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Review

Cell Adhesion Molecules in the Pathogenesis of Schizophrenia

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Abstract

The causes of schizophrenia remain obscure and complex to identify. Alterations in dopaminergic and serotonergic neurotransmission are, to date, the primary pharmacological targets in treatment. Underlying abnormalities in neural networks have been identified as cell adhesion molecules (CAMs) involved in synaptic remodeling and interplay between neurons-neurons and neurons-glial cells. Among the CAMs, several families have been identified, such as integrins, selectins, cadherins, immunoglobulins, nectins, and the neuroligin-neurexin complex. In this paper, cell adhesion molecules involved in the pathogenesis of schizophrenia will be described.

Keywords

cadherins, immunoglobulin, integrin, nectin, neurexin/neuroligins, selectin, synaptic remodeling

INTRODUCTION

Schizophrenia has complex and poorly understood origins, although research points to a role for hereditary and environmental variables. The core sign of schizophrenia is the impairment of reality testing. Patients with schizophrenia cannot distinguish and integrate their thoughts, fantasy, and imagination with external stimuli. The occurrence of positive symptoms, such as delusions and hallucinations, and negative symptoms, such as poor thoughts, poor motor initiative, flattening of affect, and social and cognitive impairment, result in difficulty in exhibiting purposeful and socially adaptive behaviors. The onset of schizophrenia occurs in early adulthood, with an incidence of 0.2/1000/year and a prevalence of about 4 per 1000.[1] The course is chronic and characterized by phases of remission to phases of relapse, with a poor prognosis of untreated disease and burdened by high mortality rates with a two- to threefold increased risk.[1] Several researchers frame schizophrenia as a neurodevelopmental disorder that recognizes as its anatomopathological substrate an 'aberrant synaptic plasticity', resulting in abnormal neurotransmission.[2] In this regard, accumulating evidence highlight that the extracellular matrix (ECM) is pivotal in the pathophysiology of schizophrenia, and cell adhesion molecules (CAMs) play an essential role in cells sticking to one another and their surroundings.[3] CAMs are a group of quaternary proteins found on the surface of cells that help cells adhere to each other and the matrix proteins. Cell surface receptors are involved in various cellular functions, from migration and differentiation to proliferation and survival and play a crucial role in synaptic plasticity, which is essential in memory and learning processes.[4] Cells can adhere to one another and communicate with their surrounding environment

because these molecules can attach to specific proteins in neighboring cells or the extracellular matrix. There are many different types of CAMs, each with its distinct structure and responsibilities in mediating cellular communication.[5] CAMs are classified into family classes: integrins, selectins, cadherins, immunoglobulins, nectins, and neurolings/neurexins.

Cancer, autoimmune disorders, and psychiatric illnesses are just a few of the numerous conditions in which CAMs play a significant role.[5] In view of the importance of CAMs in the processes of synaptogenesis, pruning, and synaptic remodeling, this review will discuss recent and intriguing data regarding CAMs as a new area of research in the study of the pathogenesis of schizophrenia. Various scientific evidence is emerging on altering the proteins involved in neuron-neuron and neuron/neuroglia adhesion. Distortion in cell-cell adhesion results in altered neurotransmission. The objective of this narrative review of the literature will be to expose the studies performed on CAMs concerning schizophrenia. This systematic search followed the PRISMA guidelines. Two authors independently searched the following databases: MEDLINE, Cochrane Central Register, EMBASE, PsycINFO, and through Mendeley for the following entries: schizophrenia or patients with schizophrenia and Integrins and Selectins and Cadherins and Immunoglobulins and Nectins and Neurolings/Neurexins. Only English-written papers were considered.

Integrins

Integrins comprise 24 members and are constituted of two subunits, alpha and beta, which are assembled to form heterodimeric transmembrane receptors that mediate signals between the cell interior and the extracellular space and play a crucial role in cell migration, proliferation, and survival.[6] Specifically, integrins are characterized by an extracellular domain that binds ECM proteins, a transmembrane domain, and an intracellular domain that initiates the intracellular signal transduction cascade and interacts with the cytoskeleton.[7] Synaptic plasticity, a vital process for proper brain development and the maintenance of appropriate neurotransmission, depends on the activity of integrins.[8] Moreover, the alpha and beta heterodimers subunits of integrins interact with the serotonin transporter (SERT)[9], affecting serotonergic neurotransmission and modulate the glutamatergic pathway by acting on the AMPA glutamate receptor.[10] Glutamatergic and serotoninergic neurotransmission are both altered in schizophrenia.[11] Among integrins family, the alpha-7 integrin is one of the most investigated in schizophrenia. Reduced alpha-7 integrin expression has been seen in the brains of people with schizophrenia, which may play a role in the misdirected migration and organization of neural progenitor cells.[12] Schizophrenia has been linked to an unusual movement of immune cells to the brain and it has been hypothesized that alpha-7 integrin expression is reduced in the blood of patients with this condition.[12] Beta-1 integrin is another integrin involved in brain development, neuronal migration, and synapse function, which has been investigated in schizophrenia.[6] People with schizophrenia have increased expression of beta-1 integrin in the brain, according to studies, which may have a role in the disordered development and maintenance of neuronal connections.[7] It has also been shown that beta-1 integrin is overexpressed in the blood of schizophrenia patients, which may contribute to the aberrant migration of immune cells to the brain.[13] Moreover, the activation of the fibronectin/beta-1 integrin pathway of microglia leads to neuroinflammation[14], and several researchers have highlighted how microglia activation and associated neuroinflammation play a key role in pathogenesis of the schizophrenia.

