Hyperkalemia Enhances the Effect of Adenosine on I_{K,ADO} in Rabbit Isolated AV Nodal Myocytes and on AV Nodal Conduction in Guinea Pig Isolated Heart

Anatoly E. Martynyuk, PhD, DSc; Timothy E. Morey, MD; Luiz Belardinelli, MD; Donn M. Dennis, MD

Background—The atrioventricular (AV) node is insensitive to changes in extracellular potassium concentration, [K\textsubscript{o}], because of the absence of the inward rectifier potassium current (I_{K1}). However, we propose that in the presence of adenosine, elevated [K\textsubscript{o}], should increase the adenosine-activated inward rectifier potassium current (I_{K,ADO}) in AV nodal myocytes and hence augment the negative dromotropic effect of the nucleoside.

Methods and Results—The effects of normal (4.8 mmol/L) and high (8.0 mmol/L) [K\textsubscript{o}] on adenosine-induced changes in resting membrane potential (V_m), I_{K,ADO}, and membrane resistance (R_m) in rabbit isolated AV nodal myocytes and in AV nodal conduction delay (atrium-to-His bundle, AH, interval) in guinea pig isolated hearts were determined with the use of whole-cell patch-clamp and His bundle electrogram techniques, respectively. High [K\textsubscript{o}], alone did not significantly affect membrane current, R_m, or V_m in AV nodal myocytes. However, high [K\textsubscript{o}], in the presence of adenosine (3 \mu mol/L) markedly increased I_{K,ADO} (0.249±0.038 to 0.571±0.111 nA, P<0.05) at −100 mV and reduced R_m (151±21 to 77±8 \Omega, P<0.02). Adenosine still hyperpolarized V_m from −48±2 to −65±1 mV (P<0.001). High [K\textsubscript{o}], alone did not significantly affect the AH interval in isolated hearts. However, high [K\textsubscript{o}], markedly lengthened the AH interval prolongation caused by adenosine (4 \mu mol/L, 7.9±0.8 vs 22.1±3.0 ms, P<0.001). The potentiating effect of high [K\textsubscript{o}] on adenosine-induced delay in AV nodal conduction was abolished by BaCl\textsubscript{2} (100 \mu mol/L).

Conclusions—By increasing I_{K,ADO} and decreasing R_m of AV nodal myocytes, elevated [K\textsubscript{o}], augments the depressant effect of adenosine on AV nodal conduction. (Circulation. 1999;99:312-318.)

Key Words: adenosine ■ atrioventricular node ■ potassium ■ myocytes

The negative dromotropic effect of adenosine underlies its therapeutic value for the acute treatment of many types of supraventricular tachyarrhythmias and its role in increasing atrioventricular (AV) nodal conduction delay during myocardial ischemia.\textsuperscript{1,2} We recently demonstrated in rabbit isolated AV nodal myocytes that adenosine hyperpolarizes the membrane potential (V_m) secondary to activation of the time-independent inward rectifier potassium current (I_{K,ADO}) and inhibits the basal and catecholamine-stimulated calcium current (I_{Ca,L}).\textsuperscript{3,4} These effects of adenosine can at least in part explain its depressant effects on AV nodal conduction.

Adenosine-activated K\textsuperscript{+} channels belong to the family of inward-rectifying K\textsuperscript{+} channels through which conductance is increased with elevation in the concentration of extracellular potassium, [K\textsubscript{o}].\textsuperscript{3,5-7} A number of studies have shown that cardiac pacemaker tissue is insensitive to changes in [K\textsubscript{o}], under normal physiological conditions.\textsuperscript{8-11} The insensitivity of pacemaker cells (ie, sinoatrial and AV nodal myocytes) to changes in [K\textsubscript{o}], has been explained by the absence of the main inward rectifier K\textsuperscript{+} current, I_{K1}.\textsuperscript{8} However, because elevated [K\textsubscript{o}], should increase the conductance of inwardly rectifying K\textsuperscript{+} channels, such as I_{K,ADO}, we hypothesized that the depressant effect of adenosine on AV nodal tissue will be greater when [K\textsubscript{o}], is elevated.

