopp 2003; McCarthy 2003). Despite significant contributions from twin studies highlighting the importance of genetics in the development of type-2 diabetes (Barnett et al. 1981; Newman et al. 1987), relatively few genes have been identified as *bona fide* susceptibility markers (Gloyn 2003). The identification of these genes is confounded by environmental factors such as diet, obesity, and a sedentary lifestyle, which may also increase susceptibility (Charles et al. 1997; Hill and Peters 1998; Sobngwi et al. 2003).

An improved understanding of the regulation of insulin secretion from the pancreatic β-cell has resulted in the proposal of candidate genes that encode dysfunctional proteins such as glucokinase, hepatic nuclear factors-1α and 4α, and insulin promoting factor-1 as contributors to the more rare monogenic maturity-onset diabetes of the young (Gloyn 2003). However, the identification of genetic mutations and/or polymorphisms contributing to the development of common type-2 diabetes has proved to be elusive, and those discovered thus far have not been fully characterized. Until

recently, the Pro12Ala polymorphism in the peroxisome proliferator-activated receptor (PPARγ; Rangwala and Lazar 2004) was the only polymorphism demonstrated to alter type-2 diabetes susceptibility in a significant percentage of the general population (Altshuler et al. 2000).

Recent studies suggest that the KCNJ11 gene, which encodes the Kir6.2 subunit of the ATP-sensitive potassium (K_{ATP}) channel, may also be a candidate diabetogenic gene. K_{ATP} channels are ubiquitously expressed throughout the body and are critical mediators of glucose homeostasis, including the proper glucose-stimulated insulin secretion (GSIS) from pancreatic β-cells. The E23K K_{ATP} channel polymorphism has received much attention recently as it is found at a higher frequency in the Caucasian type-2 diabetic population. Indeed, E23K is second only to the Pro12Ala mutation in the PPARγ protein in altering the relative risk for type-2 diabetes (Altshuler et al. 2000; Love-Gregory et al. 2003). Furthermore, a potential association of these Kir6.2 polymorphisms with obesity (Nielsen et al. 2003) suggests a role for free fatty acids (FFA) or their metabolites in altering K_{ATP} channel activity and perhaps β-cell function. Recent studies have addressed this issue by examining the functional effects of these Kir6.2 polymorphisms on the K_{ATP} channel. The purpose of this review is (1) to discuss the recent developments in the study of these polymorphisms, (2) to offer insights into the possible mechanisms that may underlie increased susceptibility to type-2 diabetes, and (3) to consider evolutionary pressures that may have selected for the high prevalence of these polymorphisms in the Caucasian population.

Nutrient-stimulated insulin secretion

K_{ATP} channel-dependent secretion

Insulin is secreted from pancreatic β-cells in response to nutrients such as glucose, fatty acids, and certain amino acids. Glucose serves as the primary stimulus. As post-prandial plasma glucose levels rise, increased glucose metabolism in the β-cell mitochondria leads to ATP formation at the expense of ADP. The increase in the cytosolic ATP-to-ADP ratio results in closure of the K_{ATP} channels and membrane depolarization via a reduced K^+ efflux. Subsequent activation of voltage-gated calcium channels is followed by transient increases in intracellular Ca^{2+}, which then triggers the exocytosis of insulin-containing granules (Ashcroft and Rorsman 1989; Fig. 1). Although other ion channels such as voltage-gated and calcium-activated potassium channels are involved in repolarizing the membrane potential, K_{ATP} channels serve to transduce the glucose-mediated metabolic signal into alterations in electrical activity that initiate and maintain insulin secretion.

Fat metabolism and K_{ATP} channels

In addition to glucose, acute FFA exposure results in increased insulin secretion via several proposed pathways. New evidence suggests the existence of a cell surface G-protein coupled receptor, GPR40, which may amplify GSIS when bound by fatty acids through direct

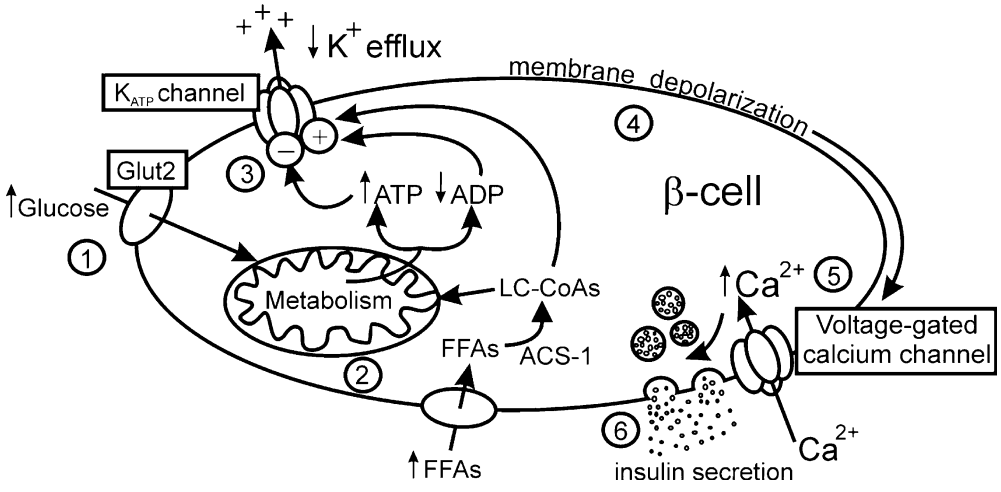

Fig. 1 K_{ATP} channel-dependent mechanism of glucose-stimulated insulin secretion (*Glut2* glucose transporter isoform 2, *FFAs* free fatty acids, *ACS-1* acyl-CoA synthetase, *LC-CoAs* long-chain acyl CoA esters, *ATP* adenosine triphosphate, *ADP* adenosine diphosphate). Glucose is transported into the pancreatic β-cell via the Glut2 transporter (*1*). Glucose oxidation in the mitochondria (*2*) leads to an increase in the cytosolic ATP-to-ADP ratio, which inhibits the activity of K_{ATP} channels (*3*). The reduction in K^+ efflux (*4*) causes membrane depolarization and activation of voltage-gated (L-type) calcium channels (*5*). Transient increases in cytosolic Ca^{2+} concentrations trigger the release of insulin-containing granules (*6*). ATP production can also arise via the esterification of FFAs by ACS-1 and subsequent β-oxidation of LC-CoAs within the mitochondria. Additional ion channels are also involved in the repolarization of the membrane potential and cessation of insulin release.

modulation of intracellular Ca^{2+} levels (Briscoe et al. 2003; Itoh et al. 2003). In addition, FFAs can diffuse or be actively transported across the plasma membrane and be converted to acyl-coenzyme A esters by acyl-CoA synthetase-1 (Corkey et al. 2000). Metabolism of these long-chain acyl-CoA esters (LC-CoAs) in the mitochondria leads to the formation of ATP and subsequent closure of the K_{ATP} channel (Fig. 1). LC-CoAs with a carbon chain length greater than 12 can also directly activate K_{ATP} channels (Branstrom et al. 1997, 1998; Gribble et al. 1998; Larsson et al. 1996). In both obese individuals and those with type-2 diabetes, circulating FFA and cytosolic acyl-CoA levels are increased (Golay et al. 1986; Reaven et al. 1988). This suggests that the accumulation of LC-CoAs in β-cells and their direct effects on K_{ATP} channel activity contribute to decreased GSIS and the development of type-2 diabetes.

Molecular aspects of the K_{ATP} channel

K_{ATP} channels of differing isoforms are expressed in a wide variety of tissues including pancreatic β- and α-cells (Ashcroft 2000; Bokvist et al. 1999). The distinctive properties of the K_{ATP} channel, as defined by its molecular composition, allow for the regulation of potassium ion efflux by intracellular metabolites such as nucleotides and LC-CoAs. This creates a unique mechanism by which cellular metabolism can be coupled to alterations in electrical activity. The pancreatic K_{ATP} channel is a hetero-octomeric complex (Aguilar-Bryan et al. 1998; Clement et al. 1997; Shyng and Nichols 1997) comprised of four inward-rectifier K^+ channel subunits (Kir6.2; Inagaki et al. 1995; Sakura et al. 1995) coupled to four high-affinity sulfonylurea receptor subunits (Aguilar-Bryan et al. 1995; Fig. 2). Kir6.2 is composed of two transmembrane domains and a pore loop that forms the central K^+-conducting pore region of the channel. Both the short N-terminus and longer C-terminus are located on the cytosolic side of the membrane (Fig. 2).

