hERG K^+ Channels

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BACK

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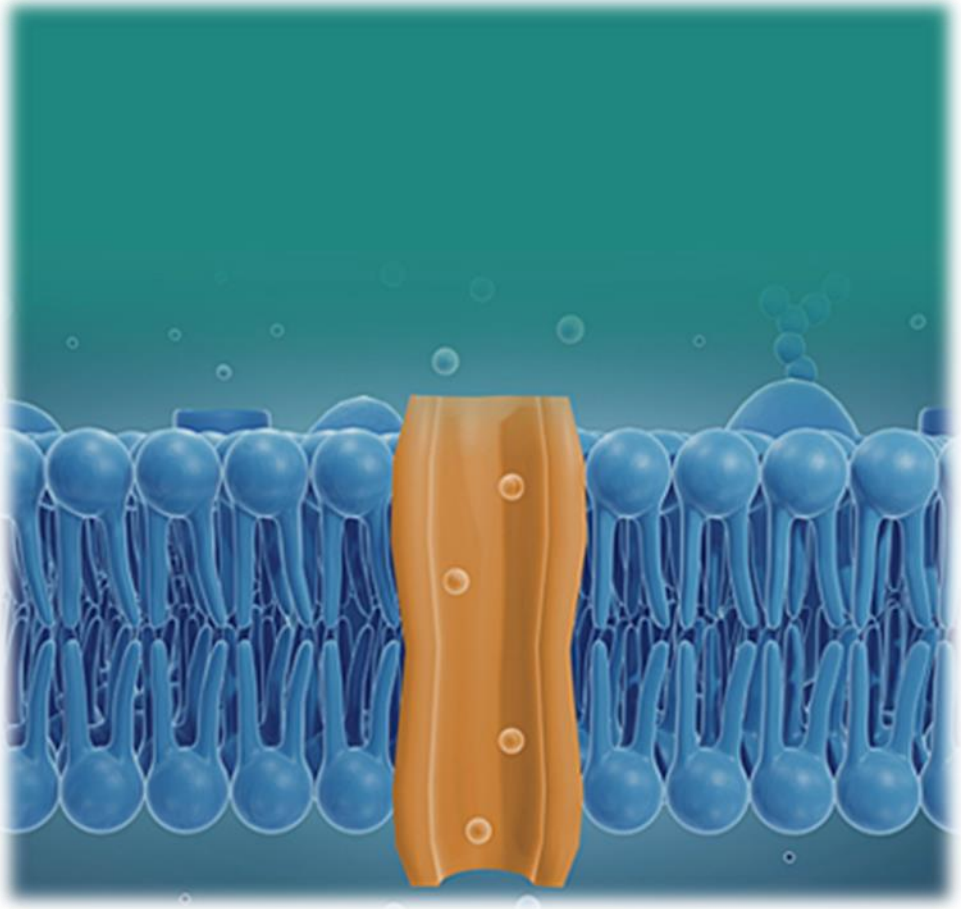


hERG Introduction

BACK

hERG (human Ether-à-go-go-Related Gene) is the Kv11.1 potassium channel. The hERG channel mediates the repolarizing I_{Kr} current in the cardiac action potential, which helps reset the hyperpolarized potential in cardiac cell in preparation for the next action potential.

This channel has received special attention by the FDA due to the fact that blockade of this channel by some approved drugs can result in a potentially fatal disorder called long QT syndrome. This syndrome can also be caused by or by rare mutations in some families [1] A number of clinically successful drugs in the market have had the tendency to inhibit hERG, lengthening the QT interval and potentially leading to a fatal ventricular tachyarrhythmia (torsades de pointes). This has made hERG inhibition an important counter screening target that must be avoided during drug development.[3]

hERG has also been associated with modulating the functions of some cells of the nervous system [4] and with establishing and maintaining cancer-like features in leukemic cells.[5]

hERG References

BACK

1) Hedley PL, Jørgensen P, Schlamowitz S, Wangari R, Moolman-Smook J, Brink PA, Kanters JK, Corfield VA, Christiansen M (2009). "The genetic basis of long QT and short QT syndromes: a mutation update". Hum. Mutat. 30 (11): 1486–511. doi:10.1002/humu.21106. PMID 19862833. S2CID 19122696.

