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An outwardly rectifying anionic background current in atrial myocytes from the human heart

H. Li [a], H. Zhang [c], J.C. Hancox [b,*], R.Z. Kozlowski [a,*,1]

[a] *Department of Pharmacology, Bristol Heart Institute, School of Medical Sciences, The University of Bristol, University Walk, Bristol BS8 1TD, UK*
[b] *Department of Physiology, Bristol Heart Institute, School of Medical Sciences, The University of Bristol, University Walk, Bristol BS8 1TD, UK*
[c] *Biological Physics Group, School of Physics & Astronomy, The University of Manchester, Manchester M60 1QD, UK*

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Abstract

This report describes a hitherto unreported anionic background current from human atrial cardiomyocytes. Under whole-cell patch-clamp with anion-selective conditions, an outwardly rectifying anion current (I_{ANION}) was observed, which was larger with iodide than nitrate, and with nitrate than chloride as charge carrier. In contrast with a previously identified background anionic current from small mammal cardiomyocytes, I_{ANION} was not augmented by the pyrethroid tefluthrin (10 μM); neither was it inhibited by hyperosmolar external solution nor by DIDS (200 μM); thus I_{ANION} was not due to basal activity of volume-sensitive anion channels. I_{ANION} was partially inhibited by the Cl^- channel blockers NPPB (50 μM) and Gly H-101 (30 μM). Incorporation of I_{ANION} into a human atrial action potential (AP) simulation led to depression of the AP plateau, accompanied by alterations to plateau inward calcium current, and to AP shortening at 50% but not 90% of complete repolarization, demonstrating that I_{ANION} can influence the human atrial AP profile.

Keywords: Action potential; Anion; Anionic; Atrium; Atrial myocyte; Background current; Cardiac; Computer modelling; Heart; Patch-clamp

The electrophysiological behaviour of cardiac myocytes from mammalian hearts is determined by the combined activity of a range of different cation and anion channel types. The reversal potential for chloride (Cl^-) ions in the heart (E_{Cl}) lies between ~−60 and −40 mV [1]. Negative to E_{Cl} outward Cl^- movement generates depolarizing ionic current, whilst positive to E_{Cl} inward Cl^- movement generates repolarizing ionic current. Therefore, the activation of Cl^- channels can influence both the resting membrane potential and the duration of cardiac action potentials (APs) ([1–3] for reviews). Several different anion channel types have been identified that may contribute to cardiac physiology and pathophysiology [1–3]. Of the cardiac anion channel currents thus far identified, the three major types are: (i) a cystic fibrosis transmembrane conductance regulator (CFTR) current-activated through cAMP-dependent phosphorylation ($I_{Cl,cAMP}$; e.g. [4–6]); (ii) a stretch- or swelling-activated Cl^- current ($I_{Cl,Swell}$; e.g. [7–9]) and (iii) a Ca^{2+}-activated Cl^- current ($I_{Cl,Ca}$; e.g. [10–12]).

Recently, an outwardly rectifying anionic background current (I_{AB}) has been identified in cardiac myocytes from two commonly studied model species (rat and guinea-pig) using whole-cell patch-clamp measurements [13,14]. I_{AB} is distinct from previously identified Cl^- currents as it has a distinct permeability sequence ($NO_3^- > I^- > Cl^-$) and is insensitive to the stilbene diphosphonate Cl^- channel inhibitor DIDS, to cell swelling and to intracellular Ca^{2+} and cAMP [13,14]. I_{AB} can also be differentiated from other major cardiac anion currents as it can be activated by the pyrethroid agent tefluthrin [14]. Anion substitution experiments have provided evidence that I_{AB} can influence AP duration (APD) [13]. There is some disagreement as to

* Corresponding authors.
E-mail addresses: jules.hancox@bristol.ac.uk (J.C. Hancox), roland.kozlowski@lectusth.com (R.Z. Kozlowski).
[1] Present address: Lectus Therapeutics Limited, Babraham Research Campus, Cambridge CB223AT, UK.

