論文の内容の要旨

論文題目　The Role of Estrogen in Takotsubo Cardiomyopathy
（たこつぼ型心筋症におけるエストロゲンの果たす役割に関する解析）

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Objective:

High cAMP-activated protein kinase A driven by acute catecholamine surge triggers β2 adrenoreceptor (β2AR) switching from stimulatory guanine nucleotide regulator protein to inhibitory guanine nucleotide regulator protein (Gi) in Takotsubo syndrome (TTS). This Gi switch avoids cardiotoxicities from excess catecholamine by upregulating survival genes, and activating extracellular signal-regulated kinase (ERK) in TTS, but depresses cardiac contractility. On the other hand, animal studies have shown short-term estrogen exposure exerts protective effects in TTS by increasing contraction. Here we explore a better mouse model for TTS and estrogen delivery for investigating the role of chronic estrogen supplementation in switching of β2AR coupling and modulating contractility.

Methods and Results:

Single dose of epinephrine was intraperitoneally injected to reproduce transient cardiodepression in ovariectomized (ovx) and ovx plus 17β-estradiol pellet-implanted (ovx+E2) mice. Ovx+E2 mice had lower cardiac performance in echocardiography and hemodynamic parameters. Six-minute post-injection, ovx+E2 mice had higher phosphorylation of cAMP response element binding protein (pCREB) that can be abolished by G protein-coupled estrogen receptor 1 (GPER) antagonist. Conversely, 30-minute post-injection, another group of ovx+E2 mice had lower pCREB and lower contractility that could be converted by GPER antagonist. Six-hour post-injection, without GPER antagonist ovx+E2 mice had significantly higher phosphorylation of ERK which indicating Gi switch. At this timepoint, E2 ameliorated nitrosative stress, inflammation, and angiogenesis. One week after stress, E2 increased exercise tolerance and cardiac reserve.

Conclusions:

Through GPER, chronic E2 supplementation facilitates acute epinephrine stress triggered-β2-AR/Gi switch which depresses cardiac contractility. E2 may trade cardiodepression for preserving cardiac reserve.