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Research Report

Vulnerability of synaptic plasticity in the complexin II knockout mouse to maternal deprivation stress

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Abstract

The alterations in brain function and structure seen in schizophrenia are mediated by genetics as well as vulnerability due to environmental factors. Postmortem studies in schizophrenic patients have shown that expression of complexin II, which is involved in neurotransmitter release at central nervous system synapses, is decreased in the brain. We examined the physiological characteristics of complexin II gene-deficient mice subjected to maternal deprivation stress to determine whether psychological stress during the early stage of life affected the development of brain function. We compared the electrophysiological properties of CA1 hippocampal pyramidal neurons and spatial memory in the Morris water maze test in the wild-type mouse and the homozygous mutant. In the non-stressed mouse, no significant differences in transsynaptic responses and synaptic plasticity or spatial memory were seen, suggesting that complexin II does not play a critical role in transmitter release or synaptic plasticity under these conditions. In contrast, under conditions of maternal deprivation stress, the knockout mouse showed a significant decrease in post-tetanic potentiation and LTP induction and a significant impairment in Morris water Maze test compared to the wild-type mouse, suggesting that complexin II plays a significant role in neurotransmitter release and synaptic plasticity under this pathological condition. Taken together, these results show that mice lacking complexin II are vulnerable to maternal deprivation stress, which raises the possibility that the complexin II gene may be a factor in the onset of schizophrenia.
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Theme: Excitable membranes and synaptic transmission
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1. Introduction

The cellular mechanisms underlying learning and memory remain unclear, but most evidence supports the idea that the precise regulation of neurotransmitter release or synaptic strength is involved, as in long-term potentiation (LTP) [5]. The principal molecular mechanism underlying neurotransmitter release is the interaction between soluble N-ethylmaleimide-sensitive fusion protein (NSF) attachment protein receptors (SNARE). Different vesicle membranes have different receptors which mediate docking and fusion prior to neurotransmitter release; the v-SNAREs, known as VAMPs, are present on synaptic vesicles and the t-SNAREs, syntaxin and SNAP-25, on the plasma membrane. Furthermore, two cytoplasmic proteins, NSF and α-SNAP, bind to and disassemble the SNARE complex.

The complexins, complexin I (CPLX I) and complexin II (CPLX II), are highly conserved proteins which are expressed differently in the brain upon the circuitry connection of the

Abbreviations: A/D converter, analog/digital converter; CPLX, complexin; D-AP5, D-2-amino-5-phosphonovaleric acid; fEPSP, field excitatory postsynaptic potential; I/O relationship, input/output relationship; LFS, low-frequency stimulation; LTD, long-term depression; LTP, long-term potentiation; PPF, paired-pulse facilitation; PTP, post-tetanic potentiation; SNARE, soluble *N*-ethylmaleimide-sensitive fusion protein attachment protein receptor

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neuron [10]. In the hippocampus, CPLX II is preferentially expressed in the excitatory neurons [13]. CPLXs were identified as presynaptic proteins that bind to the neuronal SNARE complex following vesicle fusion [16,32]. In vitro, they bind with a 1:1 stoichiometry to the assembled synaptic SNARE complex, making CPLXs attractive candidates for controlling the exocytotic fusion apparatus. Although the involvement of CPLXs in synaptic vesicle exocytosis has been reported [1,19,24,33], their precise physiological role and mode of action remain unclear.

Changes in CPLXs have been implicated in mental disease, including schizophrenia. Patients with schizophrenia have decreased levels of CPLX mRNA and protein in the hippocampal formation associated with a greater loss of CPLX II than CPLX I [6] and have decreased levels of CPLX II mRNA and protein in the cerebellar cortex [7]. Because the changes in expression of CPLX proteins observed in brain tissue from schizophrenic patients are specific in terms of the region of the brain and the isoform involved, these findings support the idea that altered circuitry caused by abnormal synaptic function is a component of the pathophysiology of schizophrenia.

