The mouse voltage-gated K\(^+\) channel gene, Kv1.4, is expressed in brain and heart as a 4.5- and 3.5-kilobase (kb) transcripts. Both mRNAs begin at a common site 1338 bp upstream of the initiation codon, contain 3477 and 4411 nucleotides, respectively, and are encoded by two exons; exon 1 contains 0.5 kb of the 5'-noncoding region (NCR), while exon 2 encodes the remaining 0.8 kb of the 5'-NCR, the entire coding region (2 kb), and all of the 3'-NCR. The 3.5-kb transcript terminates at a polyadenylation signal 177 bp 3' of the stop codon, while the 4.5-kb mRNA utilizes a signal 94 bp farther downstream. Although the proteins generated from either transcript are identical, the two mRNAs are functionally different, the 3.5-kb transcript producing 4-5-fold larger currents when expressed in Xenopus oocytes compared to the 4.5-kb mRNA. The decreased expression of the longer transcript is due to the presence of five ATTTA repeats in the 3'-NCR which inhibit translation; such motifs have also been reported to destabilize the messages of many other genes and might therefore shorten the life of the 4.5-kb transcript during its natural expression. The Kv1.4 basal promoter is GC-rich, contains three SP1 repeats (CCGCCC, –65 to –35), lacks canonical TATAAA and GGCAATCT motifs, and has no apparent tissue specificity. One region enhances activity of this promoter. Thus, transcriptional and post-transcriptional regulation of mKv1.4, coupled with selective usage of the two alternate Kv1.4 mRNAs, may modulate the levels of functional Kv1.4 channels.

Nineteen known genes grouped into four families (Kv1–Kv4) encode voltage-gated K\(^+\) channels in mammals (reviewed in Ref. 1). Despite having intronless coding regions of only 1.5–2.0 kb\(^\text{1}\) (e.g. Refs. 2 and 3), mammalian Kv1 family genes have transcripts as large as 9.5 kb due to the presence of extensive NCRs which exhibit a high degree of evolutionary conservation (1, 3–5). None of these transcripts has been mapped completely, and the role of the NCRs remains obscure.

The Kv1.4 gene, located on mouse chromosome 2 and human chromosome 11p14.1 (3), encodes a rapidly inactivating, 4-aminopyridine-sensitive K\(^+\) channel with phenotypic properties resembling the neuronal after-hyperpolarization-inducing current (6), and the 4-aminopyridine-sensitive component of the cardiac I\(_{\text{Na}}\) current (7–9). Two distinct Kv1.4 transcripts, ~3.5 and ~4.5 kb in length, are present in rat heart and brain (4, 10, 13). Here we report the characterization of the entire transcriptional unit of mouse Kv1.4 (mKv1.4) which may represent the first such analysis for any member of the extended voltage-gated ion channel gene family.

MATERIALS AND METHODS

Northern Blots

A multiple-tissue mouse mRNA blot obtained from Clontech (Palo Alto, CA) was probed with different regions of the 11-kb mKv1.4 genomic clone (stringency = 0.5 × SSC, 0.1% SDS and 60 °C, exposure = 3–7 days). Blots were stripped of probe by boiling in 0.1% SDS and cooling to room temperature, and reused after ensuring that no residual probe remained.

pLuciferase Vectors and Luciferase Assays

Promega pLuciferase Constructs—Three luciferase-containing constructs were used in this study. The control vector contains the SV40 enhancer and promoter elements upstream of the luciferase gene. The enhancer vector contains (from 5' to 3') the SV40 enhancer, a multiple cloning site for introducing the putative promoter-containing element, and the luciferase reporter gene. The basic vector includes only the luciferase gene with an upstream multiple cloning site for introducing the putative promoter fragment.

Deletion Constructs—Several 5'-flanking fragments from the mKv1.4 genomic clone were cloned into the enhancer or basic vectors using appropriate restriction enzymes, and their ability to induce luciferase activity was determined. The integrity of all constructs was confirmed by restriction mapping and/or by sequencing.

