DOI: 10.1111/bph.16031

CORRECTION

Correction to "An in silico-in vitro pipeline for drug cardiotoxicity screening identifies ionic proarrhythmia mechanisms"

Clark, A. P., Wei, S., Kalola, D., Krogh-Madsen, T., & Christini, D. J. (2022). An in silico–in vitro pipeline for drug cardiotoxicity screening identifies ionic pro-arrhythmia mechanisms. British Journal of Pharmacology, 179(20), 4829–4843. https://doi.org/10.1111/bph.15915

There has been a discrepancy between the methods reported in the above manuscript and the actual experimental implementation. The text below (1) details this discrepancy and (2) demonstrates that this discrepancy would not impact the manuscript conclusions.

The authors discovered that the Ishihara I_{K1} dynamic clamp module used has an incorrect formulation. The module used in the paper was missing three sets of parentheses within the alpha and beta equations of the model in Table 1.

Figure 2 displays the effect of the difference between the implementation in the manuscript and the correct Ishihara implementation. The main difference is that the correct Ishihara implementation (red, dotted) conducts a small outward current over the duration of the action potential, while the formulation used in the experiment (black, solid) does not. The formulation used in the experiment (black) was more like the baseline Kernik–Clancy I_{K1} current (blue dashed).

The authors have also simulated Kernik–Clancy drug block experiments with the correct and incorrect I_{K1} formulations (Figure 3). These experiments show similar results for both formulations.

The discrepancy between author's implementation and the correct Ishihara model has no effect on the conclusions of this manuscript: An I_{K1} dynamic clamp was still applied but produced I_{K1} more like that of the Kernik–Clancy than Ishihara model. With this incorrect formula-

TABLE 1 The correct Ishihara model

$$I_{K1} = G_{K1} \cdot (V - E_K) \cdot (\text{phi} \cdot f_O \cdot y_1 + [1 - \text{phi}] \cdot y_2)$$
$$G_{K1} = 2.5 \cdot ([K^+]_o/5.4)^{0.4}$$

High-affinity channel

$$\alpha = 0.17 \cdot \exp(-0.07 \cdot ((V - E_K) + 8 \cdot [Mg^{2+}]_i)) / (1 + 0.01 \cdot \exp(0.12 \cdot ((V - E_K) + 8 \cdot [Mg^{2+}]_i)))$$
$$\beta = [SPM]_i \cdot 280 \cdot \exp(0.15 \cdot ((V - E_K) + 8 \cdot [Mg^{2+}]_i)) / (1 + 0.01 \cdot \exp(0.13 \cdot ((V - E_K) + 8 \cdot [Mg^{2+}]_i)))$$
$$K_{dMg} = 0.45 \cdot \exp(-(V - E_K)/20)$$
$$f_O = 1/(1 + [Mg^{2+}]_i/K_{dMg})$$
$$dy_1/dt = \alpha \cdot (1 - y_1) - \beta \cdot (f_O)^3 \cdot y1$$

Low-affinity channel

$$K_{dSPM\_L} = 0.04 \cdot \exp(-(V - E_K)/9.1)$$
$$y2 = 1/(1 + [SPM]_i/K_{dSPM\_L})$$

Note: The bolded red parentheses were incorrectly omitted from the dynamic clamp implementation.

