The SK3 Subunit of Small Conductance Ca$^{2+}$-activated K$^+$ Channels Interacts with Both SK1 and SK2 Subunits in a Heterologous Expression System* 

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The aim of this study was to determine whether functional heteromeric channels can be formed by co-assembly of rat SK3 (rSK3) potassium channel subunits with either SK1 or SK2 subunits. First, to determine whether rSK3 could co-assemble with rSK2 we created rSK3VK (an SK3 mutant insensitive to block by UCL 1848). When rSK3VK was co-expressed with rSK2 the resulting currents had an intermediate sensitivity to UCL 1848 (IC$_{50}$ of $\sim$5 nM compared with 120 pM for rSK2 and $>$300 nM for rSK3VK), suggesting that rSK3 and rSK2 can form functional heteromeric channels. To detect co-assembly of SK3 with SK1, we initially used a dominant negative construct of the human SK1 subunit (hSK1YP). hSK1YP dramatically reduced the SK3 current, supporting the idea that SK3 and SK1 subunits also interact. To determine whether these assemblies were functional we created rSK3VF, an rSK3 mutant with an enhanced affinity for tetraethylammonium chloride (TEA) (IC$_{50}$ of 0.3 mM). Co-transfection of rSK3VF and hSK1 produced currents with a sensitivity to TEA not different from that of hSK1 alone (IC$_{50}$ $\sim$15 mM). These results suggest that hSK1 does not produce functional cell-surface assemblies with SK3. Antibody-staining experiments suggested that hSK1 may reduce the number of functional SK3 subunits reaching the cell surface. Additional experiments showed that co-expression of the rat SK1 gene with SK3 also dramatically suppressed SK current. The pharmacology of the residual current was consistent with that of homomeric SK3 assemblies. These results demonstrate interactions that cause changes in protein trafficking, cell surface expression, and channel pharmacology and strongly suggest heteromeric assembly of SK3 with the other SK channel subunits.

Small conductance Ca$^{2+}$-activated potassium channels (SK channels) are widely expressed throughout the central and peripheral nervous systems. In many neurons SK channels underlie some components of the post-spike after-hyperpolarization (see e.g. Ref. 1). They also have important functions in non-neuronal tissues. Native SK channels have a characteristic pharmacology. They can be blocked by the bee venom toxin apamin and several selective small molecule blockers that we have developed (such as UCL 1848) that are active at nanomolar or subnanomolar concentrations (2–4).

Molecular cloning studies have identified three closely related genes (SK1, -2, and -3) which code for SK channel subunits in mammalian cells (5–7). In both Xenopus oocytes and mammalian cell lines, expression of the rat homologues of SK2 and SK3 (rSK2 and rSK3 respectively) results in the formation of functional homomeric SK channels. Further, both homomeric rSK2 and homomeric rSK3 channels can be blocked by either apamin or UCL 1848 at concentrations that are similar to those reported for native channels (8). The potencies of both compounds depend on the subunit composition of the channel, with the IC$_{50}$ for blocking homomeric SK2 channels being $\sim$18-fold lower than for SK3.

The behavior of SK1 is different to that of other SK genes. Initial expression studies of the human SK1 gene (hSK1) showed that it can produce functional channels in the Xenopus oocyte expression system and these channels are insensitive to apamin at concentrations of up to 100 nM (5). Subsequent work, however, expressing hSK1 in mammalian cell lines, showed that most cells produce channels that are blocked by apamin with an IC$_{50}$ of $\sim$3–12 mM. A few cells also produce an apamin-insensitive current component (9, 10). More recent oocyte work suggests that, in fact, expression of the human SK1 gene also produces some apamin-sensitive channels in this system (11). The reason for this behavior is unclear and it consequently remains unknown whether SK1 forms apamin-sensitive channels or apamin-insensitive channels, or both, in vivo. Interestingly, the rat SK1 gene differs from its human counterpart because it does not produce functional channels when expressed alone in either oocytes or mammalian cell lines (12).