Selectins

Selectins are carbohydrate-binding proteins on the surface of cells involved in the rolling and tethering processes between leukocytes and endothelium, thus promoting the initial stages of inflammation. Three types of selectins have been classified: P-selectin (platelet selectin), E-selectin (endothelial selectin), and L-selectin (leukocyte selectin).[15] Also, selectins contribute to the development of schizophrenia by permitting immune cells stick to the inside of blood vessels, which in turn causes persistent and mild neuroinflammation.[16] Peripheral immune activation triggered by microorganisms, autoimmunity, or other systemic conditions can lead to P-selectin-mediated trafficking of inflammation into the brain.[17] Interestingly, higher selectin values were found in first-episode patients with schizophrenia than in chronic or drug-treated patients.[18] This is supported by research showing elevated selectin and inflammatory marker levels in the blood and cerebrospinal fluid of people with schizophrenia.[19]

Cadherins

Another class of proteins involved in cell-to-cell adhesion processes and intracellular signal transduction is cadherins, of which about 100 have been identified in the brain. The cadherin family includes classical cadherins, desmosomal cadherins, and protocadherins.[20] Specifically, protocadherins are involved in the formation and maintenance of neuronal circuits and are most highly expressed in the hippocampus and basal ganglia[21]; they also have multiple and more complex functions; in fact, their involvement in neuronal migration, synaptic remodeling, and gray matter differentiation has been described[22]. Changes in the expression of placental cadherins have been connected to the prenatal period, which is critical for developing mental issues. On the other hand, epithelial cadherins help keep the blood-brain barrier, which keeps hazardous chemicals out of the brain and out of circulation, intact.[23] Several neuropsychiatric illnesses, including schizophrenia, have been linked to blood-brain-barrier disruptions. Cadherins are involved in proper embryonic brain development and

brain maturation during early postnatal life; mutations in genes coding for cadherins are a risk factor for schizophrenia.[24] In this regard, genetic studies in Ashkenazi Jewish samples have shown that specific mutations in genes associated with cadherins/protocadherins are related to the development of schizophrenia[25], and the allelic variants of cadherins predispose to early-onset schizophrenia[22].

Immunoglobulins

It is challenging to adequately explain the involvement of immunoglobulins in the etiology of schizophrenia due to the complexity of the disease and our limited knowledge of its underlying causes.[26] However, several hypotheses may be supported by the data that has been put out. Immunoglobulins have been hypothesized to add to brain inflammation and oxidative stress.[27] Evidence suggests that the immune system is activated in people with schizophrenia, as they have been found to have elevated levels of immunoglobulins.[28] Among the immunoglobulin family, L1CAM, because of its involvement in central nervous system development, is the one most involved in the pathogenesis of schizophrenia.[29] A case-control study involving 267 schizophrenic patients and 234 healthy controls revealed that polymorphism of a gene encoding for the L1CAM protein is a predisposing factor for the development of schizophrenia.[29]

Nectins

Nectins are immunoglobulin-like CAMs that are involved in synaptic remodeling processes. To date, four subunits have been identified: nectin-1, nectin-2, nectin-3, and nectin-4. Among these forms, nectin-2 plays a role in synapse development and homeostasis of astrocytes and neurons.[30] Cell adhesion and migration are just two of the many functions that nectins, a class of cell adhesion molecules, perform.[31] The amygdala, the hippocampus, and the cortex all express nectins; these regions are each responsible for a distinct part of cognition, emotion, and sensory processing.[32] Also, multiple genetic studies have connected polymorphisms in the nectin genes to an elevated schizophrenia risk.[33]

