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COMMENTARY

Ranolazine and late cardiac sodium current – a therapeutic target for angina, arrhythmia and more?

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Ranolazine is a new antianginal drug approved for clinical use in the United States in January 2006. A study published in this same issue of the *British Journal of Pharmacology* characterizes ranolazine block of late sodium current caused by the long QT syndrome 3 mutations. This commentary discusses the implications of that study and the background and implications for block of late cardiac sodium current in general.
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Abbreviations: I_{Na}, sodium current; I_{NaL}, late sodium current

Ranolazine – a selective blocker of late Na current (I_{NaL})

The paper by Fredj *et al*. (2006), in this issue of *British Journal of Pharmacology* uses cloned and expressed cardiac Na channels (SCN5A) in HEK cells, and in native cardiac myocytes from a transgenic mouse arrhythmia model, to further our knowledge of the interaction of ranolazine with SCN5A. The major new finding is the evidence that ranolazine interacts with SCN5A at the same site on the domain IV S6 as other local anesthetic and antiarrhythmic drugs (Ragsdale *et al*., 1994). This places ranolazine firmly in the category of typical Na channel blocking drugs, but with a distinct profile in regard to that it preferential block of I_{NaL} relative to peak sodium current (I_{Na}). Ranolazine block of I_{NaL} was 10 times more potent than block of peak I_{Na} for two different SCN5A mutations that cause inherited long QT syndrome (LQTS) type 3 (LQT3) (Fredj *et al*., 2006). These results extend previously published results showing a relatively selective ranolazine block of I_{NaL} in myocytes using ATX-II to induce I_{NaL} (Antzelevitch *et al*., 2004; Song *et al*., 2004). Selective block of I_{NaL} over peak I_{Na} has been shown previously for drugs such as mexiletine (Dumaine *et al*., 1996) and flecainide (Nagatomo *et al*., 2000), but ranolazine appears to be even more selective. For example, flecainide was only three times more potent in blocking I_{NaL} compared to peak I_{Na} (Nagatomo *et al*., 2000). Ranolazine also shortened action potential duration (APD) in native cardiac myocytes just as it did for the ATX-II model (Antzelevitch *et al*., 2004; Song *et al*., 2004). These data provide support for a possible role for ranolazine in treating LQT3 patients where I_{NaL} may play a role in triggered cardiac arrhythmia, and also perhaps in acquired arrhtymia symdromes in which I_{NaL} may play a role.

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Ranolazine as antianginal drug

Ranolazine was developed and will soon come into clinical use as an antianginal medication (Chaitman *et al*., 2004a, b). Clinically, ranolazine has been shown to be distinct from other conventional antianginal agents such as beta blockers, calcium channel blockers, and nitrates in that it did not have a clinically significant effect on heart rate or blood pressure (Chaitman *et al*., 2004a, b). This implies a molecular mechanism of action that may be distinct from these conventional agents. Initial attention was directed at investigations of ranolazine to partially decrease fatty acid oxidative metabolism (pFOX inhibition) (McCormack *et al*., 1998). This effect, however, occurred at levels greater than the therapeutic range ($>10\,\mu$M). Later investigations of the electrophysiological effects of ranolazine found a potent and selective block of I_{NaL} in heart at concentrations ($\sim 6\,\mu$M), well within the therapeutic range (Antzelevitch *et al*., 2004). This concentration was also lower than the blocking effects of ranolazine for other cardiac ion channels (Antzelevitch *et al*., 2004) and lower than the concentration required for the pFOX effects (McCormack *et al*., 1998). Could this block of I_{NaL} be a mechanism of action for the antianginal effects?

Changes in ion homeostasis in acute ischemia are immediate, and the mechanisms are complex. Intracellular sodium and intracellular calcium rise in parallel along with internal protons and extracellular potassium (Steenbergen *et al*., 1993). The increase in calcium may be caused at least in part by sodium induced calcium overload through a decreased activity or actual reversal of the sodium–calcium exchanger, although the role for internal sodium in this process has been questioned recently (Imahashi *et al*., 2005), and protons and sodium–hydrogen exchange may also play an important role (Anderson *et al*., 1990). In any event, the rise in intracellular calcium in myocardial cells increases diastolic wall tension and increases end-diastolic pressure, which increases oxygen demand while at the same time decreases oxygen supply because of decreased diastolic flow. In the laboratory setting,

cardiac I_{NaL} has been shown to be acutely increased in conditions found in ischemia such as hypoxia (Ju *et al*., 1996) and increased concentrations of ischemic metabolites such as lysophosphatidylcholine (Undrovinas *et al*., 1992; Shander *et al*., 1996). Belardinelli *et al*. (2004) proposed that ranolazine block of late I_{NaL} ameliorates ischemia induced accumulation of intracellular Na, preventing Na-induced calcium overload and the subsequent deleterious effects on left ventricular end-diastolic pressure that exacerbates angina.

