Neuronal nitric oxide synthase inhibition exacerbates atrial electrical remodeling via small-conductance Ca2+-activated K+ channel activation

Doctor Koya T1.; Doctor Watanabe M1.; Doctor Natsui H1.; Doctor Kadosaka T1.; Doctor Koizumi T1.; Doctor Nakao M1.; Doctor Hagiwara H1.; Doctor Kamada R1.; Doctor Temma T1.; Professor Anazai T1.

Hokkaido University, Sapporo, Japan

Funding Acknowledgements: Type of funding sources: Public Institution(s). Main funding source(s): The Japan Society for the Promotion of Science KAKENHI

Background: The presence of atrial fibrillation (AF) is associated with electrical remodeling processes that promote a substrate for the maintenance of AF itself. Small conductance Ca2+-activated K+ (SK) channels; K+-selective and voltage-independent ion channels are key factors in the atrial electrical remodeling (2, 3). However, the mechanism of its activation remains unclear. A recent study showed that neuronal nitric oxide synthase (nNOS) expression and activity are reduced in AF patients and that nNOS depletion causes the abbreviation of action potential duration (APD), leading to increased AF inducibility in animal experiments (4). Decreased NO production, especially driven by nNOS inhibition, might play a key role in the atrial electrical remodeling, and the downstream alteration of SK channels might result from this process.

Purpose: We aimed to evaluate the potential of SK channel blocking to mitigate abnormal electrophysiological properties and the inducibility of atrial tachyarrhythmia (ATA) which was induced by nNOS depletion, and to describe the related mechanism.

Methods: Atrial tachyarrhythmia induction and optical mapping were performed in perfused rat hearts. nNOS was pharmacologically inhibited by S-methylthiocitrulline (SMTC, 100 nM). The influence of the SK channel was examined by a specific channel inhibitor, apamin (100 nM). APD, conduction velocity, and calcium transient (CaT) parameters (CaTD, rise time, time to 50% decay, and tau) were evaluated by voltage and calcium dual optical mapping. Dominant frequency was evaluated to analyze the wave dynamics of AF.

Results: SMTC increased the inducibility of ATA and apamin mitigated the nNOS inhibition-induced arrhythmogenicity (0% [0/7] vs 62% [8/13] vs 15% [2/13] in control, SMTC and SMTC + apamin). SMTC caused the abbreviation and enhanced spatial dispersion of APD, which were reversed by apamin. In contrast, conduction velocity was not affected by SMTC or apamin. Moreover, apamin reduced the dominant frequency of SMTC-induced ATA. In voltage and calcium optical mapping, SMTC and apamin did not alter the parameters associated with CaT, however, SMTC caused the abbreviation of APD, which was reversed by apamin (APD80: 48.4 ± 2.7 msec in control group, 30.8 ± 1.5 msec in SMTC group, p <0.0001 vs. control, 41.8 ± 1.5 msec in SMTC + apamin, p = 0.01 vs. SMTC by One-way ANOVA and Tukey’s multiple-comparison test) (Figure A-C).

Conclusion: Acute nNOS inhibition abbreviated APD via activating SK channels. A specific SK channel blocker mitigated APD abbreviation without the alteration of CaT, implying an underlying mechanism of post translational modification of SK channels.

A (msec) B (msec) C (msec)

mean ± SEM. *p < 0.05 vs CON, †p < 0.05 vs SMTC