The regulatory SUR subunit bestows rich pharmacological properties upon the K_{ATP} channel complex and contains the binding domains for anti-diabetic sulfonylurea drugs, such as glibenclamide and glipizide, and for the K_{ATP} channel-opener diazoxide, which is used in the treatment of some forms of persistent hyperinsulinemic hypoglycemia of infancy (Babenko et al. 2000; Huopio et al. 2002; Matsuoka et al. 2000; Uhde et al. 1999). The three SUR subunits so far identified are termed SUR1, SUR2A, and SUR2B. In recombinant systems, the co-expression of SUR1 with Kir6.2 forms channels with properties identical to those channels found in pancreatic β-cells (Inagaki et al. 1995), α-cells (Bokvist et al. 1999), glycolipoprotein-1 (GLP-1)-secreting L-cells (Reimann and Gribble 2002), and certain neurons in the brain (Karschin et al. 1998; Zawar et al. 1999). K_{ATP} channels incorporating the SUR2A subunit are found in the sarcolemmal membrane of the heart and in skeletal muscle, whereas those incorporating SUR2B are found in vascular smooth muscle (for a review, see Seino 2003).

Both Kir6.2 and SUR1 contribute to the nucleotide sensitivity of the β-cell K_{ATP} channel. The Kir6.2 subunit confers ATP sensitivity to the channel complex (Aguilar-Bryan and Bryan 1999; Tucker et al. 1997), whereas Mg-ADP interacts with the second nucleotide-binding fold (NBF-2) on SUR1, antagonizing ATP-mediated channel closure (Gribble et al. 1997; Nichols et al. 1996; Shyng et al. 1997). Anionic lipid mediators such as LC-CoAs and PIP_2 can further increase K_{ATP} channel activity through interaction with the Kir6.2 subunit (Branstrom et al. 1997; Larsson et al. 1996; Manning Fox et al. 2004; Schulze et al. 2003a; Shyng and Nichols 1998).

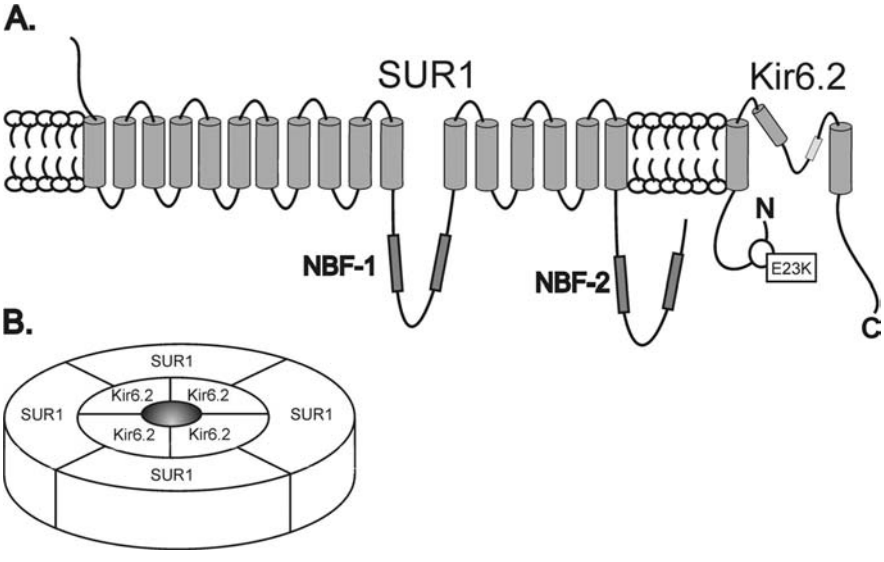

Fig. 2 **a** Schematic representation of K_{ATP} channel subunits SUR1 and Kir6.2. The relative position of the Kir6.2 E23K polymorphism in the proximal N-terminus is highlighted. **b** The K_{ATP} channel is a hetero-octomeric complex comprised of four Kir6.2 subunits that together form the K^+-specific pore, surrounded by four SUR1 subunits

Genetic variations in K_{ATP} channels

SUR1 subunit

Although several variants in the gene encoding the SUR1 subunit (ABCC8 gene) have been associated with type-2 diabetes, no changes in K_{ATP} channel function or GSIS have been observed in individuals with polymorphisms in either the coding region of SUR1 or its promoter sequence (Gloyn et al. 2001; Hani et al. 1997; Hansen et al. 2001; Hart et al. 1999). New evidence suggests polymorphisms in SUR1 that are associated with type-2 diabetes may indeed be in linkage disequilibrium with polymorphisms in the adjacent KCNJ11 gene, which encodes the Kir6.2 subunit of the K_{ATP} channel (Barroso et al. 2003; Florez et al. 2004). To date, no functional significance of these SUR1 polymorphisms has been demonstrated.

Kir6.2 subunit

The Kir6.2 subunit forms both the pore region, which conducts potassium ions, and the ATP sensor. Therefore, mutations that decrease the ability of the channel to respond to ATP may cause reduced insulin secretion and increased susceptibility to type-2 diabetes. Increasing numbers of mutations within the Kir6.2 subunit have been associated with alterations in glucose homeostasis. Intensive research has been focused on three particular single nucleotide polymorphisms (E23K, L270V, and I337V) found in several Caucasian populations (Hani et al. 1998; Hansen et al. 1997; Inoue et al. 1997; Sakura et al. 1996). Although L270V and I337V are found at a similar frequency in both healthy and type-2 diabetic individuals, the E23K polymorphism appears at higher frequency in type-2 diabetic populations. The E23K and I337V polymorphisms are highly linked with reported concordance rates between 72% and 100% (Hani et al. 1998; Hansen et al. 1997; Sakura et al. 1996) depending on the population studied. In addition, a recently published study indicates that six Kir6.2 single nucleotide polymorphisms (SNP), including the activating R201H mutation, contribute to permanent neonatal diabetes (Gloyn et al. 2004).

E23K polymorphism

E23K is a missense SNP (gag → aag) located in the cytosolic proximal (5′) N-terminal tail of the Kir6.2 subunit (Fig. 2) and results in the substitution of a highly conserved glutamate (E) residue with lysine (K) and a subsequent negative-to-positive shift in residue charge. Although E23K is linked (>72%) with I337V (atc → gtc; no charge change), no discernable functional relevance of the I337V polymorphism has been determined to date (Schwanstecher et al. 2002a, 2002b). However, the high concordance between E23K and I337V suggests that these polymorphisms may have originated in a common ancestor, further indicating a possible evolutionary advantage to their maintenance in the general population.

Initial studies with small cohorts of 150–350 subjects failed to detect an association between E23K and type-2 diabetes ('t Hart et al. 2002; Hansen et al. 1997; Inoue et al. 1997; Sakura et al. 1996; Tschritter et al. 2002; Yamada et al. 2001). More recent examinations of the allelic or genotypic frequencies of the E23K polymorphism have employed larger study populations. The genotypic frequencies for previous case-control studies (including the UK Prospective Diabetes Study, and studies of French, Utah, and Danish Caucasian populations) have recently been summarized by Nielsen and co-workers (2003) yielding an average genotypic frequency of 18% K/K for type-2 diabetic individuals versus 10.5% K/K in the control glucose-tolerant subject cohort (Table 1). This work is supported by two additional large-scale studies that have independently confirmed the E23K association with type-2 diabetes (Florez et al. 2004; Gloyn et al. 2003), yielding odds ratios between 1.15 and 1.65 and further highlighting the

Table 1 Genotype frequencies of the Kir6.2 E23K polymorphism in all population studies performed to date. Data are fractions of each group with the indicated genotype; the numbers of subjects in each group are given in *parentheses*

Reference	Percentage glucose-tolerant cohort (*n*)			Percentage type-2 diabetic cohort (*n*)		
	E/E	E/K	K/K	E/E	E/K	K/K
Sakura et al. (1996)	0.54 (44)	0.33 (27)	0.13 (11)	0.38 (38)	0.45 (45)	0.17 (17)
Inoue et al. (1997)	0.36 (59)	0.59 (96)	0.05 (9)	0.43 (124)	0.46 (133)	0.12 (34)
Hani et al. (1998)	0.40 (45)	0.46 (53)	0.14 (16)	0.28 (53)	0.45 (87)	0.27 (51)
Gloyn et al. (2001)	0.41 (125)	0.50 (152)	0.09 (30)	0.37 (133)	0.45 (161)	0.18 (66)
't' Hart et al. (2002)	0.40 (26)	0.49 (32)	0.11 (7)	0.36 (34)	0.53 (50)	0.11 (10)
Gloyn et al. (2003)	0.42 (491)	0.45 (534)	0.13 (157)	0.36 (308)	0.48 (412)	0.16 (134)
Nielsen et al. (2003)	0.39 (330)	0.47 (408)	0.14 (124)	0.36 (287)	0.47 (382)	0.17 (134)
Average (total *n*)	0.42 (1120)	0.47 (1302)	0.11 (354)	0.36 (977)	0.47 (1270)	0.17 (446)
Hani et al. (1998)[a]	0.436 (160)	0.452 (166)	0.112 (41)	0.353 (184)	0.453 (236)	0.194 (101)
Nielsen et al. (2003)[b]	0.378 (521)	0.518 (657)	0.105 (173)	0.363 (525)	0.458 (685)	0.18 (263)

[a]Recently performed meta-analysis
[b]Averaged data from individual population studies by Nielsen et al. (2003), Gloyn et al. (2001), Hani et al. (1997), and Inoue et al. (1997)

importance of statistical power in genetic association studies.

