Illuminating the mechanism of hERG channel activators using voltage clamp fluorometry

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hERG (human ether-á-go-go related gene) encoded channels are voltage-sensitive potassium ion channels that mediate cardiac repolarisations due to their unusual gating kinectics. In particular the mechanism of slow activation is not well understood. There are many drugs and compounds which cause block of hERG channels but recently a novel class of compounds which activate hERG channels has been discovered. Here we use voltage clamp fluorometry as a measure of voltage sensor movement to unravel the mechanism of hERG channel activators.

Methanthiosulfonate-rhodamine (MTSR) fluorescence at position E518C of hERG channels was used to track voltage sensor movement. Depolarisation of E518C channels caused an increase in the fluorescent signal fit with a Boltzmann function with a $V0.5 = -6.3 \pm 1.1$. Application of hERG channel activator NS1643 (50μmol/L) caused a shift of the fluorescence response to $V0.5 = -22.6 \pm 2.9$. In addition NS1643 increased the rate of increase of the fluorescent signal. Previous studies have shown that NS1643 causes both a shift in the voltage dependence of current activation as well as an increase in the rate of action.

The results indicate that NS1643 causes a shift in the voltage dependence of current which is related to a shift in the voltage dependence of voltage sensor movement. In addition, NS1643 causes an increase in the rate of activation which is related to an increased rate of voltage sensor movement.