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Anti-NMDAR antibodies, the blood–brain barrier, and anti-NMDAR encephalitis

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Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is an antibody-related autoimmune encephalitis. It is characterized by the existence of antibodies against NMDAR, mainly against the GluN1 subunit, in cerebrospinal fluid (CSF). Recent research suggests that anti-NMDAR antibodies may reduce NMDAR levels in this disorder, compromising synaptic activity in the hippocampus. Although anti-NMDAR antibodies are used as diagnostic indicators, the origin of antibodies in the central nervous system (CNS) is unclear. The blood–brain barrier (BBB), which separates the brain from the peripheral circulatory system, is crucial for antibodies and immune cells to enter or exit the CNS. The findings of cytokines in this disorder support the involvement of the BBB. Here, we aim to review the function of NMDARs and the relationship between anti-NMDAR antibodies and anti-NMDAR encephalitis. We summarize the present knowledge of the composition of the BBB, especially by emphasizing the role of BBB components. Finally, we further provide a discussion on the impact of BBB dysfunction in anti-NMDAR encephalitis.

KEYWORDS

anti-NMDAR encephalitis, blood–brain barrier, neurovascular unit, NMDAR receptor, autoimmune disorder

1 Introduction

Anti-NMDAR encephalitis is the most common antibody-related autoimmune disease, accounting for approximately 81% of autoimmune encephalitis cases (1). It was first described in 2007 by Dalmau (2). According to a survey, anti-NMDAR encephalitis is more common in young patients than any specific viral etiology (3). Most young and female patients are affected (4). This disease usually presents with acute behavioral changes, psychiatric symptoms, seizures, and memory deficits (5). The reduction in NMDAR surface density and synaptic localization by anti-NMDAR antibodies is thought to be the main mechanism of the disease (6). It also involves B cells in the CNS, which can produce antibodies intrathecally. In a normal state, a low level of circulating B cells passes across the BBB (7). However, in anti-NMDAR encephalitis, there is a significant increase in B cells. It is well known that the brain is devoid of autoimmune cells and antibodies due to the BBB. Impaired BBB may play an important role in this disease. Several CNS diseases involve BBB dysfunction, including neurodegenerative disorders (8), encephalitis (9), epilepsy (10), and multiple sclerosis (11). However, less attention has been given to the role of BBB in anti-NMDAR encephalitis.

In this review, we introduce the NMDA receptor and anti-NMDAR encephalitis. We then outline the structural and physiological roles of the BBB, including a set of BBB elements. The role of the BBB in therapy is also mentioned. Finally, we examine the role of the BBB in anti-NMDAR encephalitis. We hope to provide a novel perspective for understanding the pathogenesis of this disease.

2 Anti-NMDAR encephalitis and NMDA receptors

2.1 NMDA receptors

NMDAR, as a heterotetrameric transmembrane ion channel, is a subtype of glutamate receptor. It is formed by the combination of two necessary GluN1 subunits and two other subunits, including GluN2 or GluN3 subunits. It is widely expressed in various CNS cells (12), including neurons, endothelial cells, microglia, oligodendrocytes, and astrocytes. Here, we focus on its function in neurons and endothelial cells (the function of endothelial cells is described in part 3.1). In the CNS, NMDARs are predominantly expressed by neurons and are mainly distributed in the prefrontal cortex, hippocampus, amygdala, and hypothalamus (13). It widely exists in CNS neurons and is involved in a series of neural activities. As glutamate receptors, NMDARs can regulate the survival of neurons and the development of dendrites and axons. NMDARs are also involved in synaptic transmission and plasticity, as well as higher nervous activity such as learning, memory, and emotion (14, 15). However, excessive NMDAR activity leads to excitotoxicity and promotes cell death (16). Glutamate and glycine (or d-serine) are NMDAR agonists. NMDARs may also be blocked by magnesium. Activated NMDARs play an important role in regulating long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission (17) by mediating Ca^{2+} permeability.

