

## Chronic histamine decrease in adult mice induced depression-like behavior and impaired sleep-wake cycle

Yo Yamada<sup>1</sup>, Takeo Yoshikawa<sup>1</sup>, Fumito Naganuma<sup>1,2</sup>, Kazuhiko Yanai<sup>1</sup>

<sup>1</sup>*Dept. Pharmacol., Grad. Sch. Med., Tohoku Univ.*, <sup>2</sup>*Div. Pharmacol., Tohoku Med Pharm Univ.*

Histamine acts as a neurotransmitter in the brain. Histamine is synthesized from histidine by histidine decarboxylase (HDC). In the central nervous system, HDC-positive neurons exist in tuberomammillary nucleus (TMN) of posterior hypothalamus and project their axons to entire brain. Recent studies showed that chronic histamine decrease in adult was observed in several neurological disorders such as narcolepsy and Alzheimer's disease. However, it is still unknown whether this histamine decrease plays a causative role in the disorders or not. In present study, we induced chronic histamine deficiency in adult mice to reveal the direct involvement of impaired histaminergic nervous system in brain dysfunction. We stereotaxically microinjected adeno-associated virus expressing Cre-recombinase into TMN of adult HDC flox mice (HDC cKO mice) for long-term brain histamine decrease. Immunohistochemical analysis showed Cre expression in TMN in HDC cKO mice. We confirmed the reduced HDC mRNA expression and the decreased histamine content in HDC cKO brain. In the tail suspension test, immobility time was prolonged in HDC cKO mice. In home-cage locomotor activity test, activity counts during light period were decreased in HDC cKO mice. Additionally, we performed sleep analysis by measuring electroencephalogram and electromyogram. The analysis showed that cKO mice exhibited decreased wakefulness during light period. These results indicated that chronic dysfunction of histamine system caused depression-like behavior and impaired sleep-wake cycle in mice.