Cell Culture, Transfection of Constructs, and Luciferase Assays—C\(_2\)C\(_2\) myoblast cells were grown in minimum essential medium (Cell Grow Mediatech, Washington, D. C.) containing 4.5 g/liter glucose, 10% fetal bovine serum (Summit Biotechnology, Greeley, CO), 0.1 IU/ml penicillin, and 0.1 mg/ml streptomycin (ICN Biomedicals Inc., Costa Mesa, CA). NIH-3T3 mouse fibroblasts were maintained under almost similar conditions, except for a lowered glucose concentration (1 g/liter) in the minimum essential medium. One day prior to transfection, 5 × 10\(^5\) cells/dish were plated into 100-mm Petri dishes, and fresh medium was added 1 h prior to transfection. Cells in each plate were transfected with 20 µg of DNA (isolated using the Qiagen Maxi-prep, Qiagen Inc., Chatsworth, CA) for 16 h by the calcium phosphate method and placed into fresh medium. Seventy-two hours post-transfection, the cells were washed with 1 × phosphate-buffered saline, harvested, and lysed for 20 min in 200 µl of Promega lysis reagent (Promega, Madison, WI). The cell lysates were pelleted, and the supernatants were frozen until assayed using the Luciferase Assay Kit (Promega) in a Monolight 2010 Lumino- meter (Analytical Luminescence Laboratory, San Diego, CA).
Generation of Constructs and Analysis of mkV1.4 Expression in Xenopus Oocytes

Expression Constructs—The Kv1.4 coding region was cloned into the pTM-1 vector (3). The Kv1.3/kv1.4 chimeric construct was created as follows: the 3′-NCR BglII/EcoRI fragment of mkV1.4 (containing five ATTTA motifs) was inserted downstream of the coding region of the reporter molecule, Kv1.3, containing an antibody-recognizable epitope (gene 10) at its N terminus. This construct was linearized at either a SalI/EcoRI site in the ATTTAs (or an EcoRI site downstream of all five ATTTAs), and cRNA was prepared. In a second chimeric construct, an oligonucleotide (Chemgenes, Needham, MA) corresponding to nt 395–447 of the 3′-NCR of mkV1.4 (ATTTAs 1–3) was linked to the 3′-end of Kv1.3. In a third construct, an oligonucleotide containing AGTGA in place of the three ATTTAs motifs (bp 395–447 of the 3′-NCR) was attached to the 3′-end of Kv1.3. The latter two constructs were linearized at the EcoRI site (downstream of the three ATTTAs or three AGTGA), and cRNA was prepared. The cRNAs from all these constructs are identical in their Kv1.3-derived sequences (5′-NCR, coding region, and proximal 0.2 kb of the 3′-NCR), and differ only in the lengths of the Kv1.4-derived 3′-NCRs which they contain. cRNA from each construct was injected into Xenopus oocytes and evaluated as described (3, 11).

Analysis of mRNA Isolated from Oocytes—cRNA for each of these constructs was synthesized and radiolabeled with [32P]CTP. Unincorporated nucleotides were removed by centrifugation through a Sephadex G-50 chromatography column (Boehringer Mannheim) followed by ethanol precipitation, and the cRNA concentration was adjusted to 1 ng/ml. Forty-six ng of cRNA were injected into each oocyte, and total RNA was extracted from 7 oocytes for each data point, either at time 0 (immediately after injection) or after 48 h. Oocytes were lysed in 2 ml of cell lysis solution (Promega), RNA-extracted, and run on a 1.5% agarose gel, autoradiographed to quantitate the levels of extracted RNA.

Ribonuclease Protection Assays

Total RNA was extracted from mouse brain using Promega’s total RNA isolation kit (Promega). This RNA (10 μg) was hybridized to an antisense cRNA probe derived from the mkV1.4 genomic clone. The 1.4-kb Sad/BamHI fragment was linearized at Mspl (580 bp), and a [32P]dCTP (ICN, Costa Mesa, CA) radiolabeled antisense cRNA probe was generated using T7 RNA polymerase. The total RNA and probe were hybridized overnight at 47°C in hybridization buffer (4 M NaCl, 400 mM PIPES, 10 mM EDTA, and 80% formamide). The reaction was digested with RNase A and T1 (Sigma) for 1 h at room temperature. The digestion reaction was stopped with 10% SDS, followed by phenol/2.

