論 文 要 旨

Involvement of brain fractalkine-CX3CR1 signaling in cognitive deficiency of diabetic mice

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PART Ⅰ：Reduced brain fractalkine-CX3CR1 signaling is involved in the impaired cognition of streptozotocin-treated mice

Patients with diabetes mellitus are predisposed to cognitive impairment. Fractalkine-CX3CR1 in the brain signaling represents a primary neuron-microglia inter-regulatory system for several brain functions including learning and memory processes. The present study addressed whether fractalkine-CX3CR1 signaling in the hippocampus contributes to the cognitive deficits observed in streptozotocin (STZ)-treated mice. Our results showed that STZ-treated mice exhibited significant cognitive deficits in the Y-maze test, and a decrease in fractalkine and CX3CR1 levels in the hippocampus. Moreover, intracerebroventricular injection of the CX3CR1 antagonist 18a in normal mice induced significant cognitive deficits in the Y-maze test. STZ-treated mice showed a significant increase in plasma corticosterone levels and a decrease in plasma and hippocampal levels of insulin-like growth factor-1 (IGF-1). Therefore, we examined the effects of corticosterone and IGF-1 on regulation of fractalkine and CX3CR1 expression. Dexamethasone (DEX) application significantly decreased the mRNA expression of fractalkine in primary neuron and astrocyte cultures, and of CX3CR1 in primary microglia cultures. On the other hand, IGF-1 application significantly increased the mRNA expression of fractalkine in primary neuron cultures and CX3CR1 in primary microglia cultures. In addition, administration of DEX and the IGF-1 receptor tyrosine kinase inhibitor picropodophyllin significantly reduced the mRNA expression of fractalkine and CX3CR1 in the hippocampus. These findings indicate that impaired cognition in STZ-treated mice is associated with reduced fractalkine-CX3CR1 signaling in the hippocampus which may be induced by an increase in corticosterone and a decrease in IGF-1.

PART Ⅱ：Impaired brain fractalkine-CX3CR1 signaling is implicated in cognitive dysfunction in diet-induced obese mice

Introduction A diet high in saturated fat is well known to affect neuronal function and contribute to cognitive decline in experimental animals and humans. Fractalkine released from neurons acts on its receptor, CX3CR1 in the microglia to regulate several brain functions. The present study addressed whether fractalkine-CX3CR1 signaling in the brain, especially the hippocampus,

contributes to the cognitive deficits observed in diet-induced obese (DIO) mice.

Research design and methods Mice were given 60% high-fat diet for 16 weeks. The expression of fractalkine and CX3CR1 in the hippocampus, amygdala and prefrontal cortex of DIO mice was analyzed. Cognitive ability in the Y-maze test and hippocampal glutamate receptors and synaptic markers were observed in DIO and CX3CR1 antagonist-treated mice. Regulation of fractalkine and CX3CR1 expression in the hippocampus were examined following administration of a selective insulin-like growth factor-1 (IGF-1) receptor inhibitor and a TrkB antagonist in normal mice.

Results DIO mice exhibited significant cognitive deficits in the Y-maze test and decrease in fractalkine and CX3CR1 in the hippocampus and amygdala compared with mice fed a control diet (CD mice). Administration of the CX3CR1 antagonist 18a in normal mice induced significant cognitive deficits in the Y-maze test. DIO mice and CX3CR1 antagonist-treated mice exhibited significant decreases in protein levels of NMDA receptor subunit (NR2A), the AMPA receptor subunit (GluR1) and post synaptic density protein 95 in the hippocampus compared with their respective controls. Furthermore, plasma IGF-1 and hippocampal brain-derived neurotrophic factor were significantly decreased in DIO mice compared with CD mice. Administration of a selective IGF-1 receptor inhibitor and a TrkB antagonist in normal mice significantly decreased fractalkine and CX3CR1 in the hippocampus.

Conclusions These findings indicate that the cognitive decline observed in DIO mice is due, in part, to reduced fractalkine-CX3CR1 signaling in the corticolimbic system.