Glucocorticoid Induction of Kv1.5 K⁺ Channel Gene Expression in Ventricle of Rat Heart

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Abstract  Multiple voltage-gated K⁺ channels contribute to the repolarization phases of the cardiac action potential and are targets of several antiarrhythmic drugs. The Kv1.5 K⁺ channel gene is expressed in the heart, and heterologous expression of this gene generates a slowly inactivating K⁺ current. Previously, we found that glucocorticoids specifically upregulate pituitary Kv1.5 gene expression. To test whether these steroids might also induce Kv1.5 gene expression in the heart, cardiac channel mRNA and protein were measured by RNase protection assay and by immunoblotting with antibody specific for the extracellular domain of Kv1.5 polypeptide. Kv1.5 mRNA and immunoreactive protein appeared to be more abundant in rat ventricle than atrium. Reduction of endogenous glucocorticoids by adrenalectomy decreased ventricular Kv1.5 mRNA ~8-fold, which was estimated by using cyclophilin mRNA as an internal control. Kv1.5 immunoreactive protein also decreased ~6-fold. Injection of dexamethasone into adrenalectomized rats acted within a day to increase ventricular Kv1.5 mRNA and immunoreactive protein ~50-fold and ~20-fold, respectively. In contrast, atrial Kv1.5 mRNA expression was unaffected by either adrenalectomy or injection of the glucocorticoid agonist. Furthermore, dexamethasone-induced upregulation was specific for Kv1.5, since whole-heart Kv1.4 and Kv2.1 mRNA levels, as well as ventricular Kv2.1 mRNA expression, were unchanged. Thus, dexamethasone specifically upregulates Kv1.5 K⁺ channel gene expression in rat ventricle but not atrium. Glucocorticoids may affect excitability of ventricular myocytes and the efficacy of clinically useful drugs by changing the expression of the Kv1.5 K⁺ channel. (Circ Res. 1994;75:1006-1013.)

Key Words • voltage-gated K⁺ channels • gene regulation • adrenalectomized rats • dexamethasone

Materials and Methods

Animals

Female Sprague-Dawley rats weighing 200 to 225 g (7 to 8 weeks old) were obtained from Zivic-Miller (Zelienople, Pa.). For examining the effect of glucocorticoids, rats were either
sham-operated or bilaterally adrenalectomized (Zivic-Miller) and kept in plastic cages with free access to food and drinking water. Adrenalectomized rats were given 0.9% NaCl as drinking water. Seven days after the operation, the rats were injected intraperitoneally with 10 mg dexamethasone in 0.5 mL sesame oil or with vehicle alone. Twenty-four hours after injection, the rats were anesthetized by inhalation of methoxyflurane and decapitated. The atria and ventricles were dissected and immediately frozen on dry ice.

**Transfections**

The full-length cDNAs encoding rat K⁺ channels from Kv3.2 (Kv1.3), Kv3.1 (Kv1.4), and Kv1.5 (Kv1.5) were subcloned into pRc/CMV (Invitrogen). Chinese hamster ovary (CHO) cells were transfected with one of these plasmid DNAs or with the parental plasmid pRc/CMV by the calcium phosphate precipitation method (Transfintinity, BRL). Transfected cells were selected with 0.2 mg/mL neomycin. After three rounds of subclonings, cloned cells were tested for expression of K⁺ channel mRNA by Northern blot hybridization.3,19 and for K⁺ currents by the standard whole-cell patch-clamp method.25

**RNA Isolation and Measurements**

Total RNAs were isolated from a part of the frozen tissues by a one-step method with acid phenol guanidium thiocyanate with additional extractions. Briefly, the obtained RNA pellet was dissolved in solution D and extracted repeatedly with an equal volume of phenol-chloroform-isomylalcohol (25:24:1) until an intermediate layer of proteins became invisible. RNA concentrations were determined spectrophotometrically by using absorbance at 260 nm (A260=40 mgRNA).