Functional consequences of Kir6.2 polymorphisms

In Vivo studies

The underlying mechanistic alterations of K_{ATP} channel function caused by the E23K polymorphism have to be characterized, including the effects of heterozygous and homozygous variants, in order to determine the impact of this polymorphism on the development of type-2 diabetes. Studies involving human subjects have been performed by a number of groups with the common goal of demonstrating altered insulin secretion in patients with the polymorphism. The initial study by Hansen et al. (1997) showed no significant difference in first-phase insulin or C-peptide release in response to an intravenous glucose injection, nor any difference in tolbutamide-stimulated insulin secretion between individuals carrying the E23K/I337V double polymorphism and those with wild-type K_{ATP} channels. However, a subsequent study revealed a slight decrease in insulin secretion during a 3-h hyperglycemic clamp ('t Hart et al. 2002). This difference did not reach statistical significance, a problem that may have been resolved with a larger study cohort. The polygenic and multifactorial nature of type-2 diabetes and the likely small contribution to increased relative risk by any one genetic polymorphism make it difficult to detect subtle changes in glucose homeostasis in small populations. A more recent and larger study suggests that insulin secretion is significantly reduced in both heterozygous (E/K) and homozygous (K/K) polymorphic individuals following an oral glucose challenge (Nielsen et al. 2003). This work has recently been confirmed by Florez and colleagues (2004) in a large scale study of 674 Scandinavian non-diabetic individuals. Siblings discordant for the E23K genotype were examined by the oral glucose tolerance test to obtain their insulinogenic indices. Those siblings who were homozygous for the K allele were found to have a 20%–30% decrease in β-cell function when compared with siblings with an E/E or E/K genotype (Florez et al. 2004). These studies raise the possibility that the route of glucose administration (intravenous vs. oral) may determine whether the E23K polymorphism alters insulin secretion (Nielsen et al. 2003). With oral administration of glucose, additional systems that modulate the secretion of insulin and other hormones essential to glucose homeostasis play a role, including neuronal and enteric (e.g., GLP-1) regulatory pathways (Clement et al. 2002; MacDonald et al. 2002; Miki et al. 2001; Thorens 2003). These pathways are regulated in part by processes involving K_{ATP} channels containing the Kir6.2 subunit. An assessment of the function of these pathways within their respective tissues will be important in the light of the potential alterations in K_{ATP} channel activity resulting from the E23K polymorphism.

Recombinant K_{ATP} channel Studies

The functional effect of the E23K polymorphism on the properties of the K_{ATP} channel is now being investigated. In the initial study by Sakura and colleagues (1996), wild-type or E23K Kir6.2 subunits were co-expressed with SUR1 in *Xenopus* oocytes. Both the wild-type and E23K-containing K_{ATP} channels were ATP-sensitive, being similarly activated by ATP-depletion induced by metabolic inhibition. However, metabolic inhibition gives only an indication as to whether the expressed channels are sensitive to large changes in intracellular ATP levels. The limited power of this experiment does not allow for the detection of subtle, yet important, changes in K_{ATP} channel properties such as the "open" probability or their regulation by other K_{ATP} channel modulators that may underlie the pathophysiological relevance of the E23K polymorphism. For example, ~99% of K_{ATP} channels are estimated to be closed in the presence of basal glucose concentrations. Therefore, a change in K_{ATP} channel activity of less than 1% could significantly affect insulin secretion (Cook et al. 1988).

Functional studies have primarily involved the clinical assessment of insulin secretion (as measured by plasma insulin levels during a hyperglycemic clamp or oral glucose challenge) or response to sulfonylureas. E23K does not significantly affect sulfonylurea potency at the single K_{ATP} channel level or in individuals with a polymorphic genotype (Gloyn et al. 2001; Hansen et al. 1997; Schwanstecher and Schwanstecher 2002).

Free nucleotide diphosphate concentrations in resting β-cells have been estimated to be between 10 μM and 20 μM (Ronner et al. 2001), whereas resting ATP levels are in the low millimolar range (Gribble et al. 2000; Kennedy et al. 1999). E23K channels appear to have reduced ATP sensitivity in the presence of 300 μM guanosine 5′-diphosphate (GDP), an activating nucleotide thought to interact only with the SUR1 subunit (Schwanstecher et al. 2002b). These results by Schwanstecher and colleagues (2002b) indicate that the transduction between nucleotide diphosphate binding and channel activation may be slightly altered in polymorphic K_{ATP} channels at low ATP and high GDP concentrations, but do not support the altered clinical success of sulfonylurea therapy for type-2 diabetic individuals.

Several studies have examined the structure of the K_{ATP} channel for the ATP-binding site. Positively charged residues in the cytosolic N-terminus, including R50, R54, and the cytosolic C-terminal residue K185, are thought to interact forming a putative ATP-binding region (Cukras et al. 2002; John et al. 2003; Trapp et al. 2003; Tucker et al. 1998). Interestingly, mutations within the N-terminus encompassing amino acids 16–29 also

significantly alter K_{ATP} channel activity (Cukras et al. 2002) suggesting that positively charged residues in this region (E23K?) may contribute to ATP binding.

Initial studies examining the effects of E23K on K_{ATP} channel function performed by Schwanstecher et al. (2002a) revealed an approximate 1.6-fold increase in open probability. This increase in open probability in E23K polymorphic K_{ATP} channels results from a slight reduction in ATP sensitivity. The negative-to-positive change in charge that accompanies the E-to-K mutation and the proximity of E23 to residues implicated in ATP sensitivity suggests that the E23K polymorphism alters ATP binding or the steric transduction of ATP binding to K_{ATP} channel closure.

We have performed similar studies on both wild-type and E23K/I337V double polymorphic K_{ATP} channels in the absence of ATP and obtained similar values of spontaneous open probability in both wild-type and polymorphic channels (Riedel et al. 2003). The use of the single E23K polymorphism versus the double E23K/I337V polymorphism (used in our study) might contribute to the observed differences. In addition, we were unable to reproduce the rightward shift in ATP sensitivity of polymorphic K_{ATP} channels (Schwanstecher et al. 2002a) in the absence of additional channel modulators (Riedel et al. 2003). The exact cause of this discrepancy is not currently understood, warranting further examination of the effects of nucleotides on polymorphic K_{ATP} channel behaviour.

Interestingly, a large shift in IC_{50} (inhibitory concentration 50%) for ATP sensitivity is not a prerequisite for altered insulin secretion. Gloyn et al. (2004) have recently described an activating human mutation (R201H) that, in the heterozygous state, results in permanent neonatal diabetes mellitus. Although the mutation alone evokes a significant decrease in ATP sensitivity, a 1:1 mixture of mutant and wild-type channels (to simulate the heterozygous phenotype) has a similar IC_{50} to that of wild-type channels. In addition, the effect on whole cell current is minimal and not significant. These results indicate that even severe mutations that result in permanent diabetes from birth may not significantly alter IC_{50} or spontaneous open probability values. Similar to our E23K results, a shift in the hill coefficient of ATP binding in the R201H mutant permits an increase in K_{ATP} channel activity at millimolar ATP levels (Gloyn et al. 2004).

The effects of LC-CoAs on K_{ATP} channel function

The E23K variant has been linked to an increase in body mass index (BMI; Nielsen et al. 2003), an indication of obesity. In both obese and type-2 diabetic individuals, circulating levels of long chain FFAs are chronically elevated, leading to cellular accumulation of fatty acids and their metabolites, the LC-CoAs (Corkey 1988; Corkey et al. 2000; Prentki and Corkey 1996). In β-cells, the interaction of these LC-CoA molecules with the K_{ATP} channel results in increased channel activity and K^+ efflux (Branstrom et al. 1997, 1998; Gribble et al. 1998; Larsson et al. 1996). The observed increase in K_{ATP} channel current in the presence of LC-CoAs may therefore lead to a reduction in β-cell electrical excitability, contributing to the impairment of insulin secretion, a common dysfunction in type-2 diabetes.

