Automated Patch clamp System Introducing Simulated $I_{K1}$ Into stem cell-derived Cardiomyocytes Using Dynamic Clamp

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Introduction
Dynamic clamp is a powerful tool to inject real-time simulated currents into patch clamped cells. This has been shown using conventional patch clamp whereby the inward rectifier current $I_{K1}$ was introduced into human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs). $I_{K1}$ is typically expressed at low levels in these cells, hence their membrane potential is more depolarized than that of primary cardiomyocytes. Limiting their use in safety pharmacology. Introducing simulated $I_{K1}$ into hiPSC-CMs may render them a viable alternative to scarcely available adult human cardiomyocytes.

In this study, we combined dynamic clamp with an automated patch clamp (APC) system to demonstrate that $I_{K1}$ conductance can be added to hiPSC-CMs on this platform, while at the same time, applying automatic $R_{seal}$ compensation (SC)⁴. Our results show that virtual $I_{K1}$ can be successfully injected into hiPSC-CMs in up to 8 cells simultaneously and that $R_{seal}$ is correctly compensated avoiding overcompensation. Our approach results in more stable resting membrane potentials and action potential duration (APD) values. Action potential (AP) shape is also improved. L-Type calcium channel opener BayK 8644 and channel blocker nifedipine were also tested. In addition, we compared the shape of APs at physiological versus ambient temperature.

Combining dynamic clamp with APC

Theory of Seal Resistance compensation

Effect of seal compensation and simulated $I_{K1}$ on the shape of hiPSC-CM

Effect of applying seal compensation and simulated $I_{K1}$ to hiPSC-cardiomyocytes on AP shape and pharmacology

Conclusions

- $I_{K1}$ and seal compensation were successfully applied to hiPSC-CMs in multiple cells simultaneously and effects on RMP and AP duration.
- Combined with the Patchcliner® Octo, Dynamite® enabled the recording of stable APs from hiPSC-CM at a higher throughput.
- Ca²⁺ channel activator, Bayk 8644, and blocker, nifedipine, prolonged and shortened AP duration, respectively, as expected and a complete concentration-response curve was recorded on an individual cell.
- APs at physiological temperature were also measured.
- Future goals:
  - Test effects of the set of drugs defined by CiPA on action potentials using dynamic clamp.
  - Upgrade technique to higher throughput devices, e.g. SyncroPatch 384i.

References