Voltage-gated K⁺ channel subunits must reach the plasma membrane to repolarize action potentials. Yet the efficiency of cell surface targeting varies among Kv subunits with some requiring auxiliary subunits for optimal expression. Here we identify a conserved motif located in the variable C-terminal region of Kv1 channels that controls the efficiency of functional channel expression. Variations among wild type channels in the optimal sequence VXXSL produce differences in distribution and the requirement for auxiliary subunits. Furthermore, deletion of this motif decreases subunit glycosylation and surface localization but does not prohibit subunit multimerization. Finally, the action of the essential sequence is shown to be independent of the chaperone effect of Kvβ subunits. Thus, the newly identified C-terminal motif governs processing and cell surface expression of Kv1 voltage-gated K⁺ channels.

Voltage-gated K⁺ channels are essential for controlling action potential repolarization and frequency in neurons, muscles, and other excitable cells. The mammalian Kv gene family that encodes these channels is comprised of more than 30 genes that produce subunits that differ in gating and permeation properties, subcellular distribution, and regulation of expression (1, 2). Furthermore, certain Kv channels require auxiliary subunits to be efficiently expressed on the cell surface, while many members of this family express well as homotetrameric complexes (3). The importance of efficient trafficking to the plasma membrane has been recently revealed by the finding that genetic diseases can be caused by mutations that alter processing and cell surface expression of voltage-gated K⁺ channels (4, 5). However, despite intense structure-function analysis and studies of subunit multimerization and processing (6–8), the identity of domains that account for variations in wild type Kv channel expression is obscure.

Recent studies suggest that C-terminal sequences are significant for expression of functional voltage-gated K⁺ channels. Human genetic diseases such as juvenile epilepsy, Jervell and Lange-Nielson syndrome, Romano-Ward syndrome, and episodic ataxia are associated with loss of large stretches of the native C-terminal region of KCNQ2, KvLQT1, HERG, and Kv1.1, respectively (9–12). In the case of HERG, it is known that a 104-amino acid C-terminal sequence is critical for production of functional channels (13). However, it remains unclear whether this region is required for gating or channel targeting.

Here we identify a new 3-amino acid motif located in a highly variable C-terminal region of Kv1 subunits that influences cell surface expression. Loss of the motif disrupts plasma membrane localization and glycosylation. Variations in this motif found in wild type Kv family members cause differences in basal and Kvβ-dependent cell surface expression. Thus, this new motif is a major determinant of Kv channel processing and cell surface expression.

EXPERIMENTAL PROCEDURES

Constructs—GFP-Kv1.4 cDNA was constructed by subcloning most of the coding region of rat Kv1.4 cDNA (RK3, nucleotides 556–2693) (14) into pEGFP-C1 (enhanced GFP; CLONTECH, Palo Alto, CA) as described previously (15). GFP-Kv1.5 cDNA was made by subcloning BglII-3′ end HindIII fragment of rat Kv1.5 cDNA (Kv pGEMA, nucleotides 299–2431) (16) into the corresponding site of pEGFP-C1. The reading frame was shifted by digestion with BglII and filling-in with Klenow. The resulting fusion protein lacks the first two amino acids (ME) of rat Kv1.5 polypeptide and contains SGLRS in the border between EGFP and Kv1.5. GFP-Kv1.2 was constructed using polymerase chain reaction with primer containing the 5′ end of the rat Kv1.2 cDNA (17) and a BglII site. The resultant fusion protein consists of EGFP, the linker sequence SGLRS, and all of the Kv1.2 coding sequence. Deletion, interchange, and mutation constructs were prepared from GFP-Kv1.4, GFP-Kv1.5, or GFP-Kv1.2 using endogenous restriction enzyme sites and/or by polymerase chain reaction-based methods. All the obtained constructs were verified by DNA sequencing.

Imaging and Electrophysiology—HEK 293 cells were obtained from ATCC and grown in 10% fetal bovine serum in Dulbecco’s modified Eagle’s medium without bicarbonate was supplemented with 25 mM hemisodium Hepes (pH 7.5), and cells were grown at 26 °C in air.