Our group has recently examined the effects of LC-CoAs on the activity of polymorphic K_{ATP} channels. We have found that the addition of physiological (i.e., nanomolar) unbound/free concentrations (Corkey et al. 2000; Deeney et al. 1992) of palmitoyl-CoA (a common 16-carbon saturated fatty acid) results in a significant increase in polymorphic (E23K/I337V) K_{ATP} channel current compared with wild-type (Riedel et al. 2003). In the presence of similar LC-CoA concentrations, this would have the effect of reducing cellular excitability via increased K^+ efflux in β-cells possessing polymorphic K_{ATP} channels compared with those with wild-type

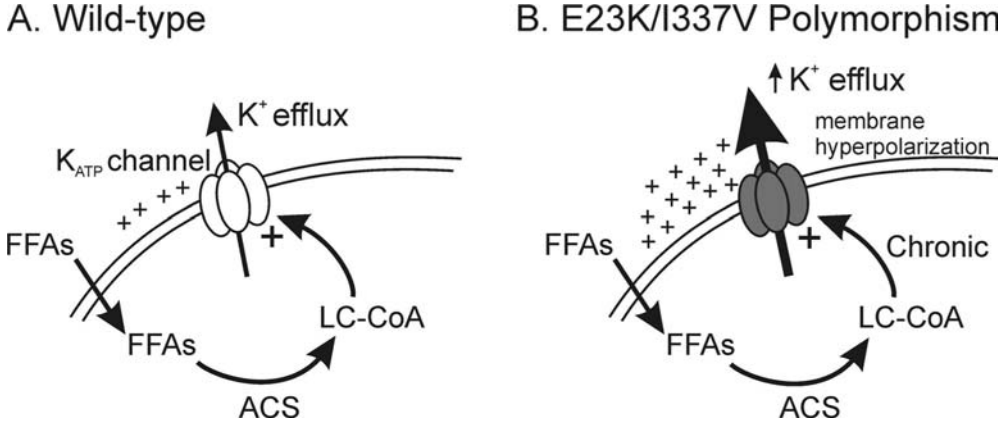

Fig. 3 Long chain acyl CoA esters (*LC-CoA*) such as palmitoyl-CoA directly activate K_{ATP} channels. Chronic exposure to free fatty acids (*FFAs*) results in cytosolic accumulation of *LC-CoAs* and increased K_{ATP} channel activity, a situation that may lead to impaired insulin secretion. K_{ATP} channels carrying the homozygous K/K genotype are more susceptible to activation by *LC-CoAs*. An increased K^+ efflux may reduce β-cell activity, contributing to hyperglycemia and type-2 diabetes

channels (Fig. 3). The increase in K_{ATP} channel activity is attributed to a reduction in the hill co-efficient of ATP inhibition, leading to a rightward shift in ATP sensitivity in the E23K/I337V polymorphic versus wild-type K_{ATP} channels at millimolar ATP concentrations (Riedel et al. 2003).

The molecular mechanism by which the E23K amino acid shift alters the ability of the K_{ATP} channel to sense changes in either ATP or LC-CoAs is currently unknown. A clear picture of the structure of the K_{ATP} channel may hold the key to determining the precise mechanism by which LC-CoAs alter channel activity and the way in which the E23K polymorphism affects this process. The recent crystallization of related inward-rectifier potassium channels KirBac1.1 and GIRK (Kuo et al. 2003; Nishida and MacKinnon 2002) may facilitate our understanding of the actions of polymorphisms on the binding of channel ligands such as ATP, PIP_2, and LC-CoAs, three molecules that act directly on the Kir6.2 subunit of the K_{ATP} channel (Schulze et al. 2003b). Although neither of these crystal structures currently includes the distal N-terminus (and therefore the E23 residue), significant progress is being made and may soon lead to a more complete model of the K_{ATP} channel at the molecular level. Indeed, our own molecular mechanistic studies suggest that the process of LC-CoA-mediated K_{ATP} channel activation involves both the binding of the negatively charged CoA head group to a region close to the ATP-binding region and an interaction of the long chain hydrophobic acyl tail with the plasma membrane (Manning Fox et al. 2004).

Evolutionary aspects of the E23K polymorphism

Given the high allelic frequency of E23K in the general population, speculation has been made regarding the evolutionary advantage of this polymorphism. Schwanstecher et al. (2002a) first proposed that a potential discrete regulation of insulin secretion in heterozygotes as a result of slightly higher K_{ATP} channel activity may reduce glucose uptake in muscle and adipose tissue, thus providing an evolutionary advantage by improving substrate supply for tissues with insulin-independent mechanisms of glucose uptake, especially the brain (Schwanstecher et al. 2002a). In the light of recent evidence highlighting a link between increased BMI, chronically elevated fatty acids, and the E23K polymorphism (Nielsen et al. 2003), including our work on the interaction of LC-CoAs with polymorphic K_{ATP} channels (Riedel et al. 2003), we can now speculate further regarding the systemic effects of E23K and the potential advantage of maintaining this polymorphism at such high allelic frequency in the general population.

The heterozygous E23K genotype has previously been suggested to represent a ''thrifty gene'' variant, a term coined by James Neel in 1962 (Neel 1962). The ''thrifty gene'' hypothesis suggests that, during human evolution, genes primarily promoting efficient energy storage and/or utilization were preferentially selected for, resulting in improved survival during the regular periods of food shortage (Neel 1962). In present times, the adoption of a ''Western lifestyle'' with abundant and easily accessible high caloric food sources and reduced exercise may predispose individuals carrying these thrifty genes to obesity and increase their risk of developing type-2 diabetes. However, the homozygous wild-type (E/E) genotype may itself constitute a ''thrifty gene'' variant, given the potential for improved insulin release in response to glucose (Nielsen et al. 2003) and reduced activity of K_{ATP} channels in the absence of ATP (Schwanstecher et al. 2002a) and presence of LC-CoAs (Riedel et al. 2003). An additional decrease in glucagon secretion in E/E individuals vs. those carrying one or both E23K polymorphic alleles further supports this hypothesis (Tschritter et al. 2002). These observations suggest that carriers of the E/E genotype are capable of more efficient energy storage, a characteristic of a ''thrifty gene''.

Recent population studies indicate that there remains an unexpectedly high (11%) average occurrence of this polymorphism in the glucose-tolerant Caucasian population ('t Hart et al. 2002; Gloyn et al. 2001, 2003; Hani et al. 1998; Hansen et al. 1997; Inoue et al. 1997; Nielsen et al. 2003; Sakura et al. 1996; Table 1). These data indicate that there may have been some evolutionary advantage in the maintenance of the K/K allelic combination. Chakravarthy and Booth (2004) have proposed that genes promoting improved muscular performance and the efficient utilization of fuels may also be considered ''thrifty''. In accord with this notion, we speculate that the high prevalence of the K/K genotype represents not a classical ''thrifty-storage gene'' but perhaps more appropriately a ''thrifty-utility gene'', viz., one that confers improved substrate supply for all tissues and improved muscle performance during sustained exercise (Fig. 4). The reasons for this suggestion are as follows. Studies have shown that, in K/K individuals, glucagon secretion is increased (Tschritter et al. 2002), insulin secretion is decreased (Nielsen et al. 2003), and K_{ATP} channel activity is upregulated in the presence of LC-CoAs (Riedel et al. 2003). Physiologically, this would effectively maintain slightly higher plasma glucose concentrations, thereby improving substrate supply for glucose-utilizing tissues such as skeletal and cardiac muscle (Fig. 4). The slight shift in the threshold of insulin secretion to higher glucose concentrations may have been counter-balanced by improved insulin sensitivity in the skeletal muscles of our ancestors, an effect that can be mimicked today by continuous endurance training (Dela et al. 1992; Russell et al. 2003). Improved insulin-independent glucose uptake via the contraction-induced activation of AMP-regulated protein kinase (Bergeron et al. 1999; Hayashi et al. 1998; Kurth-Kraczek et al. 1999) also contributes to improved substrate utilization in exercising muscle. Studies to date have failed to demonstrate a strong association of the E23K polymorphism with alterations in fasting glucose

