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COMMENTARY

Persistent (current) in the face of adversity . . . A new class of cardiac anti-ischaemic compounds on the horizon?

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Although a persistent component of the sodium current (INaP) was described in cardiac tissue about three decades ago, its physiological role and potential as a therapeutic target was not immediately apparent. Subsequent demonstrations that INaP is enhanced by hypoxia and ischaemia, and that Na^+ influx via INaP may contribute to cellular damage, diastolic dysfunction and arrhythmias during ischaemia and reperfusion, raised interest in INaP as a target for anti-ischaemic drugs. Several agents have now been developed to clinical stages, which have INaP block as either their main action, or as a useful co-effect. In this issue of the *British Journal of Pharmacology*, Vacher *et al.* report the anti-ischaemic actions of F15845, which appears to exhibit the most selective block of INaP yet described. Its efficacy in animal models of angina raises the prospect of new, specific, INaP blockers that may represent a largely unexploited opportunity for a new class of anti-ischaemic compounds.
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Abbreviations: INaP, persistent sodium current; INaT, transient (voltage-dependent) sodium current; NCX, sodium-calcium exchanger; NHE, sodium-hydrogen exchanger

It first became apparent that the sodium current, INa, has a persistent (i.e. non-inactivating) component almost 30 years ago. In Purkinje fibres, low concentrations of tetrodotoxin (TTX) [3.3×10^{-8}M, well below those that block the rapidly inactivating, transient sodium current (INaT)] were shown to shorten the action potential (Coraboeuf *et al.*, 1979), implying the existence of a sodium current flowing throughout the duration of the action potential. This TTX-sensitive current was subsequently shown directly by voltage clamp and the channels responsible revealed by patch clamp. The current has now been directly observed in rat, mouse, rabbit and human ventricle cells (Saint, 2008). However, at the time it was first observed, the physiological role of this current was not apparent – persistent sodium current (INaP) normally has an amplitude of about 0.5% of peak INaT, and it was not clear how such a comparatively small current could be important. As a consequence, INaP, in the cardiac context at least, languished for want of a physiological or pathophysiological role. This started to change when it was demonstrated that the persistent current was enhanced by mutations in Na^+ channels, which were also linked to serious clinical arrhythmias (Marban, 2002), and, perhaps more far reaching, by demonstrations that INaP was enhanced in hypoxia and ischaemia (Ju *et al.*, 1996). These latter results suggested an important role for INaP in the pathophysiology of ischaemia. Indeed, INaP has now been implicated as one of the culprits in the cascade of events leading to cellular calcium overload and subsequent cellular damage and/or arrhythmias.

During ischaemia and reperfusion, increased $[Na^+]_i$ reduces the Na^+ gradient available to the sodium-calcium exchanger (NCX), leading to reduced calcium pumping (or, *in extremis*, reversal of NCX producing a calcium influx) – the 'coupled exchanger' theory (Tani and Neely, 1989). The increase in $[Na^+]_i$, is due to a combination of reduced sodium pump activity and increased sodium-hydrogen exchanger (NHE) activity. However, the observation that TTX can attenuate the rise in $[Na^+]_i$ and the consequences of ischaemia suggests that a good portion of the Na^+ influx is occurring through INaP channels (Eigel and Hadley, 1999). It has also been suggested that some of the beneficial effect of NHE blockers in this situation is due to block of INaP (Williams *et al.*, 2007). This involvement of INaP in the genesis of ischaemic and reperfusion damage (and possibly arrhythmias) has led to increased