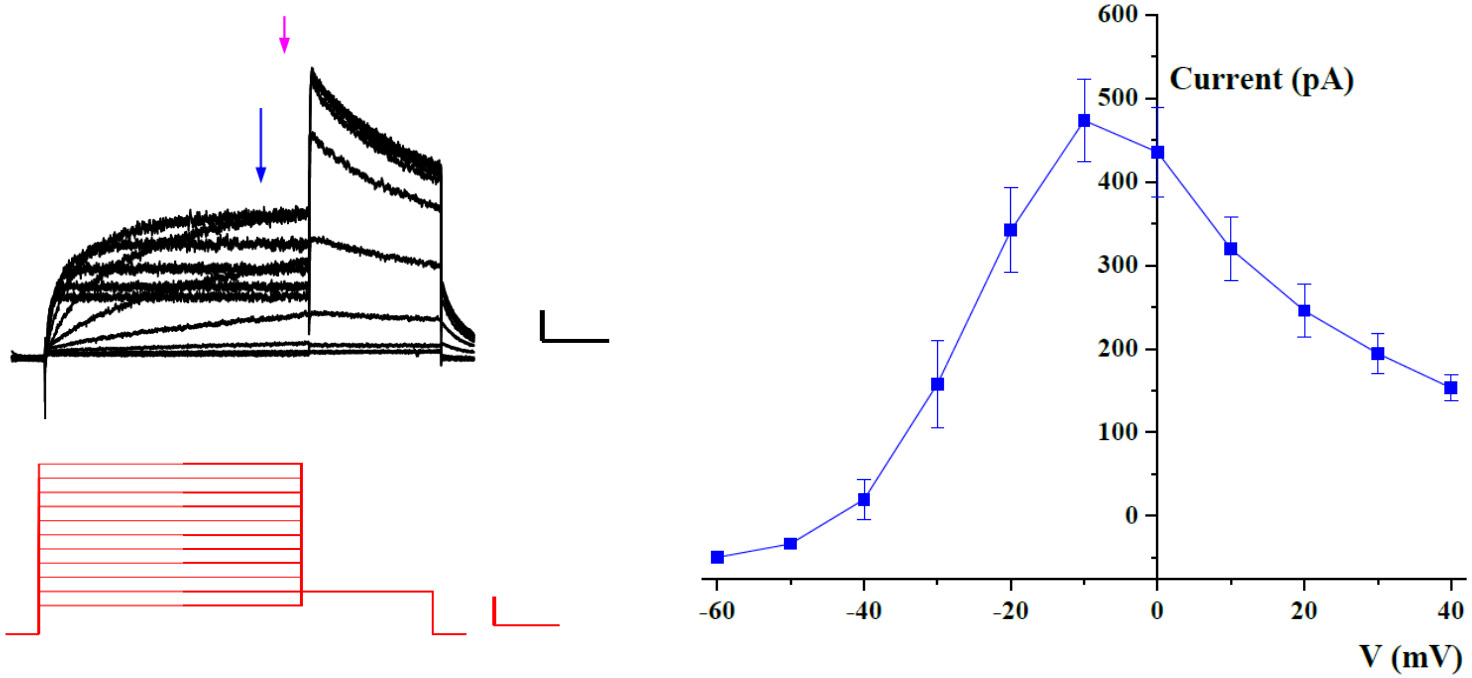
2) Bjerregaard, Preben (2018-03-02). "The diagnosis and management of short QT syndrome". Heart Rhythm. 15 (8): 1261–1267. doi:10.1016/j.hrthm.2018.02.034. ISSN 1556-3871. PMID 29501667. S2CID 4519580.

3) Sanguinetti MC, Tristani-Firouzi M (March 2006). "hERG potassium channels and cardiac arrhythmia". Nature. 440 (7083): 463–9. Bibcode:2006Natur.440..463S. doi:10.1038/nature04710. PMID 16554806. S2CID 929837.

4) Chiesa N, Rosati B, Arcangeli A, Olivotto M, Wanke E (June 1997). "A novel role for HERG K+ channels: spike-frequency adaptation". J. Physiol. 501 (2): 313–8. doi:10.1111/j.1469-7793.1997.313bn.x. PMC 1159479. PMID 9192303.

