Human TREK2, a 2P Domain Mechano-sensitive K\(^+\) Channel with Multiple Regualtions by Polyunsaturated Fatty Acids, Lysophospholipids, and G\(_s\), G\(_i\), and G\(_q\) Protein-coupled Receptors*

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Mechano-sensitive and fatty acid-activated K\(^+\) belong to the structural class of K\(^+\) channel with two pore domains. Here, we report the isolation and the characterization of a novel member of this family. This channel, called TREK2, is closely related to TREK1 (78% of homology). Its gene is located on chromosome 14q31. TREK2 is abundantly expressed in pancreas and kidney and to a lower level in brain, testis, colon, and small intestine. In the central nervous system, TREK2 has a widespread distribution with the highest levels of expression in cerebellum, occipital lobe, putamen, and thalamus. In transfected cells, TREK2 produces rapidly activating and non-inactivating outward rectifier K\(^+\) currents. The single-channel conductance is 100 pico siemens at +40 mV in 150 mM K\(^+\). The currents can be strongly stimulated by polyunsaturated fatty acids such as arachidonic, docosahexaenoic, and linoleic acids and by lysophosphatidylcholine. The channel is also activated by acidification of the intracellular medium. TREK2 is blocked by application of intracellular cAMP. As with TREK1, TREK2 is activated by the volatile general anesthetics halothane, isoflurane, and by the neuromuscular-blocking agent succinylcholine. TREK2 can be positively or negatively regulated by a variety of neurotransmitter receptors. Stimulation of the G\(_i\)-coupled receptor 5HT4R or the G\(_i\)-coupled receptor mGlur1 inhibits channel activity, whereas activation of the G\(_i\)-coupled receptor mGlur4 increases TREK2 currents. These multiple types of regulation suggest that TREK2 plays an important role as a target of neurotransmitter action.

Potassium channel subunits containing two pore domains form a novel class of background K\(^+\) channels. These K\(_p\) channels have unique pharmacological and functional properties (1–10). They are active at all membrane potentials and display very rapid kinetics of activation and deactivation, and no inactivation. Their widespread tissue distribution suggests that one of their major physiological role is the setting of the resting membrane potential in many different cell types. However, background K\(^+\) channels with specific functional and regulatory properties, as well as unique tissue distribution, have been cloned. These channels could be involved in more specific functions such as epithelial K\(^+\) transport and regulation of neuronal and muscular excitability (11).

Various K\(^+\) currents have been recorded in vivo from neuronal, cardiac, and smooth muscle cells that form a subfamily of background K\(^+\) currents sensitive to fatty acids (12–15). Recently, fatty acid-activated K\(^+\) channels have been cloned from mouse and human (2, 6, 16). These channels, named TREK1 (TWIK-related K\(^+\) channel) and TRAAK (TWIK-related arachidonic acid-stimulated K\(^+\) channel), produce quasi-instantaneous currents that are outwardly rectifying in physiological K\(^+\) gradient. These channels have a low basal activity compared with TASK background channels (3–5). However, they can be strongly activated by application of arachidonic acid. This effect is specific of unsaturated fatty acids. Oleate, linoleate, eicosapentaenoate, and docosahexaenoate all strongly activate TREK1 and TRAAK, whereas saturated fatty acids such as palmitate, stearate, and arachidate are ineffective (6, 17). Another efficient way for activating these channels is the application of a stretch to the cell membrane (17, 18). Both channels are activated by shear stress, cell swelling, and negative pressure. They are mecano-sensitive K\(^+\) channels. Compared with TRAAK, TREK1 has additional features. TREK1 is inhibited by activators of protein kinases C (PKC) and A (PKA). The site for PKA phosphorylation has been localized in the cytoplasmic carboxyl-terminal part of the channel (17). TREK1 but not TRAAK is opened by internal acidification (19). Lowering pH shifts the pressure-activation relationships toward positive values and leads to channel opening at atmospheric pressure. TREK1 but not TRAAK is activated by inhalational general anesthetics, halothane and isoflurane, at concentrations used in human general anesthesia (16). Finally, TREK1 and TRAAK have different tissue distributions, the expression of TRAAK being more restricted to neuronal cells than TREK1 (2, 6, 20).