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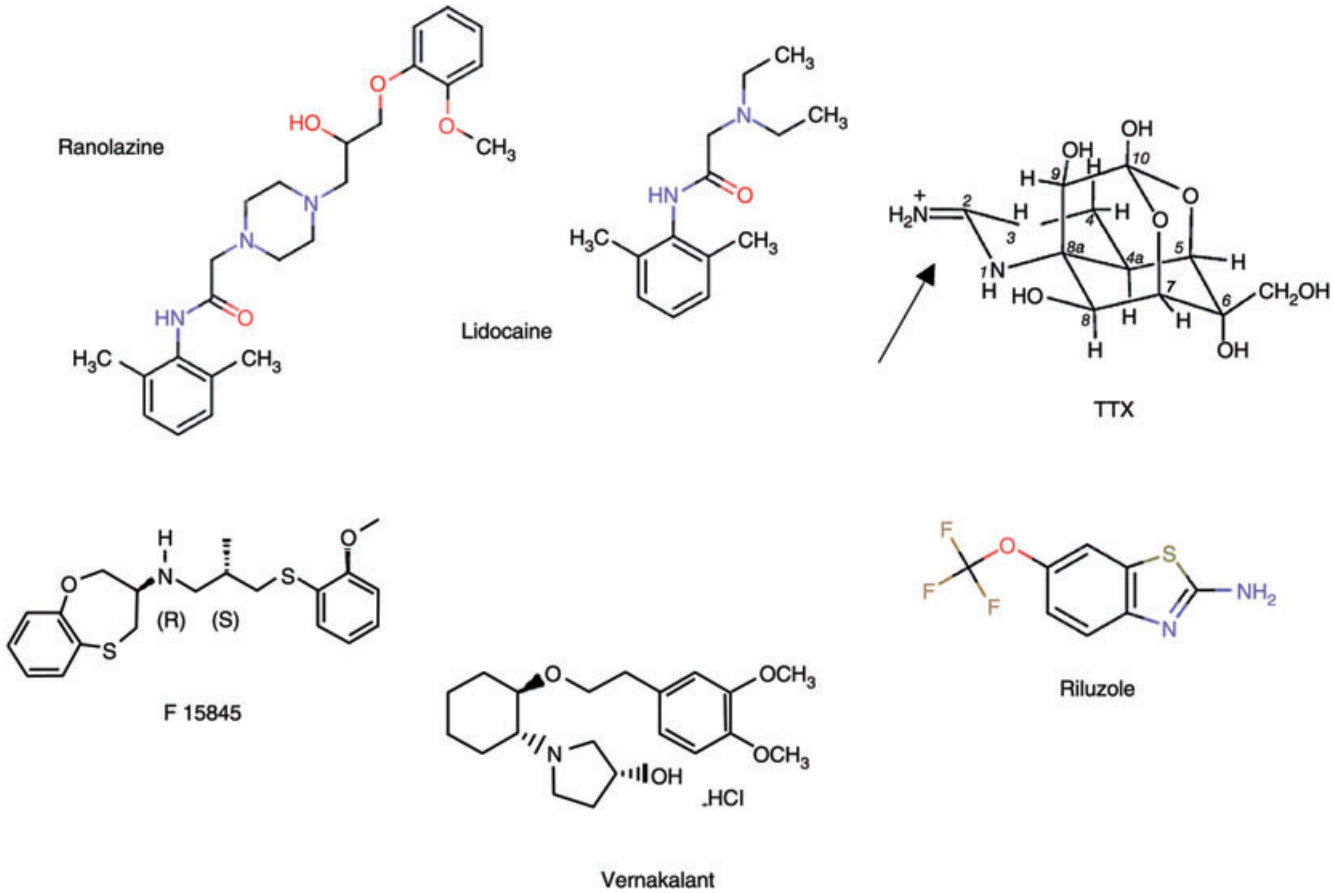

Figure 1 Compounds that show relative selectivity for block of persistent sodium current (INaP) over transient sodium current (INaT). Tetrodotoxin (TTX) has a guanidino-group (arrowed), which is similar to the combined tertiary and secondary amines in lidocaine and ranolazine. F15845 and vernakalant have secondary or tertiary amines. TTX shows reasonable selectivity for INaP over INaT; lidocaine is about one order of magnitude more selective for INaP. Ranolazine and vernakalant show some selectivity for block of INaP over INaT, but block other channels with similar potencies also. F15845 appears to be about an order of magnitude different in EC_{50} for INaT and INaP block [10^{-5}M blocks INaT by about 25% and INaP (induced by veratridine) by about 75%], with little block of other ion channels. Riluzole has been reported to preferentially block INaP over INaT in neuronal cells.

interest in the development of selective blockers of INaP as therapeutic tools.

However, tailoring selectivity of block of INaP over INaT or other ion channels has been difficult. TTX and lidocaine show some selectivity (Ju *et al.*, 1992; Saint *et al.*, 1992), but more selective compounds have proved elusive. Ranolazine is reasonably selective, but blocks other channels also (Antzelevitch *et al.*, 2004). Interestingly, the structures of compounds, which show selectivity for block of INaP over INaT, have little in common (Figure 1). The lack of highly selective compounds has impeded progress, although a serendipitous block of INaP by compounds developed to target other channels (such as vernakalant) has led to suggestions that a block of INaP might be beneficial in producing an anti-torsadogenic effect (by shortening the action potential), which can counteract the effect of IK_r block (Orth *et al.*, 2006). One therapeutic area where block of INaP may be useful is angina, and ranolazine has reached the clinical stage of development as an anti-anginal, with INaP block as its purported mode of action.