5) Arcangeli A (2005). "Expression and role of hERG channels in cancer cells". The hERG Cardiac Potassium Channel: Structure, Function and Long QT Syndrome. Novartis Found. Symp. Novartis Foundation Symposia. Vol. 266. pp. 225–32, discussion 232–4. doi:10.1002/047002142X.ch17. ISBN 9780470021408. PMID 16050271.

hERG-CHO (CYL3038)

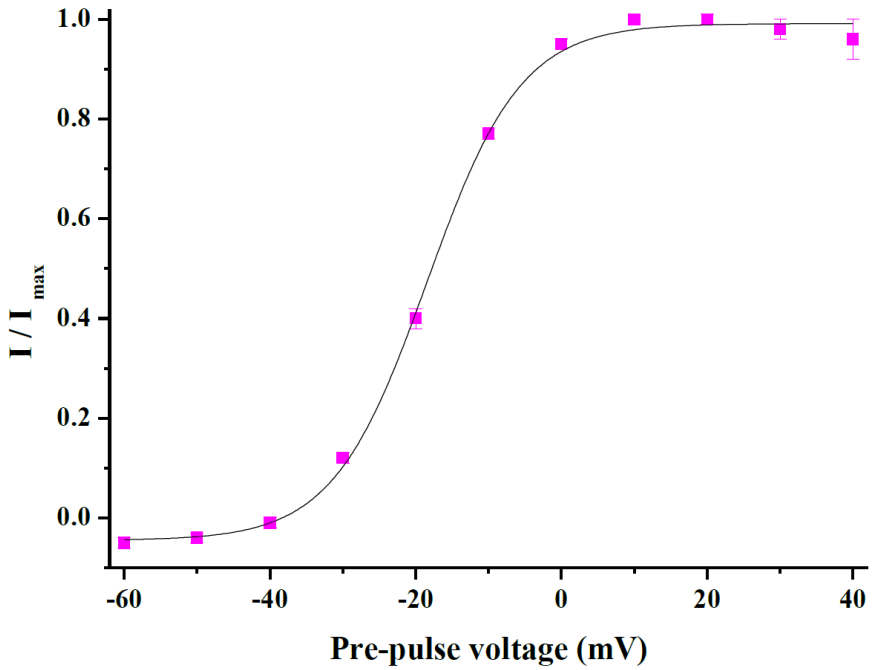


BACK

hERG Raw Currents and Current-Voltage Relationship: **Left:** hERG currents evoked by depolarizing voltage steps. Membrane currents (upper panel) elicited by 4 s depolarizing voltage pulses (lower panel), stepped in 10 mV increments from –60 mV to + 40 mV from a holding potential of –80 mV every 15 s. Scale bars represent 1 s and 100 pA (upper panel) and 1 s and 20 mV (lower panel). The blue arrow denotes where membrane current was measured for the current voltage relationship **(Right).** The purple arrow denotes the point at which tail currents were measured for the activation curves in a subsequent figure **Right:** The isochronal I/V relationship of the hERG current. The current was measured at the end of the depolarizing step and plotted against voltage (mean ± S.E.M, n= 7-8 cells) (Manual Patch Clamp Data)

