（学位第３号様式）

学 位 論 文 要 旨

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題　目	Elucidation of the mechanism of abnormal emotional behavior in Neu1-knockout zebrafish and its potential as a model of psychiatric disorders （シアリダーゼ Neu1 遺伝子欠損ゼブラフィッシュの 情動行動異常メカニズムの解明と精神疾患モデルとしての可能性）

Psychiatric disorders exhibit emotional abnormal symptoms such as depression, bipolar disorder, and schizophrenia. Recently, it has been reported that intracellular sialoglycoconjugate remodeling and the activity of the lysosomal autophagy system are dramatically altered in emotional abnormalities, but the details of these mechanisms are still unknown. Sialidase Neu1 is a glycosidase that is highly expressed in the brain and is responsible for the catabolic degradation of sialo-glycans in lysosomes. It is expected that the involvement of Neu1 in the remodeling of sialoglycoconjugates in emotional abnormalities, but the evaluation of the function regulatory by Neu1 in emotional abnormalities has not been conducted. In this study, we aimed to elucidate the alteration of emotional behavior by Neu1 deficiency and its mechanism by using Neu1-knockout zebrafish (Neu1-KO).

In normal behavioral tests, Neu1-KO had suppressed shoaling and aggression, suggesting reduced sociality. In the 3-Chambers test, Neu1-KO showed strong interest toward different fish species, whereas the wild type showed avoidance behavior. These changes in emotional behavior were consistent with down-regulated the mineralocorticoid receptor (mr), neuropeptide Y (npy), and isotocin (human oxytocin homolog, ist) genes in Neu1-KO. We then analyzed neuronal and glial cells properties to elucidate the mechanism of the abnormal emotional behavior in Neu1-KO. In microglia, accumulation of α2-3 sialo-oligosaccharides and enhancement of lysosomal exocytosis induced by sialylation of Lamp1a were observed in the Neu1-KO brain. The microglia of Neu1-KO were transformed to a neuropathic (M1) action accompanied by the secretion of inflammatory cytokines, resulting in neuronal degeneration occurred based on the necroptosis. Furthermore, the astrocyte was also activated in Neu1-KO, but the expression of their glutamate transporter-related genes was down-regulated. The expression of glutamate receptor genes in postsynaptic cells and downstream neuroplasticity-related genes were also decreased, suggesting reduced glutamatergic neuronal activity in Neu1-KO.

Our results suggest that abnormal microglial activation would trigger neuronal and glial cells alterations in Neu1-KO, resulting in reduced sociality and anxiety due to suppression of the hypothalamic-pituitary-adrenal system. In addition, the observed emotional behavior and alterations of neuronal and glial cells in Neu1-KO were quite similar to human psychiatric disorders such as autism spectrum disorder. We suggest the potential of Neu1-KO as a model of human psychiatric disorders.