Isolation of Protein from Oocytes and Western Blot Analysis—For each experiment, cRNA was injected into six oocytes; 48 h later, the oocytes were washed in fresh, ice-cold oocyte Ringer solution (96 mM NaCl, 1.8 mM CaCl2, 1 mM MgCl2, 5 mM Hepes, pH 7.4, 290–320 mosm) and completely lysed in ice-cold buffer (7.5 mM Na2HPO4, pH 7.4, 1 mM EDTA) containing a mixture of protease inhibitors (1 mg/ml leupeptin, 20 mg/ml phenylmethylsulfonyl fluoride, and 1 mg/ml pepstatin A (Sigma), Oocyte yolk was removed by centrifugation (4000 × g, 5 min at 4°C), the membranes were pelleted (12,000 × g, 30 min, 4°C), washed once in lysis buffer, and resuspended in Laemmli loading buffer (12). The membrane-associated proteins were electrophoresed in a 10% SDS-polyacrylamide gel (12), electroblotted onto a polyvinylidene difluoride membrane (Millipore Corp.) in Towbin buffer (192 mM glycine, 25 mM Tris base in 20% methanol), and blocked with 5% powdered milk. Western blot analysis was then performed using the mouse anti-gene 10 antibody (7-7 Tag, Novagen, Madison, WI; 1:4000 dilution) and the horseradish peroxidase-labeled goat-anti-mouse second antibody (Caltag, San Francisco, CA, 1:2000 dilution) as immunoprobes; the bands were visualized by the Enhanced Chemiluminescent System (Amersham) and exposed to Hyperfilm (Amersham, Buckinghamshire, UK) for 1–5 min. Autoradiographs were scanned and analyzed as described.

Structure of mkV1.4 transcripts. A, organization of the mouse Kv1.4 genomic clone. All of the known mouse Kv1.4 gene is contained within an 11-kb HindIII fragment. The coding region is shown as a shaded box with S1–S6 indicated by black stripes. Restriction sites are: H, HindIII; S, Sad; P, PstI; B, BamHI; E, EcoRI; Bg, BglII. The heavy horizontal lines in the map represent NCRs within the 2 exons of Kv1.4. The lines numbered 1–6 below the restriction map represent the probes used for mapping the transcripts. B, Northern blots of mouse brain poly(A)+ mRNA. Six lanes of mouse brain mRNA were probed using each of the numbered probes shown in A. Exposure times were 4 days for lanes 1–4, 5 days for lane 5, and 6 days for lane 6. +, lane 6 stripped and reprobed with probe 4, *; PstI site close to transcription initiation site.
chloroform extraction and ethanol precipitation. The precipitated pellet was resuspended in 5 μl of water and 4 μl of loading buffer, heated at 85 °C, and then loaded onto a 6% denaturing polyacrylamide gel. The gel was dried and autoradiographed. 

In the negative control, yeast RNA was substituted for the mouse brain RNA. A separate lane contained the full-length undigested probe.

Primer Extension Experiments to Define the Transcription Start Site

A synthetic oligonucleotide, 5'-GACAGCGAGCGTACCTTG-3', representing the sequence 53–70 nt downstream of the Pst I site in the genomic region thought to be near the 5' end of mKv1.4 (3), was annealed to 3 mg of total mouse brain RNA at 55 °C for 3 min and placed on ice. To this was added [γ-32P]ATP (25 mCi in 1 ml, 3000 Ci/mmol) and a mixture consisting of unlabeled deoxynucleotides (1 mM each dATP, dGTP, dTTP, Perkin-Elmer Corp., Norwalk, CT), reverse transcriptase (20 units, Promega), and RNase inhibitor (20 units, Boehringer Mannheim) in a final reaction volume of 50 μl, and the mixture was incubated for 10 min at 24 °C, followed by 1 h at 40 °C. The product was concentrated, mixed with acrylamide gel loading dye, and loaded onto a 6% acrylamide sequencing gel (6 ml/lane) adjacent to a sequencing reaction (280-bp fragment from RNase digestion, while the length undigested probe. 

