C-Terminal Tails of Sulfonylurea Receptors Control ADP-Induced Activation and Diazoxide Modulation of ATP-Sensitive K⁺ Channels

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Abstract—The ATP-sensitive K⁺ (K₁ATP) channels are composed of the pore-forming K⁺ channel Kir6.0 and different sulfonylurea receptors (SURs). SUR1, SUR2A, and SUR2B are sulfonylurea receptors that are characteristic for pancreatic, cardiac, and vascular smooth muscle–type K₁ATP channels, respectively. The structural elements of SURs that are responsible for their different characteristics have not been entirely determined. Here we report that the 42 amino acid segment at the C-terminal tail of SURs plays a critical role in the differential activation of different SUR-K₁ATP channels by ADP and diazoxide. In inside-out patches of human embryonic kidney 293T cells coexpressing distinct SURs and Kir6.2, much higher concentrations of ADP were needed to activate channels that contained SUR2A than SUR1 or SUR2B. In all types of K₁ATP channels, diazoxide increased potency but not efficacy of ADP to evoke channel activation. Replacement of the C-terminal segment of SUR1 with that of SUR2A inhibited ADP-mediated channel activation and reduced diazoxide modulation. Point mutations of the second nucleotide-binding domains (NBD2) of SUR1 and SUR2B, which would prevent ADP binding or ATP hydrolysis, showed similar effects. It is therefore suggested that the C-terminal segment of SUR2A possesses an inhibitory effect on NBD2-mediated ADP-induced channel activation, which underlies the differential effects of ADP and diazoxide on K₁ATP channels containing different SURs. (Circ Res. 2000;87:873-880.)

Key Words: K₁ATP channel ■ sulfonamide receptor ■ C-terminus ■ ADP ■ diazoxide
tissue, although it has almost no effect on SUR2A/Kir6.2 channel heterologously expressed in mammalian cells. D’haen et al. recently showed that diazoxide activation of the reconstituted SUR2A/Kir6.2 and native cardiac KATP channels requires the presence of high concentrations of intracellular ADP, which is analogous to the effect of nicorandil on cardiac KATP channel.2,20,22 SUR2A and SUR2B are generated from a single gene and differ only in their 42 amino acid residue C-terminal tails (C42). The C42 of SUR2B shares ~30% homology with that of SUR2A, but it shares ~70% homology with that of SUR1. Therefore, we considered that the C-terminal segment of SURs might be involved in the SUR subtype–dependent activation of KATP channels by diazoxide, although it has been reported that the replacement of the C-terminus of the diazoxide-insensitive SUR2A with the C-terminus of the diazoxide-sensitive SUR1 did not confer diazoxide sensitivity to the chimera.

To examine this possibility, we compared the effects of intracellular ADP and diazoxide on KATP channels containing wild-type, mutant, and chimeric SURs. We found that in the presence of ATP, much higher concentrations of ADP were needed to activate SUR2A/Kir6.2 channels than SUR1 or SUR2B/Kir6.2. In all SUR/Kir6.2 channels, diazoxide increased the potency of ADP for channel activation without significantly affecting its efficacy. The chimera of SUR2A whose C42 was replaced with that of SUR1 formed a KATP channel effectively responding to ADP and diazoxide. When the SUR2A-C42 was adopted to SUR1, the chimera SUR1-2A/Kir6.2 channel was hardly activated by ADP and diazoxide. Mutations in the second nucleotide-binding domain (NBD2) of SUR1 and SUR2B that are known to reduce the binding of ADP resulted in behavior similar to that of the SUR2A-C42 was adopted to SUR1, the chimera SUR1-2A/Kir6.2 channel is 70% homology with that of SUR1. Therefore, we considered that the C-terminal segment of SURs might be involved in the SUR subtype–dependent activation of KATP channels by diazoxide, although it has been reported that the replacement of the C-terminus of the diazoxide-insensitive SUR2A with the C-terminus of the diazoxide-sensitive SUR1 did not confer diazoxide sensitivity to the chimera.

