Editorial

Is cardiac $I_{Ks}$ a relevant drug target?

Michael J. Curtis

Cardiovascular Research, The King’s Centre for Cardiovascular Biology and Medicine, The Rayne Institute, St Thomas’ Hospital, London, SE1 7EH, UK

Received 22 December 2003; accepted 2 January 2004

See article by Nakashima et al. (pages 705–714) in this issue.

It is with pleasure that I write a commentary on a new work from Stanley Nattel’s laboratory. Nakashima et al. (Cardiovascular Research, this issue) have examined the actions of a relatively selective $I_{Ks}$ blocker on a variety of cardiac electrophysiological variables in anesthetized dogs. There is an important underlying question driving this work, namely: to what extent does $I_{Ks}$ represent a potential target for modulation of cardiac rhythm by drugs? Modulation, it should be noted, encompasses pro-arrhythmic as well as antiarrhythmic actions.

Since the first full characterization of $I_{Ks}$ as a component of the composite current, $I_K$, it has been clear that drugs differ in their selectivity for $I_{Ks}$ versus its cohabitee in repolarization, $I_{Kr}$ [1]. The number of relatively selective $I_{Ks}$ blockers developed over the years as antiarrhythmics far outweighs the number of relatively selective $I_{Kr}$ blockers, owing in part to the use of D-sotalol as the prototype containing the presumed pharmacophore that has directed the synthesis of agents such as dofetilide [2]. Likewise, and perhaps not unconnectedly, $I_{Kr}$ has been the focus for concern in the field of torsades de pointes-susceptible preparations. Parallel transgenic approaches are problematic owing to the underlying peculiarities inherent in mouse cardiac repolarization, and in the electrophysiology of the heart of this newly favoured species in general (peculiarities that result in their being, for example, no publications to my knowledge that report ventricular fibrillation occurring in murine hearts during regional ischaemia). Single cell work using muscle strips or cardiomyocytes is of interest [3,4]. However, the influence of the syncytium, the heart rate, circulating hormones and other factors mandates the use of in vivo preparations for determining the true role of $I_{Ks}$. A conscious primate would be the most ideal pre-clinical preparation. Ethics and cost, however, prevail. In the Nakashima study, a compromise preparation (anesthetized dog) was chosen.

In the absence of a suitable transgenic preparation, and in the face of the technical restrictions imposed by an intact beating heart in vivo that limit scope for gaining a direct measure of channel activity and function, the best remaining avenue of investigation for testing the role of an ion channel in cardiac homeostasis is an in vivo pharmacological approach (use of drugs to block or activate specific targets in whole animals). In this regard, it is essential that the chosen pharmacological tool is specific and selective for the study target. The conclusions of the present paper rest on the integrity of HMR 1556 as a tool to probe $I_{Ks}$. In view of it having no known molecular target promiscuity over a reasonable concentration range, and in the light of the present and previously published findings (which are reiterative), there are no obvious concerns about HMR 1556 meaning that Nakashima et al. have added value to the knowledge body, although future discoveries may conceivably change this.

The Nakashima et al. data are interesting. It would appear that $I_{Ks}$ plays a role in repolarization that may become markedly accentuated in the presence of $I_{Kr}$ dysfunction. This confirms what would seem to be intuitive, and accords with the concept of repolarization reserve.
The relevance of the findings to antiarrhythmic drug development may be debatable. However, the relevance to drug-induced torsades de pointes is more apparent, and the findings are potentially alarming: with a compromised $I_{Kr}$, the threshold for $I_{Kr}$-induced torsades de pointes might be expected to be reached much more easily. The role of $I_{Ks}$ in drug-induced torsades de pointes has yet to be fully explored. Therefore the important message to me from the study, although perhaps being not the most obvious focus of the work, is that $I_{Ks}$ may require more close attention in future drug safety evaluation.

It is noteworthy that the prevailing obsession with $I_{Kr}$ appears to be beginning to recede. There are suggestions that other repolarising currents need to be factored into the equation, since selective $I_{Kr}$ blocking interventions are less proarrhythmic than repolarization-altering interventions that also fundamentally alter action potential shape as well as duration [5]. Moreover, it has been shown that the risk of torsades de pointes with a range of heterogenous drugs of a common therapeutic class correlates better with threshold concentration for APD widening than simply with $I_{Kr}$ blocking potency [6]. Thus $I_{Kr}$ is not the beginning and the end.

The present findings differ quantitatively but not qualitatively from those of Varro et al. [3]. Nakashima et al. rightly attribute the discrepancy to differences in model (not least the influence of the setting: in vivo vs. in vitro). This is important for two reasons. First, the findings from Varro et al. [3] and Nakashima et al. broadly point in the same direction, which would suggest that they are probably correct. Second, they emphasize that in this area, as with so many areas in biology, relevance of preclinical findings to human physiology and pathophysiology can be speculated but never confidently anticipated. This speaks to the general relevance of preclinical research (even that using human cultured cells). In other words, any target for therapeutic or adverse manipulation postulated from preclinical studies may or may not be a relevant target, and clinical relevance can be ascertained only by clinical studies. All we get from preclinical investigation is hints (albeit, sometimes very good hints).

Time will tell whether $I_{Ks}$ is a relevant target for suppression of atrial tachyarrhythmias, or its block an important trigger for torsades de pointes. The present investigation provides good reason for further study.

References