It is believed that the functions of NMDARs mainly involve two kinds of diseases. Excitation is the first concern. It is associated with a series of diseases, such as stroke and epilepsy. Stimulation by glutamate of NMDARs can result in the death of neurons in these disorders. The other is NMDAR hypofunction, which may induce the elimination of synaptic activity mediated by NMDARs, resulting in memory, cognition, and behavioral defects. It is associated with schizophrenia and anti-NMDAR encephalitis (18, 19). The extracellular N-terminal domain of the NR1 subunit is the main targeting epitope (2). NMDAR hypofunction may induce a selective and reversible decrease in NMDAR quantity on the cell surface, mainly in the hippocampus (6, 19).

2.2 Anti-NMDAR encephalitis and anti-NMDAR antibodies

2.2.1 Essential clinical characteristics of anti-NMDAR encephalitis

Anti-NMDAR encephalitis, characterized by CSF anti-NMDAR antibodies, is an antibody-related autoimmune encephalitis. Compared to other patients, anti-NMDAR encephalitis patients have a longer intensive care unit length

of stay and a greater percentage of mental symptoms, motor disorders, and autonomic dysfunction (20). Following its initial reported in 2007, the number of diagnosed cases is increasing (2), and it is receiving increasing attention.

In general, anti-NMDAR encephalitis often affects young individuals and women. It also occurs in children and elderly individuals. This disease is commonly associated with ovarian teratoma and herpes simplex encephalitis. However, the mechanism is not very clear. The main symptoms of this disorder are mental symptoms, accompanied by memory impairment, autonomic nervous symptoms, seizures, and respiratory failure in over half of the patients. At the onset, psychiatric or behavioral symptoms are the most common, making it difficult to distinguish between anti-NMDAR encephalitis and primary psychosis (21). Sometimes, anti-NMDAR encephalitis is accompanied by other immune diseases, such as progressive systemic sclerosis (22) and myelin oligodendrocyte glycoprotein antibody-associated encephalitis (23).

Human autoimmunity plays an important role in this disorder. T lymphocytes and B lymphocytes have been found in brain samples from patients with anti-NMDAR encephalitis (24). Single-cell sequencing confirmed the activation and differentiation of B lymphocytes and the amplification of plasma cells in anti-NMDAR encephalitis (25). Mild perivascular lymphocytic cuffing, microglial activation, and a decrease in NMDAR density have been observed in the hippocampus during a brain biopsy or autopsy (2, 24). Compared to non-inflammatory neurological disease patients, the proportion of CD19+ B lymphocytes in the CSF of anti-NMDAR encephalitis patients is higher (26). Both oligoclonal bands and the production of many intrathecal immunoglobulins are characteristics of anti-NMDAR encephalitis (27–29). Obvious microglial proliferation and IgG deposition were detected in a series of brain regions, including the hippocampus and forebrain, accompanied by rare inflammatory infiltration (24, 30). Rituximab may relieve anti-NMDAR encephalitis in patients who fail to respond to first-line treatment (31). This provides evidence that B cells may be crucial for anti-NMDAR encephalitis development.

2.2.2 Anti-NMDAR antibodies and their role in anti-NMDAR encephalitis

Antibodies against NMDAR play an important role in anti-NMDAR encephalitis. They are very common in the blood and CSF of patients with this disorder and are rarely present in other diseases. Studies have shown that anti-NMDAR antibodies from patients can selectively mediate the internalization of surface NMDARs, leading to a decrease in the surface density of synaptic NMDAR clusters and a reduction in glutamate synaptic function (6, 32). Initially, antibodies were detected in young women with teratomas. Ectopic neurons in teratomas are thought to be immune triggers and sources of autoantigens (2). Recent research shows that NMDAR antibodies may be produced from the tertiary lymphatic structure of tumors and traditional secondary lymphatic organs (33).

The anti-NMDAR antibody level is associated with the severity of disease symptoms, outcomes, and prognosis. Compared to

patients without anti-NMDAR antibodies, patients with antibodies present with more aggression, exaltation, and disinhibition (20). Although there was no significant difference between severe patients and non-severe patients ($P = 0.062$), the strong positive rate of severe patients was higher than that of non-severe patients (48.7% vs. 29.2%) (34). There is also a certain correlation between antibody levels and symptoms. Patients with higher antibody titers were found to more commonly present a psychiatric symptom as the primary symptom and to display more severe clinical features than those with lower antibody titers. EEG background activity and symptoms were linked to CSF antibody titers. Serum titers decreased in patients with improved symptoms (19).