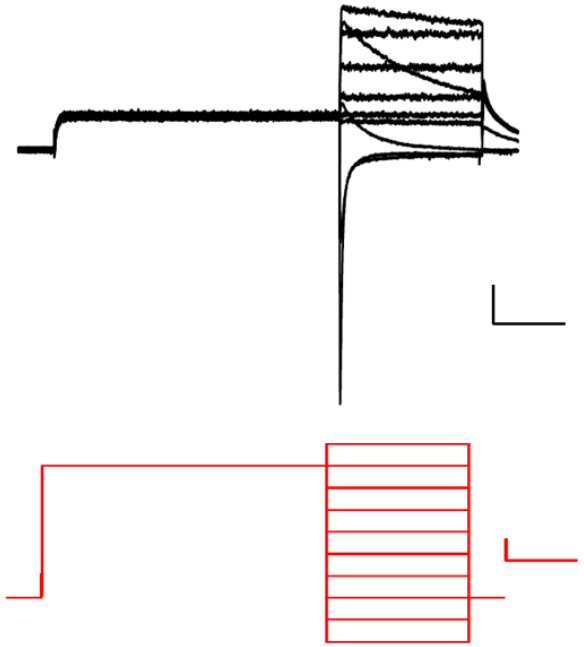
hERG-CHO

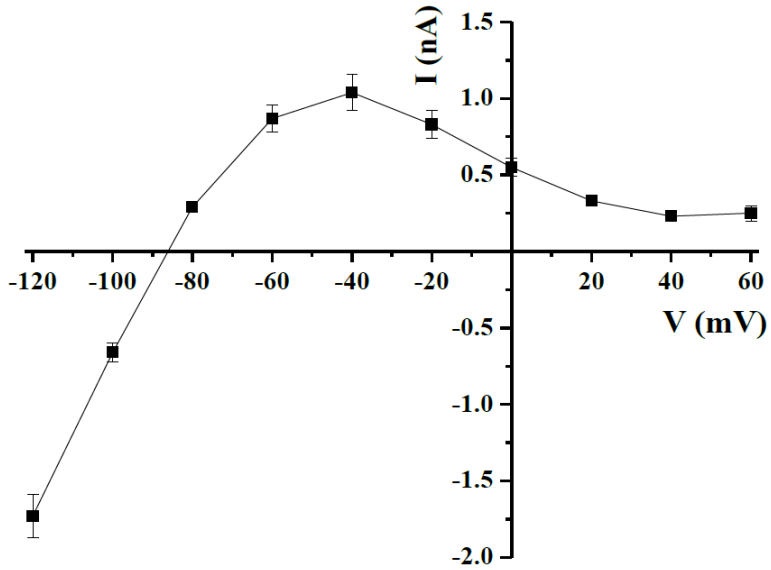
BACK



hERG activation curve measured with tail currents. Data was fitted with a single Boltzmann equation. V½ = - 18.5 ± 0.7 mV and slope (k) = 6.4 ± 0.1. Data normalized to current at 10 mV. Mean current at 10 mV = 832 ± 46 pA. Values represent mean ± S.E.M. (n = 6 cells) (Manual Patch Clamp Data)