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whether or not a basally active anionic current exists in human atrium [15,16] and there is no information as to whether humans exhibit an I_{AB} with the characteristics of that seen in small mammal hearts. Therefore, the present study was undertaken to determine whether or not I_{AB} exists in adult human cardiac myocytes. The resulting findings indicate the presence in human atrial myocytes of an outwardly rectifying anionic background current (I_{ANION}). Notably, the I_{ANION} observed in this study has the potential to contribute to human atrial electrophysiology, but is distinct from both the I_{AB} recorded previously from myocytes from small mammal hearts [13,14] and from outwardly rectifying stilbene diphosphonate-sensitive anionic currents recorded previously from human atrium [17].

Methods

Atrial myocyte isolation

The study was approved by the local Central and South Bristol Research Ethics Committee and was conducted in accordance with the principles of the Declaration of Helsinki. Human right atrial appendages were obtained, with consent, from 32 patients (27 males, 5 females, average age 69.7 ± 1.7 years) undergoing coronary artery bypass surgery. Single human atrial myocytes were isolated from right atrial appendages by mechanical and enzymatic dispersion. Tissue samples were quickly immersed in cardioplegic solution (see Table 1; solution G, 100% O_2, ice cold). The samples were chopped into small chunks and washed with an EGTA-containing solution (see Table 1; solution H) gassed with 100% O_2 for 15 min at 37 °C. The chunks were then incubated in the same solution from which EGTA was excluded and protease type XXIV (3 U/ml, Sigma) and collagenase type V (250 U/ml, Sigma) were added. The medium was continuously gassed with 100% O_2 at 37 °C. After 15 min, the incubation medium was substituted for the same solution containing collagenase only. Myocytes were progressively released from the chunks into the supernatant and their yield monitored under a microscope. The suspension was washed in enzyme-free solution and the myocytes were stored at room temperature until use (within ~8 h of cell isolation).

Electrophysiology

Solutions used. Experimental solutions for the investigation of anionic current were similar to those used previously to study I_{AB} [14]; the composition of all solutions used is given in Table 1. Osmolarity values given for each of the solutions listed in Table 1 were measured using a micro-osmometer employing a freezing-point method (Advanced Instruments, Norwood, MA, USA). Myocytes used in whole-cell voltage-clamp experiments were superfused (20–25 °C) with a standard Hepes-buffered Tyrode's solution (see Table 1; solution A) until the whole-cell recording configuration had been obtained. For isolation of background anion current, sodium-free Tyrode's solutions were used (solutions B–E) in which Na was replaced by *N*-methyl-D-glucamine (NMDG), with one of several possible dominant anions: solution B, chloride; solution C, aspartate; solution D, iodide; solution E, nitrate. All drugs used were added to solution E from stock solutions made in dimethyl sulfoxide

