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REVIEW: FRONTIERS IN PHARMACOLOGY

Inhibition of late sodium current to reduce electrical and mechanical dysfunction of ischaemic myocardium

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This commentary on the review by DA Saint in the current issue of the British Journal of Pharmacology focuses on the pathological role of late I_{Na} in the heart, the evidence supporting inhibition of late I_{Na} as a therapeutic target in ischaemic heart disease, and the therapeutic applications and challenges for development of new late I_{Na} inhibitors. Recent reports from a large clinical outcome trial (MERLIN) of ranolazine, a drug known to inhibit late I_{Na}, indicated that it was safe and reduced recurrent ischaemia and arrhythmic activity. In combination with other results indicating that inhibition of late I_{Na} reduces ischaemia, myocardial Ca^{2+} overload, and electrical and mechanical dysfunction when late I_{Na} is increased, the new clinical trial results suggest that reduction of cardiac late I_{Na} is safe and therapeutically beneficial.
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Keywords: late I_{Na}; angina; diastolic dysfunction; ischaemia; ranolazine; Ca^{2+} overload; sodium channel; heart failure; lusitropy

Abbreviations: AP, action potential; APD, action potential duration; DAD, delayed afterdepolarization; EAD, early afterdepolarization; I_{Na}, sodium current; LV, left ventricle; NCX, Na^+–Ca^{2+} exchange

Introduction

The review by David Saint of the properties of the cardiac persistent late sodium current (I_{Na}) (Saint, 2007), and of the potential therapeutic role(s) of drugs that inhibit this current, recognizes that late I_{Na} may be increased in ischaemic and failing hearts and thus may be of general pathologic importance in heart disease. The discussion of blockers of late I_{Na} in the review is timely, given the recent FDA approval of ranolazine for the treatment of chronic angina (the primary symptom of ischaemic heart disease) and the publication of results from a large clinical outcome trial with the drug (Morrow *et al.*, 2007; Scirica *et al.*, 2007).

Why is enhanced late I_{Na} pathologic?

Enhancement of late I_{Na} is pathologic because it increases the intracellular concentration of Na^+, Na^+–Ca^{2+} exchange (NCX), Ca^{2+} entry into myocytes and duration of the myocardial action potential (AP). The increase of Ca^{2+} entry may be of sufficient magnitude to cause Ca^{2+} overloading with mechanical (e.g., impaired ventricular diastolic relaxation and reduction of diastolic coronary blood flow) and electrical (e.g., early and delayed afterdepolarizations: EADs and DADs) dysfunction (Belardinelli *et al.*, 2006). Enhancement of late I_{Na} greatly increases Na^+ entry during phase 2 of the ventricular AP (Makielski and Farley, 2006). Because net outward current is small during phase 2, an enhanced late I_{Na} reduces repolarization reserve and increases AP duration (APD). When phases 2 and 3 are prolonged, Ca^{2+} and Na^+ channels may reopen, and the subsequent cation influx may lead to further APD prolongation and EADs. Spatial heterogeneity of prolongation of APD in the ventricle due to enhanced late I_{Na} may set the stage for triggered and re-entrant arrhythmias.

Enhanced late I_{Na} disrupts Na^+ and Ca^{2+} homeostasis. Sodium entry leads to increases of intracellular Na^+ concentration, reverse mode (3 Na^{2+} out for 1 Ca^{2+} in) NCX and Ca^{2+} entry. The increase of Ca^{2+} entry during phase 2 of the AP plateau may not only support systolic contraction, but also cause Ca^{2+} overload. Acute cellular Ca^{2+} overloading has negative consequences. Accumulation of Ca^{2+} by the sarcoplasmic reticulum is increased, but an elevation of both stored Ca^{2+} and cytosolic Ca^{2+} concentrations facilitates the occurrence of spontaneous

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sarcoplasmic reticulum Ca^{2+} release during diastole (Bers, 2001). Spontaneous release of Ca^{2+} from the sarcoplasmic reticulum during diastole increases NCX (Bers, 2001). NCX is electrogenic, and its operation in the forward mode (3 Na^+ in for 1 Ca^{2+} out) creates a transient inward current that can generate a DAD and triggered arrhythmic activity, as well as an aftercontraction (i.e., force production during diastole). Thus, both reverse (phases 1 and 2 of the AP) and forward (phases 2 and 3 and diastole) modes of NCX are enhanced subsequent to increases of late I_{Na} and intracellular [Na^+], although at different times during the cardiac cycle. The late I_{Na}-enhanced oscillatory increases and decreases of the forward and reverse modes of the electrogenic NCX may become electrically destabilizing and cause formation of DADs.