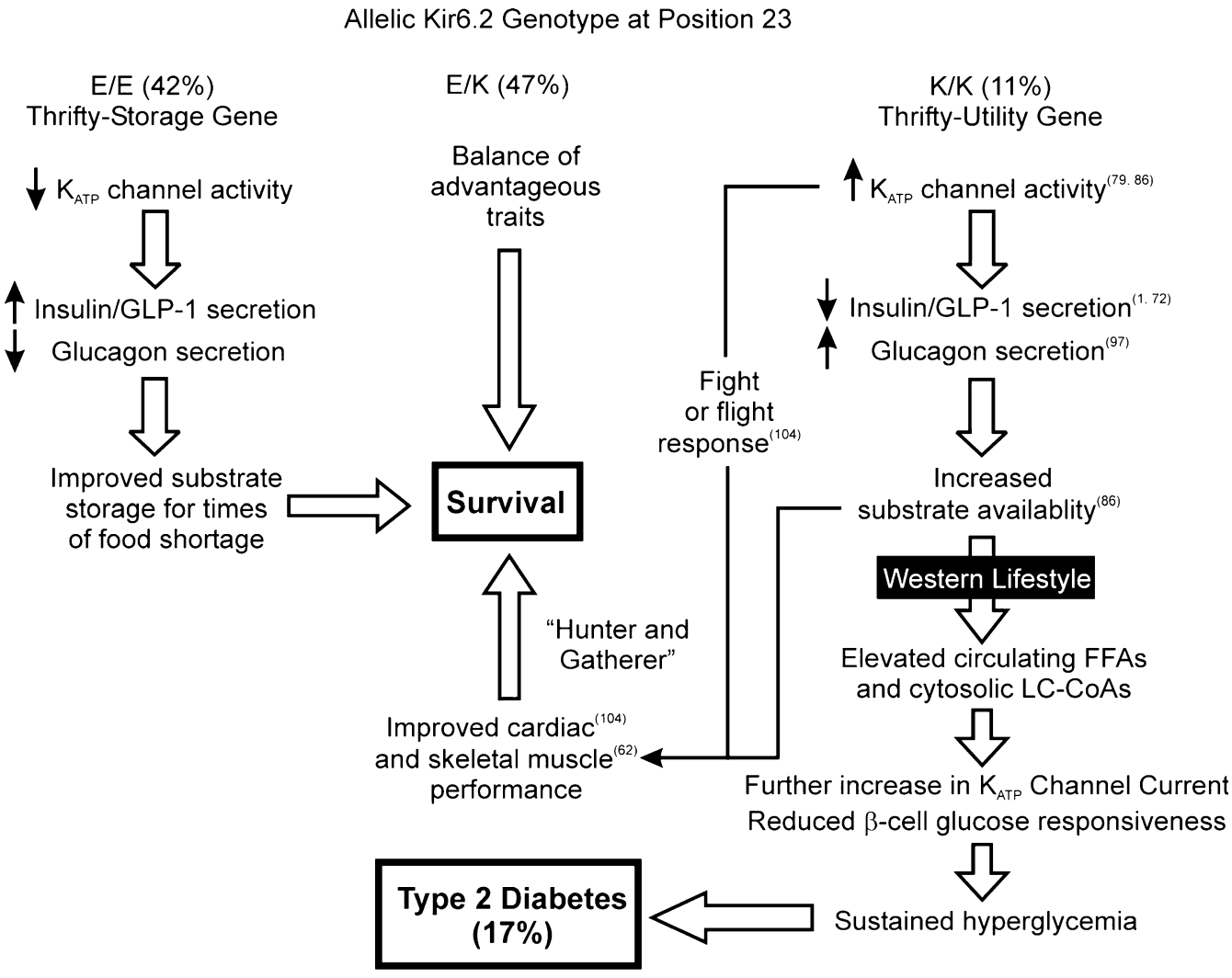

Fig. 4 Representation of the selection pressure that may maintain a high prevalence of the various genotypes at residue position 23 of the Kir6.2 subunit of the K_{ATP} channel. Given in *parentheses* are the average genotypic frequencies of each allelic combination in the general Caucasian population as calculated in Table 1. The evolutionary advantage of the K/K genotype may be lost in the presence of a *Western Lifestyle*. A high caloric diet coupled with reduced physical activity leads to an increased risk of type-2 diabetes, which in turn may contribute to the increased prevalence of the K/K genotype within this population

or insulin levels ('t Hart et al. 2002; Nielsen et al. 2003); however, there is evidence of slightly reduced fasting serum insulin levels in individuals carrying the homozygous K/K genotype (Hansen et al. 1997). Additional large-scale studies designed to examine fasting glucose and insulin levels are therefore warranted.

The activation of K_{ATP} channels has further been implicated in optimizing skeletal muscle contractility during exercise through increasing blood flow and potentiating force development via increased extracellular K^+ levels (Gramolini and Renaud 1997; Renaud 2002). Interestingly, a recent study has shown that decreased pH results in a relative decrease in ATP sensitivity in recombinant Kir6.2(E23K)/SUR2A (skeletal muscle and cardiac type) K_{ATP} channels versus wild-type (Li et al. 2004). As anaerobic metabolism produces excess protons and decreases muscle pH, a population of polymorphic K_{ATP} channels may open more rapidly in response to an anaerobic exercise stimulus than a population of wild-type channels. Sensitization of the E23K polymorphic K_{ATP} channel to a decrease in pH may therefore improve skeletal muscle performance in these individuals. In addition, K_{ATP} channels may be activated in the heart during stress, thereby reducing action potential duration and improving cardiac function in response to β-adrenergic stimulation improving the "fight or flight" response (Zingman et al. 2002). Goodwin and Taegtmeyer (2000) have also suggested that this response may be strengthened in the presence of elevated LC-CoAs. They have shown that the increase in LC-CoA levels that occurs during exercise results in improvement in the β-oxidation and substrate supply required to maintain energy homeostasis in the contracting heart

(Goodwin and Taegtmeyer 2000). Taken together, these results suggest that the increased activity of K_{ATP} channels, as observed in the presence of the E23K polymorphism (Riedel et al. 2003; Schwanstecher et al. 2002a), result in improved cardiac and skeletal muscle performance during exercise. The K/K genotype may therefore have conferred an evolutionary advantage to our "hunter-gatherer" ancestors by allowing them to maintain intense physical activity for prolonged periods of time, such as would have been required for the procurement of food through hunting (Cordain et al. 1998). The evolutionary downside to possessing the E23K polymorphism may perhaps have become apparent when homozygous individuals adopt the modern "Western lifestyle," i.e., reduced physical activity coupled with increased fat and carbohydrate intake, enhancing their likelihood of developing obesity and contributing to the onset of type-2 diabetes. Selection against the E23K polymorphism may not have occurred in our ancestral past as enforced fasting and obligatory physical activity probably balanced periods of high caloric intake and physical inactivity.

The evolutionary benefits of each homozygous genotype - the K/K "thrifty-utility" vs. the E/E "thrifty-storage" gene (Fig. 4) - may be balanced in heterozygotes, contributing to the high prevalence of the E/K genotype in both the general and type-2 diabetic population (Gloyn et al. 2003; Hani et al. 1998; Nielsen et al. 2003) and, in present times, conferring only a slight increase in risk for the development of type-2 diabetes (Love-Gregory et al. 2003; Schwanstecher and Schwanstecher 2002).

Physiological relevance

There is now strong evidence to suggest that the frequency of the homozygous E23K polymorphism is higher in Caucasian type-2 diabetic individuals than in the general Caucasian population (Gloyn et al. 2003; Hani et al. 1998). However, the way in which the E23K polymorphism precisely contributes to the development of the type-2 diabetes currently remains unclear. Although genetic predisposition is considered a major risk factor, a significant contribution also originates from environmental factors such as diet and lifestyle. For example, our recent findings that LC-CoA sensitivity is significantly increased in polymorphic K_{ATP} channels (Riedel et al. 2003) provides a plausible explanation as to why alterations in glucose homeostasis are seen only in certain studies. These results coupled with those of Schwanstecher et al. (2002a) who have reported increased K_{ATP} channel activity in the presence of physiological nucleotide concentrations indicate that the E23K polymorphism alters the binding of several channel modulators. Interestingly, a potential link has been made between the presence of E23K and increased BMI (Nielsen et al. 2003). This is in contrast to an earlier report by Hansen and colleagues (1997) in which no interaction between obesity (defined as BMI > 25) and E23K could be detected. An examination of the populations used in each of these studies yields a possible explanation for the discrepancy. In the study by Hansen and colleagues (1997), the population comprised of 346 young adults with average BMI values in the range of 22 to 24. The low BMI values among participants may have prevented the authors from noting any effects attributable to obesity. Conversely, participants in the Nielsen study had BMI values above 25, and there was a noted significant difference between BMI values of wild-type individuals and those that were homozygous for the E23K polymorphism (Nielsen et al. 2003). In vivo studies dedicated to examining the effects of elevated LC-CoAs caused by obesity have yet to be completed.

K_{ATP} channels are involved in the secretion of many hormones that regulate plasma glucose levels. The expression of E23K polymorphic K_{ATP} channels in various tissues probably affects cellular processes including glucagon and GLP-1 secretion, central-nervous-system-mediated appetite regulation, and cardiac and skeletal muscle function. Individuals homozygous for the E23K polymorphism who possess elevated LC-CoA levels may exhibit reduced responsiveness in these tissues possibly contributing to chronic hyperglycemia. The finding that E23K is associated with individuals with increased BMI (Nielsen et al. 2003) supports this hypothesis. Recent studies have indicated that both insulin (Nielsen et al. 2003) and glucagon (Tschritter et al. 2002) secretion is altered in individuals carrying the E23K polymorphism. Additional studies in extra-pancreatic tissues will be required to understand fully the impact of the polymorphism on glucose homeostasis and energy balance. Furthermore, transgenic animal models of the homozygous E23K polymorphism should be designed to allow the characterization of the polymorphism in a variety of tissues and in response to such environmental stresses as dietary manipulation and exercise.

Recent studies have addressed the issue of acute versus chronic FFA exposure of otherwise healthy patients with or without a family history of type-2 diabetes (Kashyap et al. 2003). Both the insulin secretion rate and plasma C-peptide levels significantly decreased in patients with a family history, but only after they had been given a multi-day lipid infusion chronically to raise plasma FFA levels to those seen in obese and type-2 diabetic individuals (Kashyap et al. 2003). Accordingly, long-term (24 h) fatty acid infusion has recently been shown to lead to significant reductions in first-phase insulin secretion in glucose-intolerant relatives of type-2 diabetic individuals but not in glucose-tolerant controls (Storgaard et al. 2003). The observed decrease in first-phase insulin secretion in these studies is consistent with the involvement of the K_{ATP} channel-dependent mechanism of insulin secretion in the development of type-2 diabetes (Henquin 2000). The underlying genetic difference between those individuals with and without a

family history of type-2 diabetes, including any possible involvement of the E23K polymorphism, remains to be identified.

