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Spine Homeostasis as a Novel Therapeutic Target for Schizophrenia

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Abstract

Schizophrenia is a complex disorder with positive, negative and cognitive symptoms. Previously, great reduction in spine number has been reported in schizophrenia patients. Mutations in numerous genes that encode synaptic proteins are known as genetic risk factors. In addition, antipsychotic drugs change the number of spines, suggesting that disturbance in spine homeostasis is deeply involved in the pathogenesis of schizophrenia. On the other hand, abnormal release of dopamine is also reported to play a role in the disease. However, the relationship between the spine homeostasis and the dopaminergic system is largely unknown. Here, we review the related articles that can give us useful insight about spine homeostasis in schizophrenia. We hypothesize that the treatment for spine homeostasis can be a novel therapeutic method for schizophrenia.

Spine Disturbances in Schizophrenia

Schizophrenia is a complex disorder with positive, negative and cognitive symptoms [1]. In schizophrenia, a reduction in the number of dendritic spines on excitatory glutamatergic pyramidal neurons is reported in the frontal and temporal association cortex [2,3]. In addition, spine density of pyramidal neurons decreased in the dorsolateral prefrontal cortex [4]. The spine homeostasis in pyramidal neurons, playing important roles in corticocortical connectivity and working memory, is disturbed in schizophrenia. Also, the synaptic homeostasis in hippocampal formation is morphologically impaired [5,6].

The mutations in numerous genes that encode synaptic proteins in schizophrenia patients, such as *DISC1, neuregulin-1*, and *dysbindin*, have been reported [7]. DISC1, disrupted in schizophrenia, which was identified at the break point on chromosome 1q42 in Scottish family, is expressed at synapses of dendritic spines in the prefrontal and parietal cortex [8]. DISC1 is localized to mitochondria in cortical neurons and DISC1/FEZ1 complex is needed for the transportation of mitochondria from soma to axon and dendrites [9,10]. Neurons cannot extend their neurites without those mitochondria [11]. These results suggest that DISC1 is an important component to keep spine homeostasis. Type I transmembrane protein Neuregulin-1 (NRG1), also known as heregulin or NDF, is expressed in cortical neurons and their synaptic terminals on spines, and its receptor ErbB4 is located in postsynaptic spines [12,13]. NRG-1 released from nerve terminals modulates transmission at excitatory synapses by modifying postsynaptic receptors [14]. Prevention of NRG1/ErbB4 signaling destabilizes AMPA receptors and leads to loss of synaptic NMDA currents and decrease in spine size [15]. The hypofunction of NMDA signaling via increased NRG1/ErbB4 signaling was reported in post-mortem brains of schizophrenia [16]. In deed, the mutations of *NRG1/ErbB4* have been reported as genetic risk factors in schizophrenics [17-20]. Dysbindin-1 expressed in the cortex is associated with microtubles and postsynaptic densities of spines at certain synapses [21]. At glutamatergic presynaptic terminals, Dysbindin-1 is also binding to Snapin, which primes synaptic vesicles for exocytosis [22]. Over-expression and SNP association of dysbindin is reported of Dysbindin-1 results in enhanced glutamate release at synapses and SNP association of *dysbindin* is reported [23]. Since these molecules play important roles in synaptic transmission, dysfunction of these molecules by genetic mutations may cause synaptic loss with disturbance of spine homeostasis and disruption of neural networks with loss of dendrites.

Okubo et al. [24] found that dopamine D1 receptor was reduced in prefrontal cortex in schizophrenia patient. The reduction correlates with the severity of the negative symptoms. Therefore, the disturbance of spine homeostasis may result in negative symptoms and cognitive deficits in schizophrenia.

Spine Homeostasis and Dopamine D1 Receptor System

Spine homeostasis is an important phenomenon to keep brain functions. Spine plasticity consists of two categories. One is short-term plasticity, which is regulated by conductance changes of ion channels located in spines, and plays a pivotal role in working memory [25]. The functions of prefrontal cortical working memory depend on pyramidal cell networks that interconnect on dendritic spines. The strength of prefrontal cortical network connections can be rapidly increased or decreased by molecular signaling events within spines. This form of neuroplasticity provides great adaptability in mental state, but also gives vulnerability and limits mental capacity [25]. Many genetic and/or environmental insults to this short-term plasticity are associated with cognitive disorders [25]. The other is long-term plasticity, which needs protein synthesis and rearrangements of cytoskeleton in spines, playing a pivotal role in memory and learning [26]. In the mammalian forebrain, spines are very plastic and can rapidly change the shapes in response to numerous stimuli. This dynamic remodeling of dendritic spines is thought to be important for processing, cognition and memory of information [26].

