Phenotypic differences in transient outward K⁺ current of human and canine ventricular myocytes: insights into molecular composition of ventricular I\(_{to}\)

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ALTHOUGH THE CA\(^{2+}\)-INDEPENDENT, voltage-gated transient outward K⁺ current (I\(_{to}\)) plays a critical role in cardiac repolarization of several species, its precise role in normal and diseased human ventricular myocardium remains controversial (11). Despite elucidation of the molecular basis underlying I\(_{to}\) in the atrium of several species (36), the exact molecular makeup of this current in human and canine ventricular myo-
cardium also remains controversial. Canine models of disease states, including ischemia, heart failure, and Brugada syndrome have implicated I\(_{to}\) in the mechanism of arrhythmias in these pathologies. Unfortunately, the phenotypic similarity of I\(_{to}\) in human and canine ventricular myocytes remains unex-plored. Because technical factors, including isolation procedure, extracellular and intracellular solutions, temperature, and recording methods, influence the electrophysiological properties of ionic currents, such detailed comparison requires that the measurements be performed under identical conditions.

Ventricular I\(_{to}\) is highly regulated both temporally and regionally in normal hearts (35) and is significantly modulated in a wide variety of structural heart diseases (23). For instance, action potential duration (APD) prolongation in heart failure is associated with a concomitant reduction of the phase 1 repolarizing notch of the action potential, which is inscribed by I\(_{to}\) (15). In ischemia, I\(_{to}\) is thought to play a critical role in the protection of epicardial cells against metabolic inhibition by contributing to abrupt shortening of epicardial APD (22). Moreover, regional and transmural differences in the balance between I\(_{to}\) and Na⁺ current (I\(_{Na}\)) may underlie ventricular fibrillation and sudden death in patients with inherited arrhythmias such as Brugada syndrome (9, 40). Finally, inhibition of I\(_{to}\) by several antiarrhythmic agents such as flecainide, quinidine, and propafenone contributes to both their therapeutic and proarrhythmic effects (24, 33, 42). Therefore, defining the molecular identity and electrophysiological properties of ventricular I\(_{to}\) is essential for a comprehensive understanding of arrhythmia mechanisms in a wide variety of pathologies and may aid in the proper choice and design of antiarrhythmic drug therapy.

Measurements of human I\(_{to}\) require the availability of ex-planted hearts from patients with heart failure or nonfailing donor hearts that are deemed technically unsuitable for transplantation. Because of the difficulties associated with obtaining appropriate human cardiac samples and the confounding complexities associated with disease etiology and therapy in humans, animal models of cardiovascular disease, especially in dog, have been widely used. The usefulness of these models is dependent on their mimicry of human physiology and disease. Therefore, the exact identity of human I\(_{to}\) and its variation from the canine counterpart must be investigated in detail.

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Kv4.3 has emerged as the leading candidate K⁺ channel gene likely to encode cardiac Iₘ₀ in large mammals such as dogs and humans (10, 14, 32, 34, 44). Moreover, Kv4 subunits may form heteromeric complexes with a class of Kv channel-interacting proteins. K⁺ channel accessory proteins (KChIPs), in vivo (2, 5, 6, 8, 28, 31). Although KChIP2 significantly modulates Kv4.3 function when expressed in heterologous systems (5, 6, 8, 28), it remains unknown whether KChIP2 or other accessory subunits, such as KChA/P (1, 18, 37) or Kv8 (8, 19, 41), merely act to increase the sarcolemmal expression of Kv4.3 or, in fact, directly participate in the formation of native ventricular Iₘ₀.

In the present study, the electrophysiological and pharmacological properties of human and canine Iₘ₀ were compared. Human ventricular Iₘ₀ differs appreciably from canine Iₘ₀ in both steady-state inactivation and recovery from inactivation. Moreover, differences in the pharmacological profiles of human and canine Iₘ₀ suggest differences in the molecular architecture of the channel pore in these two species. Western blots of human and canine tissues demonstrate expression of Kv4.3, Kv1.4, and KChIP2 in both species but with distinctive variations in apparent molecular weights. Such differences may underlie the heterogeneity of the biophysical fingerprint of Iₘ₀ across species. Functional differences in human and canine ventricular Iₘ₀ may be attributable to intrinsic variations in Kv4.3 between dog and human, functional expression of other, yet to be identified α- or β-subunits, and/or differences in posttranscriptional or translational modification of the two isoforms.

