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Short-chain fatty acid butyrate against TMAO activating endoplasmic-reticulum stress and PERK/IRE1-axis with reducing atrial arrhythmia

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Abstract

Introduction: The accumulation of microbiota-derived trimethylamine N-oxide (TMAO) in the atrium is linked to the development and progression of atrial arrhythmia. Butyrate, a major short-chain fatty acid, plays a crucial role in sustaining intestinal homeostasis and alleviating systemic inflammation, which may reduce atrial arrhythmogenesis.

Objectives: This study explored the roles of butyrate in regulating TMAO-mediated atrial remodeling and arrhythmia.

Methods: Whole-cell patch clamp experiments, Western blotting, and immunocytochemistry were used to analyze electrical activity and signaling, respectively, in TMAO-treated HL-1 atrial myocytes with or without sodium butyrate (SB) administration. Telemetry electrocardiographic recording and echocardiography and Masson's trichrome staining and immunohistochemistry were employed to

examine atrial function and histopathology, respectively, in mice treated with TMAO with and without SB administration.

Results: Compared with control cells, TMAO-treated HL-1 myocytes exhibited reduced action potential duration (APD), elevated sarcoplasmic reticulum (SR) calcium content, larger L-type calcium current (I_{Ca-L}), increased Na^+/Ca^{2+} exchanger (NCX) current, and increased potassium current. However, the combination of SB and TMAO resulted in similar APD, SR calcium content, I_{Ca-L}, transient outward potassium current (I_{to}), and ultrarapid delayed rectifier potassium current (I_{Kur}) compared with controls. Additionally, TMAO-treated HL-1 myocytes exhibited increased activation of endoplasmic reticulum (ER) stress signaling, along with increased PKR-like ER stress kinase (PERK)/IRE1α axis activation and expression of phospho-IP3R, NCX, and Kv1.5, compared with controls or HL-1 cells treated with the combination of TMAO and SB. TMAO-treated mice exhibited atrial ectopic beats, impaired atrial function, increased atrial fibrosis, and greater activation of ER stress signaling with PERK/IRE1α axis activation compared with controls and mice treated with TMAO combined with SB.

Conclusion: TMAO administration led to PERK/IRE1α axis activation, which may increase atrial remodeling and arrhythmogenesis. SB treatment mitigated TMAO-elicited ER stress. This finding suggests that SB administration is a valuable strategy for treating TMAO-induced atrial arrhythmia.

Keywords: Atrial remodeling; Butyrate; Endoplasmic reticulum stress; Short-chain fatty acid; Trimethylamine N-oxide.

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