hERG-CHO

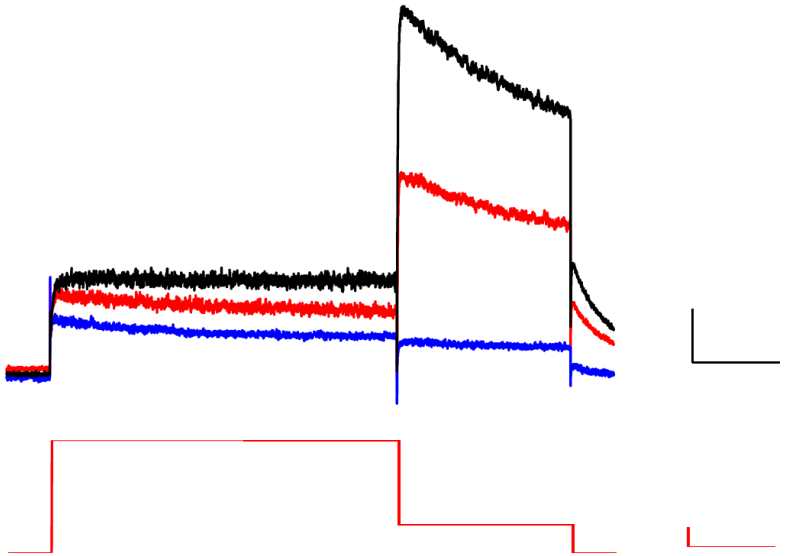


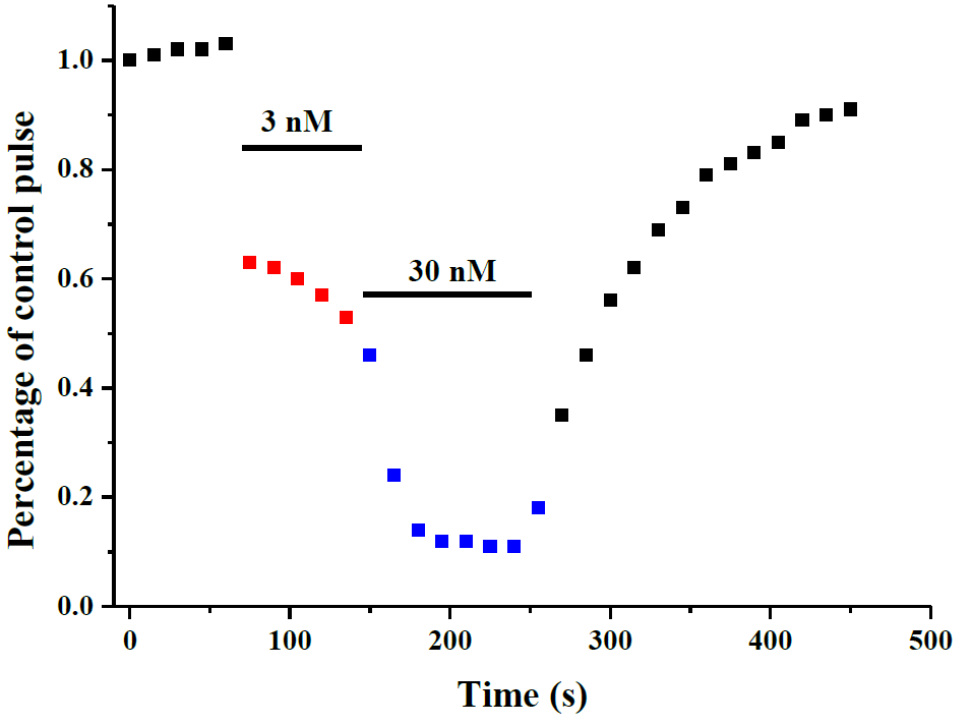


BACK

hERG Fully Activated Current-Voltage Relationship: In order to obtain the fully activated current voltage relationship, cells were clamped at a holding potential of -80 mV and then voltage pulses were applied as described. At potentials negative to the reversal potential (i.e. - 120 mV and -100 mV), large deactivating inward tail currents were recorded. The current reversed direction on stepping to -80 mV and stepping to more depolarized levels lead to progressively larger outward tails up to -40 mV and then lead to progressively smaller time-independent currents up to +40 mV. **Left:** hERG current evoked by repolarizing voltage steps. Membrane currents (upper panel) were elicited by the voltage protocol shown in the lower panel i.e. the membrane was stepped to +40 mV for 4 s followed by repolarizing steps from -120 mV to +60 mV in 20 mV increments for 2 s. Scale bars represent 1 s and 250 pA (upper panel) and 1 s and 20 mV (lower panel). **Right:** The fully activated I/V relationship of the hERG current. The voltage protocol described in Figure 4 was applied every 15 s. Peak current (measured on stepping back to the various test voltages) is plotted against membrane voltage (mean ± S.E.M, n=5 cells) (Manual Patch Clamp Data)

