A Novel Two-pore Domain K⁺ Channel, TRESK, Is Localized in the Spinal Cord*

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The potassium (K⁺) channel was first identified and characterized as Drosophila Shaker. It is activated by a change in membrane potential and induces selective permeation of K⁺ (1–3). To date, more than 70 K⁺ channel genes have been identified in mammals and are divided into several subfamilies based on the basis of their sequence similarities and channel properties (4). The K⁺ channels are characterized by having two, four, or six transmembrane domains and one or two pore-forming domains that are essential for selective permeation of K⁺. It was reported that the K⁺ channel is present in all living cells and organs and is involved in a variety of cellular functions, including regulation of the neuronal firing rate, heart rate, muscle contraction, and hormone secretion (5, 6).

The most recently identified K⁺ channels were two-pore domain K⁺ channels, which have four transmembrane domains (TM1–4), two pore-forming domains (P1, P2), cytoplasmic N- and C-terminal regions, and an extended extracellular loop between TM1 and P1, which are evolu-

tioned as coding for the two-pore domain K⁺ channel. From the human draft sequencing data base and database. Many channel genes have been isolated and analyzed for their cellular mechanisms. This has been especially true for two-pore domain K⁺ channel genes. In this paper we describe the cloning of a novel two-pore domain K⁺ channel, TRESK, from the human draft sequencing data base and describe its tissue distribution and electrophysiological and pharmacological properties.

EXPERIMENTAL PROCEDURES

Molecular Cloning and Isolation of TRESK—The human TWIK-1 amino acid sequence was used for a TBLASTN search against the human draft genome sequencing data base at the National Center for Biotechnology Information (NCBI). The genomic clone (GenBank™ accession number AL731557) was identified, and some fragments of AL731557 showed the highest similarity to human TREK1. To identify the 5' and 3' ends of the cDNA corresponding to this fragment, 5' and 3' rapid amplification of cDNA ends was performed with human spinal cord poly(A)⁺ RNA using a Marathon cDNA amplification kit (Clontech) and primers derived from the genomic fragment. Amplified fragments were directly cloned into the plasmid pCR-TOPO (Invitrogen) and sequenced on both strands (Applied Biosystems, model 3700). Sequencing of the rapid amplification of cDNA ends products revealed that this genomic fragment was a part of a cDNA. The determined sequences were assembled into one contiguous sequence with an open-reading frame encoding 385 amino acids. This is called human TRESK.

Finally, to verify that human TRESK cDNA including the entire open-reading frame could be cloned from an independent source, human spinal cord poly(A)⁺ RNA (Clontech) was used for the reverse translation.
transcription (RT)-PCR. The RT reaction was primed with random hexamer. The primers for PCR were 5'-H11032-TCAGGGACGATGGAGGTCT-3' and 5'-H11032-AAAACCAGCTCAGCCAGTG-3'. PCR was performed for 35 cycles at 98 °C for 15 s, 60 °C for 30 s, and 72 °C for 2 min with Taq polymerase (TAKARA). The amplified fragment was subcloned into the pCR-TOPO vector and sequenced on both strands.

RT-PCR Analysis—Multiple human poly(A)/H11001 RNA (Clontech) was reverse-transcribed to generate first-strand cDNA with an Advantage RT-for-PCR kit (Clontech). PCR was carried out with this first-strand cDNA, corresponding to 5 ng of poly(A)/H11001 RNA. PCR primers were designed from the human TRESK cDNA sequence, 5'-H11032-TGCTTTCTGGTGACCTACGC-3' and 5'-H11032-GCTGCACAGGAAATGTAGGC-3'. PCR was performed for 45 cycles at 98 °C for 15 s and 70 °C for 1 min using Taq polymerase. The PCR products were run on 1.5% polyacrylamide gels. Ethidium bromide-stained gels were examined under UV illumination. Amplified fragments were subcloned into the pCR-TOPO vector and sequenced on both strands to confirm the PCR product as human TRESK. As a control, glyceraldehyde-3-phosphate dehydrogenase was amplified using specific primers (Clontech).

Transfection of TRESK—The previously amplified cDNA of TRESK was cloned into the pcDNA3.1 vector (Invitrogen). L929 cells were transfected with TRESK cDNA for electrophysiological studies as described elsewhere (31–33). Cells were co-transfected with the TRESK expression vector described previously and the green fluorescent protein expression vector phGFP S65T (Clontech) using FuGENE 6 (Roche Applied Science). The cells were cultured in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum. Transfected cells were identified by observing green fluorescent protein fluorescence with an epifluorescence microscope. Electrophysiological studies were carried out 1–3 days after transfection.

