The selective late sodium current inhibitor eleclazine reduces atrial fibrillation dominant frequency and facilitates the suppression of arrhythmia in HL-1 cells

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Background: The cardiac late sodium current (INaL) has been increasingly implicated in the initiation of atrial fibrillation (AF). In fact, it has been reported that the augmentation of INaL in pathophysiological conditions prolongs repolarization and facilitates the appearance of afterdepolarizations, which can act as triggers of arrhythmic activity. Eleclazine is a novel selective inhibitor of INaL and is undergoing clinical testing for the treatment of cardiac arrhythmias.

Purpose: The aim of this study was to investigate the effects of eleclazine on spectral characteristics of atrial fibrillation in cultured atrial myocyte monolayer in order to assess whether this inhibitor could protect against cardiac arrhythmias.

Methods: Confluent HL-1 murine atrial myocyte monolayer with spontaneous fibrillatory activity was cultured in 1.5 cm diameter petri dishes (n=10). A high-resolution optical mapping system was used to record fibrillatory activity under basal conditions (without drug), and under eleclazine at increasing concentrations (1, 3 and 5 μM). Power spectra of optical signals were estimated by using Welch periodogram and dominant frequency (frequency with the largest peak in the spectrum between 0.05 and 30 Hz) was determined. The incidence of spontaneous defibrillation was analyzed under control and drug conditions. An ANOVA and a chi-squared test were used. Significance was reached when $p<0.05$.

Results: Eleclazine at 1, 3 and 5 μM significantly decreased dominant frequency with respect to basal conditions (basal: 4.74±1.31 Hz; 1μM: 3.59±1.17 Hz, $p<0.001$; 3μM: 3.19±0.64 Hz, $p<0.01$; 5μM: 2.58±0.40 Hz, $p<0.01$). The magnitude of drug-induced decrease in AF activation frequency was enhanced by increasing concentrations (1μM: 27%, 3μM: 42%; 5μM: 46%; $p<0.05$). After the analysis of optical signals, we observed that the incidence of spontaneous defibrillation in atrial monolayers was significantly greater under eleclazine 5μM action than under control conditions (chi-square=5.00, p=0.025). In fact, under the action of eleclazine 5μM, fibrillatory activity was suppressed in 4 of the 10 monolayers, phenomenon that did not occur in any case of control situation.

Conclusions: Selective late INa inhibition with eleclazine reduced dominant frequency of atrial fibrillation and facilitates the termination of arrhythmia in cultured atrial myocyte monolayer.

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