For Northern blotting, an aliquot of total RNA was electrophoresed on 1% formaldehyde-agarose gel and transferred to nylon membrane by capillary action. Prehybridization and hybridizations were performed as described previously18,19 by using random priming-labeled cDNA probes: EcoRI-HindIII fragment of Kv1.2 for Kv1.5, HindIII-BamHI fragment of dhk127 for Kv2.1, Pst I-BamHI fragment of pBl1528 for cyclophilin, Pst I-Pst I fragment of pGAPDH29 for glyceraldehyde phosphate dehydrogenase, and Pst I-Pst I fragment of pANF-130 for atrial natriuretic factor. Densitometric measurements of autoradiograms (LKB 2400 Gel Scan, LKB, version 1) was used to quantify hybridization signals. K⁺ channel mRNA levels were normalized by reprobing blots with cyclophilin cDNA probe.19

For RNase protection assay, parts of rat Kv1.5 cDNA and cyclophilin cDNA were subcloned into pGEM1 (Promega). The 5'-end EcoRI-blunted blunt Bgl II fragment of rat Kv1.5 cDNA (pGEM-A-Kv1.5) corresponding to the sequence 295 to 4 was subcloned into the EcoRI-Sma I site of pGEM1 (pKv1 EB300). The 5'-end Pst I-Asp 700 fragment of rat cyclophilin cDNA (p1B15) corresponding to the sequence 6 to 104 was subcloned into the Pst I-Sma I site of pGEM1 (pcyc PA100). RNA probes were prepared from EcoRI-digested pKv1 EB300 (the 5'-end Kv1.5 probe), HindIII-digested pCyc PA100 (internal control probe), or Xba I-digested pGEM-A-Kv1.5 (the 3'-end Kv1.5 probe) by using either SP6 or T7 polymerase. Solution hybridization was performed with 5×10⁶ cpm of one of the Kv1.5 probes and cyclophilin probe, as described previously.18 RNase digestion, recovery of protected RNAs, and running a denaturing gel were performed as described previously.18 Kv1.5 mRNA levels were determined by densitometric measurements of autoradiograms (LKB 2400 Gel ScanXL, version 1) using cyclophilin mRNA levels as internal controls.

**Antibody Production and Immunoblot Analysis**

Polyclonal anti-Kv1.5 antisera were generated by immunization of rabbits (HTI Bio-Products, Ramona, Calif) with a fusion protein containing a part of the extracellular loop between S1 and S2 domains of rat Kv1.5 polypeptide (amino acids 272 to 312, K41E) and bacterial glutathione S-transferase (GST).

The frozen ventricles (=0.5 g) were thawed on ice and homogenized in 10 vol of a solution (0.25 mol/L sucrose, 1 mmol/L EDTA, 1 mmol/L phenylmethylsulfonyl fluoride, and 1 mmol/L iodoacetamide). Nuclear debris and undisrupted tissues were removed by centrifugation of the homogenate at 1000g for 10 minutes. The low-speed supernatant was then centrifuged at 100,000g for 1 hour. The resulting pellet was washed with a solution containing (mmol/L) Tris-HCl 20 (pH 7.4), EDTA 1, phenylmethylsulfonyl fluoride 1, and iodoacetamide 1 and referred to as post–nuclear membrane fraction. Cultured cells were lysed in a hypotonic solution, and the lysed cells were centrifuged at 15 000g for 20 minutes. The post–nuclear membrane fraction was then prepared by homogenization and differential centrifugation of the pellet total membrane fraction, as described for the ventricular tissues. Protein concentrations were determined by using Bio-Rad protein assay solution with human immunoglobulin as a standard. The post–nuclear membrane proteins were separated on a 7.5% sodium dodecyl sulfate–polyacrylamide gel and transferred to nitrocellulose membrane. The nitrocellulose membrane was washed with 2×10 vol of SDS-PAGE buffer and then transferred to phosphate-buffered saline containing 0.1% Tween 20. The coated membrane was probed with 1/2000 dilution of anti-K41E serum or 1/200 dilution of affinity-purified anti-K41C18 in the coating solution. Bound antibodies were detected with sheep anti-rabbit IgG conjugated with horseradish peroxidase and visualized with enhanced chemiluminescence reagents (ECL, Amersham). Kv1.5 immunoreactive proteins were measured by densitometry using enhanced laser scanning (LKB 2400 Gel ScanXL, version 1), as described previously.18