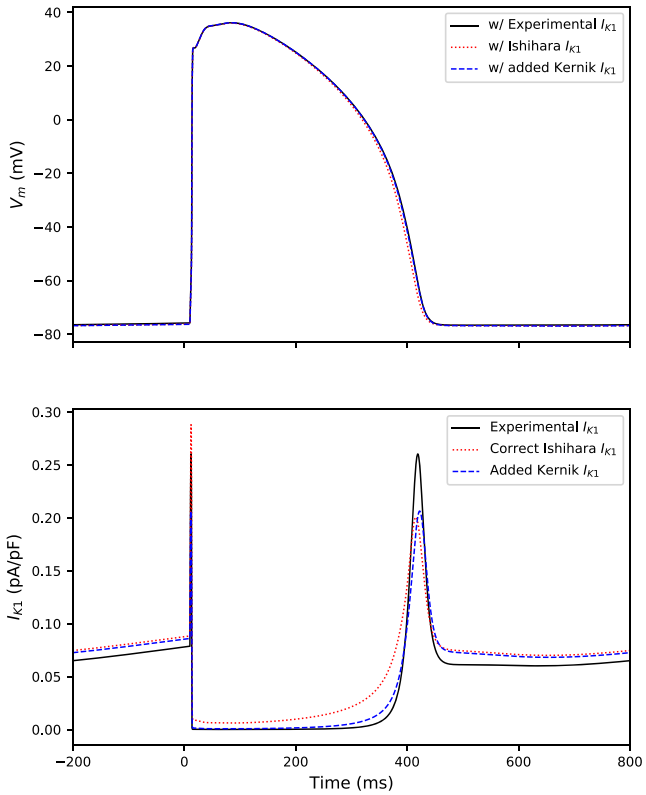

FIGURE 2 Top: Action potentials with I_{K1} current increased until spontaneous behavior stopped and then paced at 1 Hz. Action potentials from the Kernik–Clancy model with the incorrect dynamically clamped I_{K1} used in our experiments (black, solid), the correct Ishihara I_{K1} (red, dotted), and the baseline Kernik-Clancy model with increased I_{K1} (blue, dashed). Bottom: The I_{K1} for each of these models

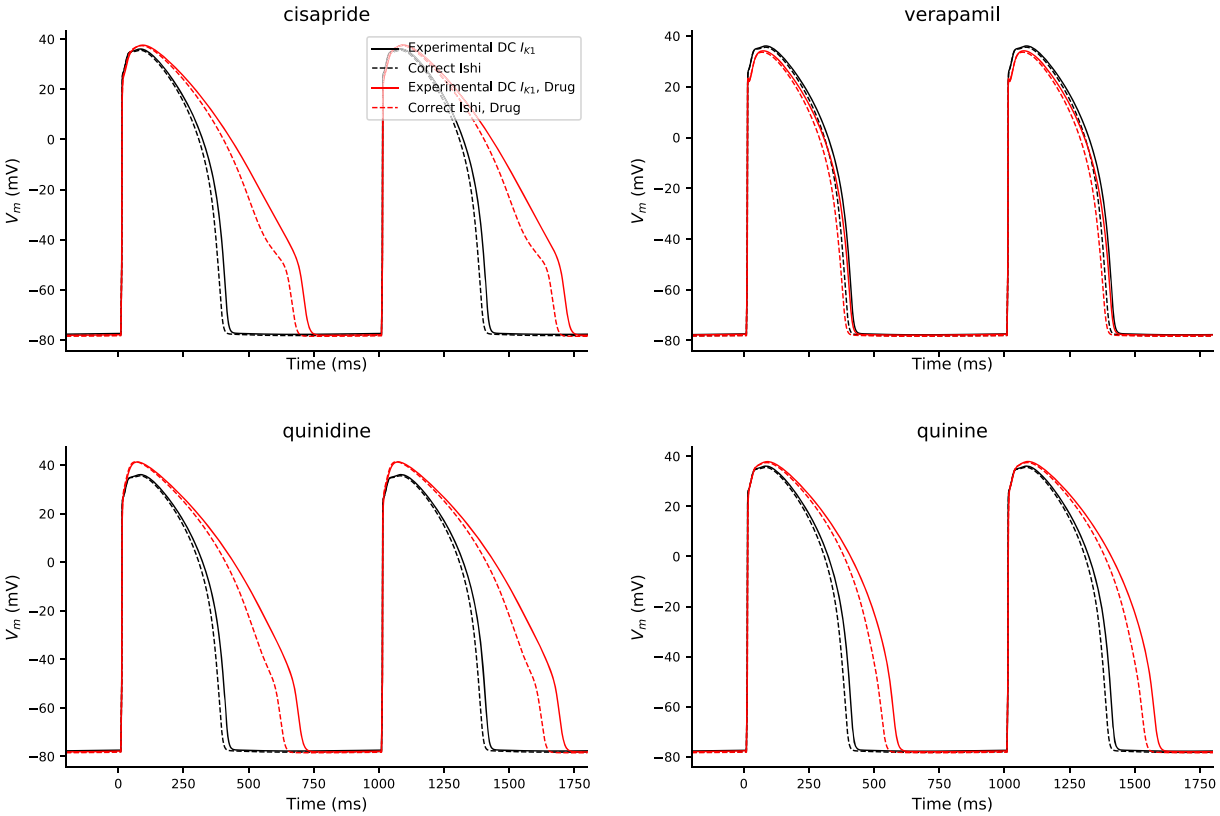

FIGURE 3 Effect of each drug (cisapride, verapamil, quinidine, and quinine) on the Kernik–Clancy AP with either the correct (dashed) or incorrect (solid) Ishihara I_{K1} formulation

tion, the authors were still able to maintain a resting membrane potential for the iPSC-CMs during their dynamic clamp experiments, which allowed authors to pace them at 1 Hz and detect AP prolongation in their treatment group. Ultimately, one would have to implement this incorrect formulation of the Ishihara model to fully reproduce the results, but the authors would suggest applying the Ishihara model as originally described in future studies.

The authors apologize for these errors.