This article describes the cloning, the genomic organization, the localization, and the functional characterization of a novel human K\(^+\) channel with two pore domains. The molecular and functional properties of this channel indicates that it too belongs to the particular subclass of mecano-sensitive and unsaturated fatty acid-activated K\(^+\) channels. TREK2 is more related to TREK1 than to TRAAK, and like TREK1, it is activated by general anesthetics at clinical concentrations. TREK2 is modulated by different types of neurotransmitter receptors.

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† The abbreviations used are: TREK, TWIK-related K\(^+\) channel; TWIK, Tandem of P domains in a Weak Inward rectifying K\(^+\) channel; TRAAK, TWIK-related arachidonic acid-stimulated K\(^+\) channel; TASK, TWIK-related acid-sensitive K\(^+\) channel; PKC, protein kinase C; PKA, protein kinase A; RACE, rapid amplifications of cDNA ends; PCR, polymerase chain reaction; kb, kilobase(s); contig, group of overlapping clones.
**Molecular Cloning of TREK2—DNA sequences produced in the frame of the human genome sequencing program are rapidly accumulating in the public high throughput genomic sequences (HTGS) data base. Searches of this data base using the Blast sequence alignment program (21) led to the identification of human sequences restrained to a single genomic contig. The analysis of these sequences suggested the presence of introns and exons forming a gene coding for a novel K_2P_ subunit. Oligonucleotides were deduced from the potential exon sequences and used to clone cDNA fragments from human brain by using RACE-PCR. The sequence deduced from these cDNAs is 2730 base pairs long and contains an open reading frame of 1617 nucleotides, predicting a 538-amino acid polypeptide (Fig. 1A). This protein has the same overall structure than the previously cloned K_2P_ subunits. It displays four membrane-spanning segments (M1 to M4), two P domains (P1 and P2), and an extended loop between M1 and P1. The dendrogram shown in Fig. 1C clearly indicates that this subunit is more related to TREK1 and TRAAK than to other K_2P_ subunits. Therefore, this novel K_2P_ subunit was named TREK2 (gene KCNK10 in the human genome organization (HUGO) nomenclature). TREK2 shares 63% identity and 78% homology with TREK1. The homology level falls to 69% with TRAAK and to 50–55% with the other K_2P_ subunits.**

**TREK2 Gene Organization and Location—The genomic organization of TREK2 was deduced from the alignment of the cloned cDNAs with the genomic sequences available in the high throughput genomic sequences (HTGS) DNA data base.**

The open reading frame is composed of six introns and seven exons. The amino terminus of TREK2 is encoded by exon 1, the M1 domain by exon 2, M2 by exon 4, M3 by exon 5, and M4 by exon 6. The third exon codes for the carboxyl-terminal part of the M1P1 interdomain, and the seventh one encodes the large carboxyl terminus of the channel (Fig. 1A). The length of introns 2–6 varies from 1.8 kb to 35 kb (Fig. 1B). The first exon being out of the genomic contig, the size of the first intron is not known. At this point, it cannot be excluded that the 5'-untranslated sequence corresponds to more than one exon. This organization is different than TWIK1 and TASK3 gene organizations. TWIK1 contains three exons separated by two large introns (23), and TASK3 contains only one short intron (10). However, genomic organization of TREK2 is very close to the genomic organization of both TRAAK (24) and TREK1 channel 2 genomic organizations. Introns 2 to 6 are found in the same positions. This observation confirms that these three channels are closely related and suggests that they have arisen by gene duplication from a common ancestor. A particular feature found in TWIK1, TASK1, TREK1, TREK2, TRAAK, TASK2, and TASK3 genes is the presence of a conserved intron in the sequence coding the P1 domain (third intron in the TREK2 gene). The intron site is between the first and the second nucleotides of the codon coding for the first glycine residue of the pore signature sequence G/Y/F/L/G. An intron in the same position is found in 20 genes among the 36 examined that encode potential K_2P_ channels in the nematode Caenorhabditis elegans (25) and in 8 genes among 11 in the Drosophila, as determined by analyzing its recently released genomic sequences. The significance of this conserved intron position is not known; however, it is worth noting that this intron has been conserved in mammals, where it might eventually have the same role as in the nematode. The analysis of genomic contig bearing the TREK2 gene showed that this sequence
contains two sequence tag sites, D14S1058 and WI-6710. WI-6710 has been placed on the WICGR radiation hybrid map 308.53 centiRay from the top of the Chr14 linkage group, and D14S1058 has been mapped by Genethon 86.3 centimorgan from the top of the Chr14 linkage group. These results are in agreement and indicate that the chromosomal location of TREK2 gene is 14q31. This location is different from those of TREK1 (1q41) (26) and TRAAK (11q13) (24).