**Results**

**Kv1.5 K⁺ Channel Expression in Rat Heart**

It has been shown that Kv1.5 mRNA is significant in both rat atrium and ventricle by Northern blot analysis.1 To obtain more quantitative information about cardiac Kv1.5 mRNA expression, we used RNase protection assays with the two distinct regions of the rat Kv1.5 cDNA as probes (Fig 1). Various amounts of total RNAs isolated from young (7- to 8-week-old) adult female atria and ventricles were used to compare the abundance of Kv1.5 mRNA in these two tissues. The two probes detected significant signals of Kv1.5 mRNA in both the atrium and ventricle (Fig 1). Densitometric measurements of the signals indicate that the two probes gave consistent results, suggesting that no alternatively spliced transcripts for Kv1.5 mRNA are present in the rat heart. The steady state concentration of Kv1.5 mRNA measured in two independent experiments was estimated to be ~18-fold higher in the ventricle than in the atrium. Therefore, Kv1.5 mRNA expression varies between the atrium and ventricle.

To examine cardiac Kv1.5 protein expression, we generated a polyclonal antibody specific for the Kv1.5 polypeptide (anti-K41E). This antibody was produced against a fusion protein containing a portion of the extracellular loop between S1 and S2 transmembrane domains of the Kv1.5 polypeptide corresponding to amino acids 272 to 312,3 which is unique for Kv1.5 channel (Fig 2A). The specificity of the antibody was tested by immunoblot analysis with the post–nuclear membrane fractions prepared from CHO cells stably transfected with one of three rat Shaker-related K⁺ channel genes (Kv1.3, Kv1.4, and Kv1.5; Fig 2B). These transfected cells express significant amounts of the
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Fig 1. RNase protection assay of rat ventricular and atrial RNAs with Kv1.5 probes. Total RNAs were isolated from the ventricles and atria of adult rats. Various amounts of total RNAs (2, 5, and 10 μg) as well as 10 μg of yeast RNA (negative control) were hybridized with either the 3' end (nucleotides 1803 to 2227) or the 5' end (nucleotides -296 to 4) Kv1.5 RNA probe and cyclophilin probe (nucleotides -6 to 104, internal control). After RNase digestion, the protected RNAs were isolated and separated on a 4% polyacrylamide gel containing 7.8 mol/L urea. Undigested RNA probes were also applied to the gel (probe). The gels were dried and exposed to an X-ray film for various times to quantify the signals. The probes consist of the sequences corresponding to channel cDNA and a part of the vector: the 3' end Kv1.5 probe, 445 (424+21) bases; the 5' end Kv1.5 probe, 357 (299+58) bases; and the cyclophilin probe, 166 (111+55) bases. The lengths of the protected fragments were consistent with the cDNAs inserted in the vector. Smaller fragments seen in the figure were mostly due to shorter (not fully extended) RNA probes. Kv1.5 mRNA in the ventricle was estimated to be 18-fold more abundant than that in the atrium (the average of the two independent experiments with the two different probes).

Fig 2. Anti-K41E (anti-Kv1.5) antibody detects a 76-kD membrane protein in transfected cells and many tissues. A, Amino acid sequences between S1 and S2 domains of rat Shaker subfamily K⁺ channels. Dashes indicate the sequences identical to Kv1.5 polypeptide. The fusion protein used to produce antisera contains the amino acid 272-312 of Kv1.5 polypeptide. B, Immunoblot analyses with anti-K41E antisera. Proteins (50 μg) from the post-nuclear membrane fractions of transfected Chinese hamster ovary (CHO) cells and rat tissues and protein (10 μg) from the post-nuclear membrane fraction of GH₃ cells were subjected to immunoblot analysis. C, Two different amounts of proteins from the post-nuclear membrane fractions of normal rat ventricles and atria were applied to the gel to compare the abundance of Kv1.5 immunoreactivity in these two tissues. The 76-kD immunoreactive protein was estimated to be approximately eightfold more abundant in the ventricle than the atrium (the average of the two independent experiments).
group; Fig 3). Kv1.5 probe exhibits a single band of 3.5 kb on a Northern blot, whereas Kv1.4 and Kv2.1 probes detect multiple bands (Fig 3A). The 3.5-kb Kv1.5 mRNA was significantly decreased by adrenalectomy (Adex versus sham, *P* < .05 by two-tailed Bonferroni test) and increased by injection of dexamethasone into the adrenalectomized rats (Adex + Dex versus Adex, *P* < .01; Fig 3B). In contrast, the larger sizes of mRNAs detected by the latter two probes (14 kb for Kv1.4 and 12 kb for Kv2.1; Fig 3B) as well as the smaller ones (4.5 kb for Kv1.4 and 4 kb for Kv2.1; data not shown) were unaffected. Hence, glucocorticoids specifically induce the expression of Kv1.5 mRNA without affecting Kv1.4 and Kv2.1 mRNA levels in rat heart.

