High Throughput Pharmacology of cardiac L-type Ca^{2+} Channels in overexpressing cell lines and iPSC-cardiomyocytes

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The new paradigm in cardiac drug safety screening, the Comprehensive In-vitro Proarrhythmia Assay (CiPA) initiative, is being introduced to provide a more complete assessment of proarrhythmic risk by evaluating and implementing currently available high throughput methods. An important part of this initiative is an extension of the electrophysiological evaluation beyond hERG to include other cardiac channels such as $Na_V1.5$, $Ca_V1.2$, KV-LQT1 and $K_{ir}2.1$.

A typical difficulty when performing patch clamp measurements of ion channels is the spontaneous loss of current amplitude over time, a phenomenon described as run-down. This phenomenon is particularly pronounced in $Ca_V1.2$ channels which dramatically impair stable recordings and thus reliable pharmacological assessment, especially in the study of slow or use-dependent compounds. Specialized high throughput, gigaseal platforms have shown to be successful in delivering ion channel electrophysiological measurements, and overcoming these difficulties.

Here we present data on the full CiPA ion channel panel with a focus on the $Ca_V1.2$ assay, utilizing overexpressing cells and iPS cardiomyocytes on an automated patch clamp system. We depict very stable recordings of $Ca_V1.2$ over an extended period of time (> 25 min), which permits cumulative compound application. Furthermore, we demonstrate $Ca_V1.2$ activation from different states which allows to discriminate state- and use-dependent drug effects.

Additionally, the effect of drugs on action potentials as recorded in iPSC-cardiomyocytes is important for assessing the interaction of the cardiac ion channel ensemble. We present our advances in development of iPSC-cardiomyocytes "ready-to-use" assays for automated patch clamp, with focus on the compound effects of L-type Ca2+ channel inhibitors on action potentials of these cells.

In summary, our assay development demonstrates how accurate pharmacology and high throughput recordings of even difficult targets like $Ca_V1.2$ can be achieved in a reproducible and reliable manner with excellent success rates.