Chronic mitochondrial fusion promotor as a novel pharmacological intervention to alleviate left ventricular dysfunction in rats with chronic myocardial infarction

C. Piamsiri, K. Jinawong, C. Maneechote, B. Arunsak, S.C. Chattipakorn, N. Chattipakorn
Chiang Mai University, Cardiac Electrophysiology Research and Training Center, Chiang Mai, Thailand

Funding Acknowledgement: Type of funding sources: Public grant(s) – National budget only. Main funding source(s): 1. The National Science and Technology Development Agency Thailand2. The Thailand Research Fund (RGJ)

Background: Decreased cardiac mitochondrial fusion associated with increased mitochondrial dysfunction has been demonstrated in acute myocardial infarction pathology. However, whether this pathophysiologic process is associated with myocardial injury in chronic myocardial infarction (CMI) is still unclear. Recently, a novel pharmacological intervention to promote mitochondrial fusion using mitochondrial fusion promotor-M1 (M1) has been shown to exert cardioprotection against myocardial ischemia and reperfusion injury. However, the roles of M1 in CMI has never been investigated.

Purpose: We investigated the potential cardioprotective benefits of chronic treatment with mitochondrial fusion promotor-M1 in rats with chronic MI model.

Methods: Adult male Wistar rats were assigned to the sham group (n=5) and the CMI group (n=15), which was induced by a permanent left anterior descending coronary occlusion. After 1 week of operation, rats in the CMI group were randomly divided into 3 subgroups which was treated with one of the followings: 1) vehicle (3% DMSO/day, ip, CON, n=5), 2) enalapril (10 mg/kg/day, po, ENA, n=5), or 3) mitochondrial fusion promotor-M1 (2 mg/kg/day, ip, M1, n=5) once daily for 4 weeks. In the end, echocardiography for the left ventricular (LV) function was performed, and the heart was removed to determine the mitochondrial function and malondialdehyde (MDA) level for oxidative stress.

Results: CMI rats that received vehicle showed significantly impaired LV function and cardiac mitochondrial function as evidenced by a 60% reduction in LV ejection fraction (LVEF) along with increased mitochondrial reactive oxygen species (ROS) production, mitochondrial depolarization and mitochondrial swelling, respectively, when compared with the sham rats (Fig. 1A–D). The CMI rats also exhibited a higher cardiac tissue MDA level than those of sham rats, further indicating cardiac oxidative stress (Fig. 1E). Interestingly, chronic treatment with either enalapril or M1 effectively attenuated CMI-induced mitochondrial dysfunction and oxidative stress up-regulation, thus increasing LVEF (27% improvement for both ENA and M1), when compared with the vehicle group (Fig. 1A).

Conclusion: Long-term promotion of mitochondrial fusion mitigated cardiac mitochondrial dysfunction and oxidative stress, eventually culminating in improved LV function in rats with CMI. These findings suggest that chronic modulation of mitochondrial fusion could be a promising pharmacological intervention to improve LV function in CMI.