**Identification of Specific Pore Residues Mediating KCNQ1 Inactivation**

**A NOVEL MECHANISM FOR LONG QT SYNDROME**

KCNQ1 inactivation bears electrophysiological characteristics different from classical N- and C-type inactivation in Shaker-like potassium channels. However, the molecular site of KCNQ1 inactivation has not yet been determined. KCNQ2 channels do not exert a fast inactivation in contrast to KCNQ1 channels. By expressing functional chimeras between KCNQ1 and KCNQ2 in *Xenopus* oocytes, we mapped the region of this inactivation to transmembrane domain S5 and the pore loop H5 and finally narrowed down the site to positions Gly272 and Val307 in KCNQ1. Exchanging these two amino acids individually with the analogous KCNQ2 residue abolished inactivation. Furthermore, a KCNQ1-like inactivation was introduced into KCNQ2 by mutagenesis in the corresponding region, confirming its relevance for the inactivation process. As KCNQ1 inactivation involves the regions S5 and H5, it exhibits a geography distinct from N- or C-type inactivation. Native cardiac *I*_Ks* channels comprising KCNQ1 and accessory MinK subunits do not inactivate because of the functional interaction of KCNQ1 with MinK. Mutations in KCNQ1 can lead to long QT1 syndrome, an inherited form of arrhythmia. The long QT1 mutant KCNQ1(L273F) displays a pronounced KCNQ1 inactivation. Here we show that when expressing mutant *I*_Ks* channels formed from KCNQ1(L273F) and MinK, MinK association no longer eliminates KCNQ1 inactivation. This results in smaller repolarizing currents in the heart and therefore represents a novel mechanism leading to long QT syndrome.

Ion channels regulate the membrane potential of excitable cells. These are proteins containing aqueous pores and undergo conformational changes leading to the defined gating states “open” and “closed,” where open channels are conducting and closed channels are nonconducting. In many channels there are additional “inactivated” states, which are also nonconducting and which follow the open states because of an activating physiological stimulus. Among voltage-gated potassium channels, there are two major types of inactivation. N-type inactivation is mediated by an intracellular “ball,” located within the N terminus of either the pore-forming protein or a modulatory β-subunit, which plugs the ion channel pore (1–4). In C-type inactivation the outer vestibule of the pore itself undergoes conformational changes (5).

Inactivation plays an important physiological role such as determining the sodium spike in neurons and myocytes. Genetic defects, resulting in impaired inactivation of sodium channels, can cause myotonia and a form of long QT syndrome (LQTS) (6, 7).

The KCNQ gene family represents a group of recently identified voltage-gated potassium channels, and disease-causing mutations have been identified in 4 of 5 known KCNQ genes (8–13). KCNQ1 (formerly called KvLQT1), the founding member of this family (8), coassembles with MinK (also called IsK or KCNE1) protein (14) generating slowly activating potassium currents. These constitute the cardiac *I*_Ks* conductance, one component of the delayed rectifier repolarizing current in ventricular myocytes. Mutations in either cause LQTS, whereby LQT1 mutations occur in KCNQ1 and LQT5 mutations in MinK (8, 15–21).

Homomeric KCNQ1 channels are characterized by fast activation and delayed inactivation. Delay of inactivation was explained by two open states separating closed and inactivated states in a linear gating scheme. Inactivation of KCNQ1 is incomplete, supposedly resulting from a weak voltage sensitivity of the rates of both onset of and recovery from inactivation. Alternatively, the partial inactivation can also be caused by subconductance states. The lack of sensitivity to high extracellular TEA and potassium, together with delayed onset distinguishes KCNQ1 inactivation from classical C-type inactivation in Shaker-like channels. The weak voltage sensitivity of KCNQ1 inactivation and the lack of a Shaker-like ball structure within KCNQ1 differ from N-type inactivation (22, 23).

In contrast to the existing biophysical data on KCNQ1 inactivation, its molecular determinants have only been discussed tentatively so far. Franquena et al. (24) analyzed three different LQT1 mutations located within or close to the intracellular linker between the S4 and S5 transmembrane domains. After expression in *Xenopus* oocytes, some mutants showed overall altered gating characteristics compared with KCNQ1-WT, but in none of them inactivation was abolished. The LQT1 mutation L273F (8) exhibited a pronounced macroscopic inactivation when expressed in *Xenopus* oocytes (19). (The position number according to Shalaby et al. (19) is L272F.) The mutation is located in transmembrane segment S5, indicating a possible involvement of the S5 region in channel inactivation.