The overlapping patterns of expression for SK1, SK2 and SK3 within the CNS (5, 13, 14) raise the possibility that heteromeric assembly of SK subunits may occur. That co-assembly may occur is also suggested by the work of Ishii et al. (15) where it was shown that injection of an SK1-SK2 dimer or co-injection of mRNA for hSK1 and rSK2 into Xenopus oocytes resulted in currents with an apamin sensitivity between that of homomeric hSK1 and rSK2. Following this observation we have recently shown that co-transfection of the rat SK1 and SK2 genes in HEK cells produces channels with a novel pharmacology, suggesting that subunits from these genes can also assemble to form functional heteromeric channels (16). Despite the progress being made toward understanding SK1/SK2 interactions, much less is known of the interactions between SK3 and the other SK subunits. Interestingly, however, it has been...
reported that a fragment of SK3, when transfected into the Jurkat cell line, acts as a dominant negative, suppressing the endogenously expressed SK2 current (17). This finding suggests that SK2 and SK3 may be able to form a heteromeric complex. The principle aim of the present work was to examine, in more detail, the possibility that SK3 interacts with the other SK channel subunits; SK1 and SK2.

**EXPERIMENTAL PROCEDURES**

**Constructs**—The rat SK1, SK2, and human IK1 (SK4) genes sub-cloned into the pTracer or pcDNA mammalian expression vectors were a generous gift from Prof. Len Kaczmarek and Dr. William Joiner (Yale University). The rat SK1 clone (accession number AF000227) encoded the full-length transcript and was re-engineered to eliminate the 5'-untranslated region and replace it with an optimal Kozak sequence (g-cacc) just prior to the start methionine (starting protein sequence MSSRSH...). The rat SK3 gene (accession number AF291239) was previously cloned from a rat SCG library (8) and subcloned into the pcDNA 3.1 Zeo+ plasmid (Invitrogen). The human hSK1 clone (accession number U69885) was a generous gift from Prof. J. P. Adelman (Vollum Inst.). Mutations were made using the QuikChange Site-directed Mutagenesis kit (Stratagene) or by standard overlap extension PCR. Constructs were sequenced on an ABI 377 sequencer using the Big Dye II sequencing kit. The TEA-sensitive mutations, which substitute phenylalanine for valine in rSK2 (SK2VP) and rSK3 (SK3VP) are at structurally equivalent amino acid positions (366 and 515 in rSK2 and rSK3, respectively). The UCL 1845-insensitive mutation of rSK3 (SK3VK) substitutes a lysine residue for a valine at position 491. In the dominant negative construct of hSK1 (hSK1YP) proline is substituted for tyrosine at position 351. Plasmid DNA for transfection was purified using Maxi Prep or Midi Prep kits (Qiagen).

**Maintenance and Transient Transfection of HEK 293 Cells**—HEK 293 cells were maintained in Dulbecco's modified Eagle's medium supplemented with 10% fetal calf serum, 2 mM l-glutamine, penicillin (100 units/ml), and streptomycin (100 µg/ml). Cells were plated into 35-mm culture dishes and transfected using LipofectAMINE 2000 (Invitrogen). The ratio of DNA for transfection of HEK cells was varied slightly for each experiment where hSK1YP or rSK1 were co-expressed with another SK gene we used 2 µg of rSK3 together with 4 µg of QBI plasmid DNA (Qbiogene), which expresses GFP, allowing identification of transfected cells. LipofectAMINE 2000 (1 µg DNA) and plasmid DNA were mixed in Opti-MEM and added to cells plated at 50% confluence. After incubation overnight the cells were re-plated into 35-mm dishes and used within 2 days for recording. Cells used for immunohistochemistry were plated on 18-mm square glass coverslips.

**Immunohistochemistry**—Transfected cells plated on glass cover slips were washed three times in phosphate-buffered saline (PBS) before being fixed for 10 min using freshly made 4% w/v paraformaldehyde (in PBS). Cells were washed in PBS again and permeabilized using 100% methanol for 10 min. After a further wash in PBS the cells were then left in an antibody-blocking solution (ABS) consisting of 2% w/v bovine serum albumin and 2% w/v horse serum in PBS for 1 h. The cells were then incubated for 4 h in the primary anti-rSK3 antibody (Chemicon) at a concentration of 0.3 µg/ml. To remove excess primary antibody, the cells were washed three times in PBS containing 0.1% v/v Tween-20 and then incubated in a 1:200 dilution of a Cy3-conjugated goat anti-rabbit secondary antibody (Chemicon) for 1 h. All antibodies were diluted in ABS. Following incubation, cells underwent a final wash in PBS with 0.1% v/v Tween-20. Coverslips were mounted onto slides (previously cleaned with ethanol) using a small drop of antifade mount (Vector Laboratories Inc.). All staining operations were carried out at room temperature (22 °C). Stained cells were viewed with a Leica TCS confocal microscope.