85°C, and then loaded onto a 6% denaturing polyacrylamide gel. The probe is visible in

Mapping the Kv1.4 Transcription Unit

RESULTS

Tissue Distribution of Kv1.4 in the Mouse — A Northern blot probed with a mKv1.4-specific 3'-NCR fragment revealed hybridizing -3.5- and -4.5-kb bands in mouse brain and heart poly(A)+ mRNA, a weakly hybridizing -2.5-kb band in skeletal muscle, and additional faint signals in both lung and muscle; the probe did not hybridize detectably to mRNA from spleen, muscle, and additional faint signals in both lung and muscle; the probe did not hybridize detectably to mRNA from spleen, liver, kidney, or testes (Fig. 1). These results are consistent with previous reports describing the tissue distribution of the rat and human Kv1.4 homologues (4, 5, 10, 13).

Mapping the Mouse Kv1.4 Transcripts — DNA fragments derived from six regions of the genomic clone (Fig. 2A) were used to probe poly(A)+ mRNA from mouse brain (Fig. 2B). The 4.5-kb band was found to hybridize with probes 1–5, while the 3.5-kb band was only detected by probes 1–3. Probe 6 hybridized to neither transcript, although it did hybridize to the Kv1.4 genomic clone used as a positive control (not shown); reprobing this lane with probe 4 revealed the expected 4.5-kb hybridizing band, indicating that the lack of hybridization to probe 6 was not due to the absence of mRNA in this lane. These hybridization patterns show that both of the mouse Kv1.4 transcripts share the 5'-end of the transcript, the entire coding region, and at least 0.2 kb of the 3'-NCR (probe 3), while the 4.5-kb mRNA contains an additional ~900 nt in the 3'-NCR, the region spanned by probes 4 and 5.

Examination of the 3'-NCR sequence reveals a consensus poly(A)+ signal (AATAAA) 177 bp downstream from the stop codon (Figs. 2A and 3). The 3.5-kb transcript must terminate at or near this poly(A)+ signal, since it does not hybridize with probe 4 (Fig. 2B) which begins 40 bp farther downstream (Figs. 2A and 3). The 4.5-kb transcript terminates at or close to a second poly(A)+ signal located 934 bp 3' of the first, since it shows no hybridization with probe 6 which begins 40 bp downstream of this signal (Figs. 2A and 3). The significance of the A/T-rich motifs in the 3'-NCR (Fig. 3B) is discussed below.

To delineate more precisely the 5' end of the transcript, we used a 580-bp MspI/BamHI probe (Fig. 4A) in RNase protection assays. Mouse brain RNA (lane 3, Fig. 4B) protected a radio-labeled 280-bp fragment from RNase digestion, while the probe did not survive RNase treatment when incubated with control yeast tRNA (lane 2); the full-length undigested 580-bp probe is visible in lane 1. The size of the protected fragment suggests that the transcription initiation site is likely to be at or very close to the Pst I site indicated by the asterisk in Fig. 2A.
Mapping the Kv1.4 Transcription Unit

FIG. 4. Transcription initiation site of mKv1.4. A, genomic map of Kv1.4 exon 1 and 3'-flanking region. The PstI site indicated by the arrowhead is close to the transcription start site shown in Fig. 2A. Lane 1, HindIII; lane 2, EcoRI; lane 3, BamHI; lane 4, XhoI; lane 5, PstI. B, RNase protection. The probe used in lane 2 is shown. Lane 1, 32P-labeled probe alone shows a single band of 580 bp; lane 2, yeast tRNA, did not protect any visible fragment of the 5'-flanking region 53–70 bp downstream of the PstI site. Lane left, primer extension fragment from mouse brain mRNA. Right-hand four lanes, sequencing reaction of mouse Kv1.4 genomic clone using the same primer. The nucleotide corresponding to the extended 5'-end is shown. The probe used in lane 3, brain RNA, protected 280 bp of probe from digestion. C, Primer extension fragment from DIG-labeled probe alone shows a single band of 580 bp (90-bp vector sequence from mouse brain mRNA.