Genetic epidemiological investigations, including family, twin and adoption studies, suggest that psychiatric conditions, such as schizophrenia and mood disorders, reflect a combination of genetic and environmental factors [34]. A study of identical twins showed that average concordance rates are far lower than would be expected on the basis of genetic equivalence alone, suggesting an effect of environmental factors on neurodevelopmental processes during the early (pre- and perinatal) and late (postnatal and adolescent) period and on the etiology and pathophysiology of schizophrenia [3,35]. A growing body of evidence supports the hypothesis that psychosocial stress plays a role in the expression of symptoms in schizophrenia, as it interacts with the latent neural vulnerability that stems from genetic liability and early environmental insult [15,20,27]. Advances in the understanding of the neurobiology of the stress cascade in both animal and human studies have led to a plausible model in which this interaction would occur through neurotoxic effects on the hippocampus that may involve synaptic remodeling. Precise biological mechanisms that result in behavioral changes in adulthood caused by stress in the early stage of life have been reported. Zhang et al. [38] reported that prolonged maternal deprivation stress can alter normal brain development by increasing cell death of neurons and glia in the cerebral and cerebellar cortex with an induction of nerve growth factor (NGF) which is one of neurotrophins involved in growth and differentiation of neurons. Cirulli et al. [4] reported that early maternal separation in neonatal rats resulted in increased expression of NGF mRNA in the dentate gyrus and the hilus of the hippocampus. These observations provide a potential mechanism by which early environmental stressors may influence subsequent behavior.

Clinical studies have indicated a correlational link between hippocampal pathology and mental stress. Individuals with the stress-related psychiatric condition, posttraumatic stress disorder, have a smaller hippocampal volume, which is possibly related to the hippocampal dysfunction [36], and there is a significant association between the size of the hippocampal fissure and symptoms during the onset of schizophrenia [30]. Although there is no conclusive evidence that psychological stress is a factor in the pathogenesis of schizophrenia, these facts indicate that hippocampal abnormality generated during an early stage of life may be involved [2,12]. In this report, we developed CPLX II gene-deficient mouse and applied maternal deprivation stress, a typical psychological stress, to this knockout mouse at the early stage of life, then the physiological property of hippocampal function at the developed stage was examined to show the hypothesis that decreased CPLX II is a genetic factor involved in the pathogenesis of schizophrenia.

2. Materials and methods

2.1. Animals

To examine whether the above-mentioned changes in genetic factors seen in psychiatric patients cause vulnerability to stress during the postnatal period, we have used the CPLX II gene knockout mouse, which were developed in our laboratory [31]. As a neurodevelopmental model, we examined the effect of maternal deprivation stress, a physiological form of psychological stress, on subsequent behavior and hippocampal function. The homozygotes were back-crossed to C57Bl/6 mice for more than 10 generations to stabilize the genetic background before use, and heterozygous mutant mice (+/−) were interbred to obtain mice homozygous for the inactive CPLX II gene. The heterozygous and homozygous mutants grew normally and exhibited no obvious physical abnormalities up to at least the age when we ended our study, generally at 9 weeks. Genotypes were confirmed by an allele-specific polymerase chain reaction on tail tips. Each litter, regardless of genotype and sex, was housed together in a plastic cage at 22 °C on a 12-h light/dark cycle (lights on at 7:00 and off at 19:00) until 30 days old, thereafter they were housed separately according to their sex. Each litter was housed with its natural mother. Food and water were provided ad libitum. Homozygous mutant (CPLX II −/−) and wild-type (wild-type +/+) mice were used in the experiments.

2.2. Maternal deprivation stress

The maternal deprivation procedure was performed by removing the pup from the home cage and by placing it in a separate clean cage at ambient temperature. This process was carried out once daily for 1 h from post natal day (PND) 2 to PND 15. The mice were otherwise left undisturbed, except for routine cage maintenance, which was performed once a week. Immediately after the last session (PND 15),

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