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Aberrant endoplasmic reticulum stress mediates coronary artery spasm through regulating MLCK/MLC2 pathway

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Abbreviations: ER, endoplasmic reticulum; CAS, coronary artery spasm; MLCK, myosin light chain kinase; MLC2, myosin II regulatory light chain; VSMCs, vascular smooth muscle cells; 4-PBA, 4-phenylacetic acid; Tm, tunicamycin; UPR, unfolded protein reaction; IRE1, inositol requiring enzyme 1; PERK, double-stranded RNA-activated protein kinase (PKR)-like ER kinase; ATF6, activating transcription factor 6; ECG, electrocardiograph; qRT-PCR, quantitative real-time polymerase chain reaction; ACh, acetylcholine; 5-HT, 5-hydroxy tryptamine.

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Abstract

Coronary artery spasm (CAS) is a pathophysiological phenomenon that may cause myocardial infarction and lead to circulatory collapse and death. Aberrant endoplasmic reticulum (ER) stress causes accumulation of misfolding proteins and has been reported to be involved in a variety of vascular diseases. The present study investigated the role of ER stress in the development of CAS and explored the possible molecular mechanisms. Initially, it was found that ER stress markers were elevated in response to drug-induced vascular smooth muscle cells (VSMCs) contraction. Pharmacologic activation of ER stress using Tunicamycin (Tm) persistently induced CAS and significantly promoted Pituitrin-induced CAS in mice as well as in a collagen gel contraction assay. On the contrary, pharmacologic inhibition of ER stress using 4-phenylacetic acid (4-PBA) completely blunted Pituitrin-induced CAS development in mice. Moreover, during the drug-induced VSMCs contraction, expression of ER stress markers were increased in parallel to those of myosin light chain kinase (MLCK) and phosphor-MLC2 (p-MLC2, at Ser19). After inhibiting MLCK activity by using its specific inhibitor ML-7, the ER stress activator Tm failed to activate the MLCK/MLC2 pathway and could neither trigger CAS in mice nor induce VSMCs contraction *in vitro*. Our results suggested that aberrant ER stress mediated CAS *via* regulating the MLCK/MLC2 pathway. ER stress activators might be more robust than the common drugs (Pituitrin or acetylcholine) as to induce vasocontraction and thus may serve as potential therapeutics against chronic bleeding, while its inhibitor might be useful for treatment of severe CAS caused by other medication.