Inactivation of KCNQ1 is abolished by coassembly with MinK (22, 23), suggesting that interacting domains of these two proteins might also influence the inactivation process itself. Pusch et al. (25) have presented evidence for MinK interaction with the outer vestibule of KCNQ1. MinK also might

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1 The abbreviations used are: LQTS, long QT syndrome; LQT, long QT; TEA, tetraethylammonium; WT, wild type.
directly interact with the pore region of KCNQ1 as suggested by both a yeast two-hybrid study and a cysteine-scanning study in MinK (26, 27).

It was our aim to gain insights into the as yet unknown molecular mechanism underlying KCNQ1 inactivation and its possible pathophysiological relevance.

**EXPERIMENTAL PROCEDURES**

**Molecular Biology**—For the construction of chimeras, silent point mutations were introduced producing restriction endonuclease sites at corresponding positions in KCNQ1 and KCNQ2, namely a SacI site (at KCNQ1 amino acids Glu261-Leu262), an NsiI site (at KCNQ1 amino acids Asp231-Ala232-Leu233), and a BamHI-site (at KCNQ1 amino acids Gly268-Ser269). Other chimeric joining regions were created by recombinate polymerase chain reaction resulting in constructs described in Fig. 1.

Site-directed mutagenesis was performed by polymerase chain reaction using cloned *Pyrococcus furiosus* DNA polymerase (Strategen). All constructs were reconfirmed by automated DNA sequencing. For *Xenopus* oocyte expression, capped cRNA was synthesized using the SP6 and T7 mMessage mMachine kits (Ambion). GenBank*®* accession numbers used are as follows: hKCNQ1, AJ006345; hKCNQ2, NM004518; and MinK(KCN1E1), M26685.

**Two Electrode Voltage Clamp Technique—** *Xenopus* laevis oocytes were obtained from tricaine-anesthetized animals. Ovaries were collagenase-treated (1 mg/ml, Worthington, type II) in OR2 solution (NaCl 82.5 mM, KCl 2 mM, MgCl2 1 mM, HEPES 5 mM, pH 7.4) for 120 min and subsequently stored in recording solution ND96 (NaCl 86 mM, KCl 2 mM, CaCl2 1.5 mM, MgCl2 1 mM, HEPES 5 mM, pH 7.4) with additional sodium pyruvate (275 mg/liter), theophylline (90 mg/liter) and Gentamycin (50 mg/liter) at 18 °C. Oocytes were individually injected with 10 ng of cRNA encoding WT or mutant KCNQ1 subunits, or co-injected with 10 ng of cRNA of WT or mutant KCNQ1 and 5 ng of hMinK cRNA.

Standard two electrode voltage clamp recordings were performed at 22 °C with a Turbo Tec 10CX (NPI) amplifier, an ITC-16 interface combined with LabSoft (Heka), and Origin version 5.0 (Microcal Software) for data acquisition. Macroscopic currents were recorded 3–4 days after injection. The pipette solution contained 3 M KCl. All fitting procedures were based on the simplex algorithm. Student’s t test was used to test for statistical significance, which was assumed with p < 0.05.

To calculate the fraction of inactivated channels, a double exponential fit to the tail currents was done according to the formula: I(t) = A0 × exp(−t/τ1) − A1 × exp(−t/τ2). The faster and the slower component represent recovery from inactivation and deactivation respectively, whereby A0 and τ are the amplitude and time constant for the slow component, and A1 and τ are the amplitude and time constant for the fast component. The fraction of inactivated channels is given by A/A0, where the amplitude A is related to the degree of activation, and the amplitude A indicates the degree of inactivation. The method was previously described in detail (22, 23).