Antipsychotic drugs, clozapine and haloperidol, change the number of spines, suggesting that disturbance in spine homeostasis is deeply involved in the pathogenesis of schizophrenia [27]. On the other hand, abnormal release of dopamine is also reported to play a role in the disease [28].

Interestingly, dopaminergic D1 system is involved in both types of spine plasticity. For the short-term plasticity, dopamine acts at D1 receptors on spines to sculpt network inputs to decrease noise

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in the prefrontal cortex [29]. D1 receptors exist on dendritic spines near excitatory network inputs in the prefrontal cortex [30]. The microcircuits consist of recurrent excitatory pyramidal cell networks that interconnect on spines, and excite each other via NMDA receptor signaling. Persistent firing of pyramidal cells is sculpted by lateral inhibition from GABAergic basket and chandelier cells, thus creating tuned, persistent firing needed for accurate representational knowledge [29]. The strength of pyramidal cell network connections is weakened by dopamine D1 receptors via opening hyperpolarization-activated cyclic nucleotide-gated channels in dendritic spines, resulting in decreased noises [31]. Thus, dopamine D1 receptor plays an important role to keep short-term spine homeostasis.

In addition, the dopaminergic D1 system is involved in synaptic stability and long-term plasticity. Epac2, a GEF for the small GTPase Rap, has recently been described as a novel cAMP target localized to dendritic spines [32]. Signaling of Epac2 in response to pharmacological stimulation or cAMP accumulation, via dopamine D1 receptors, activates Rap and promotes structural destabilization of dendritic spines and functional depression due to removal of glutamate receptor (GluR2/3)-containing AMPA receptors [26]. Brief exposure to a D1 agonist increased surface expression of GluR1-containing AMPA receptors by increasing their rate of externalization at extra-synaptic sites and promoted LTP [33]. Taken together, both short-term and long-term spine plasticity are tightly regulated by dopamine D1 receptors.

Compensatory Dopaminergic Changes

Dopamine D1 signaling keeps adequate functions in the prefrontal cortex. If spine homeostasis is disturbed and cognitive deficits appear, an intrinsic compensation system for dopamine may be activated to increase the amount of dopamine to keep the adequate functions in the prefrontal cortex. The prefrontal cortex receives dopaminergic fibers from the ventral tegmental area. Dopaminergic neurons are known to show several patterns of activity [34,35]. The population activity, i.e. the proportion of dopamine neurons firing spontaneously, is regulated by the ventral subiculum of the hippocampus [36,37]. In contrast, burst firing, related to the behaviorally important out-put of the dopamine system, is driven by the brainstem pedunculopontine tegmentum [37,38]. When an animal is exposed to a behaviorally important stimulus, the pedunculopontine tegmentum elicits a burst of action potentials in dopamine neurons. However, this bursting only happens in the portion of the dopamine neuron population that is firing spontaneously [38]. This proportion is regulated by the ventral subiculum. Therefore, the ventral subiculum provides the gain for the behaviorally important stimulus. Interestingly, the anterior hippocampus, the human homolog of the ventral subiculum, is overactive in schizophrenia patients [39-43]. The over-activation in the anterior hippocampus may increase the proportion of dopaminergic neurons firing spontaneously, resulting in the hyperactive states of dopaminergic system. Therefore, antagonist of dopamine D2 receptor, such as Chlorpromazine, seemed to be useful treatment for positive symptoms.

Consequences

As consequences, we want to postulate a story for the pathogenesis of schizophrenia as follows. Epigenetic vulnerability, prenatal events, developmental events, emotional factors and environmental factors may disturb spine homeostasis. And, the disturbance of spine homeostasis may result in negative and cognitive deficits. To adapt these conditions, dopamine D1 receptors are activated by compensatory dopaminergic hyperactivity. This hyperactivity secondly over-activates dopamine D2 receptors, resulting in positive symptoms. Many antipsychotic drugs antagonize dopamine D2 receptors. However, these drugs are not so effective to negative symptoms, suggesting that dopamine D2 receptor over-activation is secondary as we postulate. As therapeutical issues, since there are many kinds of receptors in spine to keep its homeostasis, these receptors are the targets to develop new drugs. Thus, we want to emphasize that spine homeostasis can be a novel therapeutic target for schizophrenia

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