An understanding of the mechanism(s) whereby adenosine regulates AV nodal function in the setting of hyperkalemia has both physiological and pathophysiological importance. If elevated [K\textsubscript{o}], indeed sensitizes the AV node to the depressant effects of adenosine, it is reasonable to postulate that adenosine-mediated AV nodal conduction block can occur even at interstitial concentrations of adenosine that are subthreshold for its negative dromotropic effect during normokalemic conditions. Thus accumulation of [K\textsubscript{o}], may play an important mechanistic role in potentiating the negative dromotropic effect of adenosine and prove to be relevant for the understanding of the mechanisms underlying the rate-dependent actions of adenosine on AV nodal conduction.

Received April 29, 1998; revision received August 17, 1998; accepted September 9, 1998.

From the Departments of Anesthesiology (A.E.M., T.E.M., D.M.D.), Medicine (L.B.), and Pharmacology (L.B., D.M.D.), University of Florida, Gainesville.

Correspondence to Donn M. Dennis, MD, Department of Anesthesiology, University of Florida, PO Box 100254, 1600 SW Archer Rd, Gainesville, FL 32610-0254. E-mail Dennis@anest2.anest.ufl.edu

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Therefore, we studied the effects of hyperkalemia ([K⁺]₀ = 8.0 mmol/L) on adenosine-induced changes in the electrophysiological properties of rabbit isolated single AV nodal myocytes and in AV nodal conduction delay in guinea pig isolated hearts. Recognizing that nodal myocytes may be mixed with atrial myocytes during the AV nodal cell isolation procedure, we also carried out experiments in isolated atrial myocytes.

Methods

**Isolated AV Nodal and Left Atrial Myocytes**

All protocols were reviewed and approved by the Animal Use Committee of the University of Florida Health Sciences Center. Single AV nodal and left atrial myocytes were obtained from rabbit hearts (n = 17) by enzymatic and mechanical dispersion of the tissues as previously detailed. The gigaseal technique for whole-cell patch-clamp recordings was used. Voltage-clamp recordings of the inward rectifier potassium currents (Iₖᵢ, Iₖᵢ,ADO) and the high-threshold basal and stimulated calcium current (Iₖᵢ,ADO) were obtained as previously described. The equilibrium potential of potassium (E₅) was calculated with the Nernst equation:

\[ E_5 = \frac{RT}{F} \ln \left[ \frac{[K_o]}{[K_i]} \right] \]

where RT/F is 26.55 mV. In the experiments with adenosine, the concentrations of adenosine used (eg, 3 to 4 μmol/L) were similar to those reported to be the interstitial concentration of adenosine measured during myocardial hypoxia or ischemia.

**Isolated Perfused Hearts**

Hartley guinea pig hearts were isolated and prepared with the Langendorff method as previously described. Electrocardiograms were recorded with the use of unipolar electrodes placed on the surface of the left atrium and in the His bundle position according to the method of Jenkins and Belardinelli. The atrial-to-His bundle (AH) interval, a measure of AV nodal conduction time, was measured from the atrial and His bundle electrograms with the use of cursors (Snapshot Storage Scope, HEM Data Corp.). Unless otherwise noted, if any of the interventions caused second- or third-degree AV nodal block, the most stable measured response value (longest AH interval) before the onset of AV nodal conduction block was used for data analysis.

Statistical Analysis

Values are presented as mean ± SEM. Tests of statistical significance were performed with a paired t test and a 1- or 2-way, repeated-measures ANOVA followed by Student-Newman-Keuls testing (SSPS version 7.5, SPSS, Inc). A value of \( P < 0.05 \) was considered statistically significant.

Results

**Isolated AV Nodal and Left Atrial Cells**

**Effect of Elevated [K⁺]₀, on Electrophysiological Properties of Atrial and AV Nodal Myocytes in the Absence of Adenosine**

Atrial and AV nodal myocytes were distinguished on the basis of morphology and electrophysiological properties. High [K⁺]₀, caused different responses in atrial and AV nodal cells (Figure 1, A and B). Increase of [K⁺]₀ from 4.8 to 8.0 mmol/L depolarized atrial myocytes from −77 ± 1 to −65 ± 1 mV (n = 4, \( P < 0.001 \)). In contrast, the \( V_m \) of AV nodal myocytes was insensitive to changes in [K⁺]₀; \( V_m \) was −49 ± 2 and −48 ± 2 mV in the presence of 4.8 and 8.0 mmol/L [K⁺], respectively (n = 5, \( P = 0.74 \)).

