Catecholaminergic polymorphic ventricular tachycardia and calcium handling proteins

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Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an inherited arrhythmia characterized by adrenergic induced polymorphic ventricular tachycardia, frequently leading to sudden death. CPVT stems from mutations in the ryanodine receptor (RyR2), the Ca^{2+} buffering protein in the sarcoplasmic reticulum (SR), calsequestrin or cytoplasmic Ca^{2+} regulating protein, calmodulin. All these genes control cardiac Ca^{2+} release from the SR.

Although excess Ca^{2+} release through RyR2 in diastole is a key factor in CPVT, not all RyR2 antagonists have an antiarrhythmic action. Our previous studies comparing the anti-arrhythmic blocking action of flecainide with the pro-arrhythmic blocking action of tetracaine found that flecainide reduced the amount of Ca^{2+} released during localised diastolic release events (Ca^{2+} sparks) but increased their frequency. As a result, flecainide had no effect on overall SR Ca^{2+} leak or SR Ca^{2+} content. However, the likelihood that each Ca^{2+} spark could generate an arrhythmogenic Ca^{2+} wave was reduced because the Ca^{2+} sparks were smaller. In contrast, tetracaine decreased spark-mediated SR Ca^{2+} leak but significantly increased SR Ca^{2+} content, Ca^{2+} released during a spark and frequency of Ca^{2+} waves. These results suggested that the flecainide-induced reduction in Ca^{2+} spark size contributes to its anti-arrhythmic action by reducing the probability of saltatory wave propagation between adjacent Ca^{2+} release sites.

In this study, we examine the inhibiting action of flecainide and tetracaine on RyR2 activity in lipid bilayers with a view to understanding the opposite actions of these drugs on heart rhythm. For both flecainide and tetracaine, we identified two similar mechanisms underlying these actions. First, a slow inhibition in which luminal and cytoplasmic drugs induce long closed events (~100-1000 ms). The apparent binding rate is proportional to the RyR closed probability, indicating that it only operates on closed channels. Second, is a fast inhibition in which the drugs induce relatively short closed events (~2 ms) which operate on both open and closed channels.

We develop a kinetic model for tetracaine and flecainide inhibition which predicts that under diastolic conditions, i.e. when RyRs are mainly closed, tetracaine blocks primarily *via* the slow mechanism (IC_{50} (slow) = 0.2 mmol/l; IC_{50} (fast) = 2 mmol/l) whereas flecainide blocks mainly by the fast mechanism (IC_{50} (slow) = 0.23 mmol/l; IC_{50} (fast) = 0.11 mmol/l). These two forms of RyR blockade are likely to have very different actions on SR Ca^{2+} release. During periods of Ca^{2+} release, *i.e*. when RyRs are open, the slow mechanism becomes ineffective, leaving only the fast inhibition as the dominant mechanism. Hence tetracaine loses its blocking efficacy whereas flecainide inhibition is sustained. In the case of tetracaine, this has the effect of increasing the positive feedback on SR Ca^{2+} release generated by intracellular Ca^{2+} which would increase the amplitude of Ca^{2+} sparks, destabilise Ca^{2+} cycling by the SR and cardiac rhythm. Therefore, the mechanisms underlying inhibition of the RyR2 by drugs are crucial to their successful use as therapeutic agents.