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The role of integrin beta in schizophrenia: a preliminary exploration

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Review

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Abstract

Integrins are transmembrane heterodimeric (αβ) receptors that transduce mechanical signals between the extracellular milieu and the cell in a bidirectional manner. Extensive research has shown that the integrin beta (β) family is widely expressed in the brain and that they control various aspects of brain development and function. Schizophrenia is a relatively common neurological disorder of unknown etiology and has been found to be closely related to neurodevelopment and neurochemicals in neuropathological studies of schizophrenia. Here, we review literature from recent years that shows that schizophrenia involves multiple signaling pathways related to neuronal migration, axon guidance, cell adhesion, and actin cytoskeleton dynamics, and that dysregulation of these processes affects the normal function of neurons and synapses. In fact, alterations in integrin β structure, expression and signaling for neural circuits, cortex, and synapses are likely to be associated with schizophrenia. We explored several aspects of the possible association between integrin β and schizophrenia in an attempt to demonstrate the role of integrin β in schizophrenia, which may help to provide new insights into the study of the pathogenesis and treatment of schizophrenia.

Introduction

Integrins are heterodimeric (αβ) extracellular matrix (ECM) receptors that mediate cell-matrix and cell-cell adhesion. Integrin β is an essential subunit in heterodimers, and eight different β subunits have been identified that can form a variety of integrin αβ heterodimer combinations with different α subunits, which are important in the developmental maturation of the nervous system. In particular, integrins containing β1 and β3 subunits have been most studied. β-class integrins are closely associated with synapses and play a critical role in the regulation of synaptic function. Integrin β family members also regulate a variety of neurotransmitters, hormones, and protein peptides, such as serotonin (5-HT), glutamate, estrogen, and neurotrophic factors.

Schizophrenia is a polygenic disorder characterized by psychosis, apathy, social withdrawal, and cognitive impairment.[1] It consists of three types of symptoms, negative, positive, and cognitive.[2] Its etiology is currently unknown, but it is associated with developmental processes in the brain and multiple neurotransmitters in the brain, and several different hypotheses have been proposed, including neurodevelopmental and neurochemical hypotheses.[2] Due to the pathogenesis of schizophrenia remains unclear, its treatment presents many challenges.

In schizophrenia-related studies, despite growing evidence of an association between integrin β and schizophrenia, it remains difficult to understand why and how altered integrin β adhesion and signaling can lead to the onset or development of schizophrenia. Here, we discuss the evidence linking integrin β to schizophrenia. We focus on common mechanisms and recurrent signaling pathways in an attempt to connect the dots between integrin β molecular structure, signaling, synaptic function, and schizophrenia and to suggest clinical ideas for exploring the pathogenesis of schizophrenia and studying the treatment related to integrin β and schizophrenia.

Integrin β and DISC1

In earlier years, a study found significantly increased expression of platelet integrin αIIbβIIIa in drug-naive, first-episode schizophrenic patients by comparison with healthy controls.[3] Subsequently, another study identified polymorphisms in the integrin β3 gene (ITGB3) associated with the age of onset of schizophrenia through statistical analysis of big data.[4] Disrupted-in-schizophrenia 1 (DISC1) is a major psychiatric disease susceptibility gene associated with the molecular mechanisms of schizophrenia,[5] and it is involved in many critical neurodevelopmental

processes, including neurite growth, neuronal migration, and differentiation.[6-8] In which, it has been shown that DISC1 regulates cell adhesion by increasing the expression of integrin β1, which promotes neurite growth.[7] Therefore, integrin β can be linked to schizophrenia through DISC1. Integrin β has also been associated with several symptoms of schizophrenia. Integrin β3 knockout mice exhibit diminished preference for social novelty in a novel environment, increased repetitive behavior[9] as well as abnormal anxiety-like behavior,[10] exaggerated vulnerability under chronic unpredictable stress, and changes in midbrain synaptophysin and dopamine metabolism,[11] which are similar to some of the symptoms present in schizophrenia.