GFP-tagged channel proteins were imaged using a 2001 scanning laser confocal microscope (Molecular Dynamics) using 488 nm illumination (15, 18). GFP-positive cells that displayed a clear ring of fluorescence on an equatorial optical section that corresponded with the location of the cell surface as viewed by standard light microscopy were scored positive for cell surface expression. The number of such positive cells out of the total counted (≈100 cells) in at least two independent experiments yielded the reported percentage of cells with cell surface expression. Similar morphological measurements have been shown to correlate with biochemical and electrical determinations of cell surface expression of Kv channels (3, 5).

The abbreviations used are: GFP, green fluorescent protein.
Voltage-gated K⁺ currents in fluorescent cells were measured by the standard whole cell patch clamp method 2 days after transfection. The bath solution contained 140 mM NaCl, 5.4 mM KCl, 2 mM CaCl₂, 0.8 mM MgCl₂, 10 mM glucose, and 10 mM NaHepes (pH 7.5). The pipette solution contained 140 mM KCl, 1 mM Na₃EGTA, 3 mM MgCl₂, 10 mM NaHepes (pH 7.2). A holding potential of −60 mV was used, and recordings were performed at room temperature.

Biochemical Protocols—Cells were grown in 100-mm plastic tissue culture dishes and transfected with a total of 20 μg of DNA. Two days later, the cells were washed and collected with phosphate-buffered saline supplemented with 2 mM EDTA and then lysed with 10 mM Tris-HCl (pH 7.5) supplemented with 1 mM EDTA, 1 mM iodoacetamide, and 0.1 mM phenylmethyl sulfoxide (Buffer A) (19, 20). A total membrane fraction was obtained by centrifugation of the cell lysate at FIG. 1.
40,000 \times g for 30 min. The pelleted material was then suspended in a small volume of Buffer A containing 1% Triton X-100 and sonicated for 10 s. Solubilized material was obtained by centrifugation at 14,000 rpm for 5 min.

Protein concentration was determined by Bio-Rad protein assay solution with bovine serum albumin as a standard. Each sample (20 \mu g of protein) was separated on a 7.5% SDS-polyacrylamide gel and transferred to nitrocellulose membrane. The membrane was coated with 5% nonfat dry milk in phosphate-buffered saline supplemented with 0.1% Tween 20 at room temperature for 2 h. The coated membrane was probed with polyclonal anti-GFP antibody (Medical and Biological Laboratories, Watertown, MA) at 1:2000 to 1:3000 dilution in the coating solution for overnight at 4 °C. The membrane was washed four times with Tween-containing phosphate-buffered saline, incubated with secondary peroxide-conjugated antibody, and washed four times with the same washing solution. Immunoreactive proteins were detected using enhanced chemiluminescence reagents (NEN Life Science Products).

For glycosidase treatment, the total membrane fraction was resuspended in Buffer A containing 0.25 M sucrose with a Dounce homogenizer. A nuclei-free membrane fraction was then obtained by differential centrifugation as described previously (20). The pelleted membrane was suspended in a small volume of solution containing 20 mM Tris-HCl (pH 7.2) and 1% SDS and boiled for 2 min, followed by 10-fold dilution to a concentration of 20 mM Tris-HCl (pH 7.2), 50 mM EDTA, 10 mM NaF, and 0.5% Triton X-100. An aliquot of the diluted sample was incubated with or without endoglycosidase F for 2–3 h at 37 °C. Digested samples were then subjected to immunoblot analysis, following SDS-polyacrylamide gel electrophoresis.

To test for coassembly between deletion mutants and wild type Kv1.4 proteins, cells were transfected with Kv1.4 cDNA and GFP-tagged Kv1.4 or Kv1.5 cDNA. Membrane extracts were prepared 3 days after transfection using 1% Triton as described above. Extracts were precleared with protein A-containing fixed bacteria (Pansorbin, Calbiochem, San Diego, CA) and mixed with anti-GFP antibody (Medical and Biological Laboratories) and Pansorbin overnight at 4 °C. The complexes were precipitated and washed with Buffer A four times. Bound materials were eluted with 2× SDS sample buffer and subjected to immunoblot analysis.

