DYNAMICS OF THE LATE SODIUM CURRENT UNDER THE ACTION POTENTIAL IN GUINEA PIG, CANINE AND HUMAN VENTRICULAR MYOCARDIUM

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Many aspects of the late sodium current ($I_{Na,late}$) are still poorly understood. We studied the true profile of $I_{Na,late}$ in different species. We also aimed to find out if there is a sharp difference in frequency-dependent $I_{Na,late}$ blockade between the so-called "selective late sodium current inhibitors" and "general" class I/B sodium channel blockers.
$I_{Na,late}$ was defined as tetrodotoxin-, mexiletine-, or GS458967-sensitive current, recorded under action potential voltage clamp (APVC) or conventional voltage clamp. Action potential measurements were carried out with sharp microelectrodes.
Under APVC conditions the density of canine and human $I_{Na,late}$ monotonically decreased, whereas in guinea pig, it continuously increased during the AP plateau. Conventional voltage clamp experiments revealed that the "increasing" $I_{Na,late}$ profile in guinea pig is determined by the slow decay of $I_{Na,late}$ in this species.
In guinea pig cells, facilitation of $I_{Na,late}$ prolonged APD and induced arrhythmogenic activities; triggered by spontaneous Ca^{2+} release from the sarcoplasmic reticulum.
CaMKII inhibition using KN-93 reduced $I_{Na,late}$ magnitude throughout the time course of AP. Meanwhile, increasing Ca^{2+}-load did not further increase $I_{Na,late}$, indicating that the Ca^{2+}-CaMKII modulation of $I_{Na,late}$ can already be saturated under baseline condition.
Like mexiletine, GS458967 inhibited both the early and late components of the sodium current. On the basis of its kinetic properties, GS458967 can be classified as a I/B antiarrhythmic drug in Vaughan-Williams classification. Based on our experiments, the sharp distinction between "selective" $I_{Na,late}$ inhibitors and the frequency-dependent $I_{Na,late}$ inhibition described for "general" class I/B sodium channel inhibitors is highly questionable.

Keywords: late sodium current, cardiac myocyte, action potential, antiarrhythmic drug

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