Tissue Distribution of TREK2—The expression of TREK2 in various adult human tissues was examined by reverse transcription-PCR analysis. As shown in Fig. 2A, TREK2 is abundantly expressed in kidney and pancreas and more moderately in testis, brain, colon, and small intestine. Only very faint signals were obtained in liver, heart, prostate, and thymus. This expression pattern contrasts with the TREK1 and TRAAK tissue distributions (Fig. 2A). Some tissues express only one of these channels: for instance, pancreas and colon (TREK2), placenta (TRAAK), and ovary (TREK1). Other tissues do not express these channels or only to modest levels: heart, skeletal muscle, lung, peripheral blood leukocytes, and spleen. Finally, some tissues express two or three of these related channels: brain, testis, and small intestine. Distributions of TREK1, TREK2, and TRAAK in the different areas of the human brain were analyzed by Northern blot. As shown in Fig. 2B, the TREK2 probe detected two transcripts of 4 and 7.5 kb. TREK2 is mainly expressed in cerebellum, occipital lobe, putamen, and thalamus and to lower levels in the other examined areas. No expression was detected in amygdala and spinal cord. The 4-kb transcript is expressed at a higher level than the 7.5-kb transcript except in occipital lobe and cerebellum. As expected from the previous studies on TREK1 and TRAAK expression in rodent central nervous system (2, 6, 20), these two channels have a widespread distribution in the human brain. The 3-kb TRAAK transcript and the 2.7- and 3.3-kb TREK1 transcripts are well expressed in areas where TREK2 is mainly expressed: putamen and thalamus. In the brain cortex (occipital, frontal, and temporal lobes), TRAAK is also highly expressed. Finally, TREK1 is the only channel of this family to be expressed in the spinal cord.