**RESULTS**

Inactivation in KCNQ1 channels becomes apparent in a hook in the tail current when repolarizing the membrane potential after a depolarizing pulse (Refs. 22, 23, and Fig. 1D). This trait is also described for HERG channels where it is even more pronounced (28, 29). The hook is attributed to rapid recovery of currents from inactivation at a rate much faster than deactivation (Fig. 1D). Onset of KCNQ1 inactivation can be revealed using a double-pulse protocol (23, 29, 30). A conditioning 2-s pulse to 40 mV is applied to activate and inactivate channels followed by a 20-ms hyperpolarizing interpulse, which transiently removes inactivation. During a final test pulse to 40 mV, onset of inactivation becomes visible (Fig. 1C). Throughout this study we considered both the hook and the onset of inactivation as a marker for the presence or absence of inactivation in mutant KCNQ1 channels.

To define the structural determinants of KCNQ1 inactivation, we constructed a series of functional chimeras between the closely related channels KCNQ1 and KCNQ2. KCNQ2 is a component of the neuronal noninactivating M-current and is mutated in neonatal epilepsy (9, 10, 31). As shown in Fig. 1, KCNQ2 did not inactivate like KCNQ1. In a gain of function approach, we transferred the ability to inactivate from KCNQ1 to KCNQ2. Substituting the S5/S6 domain from KCNQ1 into KCNQ2, caused a dramatic change in the biophysical characteristics of the resulting construct (Q5S5-S6Q1) compared with KCNQ2-WT (Fig. 1). Macroscopic inactivation is conferred at positive voltages, suggesting that this part of the protein is necessary for the inactivation process.

By contrast it was possible to substitute large segments of KCNQ2 into KCNQ1 without abolishing inactivation. A KCNQ1 construct including substituted KCNQ2 amino acids from the end of H5 to the end of S6 (Q5S5Q6Q2, Fig. 1) maintained inactivation. Interestingly the KCNQ2 S6 region somehow enhances intrinsic KCNQ1 inactivation. Another KCNQ1 chimeric construct containing the KCNQ2 S5/S6 linker (Q1S5/H5 linker Q2) revealed that exchanging this region does not remove inactivation (Fig. 1). Thus the borders of the crucial region for inactivation could be assigned to the S5 segment and part of the H5 pore loop.

Fig. 1A illustrates differences in the protein sequences of the related KCNQ channels in the described regions. With site-directed mutagenesis, we exchanged the different amino acids in KCNQ1 to the corresponding residues in KCNQ2. Expression of these point mutants showed that two single amino acid substitutions, G272C and V307L, are capable of abolishing inactivation (Fig. 1). Mutation G272C, adjacent to the site of clinical mutation L273F (as described above), caused additionally slowed activation kinetics. To exclude the possibility that the introduced cysteine might be stabilizing the channel via formation of novel intramolecular disulfide bonds, we substituted glycine with threonine at this position. Now, activation and deactivation kinetics of G272T were very similar to KCNQ1-WT (Table I); however inactivation still was completely abolished. The other key mutation V307L located in the pore loop showed slightly slowed activation and deactivation kinetics compared with KCNQ1-WT (Table I), but again abolished inactivation. The slight changes in activation kinetics are not reflected by altered current-voltage relationships and thus shifted voltage dependence of activation cannot account for the lack of inactivation. A further observation was that in the noninactivating mutants, the slow component of deactivation was decreased or abolished (Table I). Possibly the slow component of deactivation in KCNQ1 is somehow connected to the inactivation process.

To corroborate our results, we made additional point mutations in the inactivating KCNQ2 chimera Q5S5-S6Q1. Analogous substitution of glycine 272 in S5 (KCNQ1 numbering) and valine 307 in H5 (KCNQ1 numbering) by cysteine and leucine, respectively, again abolished inactivation in this chimeric construct. Effects on activation and deactivation kinetics were only minor (Fig. 2, A and B).