Elevation of the intracellular Ca^{2+} concentration secondary to an enhanced late I_{Na} in ventricular myocytes impairs diastolic relaxation, that is, slows active relaxation of the ventricle (a negative lusitropic effect). Maintenance of contractile tension during a prolonged period of active ventricular relaxation increases myocardial oxygen consumption and reduces coronary blood flow during left-ventricular (LV) isovolumic relaxation, when flow is normally at its peak. A reduction of diastolic coronary flow in a region of the myocardium with already reduced flow reserve only worsens the tenuous balance between oxygen supply and demand (see Figure 1 and Belardinelli *et al.*, 2006). An increase of late I_{Na} exacerbates the situation by facilitating AP prolongation, EADs and DADs. These acute electrical events are associated with increases in the cytosolic Ca^{2+} concentration, force production and delayed or reduced diastolic relaxation that further increase oxygen demand while concurrently reducing diastolic blood flow and myocardial oxygen supply. Thus, increases of late I_{Na} and intracellular Ca^{2+} worsen LV function. Furthermore, although the role of late I_{Na} in chronic calcium overloading is unknown, late I_{Na} is reported to be increased in myocytes from failing hearts and from post-infarction remodeled myocardium (Huang *et al.*, 2001; Undrovinas *et al.*, 2006). Heart failure appears to be a condition of chronic Ca^{2+} overloading that is associated with down-regulation of $I_{Ca,L}$, increased NCX, prolongation of APD, decreased contractility and a proarrhythmic state (Bers, 2001).

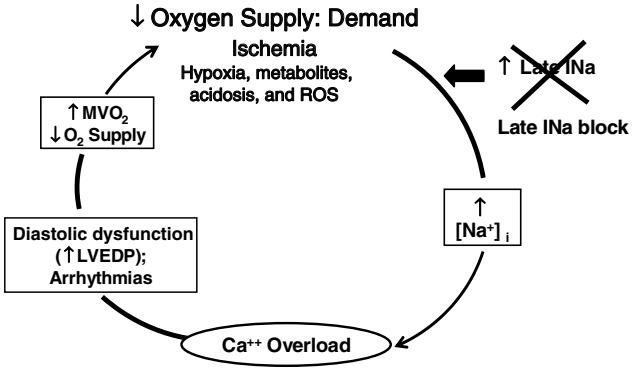

Figure 1 Block of late I_{Na} interrupts a deleterious positive feedback cycle during ischaemia by reducing [Na+]i-dependent calcium overload.

Regional differences in the magnitude of late I_{Na} in ventricular myocardium have been reported, and augmentation of these differences is proarrhythmic (Antzelevitch *et al.*, 1999; Antzelevitch and Belardinelli, 2006). In ischaemic and structurally abnormal hearts, it is doubtful that increases of late I_{Na} and cellular Ca^{2+} overloading occur simultaneously and equally throughout the ventricle. Consequently, cell-to-cell and regional dispersion of increases of late I_{Na} and Na^+-induced Ca^{2+} overloading during ischaemia may lead to focal regions of EAD and DAD formation that increase the dispersion of ventricular repolarization. These events alter the conduction and chronology of ventricular electrical (and mechanical) activity, facilitate triggered and re-entrant arrhythmic activity, prolong the time needed for relaxation of systolic contraction and reduce contractile efficiency and diastolic blood flow (oxygenation) in the myocardium.

Much evidence suggests that late I_{Na} is enhanced in ischaemia, although quantization of late I_{Na} in an intact, blood-perfused heart during ischaemia cannot be done. Myocardial-cell Na^+ content increases during ischaemia (Bers, 2001). Myocardial-cell Ca^{2+} overload and dysfunction caused by ischaemia and reperfusion can be prevented by blockade of membrane Na^+ channels or cardiac-specific ablation of NCX, thus implicating increased Na^+ entry into cells as a proximate cause of Ca^{2+} overload (Belardinelli *et al.*, 2006). Hypoxia is known to impair inactivation of Na^+ channels and increase late I_{Na} (Saint, 2006). Tissue hypoxia and reperfusion of ischaemic myocardium are reported to generate metabolites (e.g., palmitoyl-L-carnitine and lysophosphatidylcholine) and reactive oxygen/nitrogen species (e.g., hydrogen peroxide and nitric oxide) that increase late I_{Na} in ventricular myocytes.