Typical records of steady-state current-voltage relations of atrial and AV nodal myocytes measured in response to a voltage ramp protocol (during which \( V_m \) was changed from −120 to +40 mV over 6 seconds) are shown in panels C and D, respectively, of Figure 1. In atrial cells there was a marked inward rectification at \( V_m < 50 \) mV that corresponded to activation of the inwardly rectifying potassium current, Iₖᵢ. High [K⁺]₀ increased the inward component of Iₖᵢ over a certain range of negative potentials. For instance, the amplitude of the inward component of Iₖᵢ at −100 mV was increased from −0.190 ± 0.028 to −0.580 ± 0.108 nA (n = 5, \( P = 0.02 \)). There was also a small increase in the outward component of Iₖᵢ measured at −40 mV from 0.049 ± 0.008 to 0.056 ± 0.008 nA (\( P = 0.55 \)). In addition, in atrial cells, hyperkalemic conditions caused a 12 ± 1 mV (\( P < 0.001 \)) shift of the reversal membrane potential (\( V_{rev} \)) in the positive direction. In contrast, Iₖᵢ was absent in AV nodal cells that had a relatively small background current with little inward rectification at \( V_m < 50 \) mV (Figure 1D).

**Effect of Elevated [K⁺]₀, on Electrophysiological Properties of AV Nodal and Atrial Myocytes in the Presence of Adenosine**

In the presence of high [K⁺]₀, adenosine (3 μmol/L) still significantly hyperpolarized the membrane potential of AV

![Figure 1](https://example.com/f1.png)

**Figure 1. Effects of [K⁺]₀ on \( V_m \) and membrane current in atrial and AV nodal (AVN) myocytes.** Shown are typical examples of membrane potentials recorded from atrial (A) and AV nodal (B) myocytes and of the current-voltage relation of atrial (C) and AV nodal (D) myocytes recorded in response to a voltage ramp in the presence of 4.8 and 8.0 mmol/L [K⁺].
Elevated Extracellular K⁺, Adenosine, and AV Node

nodal myocytes from -48 ± 2 to -65 ± 1 mV (Figure 2A), although the magnitude of hyperpolarization was less than that caused at normal $[K^+]_o$ (from -49 ± 2 to -73 ± 2 mV). In contrast to AV nodal myocytes, adenosine (3 μmol/L) caused only minimal hyperpolarization in atrial myocytes (Figure 2B) at normal (from -77 ± 1 to -78 ± 1 mV) and high $[K^+]_o$ (from -65 ± 1 to -66 ± 2 mV).

The steady-state current-voltage relations of AV nodal and atrial myocytes measured in response to a voltage ramp protocol before and after the application of adenosine are shown in Figure 3. In contrast to control conditions (ie, absence of adenosine, Figure 1D), elevation of $[K^+]_o$ to 8.0 mmol/L in the presence of 3 μmol/L adenosine significantly augmented the membrane current in AV nodal cells (Figure 3, A and B). The inward component of this current measured at -100 mV (ie, background $I_{K,ADO}$) increased from -0.249 ± 0.038 nA (normal $[K^+]_o$) to -0.571 ± 0.111 nA (high $[K^+]_o$, n=7, P<0.05). Despite a decrease in the potassium driving force ($E_M-E_K$), the outward component of this current measured at -40 mV increased from 0.064 ± 0.019 to 0.079 ± 0.021 nA in response to elevation of $[K^+]_o$. In the presence of adenosine, the $V_{rev}$ was shifted from -76 ± 2 to -64 ± 1 mV in the presence of 4.8 and 8.0 mmol/L $[K^+]_o$, respectively (P<0.001).