To test whether this regulation of Kv1.5 mRNA expression might occur in both the ventricle and atrium, total RNAs were isolated from the ventricles and atria of another set of animals, and RNase protection assays were performed (*n* = 4 for each group; Fig 4). In the ventricle, reduction of endogenous glucocorticoids by adrenalectomy decreased the steady state level of Kv1.5 mRNA = 8-fold, estimated by using cyclophilin mRNA levels as internal controls (Adex versus sham, *P* < .01 by two-tailed Bonferroni test; Fig 4A and 4C). Furthermore, injection of dexamethasone in the adrenalectomized rats caused an increase in ventricular Kv1.5 mRNA level = 50-fold within 24 hours (Adex + Dex versus Adex, *P* < .01). Since ventricular cyclophilin mRNA expression might be affected by these operations, we compared cyclophilin mRNA levels with glyceraldehyde phosphate dehydrogenase (GAPDH) mRNA expression, another constitutively expressed gene, by Northern blot analysis. The results indicate that the expression of cyclophilin mRNA is = 30% higher in the Adex group than in the sham and Adex + Dex groups on the basis of GAPDH mRNA levels (data not shown). Thus, with GAPDH mRNA expression assumed to be constant, Kv1.5 mRNA levels as decreased by = 6-fold by adrenalectomy and increased by = 38-fold by injection of dexamethasone.

Although the expression of whole-heart Kv1.4 and Kv2.1 mRNA levels was unchanged, these channel mRNA levels might be regulated only in the ventricle. To test this possibility, we attempted to measure ventricular Kv1.4 and Kv2.1 mRNA levels. We found that ventricular Kv2.1 mRNA expression was unaffected by either adrenalectomy or injection of dexamethasone (Fig 5) and that Kv1.4 mRNA was nearly undetectable in the ventricle from all three groups of animals (data not shown). Thus, Kv1.5 mRNA expression in the ventricle is specifically and dramatically upregulated by glucocorticoids.

In contrast to the dramatic changes in ventricular Kv1.5 mRNA expression, neither adrenalectomy nor dexamethasone injection significantly affected atrial channel mRNA expression (Fig 4B and 4C). This failure of the glucocorticoid agonist to regulate atrial Kv1.5 mRNA expression is not due to a lack of the functional steroid receptors, since an upregulation of atrial natriuretic factor (ANF) mRNA expression was seen in the same RNA samples (data not shown). ANF mRNA was decreased by = 30% by adrenalectomy (Adex compared with sham) and increased = 2.2-fold by the subsequent injection of dexamethasone (Adex + Dex com-
pared with Adex) with the GAPDH mRNA level used as a control. Hence, glucocorticoids specifically upregulate Kv1.5 mRNA expression in the ventricle but not the atrium.

**Glucocorticoid Induction of Kv1.5 Immunoreactive Protein Expression**

To test whether the upregulation of ventricular Kv1.5 mRNA might be associated with changes in Kv1.5 protein, Kv1.5 immunoreactivity was measured by using antibody specific for the extracellular loop of Kv1.5 polypeptide (anti-K41E). Post-nuclear membrane fractions were prepared by homogenization and differential centrifugation of the ventricles (the same tissues used for channel mRNA measurement in Fig 4, n=4 for each group). The membrane proteins were then subjected to immunoblot analysis (Fig 6A and 6B). Densitometric measurements of the 76-kD Kv1.5 immunoreactive protein revealed that this protein decreased ≈6-fold by adrenalectomy (Adex versus sham, *P* < .05 by two-tailed Bonferroni test). Moreover, dexamethasone injection into the adrenalectomized rats increased the Kv1.5 immunoreactive protein ≈20-fold (Adex+Dex versus Adex, *P* < .01). Qualitatively similar results were also seen when Kv1.5 immunoreactivity was measured from whole heart (n=3 for each group). Therefore, glucocorticoids act within a day to dramatically increase the expression of Kv1.5 immunoreactive protein in rat ventricle.