Integrin β and synapses

The function of synapses, that is, the connections between neurons, is important for brain function. Abnormalities in synaptic transmission and plasticity during neural development can lead to the development of schizophrenia.[12-15] And disruption of the glutamatergic signaling pathways associated with synaptic plasticity has also been linked to the etiology of schizophrenia.[16] In addition, schizophrenia susceptibility genes that play key roles in synaptic function,[17] such as D2 dopamine receptor (D2 DR), DISC1, neuregulin 1 (NRG1) and its receptor ErbB4, and voltage-gated calcium channels (VGCC) associated with schizophrenia etiology, have been widely reported for their regulation of synaptic plasticity and also interact with postsynaptic N-methyl-D-aspartate acid receptor (NMDAR).[18]

Not surprisingly, the close association between synapses and schizophrenia is described above, and integrin β is also known to play an important part in synapses (Figure 1). β1 integrins are essential for synapse formation,[19] and β1 integrins that aggregate post-synaptically can also function as adhesion proteins to mediate synaptic adhesion.[20] In hippocampal CA1 pyramidal neurons, ablation of α3 or β1 integrins at specific times during embryonic and postnatal life respectively affects the structure and function of excitatory synapses.[21-24] α3β1 integrin regulates synaptic and dendritic stability by binding to the ECM protein laminin α5,[25] and intracellularly it interacts with and activates the Abl2/Arg (Abl-related gene) non-receptor tyrosine kinase, thereby affecting actin remodeling in dendrites and spines.[21,22,26-28] β3 integrins affect synaptic strength by regulating the quantal size and content of excitatory synaptic transmission.[29,30] Integrin β also modulates synaptic plasticity. Synaptic plasticity in the adult hippocampus requires β1 integrins,[24] but β3 integrin is dispensable for Hebbian forms of plasticity in the hippocampus.[10] β1 class integrins also affect neuronal cytoplasmic calcium levels, thereby modulating the lasting synaptic plasticity in forebrain neurons.[31] Postsynaptic plasticity-related gene 1 (PRG-1) also affects synaptic plasticity in a cell-autonomous fashion by activating integrin β1.[32] Long-term potentiation (LTP) is a form of synaptic plasticity, and deletion of β1 integrins impairs LTP,[10,33] and in recent years it has also been shown that β1 integrins are involved in a novel form of cognition-related LTP triggered by endocannabinoid signaling in the hippocampus.[34] Synaptic homeostasis is also a form of synaptic plasticity, and β3 integrins are required in homeostatic plasticity.[29] In addition, integrins composed of β1 and α3 subunits are involved in the regulation of inhibitory synaptic plasticity.[35] Thus, alterations of integrin β activation and adhesion might therefore underlie some of the structural defects found in schizophrenic patients.