Electrophysiological Study—Electrophysiological recordings of TRESK transfectants were performed using a voltage-clamp technique (34). Recordings were made with an Axopatch 1D amplifier (Axon Instruments) using patch electrodes with a resistance of 3–5 megohms. The internal pipette solution contained 149 mM KCl, 1.8 mM MgCl2, 4.5 mM EGTA, and 9 mM HEPES-K (pH 7.3). The external solution contained 149 mM NaCl, 5 mM KCl, 2 mM MgCl2, and 10 mM HEPES-Na (pH 7.3). All recordings were performed at room temperature (22 °C). Analysis was carried out on a personal computer using pCLAMP6 software (Axon Instruments). All values are expressed as means ± S.E. Statistical significance was tested with Student’s t test.

RESULTS

Molecular Cloning of Human TRESK—The two-pore domain K+ channel-related sequence, accession number AL731557, was identified in the human draft genome sequencing data base of GenBankTM using a TBLASTN search for the amino acid sequence of human TWIK-1. Genomic clone AL731557 consists of 142,068 bases, and has been assigned to chromosome 10 of the human genome. Sequence alignment with the CDS and AL731557 revealed that the CDS consisted of 14 exons, of which 13 are coding. The coding region of TRESK is 1158 bases, which encodes 385 amino acids (Fig. 1). A novel two-pore domain K+ channel, TRESK, has been cloned from human genomic clone AL731557, which contains a region encoding 1158 bases and 385 amino acids. The alignment revealed that the CDS consists of 3 exons composed of 222, 129, and 804 bases and two introns spanning 12,811 bases.
Hydropathy analysis of the amino acid sequence showed that the new clone belongs to the K⁺ channel family since it has two pore-forming domains (P) and four transmembrane domains (TM) (Fig. 1, A and B). Two N-glycosylation sites are present in the TM1-P1 linker region (Fig. 1, A and C). Because the N-terminal region is located on the intracellular side, similar to other two-pore domain K⁺ channels, the putative K⁺ channel has a short N-terminal region, extended intracellular loop between TM2 and TM3, and a short C-terminal region (Fig. 1C).

Searching the GenBank™ database with the BLAST sequence alignment program revealed that the full amino acid sequence of the new clone shows the greatest similarity to human TREK2, but even so, it still shares only 34% identity. Alignment of the amino acid sequence of the new clone with human TREK2, but even so, it still shares only 34% identity. Also, phylogenetic analysis suggested that this clone has a common ancestor with previously reported two-pore domain K⁺ channels but represents an additional branch in this family of the channels (Fig. 2). These results indicate that this new clone belongs to the K⁺ channel family, including TRESK.

**Phylogenetic tree of the human two-pore domain K⁺ channel family, including TRESK.** The tree was generated using the neighbor-joining algorithm of the Phylip program on the basis of a multiple alignment of conserved sequences of the pore-forming domain analyzed with the ClustalW program.

**Basic Electrophysiological Properties of TRESK**—To characterize the electrophysiological properties of TRESK using the whole-cell voltage clamp technique, L929 cells were transiently transfected with the TRESK expression vector. The cells were clamped at a holding potential of −80 mV and were depolarized to voltages between −120 and +100 mV. In TRESK-transfected cells, large currents were recorded (Fig. 4A) that were not present in the control cells (data not shown). The activation kinetics of TRESK current was rapid. Depolarization steps induced a two-step current composed of large instantaneous and delayed components (Fig. 4A). The ion selectivity of TRESK was studied by changing the concentration of K⁺ in the external solution from 5 to 150 mM while maintaining the pipette [K⁺] constant at 150 mM. The current-voltage (I-V) relationship is outwardly rectifying, and almost no inward currents were recorded in an external medium containing 5 mM K⁺ (Fig. 4B). The plots of the reversal potential as a function of [K⁺] showed that the slope was 49.0 ± 0.8 mV/decade (n = 3), which is close to the calculated Nernst value of 58 mV, as expected for a highly selective K⁺ channel (Fig. 4C). As previously reported for other two-pore domain K⁺ channels, the membrane potential of TRESK-expressed L929 cells with a high current density was strongly polarized (Fig. 4D). In contrast, the membrane potential of TRESK-expressed cells that had a low current density was not polarized (Fig. 4D).