Mapping the Kv1.4 Transcription Unit

FIG. 5. Sequence of the 5'-flanking region containing the promoter, enhancers, and potential transcription initiation sites. An ~1000-bp region of sequence from the genomic clone, flanking the PstI site indicated by the asterisk in Fig. 2A, is shown. The underlined nucleotide at position +1 indicates the transcription initiation site observed in primer extension experiments. Consensus sequences for SP-1 (CCGCCCC), AP-2, and the fibroblast enhancer element are shown, as are four E box repeats and two MspI sites. The sequence extends through the end of exon 1. The upstream ATGs in the 5'-NCR sequence contained in exon 1 are italicized and underlined. An additional seven ATGs are present in the 3'-NCR sequence contained in exon 2 (3).

Mapping the Kv1.4 Transcription Unit

FIG. 6. Kv1.4 expression in oocytes. A, constructs. The Kv1.4 construct linearized at either BglII (left) or EcoRI (right) sites in the 3'-NCR. The arrowheads represent the five ATTTA motifs. B, oocyte recordings. Representative traces from oocytes expressing the BglII or EcoRI mKv1.4 cRNAs. C, average current values. Average values of Kv1.4 currents in oocytes expressing either the BglII or the longer ATTTA-containing EcoRI cRNA closely to the 3.5-kb mRNA, while the EcoRI-linearized form terminates 892 bp farther 3' and represents the longer transcript. Both cRNAs produced typical rapidly inactivating K+ currents when expressed in Xenopus oocytes, although the shorter transcript produced 4–5-fold more mKv1.4 currents than the longer one (Fig. 6B). Clearly, the presence of the additional 3'-NCR sequence in the 4.5-kb mRNA reduces functional channel expression in oocytes (Fig. 6, B and C).

This region is 66% AU-rich and contains five AUUUAs repeats that are conserved in rat and bovine homologues of Kv1.4 (Fig. 3B and 1). These motifs are also present in the 3'-NCRs of many other genes expressed in diverse mammalian cell types (14–18). The presence of three or more such repeats, either by themselves or as part of the larger nonanucleotide motif (UUAAUUUAU(AU)(AU)), has been reported to reduce mRNA stability in almost every case examined (e.g., Refs. 14–18). In view of this, it seems very likely that the 3'-NCR of Kv1.4 has a destabilizing effect on the 4.5-kb transcript in mammalian cells. In Xenopus oocytes, however, AUUUU-mediated mRNA degradation is minimal; this mechanism therefore cannot account for the decreased expression of the 4.5-kb transcript in oocytes.

The octanucleotide repeat, UUAUUUUAU, has been reported to inhibit translation of diverse messages in oocytes and in vitro translation systems (19–23). While the 3'-NCR of mKv1.4 does not contain this octanucleotide motif (Fig. 5), we considered the possibility that the shorter AUUUA motif might possess translation inhibitory activity. To test this idea, we coupled a reporter gene (gene-10-containing Kv1.3) to mKv1.4 3'-NCR sequences containing 0–5 ATTTA repeats (Fig. 7A). The presence of 5 AUUUA decreased expression of the reporter protein 11-fold, while three AUUUAs caused 3.5-fold suppression (Fig. 7C); mutating these three AUUUAAs to AGUGA completely relieved the suppression. The total amount of protein loaded in each of these lanes was roughly equal, as evidenced by the Coomassie stain of a 100-kDa endogenous oocyte protein (Fig. 7D).

The presence of the AUUUAs repeats did not appreciably alter levels of Kv1.4 cRNA during the course of the experiment (Fig. 7B). The levels of [32P]CTP-labeled reporter-gene cRNA remained unchanged even after 48 h, regardless of the presence or absence of AUUUAs (Fig. 7B), and densitometric analysis revealed no more than an 8% difference in the intensity of the bands. Thus, the observed AUUUUA-mediated reduction in functional expression of the longer 4.5-kb transcript in oocytes must be mediated via suppression of translation. Using the reasoning of Kruys and co-workers (19–23), we argue that the AUUUUAA motifs in the Kv1.4 3'-NCR might also reduce translational efficiency of the 4.5-kb mRNA in mammalian cells.
Identifying the mKv1.4 Promoter and Enhancer(s)—To identify the mKv1.4 promoter, 5'-flanking regions upstream of exon 1 were engineered either into the pUC-luciferase-enhancer or the basic vector (see "Materials and Methods"). These were transfected into two cell lines (C2C12, NIH-3T3), and luciferase activity was measured; of the two, only C2C12 cells are known to express Kv1.4 (10).

