PKC gamma-mediated signaling and schizophrenia

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Schizophrenia is a complicated mental disorder. Although multiple hypotheses have been proposed to interpret the molecular mechanisms underlying the pathogenesis of the disease, the key pathological process is yet blurry. Early clinical studies have implicated a role of the histidine triad nucleotide-binding protein-1 (Hint1) in the pathogenesis of schizophrenia. A most recent investigation by Zhang et al has defined the activity of protein PKC gamma (PKCγ) in the brain using Hint1-knockout animal model. Their finding that Hint1-deficiency causes a compromised PKCγ signaling in the brain may shed a new light on the glutamate hypothesis of schizophrenia.

Keywords: schizophrenia; protein kinase C gamma; phosphorylation signaling

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Schizophrenia is a complicated psychiatric disorder that afflicts more than 60 million people worldwide (1% of the population) [1]. This disorder is characterized by breakdown of thought processes and emotional responses and featured by positive or negative clinical findings, which significantly hamper patient’s abilities in learning, work, and socialization. Etiologically, both genetics and environment influences, such as a family history of schizophrenia or long-term pressure/anxiety, have been shown to be important contributory factors for the development of schizophrenia. In past decades, although the dopamine hypothesis of schizophrenia, the 5-hydroxytryptophan (5-HTP) hypothesis of schizophrenia, and the glutamate hypothesis of schizophrenia have been proposed to explain the development of the disease, the key pathological event underlying schizophrenia remains unclear.

To explore the critical mechanisms underlying the pathogenesis of schizophrenia, Zhang et al recently applied Hint1-knockout animal to investigate the activity of PKCγ in the brain [2]. The histidine triad nucleotide-binding protein-1 (Hint1), a member of the histidine triad protein family, has been found significantly down-regulated in the prefrontal cortices of patients with schizophrenia in RNA and protein levels in clinical studies [3-5]. And also Hint1 null mice have been showed to exhibit increased anxiety and enhanced sensitivity to aversive environment and psycho-stimulation [6-8]. In the study, Zhang et al found that Hint1 deficiency impaired the normal phosphorylations response of the signaling molecule PKCγ upon psycho-stimulation, particular at the sites required for the full activation of PKCγ, in the brain structures that involved in cognition and emotion-control. This finding indicates for the first time an abnormally PKCγsignaling in the anxiety-related brain [2].

PKCγ is a member of serine/threonine-specific protein kinase family. The expression of PKCγ is solely in neurons with predominant distribution at postsynaptic sites. In the brain, most abundant PKCγ proteins localize in the structures that are involved in learning, memory, and emotion control, such as hippocampus, amygdale et al. Physiological studies have shown that several neuronal functions, including long...
term potentiation (LTP) and long term depression (LTD), specifically require PKCγ [9]. Synaptic plasticity, a property of neuron modulated by the ionotropic glutamate receptors (iGluRs) and the metabotropic glutamate receptors (mGluRs), is vital for LTP and LTD. iGluRs are Ca²⁺ channels that mediate the majority of excitatory neurotransmission in the brain. Any increase or decrease in the number of iGluRs at the postsynaptic membrane can change synaptic efficacy and strength, which represents a critical molecular mechanism underlying the response or adaptation of neuron for outside stimulation to form LTP or LTD. mGluRs are not ion channels but G-protein-coupled receptors. Instead, mGluRs activate biochemical cascades to modify downstream proteins such as ion channels to regulate synaptic plasticity. PKCγ is a crucial kinase involved in such modification process via regulating the distribution and translocation of ion channels at the postsynaptic membrane, particularly the N-methyl-D-aspartate receptor (NMDAR) and the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), to affect synaptic strength [9-12]. Intracellular PKCγ can be directly activated by diacylglycerol (DAG), a rapid product of mGluRs input, in presence of Ca²⁺. In physiology, PKCγ activation is actually a consequence of the synergistic interplay between mGluR input (DAG production) and iGluR input (Ca²⁺ generation) [10]. Therefore, PKCγ may act as a molecular coincidence detector that integrates signals from the two groups of receptor to tune the synaptic efficacy and strength.

Such finely tuning of PKCγ activity is clearly interrupted in Hint1-deficient brain. How Hint1 affects the activation of PKCγ is yet lacking of clues, because the physiological function of Hint1 per se is largely unknown. While the compromised response of PKCγ in Hint1-deficient brain upon psycho-stimulation strongly imply a failed PKCγ-mediated signaling in neuron, which could be a highly possible factor contributing to abnormally regulated synaptic plasticity in cognition/emotion-related disorders, such as schizophrenia. Notably, mice lacking PKCγ also exhibited altered anxiety-related behaviors [13]. As a matter of fact, hypofunction of glutamtergic signaling in schizophrenia (the glutamate hypothesis of schizophrenia) has become one of most acceptable explanations for the disease, despite that detailed mechanism is under investigation. So the abnormalities in PKCγ-mediated signaling in synaptic plasticity might be next valuable research area to understand the pathogenesis of schizophrenia.

**Announcement**

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**References**