Table 1
Composition of solutions used in this study

Chemical	Solution (concentration, mM)								
	A[1]	B[2]	C[2]	D[2]	E[2]	F[2]	G[3]	H[1]	I[2]
NaCl	145	–	–	–	–	–	–	137	–
KCl	4	–	–	–	–	–	–	–	–
$MgCl_2$	1	2.5	2.5	2.5	2.5	2.5	–	–	0.5
$CaCl_2$	2	–	–	–	–	–	–	–	–
Glucose	10	10	10	10	10	10	140	10	–
HEPES	10	5	5	5	5	5	10	5	–
NMDG-Cl	–	135	–	–	–	–	–	–	–
NMDG-Aspartate	–	–	135	–	–	–	–	–	–
NMDG-I	–	–	–	135	–	–	–	–	–
NMDG-NO_3	–	–	–	–	135	135	–	–	–
TEACl	–	5	5	5	5	5	–	–	–
$BaCl_2$	–	2	2	2	2	2	–	–	–
$CdCl_2$	–	0.5	0.5	0.5	0.5	0.5	–	–	–
Sucrose	–	–	–	–	–	70	–	–	–
Cs glutamate	–	–	–	–	–	–	–	–	75
CsCl	–	–	–	–	–	–	–	–	20
CsEGTA	–	–	–	–	–	–	–	–	0.05
MgATP (tris-salt)	–	–	–	–	–	–	–	–	10
Tris-phosphocreatine	–	–	–	–	–	–	–	–	5
Tris-GTP	–	–	–	–	–	–	–	–	0.1
Pyruvic acid	–	–	–	–	–	–	–	–	5
[4]Pipes	–	–	–	–	–	–	–	–	30
Adenosine	–	–	–	–	–	–	5	–	–
EGTA	–	–	–	–	–	–	–	0.2	–
KH_2PO_4	–	–	–	–	–	–	50	5	–
Mannitol	–	–	–	–	–	–	100	–	–
$MgSO_4$	–	–	–	–	–	–	8	1	–
Cl^- concentration	155	150	15	15	15	15	0	137	21
Osmolarity (mOsm)	308 ± 2.5	305 ± 1.2	306 ± 0.3	310 ± 3	305 ± 0.2	365 ± 1.5	383 ± 0.3	282 ± 0.6	308 ± 1.2

Osmolarities for each solution are measured values (see Methods).
Note. pH 7.4 with [1]NaOH, [2]CsOH, [3]KOH; [4]pH 7.1 with $CsCO_3$. Minus sign indicates absence.

(DMSO) with an exception of *N*-(2-naphthalenyl)-((3,5-dibromo-2,4-dihydroxyphenyl)methylene)glycine hydrazide (Gly H-101), which was solved in distilled water. The hyperosmotic external solution (solution F) was prepared by adding 70 mM sucrose to solution E. A Cs-based pipette solution (solution I) was used for all experiments. Solution I was sodium-free to prevent contamination of chloride currents by the sodium–calcium exchanger current.

Drugs. Diisothiocyanostilbene-2,2′-disulfonic acid (DIDS, final concentration 200 μM), 5-nitro-2-(3-phenylpropylamino)benzoic acid (NPPB, final concentration 50 μM) and tefluthrin (TEF, final concentration 10 μM) were purchased from Sigma Chemical Co. (Poole, UK). *N*-(2-naphthalenyl)-((3,5-dibromo-2,4-dihydroxyphenyl)methylene)glycine hydrazide (Gly H-101, final concentrations of 10 and 30 μM) was purchased from Merck (Frankfurt, Germany). All the drug-containing solutions were protected from light throughout.

Electrophysiological recording

In electrophysiological experiments, junction potential changes were minimized by immersing the reference Ag/AgCl electrode in a 3 M KCl solution with a continuous agar bridge (4% agar in 3 M KCl). Borosilicate glass pipettes (Harvard Apparatus, UK) were pulled using a vertical two-step Narishige PP-830 microelectrode puller (Narishige, Japan) and had a tip resistance of 5–7 MΩ when filled with the pipette solution. During anion substitution experiments, background anion current was elicited from voltage-clamped myocytes (superfused with solutions B, C, D and E in the whole-cell configuration) by depolarizing ramps from −90 to +70 mV from a holding potential of −50 mV (ramp rate of 0.32 V s^{-1}; sweep duration 1.03 s). A holding potential of −50 mV was used to inactivate the Na^+-current and T-type Ca^{2+}-current.

Recordings were made using an Axopatch 200A amplifier, and data were recorded on computer using pClamp v. 9.0 software (Axon Instruments, Forster City, CA). Data were analyzed using the Clampfit program of pClamp v. 9.0.