**Pharmacological Properties of TRESK**—The effect of various pharmacological agents on currents elicited by voltage pulse to 0 mV have been studied in TRESK-transfected cells using whole-cell recording. The classical K⁺ channel blocker, Ba²⁺, applied extracellularly at 3 mM inhibited TRESK current. This inhibition was gradually released by depolarization to voltages from −20 to +80 mV (Fig. 5A). To clarify the inhibition by Ba²⁺, we tested the effect of Ba²⁺ at the start and end of pulses at different voltages. The inhibition by Ba²⁺ at the end of the pulse was significantly decreased at depolarized potentials. On the other hand, the inhibition at the start of the pulse was not affected by the depolarization (Fig. 5B). These results suggest that Ba²⁺ acts as an open channel blocker. TRESK was insen-
Fig. 4. Electrophysiological studies of TRESK. A, voltage-dependent outward currents in L929 cells transfected with TRESK cDNA (upper traces). Cells were held at −80 mV and depolarized to a voltage between −120 and +100 mV (lower traces). B, the current-voltage (I-V) relationship plotted at different [K⁺]. C, reversal potential of TRESK currents as a function of [K⁺]₀. Experimental values were fit by linear regression (slope, 49 mV/decade). D, the relationship of current density (Iₒ) at 0 mV to the resting membrane potential (Eₘ) in each TRESK-expressing L929 cell.

Fig. 5. Pharmacological properties of TRESK. A, the addition of 3 mM Ba²⁺ to the bath solution reversibly reduced the TRESK current. Cells were held at −80 mV and depolarized to a voltage between −120 and +100 mV. B, inhibition of TRESK currents by 3 mM Ba²⁺ at the start and end of pulses at different voltages. Cells were held at −80 mV and depolarized to a voltage between −20 and +80 mV. C, inhibition by various K⁺ channel inhibitors, 50 μM propafenone, 50 μM gliburide, 1 mM lidocaine, 0.1 mM quinine, 0.1 mM quinidine, and 2 mM triethanolamine (TEA), of TRESK currents elicited by 0 mV pulse.

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(3 mM Ba²⁺), and glipizide (ATP-sensitive K⁺ channel blocker) when applied extracellularly at 100 μM. Propafenone, gliburide (ATP-sensitive K⁺ channel blocker), lidocaine (Na⁺ channel blocker), quinine, quinidine, and triethanolamine (non-selective K⁺ channel blocker) inhibited TRESK currents by 95.3 ± 1.8% (n = 3), 76.8 ± 8.6% (n = 4), 75.7 ± 5.4% (n = 5), 75.2 ± 7.1% (n = 4), 90.6 ± 1.5% (n = 4), and 34.4 ± 1.0% (n = 3), respectively (Fig. 5C). Because these compounds were reported to inhibit K⁺ channels, the results suggest that TRESK has the property of K⁺ channels.

