Late Sustained Sodium Current in Adult Human Primary Cardiomyocytes

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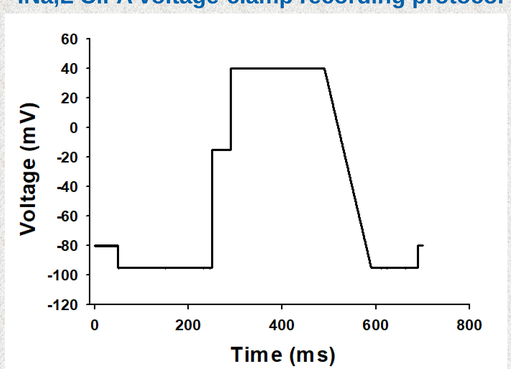
Introduction

The late sustained sodium current (INa,L), a depolarizing current that persists throughout the action potential (AP) plateau, contributes to the AP duration and maintains the intracellular homeostasis of Na^+. Increase or inhibition of INa,L is often associated with arrhythmogenicity or mitigation of pro-arrhythmia risk, respectively. Indeed, an increased INa,L has been associated with the long QT syndrome type 3 (LQT 3). Since INa,L was one of the selected channels for the CiPA initiative and drugs that block the hERG channel and also inhibit INa,L are not associated with pro-arrhythmia in humans, identifying the effect of compounds on INa,L in human cardiomyocytes during preclinical development can aid in the determination of pro-arrhythmia risk for new drugs.

Methods

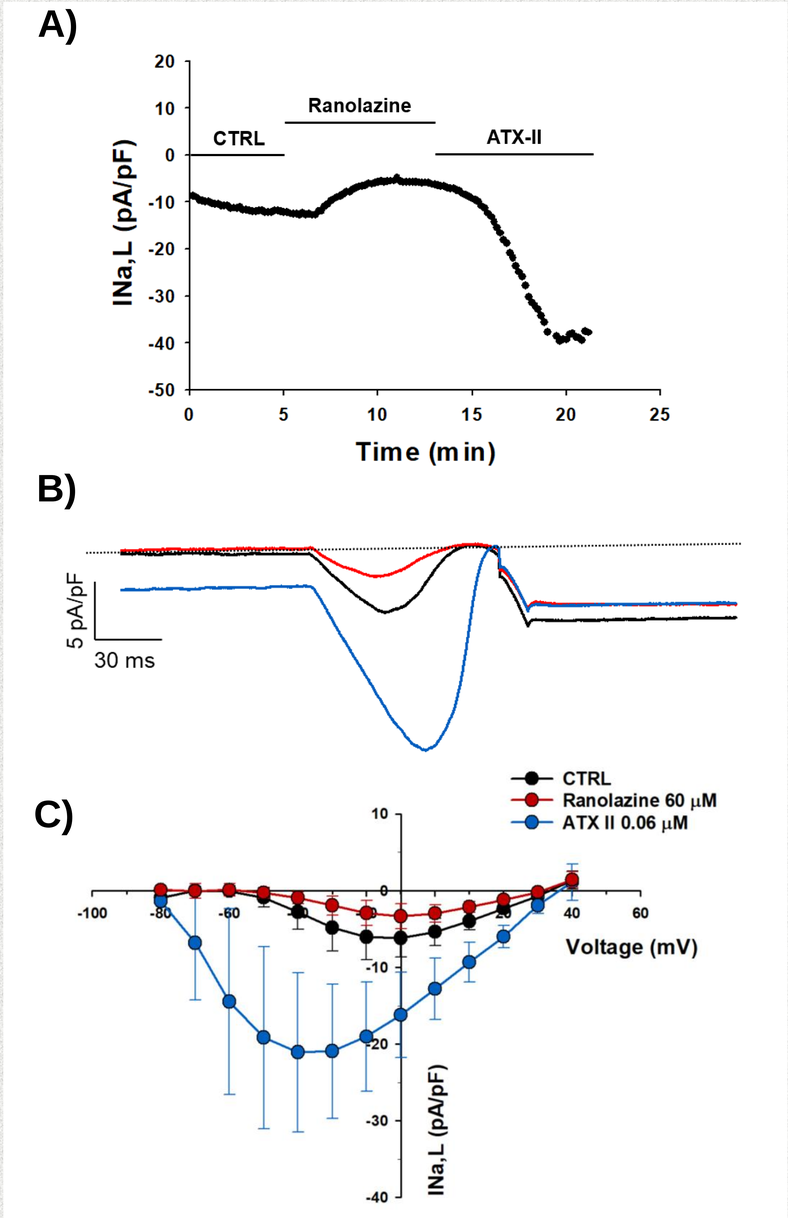
In order to better understand the properties of this current, we performed voltage-clamp recording of INa,L, at physiological temperature, in whole-cell patch-clamp experiments using adult human primary cardiomyocytes isolated from ethically consented donor hearts. Test articles were applied until steady state effect was achieved.