hERG-CHO

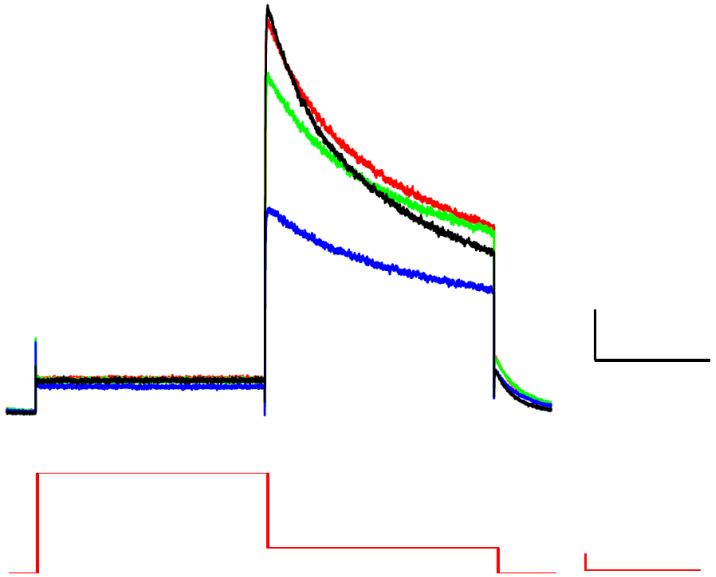


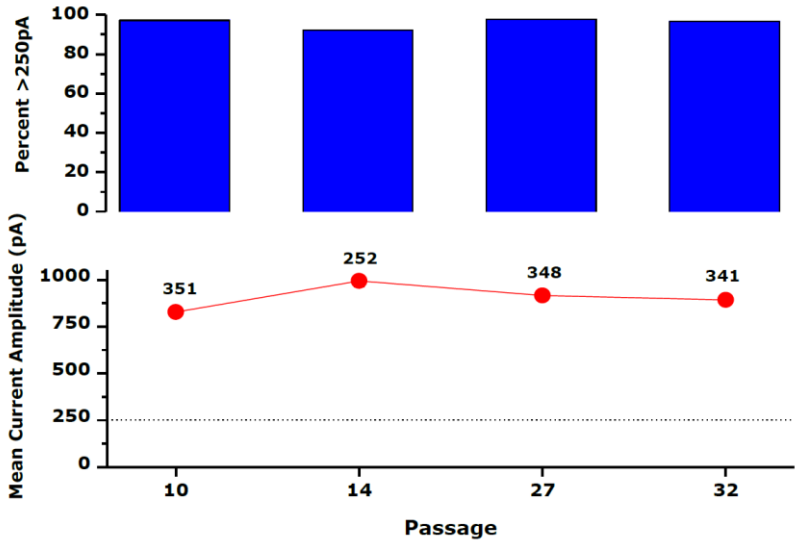


BACK

hERG Current Blockade by Cisapride: Left: Currents were evoked by a voltage protocol (lower trace) stepping to +40 mV for 4 s from a holding potential of –80 mV then stepping back to –50 mV every 15 s. Typical currents recorded before the addition of cisapride (control - black trace) and after addition of 3 nM (red) and 30 nM (blue) cisapride respectively. Scale bars represent 1s and 100 pA (upper panel) and 1 s and 20 mV (lower panel). **Right:** The effect of cisapride on the hERG tail current. Tail currents were evoked continuously (1 every 15 s). Peak tail currents (normalized to control current) are plotted against time. The labeled black bars depict the presence of 3 and 30 nM cisapride. (Manual Patch Clamp Data)