The mechanism of action of ranolazine to reduce electrical and mechanical dysfunction of the ischaemic myocardium

Ranolazine, at concentrations within its therapeutic range ($\leqslant$10 μM), significantly reduces late I_{Na} and reverses or prevents the consequences of increase of late I_{Na} (Belardinelli *et al.*, 2006). Ranolazine reduces late I_{Na} in mouse myocytes in which late I_{Na} is enhanced due to expression of the long-QT syndrome 3 mutant sodium channel, ΔKPQ (Fredj *et al.*, 2006), in ventricular myocytes isolated from normal dogs and from dogs with heart failure (Undrovinas *et al.*, 2006), in guinea pig isolated ventricular myocytes exposed to anemone toxin-II or hydrogen peroxide (H_2O_2) (Song *et al.*, 2004, 2006) and in HEK293 cells expressing human $Na_V1.5$ channels (Rajamani *et al.*, 2007). The range of values of IC_{50} (potency) is 5.9–15 μM for ranolazine to reduce late I_{Na} in various preparations. Ranolazine (1–10 μM) reduced APD and temporal dispersion of APD, and abolished EADs of guinea pig isolated ventricular myocytes in the presence of either anemone toxin-II or H_2O_2, both of which increase late I_{Na} (Song *et al.*, 2004, 2006), thus supporting the concept that reduction of an increased late I_{Na} is anti-arrhythmic. Ranolazine (5–20 μM) reversibly and significantly shortened the APD of myocytes isolated from dogs with heart failure, in which late I_{Na} is increased, and reduced variability of APD

(Undrovinas *et al.*, 2006). Ranolazine decreased cellular Ca^{2+} overload caused by anemone toxin-II or ischaemia/reperfusion in rat isolated hearts, and it enhanced recovery of post-ischaemic LV function, coronary flow and coronary vascular conductance (Fraser *et al.*, 2006). As expected, ranolazine had no effect on intracellular diastolic Ca^{2+} concentration, Ca^{2+} transient amplitude, LV function, coronary flow or coronary vascular conductance during aerobic conditions (Fraser *et al.*, 2006). Ranolazine-mediated block of late I_{Na} was significantly reduced by mutation of a single amino-acid residue (F1760A) in the putative local anaesthetic binding site of the cardiac Na^+ channel $Na_V1.5$ (Fredj *et al.*, 2006). Thus, a putative site of 'binding' of ranolazine in the cardiac Na^+ channel has been identified. In sum, the above findings strongly suggest that ranolazine alters the pathophysiology associated with Na^+-dependent Ca^{+2} overloading in myocardium by inhibiting late I_{Na}.

The anti-ischaemic effects of ranolazine occur in the absence of haemodynamic changes. Although ranolazine has been reported to antagonize α_1- and β-adrenergic antagonist activity in radioligand binding and *in vitro* tissue assays (Letienne *et al.*, 2001), at therapeutic concentrations (1–10 μM), it does not cause bradycardia or hypotension in animals (Wang *et al.*, 1999) or in resting and exercising humans (Pepine and Wolff, 1999; Chaitman *et al.*, 2004a, b; Rousseau *et al.*, 2005). In dogs that are awake, ranolazine at steady-state concentrations $\leqslant$18 μM did not cause significant slowing of heart rate or lowering of arterial blood pressure and did not affect coronary blood flow, coronary vascular resistance or LV contractility (CV Therapeutics, 2003). These findings suggest that effects of ranolazine *in vivo* on haemodynamic parameters that are regulated by α_1- or β_1-adrenergic-mediated activity are not significant in normal dogs with intact autonomic nervous control mechanisms. Furthermore, ranolazine is cardioprotective in ischaemic protocols, wherein hearts are both electrically paced and perfused at constant rates, and in models using cytotoxic ischaemic metabolites (Belardinelli *et al.*, 2006), wherein selective β-adrenergic-receptor-blocking drugs are not cardioprotective. Thus, the data available to date do not indicate any contribution of the sympatholytic action of ranolazine to its anti-ischaemic and anti-anginal effects.