Mean values of averaged original signals over five command pulses were used for statistical analysis. Hyperpolarizing voltage steps of −20 mV and 5 ms duration were applied at 20 Hz to record the capacitance transients required for direct integration and the calculation of cell capacitance. The statistical significance between control and the drug periods or NO_3^- and other anions were determined by the Paired Student's *t*-test using either Microsoft Excel or GraphPad Prism v. 4.0. The statistical significance between the normal and hyperosmotic NO_3^- solutions was calculated with two-way ANOVA test using GraphPad Prism v. 4.0. Statistical significance was considered to refer to the 95% level of confidence ($p < 0.05$).

Human atrial action potential simulations

The Courtemanche et al. human atrial action potential (AP) model [18] was modified to incorporate a formulation for I_{ANION} based on the experimental data obtained with NO_3^- and Cl^- in Figs. 1 and 2. Readers are referred to [18] for the general equations required to set up the model. The following equation was used to simulate anionic background current (I_{ANION})

$$I_{ANION} = g_{ANION} \frac{(V - E_{ANION})}{1 - c \times e^{(d \times (V - E_{ANION}))}} \quad (1)$$

where E_{ANION} represents the current reversal potential and g_{ANION} is the conductance of I_{ANION}. By fitting Eq. (1) to experimental data shown in Fig. 1B and scaled to the mean data shown in Fig. 2A, we obtained $g_{ANION} = 0.37$ pS/pF, $E_{ANION} = -45.64$ mV, $c = 0.87$, $d = 8.4 \times 10^{-4}$ mV^{-1} for the NO_3^--sensitive I_{ANION}, and $g_{ANION} = 0.19$ pS/pF, $c = 0.94$, $d = 2.5 \times 10^{-4}$ mV^{-1} for the Cl^--sensitive I_{ANION}.

Results and discussion

The voltage protocol used for these experiments was similar to that used previously to study I_{AB} present in cardiomyocytes from small mammal hearts [14] and is shown as an inset to Fig. 1A. From a holding potential of −50 mV, ascending voltage ramps were applied between −90 and +70 mV. This protocol was applied to cells superfused first with aspartate (Asp)-containing solution (solution C) and then with different superfusates containing more permeant anions. Fig. 1A shows an example of the net current traces obtained from a cell superfused serially with solutions containing Asp^-, Cl^-, NO_3^- and I^-. Both inward and, particularly, outward current components were greater with Cl^-, NO_3^- and I^- than with Asp^- in the external superfusate. Fig. 1B shows current traces for the same cell, obtained by subtracting the current in Asp^- from that with each of the more permeant anions. With each of Cl^-, NO_3^- and I^-, the Asp^--sensitive difference current showed marked outward rectification. Fig. 1C compares the mean outward current amplitude at +60 mV (normalized to membrane capacitance) for the three anions. Compared to NO_3^-, the observed current