**RESULTS**

Confocal microscopy and patch clamping demonstrate that GFP-tagged Kv1.4 channel protein targets efficiently to the cell surface to form functional voltage-gated K⁺ channels. Furthermore, deleting the final 15 C-terminal amino acids does not interfere with this localization (15). However, a 40-amino acid C-terminal deletion (Kv1.4ΔC40) disrupts cell surface localization measured by confocal microscopy (Fig. 1A, top panels). This inefficient targeting is accompanied by a reduction in voltage-gated channel activity to levels only slightly above controls (Fig. 1B). Further increasing the level of subunit protein expression results in accumulation in large round structures inside the cell (Fig. 1A, bottom panels). Under these conditions, the 40-amino acid C-terminal deletion reduces the fraction of cells with obvious surface expression (i.e. like Fig. 1A, left panels) from 100 to 6% (Table I). Kvβ subunits prevent the formation of the large intracellular structures but do not rescue efficient cell surface localization of the Kv1.4ΔC40 mutant. Rather, expression of either Kvβ1 or Kvβ2 auxiliary subunits induces a perinuclear localization of the pore forming subunits within the cell (Fig. 1C, compare with Fig. 1A, bottom panels). Likewise, maintaining cells at 26 °C fails to produce normal channel localization (data not shown). Thus, a C-terminal sequence is required for efficient cell surface localization of Kv1.4 channels.

Deletions of varying lengths were generated to identify the essential portion of the C-terminal region. Because the region identified initially is not conserved among Kv1 channels, a similar deletion analysis was performed with Kv1.5, a channel that has slightly less robust cell surface targeting than Kv1.4 (Table I). Previously, we used biotinylation of extracellular sugar groups to quantitate cell surface expression of Kv1.4 and Kv1.5 subunits (20). However, because glycosylation is affected by the loss of a C-terminal sequence (see below), we used confocal microscopy to determine the percentage of cells with an obvious ring of cell surface-proximal fluorescence. Measurements of deletion mutants led to the identification of 6-amino acid regions that are required for efficient cell surface expression located 32 and 14 amino acids from the C termini of Kv1.4 and Kv1.5, respectively. Specifically, the identified sequence in Kv1.4 is GVKE SL and in Kv1.5 is DLRRSL. Downstream sequences are not required for avid cell surface expression. Nor do such sequences rescue the effect of deleting the important regions. Importantly, the essential sequence from one subunit complements deletion of the analogous sequence in the other subunit. In fact, the Kv1.4 sequence was more efficient than the native Kv1.5 sequence in rescuing cell surface localization of a Kv1.5ΔC construct. Furthermore, the Kv1.5 sequence was less efficient than the native Kv1.4 sequence in targeting a Kv1.4ΔC construct (Table I). Thus, it appears that variations in the identified sequences can account for the difference in localization between these two members of the Kv1 family.

We then used site-directed mutagenesis to identify important amino acids in this region (Table I). Inverting the identified Kv1.4 6 amino acid sequence disrupted cell surface localization. Thus, amino acid composition alone is not sufficient. The sequences identified in Kv1.4 and Kv1.5 both end with SL. Replacing either of these amino acids with an alanine reduced cell surface localization more than 2-fold. Each of the SL sequences is flanked by two upstream charged amino acids. Yet replacing the KE with QQ does not affect Kv1.4 distribution. The next upstream position contains an aliphatic amino acid (Val for Kv1.4 and Leu for Kv1.5). Replacing this residue with alanine had a moderate effect. Finally, we found that replacing the Kv1.4 sequence GVKE SL with GAKEAA dramatically reduced cell surface localization. Therefore, it is evident that the VXXSL motif ensures robust expression of Kv1.4 channels at the plasma membrane.

We then set out to test whether differences in the essential motif could account for the great variations in cell surface
targeting among wild type Kv1 family members. Although Kv1.4 and Kv1.5 homomeric channels display robust plasma membrane expression in the absence of auxiliary subunits, Kv1.2 requires Kvβ subunits for optimal targeting (3). Sequence alignment reveals that VXXSL motif of Kv1.4 is replaced with VXXSN in Kv1.2 (Fig. 2A). To test whether this difference is significant, a Kv1.4L623N mutant was generated. As can be seen in Fig. 2B (top panels), this mutation reduces the efficiency of cell surface targeting. Furthermore, plasma membrane localization of this mutant is rescued upon coexpression with Kvβ1 subunits (Fig. 2B, bottom panels). Thus, the Leu to Asn switch induces Kv1.4 to behave more like Kv1.2; expression is suboptimal unless Kvβ subunits are present.