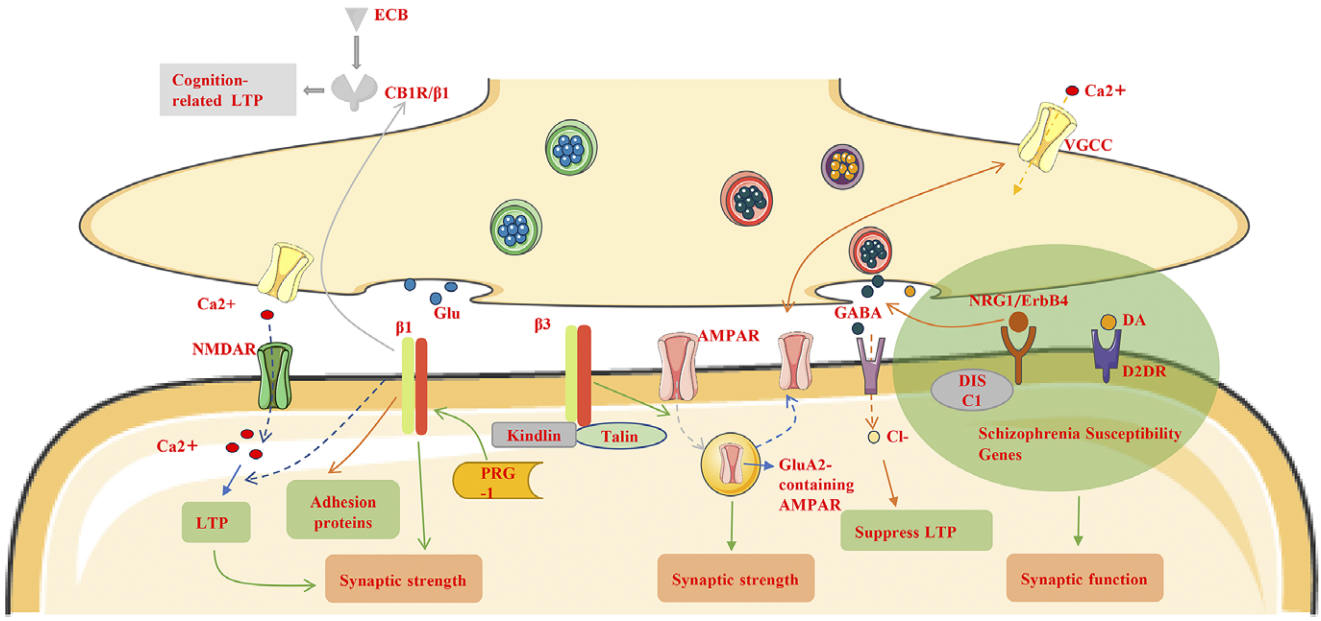

Figure 1. The association among integrin β, schizophrenia, and synapses.
Talin and Kindlin act as integrin activators, binding to the cytoplasmic tail of the integrin β subunits thereby activating integrins. LTP is a form of synaptic plasticity, and LTP induction mechanisms require synaptic NMDAR activation and Ca2+ influx to participate in downstream signaling cascades, whereas β1 integrin deficiency impairs LTP; therefore, it can be assumed that β1 integrin has a key role in NMDAR-dependent LTP-induced downstream signaling pathways.[36] PRG-1 affects synaptic plasticity in a cell-autonomous manner by activating integrin β1.[32] β1 integrin is also involved in a novel form of cognition-related LTP triggered by endogenous cannabinoid signaling in the hippocampus.[34] β3 integrins control synaptic strength by influencing alpha-amino-3-hydroxy-5-methylisoxazole-4-proprionate receptor (AMPAR). Under basal activity conditions, β3 integrins promote the internalization of GluA2-containing AMPAR, and after chronic activity stripping, β3 integrins are recruited to the cell surface via postsynaptic tumor necrosis factor signaling.[30] The green shaded section contains schizophrenia susceptibility genes (D2 DR, DISC1, NRG1, and ErbB4), which affect synaptic function in multiple ways. Of these, NRG1 can promote GABA release and thus inhibit LTP.[37-40] VGCC can interact with postsynaptic NMDAR[18] and regulate synaptic plasticity.

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Table 1. Distribution and Function of Integrin β in the Cerebral Cortex and Phenotype of Integrin β Subunit Deficient Mice

Subunits of integrin β	Classification by function[61]	Distribution of integrin β in the cerebral cortex	Phenotypes of integrin β deficient mice
β1	Mainly mediate cell–cell and cell–ECM adhesion	Widely expressed in the cerebral cortex[52,53]	a. Cortex developmental disorder and cortical lamination defects[55] b. Increased levels of N-cadherin and neuroligins[20] c. Reduced number of mature granule cells and reduced cerebellar size[46] d. Impaired LTP, selective cognitive deficits[24,33]
β2	Leukocytes specific, mediating cell rolling, and adhesion[62, 63]	–	Abnormal leukocyte adhesion and significantly reduced migration of dendritic cells to the site of infection[a64]
β3	Mainly mediate cell–cell and cell–ECM adhesion	–	a. Diminished preference for social novelty, increased repetitive behavior[9] b. Abnormal anxiety-like behavior[10] c. Exaggerated vulnerability under chronic unpredictable stress[11] e. Decreased total brain volume[47] d. Decreased platelet count, microcytic hypochromic anemia, splenomegaly[a65]
β4	Mainly mediate cell–cell and cell–ECM adhesion	–	a. Cell cycle and adhesion defects[a66] b. Abnormal collective migration of epithelial cells[a67]
β5	Mainly mediate cell–cell and cell–ECM adhesion	Widely expressed in the cerebral cortex[52,53]	Abnormal retinal function[a68,69]
β6	Mainly mediate cell–cell and cell–ECM adhesion	Neurons and oligodendrocytes in the adult cortex[52]	a. Enhanced keratinocyte proliferation and retarded hair follicle regression after depilation[a70] b. Regulating inflammation in the adult lung[a71]
β7	Leukocytes specific, mediating cell rolling and adhesion[62,63]	–	a. Diminished immune function mediated by intestine-associated lymphoid tissue[a72] b. Abnormal migration of small intestinal enterocytes[a73]
β8	Atypical integrin, mediating neither cell rolling nor adhesion	Diffusely distributed throughout the neuropil[54]	Abnormal vascular development and intracerebral hemorrhage[a74]