Using a final approach, we attempted to introduce a KCNQ1-like inactivation into KCNQ2 through single amino acid exchanges. We constructed the KCNQ2 mutations C242G, L243F, and L272V. These positions correspond to the residues Gly573-Leu573, and Val1037 in KCNQ1, which we recognized as being important for KCNQ1 inactivation. Introducing a phenylalanine at position 243 in KCNQ2 resulted in inactivating currents interestingly similar to the KCNQ1 mutant L273F (Fig. 3A). The mutant KCNQ2/L273V did not exert a KCNQ1-like inactivation as shown in Fig. 3B. In a construct containing both mutations L243F and L272V, an inactivation was apparent although the currents were small in amplitude (Fig. 3C). Substituting the cysteine at KCNQ2 position 242 by glycine individually or together with the mutations described above
FIG. 1. Chimera and point mutants identifying regions of importance for KCNQ1 inactivation. A, protein sequence alignment of hKCNQ1, hKCNQ2, and rKCNQ3 showing the important regions for KCNQ1 inactivation. Postulated transmembrane segments S5 and S6 and the inner pore loop H5 are indicated above. Gray bars indicate the KCNQ2 spanning sequence in the Q1S6Q2 and Q1S5/H5linkerQ2 chimeras. These amino acids had a low impact on the inactivation process as shown below in B, C, and D. Differences in S5 and H5 of KCNQ1 and KCNQ2/KCNQ3 are marked by arrows. Amino acids that can be exchanged in KCNQ1 without affecting inactivation are marked by gray arrowheads and those that abolish inactivation by black arrowheads. Point mutants V308I and V310L and a double mutant T365A/L366W were still inactivating (data not shown). KCNQ3 forms heteromers with KCNQ2, which are not inactivating (13). Asterisk indicates the site of the LQT1 mutant L273F. B, model of important chimeras and mutants showing the typical backbone of a voltage-dependent potassium channel with the intracellular C and N terminus and six transmembrane domains. Black and gray lines indicate KCNQ1 and KCNQ2 sequences, respectively. C, representative current traces recorded in an oocyte injected with cRNA from the respective construct shown in B. A double-pulse protocol was used to show the onset or lack of inactivation. After stepping the membrane potential for 2 s from −100 mV to 40 mV, a second 1-s pulse to 40 mV was applied following different 20-ms interpulses (to −120 mV, −90 mV, and −60 mV) abrogating inactivation. The insets magnify the important regions. D, representative current traces at different voltages recorded by stepping the membrane potential for 3 s from −100 mV to 50 mV in 10
Oocytes were injected with 10 ng of cRNA. Currents were activated by a 3-s pulse to 40 mV and followed by a hyperpolarizing pulse to −60 mV. Kinetics were analyzed by exponential fits to the rising phase for activation and to the tail current for deactivation. Values are mean ± S.E., numbers of oocytes are shown in parenthesis.

<table>
<thead>
<tr>
<th>Constants</th>
<th>WT-KCNQ1</th>
<th>KCNQ1(G272C)</th>
<th>KCNQ1(G272T)</th>
<th>KCNQ1(V307L)</th>
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<tr>
<td>Activation, $\tau_{\text{act}}$</td>
<td>33 ± 3 ms (9)</td>
<td>103 ± 7 ms (9)</td>
<td>41 ± 2 ms (8)</td>
<td>76 ± 4 ms (9)</td>
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<tr>
<td>Activation, $\tau_{\text{slow}}$</td>
<td>0.85 ± 0.09 s (9)</td>
<td>0.68 ± 0.05 s (9)</td>
<td>0.27 ± 0.0 s (8)</td>
<td>0.67 ± 0.06 s (9)</td>
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<tr>
<td>Deactivation, $\tau_{\text{act}}$</td>
<td>222 ± 2 ms (9)</td>
<td>267 ± 18 ms (9)</td>
<td>238 ± 4 ms (8)</td>
<td>420 ± 30 ms (9)</td>
</tr>
<tr>
<td>Deactivation, $\tau_{\text{slow}}$</td>
<td>1.7 ± 0.4 s (9)</td>
<td>—</td>
<td>6.5 ± 0.1 s (8)</td>
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Fig. 2. Point mutants abolishing KCNQ1 inactivation in the inactivating chimera Q2S5-S6Q1. A and B, model of the chimera Q2S5-S6Q1 including introduced mutations G272C (A) and V307L (B). Black and gray lines indicate KCNQ1 and KCNQ2 sequences, respectively. Double-pulse protocol as shown in Fig. 1 demonstrate lack of inactivation in both point mutations shown. Right, current traces at different voltages of oocytes injected with cRNA of each construct; protocols as described in Fig. 1. Insets show magnified tail currents. The respective IV relationship is shown plotted from 10 oocytes for each construct. Error bars indicate S.E. All vertical bars represent 2 µA, horizontal bars, 0.5 s.

resulted in a mutant that did not produce measurable currents under our conditions.