METHODS

Human ventricular myocardium was obtained from explanted failing hearts (n = 5) and donor hearts deemed unsuitable for transplantation (n = 2). Canine ventricular myocardium was obtained from adult male mongrel dogs (n = 5) weighing 20–25 kg. Segments of ventricular myocardium adjacent to the region from which myocytes were isolated for electrophysiological recordings were used for protein isolation. The tissue was excised from the left ventricular free wall between the left anterior descending coronary artery (LAD) and the left circumflex artery. The myocyte and protein isolation procedures selected for cells and tissue lysates from the midportion of the ventricular wall. Tissue samples were quick frozen in liquid nitrogen within 10–15 min after organ harvest and stored at −80°C until further processing. All procedures were performed according to the guidelines of the American Physiological Society and were approved by the Animal Care and Use Committee of Johns Hopkins University.

Isolation of human and canine myocytes. Human and canine midventricular myocytes were isolated from the anterior wall of the left ventricle of seven humans (5 failing, 2 normal) and five dogs by perfusion of a diagonal branch of the LAD with a nominally Ca²⁺-free solution containing collagenase and protease, as described previously (13, 15, 26, 27). Myocytes were stored at room temperature (22–23°C) in Tyrode solution consisting of (in mM) 130 NaCl, 4.5 KCl, 5 MgCl₂, 23 HEPES, 21 glucose, 20 taurine, 5 Na pyruvate, and 20 2,3-butanediol monoxime, pH 7.4. The concentration of CaCl₂ was gradually raised from 100 μM to 2 mM. Only rod-shaped cells exhibiting clear cross striations and no spontaneous contractions were selected for electrophysiological study. A total of 22 human and 21 canine myocytes were used in this study.

The objective of this work was to investigate phenotypic differences in Iₘ₀ across species. Because previously we (14) and others (4) had demonstrated that the biophysical properties of Iₘ₀ were not altered in human heart failure, we combined the electrophysiological data from cells of normal and failing human hearts because of the limited availability of normal human samples.

Electrophysiological measurements. Current recordings were obtained at 24°C with the patch-clamp technique in whole cell configuration as previously described (6, 7). Glass pipettes were prepared to have a final tip resistance of 2–3 MΩ when filled with internal solution containing (in mM) 120 KCl-glutamate, 10 KCl, 10 HEPES, 5 EGTA, and 5 MgATP. pH was adjusted to 7.2 with KOH, yielding a final K⁺ concentration of 140 mM. Cells were perfused with Tyrode solution containing (in mM) 140 NaCl, 5 KCl, 1 MgCl₂, 2 CaCl₂, 10 HEPES, and 10 glucose, adjusted to pH 7.4. CdCl₂ (0.3 mM) was added to the bath solution to eliminate voltage-activated L-type Ca²⁺ and Ca²⁺-dependent currents. Cell capacitance was estimated by integrating the area under an uncompensated depolarizing step of 10 mV from a holding potential of −80 mV. Whole cell currents were elicited with a family of depolarizing voltage steps (−40 to +80 mV) from a holding potential of −50 mV. Currents were low-pass filtered at 2 kHz and digitized at 10 kHz for offline analysis. Iₘ₀ was defined as the difference between the peak transient current and the steady-state current at the end of a 500-ms voltage clamp pulse. Current inhibition by flecainide (Sigma-Aldrich, St. Louis, MO) was measured as the percent decrease in peak current after subtraction of the steady-state current.

Whole cell currents were analyzed with custom-developed software. Pooled data are expressed as means ± SE. Statistical comparisons were performed with the unpaired Student’s t-test. Differences in data were considered significant at P < 0.05.

