Increased coupling of caveolin-1 and ER\(\alpha\) contributes to the Fragile X syndrome

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Abstract

Objective: Fragile X syndrome (FXS) is a form of inherited mental retardation in humans that results from expansion of a CGG repeat in the \textit{Fmr1} gene. Interaction between estrogen receptor (ER) and lipid raft caveolae is critical for the estrogen signaling. Here, we tested the hypothesis that impaired ER-caveolae coupling contributes to the mental retardation of Fragile X syndrome.

Methods: \textit{Fmr1} knockout (KO) mouse was used as the model of Fragile X syndrome. Multiple techniques were performed including primary neuronal culture, shRNA interference, western blot, electrophysiological recording, RNA-binding protein immunoprecipitation, RT-PCR, and behavioral tests.

Results: In this study, we reported that GluA1 surface expression and phosphorylation induced by 17\(\beta\)-estradiol (E2) were impaired in the \textit{Fmr1} KO neurons. The E2-mediated facilitation of long-term potentiation and fear memory was impaired in the anterior cingulate cortex of \textit{Fmr1} KO mice. The increased coupling of caveolin-1 (CAV1) and the membrane estrogen receptor ER\(\alpha\) under basal conditions contributed to the impairment of ER signaling in \textit{Fmr1} KO neurons. FMRP interacted with \textit{CAV1} mRNA, and knockdown of CAV1 with shRNA rescued the synaptic GluA1 delivery, plasticity, and memory in \textit{Fmr1} KO mice.

Interpretation: This is the first demonstration that the coupling between ER\(\alpha\) and lipid raft CAV1 is critical for the membrane estrogen receptor signaling in synaptic plasticity. Therefore, increased coupling of CAV1 and ER\(\alpha\) may elucidate one of the critical abnormal mechanisms for fragile X syndrome.

Key words: Fragile X syndrome; estrogen; caveolae; synaptic plasticity; learning and memory