Professor　Seki Kenjiro
School of Pharmaceutical Sciences　Ohu University

Title: Role of GABAergic Circuitry between the Central Amygdala and Bed Nucleus of the Stria Terminalis in Inflammation-Induced Depressive-Like Behavior

Background and Purpose: Major depressive disorder (MDD) has been increasing worldwide, severely affecting patients' quality of life and imposing significant burdens on families and society. In Japan alone, the estimated annual economic loss associated with MDD exceeds 2 trillion yen. Understanding the neurobiological mechanisms underlying its onset is therefore critical for the development of preventive strategies and early interventions. In the present study, we focused on the central amygdala (CeA) and the bed nucleus of the stria terminalis (BNST), subcortical regions primarily composed of GABAergic neurons that are anatomically and functionally interconnected and play central roles in emotional regulation. Using a cytokine hypothesis-based mouse model, we investigated how the GABAergic circuitry between the CeA and BNST contributes to the expression of despair-like behaviors.

Research Outline: We employed an adeno-associated virus (AAV) vector targeting GAD67 to suppress GABAergic neuronal activity in the CeA and BNST and evaluated the resulting behavioral changes. Suppression of GABAergic neurons in the CeA enhanced despair-like behavior following lipopolysaccharide (LPS) administration, whereas suppression in the BNST significantly reduced such behavior. Retrograde neuronal tracing combined with GABAergic neuron-specific AAV vectors revealed that BNST neurons received inputs from CeA GABAergic terminals, and c-fos-positive neurons were colocalized with these inputs after LPS treatment. Intra-BNST administration of the GABA receptor agonist muscimol similarly induced despair-like behavior. These findings suggest that disinhibition of local BNST circuits due to reduced CeA-derived inhibitory input may underlie inflammation-induced despair-like behavior.

Future Prospects: This study provides a mechanistic insight into central neural circuits involved in inflammation-induced depressive symptoms, highlighting the functional role of CeA-BNST GABAergic connectivity. Future studies integrating input-output mapping and characterization of neuromodulatory peptides within this circuitry are expected to advance our understanding of MDD pathogenesis and facilitate the development of novel preventive and therapeutic strategies.

Reference

GABAergic circuit interaction between central amygdala and bed nucleus of the stria terminalis in lipopolysaccharide-induced despair-like behavior.
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