The changes in ramp current recorded in response to the application of adenosine (3 μmol/L) at either 4.8 and 8.0 mmol/L $[K^+]_o$ were markedly smaller in atrial myocytes (Figure 3, C and D). In atrial myocytes the mean inward component of the current ($I_{K,ADO}+I_{K1}$) measured at -100 mV was -0.264 ± 0.028 and -0.727 ± 0.099 nA at normal and high $[K^+]_o$, respectively (n=7, P<0.001). The amplitudes of the outward component of the current measured at -40 mV were 0.109 ± 0.015 and 0.113 ± 0.015 nA at normal and high $[K^+]_o$, respectively (P=0.85). Considering the fact that elevation of $[K^+]_o$ from 4.8 to 8.0 mmol/L alone significantly increased $I_{K1}$ (from -0.190 ± 0.028 to -0.580 ± 0.108 nA measured at -100 mV), the additional increase of inward rectifier current caused by application of adenosine was similar at normal and high $[K^+]_o$ (143±11% and 130±9%, respectively).

The effects of $[K^+]_o$ on $I_{K,ADO}$ of AV nodal and atrial myocytes are summarized in Figure 4. As illustrated in Figure 4, the amplitude of $I_{K,ADO}$ was greater at 8.0 than 4.8 mmol/L $[K^+]_o$ and was larger in AV nodal cells than in atrial myocytes. This suggests that in the presence of adenosine, $I_{K,ADO}$ is a major source of the resting $K^+$ conductance in AV nodal cells but not in atrial myocytes; its role is significantly increased with elevated $[K^+]_o$.

We estimated the changes in membrane resistance ($R_m$) of single AV nodal and atrial myocytes caused by adenosine and high $[K^+]_o$. The $R_m$ of cells was calculated from the slope conductance of the steady-state current-voltage relation close to the point of zero current potential. Changes in $R_m$ of AV nodal and atrial myocytes in response to extracellular application of elevated $[K^+]_o$ and adenosine are summarized in Figure 5. The $R_m$ of AV nodal myocytes in control condition was quite high (1163 ± 314 MΩ) and was not significantly changed by elevated $[K^+]_o$ (894 ± 237 MΩ, P=0.40). The $R_m$ of atrial myocytes was much smaller (109 ± 9 MΩ) and was also not significantly changed by elevated $[K^+]_o$ (91 ± 11 MΩ, P=0.20). Application of adenosine in the presence of 4.8 mmol/L $[K^+]_o$ reduced $R_m$ of AV nodal cells by 87% (1163 ± 314 to 151 ± 21 MΩ) and of atrial myocytes by 28% (109 ± 9 to 79 ± 4 MΩ). Additional increases in $I_{K,ADO}$ caused by elevated $[K^+]_o$ further decreased $R_m$ in AV nodal myocytes.

Figure 2. Effects of $[K^+]_o$ on adenosine-induced changes in $V_m$ in AV nodal (AVN) and atrial myocytes. Shown are typical examples of effects of adenosine (3 μmol/L) on $V_m$ of AV nodal (A) and atrial (B) myocytes in the presence of 4.8 or 8.0 mmol/L $[K^+]_o$. Note transient hyperpolarization in $V_m$ depicted in A at 85 seconds is due to faster washout of $K^+$ than adenosine.

Figure 3. Effects of $[K^+]_o$ on adenosine-induced changes in membrane current in AV nodal (AVN) and atrial myocytes. Shown are typical examples of effect of adenosine (3 μmol/L) on current-voltage relation of AV nodal (A and B) and atrial (C and D) myocytes in the presence of 4.8 or 8.0 mmol/L $[K^+]_o$. A similar effect was observed in the presence of 4.8 mmol/L adenosine.
(to 77±8 μM, P<0.02) but did not significantly affect Rm in atrial myocytes (to 68±6 μM, P<0.30).

**Effect of Elevated [K+]o on the Inhibitory Effect of Adenosine on Isoproterenol-Stimulated I_{Ca,L} in AV Nodal Myocytes**

To exclude the possibility that elevated [K+]o may enhance the effect of adenosine on I_{K,ADO} by causing an increase in the affinity of the A1-adenosine receptor for adenosine, a separate set of experiments was carried out on AV nodal cells. Specifically, the effect of elevated [K+]o on A1-adenosine receptor–mediated inhibition by adenosine of isoproterenol (100 nmol/L)-stimulated I_{Ca,L} (β-I_{Ca,L}) was investigated. In contrast to its activation of I_{K,ADO}, adenosine-induced inhibition of β-I_{Ca,L} was not dependent on [K+]o. (Figure 6). Adenosine (3 μmol/L) reduced β-I_{Ca,L} from −2.04±0.11 to −1.76±0.12 nA (n=3; P<0.001) at normal [K+]o. However, the magnitude of this effect of adenosine on β-I_{Ca,L} (−1.87±0.15 nA) was not significantly changed by high [K+]o.