Ranolazine as antiarrhythmic drug?

The potential for ranolazine as an antiarrhythmic agent is apparent from its Vaughan Williams Class I sodium channel blocking properties. Block of I_{NaL} by ranolazine would be expected to shorten APD and the QT interval on ECG, but ranolazine has a minor prolonging effect on APD under control conditions (Antzelevitch *et al*., 2004; Fredj *et al*., 2006), and studies have reported a small prolongation of the QT interval in experimental models (Antzelevitch *et al*., 2004) and in patients (Chaitman *et al*., 2004a, b). As ranolazine has no effect on the QRS duration (Chaitman *et al*., 2004a, b), it would probably best be placed in the Class 1B Harrison modification (Harrison, 1983). The small amount of prolongation observed probably results from the block of the delayed rectifier potassium channels (Antzelevitch *et al*., 2004), and the prolonging effect of potassium channel block is mitigated by I_{NaL} block. It is important to note that ranolazine even at high doses does not induce early after depolarizations (EADs) that may underlie triggered tachyarrhythmia (Song *et al*., 2004) and no torsades de pointes has been observed in experimental tissue models (Antzelevitch *et al*., 2004; Schram *et al*., 2004) or so far in patients (Chaitman *et al*., 2004a, b). The negligible blocking effects of ranolazine on peak and early I_{Na} at therapeutic concentrations also suggests that a 'loss of function' mechanism for proarrhythmia would not apply. Clinical and basic data suggest no proarrhythmic effects for ranolazine, but what about antiarrhythmic effects? When EADs are induced by increased I_{NaL} in the presence of ATX-II, ranolazine shortens APD and eliminates EADs (Antzelevitch *et al*., 2004; Song *et al*., 2004; Wu *et al*., 2004). Although no EADs were observed in the present study (Fredj *et al*., 2006), ranolazine did shorten APD in the transgenic mouse LQT3 myocyte model. How useful might I_{NaL} block be in acquired arrhythmia? As mentioned above, I_{NaL} is increased in acute ischemia and the resultant electrophysiological abnormality may cause arrhythmia. Moreover, cardiac I_{NaL} is increased in heart failure (Undrovinas *et al*., 1999; Valdivia *et al*., 2005), where it has been proposed to be arrhythmogenic. Ranolazine did offer protection from ventricular fibrillation in an animal pharmacological model (Gralinski *et al*., 1994).

Remaining questions and further studies

The antiarrhythmic efficacy of ranolazine in humans is unknown, but it is an intriguing possibility in LQT3 patients as demonstrated by this study (Fredj *et al*., 2006), but it is also an intriguing possibility for acquired arrhythmia in ischemia and heart failure. Further clinical studies are needed to address this issue. In animal models, a potential for myocardial protection has been suggested (Black *et al*., 1994). An ongoing study of ranolazine in acute coronary syndrome addresses this issue (Marzilli, 2005) may test this in humans.

At the basic and preclinical level, Fredj *et al*. (2006) have shown the site of interaction of ranolazine on SCN5A, but we do not yet know the mechanism of the preferential block of I_{NaL} in general, or for the special potency of ranolazine realitive to other SCN5A blocking drugs in particular. The existing studies have used ATX-II as a model for increase I_{NaL}, and now in this study the relatively uncommon LQT3 mutations. These studies do provide 'proof of principle', but additional studies of ranolazine in even more clinically relevant models such as ischemia and heart failure (Undrovinas *et al*., 2005) will be important. It has only been two short years since block of I_{NaL} has emerged as an established hypothesis for ranolazine action. The study by Fredj *et al*. (2006) represents an important advance in our knowledge of the mechanism of action of this drug and its interesting therapeutic potential. Additional study at the basic, preclinical and clinical levels is warranted to reveal its full potential and underlying mechanism of action.

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