PERSPECTIVES

Oxidative stress fine-tunes the dance of hERG K^+ channels

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The rhythm of the heartbeat is tightly controlled by the carefully choreographed opening and closing of more than a dozen different types of ion channels. This system is remarkably resilient but when it fails, the ensuing chaotic electrical activity or arrhythmia, if sustained for more than a few minutes, can have lethal consequences. This may occur when there is a significant reduction (or increase) in the activity of a single ion channel component as, for example, occurs in the rare inherited arrhythmia syndromes. It can also occur when the system is subjected to a pathological stimulus that overwhelms the inbuilt safeguards in the system. In recent years we have made significant progress in understanding how gross defects in ion channel function contribute to the genesis of arrhythmias in monogenic arrhythmia syndromes. The challenge now is to use this knowledge to help understand how more subtle changes in ion channel function contribute to the increased risk of arrhythmias in the more common acquired arrhythmia syndromes such as those that occur during oxidative stress (Van Wagoner, 2008).

Oxidative stress is known to affect many components of cardiac electrical activity, most notably the late persistent sodium current and L-type calcium channels (Hool & Corry, 2007) but also including hERG K^+ channels (Zhang *et al.* 2006). Previous studies have shown that oxidative stress results in a decrease in hERG function via a variety of mechanisms including a decrease in protein levels as well as an acceleration of deactivation. In the study by Kolbe and colleagues reported in this issue of *The Journal of Physiology* (Kolbe *et al.* 2010) they show that the acceleration of deactivation induced by acute oxidative stress is largely mediated by a cysteine residue, Cys723, located in a linker between the pore domain and the cytoplasmic cyclic nucleotide-binding domain. Two other C-terminal cysteines, Cys740 and Cys828, make smaller contributions. In this respect, hERG K^+ channels are similar to many other ion channels where thiol modification plays a critical role in the response to oxidation (Hool & Corry, 2007).

The first implication of the work from Kolbe and colleagues is that acute oxidative stress induced by hyperglycaemia is sufficient to cause significant loss of function in hERG K^+ channels and this could contribute to an increased risk of arrhythmias in patients with diabetes mellitus (Zhang *et al.* 2006). However, it is important to remember that the deleterious effects of oxidative stress in patients with diabetes mellitus are multi-factorial and modulation of hERG currents is just one of those factors. A second clinical implication of the study is that oxidative stress, elicited by hyperglycaemia, will also reduce repolarisation reserve and so could exacerbate the effect of any other mutations (or drugs) that prolong the QT interval.

An intriguing finding in the study is that oxidative inhibition of hERG currents is dependent on the rate of deactivation of the channel, i.e. mutants or deletion constructs that have accelerated deactivation are less sensitive to oxidative modification. The biological relevance of this finding is that a naturally occurring isoform of the hERG channel, denoted the 1b isoform, that has faster deactivation than the more commonly studied 1a isoform, is less sensitive to oxidative stress. Thus, cells in which the 1b isoform is a significant component will be more resistant to oxidative stress, at least with respect to effects on the I_{Kr} current. The precise role of 1b isoforms in the heart has not been definitively established but it is very likely that native I_{Kr} channels in human cardiac myocytes are composed of a mixture of 1a and 1b subunits (Sale *et al.* 2008).

The study by Kolbe *et al.* does not directly address the mechanism(s) by which modification of Csy723 results in acceleration of deactivation nor why channels with faster deactivation are resistant to inhibition by oxidative stress. One possibility they consider is that access of the Cys723 side-chain may be state dependent. This, however, does not appear to be the case, at least with respect to modification by the thiol-modifying reagent MTSES. An alternative possibility is that Cys723 contributes to a binding surface for another domain of the channel that contributes to deactivation of the channel. The obvious candidate for this domain would be the PAS domain as it is well known to be involved in regulation of deactivation. However, N-terminal deletions in which the PAS domain was retained or deleted were no different in their response (or lack thereof) to oxidative stress. The issue of whether oxidation of Cys723 interferes with binding of another domain and if so the identity of that domain therefore remains an open question.

References

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