INa,L CiPA voltage-clamp recording protocol



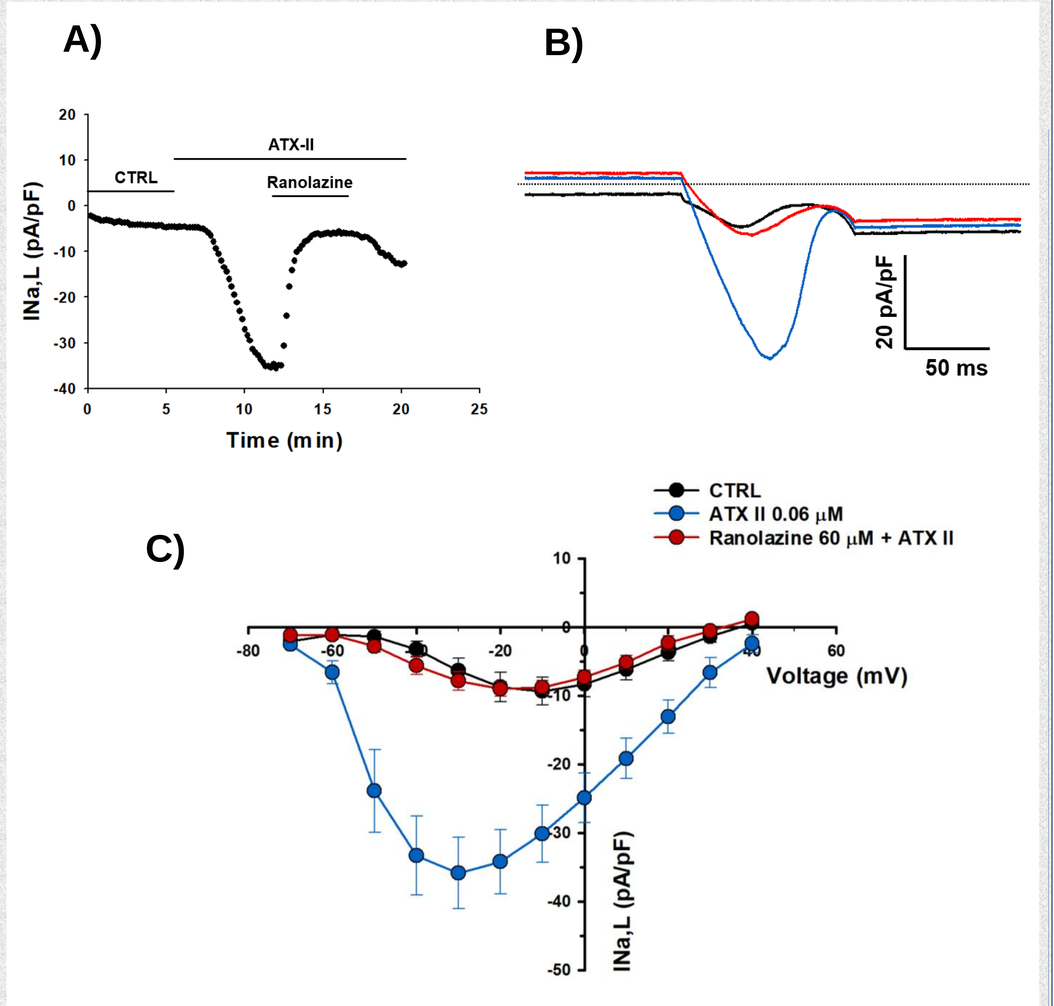
INa,L protocol was elicited every 10 s from a holding potential of -80 mV. INa,L current was measured during the step-ramp, which goes from 40 mV to -95 mV over a duration of 100 ms.

Ranolazine inhibits and ATX II stimulates INa,L



A) Myocyte was first exposed to control solution. Applications of Ranolazine and ATX II are indicated by the lines.
B) Typical INa,L traces. The dotted line indicates the zero-current level.
C) INa,L current density-voltage relationship (n=3 cells).

Ranolazine inhibits the ATX II stimulation of INa,L



A) Myocyte was first exposed to control solution. Perfusion with ATX II alone or in combination with Ranolazine are indicated by the lines.
B) Typical INa,L traces. The dotted line indicates the zero-current level.
C) INa,L current density-voltage relationship (n=6 cells).

Summary

1. Human cardiomyocytes express functional INa,L and can differentiate INa,L inhibitors from facilitators.
2. Action potential experiments are currently underway to assess INa,L role in modulating pro-arrhythmia.
3. Human cardiomyocytes could potentially provide a useful strategy for the early assessment of the ability of new multichannel blocking drugs with INa,L affinity to prevent the occurrence of pro-arrhythmia.