[a]Not phenotypes associated with schizophrenia.

Neuroanatomy of integrin β associated with schizophrenia

Most studies of schizophrenics reveal decreased volume of multiple structures in the brain.[41-44] One study showed a significant reduction in intracranial and total brain volume of 2.0% and 2.6% in medicated schizophrenia patients by meta-analysis.[45] β integrins also affect brain volume. Granule cell precursors in the cerebellum of mice with a central nervous system-restricted knockout of the integrin β1 subunit gene stop proliferating and differentiate prematurely, leading to a reduction in the final number of mature granule cells, as well as a reduction in cerebellar size.[46] Analysis of an ITGβ3 homozygous knockout mouse using MRI imaging revealed an 11% reduction in total brain volume.[47] Integrin β3 homozygous knockout mice associated with autism also had significantly smaller cerebellum than wild-type mice, with 28 out of 39 cerebellar structures smaller.[48]

Schizophrenia is associated with cortical thickness. Study finds cortical thinning in schizophrenia patients by high-resolution MRI imaging.[49,50] During cortical development, multiple β-integrins are expressed in the cortex and are closely associated with cortical formation and plasticity[51] (Table 1). β1 and β5 integrins are widely expressed and persist in the cerebral cortex,[52,53] β6 integrin is expressed in adult cortical primarily on neurons and oligodendrocytes,[52] and β8 is widely distributed throughout the neuropil.[54] Mice lacking β1 integrin have impaired cerebral and cerebellar cortex development, resulting in abnormal cortical neuronal positioning and defects in the laminar structure of the cerebral and cerebellar cortex,[55] and removal of β1 integrin at the embryonic stage in mice also results in severe cortical lamination defects.[33] β1 integrin and laminin-mediated glial-meningeal adhesive interactions are closely associated with the normal assembly of the cerebral cortex.[56]

Dysfunctional dendrites are a key feature of many developmental neurological disorders. Dendrites in prefrontal cortex (PFC) pyramidal cells are hypodense and small in schizophrenia. β integrins can also affect dendritic and axonal function. Study shows that neuronal α7β1 integrin can mediate neurite growth in the alternatively spliced region of human Tenascin-C.[57] Integrins can regulate actin reorganization in dendritic spines through NMDAR, thereby affecting dendritic spine plasticity.[58] Integrin β1 can regulate the size and complexity of hippocampal dendritic arbors through the β1- Arg-p190RhoGAP signaling cascade.[22] Integrin β1 also interacts with intercellular adhesion molecule-5 (ICAM-5) by regulating the ectodomain cleavage of ICAM-5, which in turn regulates dendritic spine morphology and synaptic maturation.[59] Integrin β3 organizes dendritic complexity of cerebral cortical pyramidal neurons along a tangential gradient.[60]

Integrin β associated with neurotransmitters in schizophrenia

Neurotransmitters have been the most active area of research on the etiology of schizophrenia. It has been shown earlier that platelet glutamate receptors may be hypersensitive in schizophrenic patients,[75] and the results support decreased glutamate function in schizophrenia.[76,77] Several studies have shown that neurotransmitters such as dopamine, serotonin, and glutamate are involved in the development of schizophrenia.[78-81] Some symptoms of schizophrenia may be due to hypofunction of NMDARs, especially in the

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PFC.[82] In addition, metabotropic glutamate (mGlu) receptors have long been used as important therapeutic targets for schizophrenia.[83-85] It has recently been shown that ITGB3, the gene encoding the ECM receptor integrin β3, can interact with mGluR5 to regulate the functional expression of synaptic mGluR5 and directly affect neuronal excitability.[86] Neurotransmitter imbalances play an important role in cognitive deficits in schizophrenia,[87] and depression and anxiety are also associated with imbalances in central nervous system 5-HT levels. And there is a close link between integrin β and several of those neurotransmitters.