Biophysical Properties of TREK2—TREK2-transfected COS cells display nonactivating currents (Fig. 3A) that are not present in control cells (not shown). The activation kinetics of TREK2 current are rapid. Depolarization pulses induce a two-step current composed of instantaneous and delayed components (Fig. 3B). 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. 3B). When cells are bathed in a K⁺-rich solution (150 mM), an inward current is revealed, and the reversal potential becomes 0 mV, as expected for a K⁺-selective channel. However, the I-V relationship is not linear and does not strictly fit the Goldman-Hodgkin-Katz equation for an open K⁺-selective pore. The current has a tendency to saturate at very negative potentials. Two-step activation kinetics and outward rectification in symmetrical K⁺ conditions have also been found for the TREK1 current (2, 17). Moreover, like TREK1, TREK2 outward currents are more important in 150 mM K⁺ than in 5 mM K⁺ for depolarizations higher than +50 mV. This effect is unusual since an increase of external K⁺ lowers the chemical driving force for outward K⁺ flux and would be expected to decrease rather than increase the currents. For TREK1, this effect has been attributed to a stimulating effect of external K⁺, as found for other types of K⁺ channels (27, 28). In addition, TREK1 has been shown to be sensitive to external Na⁺ (Na⁺). When Na⁺ was substituted by N-methyl-D-glucamine, TREK1 activity was strongly decreased (2). TREK2 is only partially inhibited by removing Na⁺ (23% of inhibition, n = 5, not shown). Single-channel properties of TREK2 are illustrated in Fig. 3C, D, and E. Basal channel activity in outside-out patches is characterized by a flickery bursting behavior (Fig. 3C). In physiological K⁺ concentrations, the I-V relationship is outwardly rectifying, and almost no inward currents were recorded as in whole-cell recording. In symmetrical conditions, inward currents were recorded in addition to outward currents, with single-channel conductances of 128 picosiemens at −40 mV and 100 picosiemens at +40 mV (n = 5) (Fig. 3C, D, and E). It is interesting to note that the single-channel I-V relationship is inwardly rectifying because the single-channel conductance in-
dine inhibited the currents (50% of inhibition at 100 μM) (not shown). Like TREK1, TREK2 is stimulated by application of the inhalational anesthetics chloroform, halothane, and isoflurane (Fig. 5, A and B). At a clinical dose of halothane (29), TREK2 is markedly activated (1.4 ± 0.1-fold increase at 0.25 mM, n = 10, at +100 mV). The maximal halothane effect is nearly obtained at 0.5 mM (2.6 ± 0.3-fold increase, n = 10, at +100 mV). The efficiency of anesthetics is different between TREK1 and TREK2. For TREK2, halothane (2.3 ± 0.3-fold increase at 1 mM, n = 6, at 0 mV) is more efficient than isoflurane (1.9 ± 0.1-fold increase at 1 mM, n = 6) and chloroform (1.8 ± 0.1-fold increase at 1 mM, n = 7). For TREK1, chloroform is more effective than halothane and isoflurane at the same concentrations (1 mM) (16). Fig. 5, C and D, show that TREK2 is also activated by application of the neuroprotective drug riluzole. As for TREK1, this activation is transient and is followed by a decrease of the activity corresponding to an inhibition. In the case of TREK1, this is due to an increase of the intracellular cAMP and a phosphorylation of the channel by PKA (30).

**Activation of TREK2 by Fatty Acids and Inhibition by Intracellular cAMP**—Fig. 6A illustrates the strong stimulating effect of 10 μM arachidonic acid on TREK2 current (8.4 ± 1.9-fold increase at 0 mV, n = 6). This effect is reversible (not shown). Like TREK1, TREK2 is activated by other polyunsaturated fatty acids, docosahexaenoic and linoleic acids, and by lysophosphatidylcholine but not by the saturated fatty acid palmitic acid (Fig. 6, B and C) (17, 31). TREK2 is also activated by 10 μM lysophosphatidylinositol (5.1 ± 0.6-fold increase at 0 mV, n = 8). Application of the permeant chlorophenylthio-cAMP (500 μM) led to 50% inhibition of TREK2 activity at 0 mV (50 ± 5, n = 8) (Fig. 6D). A similar inhibition is obtained by application of a mixture of 1 mM 3-isobutyl-1-methylxanthine, 10 μM forskolin to increase the intracellular cAMP level (72 ± 10% of inhibition, n = 8). This suggests that TREK2 as TREK1 is inhibited by PKA phosphorylation (16).

**Regulation of TREK2 by Co-expression with Gs-, Gi-, and Gq-coupled Neurotransmitter Receptors—**TREK2 was co-expressed with 5HT4sR, a Gq-coupled receptor. The stimulation of the receptor by application of 5-hydroxytryptamine is associated with a decrease of TREK2 activity, as expected for a receptor positively coupled to adenylyl cyclase (Fig. 7A). Conversely, activation of the co-expressed Gi-coupled mGlur2 receptor by glutamate leads to a stimulation of TREK2 activity (Fig. 7B). The decrease of TREK2 activity by the stimulation of 5HT4sR is rapidly reversed after washing (Fig. 7A), whereas the TREK2 increase associated with mGlur2 is much slower to reverse (more than 10 min) (Fig. 7B). A third type of G-protein-coupled receptor was co-expressed with TREK2. This receptor is the Gq-coupled mGlur1 receptor. Activation of mGlur1 by application of glutamate led to an inhibition of TREK2 activity that is rapidly reversed by washing (Fig. 7C). The Gq protein is commonly associated with activation of phospholipase C and the consequent production of diacylglycerol and inositol 1,4,5-trisphosphate. Ultimately, diacylglycerol leads to activation of PKC and inositol 1,4,5-trisphosphate to an increase of intracellular Ca2+. However, neither the application of the PKC-activator phorbol 12-myristate 13-acetate (100 nM) nor the addition of Ca2+ in the recording pipette (1 μM) was able to induce an inhibition of TREK2 (not shown).