As the effects of E23K on the overall process of glucose homeostasis are likely to be small, sufficiently large studies will be required to separate out differences between wild-type, heterozygous, and homozygous polymorphic individuals. Florez and associates (2004) suggest that 120,000 case/control pairs may be required to analyze the effects of the E23K polymorphism on type-2 diabetes susceptibility properly. Because of the multifactorial nature of type-2 diabetes, these studies may require the separation of populations based on criteria in addition to the presence or absence of the disease phenotype, including the degree and type of obesity, gender, age, and ethnic background. For example, it will be important to examine additional populations that exhibit increased susceptibility to type-2 diabetes, including North American Indians such as the Oji-Cree (Hegele et al. 2003) and Pima (Knowler et al. 1990) populations and those individuals with a family history of type-2 diabetes.

Conclusions

There is now a substantial body of evidence that suggests the E23K polymorphism plays a role in the etiology of type-2 diabetes in a significant percentage of the Caucasian population. The subtle nature of alterations in K_{ATP} channel activity induced by E23K highlights the importance of detailed probing of channel properties, including both macroscopic and single channel activity, when examining ion channel mutations. Further studies of this polymorphism are likely to highlight the multifactorial nature of the diabetic phenotype. Environmental factors such as dietary fat intake and physical inactivity further contribute to impaired glucose homeostasis in a number of tissues, increasing susceptibility to type-2 diabetes preferentially in individuals with specific genotypes.

References

Aguilar-Bryan L, Bryan J (1999) Molecular biology of adenosine triphosphate-sensitive potassium channels. Endocr Rev 20:101–135

Aguilar-Bryan L, Nichols CG, Wechsler SW, Clement JP, Boyd AE, III, Gonzalez G, Herrera-Sosa H, Nguy K, Bryan J, Nelson DA (1995) Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin secretion. Science 268:423–426

Aguilar-Bryan L, Clement JP, Gonzalez G, Kunjilwar K, Babenko A, Bryan J (1998) Toward understanding the assembly and structure of KATP channels. Physiol Rev 78:227–245

Altshuler D, Hirschhorn JN, Klannemark M, Lindgren CM, Vohl MC, Nemesh J, Lane CR, Schaffner SF, Bolk S, Brewer C, Tuomi T, Gaudet D, Hudson TJ, Daly M, Groop L, Lander ES (2000) The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. Nat Genet 26:76–80

Ashcroft FM (2000) The Yin and Yang of the K(ATP) channel. J Physiol (Lond) 528:405

Ashcroft FM, Rorsman P (1989) Electrophysiology of the pancreatic beta-cell. Prog Biophys Mol Biol 54:87–143

Babenko AP, Gonzalez G, Bryan J (2000) Pharmaco-topology of sulfonylurea receptors. Separate domains of the regulatory subunits of K(ATP) channel isoforms are required for selective interaction with K(+) channel openers. J Biol Chem 275:717–720

Barnett AH, Eff C, Leslie RD, Pyke DA (1981) Diabetes in identical twins. A study of 200 pairs. Diabetologia 20:87–93

Barroso I, Luan J, Middelberg RP, Harding AH, Franks PW, Jakes RW, Clayton D, Schafer AJ, O'Rahilly S, Wareham NJ (2003) Candidate gene association study in type 2 diabetes indicates a role for genes involved in beta-cell function as well as insulin action. PLoS Biol 1:E20

Beck-Nielsen H, Vaag A, Poulsen P, Gaster M (2003) Metabolic and genetic influence on glucose metabolism in type 2 diabetic subjects–experiences from relatives and twin studies. Best Pract Res Clin Endocrinol Metab 17:445–467

Bergeron R, Russell RR, III, Young LH, Ren JM, Marcucci M, Lee A, Shulman GI (1999) Effect of AMPK activation on muscle glucose metabolism in conscious rats. Am J Physiol 276:E938-E944

Bokvist K, Olsen HL, Hoy M, Gotfredsen CF, Holmes WF, Buschard K, Rorsman P, Gromada J (1999) Characterisation of sulphonylurea and ATP-regulated K+ channels in rat pancreatic A-cells. Pflugers Arch 438:428–436

Branstrom R, Corkey BE, Berggren PO, Larsson O (1997) Evidence for a unique long chain acyl-CoA ester binding site on the ATP-regulated potassium channel in mouse pancreatic beta cells. J Biol Chem 272:17390–17394

Branstrom R, Leibiger IB, Leibiger B, Corkey BE, Berggren PO, Larsson O (1998) Long chain coenzyme A esters activate the pore-forming subunit (Kir6. 2) of the ATP-regulated potassium channel. J Biol Chem 273:31395–31400

Briscoe CP, Tadayyon M, Andrews JL, Benson WG, Chambers JK, Eilert MM, Ellis C, Elshourbagy NA, Goetz AS, Minnick DT, Murdock PR, Sauls HR Jr, Shabon U, Spinage LD, Strum JC, Szekeres PG, Tan KB, Way JM, Ignar DM, Wilson S, Muir AI (2003) The orphan G protein-coupled receptor GPR40 is activated by medium and long chain fatty acids. J Biol Chem 278:11303–11311

Chakravarthy MV, Booth FW (2004) Eating, exercise, and "thrifty" genotypes: connecting the dots toward an evolutionary understanding of modern chronic diseases. J Appl Physiol 96:3–10

Charles MA, Eschwege E, Thibult N, Claude JR, Warnet JM, Rosselin GE, Girard J, Balkau B (1997) The role of non-esterified fatty acids in the deterioration of glucose tolerance in Caucasian subjects: results of the Paris Prospective Study. Diabetologia 40:1101–1106

Clement JP, Kunjilwar K, Gonzalez G, Schwanstecher M, Panten U, Aguilar-Bryan L, Bryan J (1997) Association and stoichiometry of K(ATP) channel subunits. Neuron 18:827–838

Clement L, Cruciani-Guglielmacci C, Magnan C, Vincent M, Douared L, Orosco M, Assimacopoulos-Jeannet F, Penicaud L, Ktorza A (2002) Intracerebroventricular infusion of a triglyceride emulsion leads to both altered insulin secretion and hepatic glucose production in rats. Pflugers Arch 445:375–380

Cook DL, Satin LS, Ashford ML, Hales CN (1988) ATP-sensitive K+ channels in pancreatic beta-cells. Spare-channel hypothesis. Diabetes 37:495–498

Cordain L, Gotshall RW, Eaton SB, Eaton SB III (1998) Physical activity, energy expenditure and fitness: an evolutionary perspective. Int J Sports Med 19:328–335

Corkey BE (1988) Analysis of acyl-coenzyme A esters in biological samples. Methods Enzymol 166:55–70

Corkey BE, Deeney JT, Yaney GC, Tornheim K, Prentki M (2000) The role of long-chain fatty acyl-CoA esters in beta-cell signal transduction. J Nutr 130:299S–304S

Cukras CA, Jeliazkova I, Nichols CG (2002) The role of NH2-terminal positive charges in the activity of inward rectifier KATP channels. J Gen Physiol 120:437–446

Deeney JT, Tornheim K, Korchak HM, Prentki M, Corkey BE (1992) Acyl-CoA esters modulate intracellular Ca^{2+} handling by permeabilized clonal pancreatic beta-cells. J Biol Chem 267:19840–19845

Dela F, Mikines KJ, Linstow M von, Secher NH, Galbo H (1992) Effect of training on insulin-mediated glucose uptake in human muscle. Am J Physiol 263:E1134-E1143

Elbein SC (2002) Perspective: the search for genes for type 2 diabetes in the post-genome era. Endocrinology 143:2012–2018

Florez JC, Burtt N, De Bakker PI, Almgren P, Tuomi T, Holmkvist J, Gaudet D, Hudson TJ, Schaffner SF, Daly MJ, Hirschhorn JN, Groop L, Altshuler D (2004) Haplotype structure and genotype-phenotype correlations of the sulfonylurea receptor and the islet ATP-sensitive potassium channel gene region. Diabetes 53:1360–1368

Gloyn AL (2003) The search for type 2 diabetes genes. Ageing Res Rev 2:111–127

Gloyn AL, Hashim Y, Ashcroft SJ, Ashfield R, Wiltshire S, Turner RC (2001) Association studies of variants in promoter and coding regions of beta-cell ATP-sensitive K-channel genes SUR1 and Kir6.2 with type 2 diabetes mellitus (UKPDS 53). Diabet Med 18:206–212

Gloyn AL, Weedon MN, Owen KR, Turner MJ, Knight BA, Hitman G, Walker M, Levy JC, Sampson M, Halford S, McCarthy MI, Hattersley AT, Frayling TM (2003) Large-scale association studies of variants in genes encoding the pancreatic beta-cell KATP channel subunits Kir6.2 (KCNJ11) and SUR1 (ABCC8) confirm that the KCNJ11 E23K variant is associated with type 2 diabetes. Diabetes 52:568–572