Western blot analysis. Left ventricular samples from normal (n = 2) and failing (n = 5) human hearts and normal canine hearts (n = 5) were rapidly frozen in liquid nitrogen after organ harvest. Proteins were prepared as previously described (7, 14). Samples were run in duplicate or triplicate on 10%, 12.5%, or 15% Tris-HCl polyacrylamide gels (Bio-Rad, Hercules, CA) in 25 mM Tris, 192 mM glycine, and 0.1% (wt/vol) SDS running buffer. A standard control sample was also run on all gels to allow for comparisons across gels. Primary antibody incubations were performed overnight at 4°C with rabbit anti-KChIP (Wyeth-Ayerst Research, Princeton, NJ), KChIP2 (6), Kv1.4 (Alamou Labes, Jerusalem, Israel), and Kv4.3 (Chemicon, Temecula, CA) polyclonal antibodies, as described previously (14). Secondary horseradish peroxidase-conjugated antibodies were obtained from Jackson ImmunoResearch (West Grove, PA). Membranes were exposed and developed with enhanced chemiluminescence (Amersham Pharmacia Biotech, Piscataway, NJ) according to the manufacturer’s instructions.

RESULTS

Species-dependent differences in activation properties. Iₘ₀ was activated by a series of depolarizing voltage steps (~40 to +80 mV in 10-mV increments) from a holding potential of −50 mV, followed by a 10-ms Iₘ₀ inactivating prepulse to −50 mV. Shown in Fig. 1A are representative whole cell currents recorded from human (top) and canine (bottom) myocytes. Activation of Iₘ₀ in both species was comparably rapid, as peak current was achieved in ~20 ms (Fig. 1A). Average peak current densities in selected myocytes from normal and failing human hearts and canine myocytes are given in Table 1. In general, Iₘ₀ density was highest in myocytes of normal canine hearts, followed by myocytes of normal and failing human hearts. Importantly, although robust Iₘ₀ was recorded in all (100%) normal human and canine myocytes studied, only a fraction (~40%) of myocytes from failing human hearts expressed appreciable Iₘ₀ density suitable for detailed electrophysiological analysis. Only failing human myocytes with Iₘ₀ density of at least 5 pA/pF were studied.

As shown in Fig. 1C, the current-voltage relationships of human and canine Iₘ₀ were linear-positive to the threshold potentials for current activation. The average slope conduc-
Fig. 1. Electrophysiological properties of transient outward K⁺ current (Iₒ). A: representative Iₒ tracings recorded from cells isolated from the left ventricular midwall of human and canine hearts. Currents were elicited by 500-ms depolarizing voltage steps (−40 to +60 mV) from a holding potential of −50 mV. B: inactivation time constants in human and canine myocytes. Time constants were obtained by fitting the current decay phase to a monoeponential function. C: voltage dependence of Iₒ activation in human and canine myocytes. D: steady-state inactivation curves for human and canine Iₒ.

Species-dependent differences in steady-state inactivation of Iₒ. The steady-state availability of Iₒ was assessed with a standard two-pulse protocol as shown in Fig. 1D. The half-maximal potential for steady-state inactivation (V₁/₂) of human myocytes isolated from normal ventricles (−27.3 ± 1.1 mV) was not significantly different from that of myocytes isolated from failing hearts (−27.7 ± 0.5 mV). However, the steady-state inactivation of Iₒ in canine myocytes was significantly (P < 0.001) shifted in the hyperpolarized direction compared with human (normal and failing) myocytes (V₁/₂ = −37.4 ± 1.1 mV). Finally, similar to our previous findings (14) in canine myocytes isolated from normal and failing hearts, myocytes from normal (4.7 ± 0.3 mV⁻¹) and failing (4.7 ± 0.4 mV⁻¹) human hearts also exhibited identical slopes of their steady-state inactivation curves. Importantly, the slope of steady-state inactivation in human myocytes was significantly greater than that in canine myocytes (4.2 ± 0.1 mV⁻¹).

Species-dependent differences in recovery from inactivation of Iₒ. Human and canine Iₒ exhibited distinctive time courses of recovery from inactivation. The recovery kinetics of both human and canine Iₒ were measured after a 500-ms depolarizing voltage step to +50 mV from a holding potential of −100 mV and a subsequent 10-ms Iₒ, inactivating prepulse to −40 mV. Myocytes from both normal and failing human ventricles recovered rapidly and almost completely (98.8 ± 1.6%) within 250 ms (Fig. 2). The recovery of human Iₒ followed a monoeponential time (τᵢ) course with time constants that did not differ in myocytes isolated from normal (τᵢ = 27.8 ± 6.3 ms at −100 mV) and failing (τᵢ = 21.3 ± 2.6 ms) human hearts.