**DISCUSSION**

**Characterization of a Novel Channel—**TREK2 is a novel member of the fatty acid-activated and mechano-sensitive K+ channel family that includes TREK1 and TRAAK. Like these channels, TREK2 is not blocked by tetraethylammonium and Ba2+ and is stimulated by polyunsaturated fatty acids, such as

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**FIG. 2. Expression of TREK2 in adult human.** A, tissue distribution analysis by reverse transcription-PCR. The amplified products were analysed by Southern blot using specific internal primers as probes. To check the integrity of cDNAs, a glyceraldehyde-3-phosphate dehydrogenase fragment was amplified. B, localization in the brain by Northern blot analysis. Blots were hybridized at high stringency with specific probes. Each lane contains 2 μg of poly(A)+ RNA.

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**DISCUSSION**

**Characterization of a Novel Channel—**TREK2 is a novel member of the fatty acid-activated and mechano-sensitive K+ channel family that includes TREK1 and TRAAK. Like these channels, TREK2 is not blocked by tetraethylammonium and Ba2+ and is stimulated by polyunsaturated fatty acids, such as
arachidonic, docosahexaenoic, and linoleic acids, by lysophospholipids and by application of a negative pressure to the cell membrane. In addition, TREK2 shares with these channels the same gene organization, indicating that the three genes probably derive from a common ancestral gene. However, TREK2 is more related to TREK1 than to TRAAK. TREK2 and TREK1

**FIG. 3.** Biophysical properties of TREK2 currents. A, whole-cell configuration. Superimposed current traces elicited by voltage steps from −150 mV to +70 mV by increments of 20 mV. B, current-voltage (I-V) relationships in physiological (5 mM K⁺) and symmetrical (150 mM K⁺) K⁺ gradients (800-ms voltage ramps from −130 to +100 mV from a holding potential of −80 mV). C, steady-state single-channel activities at the indicated potentials. Outside-out patch mode in physiological (left traces) and symmetrical (right traces) K⁺ conditions. D, single-channel I-V curves of TREK2 obtained from outside-out patches in physiological (filled square) and symmetrical (open circle) K⁺ conditions. Mean of five examined patches. Single-channel conductance was 128 picoSiemens at −40 mV and 100 picoSiemens at +40 mV when measured in symmetrical K⁺ conditions.

