221 REDUCING SARCOLEMMAL SODIUM CURRENT DECREASES SPONTANEOUS SR CA2+ RELEASE

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Aim Ca2+ waves are thought to be important in the aetiology of ventricular tachyarrhythmias. There is some evidence that INa blocking agents can reduce spontaneous sarcoplasmic reticulum (SR) Ca2+ release via effects on the RyR. We tested the hypothesis that direct modulation of INa may also be important in altering SR Ca2+ release.

Methods and Results Imaging of spontaneous SR Ca2+ release events in healthy adult rat cardiomyocytes was performed. Variation in frequency of stimulation was used to produce Ca2+ sparks or waves. When SR Ca2+ content was held constant, spark frequency, wave frequency and wave velocity were reduced by a variety of INa blockers (including flecainide, lidocaine, propafenone and TTX). To assess the contribution of INa to spark and wave production voltage clamping was used to activate contraction from holding potentials of -80mV or -40mV. This confirmed that reducing Na+ influx during myocyte stimulation is sufficient to reduce waves and that such agents only cause Ca2+ wave reduction when INa is active. It was found that Na+/Ca2+-exchanger (NCX)-mediated Ca2+ efflux was significantly enhanced by INa blockade and that the effects of INa blockade on wave frequency could be reversed by reducing [Na+]o, suggesting an important downstream role for NCX function in the changes in SR Ca2+ release. Veratridine, an INa activator, increased wave frequency and the effects were abrogated by increasing [Na]o during the wave-detection period.

Conclusions Our results show, for the first time, that reducing Na+ influx reduces spontaneous SR Ca2+ release. We have also shown that alterations in [Na+]i modulate wave frequency through alterations in NCX function. A reduction in INa, for example, can increase the [Na+]o:[Na+]i gradient, hence causing more effective Ca2+ efflux at resting membrane potentials. This not only suggests a clear mechanism for the reduction in waves seen with INa blockers, but also emphasises the detrimental effects of high [Na]i seen in disease states such as heart failure. It also allows us to understand an alternative way in which INa blockers exert their antiarrhythmic actions.