Gloyn AL, Pearson ER, Antcliff JF, Proks P, Bruining GJ, Slingerland AS, Howard N, Srinivasan S, Silva JM, Molnes J, Edghill EL, Frayling TM, Temple IK, Mackay D, Shield JP, Sumnik Z, Rhijn A van, Wales JK, Clark P, Gorman S, Aisenberg J, Ellard S, Njolstad PR, Ashcroft FM, Hattersley AT (2004) Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 350:1838–1849

Golay A, Swislocki AL, Chen YD, Jaspan JB, Reaven GM (1986) Effect of obesity on ambient plasma glucose, free fatty acid, insulin, growth hormone, and glucagon concentrations. J Clin Endocrinol Metab 63:481–484

Goodwin GW, Taegtmeyer H (2000) Improved energy homeostasis of the heart in the metabolic state of exercise. Am J Physiol Heart Circ Physiol 279:H1490-H1501

Gramolini A, Renaud JM (1997) Blocking ATP-sensitive K+ channel during metabolic inhibition impairs muscle contractility. Am J Physiol 272:C1936-C1946

Gribble FM, Tucker SJ, Ashcroft FM (1997) The essential role of the Walker A motifs of SUR1 in K-ATP channel activation by Mg-ADP and diazoxide. EMBO J 16:1145–1152

Gribble FM, Proks P, Corkey BE, Ashcroft FM (1998) Mechanism of cloned ATP-sensitive potassium channel activation by oleoyl-CoA. J Biol Chem 273:26383–26387

Gribble FM, Loussouarn G, Tucker SJ, Zhao C, Nichols CG, Ashcroft FM (2000) A novel method for measurement of submembrane ATP concentration. J Biol Chem 275:30046–30049

Hani EH, Clement K, Velho G, Vionnet N, Hager J, Philippi A, Dina C, Inoue H, Permutt MA, Basdevant A, North M, Demenais F, Guy-Grand B, Froguel P (1997) Genetic studies of the sulfonylurea receptor gene locus in NIDDM and in morbid obesity among French Caucasians. Diabetes 46:688–694

Hani EH, Boutin P, Durand E, Inoue H, Permutt MA, Velho G, Froguel P (1998) Missense mutations in the pancreatic islet beta cell inwardly rectifying K+ channel gene (KIR6.2/BIR): a meta-analysis suggests a role in the polygenic basis of type II diabetes mellitus in Caucasians. Diabetologia 41:1511–1515

Hansen L, Echwald SM, Hansen T, Urhammer SA, Clausen JO, Pedersen O (1997) Amino acid polymorphisms in the ATP-regulatable inward rectifier Kir6.2 and their relationships to glucose- and tolbutamide-induced insulin secretion, the insulin sensitivity index, and NIDDM. Diabetes 46:508–512

Hansen T, Ambye L, Grarup N, Hansen L, Echwald SM, Ferrer J, Pedersen O (2001) Genetic variability of the SUR1 promoter in relation to beta-cell function and type II diabetes mellitus. Diabetologia 44:1330–1334

Hart LM, Knijff P de, Dekker JM, Stolk RP, Nijpels G, Does FE van der, Ruige JB, Grobbee DE, Heine RJ, Maassen JA (1999) Variants in the sulphonylurea receptor gene: association of the exon 16–3t variant with type II diabetes mellitus in Dutch Caucasians. Diabetologia 42:617–620

Hayashi T, Hirshman MF, Kurth EJ, Winder WW, Goodyear LJ (1998) Evidence for 5′ AMP-activated protein kinase mediation of the effect of muscle contraction on glucose transport. Diabetes 47:1369–1373

Hegele RA, Zinman B, Hanley AJ, Harris SB, Barrett PH, Cao H (2003) Genes, environment and Oji-Cree type 2 diabetes. Clin Biochem 36:163–170

Henquin JC (2000) Triggering and amplifying pathways of regulation of insulin secretion by glucose. Diabetes 49:1751–1760

Hill JO, Peters JC (1998) Environmental contributions to the obesity epidemic. Science 280:1371–1374

Huopio H, Shyng SL, Otonkoski T, Nichols CG (2002) K(ATP) channels and insulin secretion disorders. Am J Physiol Endocrinol Metab 283:E207-E216

Inagaki N, Gonoi T, Clement JP, Namba N, Inazawa J, Gonzalez G, Aguilar-Bryan L, Seino S, Bryan J (1995) Reconstitution of IKATP: an inward rectifier subunit plus the sulfonylurea receptor. Science 270:1166–1170

Inoue H, Ferrer J, Warren-Perry M, Zhang Y, Millns H, Turner RC, Elbein SC, Hampe CL, Suarez BK, Inagaki N, Seino S, Permutt MA (1997) Sequence variants in the pancreatic islet beta-cell inwardly rectifying K+ channel Kir6.2 (Bir) gene: identification and lack of role in Caucasian patients with NIDDM. Diabetes 46:502–507

Itoh Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, Fukusumi S, Ogi K, Hosoya M, Tanaka Y, Uejima H, Tanaka H, Maruyama M, Satoh R, Okubo S, Kizawa H, Komatsu H, Matsumura F, Noguchi Y, Shinohara T, Hinuma S, Fujisawa Y, Fujino M (2003) Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. Nature 422:173–176

John SA, Weiss JN, Xie LH, Ribalet B (2003) Molecular mechanism for ATP-dependent closure of the K+ channel Kir6.2. J Physiol (Lond)552:23–34

Karschin A, Brockhaus J, Ballanyi K (1998) KATP channel formation by the sulphonylurea receptors SUR1 with Kir6.2 subunits in rat dorsal vagal neurons in situ. J Physiol (Lond) 509 :339–346

Kashyap S, Belfort R, Gastaldelli A, Pratipanawatr T, Berria R, Pratipanawatr W, Bajaj M, Mandarino L, DeFronzo R, Cusi K (2003) A sustained increase in plasma free fatty acids impairs insulin secretion in nondiabetic subjects genetically predisposed to develop type 2 diabetes. Diabetes 52:2461–2474

Kennedy HJ, Pouli AE, Ainscow EK, Jouaville LS, Rizzuto R, Rutter GA (1999) Glucose generates sub-plasma membrane ATP microdomains in single islet beta-cells. Potential role for strategically located mitochondria. J Biol Chem 274:13281–13291

Knowler WC, Pettitt DJ, Saad MF, Bennett PH (1990) Diabetes mellitus in the Pima Indians: incidence, risk factors and pathogenesis. Diabetes Metab Rev 6:1–27

Kopp W (2003) High-insulinogenic nutrition—an etiologic factor for obesity and the metabolic syndrome? Metabolism 52:840–844

Kuo A, Gulbis JM, Antcliff JF, Rahman T, Lowe ED, Zimmer J, Cuthbertson J, Ashcroft FM, Ezaki T, Doyle DA (2003) Crystal structure of the potassium channel KirBac1.1 in the closed state. Science 300:1922–1926

Kurth-Kraczek EJ, Hirshman MF, Goodyear LJ, Winder WW (1999) 5′ AMP-activated protein kinase activation causes GLUT4 translocation in skeletal muscle. Diabetes 48:1667–1671

Larsson O, Deeney JT, Branstrom R, Berggren PO, Corkey BE (1996) Activation of the ATP-sensitive K+ channel by long chain acyl-CoA. A role in modulation of pancreatic beta-cell glucose sensitivity. J Biol Chem 271:10623–10626

Li L, Shi Y, Jiang C (2004) Effects of Kir6.2 polymorphism on the ATP sensitivity of skeletal muscle isoform of KATP channels. Diabetes 53 (Suppl 2):10–11

Love-Gregory L, Wasson J, Lin J, Skolnick G, Suarez B, Permutt MA (2003) E23K single nucleotide polymorphism in the islet ATP-sensitive potassium channel gene (Kir6.2) contributes as much to the risk of type II diabetes in Caucasians as the PPARgamma Pro12Ala variant. Diabetologia 46:136–137

MacDonald PE, El Kholy W, Riedel MJ, Salapatek AM, Light PE, Wheeler MB (2002) The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. Diabetes 51 (Suppl 3):S434-S442

Manning Fox JE, Nichols CG, Light PE (2004) Activation of adenosine triphosphate-sensitive potassium channels by acyl coenzyme A esters involves multiple phosphatidylinositol 4,5-bisphosphate-interacting residues. Mol Endocrinol 18:679–686

Matsuoka T, Matsushita K, Katayama Y, Fujita A, Inageda K, Tanemoto M, Inanobe A, Yamashita S, Matsuzawa Y, Kurachi Y (2000) C-terminal tails of sulfonylurea receptors control ADP-induced activation and diazoxide modulation of ATP-sensitive K(+) channels. Circ Res 87:873–880

McCarthy MI (2003) Growing evidence for diabetes susceptibility genes from genome scan data. Curr Diab Rep 3:159–167

