CCR5 deficiency increases astrocytes activation and accelerates progression of Alzheimer's disease

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Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder characterized by progressive cognitive deterioration and memory loss. Activation of astrocyte has been known to be related with amyloid-beta (Aβ) generation and releasing pro-inflammatory molecules that lead to neuronal cell death in development of Alzheimer's disease (AD). In this study, we found that long-term and spatial memory functions were impaired in $CCR5^{-/-}$ mice. In the subsequent study, the causal relationship between activation of astrocytes and memory impairment was investigated. Immunoreactivity of glial fibrillary acidic protein (GFAP), representing the activation of astrocytes, was frequently observed in the brain of $CCR5^{-/-}$ mice compared with that of $CCR5^{+/+}$ mice. The co-localization of GFAP and CCR5 was observed in $CCR5^{+/+}$ mice, however, it was not observed in the brain of $CCR5^{-/-}$ mice even though the expression of GFAP was much higher. Paralleling with the activation of astorcytes, the $A\beta_{1-42}$ level was higher in the brain of $CCR5^{-/-}$ mice than that of $CCR5^{+/+}$ mice. The expression of β-secretase (BACE1) and its product C99 was also increased in the brain of $CCR5^{-/-}$ mice. Apoptosis of neuronal cell in the brain of $CCR5^{-/-}$ mice was higher than that of $CCR5^{+/+}$ mice by detection of TUNEL assay. Recent study suggests that lack of CCR5 can be increased CCR2, lead to activation of astrocytes, by compensative mechanism. According to this study, we performed that western blot and immunohistochemisty of CCR2. The expression of CCR2 in the brain of $CCR5^{-/-}$ mice was higher than that of $CCR5^{+/+}$ mice. Immunohistochemistry also showed that CCR2 was increased in the brain of $CCR5^{-/-}$ mice compared with that of $CCR5^{+/+}$ mice. The co-localization of GFAP and CCR2 was stronger in $CCR5^{+/+}$ mice than that of $CCR5^{-/-}$ mice. These findings suggest that lack of CCR5 increases expression of CCR2, lead to activation of astrocytes which cause to Aβ generation, and thereby impairs the memory function. Therefore, lack of CCR5 may be critical to in the progress of AD.

Key Words: CCR5, astrocytes, Aβ, memory dysfunction