**Electrophysiology**—Currents were recorded from HEK 293 cells using conventional whole cell voltage clamp methods. The bathing solution (in mM): NaCl 140, KCl 2, glucose 10, HEPES 10, and the pH was adjusted to 7.4 with NaOH. The pipette filling solution contained (in mM): KCl 130, HEPES 10, K-HEDETA 5, and CaCl2 1.2 (free Ca2+ 1 µM). The pH was adjusted to 7.2 with KOH. The free Ca2+ concentration was calculated using stability constants from Martell and Smith (18). The 50 µM (unbuffered) calcium pipette filling solution contained (in mM): KCl 140, HEPES 10, and 0.05 µM CaCl2 (pH adjusted to 7.2 with KOH). Patch pipettes were fabricated from 1.5 mm o.d. boro-silicate glass (Harvard), fire-polished, and coated with Sylgard resin. They had resistances of 1–4 MΩ when filled with the above solution. Experiments were conducted at room temperature (20–25 °C).

Membrane currents were recorded with either a List EPC7 amplifier using a Digidata 1320A interface and pClamp 8.2 software (Axon Instruments) for acquisition, or a HEKA EPC9 patch clamp amplifier under control of Pulse software. Data were filtered at 1 kHz and digitized at 5 kHz. Acquired current traces were analyzed with either Clampfit 8.2 or HEKA Puestoft.

**RESULTS**

**SK3 Can Co-assemble With SK2 Forming Functional Channels**—It has previously been reported that expression of a dominant negative of SK3 can suppress SK2 currents in Jurkat cells (17), suggesting that SK3 and SK2 subunits co-assemble in this expression system. However, it is not yet clear whether functional channels are made by co-assembly of SK2 and SK3. We addressed this question using a mutant of SK3, SK3VK, which is very insensitive to block by apamin2 and UCL 1848, a selective small molecule blocker developed in our laboratories (2, 3). In control experiments on cells expressing SK3VK alone, 300 nM UCL 1848 had little or no effect on the amplitude of currents (Fig. 1, B and D). The advantage of using UCL 1848 as a blocker (rather than apamin) is that it has a similar potency for blocking SK2 to apamin but, unlike apamin, its action on SK2 is much more rapidly reversed, so we were able to obtain full recovery after ~3 min washout (Fig. 1, A and C). This cannot be obtained with apamin (10).

Cells expressing SK2 alone were blocked by UCL 1848 with an IC50 of 110 ± 26 µM (Fig. 1D), an essentially identical value to the one previously reported (8). However, when rSK3VK was co-expressed with SK2 the concentration-inhibition curve was shifted to lie between those of SK2 and SK3VK (Fig. 1, C and 2).

2 G. W. J. Moss, A. S. Monaghan, and Y. A. Shah, unpublished observations.
The intermediate sensitivity of the channels formed is particularly obvious in recordings that were sufficiently long and stable to apply multiple doses of drug; one such experiment is shown in Fig. 1C. Clearly the majority of current is mediated by SK3VK-SK2 heteromeric channels in these co-transfected cells or the second application of drug would not provide such a large increase in the fraction of channels blocked. Our results are thus consistent with the idea that SK3, like SK1, can assemble with SK2 forming functional heteromeric channels in vitro.

Effect of a Dominant Negative hSK1 Subunit on rSK3 Currents—Next, to examine possible assembly of SK3 with SK1 we used a dominant negative construct of hSK1 (hSK1YP) (Fig. 2). We performed three types of control experiments with this construct. First, we tested hSK1YP co-expression with hSK1 to make sure that it can knock down the wild-type SK1 currents. To do this we compared the size of currents in cells transfected using SK1 alone with those transfected using the same quantity of SK1 and a 2-fold excess of hSK1YP. As expected, the hSK1YP construct substantially reduced the SK1 current (Fig. 2A). Second, to confirm the effectiveness of this construct in co-assembly experiments, we expressed SK1YP with the wild-type rSK2 gene. The human SK1 gene and the rat SK2 gene have been shown to form subunits that co-assemble in oocytes.