Table 1. Electrophysiological parameters in human and canine myocytes

<table>
<thead>
<tr>
<th>Biophysical Parameter</th>
<th>Human Myocytes</th>
<th>Canine Myocytes</th>
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<tbody>
<tr>
<td>Cm, pF</td>
<td>224.6±10</td>
<td>274.5±97</td>
</tr>
<tr>
<td>G, pA/pF</td>
<td>8.5±0.7</td>
<td>7.3±1.8</td>
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<tr>
<td>V₁/₂, mV</td>
<td>27.3±1.1</td>
<td>27.7±0.5</td>
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<tr>
<td>dx, mV⁻¹</td>
<td>4.7±0.3</td>
<td>4.7±0.4</td>
</tr>
<tr>
<td>τᵣ, ms</td>
<td>27.8±2.6</td>
<td>21.3±2.6</td>
</tr>
<tr>
<td>τᵢ, ms</td>
<td>71.2±1.7</td>
<td>61.4±1.7</td>
</tr>
<tr>
<td>Nᵢ/n</td>
<td>2.5</td>
<td>5.17</td>
</tr>
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Values are means ± SE. N, total no. of hearts from which cells and tissue samples were selected; n, total no. of cells selected for electrophysiological measurements; Cm, membrane capacitance; G, conductance; V₁/₂, half-maximal potential for inactivation; dx, slope of steady-state inactivation; τᵣ, time constant for recovery from inactivation; τᵢ, time constant for transient outward K⁺ current decay.
In contrast, canine $I_{to}$ exhibited a biexponential recovery from inactivation. The fast and slow time constants for canine $I_{to}$ recovery were $69.1 \pm 13.5$ ms (40.5 \pm 6\% of peak $I_{to}$) and $316 \pm 44$ ms (59.4 \pm 11\% of peak $I_{to}$), respectively. As illustrated in Fig. 2C, \(\sim\)90\% of the current peak was consistently recovered within 1 s of the initial depolarizing voltage step.

Species-dependent differences in pharmacological sensitivity of $I_{to}$. Flecaïnide (to block Kv4.3-encoded current) and H$_2$O$_2$ (to alter the inactivation kinetics of Kv1.4-encoded current) have been used to determine the contribution of these two K$^+$ channel subunits to native atrial $I_{to}$ (12, 36, 39). We assessed the contribution of Kv4.3 vs. Kv1.4 to native ventricular $I_{to}$ in dogs and humans by investigating the differential sensitivity of the current in both species to flecaïnide and H$_2$O$_2$.

Flecaïnide (10 \(\mu\)M) produced a significantly larger reduction in peak current density of $I_{to}$ in human (49\%) compared with canine (18\%) myocytes (Fig. 3). H$_2$O$_2$ (0.01\%), on the other hand, produced no measurable effect on the time course of inactivation of human or canine ventricular $I_{to}$ (Fig. 4). Also shown in Fig. 4B are action potentials recorded from a canine myocyte before (control) and after exposure to H$_2$O$_2$. Although H$_2$O$_2$ resulted in a trend toward an increase in APD, there was no change in the amplitude of the phase 1 notch. Together, these data suggest that Kv1.4 does not contribute appreciably to ventricular $I_{to}$ in either species, as it encodes a current that is highly sensitive to H$_2$O$_2$.

Subunit composition of human and canine $I_{to}$. We sought to determine the molecular basis for the differential expression of $I_{to}$ in human and canine ventricular myocardium. As shown in Fig. 5, immunoreactive Kv4.3, Kv1.4, and KChIP2 proteins are expressed in the left ventricles of both species. Kv4.3 in humans is present at a predominant band of 75 kDa, which is larger than that in canine myocardium (70 kDa). In contrast, the predominant band specific for Kv1.4 in canine ventricles (94 kDa) is appreciably larger than that in humans (86 kDa).
Finally, KChIP2, along with several splice variants including KChIP2S and KChIP2T, is also abundantly expressed in both human and canine ventricular myocardium at the nucleotide level (6). In human myocardium, KChIP2 was consistently detected as a single specific band that ran at 35 kDa, whereas in dog two bands were typically observed at 35 and 25 kDa (Fig. 5).