The effect of the complementary substitution in GFP-tagged Kv1.2 (i.e. Kv1.2N469L) was also examined (Fig. 3). Consistent with our Kv1.4 experiments, this change stimulated cell surface channel expression as much as coexpression with Kvβ subunits (i.e. each manipulation produced a 1.4-fold increase). If the VXXSL motif and Kvβ act on the same step in channel processing and expression, then the effects of auxiliary subunits and the N469L mutation should not be additive. However, the increases in cell surface expression by these manipulations were found to combine to produce a 2-fold increase (Fig. 3). Hence, the enhancement of cell surface targeting by Kvβ subunits is independent of the action of the C-terminal motif.

Biochemical experiments were then performed to gain insight into how C-terminal VXXSL sequence governs cell surface expression of functional channels. Immunoblots revealed that the Kv1.4ΔC40 mutant protein is expressed at higher levels than the wild type subunit 1–6 days after transient transfection (Fig. 4, A and B). Furthermore, a high molecular weight species seen with wild type Kv1.4 subunits is not as abundant with the C-terminal deletion mutant. Treatment of GFP-tagged Kv1.4 or wild type Kv1.4 (data not shown) proteins with endoglycosidase F collapses the two native bands on the blot into a single lower molecular weight band (Fig. 4B, left lanes). This suggests that the higher band represents fully glycosylated protein, whereas the lower band is only core glycosylated. Endoglycosidase F produces a similar effect on the GFP-tagged Kv1.4ΔC40 bands (Fig. 4B, right lanes). Therefore, the lower abundance of the high molecular weight band found after deletion of the VXXSL motif is indicative of less extensive glycosylation. Importantly, it has been shown that this glycosylation is not required for expression of functional channels (6, 7). Thus, the absence of glycosylation cannot account for the abnormal distribution of the Kv1.4ΔC40 protein. Rather, these findings argue that loss of a C-terminal sequence does not induce degradation but does alter processing of the channel subunit as well as localization to the plasma membrane.

**Fig. 3.** Kvβ subunits and the C-terminal motif act independently to increase Kv1.2 cell surface targeting. Note that coexpression with Kvβ2 or optimizing the C-SL motif with an N469L substitution produce additive stimulatory effects on cell surface expression. WT, wild type.

**Fig. 4.** Glycosylation, but not multimerization, is inhibited by a C-terminal deletion of Kv1.4. A, immunoblot analysis using anti-GFP antibody of cells 1, 3, or 6 days after transfection with vectors for GFP-Kv1.4 or GFP-Kv1.4ΔC40. B, Protein extracts from cells transfected with vectors for GFP-Kv1.4 (WT) and GFP-Kv1.4ΔC40 (ΔC40) were untreated (None) or treated with endoglycosidase F (EndF). Samples were then subjected to immunoblot analysis with anti-GFP antibody. Triangle indicates the position of a 97.4-kDa marker. Horizontal lines show the positions of the two native species and the band after endoglycosidase treatment. C, commounprecipitation of wild type Kv1.4 with GFP-Kv1.4, GFP-Kv1.4ΔC40, GFP-Kv1.5, or GFP-Kv1.5ΔC28. For the lowest panel, anti-GFP antibody was used for immunoprecipitation and the blot was probed with anti-Kv1.4 antibody. The anti-Kv1.4 antibody was raised against an N-terminal peptide sequence (19). Because a portion of the N terminus is replaced with GFP, this antibody does not interact strongly with GFP-tagged Kv1.4 protein. This is evident from the difference in molecular masses the Kv1.4 and GFP-Kv1.4 proteins in the two upper panels. As above, the triangle shows the position of a 97.4-kDa marker, and horizontal lines indicate the positions of the two native species of wild type Kv1.4. The top panel shows that truncated subunits alter the glycosylation of wild type Kv1.4 subunits. The middle and bottom panels show that anti-GFP antibody co precipitated Kv1.4 protein regardless of the presence or absence of a C-terminal region in GFP-tagged Kv1.4 or Kv1.5.
The poor glycosylation of the ΔC mutants might be caused by inhibition of the rapid, cotranslational multimerization of Kv1 subunits in the endoplasmic reticulum. To test whether the C-terminal motif disrupts processing by interfering with multimerization, C-terminal deletion constructs were coexpressed with wild type subunits and then immunoprecipitated. As can be seen in the top panel of Fig. 4C, coexpression with ΔC mutants promotes the appearance of the less glycosylated species of the wild type Kv1.4. Furthermore, the lower panel of Fig. 4C shows that wild type Kv1.4 subunits immunoprecipitate equally well with full length or truncated GFP-tagged Kv1 subunits. Hence, the poor glycosylation of wild type subunits was likely caused by their association with the ΔC mutant subunits. This implies that the VXXSL motif must be important for a step following multimerization but preceding full glycosylation.