We therefore expected to see knock down of SK2 current. Again we compared the size of currents in cells transfected using SK2 alone with those of cells transfected using the same quantity of SK2 and a 2-fold excess of hSK1YP. As expected, there was a substantial reduction in currents when cells were co-transfected with the dominant negative (Fig. 2, B and D). This result is consistent with the idea that in mammalian cells, as well as in oocytes, SK1 and SK2 can co-assemble (even though the pharmacological properties of hSK1 appear to be quite different in the two expression systems). Interestingly, there was more current remaining than would be predicted if both constructs express equally well, subunits assembled at random and only a single subunit of hSK1YP were sufficient to render SK1/SK2 channels nonfunctional. The reason for this is not clear. It may
reflect either a partial recovery of function, preferred stoichiometries of the SK1/SK2 interaction or variations in expression levels. However, to ensure that overexpression of a competing plasmid does not itself cause the apparent reduction in SK currents, we performed a final control experiment testing the effect of hSK1YP on the current in cells transfected with hIK1. As in the previous cases, we used a 2-fold excess of the hSK1YP construct over the hIK1 plasmid and compared the currents against those obtained using hIK1 alone. In these experiments the magnitude of the mean hIK1 current was slightly, but not significantly, reduced as a result of co-transfection with the hSK1YP construct (Fig. 2, A and D). This suggests that competition for expression by a 2-fold excess of the hSK1YP construct does not account for the reduced currents seen when hSK1YP is transfected with wild-type SK1 or SK2. The hSK1YP construct thus seems suitable for assessing subunit co-assembly. Having completed these control experiments, we compared cells transfected with SK3 alone or cells transfected with the same quantity of SK3 and a 2-fold excess of dominant negative. The records shown in Fig. 2, B and C, demonstrate that SK3 currents were greatly depressed in the presence of hSK1YP. Thus, the effect of hSK1YP on rSK3 currents strongly suggests an interaction occurs between these two channel subunits. However, this result does not prove that hSK1 and rSK3 can co-assemble to form functional channels at the cell surface. In an attempt to detect the presence of functional heteromeric channels we therefore used the change-of-function strategy described in the next section.

**TEA-sensitive SK3 and SK2 Mutants**—Expression of hSK1 in HEK 293 cells produces currents, which are relatively insensitive to block by TEA (Fig. 3A). In our control experiments, TEA blocked homomeric hSK1 channels, rSK2 channels, or rSK3 channels, with IC50 values of 14.1 ± 1.0, 2.8 ± 0.7, and 8.7 ± 1.8 mM respectively (Fig. 3B, C and D). Surprisingly, rSK3VF co-expression (Fig. 3C, D) resulted in a marked increase in sensitivity to TEA; the concentration-inhibition curve between that of SK1 and SK2VF was virtually identical to that of SK1 and SK2VF, with IC50 values of 14.1 ± 1.0, 0.31 ± 0.05, and 3.5 ± 0.9 mM, respectively.

To validate the approach used above we repeated the experiment by creating rSK2VF, an equivalent mutation in the SK2 channel. We would expect to be able to obtain a dose response curve between that of SK1 and SK2VF when these subunits are co-expressed because assembly of SK2 with hSK1 has been previously described (15). It would also be expected from our dominant negative studies. In control experiments, SK2VF, like SK3VF, displays a marked increase in sensitivity to TEA; the IC50 for block being 0.51 ± 0.05 mM, nH 1.0 ± 0.2 (Fig. 4A, B and C). An additional observation was that introduction of phenylalanine at this position creating the mutant rSK3VF. This mutation caused the expected increase in sensitivity to TEA; the concentration-inhibition curve was fitted to a single component Hill-Langmuir equation with an IC50 for block by TEA of 0.31 ± 0.07 mM and an nH value of 0.9 ± 0.2 (Fig. 3B, C and D). This suggests that SK3VF made little or no contribution to the observed current.
transfected with SK2VF and hSK1 tended to produce SK current with kinetics that were intermediate between those of homomeric SK2VF and homomeric hSK1 (Fig. 4B). Further, in co-transfected cells it was possible to determine that current sensitivity to TEA was between that of hSK1 and rSK2VF, as shown in Fig. 4B and by the averaged data shown in Fig. 4C. The concentration-inhibition curve for co-transfected cells has an IC$_{50}$ of 3.5 ± 0.9 mM. In addition to a change in the IC$_{50}$ if co-assembly is occurring, then one might expect the dose-response curve to become rather shallow because it would represent a number of different populations where various stoichiometries of hSK1 and rSK2VF subunits have formed. When, for the purpose of comparison, both sets of data are fitted to a single component Hill curve, the co-expressed channel data is clearly best fitted with a smaller Hill coefficient for TEA block ($n_H$ value of 0.55 ± 0.10, compared with values of 1.2 ± 0.1 and 1.0 ± 0.2 for hSK1 and rSK2VF homomers, respectively). Again this argues in favor of co-assembly. Thus, the interaction of SK2 with SK1 in mammalian cells is entirely consistent with the idea that heteromeric channel assemblies can be formed. In contrast, our studies of the interaction between SK3 and SK1 do not provide evidence of functional heteromeric assemblies.