Inhibitions by ranolazine of ion currents other than late I_{Na} do not appear to be responsible for the anti-ischaemic and anti-anginal effects of the drug. Inhibition of I_{Kr} is likely responsible for the prolongation of the QT interval by ranolazine, but blockade of I_{Kr} has not been shown to reduce ischaemic damage or angina. With other drugs, I_{Kr} block has been associated with proarrhythmic activity, whereas ranolazine reduces both atrial and ventricular arrhythmic activity in humans (Scirica *et al*. 2007). The significance of a reported inhibition by ranolazine of late I_{Ca} (Antzelevitch *et al.*, 2004) is unknown. Finally, ranolazine (1–10 μM) does not increase the duration of the QRS interval (i.e., does not slow the conduction of electrical activity), a finding consistent with its low potency to reduce peak I_{Na} in the ventricle. The potencies (IC_{50} values) of ranolazine to inhibit peak I_{Na} in ventricular myocytes isolated from normal dogs and from dogs with heart failure were 294 and 244 μM, respectively (stimulation rate, 0.1 Hz; holding potential, −140 mV) (Undrovinas *et al.*, 2006). In the same study, the IC_{50} for ranolazine to inhibit late I_{Na} was 6.5 μM. These findings are consistent with the results of a large clinical outcome trial indicating that ranolazine does not increase mortality and reduces arrhythmic activity (Morrow *et al.*, 2007; Scirica *et al.*, 2007).

Results of a recent 'proof-of-concept' study of patients with a long-QT syndrome 3 caused by a KPQ deletion in $Na_V1.5$ revealed that ranolazine (1.8–4 μM) significantly shortened the QTc interval and improved measures of the rate of diastolic relaxation of the left ventricle (data on file at CV Therapeutics Inc., Palo Alto, USA). In a different study of patients with a previous transmural myocardial infarction and with ejection fractions ranging from 13–55%, ranolazine improved diastolic function of the non-infarcted myocardium (Hayashida *et al.*, 1994). These results are consistent with the hypothesis that enhanced late I_{Na} and its phenotypic manifestations are normalized by therapeutic concentrations of ranolazine in humans, and they provide compelling evidence that ranolazine inhibits late I_{Na} of the human heart *in vivo*.

What are the potential therapeutic applications for an inhibitor of late I_{Na}?

Both preclinical experience with late I_{Na} inhibitors and the clinical experience with ranolazine indicate that inhibition of late I_{Na} improves function of the ischaemic myocardium. Cardiac angina, a symptom of myocardial ischaemia, is relieved by ranolazine (Chaitman *et al.*, 2004a, b; Rousseau *et al.*, 2005). The anti-ischaemic effect of ranolazine, demonstrated in humans by an increased time to 1-mm ST-segment depression during an exercise tolerance test (Pepine and Wolff, 1999; Rousseau *et al.*, 2005), and improved diastolic function (Hayashida *et al.*, 1994) are the likely explanations for the action of ranolazine to alleviate angina in patients with ischaemic heart disease. The observation that late I_{Na} is increased in myocytes from failing hearts of dog suggests that late I_{Na} may be increased in heart failure, and thus heart failure may yet prove to be another indication for late I_{Na} inhibitors (Maltsev *et al.*, 2007). Inhibition of late I_{Na} reduces the prolonged ventricular APD (i.e., the QT interval), dispersion of repolarization, arrhythmic activity, Ca^{2+} loading of myocardial cells and diastolic dysfunction in heart failure (Undrovinas *et al.*, 2006). Diastolic heart function is improved in ΔKPQ long-QT syndrome 3 patients (as noted above), indicating that enhanced late I_{Na} may contribute to, and reduction of late I_{Na} may alleviate, diastolic dysfunction in some patients. Other potential therapeutic applications of late I_{Na} inhibitors are neuronal and muscular disorders in which mutations in various non-cardiac Na^+-channel isoforms (e.g., $Na_V1.7$ and $Na_V1.4$) are known to underlie the pathological phenotype, as in neuropathic pain, epilepsy, sudden infant death syndrome and muscular paralysis. The past 10 years have seen remarkable advancements in the identification of pathological effects of enhanced late I_{Na}, causal mechanisms of Na^+ channelopathies and disease states in which late I_{Na} is enhanced. We speculate that increases of late I_{Na} will be

found to contribute to impairment of the functional status of excitable cells in many other situations. This is not unexpected, given that excessive late I_{Na} may disrupt the homeostasis of Na^+- and Ca^{2+}-ion concentrations that maintain normal function of myocardial, neural, muscular and secretory cells. Current evidence of a role for reactive oxygen species to increase late I_{Na} (Song *et al.*, 2006) suggests that enhancement of late I_{Na} may be a common phenomenon in processes such as ischaemia and aging.