The only crystal structure of the pore-forming part of a potassium channel presently available derives from the KcsA channel of Streptomyces lividans (32). In this structure, we checked the locations of the residues equivalent to those that we identified as being involved in KCNQ1 inactivation. Interestingly, the amino acids in the KcsA channel, Leu40 and Val70 corresponding to the clinically relevant residue KCNQ1(L273) and the residue KCNQ1(V307) respectively, are in close vicinity within one subunit. The closest distances of these amino acids are around 4 Å for all four subunits, thereby enabling attractive interactions. Within the S5/H5/S6 region, KCNQ1 shares about 36% identity and 46% homology to KcsA. Accordingly the same residues in KCNQ1 can also be expected to be in close proximity. This raises the possibility that intramolecular interaction of transmembrane segment S5 and the helical part of the pore loop H5 is involved in the inactivation process, putatively stabilizing the three-dimensional conformation of the inactivated channel. Exchange of glycine at KCNQ1 position 272 by a side chain-containing amino acid can be anticipated to change the conformation of the encompassing S5 region and therefore possibly disrupt interaction of amino acids Leu273 and Val307. Introduction of a KCNQ1-like inactivation into KcsQ2 by exchanging leucine 243 with the more extensive phenylalanine in S5 supports the hypothesis of interaction of domains S5 and H5 facilitating KCNQ1 inactivation.

We next examined the pathophysiological role of KCNQ1 inactivation by studying kinetics of the LQT1 mutant L273F, which is located next to Gly272 and in the KcsA channel model in close proximity to Val307. The mutant was analyzed previously (19); the authors reported a pronounced macroscopic inactivation of KCNQ1(L273F) as well as a reduced current amplitude of KCNQ1(L273F)/MinK compared with KCNQ1-WT/MinK. We expressed homomeric mutant and heteromeric mutant/MinK channels and compared them to KCNQ1-WT and $I_{Ks}$ channels (Fig. 4). The greatly enhanced inactivation of KCNQ1(L273F) is shown in Fig. 3B. Tail current analysis after a 3-s preconditioning pulse to 40 mV resulted in 86 ± 3% inactivated mutant channels in contrast to only 31 ± 1% in KCNQ1-WT (Fig. 4, A and B; Table II). Around 30% inactivated WT channels were also calculated previously using the same analysis (22, 23). Time courses of inactivation and recovery were significantly affected compared with WT channels as well (Table II). After coexpressing the same amounts of KCNQ1-WT or KCNQ1(L273F) cRNA together with MinK cRNA, we observed a decreased current amplitude for mutant $I_{Ks}$ channels consistent with previous data (19) (Fig. 3, C and D). The current-voltage relationship of activation was not shifted in mutant $I_{Ks}$ channels compared with WT channels (Fig. 4E). Most interestingly, using the double-pulse protocol, we demonstrated that MinK is no longer able to completely abolish the pronounced inactivation in KCNQ1(L273F) (Fig. 4D). Moreover, this inactivation in mutant $I_{Ks}$ channels was accelerated compared with homomeric KCNQ1(L273F), further indicating functional assembly of the mutant KCNQ1 subunit with MinK (Table II). Tail currents of KCNQ1(L273F)/MinK channels displayed a weak hook confirming the persistence of inactivation in these heteromers (Fig. 4D). By analyzing this hook, we calculated that more than 20% of mutant $I_{Ks}$ channels were in the inactivated state after a 3-s activating pulse to 40 mV (Fig. 4F). Thus, the significant number of inactivated, i.e. nonconducting, mutant $I_{Ks}$ channels contributes to the decreased amplitudes of KCNQ1(L273F) and KCNQ1(L273F)/MinK com-

mV increments in an oocyte injected with cRNA of the respective construct shown in B. Tail currents show a characteristic hook reflecting recovery from inactivation. The insets magnify the important regions. E, IV relationship of constructs shown in B recorded as described in D ($n = 10–16$). Amplitudes at the end of 3-s test pulses were plotted against voltage. Error bars indicate S.E. All vertical bars represent 2 µA, horizontal bars, 0.5 s.
pared with those of KCNQ1-WT and KCNQ1/MinK. *In vivo* this is expected to result in a decreased repolarizing \( I_{Ks} \) conductance constituting a new mechanism leading to LQT1 syndrome.

