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Late sodium current: A mechanism for angina, heart failure, and arrhythmia

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ABSTRACT

The peak sodium current underlies excitability and conduction in heart muscle, but a late sodium current flowing after the peak contributes to maintaining and prolonging the action potential plateau, and also to intracellular sodium loading, which in turn increases intracellular calcium with consequent effects on arrhythmia and diastolic function. Late sodium current is pathologically increased in both genetic and acquired heart disease, making it an attractive target for therapy to treat arrhythmia, heart failure, and angina. This review provides an overview of the underlying bases for the clinical implications of late sodium current block.

Key Words: Sodium current, Long-QT syndrome, Antiarrhythmic drugs.

Introduction

Late sodium current (I_{Na}) is the residual I_{Na} flowing after the large peak I_{Na} during an action potential (AP) or voltage clamp (Fig. 1). Although under "normal" conditions it is a small current (~0.5%) relative to peak I_{Na}, it is sufficiently large during the AP plateau to affect the duration, and the flow over hundreds of milliseconds during the AP contributes more to Na^+ loading than the brief transient of peak I_{Na} [1]. With the recognition that the mechanism of action for the antianginal drug ranolazine was through a relatively specific block of late I_{Na}, a role for late I_{Na} as a mechanism for pathogenesis of angina, heart failure, and arrhythmia has attracted much attention [2,3]. This article offers perspectives and observations on late I_{Na} and human cardiac disease with selective references focusing on late I_{Na}, its causes and regulation, an account of pathogenesis of cardiac disease through electrophysiology and altered Na–Ca homeostasis, and a consideration of clinically available drugs that block or increase late I_{Na}.

The role of late I_{Na} in angina, arrhythmia, and heart failure is speculative and subject to on-going studies, and the reader is referred to key and recent comprehensive reviews of late I_{Na} and ranolazine that cover the wealth of experimental and clinical data [2–8] providing additional detail and supporting references.

Background

The recognition that late I_{Na} plays a role in cardiac physiology goes back to ~50 years, when it was shown that the selective Na^+ channel blocker tetrodotoxin shortened the AP plateau [9]. This late I_{Na} and its effect on the AP were subsequently studied as "window current" [10], "steady-state" current [11], "slow inactivation" current [12,13], "late current" [14], "slow current" [15], and "persistent current" [16]. As noted below, the characteristics and mechanisms for late I_{Na} are heterogeneous; therefore, the term "late I_{Na}" is preferred as the most general term not invoking particular mechanisms or characteristics. An important issue when reading the literature is to note how long after the depolarization late I_{Na} is measured. Because I_{Na} in cardiac tissue is subject to slow

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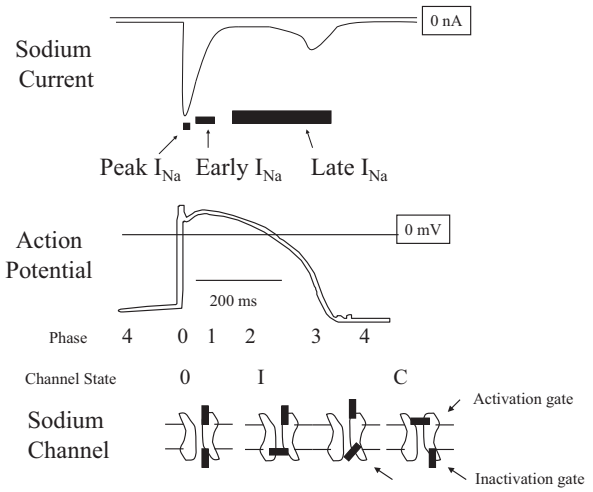

Fig. 1 – Peak, early, and late I_{Na}. Diagrams of cardiac sodium current (I_{Na}) action potential (AP), and sodium channel cartoon, lined up with time on the horizontal. Peak I_{Na} occurs in less than a millisecond and underlies the rapid upstroke or phase 0 of the AP. At this time, the activation gate and the inactivation gate on the channel are both open. Then over several milliseconds the current begins to decay, contributing to a notch in the AP called phase 1. At this time, some of the channels are inactivated (shown as "I" with the inactivation gate closed). There is no commonly accepted name for this phase of I_{Na} but here it is labeled "early I_{Na}." After several milliseconds I_{Na} normally decays to <1% of peak I_{Na}, but a residual current flows as late I_{Na} and this depolarizing current along with calcium currents supports phase 2 or the plateau of the AP. The mechanisms for late I_{Na} at the sodium channel level are multiple but can generally be thought of as incomplete inactivation. Eventually, activating potassium currents repolarize the membrane (phase 3 of the AP) and when the voltage decreases below the sodium channel threshold, the activation gate closes.