Materials and Methods

Molecular Biology

The cDNAs of mouse Kir6.2 and SURs were used.2,22,23 The coding region of each cDNA was individually subcloned into an expression vector, pcDNA3 (Invitrogen). Mutant SURs (SUR1 [K1348A] and SUR2B [K1348M]) were constructed using the GeneEditorTM in vitro site-directed mutagenesis system (Promega Corp). Chimeric SURs (SUR1-2A, SUR1-2B, and SUR2-1) were made by exchanging the C-terminal 42 amino acids of SUR1 or SUR2A with those of SUR2A, SUR2B, or SUR1 by overlap extension PCR method, respectively. All mutated and chimeric SURs were confirmed by DNA sequencing.

Functional Coexpression of SURs and Kir6.2 cDNAs

The plasmid containing Kir6.2 was cotransfected with one of the SURs into human embryonic kidney 293T cells using LipfectAMINE (Life Technology, Inc). To monitor the efficiency of transfection, pCA-GFP (S65A) was also cotransfected. The cells expressing GFP were identified by fluorescence microscopy and used for electrophysiology.

Electrophysiology

The channels expressed in the cotransfected human embryonic kidney 293T cells were recorded in the inside-out configuration of the patch-clamp technique with a patch-clamp amplifier (Axopatch 200A, Axon Instruments Inc). Pipettes were pulled from thin-walled glass tube. The tip of pipettes were coated with silgard and heat-polished. The bath was perfused with a solution containing (in mmol/L) KCl 145, EGTA 5, MgCl2 2, and HEPES-KOH 5 (pH 7.3), in which the concentration of free Mg2+ was adjusted to 1.4 mmol/L with the presence of various nucleotides. Pipettes were filled with a solution containing (in mmol/L) KCl 145, MgCl2 1, CaCl2 1, and HEPES-KOH 5 (pH 7.4). Single-channel ion currents were recorded in excised membrane patches voltage-clamped at −60 mV. All experiments were performed at room temperature (~25°C).

The data were recorded on videocassette tapes with a PCM converter system (VR-10B, Instrutech Corp). They were reproduced, low pass-filtered at 1 kHz (~3 dB) by an 8-pole Bessel filter (Frequency Devices), sampled at 5 kHz, and analyzed offline on a computer (Macintosh G3, Apple Computer Inc) using a commercially available software (Patch Analyst Pro, MT Corporation). The channel activity was expressed as relative NPo (rNPo) with reference to the maximum NPo measured in the absence of intracellular nucleotides in each inside-out patch. All data were derived from at least 4 distinct patches and expressed as mean±SE.

Results

Effects of Intracellular MgADP and Diazoxide on SUR2A/Kir6.2 and SUR2B/Kir6.2 Channels

The effects of intracellular MgADP on SUR2A/Kir6.2 and SUR2B/Kir6.2 channels and their modulation by diazoxide are compared in Figures 1A and 1B. On formation of inside-out patches, vigorous activity of KATP channels appeared. ATP (1 mmol/L) added to the internal solution almost completely suppressed the channel activity in both cases. Even in the presence of Mg2+, the SUR2A/Kir6.2 channel activity was only weakly enhanced by ADP (Figure 1A). The channel activity evoked by ADP was negligible up to 300 μmol/L, and even with 3 mmol/L ADP, rNPo was ~0.3. Diazoxide (300 μmol/L) induced little channel activity in the absence of ADP but significantly enhanced it at each concentration of ADP ([ADP]). As [ADP] was increased, diazoxide induced more channel activity, which saturated at ~0.3-0.4 in rNPo at [ADP] >300 μmol/L. The saturated rNPo value was nearly equal to that obtained by 3 mmol/L ADP alone (Figure 1A, middle panel).

Unlike the SUR2A/Kir6.2 channel, the SUR2B/Kir6.2 channel was effectively activated by ADP in a concentration-dependent fashion (Figure 1B); as [ADP] was increased from 0 to 30, 300, and 1000 μmol/L, rNPo increased from 0.03±0.03 to 0.26±0.07, 0.37±0.10, and 0.42±0.08 (n=5 for each), respectively. Diazoxide enhanced the channel activity at each [ADP]. As the concentration of the agent was raised from 0 to 30 and 300 μmol/L, the sensitivity of channel to ADP increased in a concentration-dependent fashion, but the maximum rNPo remained at ~0.4-0.5 (Figure 1B, middle panel). Thus, diazoxide mainly increased the potency but not the efficacy of ADP to enhance the KATP channel activity in both SUR2A/Kir6.2 and SUR2B/Kir6.2.