**FIG. 4.** Activation of TREK2 by a stretch of the membrane and by internal acidosis. A, reversible activation of TREK2 by membrane stretch in an inside-out patch exhibiting a low basal activity at +50 mV. B, effects of increasing stretch stimulation (in mm of Hg) on TREK2 activation in an multi-channel inside-out patch held at 0 mV. C, multi-channel inside-out patch. Effects of membrane voltage (as indicated) on TREK2 activation by the same membrane stretch (−75 mm of Hg). D, reversible activation of TREK2 by internal acidosis (pH 5.6) in a patch displaying a low basal activity. The maximum TREK2 activation is obtained in depolarized conditions. E, multi-channel inside-out patch. Voltage dependence of activation by internal acidosis at pH 5.6 is shown. In A and B, the control value of pH was kept at 7.3.
have unique functional and pharmacological properties that are not shared by TRAAK; they are negatively regulated by agents that activate PKA, positively regulated by acidification of internal medium, and strongly activated by volatile general anesthetics. Like TREK1, TREK2 is also transiently activated by riluzole, whereas TRAAK is permanently activated. For TREK1, the inhibition that follows activation by riluzole has been related to an increase of intracellular cAMP and a consequent inhibitory PKA phosphorylation of the channel (30). In molecular terms, TREK2 is also more related to TREK1, not only if one considers the overall sequence homology but also the distribution of this homology along the sequences. TRAAK, TREK1, and TREK2 have a conserved domain that extends from M1 to M4. Between TREK1 and TREK2, the homology level remains high after M4 and continues over 50 residues. This post-M4 carboxyl-terminal part is crucial for TREK1 channel sensitivity to fatty acids and stretch but also to PKA and pH (17, 16, 19). The high level of conservation in this domain between TREK1 and TREK2 explains why these channels have closely related mechanisms of regulation. Interestingly, the PKA site, which is implicated in the negative regulation by phosphorylation of TREK1 (17), is conserved in TREK2 (serine 359), suggesting that TREK2 is negatively regulated by PKA in the same way as TREK1. In TREK1, the cytoplasmic amino terminus is not important for the channel activity and for its mechanical and chemical regulations (17, 16, 19). This is also the case for TREK2 because a truncated TREK2 beginning at methionine 55 apparently conserves its properties after the removal of the first 54 residues by mutagenesis (not shown). While this manuscript was being reviewed, the cloning of a novel channel from rat has been published on line (32). This channel is clearly the rat ortholog of...
human TREK2. These channels have a similar tissue distribution, except in the kidney, where TREK2 is not expressed in the rat although it is highly expressed in the human. In addition, they share many common functional properties such as single channel conductance and sensitivity to polyunsaturated fatty acids and stretch. However, despite of a high sequence identity (more than 70%), the cytoplasmic amino-terminal part encoded by the first exon (Fig. 1A) is clearly unrelated between these two channels, suggesting alternative splicing from a single gene.

What Could Be the Physiological role of TREK2?—In neurons cultured from mesencephalic and hypothalamic areas of rat brain, several arachidonic acid-activated and mechano-sensitive K+ currents have been characterized (15). Their functional properties are very similar to the properties of TREK-related channels. Three different native currents have been identified in neurons with I-V relationships being slightly outwardly rectifying or linear or slightly inwardly rectifying in high symmetrical K+ conditions. Under the same conditions, the I-V relationship of TREK1 is slightly outwardly rectifying, and the I-V relationship of TRAAK is linear. These results together with the fact that TREK1 and TRAAK are expressed in brain areas that contain neurons expressing the native currents suggested that both cloned channels contribute to these native currents. None of the channels cloned until now corresponded to the third type of current with an inward rectification. From the Northern blot analysis, it appears that TREK2 is expressed in the same brain areas as TREK1. Since TREK2 produces currents whose I-V relationship is slightly inwardly rectifying, we propose that TREK2 could form or contribute to the formation of this third type of native arachidonic acid-activated and mechano-sensitive current with inward rectification. These channels are expected to play a role in the control of neuronal excitability and, particularly, in the control of the resting membrane potential if they are active at rest in vivo. The level of TREK2 activity can be regulated by the three different types of G-protein-coupled receptors. This indicates that TREK2 activity in neurons is probably fine-tuned by a variety of neurotransmitters and that TREK2 could play a role similar to the role of the K2P channel TASK1. In cerebellar granule cells and hypoglossal motoneurons, TASK1 has a central importance in controlling cell excitability, and the modulation of its activity by a variety of neurotransmitters acting via Gq-coupled receptors profoundly alters both resting membrane potential and excitability (33, 34). It is interesting to note that the signal transduction pathway by which Gq-coupled receptor inhibits TASK1 does not involve PKC or Ca2+ (33, 34), as also observed for TREK2. A major difference between TASK1 and TREK2 is that TREK2 is also regulated via Gi- and Gs-coupled receptors. TREK2 will probably turn out to be an important channel in charge of tuning neuronal excitability in response to a variety of neurotransmitters and hormones. The isolation and the characterization of TREK2 constitute an additional step toward the understanding of this particular class of K+ channels, which probably plays a wide variety of important physiological roles in the brain and other tissues (11) and that, because it is a target of volatile anesthetics (Ref. 16 and this article) and riluzole, a neuroprotective drug (6, 30), might have an important impact in medicine.
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