Kv1.4 Promoter Activity Is Not Cell Line-specific—A 2.1-kb SacI/BamHI fragment was found to confer very high levels of promoter activity in both cell lines (Fig. 1). Deletion of an internal 464-bp PstI fragment eliminated promoter activity suggesting that the basal promoter is located within this region. Consistent with this notion, this PstI fragment, located just upstream of the transcription initiation site (Figs. 4 and 5), induced transcription of the luciferase gene, although at a substantially lower level than the entire SacI/BamHI fragment. These data indicate the presence of additional enhancer element(s) outside the 464-bp PstI fragment.

Since DNA fragments may exhibit spurious promoter activity in the presence of powerful enhancers (e.g. SV40 enhancer), it was important to determine if the PstI fragment could induce transcription in the absence of the SV40 enhancer. For this purpose, the fragment was engineered into the basic vector (lacking an enhancer), and transcription of the luciferase gene was measured following transfection into NIH 3T3 cells. The PstI fragment clearly contains a fully functional promoter, since it is capable of initiating transcription of the luciferase gene without the help of an exogenous enhancer (Fig. 8, legend). This region, seen in Fig. 5, is 66% (G/C)-rich, lacks canonical TATAAA and GGCACTT boxes (24), contains three SP1 sites (CCGCC), multiple E-boxes (CANNNTG) (Myod-1 binding sites), one of each of the motifs for fibroblast enhancer (CCAAAT) and AP2 (ATTGTG), and resembles the promoters of many housekeeping genes (25–28).

**DISCUSSION**

We report the mapping of two mKv1.4 transcripts, 4.5 and 3.5 kb, that are expressed in brain and heart. These two are identical except in the 3'-NCR, with the longer transcript terminating at a polyadenylation signal 934 nt downstream from the signal utilized by the 3.5-kb form. Although the same coding region is utilized by both transcripts to generate identical mKv1.4 proteins, we have shown that the 3'-NCR regulates the levels of functional channels via AU-dependent regulation of translation efficiency and most likely also of mRNA stability. The presence of multiple ATGs lying upstream of the initiation methionine in the 5'-NCRs of both transcripts would be expected to decrease translational efficiency (Fig. 5). Thus, the unusually long and well conserved NCRs of Kv1.4 play important roles in modulating Kv1.4 channel expression.

The promoter for this gene has little if any tissue specificity, is located in a GC-island containing three SP1 binding sites (CCGCC), and is modulated by at least one region containing enhancer activity. The high GC content of the Kv1.4 promoter might reduce its accessibility to RNA polymerase (e.g. Ref. 29). The mechanisms responsible for tissue-specific expression of this gene have yet to be determined. Positive and negative transcriptional regulators are known to be responsible for tissue- and developmental stage-specific expression of sodium channel genes (30–32), and similar elements upstream of the SacI/BamHI fragment might be required for tissue-specific expression of mKv1.4. Alternatively, mKv1.4 gene expression might be inactivated by methylation in tissues other than the brain, heart, and skeletal muscle; this GC-rich region, in fact, contains multiple potential methylation sites (33–35). Future studies will provide answers to these questions and determine whether other K+ channels use similar mechanisms to control their expression.
of mKv1.4 expression may reflect the need to maintain the number of functional channels at closely defined levels in mammalian tissues. A rapidly inactivating K⁺ current like mKv1.4, which can open in the subthreshold range of excitation, would likely reduce the excitatory effects of depolarizing currents on neurons in a time-dependent fashion (6); a deficit of Kv1.4 current might therefore enhance neural excitability, while increased numbers of such channels may have hypoexcitatory effects. Alteration of transcriptional or post-transcriptional processes might be associated with pathological states, possibly contributing, for example, to the enhanced Kv1.4 mRNA expression seen in cardiac hypertrophy (36).

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