In contrast, pinacidil activated both SUR2A and SUR2B KATP channels even in the absence of ADP in a similar concentration-dependent fashion (Figures 1A and 1B, right panels). Also different from diazoxide, at high [ADP], the...
rNP_o evoked by even 1 μmol/L pinacidil reached a value beyond that obtained by ADP alone. Pinacidil (1 μmol/L) shifted the concentration-response relationship between [ADP] and rNP_o upward almost in a parallel fashion by 0.2-0.3 in rNP_o at each [ADP]. Pinacidil (10 μmol/L) increased the activity of both SUR2A and SUR2B/Kir6.2 channels by 0.8-0.9 in rNP_o in the absence of ADP. In the presence of various [ADP], the channel activity was enhanced by the drug essentially in an additive manner, which saturated at about 1.0 rNP_o at [ADP] >300 μmol/L. When the concentration of pinacidil was additionally increased to 100 μmol/L, channel activity decreased to 0.6-0.7 in rNP_o, probably because of nonspecific inhibitory or desensitizing effects of the drug as previously reported. Thus, it seems likely that pinacidil activates SUR2A and SUR2B-K_{ATP} channels independent of [ADP]. Therefore, it is strongly suggested that diazoxide and pinacidil enhance the SUR2-K_{ATP} channel activity by using distinct mechanisms.

SUR2A and SUR2B are splicing isoforms generated from a single gene that differ from each other only in the 42 amino acid segment at their C-terminal end. The C-terminal segment may then be responsible for the differential effects of ADP and diazoxide on the K_{ATP} channels containing these SUR2-isoforms. The C-terminal 42 amino acids (C42) of SUR2B possess only ~30% homology with those of SUR2A but ~70% with those of SUR1. Therefore, to clarify the role of C42, we examined the effect of ADP and diazoxide on the chimera SUR2-1, whose main part was SUR2, and C42 was adopted from SUR1.

Figure 1. Effects of intracellular ADP, diazoxide, and pinacidil on SUR2A/Kir6.2 (A), SUR2B/Kir6.2 (B), and SUR2-1/Kir6.2 (C) channels. Left, Effects of ADP and diazoxide (DZX) or pinacidil (PIN) on SUR2A/Kir6.2, SUR2B/Kir6.2, and SUR2-1/Kir6.2 channels. ATP, ADP, diazoxide and pinacidil were added to the bath solution as indicated by bars. Middle, Relationship between the concentration of ADP and relative NPo (rNPo) in the absence (\(V\)) and presence of diazoxide (\(U\), 30 μmol/L and \(\cdot\), 300 μmol/L). Right, Relationship between the concentration of ADP and relative NPo (rNPo) in the absence (\(\circ\)) and presence of pinacidil (\(\odot\), 1 μmol/L; \(\triangledown\), 10 μmol/L; and \(\blacklozenge\), 100 μmol/L). Relative NPo is expressed as mean±SE.
The chimera SUR2-1 formed a fully functional K<sub>ATP</sub> channel with Kir6.2 (Figure 1C). The channel activity in the inside-out patches was almost completely suppressed by ATP (1 mmol/L), and diazoxide (300 μmol/L) enhanced it to ~0.35 in rNP<sub>o</sub> in the absence of ADP. The channel activity was enhanced by ADP in a concentration-dependent fashion in a similar manner to the SUR2B/Kir6.2 channel. Diazoxide increased the channel activity at each [ADP] but did not exceed the maximum level induced by ADP also as for SUR2B/Kir6.2 channel. Therefore, the C42 of SUR1 seems to possess a similar effect on the ADP-mediated activation of the SUR2B-K<sub>ATP</sub> channel as the SUR2B-C42, which might have been suggested by the high homology between the two.