In this issue of the *British Journal of Pharmacology*, Vacher *et al.* (2009) present results on another compound under development (in Phase II), F 15845. In human $Na_v1.5$ (SCN5A) channels expressed in HEK 293 cells, F15845 blocked INaP at 10 μmol L^{-1}, without substantially affecting the peak INaT. The small amount of block of peak INaT may be explained by the shift of the inactivation curve for INaT by about 10 mV in the hyperpolarizing direction. This result is similar to that seen with lidocaine and raises the possibility that the apparent selectivity of compounds for INaP may be explainable by a combination of state-dependent binding and a non-absorbing inactivation state of the channel. It is, however, difficult to explain their finding that the block of INaP appears to depend on holding potential – how can the channel 'remember' the potential before the step depolarization? (Vacher *et al.*, 2009). A similar explanation had been proposed to account for the selectivity of TTX for INaP in a population of otherwise only weakly blocked channels, although TTX does not shift the inactivation curve of INaT. To date, no biophysical/gating models have been developed that can satisfactorily explain selective INaP block where INaP arises from a single population of channels, although the field is ripe for such an insight. Such an insight could also usefully shed light on the block of veratridine-induced INaP, which Vacher *et al.* (2009) show is blocked by F15845 with about

the same potency and intensity as 'native' INaP. While veratridine- (or other toxin-) induced INaP has been used for many studies of the effects of INaP, it has been remarked that sodium channels modified by toxins may not exhibit the same properties as INaP channels induced by hypoxia or ischaemia (Saint, 2008).

The inhibition of INaP by F15845 seems relatively selective – block of a range of other ion channels was tested, and found to be much less (although still present), reinforced by the finding that 10 μmol L^{-1} F15845 did not alter action potential morphology and had only minor effects on heart function. In this respect, F15845 is much more selective than other agents such as vernakalant and ranolazine, both of which block other channels with similar potencies to INaP. TTX, of course, is highly selective for sodium channel block over other types of ion channels.

F15845 was protective in a global ischaemia model (Vacher *et al.*, 2009); diastolic contracture induced by cessation of perfusion in an isolated guinea-pig heart was greatly reduced. This would be expected from its action to reduce INaP as similar results have been reported with TTX (Eigel and Hadley, 1999) and are consistent with the idea that INaP contributes to the cellular $[Na^+]_i$ load (and consequent $[Ca^{++}]_i$ load) during ischaemia. Sadly, Vacher *et al.* (2009) did not in this paper examine the effectiveness of F15845 on reperfusion damage. The prediction would be for this compound to be highly effective here also.

F15845 also showed good activity in both demand and supply models of angina. In both, F15845 reduced ST segment elevation. Similar results have been shown for ranolazine, which was developed as an anti-anginal before its block of INaP was fully explored. In the case of ranolazine, the issue of whether its anti-anginal effect was due to inhibition of INaP, or due to some other pharmacodynamic effect was unclear. The actions of F15845 seem less ambiguous in this regard. It is also not clear that INaP is substantially increased under the conditions of hypoxia/ischaemia prevailing in the myocardium during angina (which are presumably relatively mild compared with conditions during global ischaemia or coronary occlusion in experimental models or human myocardial infarction). Part of this lack of knowledge is due to the difficulty of assessing precisely the degree of hypoxia in the myocardium during angina, and whether this is sufficient to induce a substantial increase in INaP (and whether this can contribute to calcium overload/diastolic dysfunction in a still partially perfused myocardium). Again, however, the results of Vacher *et al.* (2009) seem to provide convincing evidence that this is indeed the case. What is needed now for an entirely convincing case to be made is a demonstration of the magnitude of INaP in the myocardium during conditions that produce angina, and a direct demonstration that blocking INaP under such conditions relieves ST segment elevation and or diastolic dysfunction. This will be difficult and perhaps impossible as measurement of INaP usually means patch clamping cells, while measuring ST segment elevation and diastolic function requires a whole heart.

Nevertheless, the gap between theory and a therapeutic application of INaP blockers appears to be closing rapidly. The clinical trial results of ranolazine are promising, and it will be interesting to see what transpires with F15845. We can, I think, expect to see a flurry of newer agents with INaP as a therapeutic target for various ischaemia-related cardiac conditions over the next few years.

Conflict of interest

David Saint is CEO of NeoViva Pty Ltd, an Australian private company developing anti-ischaemic compounds.

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