Integrin β regulates glutamate

NMDARs and AMPARs are subtypes of ionotropic glutamate receptors, and mice with reduced NMDA receptor expression exhibit manifestations similar to schizophrenia.[88] Integrins can exert regulation of synaptic NMAD-type glutamate receptor operation by activating Src kinase,[89] and the activated local kinase cascade response enhances the function of synaptic NMDA receptors in the mature hippocampus, a response that is closely associated with β1 integrins.[90] The interplay between Reelin and β1 integrins is required also for the developmental switch in NMDAR subunit composition from GluN2B to GluN2A.[91-93] AMPA-type glutamate receptor activation increases α5 and β1 integrin surface expression, adhesive function, and signaling.[94] Postsynaptic β3 integrins directly interact with GluA2 AMPAR subunits through their respective C-termini and regulate AMPAR abundance and composition to control synaptic strength.[30,95] β1 integrins and ERK1/2 can mediate astrocyte-derived Pentraxin 3 (PTX3)-induced recruitment of synaptic AMPA glutamate receptors, thereby promoting synaptic maturation.[96] Binding of β1 integrin to vascular cell adhesion molecule 1 triggers glutamine, which stimulates glutamate release from Th17 cells.[97]

Integrin β regulates 5-HT

There is a strong association between β-integrin and whole blood serotonin levels, genomic scans identified ITGB3 (encoding integrin β3) as a quantitative trait loci for whole blood serotonin,[98] and common variation in ITGB3 is associated with serotonin concentrated in males.[99] A strong association between single-nucleotide polymorphisms (SNPs) in ITGB3 and serotonin levels was found in two outbred samples,[100] after which experiments showed that it was the SNP rs2317385, located at the 5' end of the ITGB3 gene, that significantly influenced 5-HT blood levels.[101] ITGB3 haplotypes were also significantly associated with the distribution of platelet serotonin levels.[102]

The transporter protein of 5-hydroxytryptamine (SERT) is a membrane protein that transports 5HT from the synaptic gap to presynaptic neurons, and knockout mice lacking integrin β3 showed reduced platelet SERT activity.[103] SLC6A4 is the gene encoding the 5-HT transporter, and it has been demonstrated through open genomic resources that the expression of SLC6A4 and ITGB3 is correlated in several tissues in humans and mice.[104] The 5-HT transporter and integrin β3 genes interact to regulate 5-HT uptake in the mouse central nervous system.[105] Changes in integrin β3 subunit expression can also regulate the rate of SERT-mediated 5-HT transport.[106] In recent years, a study has shown an important association between integrin β and both neuropsychiatric disorders by using knock-in mice of the Itgb3 variant to phenocopies the human Pro33 variant, which produces hyperactive αvβ3 receptors in mice, and found decreased 5-HT system function and multiple behavioral deficits in mice.[107] In a study based on samples from patients with autism spectrum disorder, the promoter variant rs55827077 of ITGB3 was found to increase platelet integrin β3 protein expression and elevated blood levels of 5-HT.[108] Integrin β3 is also associated with a mode of action with selective serotonin reuptake inhibitors (SSRIs) antidepressants,[109] and reduced expression of integrin β3 subunits reduces the effective dose of SSRIs by affecting the population size of active SERT molecules.[106]