Miki T, Liss B, Minami K, Shiuchi T, Saraya A, Kashima Y, Horiuchi M, Ashcroft F, Minokoshi Y, Roeper J, Seino S (2001) ATP-sensitive K+ channels in the hypothalamus are essential for the maintenance of glucose homeostasis. Nat Neurosci 4:507–512

Neel JV (1962) Diabetes mellitus: a ''thrifty'' genotype rendered detrimental by ''progress''? Am J Hum Genet 14:353–362

Newman B, Selby JV, King MC, Slemenda C, Fabsitz R, Friedman GD (1987) Concordance for type 2 (non-insulin-dependent) diabetes mellitus in male twins. Diabetologia 30:763–768

Nichols CG, Shyng SL, Nestorowicz A, Glaser B, Clement JP, Gonzalez G, Aguilar-Bryan L, Permutt MA, Bryan J (1996) Adenosine diphosphate as an intracellular regulator of insulin secretion. Science 272:1785–1787

Nielsen EM, Hansen L, Carstensen B, Echwald SM, Drivsholm T, Glumer C, Thorsteinsson B, Borch-Johnsen K, Hansen T, Pedersen O (2003) The E23K variant of Kir6.2 associates with impaired post-OGTT serum insulin response and increased risk of type 2 diabetes. Diabetes 52:573–577

Nishida M, MacKinnon R (2002) Structural basis of inward rectification: cytoplasmic pore of the G protein-gated inward rectifier GIRK1 at 1.8 Å resolution. Cell 111:957–965

Prentki M, Corkey BE (1996) Are the beta-cell signaling molecules malonyl-CoA and cystolic long-chain acyl-CoA implicated in multiple tissue defects of obesity and NIDDM? Diabetes 45:273–283

Rangwala SM, Lazar MA (2004) Peroxisome proliferator-activated receptor gamma in diabetes and metabolism. Trends Pharmacol Sci 25:331–336

Reaven GM, Hollenbeck C, Jeng CY, Wu MS, Chen YD (1988) Measurement of plasma glucose, free fatty acid, lactate, and insulin for 24 h in patients with NIDDM. Diabetes 37:1020–1024

Reimann F, Gribble FM (2002) Glucose-sensing in glucagon-like peptide-1-secreting cells. Diabetes 51:2757–2763

Renaud JM (2002) Modulation of force development by Na+, K+, Na+ K+ pump and KATP channel during muscular activity. Can J Appl Physiol 27:296–315

Riedel MJ, Boora P, Steckley D, De Vries G, Light PE (2003) Kir6.2 polymorphisms sensitize beta-cell ATP-sensitive potassium channels to activation by acyl CoAs: a possible cellular mechanism for increased susceptibility to type 2 diabetes? Diabetes 52:2630–2635

Ronner P, Naumann CM, Friel E (2001) Effects of glucose and amino acids on free ADP in betaHC9 insulin-secreting cells. Diabetes 50:291–300

Russell AP, Feilchenfeldt J, Schreiber S, Praz M, Crettenand A, Gobelet C, Meier CA, Bell DR, Kralli A, Giacobino JP, Deriaz O (2003) Endurance Ttaining in humans leads to fiber type-specific increases in levels of peroxisome proliferator-activated receptor-gamma coactivator-1 and peroxisome proliferator-activated receptor-alpha in skeletal muscle. Diabetes 52:2874–2881

Sakura H, Ammala C, Smith PA, Gribble FM, Ashcroft FM (1995) Cloning and functional expression of the cDNA encoding a novel ATP-sensitive potassium channel subunit expressed in pancreatic beta-cells, brain, heart and skeletal muscle. FEBS Lett 377:338–344

Sakura H, Wat N, Horton V, Millns H, Turner RC, Ashcroft FM (1996) Sequence variations in the human Kir6.2 gene, a subunit of the beta-cell ATP-sensitive K-channel: no association with NIDDM in white Caucasian subjects or evidence of abnormal function when expressed in vitro. Diabetologia 39:1233–1236

Schulze D, Krauter T, Fritzenschaft H, Soom M, Baukrowitz T (2003a) Phosphatidylinositol 4,5-bisphosphate (PIP2) modulation of ATP and pH sensitivity in Kir channels. A tale of an active and a silent PIP2 site in the N terminus. J Biol Chem 278:10500–10505

Schulze D, Rapedius M, Krauter T, Baukrowitz T (2003b) Long-chain acyl-CoA esters and phosphatidylinositol phosphates modulate ATP inhibition of KATP channels by the same mechanism. J Physiol (Lond)552:357–367

Schwanstecher C, Schwanstecher M (2002) Nucleotide sensitivity of pancreatic ATP-sensitive potassium channels and type 2 diabetes. Diabetes 51 (Suppl 3):S358-S362

Schwanstecher C, Meyer U, Schwanstecher M (2002a) K(IR)6.2 polymorphism predisposes to type 2 diabetes by inducing overactivity of pancreatic beta-cell ATP-sensitive K(+) channels. Diabetes 51:875–879

Schwanstecher C, Neugebauer B, Schulz M, Schwanstecher M (2002b) The common single nucleotide polymorphism E23K in K(IR)6.2 sensitizes pancreatic beta-cell ATP-sensitive potassium channels toward activation through nucleoside diphosphates. Diabetes 51 (Suppl 3):S363-S367

Seino S (2003) Physiology and pathophysiology of K(ATP) channels in the pancreas and cardiovascular system: a review. J Diabetes Complications 17:2–5

Shyng S, Nichols CG (1997) Octameric stoichiometry of the KATP channel complex. J Gen Physiol 110:655–664

Shyng SL, Nichols CG (1998) Membrane phospholipid control of nucleotide sensitivity of KATP channels. Science 282:1138–1141

Shyng S, Ferrigni T, Nichols CG (1997) Regulation of KATP channel activity by diazoxide and MgADP. Distinct functions of the two nucleotide binding folds of the sulfonylurea receptor. J Gen Physiol 110:643–654

Sobngwi E, Boudou P, Mauvais-Jarvis F, Leblanc H, Velho G, Vexiau P, Porcher R, Hadjadj S, Pratley R, Tataranni PA, Calvo F, Gautier JF (2003) Effect of a diabetic environment in utero on predisposition to type 2 diabetes. Lancet 361:1861–1865

Storgaard H, Jensen CB, Vaag AA, Volund A, Madsbad S (2003) Insulin secretion after short- and long-term low-grade free fatty acid infusion in men with increased risk of developing type 2 diabetes. Metabolism 52:885–894

't Hart LM, Haeften TW van, Dekker JM, Bot M, Heine RJ, Maassen JA (2002) Variations in insulin secretion in carriers of the E23K variant in the KIR6.2 subunit of the ATP-sensitive K(+) channel in the beta-cell. Diabetes 51:3135–3138

Thorens B (2003) A gene knockout approach in mice to identify glucose sensors controlling glucose homeostasis. Pflugers Arch 445:482–490

Trapp S, Haider S, Jones P, Sansom MS, Ashcroft FM (2003) Identification of residues contributing to the ATP binding site of Kir6.2. EMBO J 22:2903–2912

Tschritter O, Stumvoll M, Machicao F, Holzwarth M, Weisser M, Maerker E, Teigeler A, Haring H, Fritsche A (2002) The prevalent Glu23Lys polymorphism in the potassium inward rectifier 6.2 (KIR6.2) gene is associated with impaired glucagon suppression in response to hyperglycemia. Diabetes 51:2854–2860

Tucker SJ, Gribble FM, Zhao C, Trapp S, Ashcroft FM (1997) Truncation of Kir6.2 produces ATP-sensitive K + channels in the absence of the sulphonylurea receptor. Nature 387:179–183

Tucker SJ, Gribble FM, Proks P, Trapp S, Ryder TJ, Haug T, Reimann F, Ashcroft FM (1998) Molecular determinants of KATP channel inhibition by ATP. EMBO J 17:3290–3296

Uhde I, Toman A, Gross I, Schwanstecher C, Schwanstecher M (1999) Identification of the potassium channel opener site on sulfonylurea receptors. J Biol Chem 274:28079–28082

Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 27:1047–1053

Yamada Y, Kuroe A, Li Q, Someya Y, Kubota A, Ihara Y, Tsuura Y, Seino Y (2001) Genomic variation in pancreatic ion channel genes in Japanese type 2 diabetic patients. Diabetes Metab Res Rev 17:213–216

Zawar C, Plant TD, Schirra C, Konnerth A, Neumcke B (1999) Cell-type specific expression of ATP-sensitive potassium channels in the rat hippocampus. J Physiol (Lond) 514:327–341

Zingman LV, Hodgson DM, Bast PH, Kane GC, Perez-Terzic C, Gumina RJ, Pucar D, Bienengraeber M, Dzeja PP, Miki T, Seino S, Alekseev AE, Terzic A (2002) Kir6.2 is required for adaptation to stress. Proc Natl Acad Sci USA 99:13278–13283