**Co-expression of rSK3 and rSK1**—We became concerned that the suppression of rSK3 by hSK1 could be an artifact of using the human SK1 clone in combination with rat SK3. We therefore decided to examine currents arising from expression of the rat SK1 gene with rSK3. We started by comparing Ca$^{2+}$-activated $K^+$ currents in HEK 293 cells transfected with rSK3 either alone or in combination with rSK1. As expected, cells transfected with rSK3 alone exhibited large currents with an approximately linear current-voltage relationship, which reversed close to the predicted value of $E_K$ (Fig. 5, A and D). When cells were transfected with SK3 together with rSK1, however, currents were markedly reduced (Fig. 5, A and C) although, the reversal potential was unchanged (Fig. 5D) and a small SK-like current was still clearly present. This result appears to confirm an interaction between SK1 and SK3 that reduces the SK3 current component, as was seen with the human SK1. However, a small SK current might be explained if SK1 and SK3 co-assemble to form a channel that is less sensitive to Ca$^{2+}$ activation. In order to test this possibility we repeated the experiment, this time recording with a pipette solution containing 50 $\mu$M Ca$^{2+}$. As shown in Fig. 5, B and C the results obtained were virtually identical to those with 1 $\mu$M free Ca$^{2+}$. Thus, the reduction in current does not reflect a shift in the Ca$^{2+}$ activation curve. These results might still be explained in a number of ways. It could be, for example, that this residual current is carried by SK1/SK3 channels, which have a smaller conductance or lower open probability than SK3 homotetramers. Alternatively, the remaining currents may reflect a smaller residual SK3 component. In this case, both rSK1 and hSK1 would cause similar suppression of the current carried by SK3 subunits. To address this issue we used our TEA-sensitive SK3 mutant. We compared the TEA sensitivity of channels formed by co-expression of SK3VF and rSK1 with that of channels formed by SK3VF alone. As shown in Fig. 6 the TEA sensitivity of these channels was essentially identical to those formed by expression of SK3VF alone. Further, it is clear that this mutation does not upset the subunit interaction because the TEA sensitive currents observed when rSK1 and rSK3VF are co-expressed remain much lower than those seen with rSK3VF alone (data not shown). Thus, there is no evidence of a substantial contribution from SK1 subunits and the remaining channels appear to be mainly homomeric SK3 channels that remain functional at the cell surface.

**Immunostaining**—When SK1 is transfected with SK3, the SK3 currents are suppressed. This is most dramatic with the hSK1 clone that appears to completely eliminate functional SK3 current. To investigate the mechanism of this suppression we used confocal microscopy to examine cells stained with an anti-SK3 antibody either with or without co-transfection of SK1. Cells transfected with rSK3 alone showed clear evidence of SK3 protein distributed at, or close to, the cell surface membrane (Fig. 7A). In contrast, cells transfected with both rSK3 and hSK1 displayed a punctate and largely intracellular stain-
present in Jurkat cells. These data suggest that SK2 and SK3 subunits can co-assemble. Our finding, that co-expression of the UCL 1848-insensitive rSK3 mutant (rSK3VK) with rSK2 produced a current that has an intermediate sensitivity to UCL 1848 block, provides additional evidence in support of this view. It also shows that these subunits can co-assemble into functional heteromeric channels at the cell surface. Although such functional assemblies appear to be made in vitro, it is not yet clear whether they also occur in vivo. Interestingly, Sailer et al. (20) recently reported the use of anti-SK2 and anti-SK3 antibodies to immunopurify SK channels from brain tissue. They found that anti-SK3 antibodies did not recognize anti-SK3 immunoprecipitated material and vice versa. These findings suggest that SK2 and SK3 subunits do not co-assemble to a substantial degree in the central nervous system, although they may do so elsewhere.