hERG-CHO

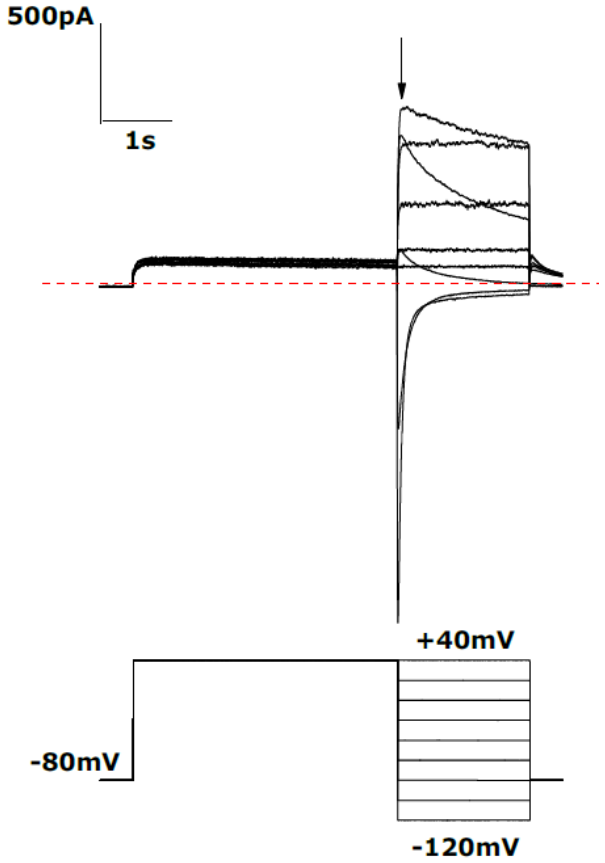


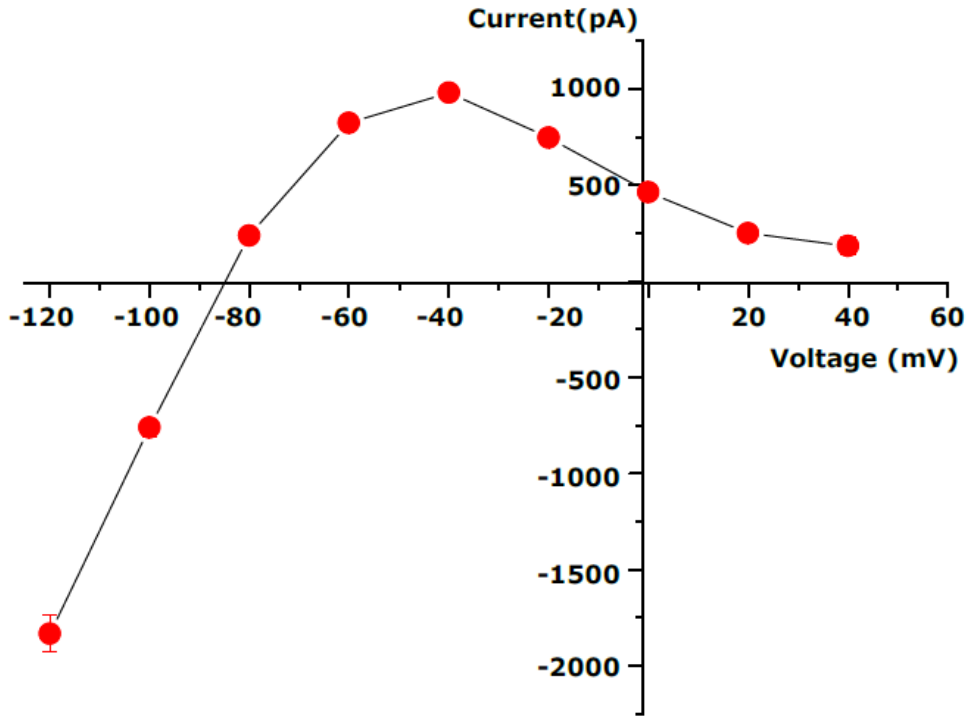


BACK

The Effect of E4031 on hERG Tail Currents and Stability of Expression Over Passage: **Left:** hERG current traces (upper trace) evoked by stepping to +40 mV for 4 s from a holding potential of –80 mV then stepping back to –50 mV every 10 s (lower trace). Typical currents recorded before the addition of E4031 (control - black trace) and after addition of 3 nM (red), 10 nM (green) and 100 nM (blue) E4031 respectively. Scale bars represent 2 s and 200 pA (upper panel) and 2 s and 20 mV (lower panel) (Manual Patch Clamp Data). **Right:** The upper panel shows the percentage of cells expressing a mean peak tail current >250 pA at –50 mV at cell passages 10, 14, 27 and 32. The lower panel shows the mean current amplitude (mean ± SEM, red circles) and the number of these cells (numbers above red circles) (IonWorks HT Data)

hERG-HEK (CYL3039)