**DISCUSSION**

Inactivation is best understood and intensively studied for classical N- and C-type mechanisms in *ShakerB* potassium channels. Fast N-type inactivation is realized by a ball plug-in mechanism, where a ball-forming domain of the channel binds to its receptor thereby blocking the ion pathway from the intracellular side (1–5). This occurs independently of the membrane potential. KCNQ1 inactivation exerts slower inactivation gating and a weak voltage dependence. Further stressing the differences from the N-type mechanism, the identified residues at KCNQ1 positions 272, 273, and 307 are not expected to be accessible for a complex ball structure from the intracellular side and thus probably cannot account for a potential receptor site.

In classical C-type inactivation, conformational changes in the outer vestibule of the pore are coupled to the inactivation process. This is reflected in the dependence of the inactivation to extracellular potassium and TEA (33, 34). In KCNQ1, TEA sensitivity of the inactivation rate is not determinable because of very low TEA affinity to the channel (22, 23, 35). However, KCNQ1 inactivation is independent of extracellular potassium concentration; a principal difference from C-type behavior. In *Shaker*-like potassium channels, certain mutations within the P-region H5 and the sixth membrane-spanning region S6 have been shown to affect the time course of inactivation (33, 36). Notably, also in our study KCNQ1 inactivation was enhanced by modification of this region (Q1S6Q2), but identified residues essential for KCNQ1 inactivation within the S5 region and the helical part of the H5 segment have not been reported to be substantially relevant for C-type inactivation. In conclusion, both C-type and KCNQ1 inactivation occur within the pore.
Oocytes were injected with 10 ng of KCNQ1 cRNA. For heteromeric expression 5 ng of MinK cRNA were added. The double-pulse protocol with two 40-mV pulses separated by a 20-ms pulse to –120 mV was used to analyze the onset of inactivation. The time constants of onset were calculated by exponential fits to the decaying phase of the currents at the beginning of the second pulse. To determine recovery from inactivation and the fraction of inactivated channels, currents were activated by a 3-s pulse to 40 mV followed by a hyperpolarizing pulse to –60 mV. Tail currents were analyzed by double exponential fits. The faster and the slower component constitute recovery from inactivation and deactivation respectively. Values are mean ± S.E. numbers of oocytes are shown in parenthesis.

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<th>τonset (ms)</th>
<th>τrecovery (ms)</th>
<th>Inactivated channels (%)</th>
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<tr>
<td>WT-KCNQ1</td>
<td>15 ± 1 (n = 12)</td>
<td>45 ± 3 (n = 13)</td>
<td>81 ± 1 (n = 12)</td>
</tr>
<tr>
<td>KCNQ1(L273F)</td>
<td>60 ± 6 (n = 6)</td>
<td>98 ± 5 (n = 6)</td>
<td>86 ± 3 (n = 6)</td>
</tr>
<tr>
<td>WT-KCNQ1/MinK</td>
<td>—</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>KCNQ1(L273F)/MinK</td>
<td>26 ± 2 (n = 8)</td>
<td>111 ± 3 (n = 8)</td>
<td>24 ± 5 (n = 12)</td>
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a Significance of homomeric KCNQ1-WT versus KCNQ1(L273F).
b Significance of homomeric KCNQ1(L273F) versus heteromeric KCNQ1/MinK.

region spanning S5 to S6, but the defined critical structures appear to be different.

In summary our results define geographical peculiarities for KCNQ1 inactivation, which were not yet reported for classical N- and C-type inactivation in Shaker-like potassium channels. KCNQ1 inactivation is characterized by an involvement of the pore region H5 and the S5 transmembrane region, putatively interacting with each other. It is believed that KCNQ1 inactivation is abolished by interaction with MinK in native heteromeric I_{Ks} channels (22, 23). As suggested previously, interaction between KCNQ1 and MinK might involve the pore region of KCNQ1 (26, 27). Our results demonstrate an essential function of the pore region for KCNQ1 inactivation, therefore allowing the interesting possibility that MinK interaction may occur in the same region that is important for inactivation. MinK possibly abolishes inactivation by weakening the interplay between H5 and S5. In the LQT1 mutant L273F this interplay might be stronger, thereby stabilizing inactivation such that MinK no longer can abolish inactivation. This in turn may contribute to the deleterious phenotype of the LQT1 mutant.

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