Long-term amiodarone exposure results in remodelling of multiple cardiac ion channels

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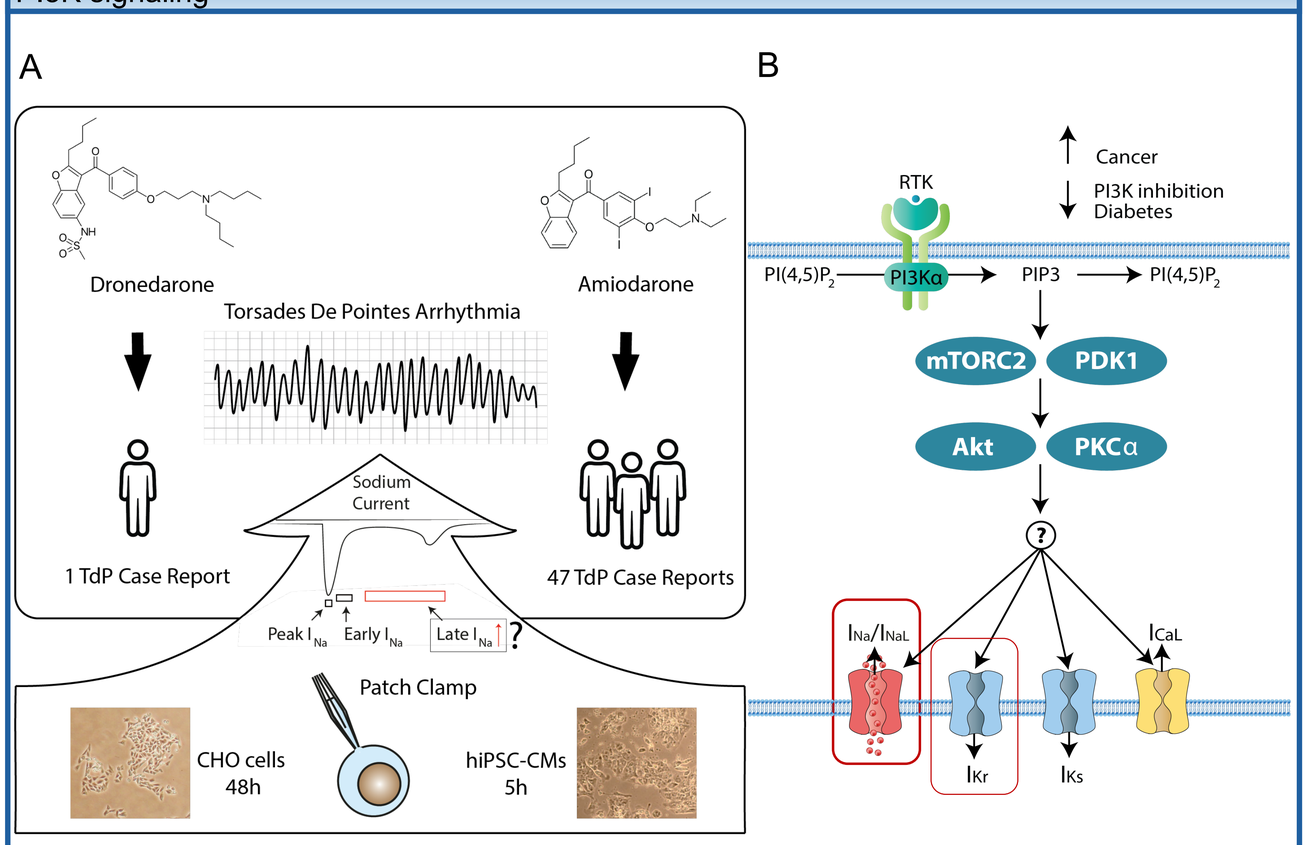
Background

- Amiodarone is an effective antiarrhythmic drug (AAD) with distinct acute and long-term electrophysiological effects. Dronedarone was developed as a less-toxic alternative (Fig. 1A), but its differential acute and long-term effects compared to amiodarone remain largely unknown.
- We aimed to investigate distinct long-term electrophysiological effects of amiodarone on cardiac ion channels. As a potential mechanism, we focused on inhibition of PI3K signaling, a pathway implicated in cancer and diabetes, which has also been shown to affect multiple cardiac ion currents including late sodium current (I_{NaL}; Fig. 1B) and rapid delayed-rectifier potassium current (I_{Kr}; Fig. 1B).

