News Release

Title

Microinjection of Reelin into the mPFC prevents MK-801-induced recognition memory impairment in mice

Key Points

- The medial prefrontal cortex (mPFC) was important to prevent MK-801-induced recognition memory by microinjection of Reelin
- The preventive effect of Reelin required to acting on its receptors
- Microinjection of Reelin suppress neural activity in the mPFC of MK-801-treated mice

Summary

The research team led by Prof. Kiyofumi Yamada (Department of Neuropsychopharmacology and Hospital Pharmacy, Nagoya University Graduate School of Medicine) showed that Reelin prevents MK-801-induced recognition memory impairment by acting on its receptors to suppress neural activity in the medial prefrontal cortex (mPFC) of mice. Several studies have reported that mutations in gene RELN and low Reelin expression are associated with schizophrenia (SCZ). Our previous report showed that microinjection of Reelin into cerebral ventricle prevents cognitive and sensory-motor gating deficits in the animal model of SCZ. However, it remains unclear whether and how Reelin ameliorates behavioral abnormalities in the SCZ model. In the present study, we evaluated the effect of recombinant Reelin microinjection into the mPFC on MK-801-induced abnormal behaviors in the SCZ model. Microinjection of Reelin into the mPFC prevented impairment of recognition memory and an increase in c-Fos-positive cells, neural activity marker, in MK-801-treated mice. A K2360/2467A Reelin that cannot bind to its receptor failed to ameliorate MK-801-induced cognitive deficits.

Research Background

The extracellular matrix glycoprotein Reelin, secreted by Cajal-Retzius cells, plays an important role in neuronal migration and layer formation during brain development. In the adult brain, Reelin is mainly produced by gamma-aminobutyric acidergic (GABAergic) interneurons, regulating neuronal plasticity and cognitive function. Reelin binds to the receptors such as apolipoprotein E receptor 2 and the very low density lipoprotein receptor, promoting phosphorylation of adapter protein Disabled-1 through the Src family kinases. Reduced Reelin expression has been involved in the pathogenesis of several neuropsychiatric disorders, including schizophrenia (SCZ). Previous reports have shown that Reelin supplementation improves or prevents abnormal behavior in animal models of Angelman syndrome and SCZ and promotes cognitive ability. However, the regions of the brain responsible for the effects of Reelin supplementation and the underlying mechanism of action remains unclear.

Research Results

To examine the effect of Reelin microinjection into the mPFC on MK-801-induced sensory-motor gating and cognitive dysfunction, mice were sequentially subjected to the prepulse inhibition (PPI), novel object recognition test (NORT), and Y-maze tests. Reelin microinjection into the mPFC had a significant protective effect on MK-801-induced impairment of object recognition memory in NORT. While, the same treatment showed a little effect against MK-801-induced impairment of performance in the PPI and Y-maze tests. To investigate the underlying mechanism of the protective effect of Reelin supplementation against MK-801-induced impairment of object recognition memory, we performed immunohistochemical analysis of c-Fos in the mPFC. Compared with the saline-treated control group, treatment with MK-801 significantly increased the number of c-Fos-positive cells in the mPFC. Microinjection of Reelin into the mPFC prevented the MK-801-induced increase in the number of c-Fos-positive cells. K2A Reelin, in which both Lys-2360 and 2467 are replaced with alanine, unable to bind to the Reelin receptor, and activate the signal transduction. We investigated the effect of microinjection of K2A Reelin into the mPFC on MK-801-induced memory impairment in NORT. While microinjection of WT Reelin significantly reduced MK-801-induced cognitive deficits, K2A Reelin had no effect.

Research Summary and Future Perspective

Our results indicated that Reelin prevents MK-801-induced recognition memory impairment by acting on its receptors to suppress neural activity in the mPFC of mice. We have previously demonstrated that inhibition of disintegrin and metalloproteinase with thrombospondin motifs-3 (ADAMTS-3), a protease that inactivates Reelin by cleavage at the N-t site, could be used to enhance Reelin signaling in the brain for the clinical treatment of SCZ. Our present findings provide further support for the use of ADAMTS-3 inhibitors in Reelin augmentation therapy for the treatment of neurodevelopmental disorders including SCZ.

Publication

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