C-Terminal Tail of SUR2A Suppresses Intracellular ADP-Activation and the Diazoxide Effect on SUR1/Kir6.2 Channel

The above results suggest that the SUR-C42 may play a specific functional role in the control of ADP-mediated activation of K<sub>ATP</sub> channels and the modulation by diazoxide. To additionally examine this possibility, we next constructed chimera SURs, whose main part was SUR1 with the C-terminal segment of either SUR2A (SUR1-2A) or SUR2B (SUR1-2B) and compared the responses of wild-type SUR1/Kir6.2 and chimeric channels (SUR1-2A/Kir6.2 and SUR1-2B/Kir6.2) toward ADP and diazoxide.

Figure 2A shows the effects of ADP and diazoxide on SUR1/Kir6.2 (A), SUR1-2A/Kir6.2 (B), and SUR1-2B/Kir6.2 (C) channels. Left, Effects of ADP and diazoxide (DZX) on SUR1/Kir6.2, SUR1-2A/Kir6.2, and SUR1-2B/Kir6.2 channels. ATP, ADP and diazoxide were added to the bath solution as indicated by bars. Right, Relationship between the concentration of ADP and relative NP<sub>o</sub> (NP<sub>o</sub>) in the absence (○) and presence of diazoxide (○, 30 μmol/L and ●, 300 μmol/L). Relative NP<sub>o</sub> is expressed as mean±SE.
effect of ADP on channel activity decreased, but the maximum rNP_o remained the same at ≈0.6 as 30 μmol/L diazoxide. However, this value was higher by ≈0.2 than the rNP_o at the highest level of channel activity induced by [ADP] alone (Figure 2A, right panel).

The chimera SUR1-2A/Kir6.2 channel was hardly activated by even high [ADP] (Figure 2B). Diazoxide (300 μmol/L) enhanced the SUR1-2A/Kir6.2 channel activity. The magnitude of the increase was the same, ≈0.2 rNP_o, at each [ADP]. Thus, the concentration-response relationship between [ADP] and rNP_o of the channel was shifted upward almost in a parallel fashion by ≈0.2 in rNP_o (Figure 2B, right panel). On the other hand, the SUR1-2B/Kir6.2 channel (Figure 2C) was as responsive to ADP and diazoxide as SUR1/Kir6.2 (Figure 2A), which confirms the functional similarity between the C42 of SUR1 and SUR2B.

Because the activation level of SUR1-2A-K ATP channel by diazoxide was nearly the same as the difference between the drug-induced maximum channel activity in the presence of ADP, the above results can be interpreted as indicating that the SUR1/Kir6.2 channel activity could be enhanced by diazoxide via two distinct mechanisms; one is ADP-dependent and the other is ADP-independent. It seems likely that the C42 of SUR2A, but not of SUR1 or SUR2B, inhibits the ADP-dependent mechanism for the activation of SUR1/Kir6.2 channel and the modulation by diazoxide.

Effects of Mutations in NBD2 of SUR2B and SUR1 on the ADP and Diazoxide Action

Like other ATP-binding cassette proteins, SURs possess 2 nucleotide-binding domains (NBD1 and NBD2, respectively). It was shown that SUR1 binds ATP at NBD1 and ADP at NBD2. The NBDs possess the Walker A and B motifs to form a portion of a nucleotide-binding pocket. In various ATP-binding proteins, Walker A motif in NBDs is responsible for binding or hydrolysis of nucleotides, where the highly conserved lysine residue plays a critical role. The mutation of this lysine residue in NBD2 extinguishes the ADP-mediated activation of SUR1 and SUR2A-K ATP channels. Therefore, we introduced mutations of the lysine residue in NBD2 of SUR2B and SUR1 (K1348M in SUR2B and K1384A in SUR1) and examined the effects of ADP and diazoxide on the mutant SUR/Kir6.2 channels (Figure 3).