Integrin β and BDNF

Brain-derived neurotrophic factor (BDNF) is a secreted peptide that is widely expressed in the nervous system and plays a key role in neuronal survival and synaptic plasticity. The role played by BDNF in schizophrenia has been extensively studied, and many studies have shown that serum BDNF levels are lower in schizophrenic patients[110-116] except that a few studies have found higher BDNF levels,[117,118] but what can be confirmed is that BDNF levels are altered in patients with schizophrenia.[119,120] Meta-analysis demonstrated a firm correlation between serum BDNF levels and the course of severe schizophrenia and major depression, suggesting that BDNF is a potential circulating biomarker for schizophrenia or depression.[121] In recent years, studies have supported that serum BDNF levels are lower in patients with first-episode schizophrenia than in healthy controls[122,123] and that abnormal signaling of BDNF increases an individual's susceptibility to schizophrenia by affecting brain function.[122] Lower BDNF levels are also associated with decreased cognitive performance in schizophrenia subjects.[124,125]

The relationship between integrin β and BDNF has not been well documented by research, but a few studies have indicated an association. Integrins bound to arginine-glycine-aspartate (RGD) matrix sequences can increase the expression of mRNAs for BDNF and its receptors TrkB and TrkC in hippocampal slices through effects on voltage-sensitive calcium channels, and although the specific integrin involved is unclear, it is likely to be related to integrin β1.[126] Neurotrophins promote the survival of newborn hippocampal neurons by promoting spontaneous GABA-dependent activity, and this survival effect requires integrin β1 signaling.[127] Integrin β1 is also involved in signaling of the glial cell line-derived neurotrophic factor (GDNF) and may function as a signaling receptor for GDNF.[128]

Integrin β and estrogen

Estrogen can function in schizophrenia by modulating the excitatory transmitter glutamate (Figure 2). In cultured hippocampal neurons, estrogen enhances glutamate release from presynaptic sites through activation of phosphatidylinositol 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK).[129] Several studies have shown that 17 β-estradiol (E2) enhances glutamatergic synaptic transmission in the hippocampus through mechanisms that increase presynaptic glutamate release probability[130,131] and postsynaptic sensitivity to glutamate.[131] Estrogen and integrin β are tightly related in many ways. Estrogen's effects on excitatory synaptic transmission entail transactivation of the BDNF receptors TrkB and β1 integrin, and β1 integrin function has a decisive role.[132] Estradiol activates integrin α5β1 to promote the attachment of striatal neurons to fibronectin, and activated integrin α5β1 also contributes to synapse formation of human-induced pluripotent stem cell-derived dopaminergic (DA) neurons.[133]

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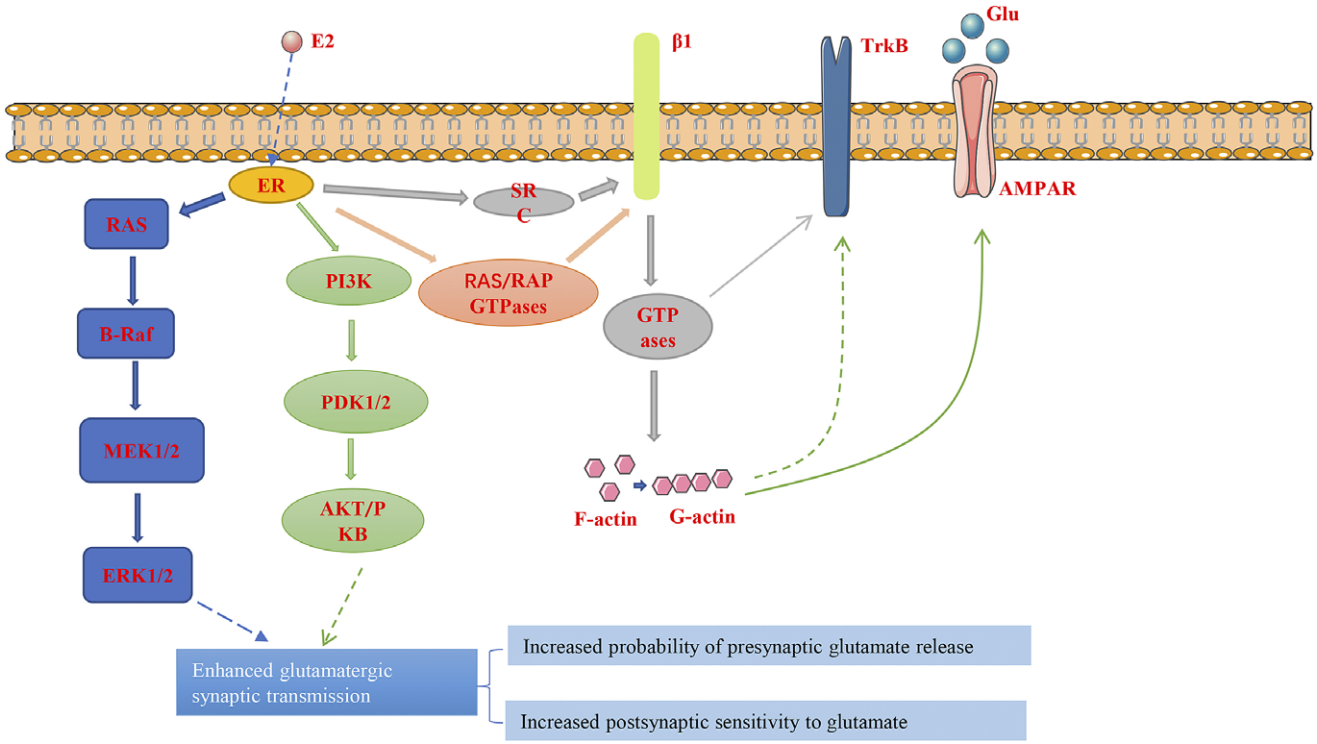

