

[課程－ 2]

審査の結果の要旨

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The present study investigated the role of chronic estrogen supplement in the pathogenesis of TTS using a novel TTS mice model.

1. The results showed that chronic estrogen supplementation via GPER facilitated epinephrine induced β 2-Gi switch which is responsible for acute cardiac dysfunction but it also exerted cardioprotective effects in antiinflammation, angiogenesis, and mitochondrial biogenesis.
2. In this model, acute epinephrine exposure induced a dose-dependent toxic effect with worst cardiac contractility 6 hours after injection and full recovery in one week. This transient cardiodepression in acute phase is Gi-dependent and exacerbated by chronic E2 supplementation and GPER signaling.
3. However, E2 regulates *Illb*, *Vegfa* and *Ppargc1a* gene expression and modifying nitrosative stress against acute catecholamine injury which may play a protective role in TTS.
4. In chronic phase, E2 confers better exercise tolerance in treadmill stress test and cardiac reserve in response to isoproterenol challenge.

This work demonstrates that GPER-dependent cardiodepression by chronic estrogen supplementation may be a trade-off for cardioprotection against acute catecholamine surge in TTS. よって本論文は博士（医学）の学位請求論文として合格と認められる。