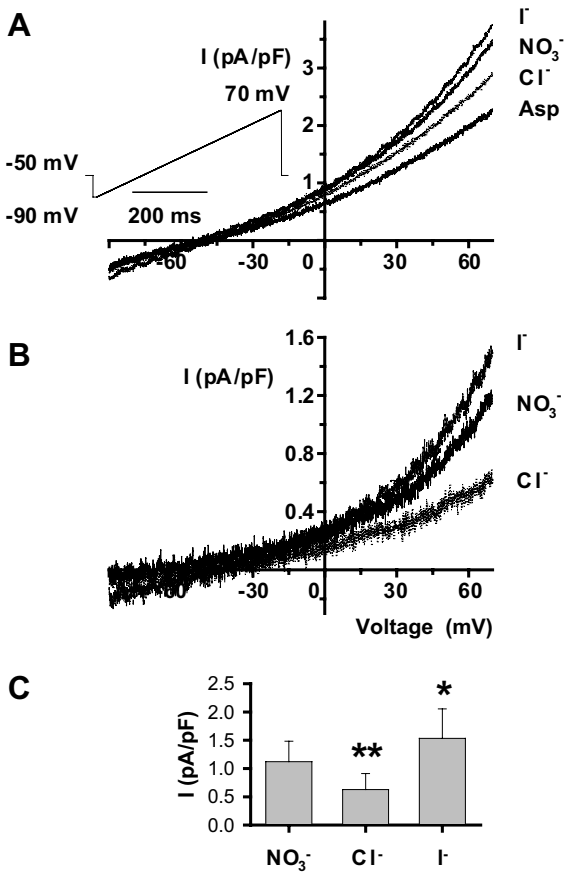

Fig. 1. (A) Representative anion-sensitive whole-cell currents (*I*, normalized to membrane capacitance) evoked by 500 ms depolarizing ramps from −90 to +70 mV from a holding potential of −50 mV (see inset) during superfusion with external solutions containing different anions (solutions C, B, E or D, respectively). (B) Representative Cl^-, NO_3^- and I^--sensitive current (*I*) for the same cell calculated by subtracting the current recorded during depolarizing ramps in the presence of aspartate from those in the presence of Cl^-, NO_3^- or I^-, respectively. (C) Mean normalized values of anion currents obtained at +60 mV (NO_3^-, $n = 7$; Cl^-, $n = 7$; I^-, $n = 6$. $^*p < 0.05$; $^{**}p < 0.001$ compared to NO_3^-).

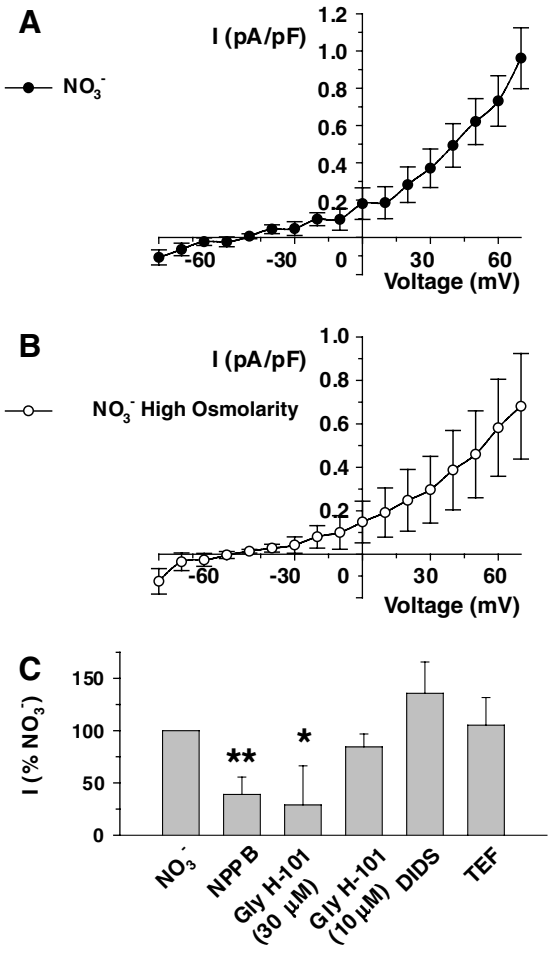

Fig. 2. (A) Plot of the mean *I–V* relations of NO_3^--sensitive current (solution E, $n = 19$). (B) Plot of the mean *I–V* relations of NO_3^--sensitive current recorded in hyperosmolar solution (solution F, $n = 8$, $p > 0.05$ vs. NO_3^- of normal osmolarity (solution E), two-way ANOVA). (C) Effects of drugs on NO_3^--sensitive current at +60 mV, expressed as percentage of the control current value before the addition of the drug (NO_3^-, $n = 15$, NPPB (50 μM), $n = 5$, Gly H-101 (30 μM), $n = 8$, Gly H-101 (10 μM), $n = 4$, DIDS (200 μM), $n = 5$ and TEF (10 μM), $n = 8$. $^*p < 0.05$; $^{**}p < 0.001$ compared to NO_3^-).

was significantly greater with I^- and smaller with Cl^- as charge carrier. These observations support the presence in human atrial cells of a basally active, anionic current (I_{ANION}); however, the relative current amplitudes with the three permeant anions differ from those observed previously with for the I_{AB} observed in myocytes from guinea-pig and rat hearts, where I_{AB} was largest with NO_3^- (permeability sequence $NO_3^- > I^- > Cl^-$; [13,14]).