**DISCUSSION**

This report identifies a new motif that governs processing and cell surface expression of voltage-gated K⁺ channels. Because the location of this sequence in the channel polypeptide is not rigid, it was not evident from previous sequence alignments. Furthermore, a role for this region of K⁺ channels was not suspected because it is not located in domains implicated in gating, ion permeation, multimerization, or channel clustering and immobilization. Yet variations in the VXXSL motif contribute to the differences in the expression and activity of wild type Kv channels. For example, our data indicate that the C-terminal motifs found in Kv1.4 and Kv1.5 account for the different efficiencies in cell surface expression of these two subunits. Furthermore, complementary mutagenesis experiments with Kv1.2 and Kv1.4 indicate that the stimulation of Kv1.2 subunit expression by auxiliary Kvβ subunits is marked because of the presence of a suboptimal VXXSN sequence. Therefore, much of the diversity in expression of normal Kv1 channels can be explained by variations in the VXXSL motif.

We also report that deletion of this sequence disrupts Kv channel activity apparently by preventing trafficking to the cell surface. This result might appear surprising in light of current recordings from truncated Kv1.5 channels expressed in L cells (21). On one hand, this difference might reflect cell type specific differences. For example, it is known that L cells express auxiliary Kvβ subunits, whereas HEK 293 cells do not (22). However, we have found that channel activity appears to saturate before cell surface expression and that transfection of expression vectors for the truncated channel at supersaturated levels can yield significant currents. This argues that very inefficient targeting can yield considerable currents with overexpression. Because the fraction of channel protein that reaches the cell surface in L cells has not been measured, the efficiency of surface expression in that system is not known. Thus, further work will be required to determine whether there is any contradiction between previous electrophysiological experiments in L cells and our conclusions regarding the requirement for the VXXSL motif for efficient surface channel expression.

It is also interesting to note that loss of a significant portion of the C termini of KvLQT1, HERG, KCNQ2, and Kv1.1 causes Jervell and Lange-Nielsen syndrome, Romano-Ward syndrome, juvenile epilepsy, and episodic ataxia in humans, respectively (9–12). These findings raise the possibility that loss of VXXSL-like motifs may contribute to disease phenotypes in human channelopathies. Indeed, preliminary experiments suggest that a region containing such a sequence may be required for functional expression of KvLQT1 channels. These findings suggest that the VXXSL motif may be important in distantly related Kv channels.

Our experiments raise the issue of how the C-terminal motif governs channel cell surface localization. Because glycosylation is less extensive after deleting the motif, it is possible that the subunits traffic inefficiently to or through the Golgi. This might occur because the C-terminal motif is required after early multimerization to exit the endoplasmic reticulum. This would be expected if the channel protein is misfolded. In favor of this interpretation, we found that large aggresome-like structures are formed after overexpression of the ΔC mutants (compare Fig. 1A, bottom panels, with Ref. 23). However, it is intriguing that Kvβ subunits, which are known to act as chaperones for Kv channels (3), prevent the formation of aggresome-like structures without rescuing efficient channel localization. Because subunit tetramerization may occur in two dimerization steps (8), it is also possible that the VXXSL motif is important for the second association step. If this were the case, subunits would be trapped in an intermediate state. Finally, our data are also consistent with the hypothesis that the VXXSL sequence is an anterograde targeting sequence recognized by cellular targeting or sorting machinery. A different C-terminal anterograde signal has been proposed to be present in SUR auxiliary subunits of KATP channels (24). Most importantly, whatever the action of this C-terminal motif is, the results presented here indicate that it is a major determinant of surface channel expression. Thus, this C-terminal sequence may serve as a useful target for therapeutic drugs to alter expression of voltage-gated K⁺ channels without affecting gating or permeation.

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C-terminal Expression Motif for Kv1 Channels

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Surface Expression of Kv1 Channels Is Governed by a C-terminal Motif
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