**Potentiation of Negative Dromotropic Effect of Adenosine by Elevated [K+]o in Isolated Hearts**

Potassium-induced changes in the negative dromotropic effect of adenosine were studied in guinea pig isolated heart. In the first series of experiments (n=5), concentration-response relations for this effect of adenosine in the presence of 4.8 and 8.0 mmol/L [K+]o were obtained (Figure 7). In the absence of adenosine, hyperkalemia did not significantly change the AH interval (39.3±2.7 at 4.8 mmol/L [K+]o vs 44.3±3.9 at 8.0 mmol/L [K+]o; n=5; P<0.23). Adenosine caused a concentration-dependent lengthening of the AH interval in hearts treated with 4.8 and 8.0 mmol/L [K+]o. However, high

**Figure 4.** Modulation of I_{K,ADO} in AV nodal (AVN) and atrial myocytes by [K+]o. Shown are typical examples of effects of 4.8 or 8.0 mmol/L [K+]o on current-voltage relation of adenosine-induced (3 μmol/L) activation of I_{K,ADO} in AV nodal (A) and atrial (B) myocytes. Values of I_{K,ADO} were obtained by subtracting currents recorded before application of adenosine from those recorded in the presence of nucleoside (Figure 3). Hatched bars indicate Vm at which amplitudes of I_{K,ADO} in AV nodal (A) and atrial (B) myocytes were measured. Summary data are expressed as mean±SEM of effect of [K+]o on I_{K,ADO} in AV nodal (C) and atrial (D) myocytes. *P<0.05 compared with 4.8 mmol/L [K+]o in AV nodal myocytes.

**Figure 5.** Effects of [K+]o on adenosine-induced changes in Rm in AV nodal (AVN) and atrial myocytes. Shown are the summary data, expressed as mean±SEM, of effects of 4.8 and 8.0 mmol/L [K+]o on adenosine-induced (3 μmol/L) changes in Rm of AV nodal (A) and atrial (B) myocytes. P<0.05: *Compared with control condition at a given [K+]o and cell type; †compared with 4.8 mmol/L [K+]o and presence of adenosine for AV nodal myocytes.

**Figure 6.** Effects of adenosine (3 μmol/L) and elevated [K+]o on isoproterenol-stimulated (1 μmol/L) I_{Ca,L} of AV nodal myocytes. Peak I_{Ca,L} is plotted versus experimental time. Current traces recorded at times 1 through 6 are shown at bottom. Calibration bars apply to all current traces. Changes in [K+]o and drug applications are indicated by horizontal bars. I_{Ca,L} was elicited by voltage-clamp steps to +10 mV from a holding potential of −50 mV of 100 ms duration at 0.1 Hz.
The data presented also support the hypothesis that \( I_{\text{K}, \text{ADO}} \). To test this hypothesis, the effect of \( [K^+]_o \) on the negative dromotropic action of adenosine (Figure 8). Medium abolished this potassium-induced potentiation of the AH interval in hearts that were exposed to elevated \( [K^+]_o \). However, the threshold concentration of adenosine required to prolong the AH interval was significantly lower (\( P<0.05 \)) in hearts perfused with 8.0 mmol/L \( [K^+]_o \) compared with wash or control at a given concentration of adenosine.

According to the single-cell data, the observed potentiation of the negative dromotropic effect of adenosine by a mechanism involving potentiation of \( I_{\text{K}, \text{ADO}} \). In addition, \( [K^+]_o \) (5.1 \( \pm \) 0.05) in hearts perfused with 8.0 mmol/L \( [K^+]_o \) were 5.26 \( \pm \) 0.03 (5.5 \( \mu \text{mol/L} \)), 5.67 \( \pm \) 0.06 (2.1 \( \mu \text{mol/L} \)), and 5.29 \( \pm \) 0.05 (5.1 \( \mu \text{mol/L} \)), respectively. In addition, addition of BaCl2 to the perfusion medium abolished this potassium-induced potentiation of the negative dromotropic action of adenosine (Figure 8).