Fig. 2A shows the mean I_{ANION}–voltage relation for 19 atrial cells, with NO_3^- as the major external anion (with I_{ANION} measured as the $NO_3^- - Asp^-$ difference current). The mean current–voltage relation for the resulting current showed clear outward rectification, with an observed reversal potential (E_{rev}) for I_{ANION} in these experiments of -45.7 ± 2.2 mV (obtained by pooling E_{rev} values from individual experiments). Previous studies provide evidence that human atrial cells exhibit $I_{Cl,\ Swell}$ (e.g. [15,17,19–21]). Therefore, in order to determine whether or not I_{ANION} could be attributed to basal activity of channels mediating $I_{Cl,Swell}$, Asp^- to NO_3^- substitutions were also made using hyperosmolar external solution [14]. The mean data from eight such experiments are shown in Fig. 2B. There was no statistically significant difference between the plotted densities of I_{ANION} from the *I–V* relation obtained in hyperosmolar solution and that shown in Fig. 2A, suggesting that I_{ANION} is distinct from $I_{Cl,Swell}$.

In order to characterize further I_{ANION} from human atrial myocytes, the sensitivity of the current to a range of pharmacological interventions was tested. Fig. 2C summarises the effects of the various interventions (expressed as % changes in NO_3^--sensitive current at +60 mV). The stilbene disulphonate DIDS failed to inhibit I_{ANION} at a concentration (200 μM) that would be anticipated to inhibit $I_{Cl,Swell}$ [19,21]. On the other hand, tefluthrin (10 μM), which we have previously reported to activate the I_{AB} seen in myocytes from guinea-pig hearts [14], failed to alter significantly the amplitude of I_{ANION} from human atrial myocytes. Together with the relative I_{ANION} amplitudes in I^-, Cl^- and NO_3^-, the lack of effect of tefluthrin indicates that I_{ANION} is distinct from the previously reported rat/guinea-pig I_{AB} [13,14]. Moreover, the lack of significant inhibition of the current by DIDS or hyperosmolar solution makes the I_{ANION} observed in the present study distinct from $I_{Cl,Swell}$ [1] and from an osmolarity- and stilbene-sensitive outwardly rectifying chloride current recently reported by Demion and colleagues [17]. NPPB (50 μM) produced a partial, statistically significant ($p < 0.05$) inhibition of I_{ANION}. The glycine hydrazide Cl^- channel inhibitor Gly H-101 failed to produce a significant blockade of I_{ANION} at 10 μM (~7-fold greater than the reported IC_{50} for CFTR channel inhibition at +60 mV [22]); but produced partial attenuation of the current at 30 μM (~20-fold the reported IC_{50} for CFTR [22]). Evidence for the presence of CFTR ($I_{Ca,cAMP}$) in human atrial cells is mixed [1,15,19–21,23], with a number of studies failing to observe the current in response to β-adrenergic stimulation, forskolin or cAMP (e.g. [15,19–21]). Previous work has failed to find evidence for $I_{Cl,Ca}$ in human atrial myocytes [24] and, moreover, the presence of EGTA in the pipette dialysate (Table 1, solution I) and external $[Ca^{2+}]$ replacement in our experiments would have inhibited any $[Ca^{2+}]_i$-activated conductances on membrane depolarization. Therefore, the I_{ANION} seen here appears to differ not only from guinea-pig and rat I_{AB} [13,14] but also from the three major reported cardiac anion conductances in: (i) being basally active and (ii) its overall pharmacological profile and sensitivity to anion substitution.