The mutant SURs formed with Kir6.2 fully functional K ATP channels, whose activity was almost completely suppressed by 1 mmol/L ATP. Figure 3A shows that ADP up to 1 mmol/L had little effect on SUR2B(K1348M)/Kir6.2 channel and that the effect of diazoxide was dramatically reduced. In contrast, pinacidil (100 μmol/L) enhanced the SUR2B(K1348M)/Kir6.2 channel to ≈0.7 in rNP_o in the absence of ADP (Figure 3A, right panel), which was the same level as the wild-type SUR2B/Kir6.2 (Figure 1B). The mutant SUR1(K1384A)/Kir6.2 channel also scarcely responded to ADP (Figure 3B). Different from the SUR2B mutant, diazoxide (30 and 300 μmol/L) enhanced the SUR1(K1384A)/Kir6.2 channel to ≈0.1 and ≈0.2 in rNP_o, respectively, irrespective of [ADP]. As a result, the concentration-response relationship between rNP_o and [ADP] was shifted by diazoxide upward almost in a parallel fashion (Figure 3B), which was similar to the reaction of the chimera SUR1-2A/Kir6.2 channel (Figure 2B).
**Discussion**

In this study, we examined the effect of intracellular ADP and diazoxide on the reconstituted K\textsubscript{ATP} channels composed of Kir6.2 and SUR1, SUR2A, or SUR2B. We found that the SUR2A/Kir6.2 channel is much less sensitive to ADP than SUR2B or SUR1/Kir6.2. In all types of SUR/Kir6.2 channels, diazoxide increased the potency of ADP for channel activation without affecting its efficacy. The experiments using chimera and mutant SURs strongly suggest that the 42 amino acids at the C-terminal end (C42) of SURs play critical roles in the ADP-mediated activation of K\textsubscript{ATP} channels and that the C42 of SUR2A may reduce ADP-mediated channel activation at NBD2. Thus, high concentrations of ADP were required for diazoxide-activation of the SUR2A/Kir6.2 channel.

**Diazoxide May Enhance SUR2/Kir6.2 Channel Activity Exclusively by an ADP-Mediated Activation Mechanism**

The modes of KCO action on native cardiac K\textsubscript{ATP} channels have been electrophysiologically classified into 3 distinct types.\(^2\) The type 1 KCOs, such as pinacidil and lemakalim, enhance the maximum response of K\textsubscript{ATP} channels and decrease the channel sensitivity to intracellular ATP (ATP\(_i\)). The type 2 KCOs, such as ER-001533 and HOE234, selectively decrease the channel sensitivity to ATP\(_i\). The type 3 KCO, nicorandil, requires the presence of intracellular ADP (ADP\(_i\)) to enhance the channel activity. Because diazoxide activation of the reconstituted SUR2A/Kir6.2 as well as native cardiac K\textsubscript{ATP} channels was shown to require the presence of high concentrations of intracellular ADP,\(^19\) diazoxide can also be classified as a type 3 KCO. The present study provides molecular insights for the type 3 action of diazoxide on various types of K\textsubscript{ATP} channels.

Although the potency was different, ADP induced openings of SUR2A and SUR2B/Kir6.2 channels in a concentration-dependent fashion. The potency of ADP for channel activation was much lower in SUR2A/Kir6.2 channel than in SUR2B/Kir6.2. Diazoxide (300 \(\mu\)mol/L) enhanced both types of K\textsubscript{ATP} channel activity at each [ADP], but the SUR2-channel activity in the presence of the drug did not exceed the maximum level of ADP-induced channel openings. Furthermore, the effect of diazoxide was largely reduced when the lysine residue at NBD2 of SUR2B was mutated. These results indicate that in the case of SUR2s, diazoxide enhances the K\textsubscript{ATP} channel activity by acting on the ADP-mediated mechanism located at NBD2 (Figure 4).

Pinacidil, the type 1 KCO for SUR2-containing K\textsubscript{ATP} channels, induced channel activation apparently in an additive manner to the channel openings induced by ADP (Figures 1A and 1B). The drug also activated the SUR2B(K1348M)/Kir6.2 channel, whose ADP-dependent activation was largely attenuated (Figure 3A, right panel). This is consistent with a recent study by Uhde et al\(^{15}\) using chimeras between SUR1 and SUR2B that showed that the TMD 16-17 and the CL 13-14 of SUR2 but not of SUR1 confer the activation by pinacidil, levocromakalin, and P1075 (Figure 4).