decay over tens of milliseconds, a measure of late I_{Na} at 10 ms will give a higher value than later measurement at 20 or 50 ms. Also note that for comparison purposes, late I_{Na} is often expressed as a percentage of the peak I_{Na} or normalized to cell size as measured by cell capacitance.

Several key features of late I_{Na} are important for understanding the clinical manifestations. An important biophysical distinction is the late I_{Na} produced by overlap of the voltage dependence of activation and inactivation to produce what is called "window current" that occurs over the voltage range of this overlap that affects AP duration. Window current is the consequence of the voltage dependence of more or less normal gating in the overall population of sodium channels and is regulated by the protein kinase C (PKC) pathway [17]. In contrast, increased late I_{Na} may involve a fundamental change or abnormality in the inactivation gate in a select population of channels. This abnormality may have diverse underlying causes and mechanisms. Another important feature of late I_{Na} addressed in more detail below is whether or not it is subject to "slow inactivation," which will lead to a frequency-dependent inactivation of the late I_{Na}. Finally, it is important to note that late I_{Na} is heterogeneous in amplitude by region in the heart [18]. Several comprehensive reviews [4,5] provide additional detail and references for these topics.

Sodium channel macromolecular complex

Cardiac I_{Na} flows through a channel formed by the α-subunit NaV1.5 encoded by the gene *SCN5A*. Although the α-subunit alone accounts for major features of I_{Na}, it is part of a macromolecular complex consisting of auxiliary subunits and associated channel interacting proteins or ChIPs. Identification of components of the macromolecular complex and how they regulate I_{Na} is a rapidly evolving field [19]. Although NaV1.5 underlies the majority of I_{Na}, other "non-cardiac" isoforms may make up an important part of cardiac I_{Na}. In particular, the nerve/brain isoforms NaV1.1 [20] and NaV1.8 [21] may underlie an important part of late I_{Na} in human heart. Other components of the complex that may play important roles in regulating late I_{Na} in human heart include α1-syntrophin (Snta1) [22], caveolin 3 (Cav3) [23], and calmodulin kinase 2(CaMKII) [24]. The β1 subunit [25,26] and β4 subunit [27] also play a role in late I_{Na}. The biophysical mechanisms by which α-subunit structure and interacting proteins in the complex affect late I_{Na} are not completely understood. Late I_{Na} is generally thought to be a modification of or failure in the inactivation process. A structure responsible for fast inactivation of I_{Na} resides in "IFM" residues on the DIII–DIV linker as a "ball" or "lid" and on the bottom of the S4–S5 linker as a receptor, but myriad mutations throughout the NaV1.5 topology cause long-QT syndrome type 3 (LQT3), so it seems that diverse perturbations in NaV1.5 structure are associated with late I_{Na}. A way to think of it is that the complex for inactivation is a fine-tuned precise machine, and there are many different ways to disrupt normal gating to make late I_{Na}. If this is true, a single final common structure–function pathway for the cell signaling and biophysical mechanisms for regulating and causing late I_{Na} may be elusive.

Causes of increased late I_{Na}

Increased late I_{Na} has been characterized under a wide variety of experimental conditions. Table 1 in a recent review [7] lists and references conditions, drugs, toxins, and diseases associated with increased late cardiac I_{Na}. Table 1 in this article lists causes most relevant to mechanisms and treatment of cardiac disease, along with possible mechanisms for their effect. It is important to note that these "causes" are not mutually exclusive but may be upstream or downstream elements in a regulatory or pathological pathway. For example, increased late I_{Na} in ischemia may be caused by acidosis and ischemic metabolites such as lysophosphatidylcholine (LPC), and late I_{Na} in LQT9 and LQT12 is caused by enhanced nitrosylation. Possible mechanisms (Table 1) at the cellular level (such as altered signaling pathways) for the increased late I_{Na} cardiac diseases are coming into focus, but as noted above, discovery of the mechanisms at the biophysical level appears less tractable.