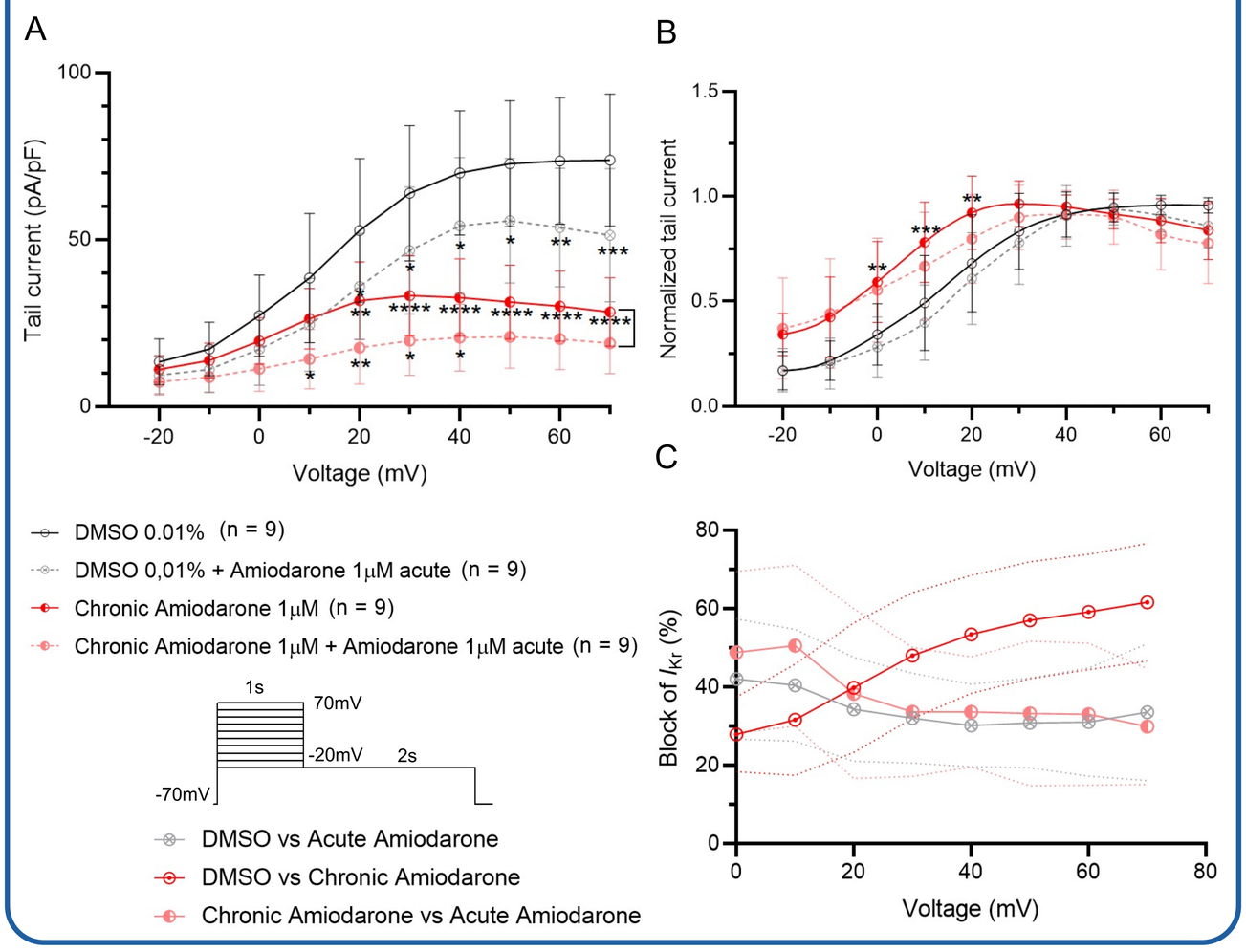
Figure 1: Differential effects of amiodarone versus dronedarone on ion channels via effects on PI3K signaling



Methods

- Membrane currents were measured using the whole-cell patch-clamp technique in Chinese Hamster Ovary (CHO) cells transiently transfected with plasmid carrying wild-type SCN5A and GFP or KCNH2 and GFP, for I_{Na} and I_{Kr} measurements, respectively. Effects of amiodarone on I_{Na} were confirmed in human induced pluripotent stem-cell derived cardiomyocytes (hiPSC-CMs).
- I_{Kr}, peak I_{Na}, and tetrodotoxin (TTX)-sensitive I_{NaL} were measured at room temperature. Cells were incubated with different AADs or Akt inhibitor (Akti 1 μM) for 5 hours (hiPSC-CMs) or 48 hours (CHO) at 37°C.