Neuroligins/Neurexins

In order for neurotransmission to be effective and efficient, neuroligins, which are expressed by the postsynaptic terminal and bind to other presynaptic CAMs known as neurexins (classified into neurexin 1, 2, and 3), are of paramount importance.[34] Interestingly, Südhof[35] states that the neuroligin/neurexin complex is a molecular code that logically guides the formation of neuronal circuits. Four proteins belong to the neuroligins family; of these, the presence of a mutation in the neuroligins two genes has been correlated with schizophrenia.[36] In addition to being expressed in the dendritic tree of neurons, neuroligins have been detected in astrocytes and oligodendrocytes.[34] Given their presence on oligodendrocytes and astrocytes, neuroligins regulate myelination and cell differentiation processes[37] and control the morphology and function of astrocytes, which are involved in nerve tissue homeostasis and in promoting synaptogenesis[38]. The neuroligins-neurexin complex could help stabilize the synapse (cooperative model) by mediating astrocytes to ensure stabilization between presynaptic and postsynaptic terminals. Alternatively, the astrocyte could create a preferential binding to only one synaptic terminal (presynaptic or postsynaptic), always mediated by the neuroligins-neurexins complex, destabilizing the synaptic connection (competitive model). These two models would underlie the processes that promote new synapse formation or pruning.[39] Specifically, neuroligin 2 is mainly expressed on GABAergic/glycinergic inhibitory synapses, while neuroligin 1 is mostly expressed on glutamatergic excitatory synapses. In contrast, the remaining neuroligins 3 and 4 are present on both synapses.[35] Pre-clinical studies performed on mice showed that overexpression of the neuroligins-2 gene in the hippocampus following early-life stress correlated with behavioral disorders, such as aggression and impaired social cognition.[40]

CONCLUSIONS

The interaction between glial cells and neurons and the development and maintenance of synaptic connections mediated fundamentally by CAMs, described in this review, and representing the neurobiochemical substrate of cellular integration, are prerequisites for the proper development and maintenance of brain networks. Thus, to ensure the integrated development of neural networks and efficient and effective neurotransmission, remodeling based on neuron-neuron and neuron-astrocyte adhesion must be adequate **(Table 1)**. In addition, the neuroinflammatory processes observed in schizophrenia are related to alterations of some specific CAMs **(Table 1)**. Genetic studies have established a significant correlation between

Table 1. The role of CAMs in neurons and neuroglia

Integrins: involved in synaptic remodeling; associated with SERT and AMPA.
Selectins: associated with the neuroinflammation.
Cadherins: involved in synaptic remodeling, neuronal migration, neurons differentiation, and BBB constitution.
Immunoglobulins: involved in development of CNS; associated with neuroinflammation.
Nectins: involved in CNS development and astrocytes homeostasis.

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allelic variants of CAMs and social affiliative behaviors (initiation and maintaining of positive social interaction, caregiving).[41] Particularly patients with negative symptoms exhibit more significant impairment in affiliative social behaviors.[42] At the microscopic level, the alterations in CAMs observed in schizophrenia produce a loss of "affiliative behavior" between neurons, which stop communicating, coordinating, and cooperating; this is what happens in the macroscopic world in which schizophrenia results in a disruption of relationships between humans. The critical role of CAMs in schizophrenia is extrinsic through the pleiotropic action performed by CAMs at different levels. Indeed, alterations in neurotransmission circuits represent the final step in a process that begins from genetic bases related to polymorphism of CAMs genes[43] and is also associated with neurodevelopmental defects, microglia hyperactivation, neuroinflammation, and synaptic dysfunction activity **(Table 1)**.

This review aimed to resume neuropathology studies in order to stimulate further and more extensive helpful research to bring new concerns regarding the neuropathology of schizophrenia and contribute to the development of new therapeutic targets.

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Competing Interests

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Молекулы клеточной адгезии в патогенезе шизофрении

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Резюме

Причины шизофрении остаются неясными и сложными для выявления. Изменения в дофаминергической и серотонинергической нейротрансмиссии на сегодняшний день являются основной фармакологической целью лечения. В основе аномалий нейронных сетей лежат молекулы клеточной адгезии (МКА), участвующие в синаптическом ремоделировании и взаимодействии между нейронами-нейронами и нейронами-глиальными клетками. Среди МКА идентифицировано несколько семейств, таких как интегрины, селектины, кадгерины, иммуноглобулины, нектины и комплекс нейролигин-нейрексин. В этой статье будут описаны молекулы клеточной адгезии, участвующие в патогенезе шизофрении.

Ключевые слова

кадгерины, иммуноглобулин, интегрин, нектин, нейрексин/нейролигины, селектин, синаптическое ремоделирование