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Palpitations, potassium and the pump

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Hypokalaemia (serum $[K^+]$ <3.5 mM) is the most common electrolyte abnormality in hospitalized patients, and has long been associated with an increased incidence of cardiac arrhythmias, often sensed as palpitations by patients. Despite increasing the driving force for outward current through K^+ channels, hypokalaemia reduces repolarization reserve by decreasing the conductances of the inward rectifier K^+ current I_{K1}, the rapid component of the delayed rectifier K^+ current I_{Kr} and the transient outward K^+ current I_{to}, thereby promoting early afterdepolarization (EAD)-mediated arrhythmias. Hypokalaemia also inhibits the Na^+–K^+ ATPase (NKA) pump, causing intracellular Na^+ and Ca^{2+} overload, which promotes delayed afterdepolarization (DAD)-mediated arrhythmias. However, the external K^+ binding site of the NKA pump is half-saturated at an extracellular $[K^+]$ (K_m) around 2.0 mM, implying that moderate hypokalaemia (2.5–3.0 mM) inhibits the NKA pump by significantly less than 50%. Perhaps for this reason, the role of NKA inhibition has received less attention as a clinically relevant arrhythmogenic factor except in severe hypokalaemia (<2.5 mM), which is relatively rare clinically compared to moderate hypokalaemia. In this issue of *The Journal of Physiology*, however, Aronsen *et al.* (2014) make a compelling case that NKA inhibition also plays an important arrhythmogenic role during moderate hypokalaemia. Using a variety of electrophysiological and fluorescent dye measurements in isolated rat ventricular myocytes, combined with computational modelling, they show convincingly that moderate hypokalaemia (2.7 mM) causes sufficient NKA pump inhibition to increase intracellular Na^+ to a level promoting intracellular Ca^{2+} overload and Ca^{2+} waves, the cause of DADs. The reason is that in cardiac myocytes, hypokalaemia inhibits the NKA pump by two mechanisms. At a constant membrane potential (e.g. around −75 mV in their study), reducing extracellular $[K^+]$ to 2.7 mM reduced the total NKA pump current by about 20%, as can be directly measured from their Fig. 3*B*. However, by negatively shifting the K^+ equilibrium potential, hypokalaemia also hyperpolarized the resting membrane potential to around −90 mV (their Fig. 2*B*). Because the NKA pump generates an outward current by exchanging 2 K^+ for 3 Na^+ ions, this hyperpolarization further inhibits the NKA pump. The combined effect of the K_m and hyperpolarization was to depress NKA pump current by more than 50% (as estimated from their Fig. 3*B*). Membrane hyperpolarization also enhances the ability of the Na^+–Ca^{2+} exchanger (NCX) to remove Na^+ from the myocyte, but NCX stimulation was not sufficient to compensate for the overall reduction in NKA pump activity, as validated in their myocyte computer model.

The authors also suggest that the NKA α_2 isoform, which requires a higher extracellular $[K^+]$ for half-maximal activation (K_m = 2.9 mM) than the NKA α_1 isoform (K_m = 1.9 mM) and therefore is more completely suppressed at 2.7 mM $[K^+]$, plays a preferential role in promoting intracellular Na^+ and Ca^{2+} overload. Although the NKA α_2 isoform contributed less than 25% of total NKA pump current (the majority being generated by the more prevalent NKA α1 isoform), selective blockade of the NKA α_2 isoform with low-dose ouabain increased the Ca^{2+} transient amplitude under normokalaemic conditions, and prevented any further increase in the Ca^{2+} transient amplitude when $[K^+]$ was subsequently reduced to 2.7 mM. Moreover, unlike NKA α_1, which is distributed ubiquitously, the NKA α_2 isoform is preferentially localized in the t-tubules, similar to the NCX. This may be a hint that there is a preferential functional relationship between NKA α_2 and NCX, as suggested previously (Swift *et al.* 2008; Despa *et al.* 2012).

The implication of these findings is that, in addition to EAD-mediated arrhythmias, clinically relevant moderate hypokalaemia can also promote sufficient intracellular Na^+ and Ca^{2+} overload by NKA inhibition to generate spontaneous diastolic Ca^{2+} waves leading to DAD-mediated arrhythmias. It could be argued that a weakness in this interpretation is that although moderate hypokalaemia increased the frequency of Ca^{2+} waves in isolated rat ventricular myocytes, the Ca^{2+} waves observed did not cause DADs of sufficient amplitude to induce triggered activity (at least as can be surmised from the example shown in their Fig. 1*B*). Moreover, the aforementioned Ca^{2+} waves were induced by rapid pacing trains, and did not appear until several seconds after termination of the train (their Fig. 1*B*). In contrast, the majority of hypokalaemia-induced atrial and ventricular ectopy in the clinical setting and intact heart models occurs during sinus rhythm in the absence of such long pauses. However, this discrepancy does not seriously detract from the overall significance of the present findings, because once Ca^{2+} overload develops, a variety of arrhythmia mechanisms, in addition to DADs, come into play. Relevant to this point, we recently reported that moderate hypokalaemia (also 2.7 mM) in isolated rat ventricular myocytes and intact rat hearts led to EAD-mediated arrhythmias that were effectively suppressed by Ca^{2+}/calmodulin-dependent protein kinase (CaMK) inhibitors (Nivala *et al.* 2014). Consistent with the experimental findings reported here, our computational model predicted that NKA pump inhibition by moderate hypokalaemia played a key role in inducing intracellular Na^+ and Ca^{2+} loading that activated CaMK, triggering EADs which further increased Ca^{2+} loading during the prolonged action potential. Thus, the initial NKA inhibition by moderate hypokalaemia triggered a positive feedback loop involving CaMK that ultimately culminated in ventricular fibrillation in intact isolated rat hearts. The key point is that once intracellular Ca^{2+} overload develops, its pleiotropic effects on many ion channels/transporters and signalling pathways can generate arrhythmias by a variety of synergistic mechanisms. By directly demonstrating significant NKA pump inhibition by moderate hypokalaemia, this study makes an invaluable contribution to our understanding of pathophysiology of

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arrhythmogenic complications arising from this common clinical condition.

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Additional information

Competing interests

None declared.