Figure 2: Chronic amiodarone induces pronounced I_{Kr} reduction, independent of channel block



Results

- In CHO cells after 48 hours of amiodarone treatment, reduced I_{Kr} even after drug wash out (Fig. 2A) and shifted I_{Kr} voltage dependence towards more negative voltages (Fig. 2B), resulting in a 30%-60% reduction in I_{Kr} depending on membrane potential (Fig. 2C).
- Acute amiodarone exposure produced similar voltage-independent channel block of ~30% when combined with control or chronic treatment (Fig. 2C).
- Long-term exposure (48 h) to amiodarone, dofetilide and Akt inhibitor in CHO cells augmented both peak I_{Na} (Fig. 3A, C) and I_{NaL} (Fig. 3B, D) ion currents. This I_{Na}/I_{NaL} increase was fully abolished by PI3K pathway activation with intrapipette phosphatidylinositol (3,4,5)-trisphosphate (PIP3; Fig. 1B; Fig. 3C,D).
- Dronedarone had no significant effect on peak I_{Na}, nor I_{NaL} and showed no significant changes with PIP3 present.
- In hiPSC-CMs, amiodarone also increased peak I_{Na} and I_{NaL} currents (Fig. 4A-D) after 5 hours of exposure.

Figure 3: Chronic exposure to amiodarone augments I_{NaL} in CHO cells via Akt

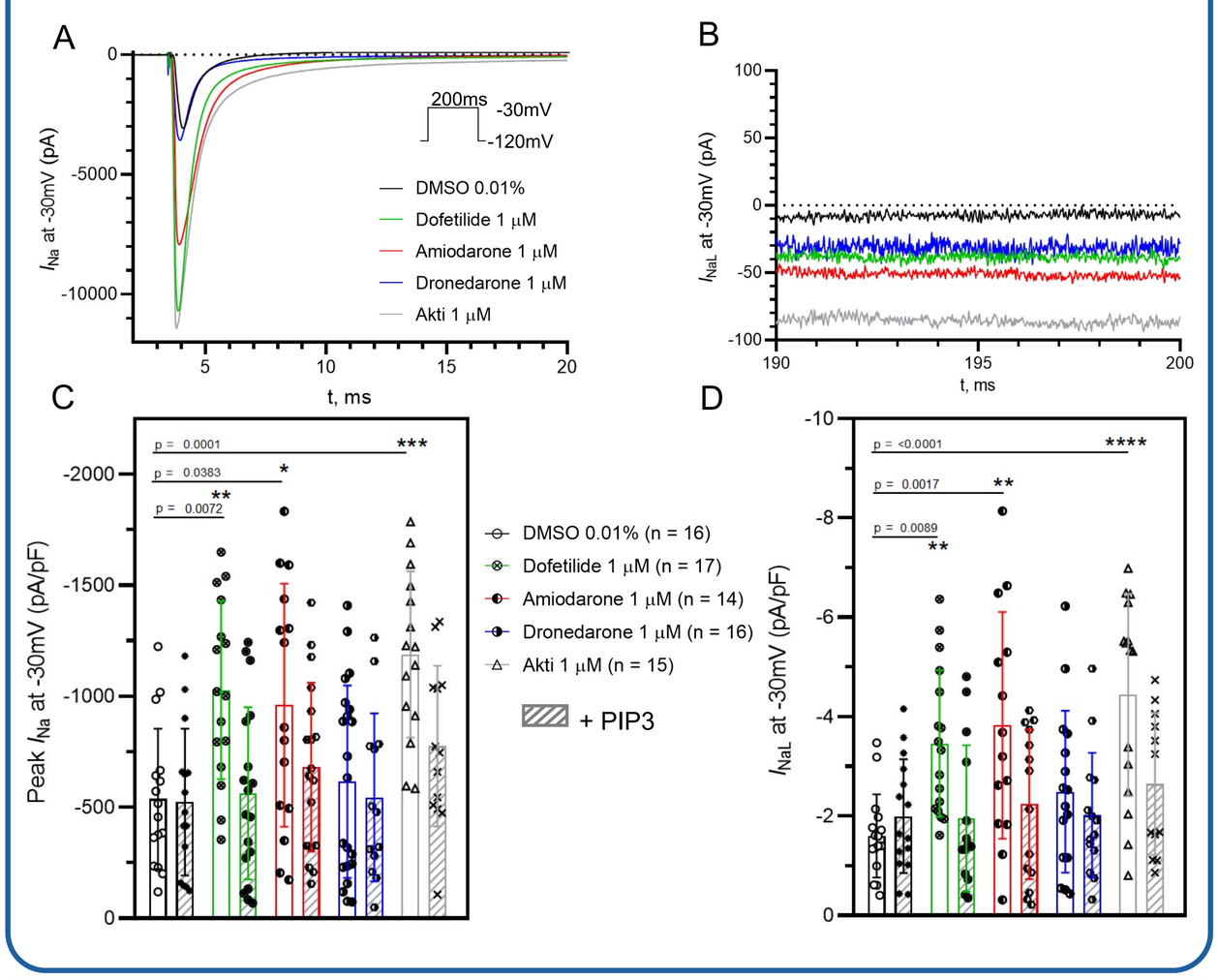
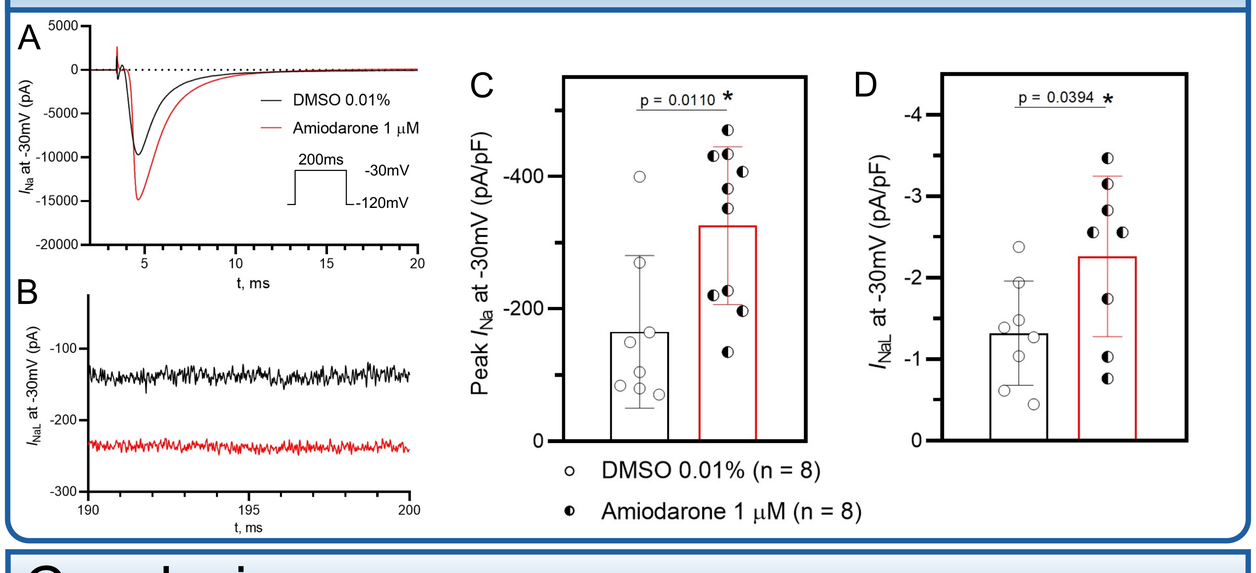


Figure 4: In hiPSC-CMs amiodarone increases I_{Na} and I_{NaL} after 5h treatment



Conclusions

- Amiodarone results in remodelling of cardiac ion channels, e.g., I_{Kr}, whereby a reduction in I_{Kr} is observed even upon drug wash out (Fig. 2A).
- Long-term amiodarone also contributes to an increase in I_{NaL}, which can potentially promote arrhythmias (Fig. 3D, Fig. 4D). Inhibition of PI3K/Akt signaling is proposed as the underlying mechanism.
- Dronedarone did not augment I_{NaL} and might therefore be considered a safer treatment option in proarrhythmia-susceptible patients.
- The differential long-term effects of amiodarone and dronedarone on I_{NaL} could contribute to the higher TdP rates with amiodarone (Fig. 1A).
- Although acute I_{Kr} block is common for all examined compounds, it is necessary to elucidate long-term drug effects on multiple ion currents, as observed with I_{Kr} and I_{NaL} in this and previous studies.

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