Figure 2. Schematic representation of the mechanism by which estrogen affects glutamatergic synaptic transmission.
E2 binds to the estrogen receptor ER and activates the classical MAPK pathway, causing phosphorylation and activation of the MAPK kinase B-Raf, the MAPK kinases MEK1/2 and the ERK1/2. E2 activates the PI3K signaling pathway, causing activation of phosphoinositide-dependent kinases (PDK1/2) and subsequently AKT/protein kinase B.[139] Both signaling pathways can enhance glutamatergic synaptic transmission. The mechanisms involved include increased presynaptic glutamate release probability[130,131] and postsynaptic sensitivity to glutamate.[131] In addition, E2 is involved in the activation of integrin β1 by acting on Src family kinases and Ras/Rap GTPases. Activated integrin β1 can drive downstream small GTPases that enable local polymerization of filamentous actin (F-actin) from actin monomers (G-actin), thereby affecting AMPAR. Activation of small GTPases can transactivate TrkB, and it has also been speculated that the aforementioned cytoskeletal reorganization also affects TrkB activation.[132]

Estrogen is additionally involved in the regulation of hippocampal synaptic plasticity.[134-136] Moreover, E2 acts as a novel neuromodulator in the forebrain, affecting synaptic plasticity and cognitive function.[137] Recently, it has been indicated that E2 receptor α induces a new form of LTP that is NMAD receptor dependent and involves AMPAR transport to the synapse.[138]

Integrin β and CHL1

Close homologue of L1 (CHL1) belongs to the immunoglobulin (Ig) superfamily cell adhesion molecules, a gene encoding neuronal cell adhesion protein that regulates the proliferation, migration, differentiation, and survival of neuronal cells.[140-142] CHL1 has been significantly associated with schizophrenia. Patients with schizophrenia present with timing impairments[143-146] as well as deficits in spatiotemporal integration,[147,148] and CHL1 knockout mice exhibit the same symptoms.[149] Furthermore, the rs2272522 polymorphism of the CHL1 locus is significantly associated with schizophrenia in the Qatari population,[150] and CHL1-deficient mice were also identified as a model for schizophrenia-like learning and attention impairments.[151] Domestic studies have shown that CHL1 interacts with DISC1 to regulate the development of neurite outgrowth and that disruption of this interaction may contribute to increased risk of schizophrenia.[152]