What are the challenges in developing an inhibitor of late I_{Na}?

Understanding of the roles of late I_{Na} in physiology and disease is still unfolding, and development of inhibitors of this current poses several challenges. Ion-channel-blocking drugs used for suppression of cardiac arrhythmias are often unselective for their given ion-channel target (e.g., amiodarone). Na^+-channel antagonists at present in therapeutic use (e.g., class I anti-arrhythmic agents), unlike many drugs (e.g., ligands of G-protein-coupled receptors), typically bind to their ion-channel targets with micromolar rather than nanomolar affinity. The goals of high potency, efficacy and selectivity that normally drive drug development may or may not be appropriate to find useful, safe blockers of late I_{Na}. In the final analysis, inhibition of ion-channel function should perhaps be rather subtle and readily reversible, and the combination of ion-channel effects of a drug may determine its success or failure.

When inhibiting cardiac late I_{Na}, it is preferable to avoid inhibition of peak I_{Na}, in the heart as well as in other excitable tissues. Drugs (e.g., flecainide, encainide) that inhibit peak I_{Na} in the ventricle were associated with increased mortality in the Cardiac Arrhythmia Suppression Trial (Echt *et al.*, 1991). This finding suggests that late I_{Na}-blocking drugs must not alter Na^+ channel opening and conductance during the AP upstroke (phase 0), to avoid slowing of impulse conduction and reduction of the wavelength of a re-entrant circuit. Reduction of peak I_{Na} by ranolazine increases with increased frequency of stimulation and decreased membrane potential and appears to be tissue (atria vs ventricle; Burashnikov *et al.*, 2007), isoform (i.e., $Na_V1.1$–1.9) and mutation (e.g., late I_{Na}s of various $Na_V1.5$-mutated channels are differentially responsive to ranolazine) dependent.

Inhibition of the *HERG* current I_{Kr} is problematic, and many drugs, including Na^+-channel blockers, reduce this current. Reduction of I_{Kr} is frequently associated with an increased incidence of torsades de pointes, a potentially fatal ventricular tachycardia. Reduction of late I_{Na} offsets the reduction of repolarization reserve and the increase of APD and antagonizes the induction of EADs caused by I_{Kr} blockers. Ranolazine reduces I_{Kr} and prolongs, although modestly, the APD, but its effect is not rate (use) dependent, and it does not have proarrhythmic activity. The twofold greater potency of ranolazine to inhibit late I_{Na} than to inhibit I_{Kr} may contribute significantly to the anti-arrhythmic effects and absence of proarrhythmic effects of the drug. In post-myocardial infarction patients without ST-segment elevation but with a QTc interval greater than 450 ms, ranolazine significantly ($P<0.001$) reduced the incidence of ventricular tachycardia ($\geqslant$8 beats at $\geqslant$100 bpm, lasting less than 30 s) during 7 days of Holter monitoring by 47% compared with placebo (Scirica *et al.*, 2007).

Lastly, how much reduction of cardiac late I_{Na} is safe? At therapeutic concentrations, ranolazine reduces late I_{Na} by about 50%. Would more be better? The answer may depend on the role of late I_{Na} in normal cardiac function. For example, Purkinje fibres have a greater late I_{Na} than other cells in the heart, and the duration of the Purkinje fibre AP is significantly shortened upon late I_{Na} block. Excessive shortening of the Purkinje fibre APD may increase the risk of re-entry. Similar concerns with blockade of physiological roles of late I_{Na} in other tissues counsel caution in the development of potent drugs for incompletely understood targets such as late I_{Na}. Nevertheless, the observation that ranolazine reduces ischaemia/angina, diastolic dysfunction and arrhythmic activity in a safe manner suggests that reduction of late I_{Na} is therapeutically beneficial. However, scientific understanding of late I_{Na} is in its infancy, and we remind ourselves that 'All scientific work is liable to be upset or modified by advancing knowledge' (Hill, 1965).

Conflict of interest

John C Shryock and Luiz Belardinelli are employees of CV Therapeutics Inc., which markets Ranexa (ranolazine).

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