Inhibition of TRESK by Free Fatty Acids—Outside-out patches were used to test whether TRESK is sensitive to free fatty acids. Arachidonic acid, which is a polyunsaturated free fatty acid, inhibited TRESK current when applied to the extracellular side of outside-out patches (Fig. 6A). We also tested whether arachidonic acid could inhibit TRESK from the cytoplasmic side of the membrane. In inside-out patches, intracellular application of arachidonic acid inhibits TRESK current (Fig. 6B). This inhibition was expressed in a concentration-dependent manner (Fig. 6C). The onset of inhibition was generally rapid (within 1 min), and steady-state inhibition was observed within 1 min after application. The relative channel current was plotted as a function of the arachidonic acid concentration in Fig. 6D. With the reasonable assumption that 50 μM arachidonic acid produces maximal inhibition of TRESK, the averaged data were fit to a Hill equation of the form $y = \frac{1}{1 + (K_{1/2}^\text{r}[\text{arachidonic acid}])^n}$, where $K_{1/2}$ is the apparent concentration of arachidonic acid that produces half-maximal inhibition, and n is the Hill coefficient (apparent $K_{1/2}$ = 6.6 μM, Hill coefficient = 1.3, n = 3). We tested whether other free fatty acids, i.e. saturated and unsaturated free fatty acids, were also able to inhibit TRESK current. When applied to the intracellular side, unsaturated free fatty acids such as docosahexaenoic acid, linoleic acid, and oleic acid significantly inhibited TRESK current at 20 μM (Fig. 6, E and F). Saturated free fatty acids such as palmitic acid and stearic acid had almost no effect on TRESK current at 20 μM (Fig. 6, E and G, n = 3 and 4, respectively). These results show that unsaturated free fatty acids inhibit TRESK current.
Regulation of TRESK Current by pH—We tested whether TRESK is sensitive to changes in the extracellular and intracellular pH. We first used whole-cell recording to test whether TRESK is sensitive to changes in the extracellular pH. The cells were clamped at a holding potential of −40 mV and then depolarized to voltages between −80 and +80 mV. TRESK currents were measured at different extracellular pH values (Fig. 7A). Changes in the extracellular pH from 7.3 to 5.6 and 8.9 resulted in inhibition (80 ± 7%, n = 3) and enhancement (120 ± 5%, n = 3) of TRESK currents, respectively, from the basal channel activity observed at pH 7.3 (Fig. 7B). Thus, the TRESK channel is sensitive to changes in the extracellular pH, acid, and alkali, but those sensitivities are not remarkable compared with other K⁺ channels. To test the effect of changes in the intracellular pH, we used inside-out patches. Fig. 7C shows that the TRESK current was remarkably inhibited by a change in the intracellular pH from 7.3 to 5.6. Changes in the intracellular pH from 7.3 to 5.6 and 8.9 resulted in inhibition (39 ± 4%, n = 3) and enhancement (140 ± 12%, n = 3) of TRESK currents, respectively, from the basal channel activity observed at pH 7.3 (Fig. 7D). These effects, especially at pH 5.6, were greater than those of the extracellular pH. These results show that TRESK is much more sensitive to changes in intracellular pH than extracellular pH.

We also tested whether TRESK is sensitive to changes in the temperature. Several two-pore K⁺ channels were also reported to be sensitive to changes in the temperature (16, 19). We recorded the TRESK current in whole-cell recording at 15, 22, 39, and 43 °C. Lowering the temperature from 22 to 16 °C had no effect on the TRESK current at −80 mV (102.7 ± 11.5%, n = 3). Raising the temperature from 22 to 39 or 43 °C also had no effect on the TRESK current (106.3 ± 5.6%, n = 3; 118.8 ± 6.4%, n = 3, respectively). These results show that TRESK is insensitive to changes in temperature.

**FIG. 6. Inhibition of TRESK by free fatty acids.** A, inhibition of TRESK current by arachidonic acid (AA) in outside-out patches in symmetric 150 mM KCl. Arachidonic acid (50 μM) was applied to the extracellular side. Cells were held at +20 mV. The inset shows the current-voltage (I-V) relationships recorded by applying a voltage ramp from −60 to +60 mV (50 mV/s) at the response for before (a) or during (b) application of arachidonic acid. B, inhibition by arachidonic acid on TRESK current recorded at +40 mV in the inside-out patches. Arachidonic acid (20 μM) was applied to the cytoplasmic side of the membrane. C, in the inside-out patches, the concentration of arachidonic acid was increased in steps from 0 to 50 μM. D, relative channel activity plotted as a function of [arachidonic acid]. E, inhibition of the TRESK current by different free fatty acids at 20 μM (n = 3 each). DHA, docosahexaenoic acid; LA, linoleic acid; OA, oleic acid; PA, palmitic acid; SA, stearic acid. F, inhibition by docosahexaenoic acid in inside-out patches held at +40 mV. Docosahexaenoic acid (20 μM) was applied to the cytoplasmic side of the membrane. G, application of stearic acid (20 μM) to the cytoplasmic side of the membrane in inside-out patches held at +40 mV.

**FIG. 7. pH-dependent changes in TRESK current.** A, the current-voltage (I-V) relationships deduced from whole-cell currents of TRESK elicited by voltage ramp ranging from −80 to +80 mV, measured at three different extracellular pH levels (5.6, 7.3, and 8.9). Iiktig, current density. B, effects of changes in extracellular pH on TRESK current at 0 mV. The current at pHin 7.3 was taken as 100%. C, inhibition of TRESK current by change in intracellular pH in inside-out patches held at +40 mV. D, effects of changes in intracellular pH on TRESK current at +40 mV. The current at pHin 7.3 was taken as 100%. The asterisks indicate a significant difference from the value at pHin 7.3, as judged by Student’s t test (p < 0.01).
nel the TWIK-related spinal cord K⁺ channel, TRESK, because this differentiates it from other two-pore domain K⁺ channels.