In order to gain insight into the physiological role of I_{ANION}, the current was incorporated into human atrial AP simulations as outlined in the 'Methods'. Fig. 3A shows the simulated APs (at an AP frequency of 1 Hz) from the Courtemanche et al. model [18] both without (Control) and with inclusion of I_{ANION}, whilst Fig. 3B shows the corresponding current profiles during the time-course of the

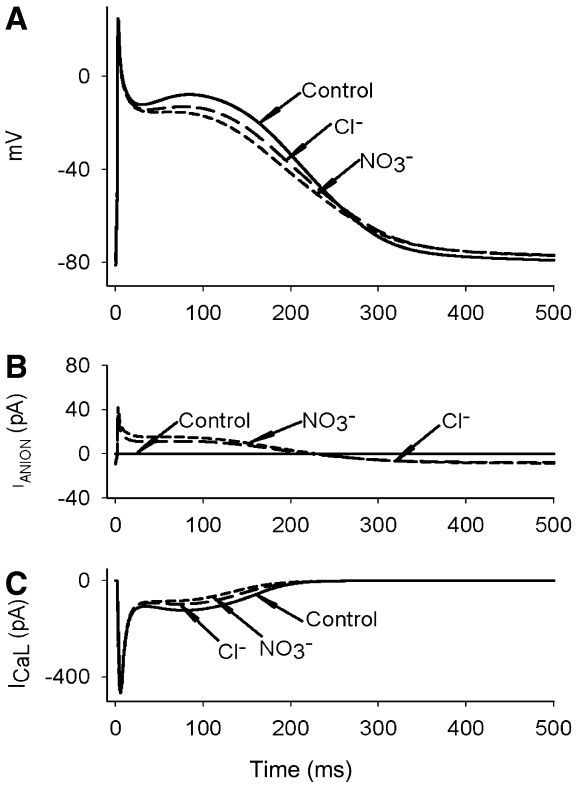

Fig. 3. (A) Simulated human atrial action potentials with and without (Control) inclusion of I_{ANION} (with each of NO_3^- and Cl^- as charge carrier). (B) Profile of I_{ANION} during each of the action potentials shown in panel A. (C) Profile of L-type Ca^{2+} current ($I_{Ca,L}$) during each of the action potentials shown in panel A, in control and with NO_3^--dependent and Cl^--dependent I_{ANION}.

AP. With either NO_3^- and Cl^- as charge carrier, incorporation of I_{ANION} into the model produced shortening of AP duration at 50% repolarization (APD_{50}; the measured APD_{50} values were 184, 165 and 159 ms for Control, Cl-sensitive I_{ANION} and NO_3-sensitive I_{ANION}, respectively). In contrast, APD_{90} was comparatively unaffected (the measured APD_{90} was ~305 ms under each condition) and resting potential also changed relatively little (with resting potential values of −81, −79 and −78 mV, respectively, for Control, I_{ANION} with Cl^- and I_{ANION} with NO_3^-). The more marked effect of I_{ANION} inclusion at less negative potentials during AP repolarization is concordant with the outwardly rectifying nature of the current. An additional observation made from the AP simulations is that incorporation of I_{ANION} also influenced the profile of L-type calcium current ($I_{Ca,L}$) during the AP plateau: the initial rapid component of $I_{Ca,L}$ was unaffected by I_{ANION} incorporation, but the sustained component during the AP plateau showed a modest reduction. Thus, both an increase in repolarizing current carried by I_{ANION} and the consequent decrease in the sustained component of $I_{Ca,L}$ combined to lead to AP plateau depression and abbreviation of APD_{50}. The results shown in Fig. 3 demonstrate clearly that I_{ANION} is able to influence human atrial AP repolarization. Further work is now warranted to determine both the extent to which the incorporation/omission of I_{ANION} influences the susceptibility of human atrial cells and tissue to arrhythmia and to pursue the underlying identity and regulation of this novel background conductance.

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