**DISCUSSION**

Species-specific differences in expression of various voltage-gated K⁺ channels have been described among dogs, rabbits, ferrets, rats, and mice (25). I\(_{\text{to}}\) exhibits characteristic regional and transmural differences in current density, kinetics, and pharmacological properties across the ventricular free wall in both humans and dogs (16, 17, 20–22, 36). However, electrophysiological properties of ventricular I\(_{\text{to}}\) between the two species have not been compared previously under identical experimental conditions.

Human ventricular I\(_{\text{to}}\) was found to differ significantly from its canine counterpart in voltage dependence and kinetics of inactivation and rate of current decay. For example, the \(V_{1/2}\) of human myocytes was significantly more depolarized than canine ventricular I\(_{\text{to}}\). The response of sarcolemmal currents such as I\(_{\text{to}}\) to membrane depolarization may have significant implications for a wide variety of human diseases, notably ischemia, in which membrane depolarization is a well-established feature. Because our data suggest that inactivation of human I\(_{\text{to}}\) is relatively resistant to membrane depolarization compared with the canine isoform, caution must be exercised when extrapolating the effects of ischemia on I\(_{\text{to}}\) in canine experimental models.

I\(_{\text{to}}\) recovery from inactivation differs significantly between canine and human myocytes. In canines, recovery from inactivation of I\(_{\text{to}}\) is described by two exponential components. The fast component has a time constant of \(~70\) ms, whereas the time constant of the slow component is over fourfold greater (\(>300\) ms). Human ventricular I\(_{\text{to}}\) follows a monoeXponential time course of recovery, which is significantly (by 61%) faster than the fast component in dogs, consistent with greater availability of human compared with canine I\(_{\text{to}}\) under similar recording conditions. Differences in the recovery kinetics of I\(_{\text{to}}\) are likely to have strong clinical importance. For example, recent reports have elegantly implicated I\(_{\text{to}}\) in the mechanism of arrhythmias associated with Brugada syndrome, whereby phase 2 reentrant excitation could occur between cells with recovered I\(_{\text{to}}\) and those with inactive I\(_{\text{to}}\) (3, 9).

Both Kv4.3 and Kv1.4 proteins are expressed in the myocardium of large mammals (29). Flecainide and H\(_2\)O\(_2\) have been used to determine the contribution of these two K⁺ channel subunits to native I\(_{\text{to}}\) (12, 36, 39). Although flecainide (low dose, 10 \(\mu\)M) suppresses peak Kv4.x current (52% mean reduction), it has little effect on Kv1.4 (only 11% mean reduction) when expressed in mammalian cells (30, 43). In our experiments, flecainide reduced the peak current density of human ventricular I\(_{\text{to}}\) without affecting the kinetics of its recovery from inactivation. In contrast, flecainide had a relatively diminished effect on canine ventricular I\(_{\text{to}}\) density. Unlike flecainide, oxidative stress did not affect the inactivation kinetics of either isoform, suggesting that Kv1.4 is not a significant contributor to human or canine ventricular I\(_{\text{to}}\).

To further investigate differences in the molecular identity of human and canine I\(_{\text{to}}\), Western blots with antibodies recognizing Kv4.3, Kv1.4, and KChIP2 were performed. Interestingly, all three subunits are expressed in the ventricles of humans and dogs. However, despite the presence of Kv1.4 mRNA (not shown) and protein (Fig. 5) in both human and canine ventricular myocardium, the electrophysiological properties of the currents and their sensitivity to flecainide and resistance to H\(_2\)O\(_2\) argue against a significant role for this subunit in native ventricular I\(_{\text{to}}\) channels. Finally, the differential sensitivity of canine and human I\(_{\text{to}}\) to flecainide and the significant variation (by –5 kDa) in the molecular mass of Kv4.3 between dog and human, suggests a difference in the primary structure or posttranslational modification of the subunit, which may underlie the distinct species-specific electrophysiological and pharmacological properties.