**Discussion**

This report is the first to demonstrate that extracellular potassium at concentrations commonly observed during various physiological and pathophysiological conditions such as physical exercise\(^{15} \) and myocardial ischemia,\(^{19} \) respectively, markedly enhances the negative dromotropic effect of adenosine by a mechanism involving potentiation of \( I_{\text{K}, \text{ADO}} \). The data presented also support the hypothesis that \( I_{\text{K}, \text{ADO}} \) plays an important role in the depressant action of adenosine on the AV node.

**Differential Effects of Elevated \([K^+]_o\), on Atrial and AV Nodal Cell Electrophysiology**

Our observation that isolated AV nodal cells, in contrast to atrial myocytes, are insensitive to changes in \([K^+]_o\), is fully consistent with results of previous studies with multicellular preparations.\(^{10} \)\(^{11} \) Likewise, DeMello and Hoffman\(^{22} \) reported that a high concentration of \( K^+ \) caused a loss of excitability of rabbit atrial muscle, whereas action potentials were still present in the AV node. In addition, \([K^+]_o\) as high as 7.5 mmol/L did not significantly affect conduction through the AV node of the rabbit isolated heart.\(^{11} \) This lack of sensitivity of the AV nodal cells to changes in \([K^+]_o\), compared with atrial myocytes, can be explained by the relatively low \( K^+ \) conductance (\( g_k \)) during diastole in nodal tissue, a feature attributable to the absence of \( I_{\text{K}}, \text{ISO} \) in AV nodal cells.

Conductance through inwardly rectifying \( K^+ \) channels can be described by the product of the potassium driving force (\( V_m-E_K \)) and \([K^+]_o\).\(^{20} \)\(^{23} \)\(^{25} \)

**Why Does Elevated \([K^+]_o\), Potentiate the Negative Dromotropic Effect of Adenosine?**

Hyperkalemia markedly sensitized the AV node to the effect of adenosine, both at the cellular and whole heart level in 2 different species, by augmenting \( I_{\text{K}, \text{ADO}} \). We suggest that potentiation of the negative dromotropic effect of adenosine by elevated \([K^+]_o\), is due to (1) a decreased space constant (\( A \)) for propagation of an action potential secondary to augmentation of adenosine-activated potassium conductance; and (2) prolongation of the refractory period of AV nodal myocytes because of (a) a slowed time course of deactivation of the delayed rectifier potassium current (\( I_{\text{K}}, \text{ISO} \)), (b) a prolonged time of recovery from inactivation of \( I_{\text{Ca,L}} \) and \( I_{\text{Ca,T}} \), (c) an increased steady-state inactivation of \( I_{\text{Ca,L}} \) and \( I_{\text{Ca,T}} \), and (d) an increased amplitude of threshold current needed to elicit an action potential. In contrast, because elevated \([K^+]_o\), did not affect the inhibition by adenosine of \( \beta-I_{\text{Ca,L}} \), an effect mediated by the \( A_1 \)-adenosine receptor, it is highly unlikely that the potentiating effects of \([K^+]_o\), on the negative dromotropic effect of adenosine is due to an increase in the inhibition of...
transmembrane potential along a cardiac fiber is described by Salata et al.30 found the time course of $I_K$ deactivation in rabbit changes in cell excitability during diastole. On the other hand, because of a low $g_K$, the resting $V_m$ of AV nodal cells is in the range of $-37\%$ of its value at the point of current application, is equal to $R_m/r_i$. Therefore, assuming that the internal or longitudinal resistance ($r_i$) of a unit length of cable is constant during activation of $I_K$, adenosine markedly reduced $R_m$ of AV nodal cells, which in turn is likely to have resulted in a decrease in $\lambda$.