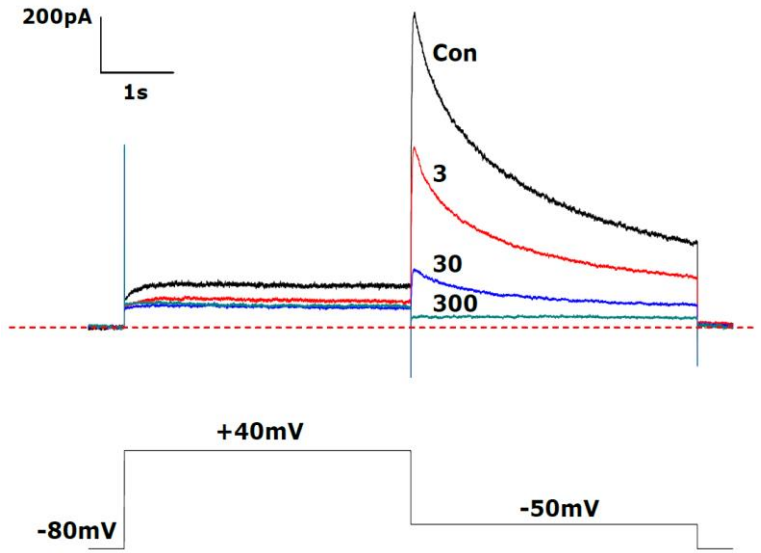


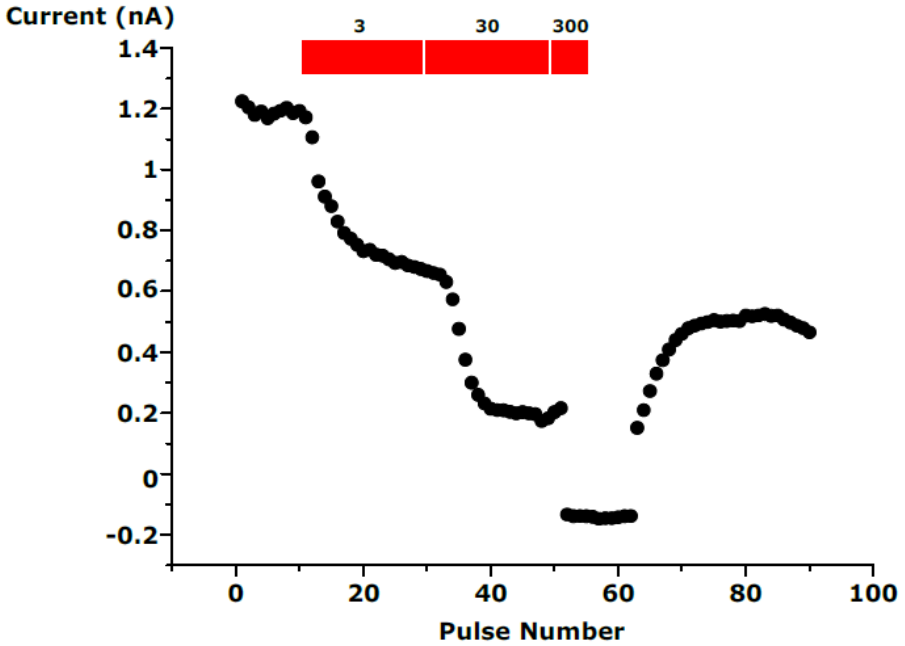


BACK

hERG Raw Data Currents and Fully-Activated Current-Voltage Relationship: Membrane currents **(Left Top Panel)** were elicited by the voltage protocol shown in the **(Left Bottom Panel),** the membrane potential was stepped to +40 mV for 4s followed by repolarizing steps from -120 mV to +40 mV in 20 mV increments). The red dotted line indicates zero current level and the arrow denotes where membrane current was measured for the current voltage relationship. **Right:** The voltage protocol described in Figure 3 was applied every 15 s. Peak current (measured on stepping back to the various test voltages is plotted against membrane voltage (mean ± S.E.M, n=4). (Manual Patch Clamp Data).

hERG-HEK



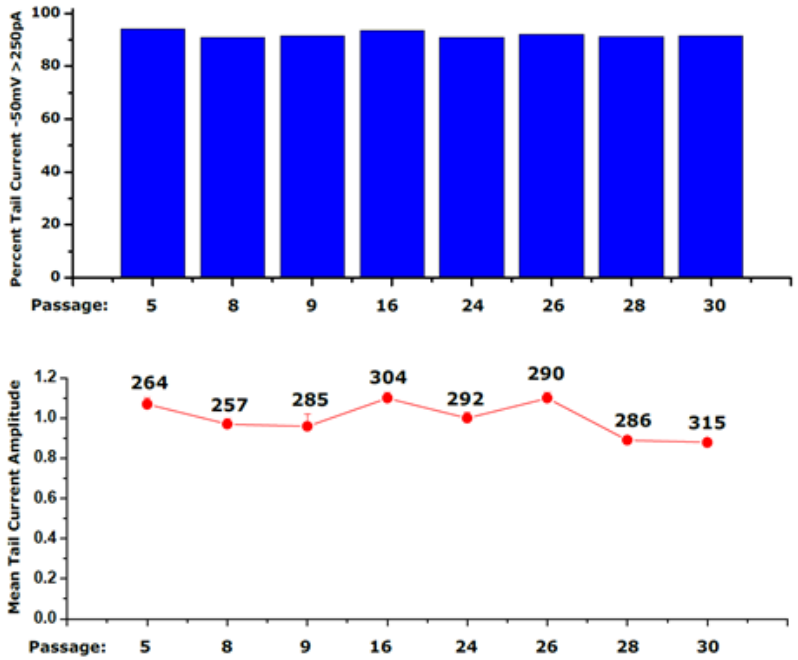


BACK

Blockade of hERG currents by Cisapride: Typical currents **(Left)** recorded before ("Con", black trace) and after 2-5 min bath application of 3 nM ("3", red trace), 30 nM ("30", blue trace) and 300 nM ("300", green trace) cisapride. The voltage protocol is shown in the lower panel and applied every 15 s. The red dotted line indicates zero current level. **Right:** Current-Time (I/t) plot of the amplitude of control currents and after the addition of 3, 30 and 300 nM Cisapride (Manual Patch Clamp Data).

hERG-HEK

BACK



Stability of expression over passage: The percentage of cells **(Top)** expressing a mean peak tail current >250 pA at –50 mV at cell passages 5, 8, 9, 16, 24, 26, 28 and 30. **Bottom:** The mean current amplitude (mean ± SEM, red circles) and the number of these cells is above the red circles (IonWorks HT Data).