Ryanodine receptor inhibition prevents ventricular arrhythmia in a murine model of hypokalaemia

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Background: Hypokalaemia-induced arrhythmia is a major cause of morbidity and mortality, affecting approximately 14% of outpatients and 20% of inpatients. Hypokalaemic inpatients have a mortality 10 times higher than their counterparts. This is due to ventricular arrhythmias initiated by early afterdepolarisations (EADs) and triggered activity. There is no antiarrhythmic drug approved for the prevention of hypokalaemia-induced ventricular arrhythmia. Recent evidence suggests that EADs can arise because of the synchronised release of Ca2+ from the sarcoplasmic reticulum, rather than the reactivation of L-type Ca2+ channels during action potential prolongation. Therefore, ryanodine receptor inhibition should prevent hypokalaemia-induced ventricular arrhythmia.

Purpose: To test the hypothesis that the ryanodine receptor inhibitors dantrolene and VKII-86 (a carvedilol analogue) are effective in preventing hypokalaemia-induced ventricular arrhythmia.

Methods: Whole heart Langendorff preparations isolated from C57BL/J6 mice were perfused with Krebs-Henseleit solution containing normal (4mM) or low (2mM) concentrations of [K+]. Surface ECG and subepicardial ventricular action potentials were simultaneously recorded. After establishing that the model reproduces EAD-mediated triggered arrhythmias in low extracellular [K+], hearts in the treatment groups were pre-treated with dantrolene or VKII-86 for 30 minutes prior to being exposed to low extracellular [K+]. The frequency of non-sustained and sustained ventricular arrhythmias occurring during a 30-minute period of exposure to low extracellular [K+] were compared between the treatment groups and controls treated with the solvent DMSO (0.1% v/v) (n=6 in each group).

Results: The mean number of non-sustained arrhythmias was 29.3±9.6 (Mean±SEM) in the control group, 3.2±1.2 in the dantrolene group and 0 in the VKII-86 group; $p<0.05$ for both treatments vs. control. The mean number of sustained arrhythmias was 1.7±0.4 in the control group, 0.17±0.17 in the dantrolene group and 0 in the VKII-86 group; $p<0.05$ for both treatments vs. control. Thus, dantrolene significantly reduced arrhythmia frequency by approximately 90%, whereas VKII-86 prevented all hypokalaemia-induced ventricular arrhythmias.

Conclusions: These results provide the first demonstration of ryanodine receptor inhibition as an effective treatment for the prevention of ventricular arrhythmia in a murine model of hypokalaemia. This study is consistent with recent studies indicating that intracellular Ca2+ load is an important mechanism underlying the development of EAD-mediated triggered arrythmia. Further studies are needed to determine whether these drugs could be re-purposed as antiarrhythmics in the setting of hypokalemia. Further development of the carvedilol analogue VKII-86 should also be considered.