Integrin β is tightly associated with CHL1 as well. CHL1 interacts with β1-containing integrins to potentiate integrin-mediated cell migration.[153] A direct link between ITGB3 and CHL1 was postulated to be involved in the regulation of serotonin uptake.[109] Subsequently, a significant correlation between the gene expression levels of CHL1 and ITGB3 in Munich Antidepressant Response Signature lymphoblastoid cell lines was found, supporting the connection between CHL1 and ITGB3.[154]

Integrin β and Reelin

Reelin is an ECM protein that is synthesized and secreted by cortical GABAergic interneurons and is involved in several aspects of brain development and function, such as neuronal migration, synaptogenesis, and synaptic plasticity. Several studies have shown that Reelin and its mRNA levels are significantly reduced in several brain regions in schizophrenia patients compared to controls,[91,155-160] and that Reelin downregulation is accompanied by a downregulation of GAD67.[158,161] Reelin can be involved in the regulation of glutamatergic synaptic maturation and plasticity by regulating synaptic NMDA receptor subunit composition and surface transport.[92] In addition, adult brain Reelin levels directly affect cognitive function and dendritic spine density.[158]

Integrin β is linked to Reelin in multiple aspects. α3β1 integrin interacts with Reelin to regulate neuronal migration and normal cortical lamination and promote neuronal adhesion to fibronectin.[91,162,163] The interaction among the amyloid precursor protein, Reelin, and α3β1 integrin promotes neurite outgrowth.[164] Reelin activates α5β1 integrin to affect the correct neuronal positioning in the mature cortex.[162] In addition, Reelin initiates a series of kinase cascade reactions to promote neurodevelopmental processes by directly binding to its receptors APOER2, VLDLR, and α3β1

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integrin and activating the downstream adapter protein DAB1.[161,165]

Integrin β and MMP9

Matrix metalloproteinase-9 (MMP9) is an extracellular protease that has been revealed in several studies to play a critical role in regulating hippocampal synaptic physiology, plasticity, and long-term memory.[166,167] It has been found that tissue inhibitor of matrix metalloproteinases-1, an endogenous inhibitor of MMP9, interacts with MMP9 to affect plasticity in the PFC,[168] and the dysfunction of the PFC is tightly associated with the development of psychiatric disorders such as schizophrenia.[169,170] A later study found increased MMP9 activity in mild cognitive impairment and that MMP9 led to a decrease in mature nerve growth factor.[171] In addition, a functional-1562 C/T polymorphism of the MMP9 gene was found to be relevant in the pathogenesis of schizophrenia by comparison with healthy controls.[172,173]

In the study of the relationship between MMP9 and integrin β, it was found that MMP9-driven LTP requires the mediation of β1-containing integrins and the activation of their downstream coenzyme protein signaling pathways.[174] Furthermore, MMP9 mediates surface transport of NMDAR through an integrin β1-dependent pathway.[175] Taken together, the interaction between integrin β and MMP9 may have an important association with schizophrenia.

Discussion

A strong correlation between integrin β and schizophrenia can be demonstrated by linking the etiology and clinical symptoms of schizophrenia to the role of integrin β in neurodevelopment, transmitter regulation, signaling, and the role it plays in states of anxiety and stress. However, we lack experimental evidence, and the pathways or mechanisms through which integrin β is involved in the effects on schizophrenia are not well understood. To date, most of our knowledge of the β integrin family in the brain has been on β1- and β3-containing integrins, and there is a lack of adequate interpretation of the physiological role of other β integrin subtypes in specific circuit-related brain functions in different brain regions,[36] and it is not clear whether these integrin subtypes are associated with schizophrenia or play a role in other brain disorders. In addition, the ECM ligands of integrins have been less studied, whereas alterations in the components of the ECM are important for brain function, and past clinical studies have demonstrated a correlation between abnormal ECM function and neuropsychiatric disorders with some degree of causality, one of the most prominent being schizophrenia. Therefore, the identification of the ECM ligand for integrin β is also helpful to study the correlation with schizophrenia. In conclusion, it remains much to be learned about the diverse functions of members of the β integrin family and the ways in which they are involved in the pathogenesis of schizophrenia, and investigating the role of different β subtypes in specific signaling pathways and potential ECM ligands could provide new clinical directions for studying the pathogenesis and treatment of schizophrenia.

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