Deactivation of $I_K$

Slow deactivation of $I_K$ has been shown to delay the recovery of excitability and cause Wenckebach periodicity in guinea pig isolated ventricular myocytes.28 Because of a slowed time course of $I_K$ deactivation, the membrane resistance is lower in the early phase of diastole and therefore a greater depolarizing current must be applied during this time to attain threshold than one applied later in diastole. In keeping with this interpretation, Howarth et al.39 showed that the kinetics of $I_K$ in rabbit AV nodal myocytes could be responsible for changes in cell excitability during diastole. On the other hand, Salata et al.30 found the time course of $I_K$ deactivation in rabbit ventricular myocytes to be highly dependent on $V_m$ (ie, marked slowing on depolarization). If voltage-dependent $I_K$ deactivation is similar in rabbit AV nodal myocytes, this can be a potential mechanism whereby elevated $[K^+]_o$ potentiates the negative dromotropic effect of adenosine because the $V_m$ of these cells is significantly more positive in the presence of adenosine and high $[K^+]_o$.

Steady-State Inactivation of $I_{Ca,L}$ and $I_{Ca,T}$

Because at high $[K^+]_o$, the adenosine-induced hyperpolarization was less than at normal $[K^+]_o$ ($-65\pm1$ mV and $-73\pm2$ mV, respectively), it is anticipated that the magnitude of $I_{Ca,L}$ and especially $I_{Ca,T}$ will be reduced because of steady-state inactivation of these calcium channels. Because the inward calcium current is the major determinant of $V_{max}$ of the AV nodal action potential, the negative dromotropic effect of adenosine should be greater in the presence of high $[K^+]_o$.

Recovery From Inactivation of $I_{Ca,L}$ and $I_{Ca,T}$

In the presence of adenosine and high $[K^+]_o$, and therefore at a less negative $V_m$, the recovery of $I_{Ca,L}$ and $I_{Ca,T}$ channels from inactivation will be slower than that in the presence of adenosine and normal $[K^+]_o$. As a result, the adenosine-induced prolongation of the refractory period of the AV node should be greater in the setting of hyperkalemia.

Threshold Current

Because of a low $g_K$, the resting $V_m$ of AV nodal cells is in the range of $-43$ to $-60$ mV, values that are considerably more positive than $E_C$ ($-90$ mV, assuming $[K^+]_o=140$ mmol/L).3,27,31 Even if $[K^+]_o$ is elevated up to $8$ mmol/L, $E_C$ remains negative to $V_m$ ($E_C$ will be $-78$ mV). In other words, the increase in $g_K$ that takes place in the presence of adenosine and high $[K^+]_o$, will still produce hyperpolarization of the membrane of AV nodal myocytes. In addition, according to the Goldman-Hodgkin-Katz equation,32 an increase in $g_K$ will increase the influence of the $K^+$ gradient on $V_m$. Therefore, at a given magnitude of hyperpolarization but with a higher level of $g_K$, a greater depolarizing current (or local circuit current) would be required to achieve $V_{th}$.

Implications

The results of this study significantly expand our understanding of the mechanisms whereby adenosine modulates single AV nodal cell electrophysiology and AV nodal conduction. Modulation of the effects of adenosine on AV nodal conduction by extracellular K+ has significant physiological and pathophysiological implications. The observation that elevated $[K^+]_o$ sensitizes the AV node to the depressant effects of adenosine provides a means whereby adenosine can cause AV nodal conduction block, even at concentrations that are ordinarily subthreshold for its negative dromotropic effect under normokalemic conditions. This finding is particularly important because adenosine and K+ may be concomitantly released in increased amounts into the interstitium under a variety of conditions.33,34 For example, during imbalances between oxygen supply and demand (eg, hypoxia or ischemia), cardiac adenosine formation is markedly increased.35 Similarly, during myocardial ischemia21 and physical exercise,36 $[K^+]_o$ may rise up to as much as 8 to 12 mmol/L. Finally, the findings here reported also provide a foundation for future studies to understand the mechanism(s) whereby drugs modulate the intrinsic rate-dependent physiological properties of the AV node.

Acknowledgments

This work was supported by the Florida Affiliate of the American Heart Association (No. 9701753), National Institutes of Health (HL-56785-01), I. Heermann Anesthesia Foundation, and FAER/Zeneca New Investigator Award.

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