Electrophysiological Behavior of TRESK—Electrophysiological studies demonstrated many profiles of the TRESK channel. The reversal potential of the current induced by expression of TRESK-cDNA in mammalian cell lines followed the calculated K⁺ equilibrium potential when the external [K⁺] was changed. This suggests that the TRESK channel selectively permeates K⁺. The whole-cell current-voltage I-V relationship in a symmetric K⁺ solution showed that TRESK induced outward rectification. When TRESK is transiently expressed in mammalian cell lines, TRESK currents are observed at all membrane potentials, including the resting membrane potential. This channel activity is also seen in other two-pore domain K⁺ channels. The basal current that is present at the resting membrane potential is thought to drive the membrane potential toward the K⁺ equilibrium potential. TRESK current is activated instantaneously by a voltage step and shows no voltage threshold for activation. Moreover, the membrane potential of TRESK-expressing cells is strongly polarized. These properties suggest that TRESK may function as a background K⁺ channel that sets the resting membrane potential.

The pharmacological profiles of the TRESK channel are similar to those of previously reported two-pore domain K⁺ channels, which are inhibited by K⁺ channel inhibitors. We analyzed the detailed mechanism of the inhibition by Ba²⁺. The inhibition by Ba²⁺ at the end of the pulse was significantly decreased at depolarized potentials, but the inhibition at the start of the pulse was not affected. These properties suggest that Ba²⁺ inhibited the open state of TRESK, and this blockage was released by depolarized stimulus.

Free Fatty Acid and pH Sensitivity of TRESK—To test for functional similarities with other members of the two-pore domain K⁺ channel family, we studied modulation of the TRESK channel by various experimental interventions such as application of free fatty acids and changes in the pH.

Like TASK-1 and TASK-3, TRESK was inhibited by intracellular and extracellular application of arachidonic acid. This inhibition was shown by intracellular application of not only arachidonic acid but also other unsaturated free fatty acids, such as docosahexaenoic acid, linoleic acid, and oleic acid. However, our studies also showed that saturated free fatty acids such as palmitic acid and stearic acid did not significantly affect the TRESK current. Thus, the TRESK channel is sensitive only to unsaturated free fatty acids, and it seems that there may be an unsaturated free fatty acid-selective site in the TRESK protein.

Furthermore, we demonstrated here that TRESK currents were inhibited and enhanced by extreme changes in the pH values from 7.3 to 5.6 and 8.9, respectively. Regulation of the channel activity by the pH is an important functional property of two-pore domain K⁺ channels. TRESK exhibited greater sensitivity to acidic conditions than alkaline conditions. Our studies also show that TRESK is more sensitive to changes in the intracellular pH than changes in the extracellular pH. This property has also been reported for TASK-3 and TREK-2 (18, 20).

Predicted Physiological Role of TRESK in the Spinal Cord—Until now, some two-pore domain K⁺ channels were reported to be expressed in the spinal cord, but they were not specific to the spinal cord (11). On the other hand, the expression of TRESK mRNA is specifically localized in the spinal cord, indicating that TRESK may play a unique role in the spinal cord that is different from other two-pore domain K⁺ channels. Actually, we revealed that the TRESK channel is regulated by free fatty acids, which have been reported to participate in the function of the spinal cord. Spinal cord trauma is known to cause a marked release of free fatty acids, especially arachidonic acid, from the cell membrane. These released free fatty acids are suggested to lead to the secondary injury to spinal cord neurons that is observed in spinal cord trauma (35). However, the specific effects of released arachidonic acid in relation to the mechanisms of spinal cord injury remain to be established. One would suspect that Ca²⁺ influx, which is known to be one of the most common cellular signaling factors, is involved in spinal cord injury. Therefore, if injured neurons show TRESK currents, released free fatty acids may cause Ca²⁺ influx via a voltage-gated Ca²⁺ channel by depolarizing the membrane potential through changing the TRESK current.

In summary, we have isolated TRESK, an outward rectifying K⁺ channel that belongs to the two-pore domain K⁺ channel family. The functional properties of TRESK show that it is sensitive to unsaturated free fatty acids and extreme changes in extracellular and intracellular pH. Furthermore, its tissue distribution and basic electrophysiological properties suggest that TRESK may be involved in regulation of the resting membrane potential in spinal cord-specific cells.

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