To further examine SK subunit assembly patterns in vitro, we have utilized both dominant negative and change-of-function approaches. We have been able to demonstrate that in mammalian cells, as in oocytes (15), hSK1 and rSK2 subunits co-assemble. It is interesting that this same pattern of behavior is seen despite dramatic differences in the reported pharmacology of hSK1. Whatever mechanism is responsible for the differences in SK1 observed in these two systems, it does not appear to disrupt SK1/SK2 subunit associations.

An additional interesting feature that emerges from our experiments is that overexpression of the hSK1 dominant negative does not substantially inhibit IK1 (SK4) currents. Although many more experiments are needed, it might eventually be shown that SK and IK channel subunits do not co-assemble in any combination. This is potentially an important point when it comes to explaining the diverse range of SK channel pharmacology reported in various tissue preparations (21). If a relatively small number of functional SK channel subunit combinations occur then perhaps SK channels rely on auxiliary β subunits for diversity (22–24).

Perhaps the most interesting aspect of our data concerns the interaction between rSK1 and rSK3. It appears that rSK1/ rSK3 subunit assembly dramatically reduces the number of functional channels at the cell surface although a small current remains (when the cDNAs are transfected in a 2:1 ratio). Similar results have previously been reported in the more extensive studies of Kv potassium channels. Silent channel subunits such as Kv8.1 and Kv9.1 can, presumably by subunit co-assembly, reduce or even abolish current otherwise produced by expression of Kv3.4 (25, 26). In some of this work there is evidence that although the silent subunits cause a reduction in current, channels reaching the cell surface have altered gating kinetics and are therefore likely to be heteromeric assemblies (26, 27). However, when we examined the remaining current seen upon co-transfection of rSK1 with the TEA-sensitive mutant rSK3VF, we found that the sensitivity of the current to block by TEA was the same as for SK3VF channels expressed alone suggesting that there was no formation of functional heteromeric channels at the cell surface. (In keeping with this idea our preliminary experiments suggest that co-expression of rSK1YP, which is not expected to form functional channels, may be shown that they are probably homotetramers of Kv3.4 (26). In contrast to the behavior seen with rSK3, we have recently shown

**FIG. 7.** The effect of human and rat SK1 on the expression pattern of SK3. A, bright field and confocal image of HEK cells transiently transfected with rSK3 showing that the expressed protein is at, or close to, the cell membrane. B, co-expression of hSK1 with rSK3 results in a more punctate and largely intracellular staining pattern for SK3. C and D, co-expression of rSK3 with rSK1 also results in a change in the pattern of SK3 staining. The degree of retention varied from cell to cell. The calibration bars show 20 μm.

**DISCUSSION**

Work by Cahalan, Chandy, and colleagues (17) has shown that an N-terminal fragment of SK3 acts as a dominant negative in suppressing the endogenous SK2-mediated current
that the opposite behavior occurs when rSK1 is co-expressed with rSK2. In this case rSK1 can interact with rSK2 to augment the levels of functional SK channels (16). It thus seems that the precise combination of subunits is critical in determining whether the complex is functional at the cell surface. This is perhaps most striking for the interaction between hSK1 and rSK3 subunits. The human homologue of SK1, unlike its rat counterpart, produces functional channels when expressed alone. SK3 also produces functional channels and one might expect therefore, that if hSK1 and SK3 co-assemble the resulting channels would, similarly, be functional and at the cell surface. However, co-expression of the TEA-sensitive rSK3VF with hSK1 led to currents with TEA sensitivity not different from that of homomeric hSK1. This finding suggests that rSK3VF subunits made little or no contribution to the observed channels.

As a first step toward understanding the mechanism of interaction between SK1 and SK3 we used an anti-SK3 antibody to study the distribution of SK3 protein. Cells co-transfected with rSK3 and either human or rat SK1 showed clear staining with rSK3VF subunits made little or no contribution to the observed channels.

Interactions between SK Channel Subunits

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