**Discussion**

Many hormones and neurotransmitters produce acute effects on excitability by modulating the gating of ion channels already present in the plasma membrane. In addition, these extracellular stimuli may cause long-term changes in excitability by regulating the expression of ion channels. It has been shown that treatment of primary cultured neonatal cardiac myocytes with high KCl, Bay K 8644, or phorbol ester increases Kv1.4 mRNA expression. Furthermore, significant changes in Kv1.4 and Kv1.5 mRNA levels are seen in hypertro-
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FIG 6. Glucocorticoids upregulate ventricular Kv1.5 immunoreactive protein. Sham indicates sham-operated and vehicle-injected rats; Adex, adrenalectomized and vehicle-injected rats; and Adex+Dex, adrenalectomized and dexamethasone-injected rats. A, Immunoblot analysis of ventricular post-nuclear membrane proteins with anti-K41E (anti-Kv1.5) serum. Post-nuclear membrane fractions were prepared from the ventricles (the same tissues used for Fig 4), and 50 μg of protein from the membrane fractions was subjected to immunoblot analysis. B, Bar graph showing Kv1.5 immunoreactivity determined by measuring the signal of the 76-kD protein by densitometry. Columns represent the immunoreactivities relative to the mean of the sham group with error bars indicating SEM (n=4). Kv1.5 immunoreactivity in the Adex group is significantly lower than that in the sham group (P<.05 by two-tailed Bonferroni test), and that in the Adex+Dex group is significantly higher than that in the Adex group (P<.01).

phied ventricles produced for months by reversal of renovascular hypertension.36 The present results demonstrate that the glucocorticoid agonist dexamethasone specifically upregulates the expression of Kv1.5 K+ channel mRNA in rat ventricle in vivo within a day. Moreover, we showed that this upregulation of the cardiac K+ channel mRNA expression is associated with a dramatic increase in K+ channel immunoreactive protein. Thus, regulation of K+ channel gene expression may constitute a novel mechanism underlying long-term control of cardiac excitability.

Glucocorticoid hormones are known to produce biological effects by inducing gene transcription via a soluble receptor protein. We have previously found that inhibition of protein synthesis does not abolish dexamethasone-induced Kv1.5 gene transcription in GH3 clonal pituitary cells.18 This suggests that the glucocorticoid-receptor complex directly acts on the regulatory region of the Kv1.5 gene to activate its transcription. This is also supported by a recent study showing the presence of a putative glucocorticoid-responsive element in the 5' flanking region of the rat Kv1.5 gene.37 Therefore, any cells that express both Kv1.5 gene and the glucocorticoid receptor might be expected to respond to dexamethasone to induce transcription of the channel gene. However, despite the fact that the glucocorticoid receptor is present in both atrial and ventricular myocytes,38 the glucocorticoid agonist upregulated Kv1.5 mRNA expression in the ventricle but not the atrium. This finding could not be due to a defect in atrial myocyte glucocorticoid action in our experiments, because we verified that ANF mRNA expression was increased by dexamethasone in the same samples. Hence, glucocorticoid induction of Kv1.5 mRNA expression differs between the atrium and ventricle. A similar differential hormone effect in the two regions of the heart is seen with thyroid hormone induction of myosin heavy chain expression: thyroid hormones markedly upregulate the expression of α- and β-myosin heavy chains in the ventricle but not the atrium.39 In addition to the heart, we also found that dexamethasone markedly increases the channel mRNA expression in the pituitary19 and skeletal muscle (K. Takimoto, unpublished data), whereas only a small change is seen in the hypothalamus and the lung (K. Takimoto and B.R. Pitt, unpublished data). Moreover, the changes in ventricular Kv1.5 mRNA produced by adrenalectomy or injection of dexamethasone are larger than those in the pituitary19 and skeletal muscle. Therefore, the glucocorticoid agonist might also indirectly affect Kv1.5 gene expression in the ventricle, in addition to directly inducing channel gene transcription. These findings suggest that the hormone induction of Kv1.5 gene might require an additional factor whose expression is confined in certain tissues. Alternatively, some tissues might possess a factor that represses hormone responsiveness. In any case, our findings demonstrate that glucocorticoids differentially regulate atrial and ventricular K+ channel gene expression.