In the case of SUR1, the effect of diazoxide could be divided apparently into 2 components. One is ADP-dependent, similar to that of SUR2-K\textsubscript{ATP} channels, and the other is ADP-independent. In the chimera SUR1-2A/Kir6.2 and the mutant SUR1(K1384A)/Kir6.2 channels, the ADP-dependent component was largely attenuated, and diazoxide (300 \(\mu\)mol/L) increased the channel rNPo, by \(\approx 0.2\) irrespective of [ADP]. Consistently, in the concentration-response relationship between ADP and wild-type SUR1/Kir6.2 channel activity, the channel rNPo in the presence of diazoxide was higher by \(\approx 0.2\) than the highest activity induced by ADP alone. Babenko et al\(^{14}\) recently showed using chimeras between SUR1 and SUR2A that TMD 6-11 and NBD1 of SUR1 are required for the activation by diazoxide and that the corresponding regions of SUR2 do not have such function. The ADP-independent component of diazoxide on the SUR1/Kir6.2 channel may be related to these regions of SUR1. But because their experiments were performed in the absence of ADP, they missed the ADP-dependent component shown in this study. This study showed that the ADP-dependent component of diazoxide activation may be conferred by the NBD2 of either SUR1 or SUR2 and the C-terminal tails of SUR1 or SUR2B (Figure 4). Therefore, diazoxide may have at least two target regions in SUR1 but only one (ie, NBD2) in SUR2 (Figure 4).

**The Functional Role of the 42 Amino Acids at C-Terminal Tail End of SUR2**

This study indicates that the difference in the 42 amino acids at the C-terminal tail (C42) of SURs plays critical roles in the control of ADP-mediated activation of the K\textsubscript{ATP} channel and the modulation of it by a KCO, diazoxide. SUR2A and SUR2B are splicing isoforms from a single gene and divergent only in C42. Therefore, the ADP-mediated activation of K\textsubscript{ATP} channels might be either inhibited by the SUR2A-tail or enhanced by the SUR2B-tail. The experiments using the chimera of SUR1 whose C-terminal segment was replaced...
with that of SUR2A strongly support the former possibility. Furthermore, the point mutation in NBD2 of SUR2B and SUR1, which is shown to reduce the binding or hydrolysis of nucleotides in other ABC proteins, abolished ADP-mediated activation of these K_{ATP} channels and also attenuated the modulation of it by diazoxide. Consistent with these results, Matsuo et al. have recently reported using photoaffinity-labeled nucleotides that the affinity of NBD2 of SUR2A for ADP binding was significantly lower than that of SUR2B and SUR1.

It is known that K_{ATP} channels in pancreatic β cells are active under physiological conditions and regulate the resting membrane potential.1 As a result, an increase of the ratio between [ATP], and [ADP], induced by high blood glucose inhibits the resting K_{ATP} channel, causes depolarization of the β cells, and generates Ca^{2+}-dependent action potentials, which triggers insulin secretion. A mutation in NBD2 of SUR1 was identified in an individual diagnosed PPHI.10 The reconstituted K_{ATP} channels possessing the mutated SUR1 exhibited a decreased sensitivity to MgADP and diazoxide and could not be opened in response to metabolic inhibition.10,12 Thus, the high channel sensitivity to ADP at NBD2 of SUR1 may play an essential role in regulation of insulin secretion in pancreatic β cells.

In some vascular smooth muscle cells, K_{ATP} channels were shown to be active under physiological conditions.31 Thus, high sensitivity to intracellular ADP allowed by the SUR2B-C42 may also be essential for the channels to play a role in physiological control of vascular tone. In contrast, the low sensitivity of SUR2A to ADP because of its particular C-terminus means that the physiological alteration of the [ATP]/[ADP] ratio may not significantly induce K_{ATP} channel activity in cardiomyocytes. But when [ADP] increases under pathophysiological conditions, however, the cardiac K_{ATP} channels would be activated and may contribute to the shortening of action potential duration.

Therefore, it is indicated that the differences in the 42 amino acid segment at C-terminal end among the subtypes of SUR may play critical roles in the physiological and pathophysiological control of K_{ATP} channels in different tissues. Additional studies are needed to elucidate the molecular mechanisms to determine how the C-terminal segments control the interaction between ADP and NBD2, how the ADP binding to NBD2 induces the K_{ATP} channel openings, and how diazoxide enhances the ADP-mediated channel activation process.

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