It appears most likely that Kv4.3 serves as the major subunit underlying ventricular I\(_{\text{to}}\) in both human and canine ventricular myocardium, because Kv4.2 is not present in either species at the mRNA level (data not shown). However, a number of ancillary subunits are known to modify Kv4.3 function. KChIP2 is a Ca\(^{2+}\)-binding accessory subunit expressed in the heart that increases expression and dramatically slows current decay of all Kv4 isoforms. Moreover, KChIP2 significantly shifts the voltage dependence of inactivation of expressed Kv4.2 (2) but not human Kv4.3 currents (6). The role of this accessory subunit in the formation of native I\(_{\text{to}}\) remains incompletely understood. We (6) previously demonstrated protein expression of KChIP2 splice variants in canine and human ventricular myocytes from both normal and failing hearts. However, heterologous expression of Kv4.3 with any combination of the KChIP2 splice variants does not fully reproduce the electrophysiological properties of native I\(_{\text{to}}\) (6). Therefore, more investigation is required to determine whether KChIP2 or
other, yet to be identified accessory subunits interact with Kv4.x to yield native $I_{to}$ channels.

**Limitations.** A reduction of $I_{to}$ is generally observed in human and animal models of heart failure. Downregulation of $I_{to}$ may be due, at least in part, to neurohormonal modulation of the current or by direct alterations in $\alpha$- or $\beta$-subunit expression in the heart. The comparisons in this study are limited by the low availability of normal human myocardium.

Transmural heterogeneity of ion channel expression, including $I_{to}$, across the ventricular wall, has been described in many species. Repolarizing $K^+$ currents in dogs are also larger in the right than the left ventricle. By design, this study was limited to myocytes obtained from the midwall of the anterior left ventricle of human and canine hearts and did not examine myocytes from epicardial or endocardial layers or other regions. Although our data provide evidence for the lack of involvement of Kv1.4 in the composition of $I_{to}$, we cannot definitively rule out the participation of Kv1.4, because an alternative mechanism(s) may protect native $I_{to}$ against oxidative stress.

Although the use of Cd$^{2+}$ to block L-type Ca$^{2+}$ current shifts the steady-state inactivation of $I_{to}$ in the depolarizing direction, differences in the voltage dependence and availability of $I_{to}$ observed in this study are not caused by differences in external divalent cations, because identical recording conditions were used in cells from both species. The tissue and cell isolation methods were also similar across species.

In conclusion, human and canine ventricular isoforms of $I_{to}$ differ significantly in their voltage dependence and kinetics of inactivation. The variant electrophysiological and pharmacological profiles of human and canine ventricular $I_{to}$ suggest differences in the molecular constituents of these channels. The relatively rapid recovery kinetics of both currents and the absence of oxidant sensitivity argue against Kv1.4 as a major component of the $I_{to}$ channel, despite its presence at the

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**Fig. 4.** Effects of H$_2$O$_2$ (0.01%) exposure for 10 min on $I_{to}$ in human and canine myocytes. A: representative current tracings and summary data of the inactivation time constants of human and canine $I_{to}$ in control and with 0.01% H$_2$O$_2$. B: effect of 0.01% H$_2$O$_2$ on the action potential in canine myocytes. Effect of H$_2$O$_2$ on $I_{to}$ steady-state inactivation (C) and recovery from inactivation (D) in canine myocytes are also shown. $\tau_m$, Time constant of $I_{to}$ decay.

**Fig. 5.** Representative Western blots of Kv4.3, Kv1.4, and Kv channel-interacting protein (KChIP)2 protein expression in canine (C) and human (H) left ventricular muscle. Human and canine KChIP2 runs between 25 and 35 kDa. Human Kv1.4 appears at 86 kDa, compared with canine Kv1.4 at 94 kDa. Kv4.3 in humans is present at a predominant band of 75 kDa, which is larger than that in canine myocardium (70 kDa).
immunoreactive protein level. Our data are most consistent with Kv4.3 as the principal subunit in both species, although we cannot conclusively rule out the contribution of other, yet to be identified subunits or factors. The appreciable differences in the function of both isoforms may result from incorporation of different ancillary subunits in the holocyclin, differences in posttranslational modification of one or more of the subunits, or even intrinsic differences in human and canine Kv4.3 genes.

REFERENCES