Previous studies from several laboratories have shown that voltage-gated K+ channel mRNA expression is regionally and developmentally regulated in rat heart. However, there are some disagreements concerning the expression of Kv1.5 mRNA: one group reported that the expression of Kv1.5 mRNA is dramatically regulated in the ventricle during development and aging,5,36 whereas the other group showed relatively constant levels of Kv1.5 mRNA throughout early development.16 Furthermore, the results from the two groups also differ concerning the levels of ventricular Kv1.4 mRNA: one group detected substantial amounts of Kv1.4 mRNA in the ventricle,36 whereas the other showed a nearly undetectable level of channel message.1 Our results indicate that Kv1.5 mRNA and immunoreactive protein are much more abundant in the ventricle than the atrium of young (7- to 8-week-old) adult rats. We also found that Kv1.4 mRNA is abundant in the atrium but not the ventricle. These discrepancies might be due to different experimental conditions that may influence channel mRNA levels. Indeed, recent findings18,19,36,37 as well as findings in the present study suggest that expression of K+ channel mRNAs is not static but is dynamically regulated under various conditions. For example, in adrenalectomized animals, Kv1.5 mRNA levels were comparable in the atrium and ventricle. Moreover, the regulation of channel mRNA expression might be regionally confined, as our results suggest. Further studies including detailed immunohistochemis-
try and in situ hybridization are needed to resolve these issues.

Expression of the Kv1.5 gene in Xenopus oocytes generates a very slowly inactivating outward K⁺ current.⁴⁻⁵ Since rat and human atrial myocytes exhibit a prominent delayed rectifying outward K⁺ current, Kv1.5 has been proposed to constitute the atrial delayed rectifier.⁶⁻¹⁴ However, our results demonstrate that Kv1.5 mRNA and immunoreactive protein are more abundant in rat ventricle than atrium. Thus, Kv1.5 protein is likely to contribute to the ventricular voltage-gated outward K⁺ current. There are two main components of ventricular voltage-gated K⁺ current in the rat:⁴⁰ a tetraethylammonium (TEA)-sensitive delayed rectifier and a TEA-insensitive and 4-aminopyridine-sensitive transient current. The fact that the heterologously expressed Kv1.5 channels differ from these native ventricular currents may be due to the association of Kv1.5 channel subunit with other proteins. Such proteins might be other Shaker subfamily K⁺ channel subunits. For example, Kv1.4 encodes a channel that rapidly inactivates in heterologous expression systems.⁴⁻⁶ Therefore, Kv1.5 protein might be present in an association with Kv1.4 protein to form the transient K⁺ current in rat ventricle. However, a previous study and our results indicate that transcripts for this gene are nearly undetectable in rat ventricle. Another possibility is suggested by the recent findings that brain dendrotoxin-binding voltage-gated K⁺ channels are associated with auxiliary β subunits⁴¹ and that the association of certain β subunits affects inactivation kinetics.⁴² Thus, it is possible that the ventricular Kv1.5 channel may encode the transient K⁺ current by associating with a β subunit. Resolving this issue will require purification and biochemical identification of cardiac K⁺ channels.

The dramatic upregulation of Kv1.5 immunoreactive protein in rat ventricle may produce many physiological and pharmacological effects. We have previously found that the dexamethasone-induced upregulation of Kv1.5 immunoreactive protein is associated with an increase in voltage-gated K⁺ current density in GH3 cells.¹⁸ Thus, the upregulation of ventricular Kv1.5 immunoreactive protein might also lead to an increase in the number of functional K⁺ channels. In patients with long QT syndrome, congestive heart failure,⁴³ or chronically infarcted regions of the ventricle,⁴⁴ action potential repolarization mechanisms are compromised. Glucocorticoid induction of Kv1.5 channel expression might be a novel therapeutic treatment to compensate for the loss of normal repolarization mechanisms. In addition to influencing basal electrical activity, hormone regulation of Kv1.5 gene expression might also affect responsiveness to hormones, autonomic inputs, and clinically useful drugs. For example, α₁-adrenergic agonists suppress the delayed rectifying K⁺ current in rat ventricular myocytes.⁴⁵ Likewise, several clinically useful drugs, especially class III antiarrhythmic drugs, act on voltage-gated K⁺ channels to produce their therapeutic effects. Heterologously expressed Kv1.5 K⁺ channels are found to be sensitive to quinidine,²⁰ verapamil,²¹ clofilium,²² tedisamil,²³ and an antihistamine.²⁴ Hence, regulation of K⁺ channel expression may influence basal electrical activity, its modulation by natural extracellular signals, and the efficacy of therapeutic drugs.

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