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5-HT2CR Deficiency Causes Affective Disorders by Impairing E/I Balance through Augmenting Hippocampal nNOS-CAPON Coupling

Authors : Hu-Jiang Shi, Li-Juan Zhu

Abstract : The implication of 5-hydroxytryptamine 2C receptor (5-HT2CR) in affective behaviors is a topic of debate, and the underlying mechanisms remain largely unclear. Here, we elucidate that the interaction between hippocampal neuronal nitric oxide synthase (nNOS) and carboxy-terminal PDZ ligand of nNOS (CAPON) contributes to the disruption of hippocampal excitation-inhibition (E/I) balance, which is responsible for the anxiety- and depressive-like behaviors caused by chronic stress-related 5-HT2CR signaling deficiency. In detail, activation or inhibition of 5-HT2CR by CP809101 or SB242084 modulates nNOS-CAPON interaction by influencing intracellular Ca^{2+} release. Notably, the dissociation of nNOS-CAPON abolishes SB242084-induced anxiety- and depressive-like behaviors, as well as the reduction in extracellular signal-regulated kinase (ERK)/cAMP-response element binding protein (CREB)/synapsin signaling and SNARE complex assembly. Furthermore, nNOS-CAPON blockers restore the impairments caused by SB242084, including the reduction in SNARE assembly-mediated γ-aminobutyric acid (GABA) vesicle release and a consequent shift of the E/I balance toward excitation in CA3 pyramidal neurons. Conclusively, our findings disclose the regulatory role of 5-HT2CR in anxiety- and depressive-like behaviors and highlight the hippocampal nNOS-CAPON coupling-triggered E/I imbalance as a pivotal cellular event underpinning the behavioral consequences of 5-HT2CR inhibition.

Keywords : 5-HT2CR, anxiety, depression, nNOS-CAPON coupling, excitation-inhibition balance, neurotransmitter release
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