Currently, several anti-NMDAR encephalitis models are being built, including models induced by the herpes simplex encephalitis virus, selected peptides, patient CSF, and so on (35–37). All of these findings support the importance of antibodies in this disorder. Antibodies are so important for this disorder that they have been included in the anti-NMDAR encephalitis diagnostic criteria (38).

Although the important role of anti-NMDAR antibodies in this disease has been recognized, there is some controversy regarding the involvement of these antibodies in anti-NMDAR encephalitis. First, it has been proven that all natural anti-NMDAR1 antibodies have pathogenic potential (39, 40). The seroprevalence of anti-NMDAR antibodies was found to be similar between schizophrenic patients and healthy individuals (41). Second, the antibody titer is related to the severity, but alleviation of the disease may not be completely related to the decrease in titer. Studies have found that intrathecal synthesis can still exist for several years after symptoms recover (42). Although the CNS is an immune-privileged organ, peripheral diseases are known to affect the CNS. Some underlying tumors in the periphery may trigger several neurologic deficits, such as paraneoplastic neurological syndrome (43). The first anti-NMDAR encephalitis patient was diagnosed with ovarian teratoma in 2007 (2). The presence of nervous tissues in ovarian teratomas may play a role in the pathogenesis of anti-NMDAR encephalitis. The resection of teratomas is beneficial for the relief of symptoms in patients (44). The controversy surrounding the role of anti-NMDAR antibodies and the impact of the peripheral immune system on anti-NMDAR encephalitis is a topic that requires further investigation. Maybe, there is another mechanism that plays a role in this disease.

3 Structural, physiological, and pathological roles of the BBB

The brain is separated from the circulatory system mainly by the BBB. It can regulate molecular transport between the CNS and blood, which is necessary to maintain homeostasis of the brain. The BBB is composed of brain microvascular endothelial cells, astrocytes, pericytes (PCs) and basement membrane (45) (Figure 1). Substances pass through the BBB in the following ways: (1) paracellular transport via damaged tight junction proteins (TJs) between endothelial cells and (2) transcellular transport via endocytosis vesicles or transport proteins (46). Neurons and microglia have the potential to influence the function of the BBB. Together with the elements of the BBB, they form the neurovascular

unit (NVU), which plays a crucial role in maintaining the normal function of the CNS.

3.1 Endothelial cells

Endothelial cells (ECs) are the core components of the BBB and have always been a research hotspot for the BBB. Neurons, astrocytes, microglia, and pericytes influence BBB integrity by regulating the ECs. ECs lack endothelial fenestrations and have relatively few caveolar vesicles (47–49). They protect the brain by restricting paracellular and transcellular transport. Cytoplasmic proteins and transmembrane proteins, which are the focus of BBB research, determine the function and structural stability of TJs (50–53).

3.1.1 Paracellular transport

TJs include claudin-5, occludin, and junction adhesion molecules, which promote the maintenance of cell polarity. Occludin, claudin-5, and ZO-1 are the main structural barrier proteins and are considered sensitive indicators of normal and disrupted BBB function (54).

3.1.1.1 Claudin-5

Many elements of the claudin family with a molecular mass of 20–27 kDa are assumed to contribute to BBB integrity. Claudin-5 is the most enriched isoform in the claudin family (55). It is always expressed in ECs that form capillaries, which is the main components of TJs and is essential for maintaining BBB integrity (56, 57). Claudin-5 exclusively limits the paracellular permeability of molecules larger than the size-selective threshold (<800 Da) across the BBB (56). The *in vitro* and *in vivo* data indicate that the decrease in claudin-5 may cause BBB disruption (58). Claudin-5 knockout and redistribution from the membrane to the cytoplasm can lead to increased BBB permeability (56, 59). The expression and regulation of claudin-5 are influenced by multiple factors. Several factors, such as vascular endothelial (VE)-cadherin, glucocorticoids, glial cell line-derived neurotrophic factor (GDNF), and estrogen, can upregulate claudin-5 expression (60–63). Vascular endothelial growth factor (VEGF) (64) and transforming growth factor- β (TGF- β) (65) downregulate the expression of claudin-5, resulting in a decrease in BBB integrity. Autophagy may alleviate hypoxia-induced BBB injury by regulating claudin-5 redistribution in stroke (66). Other claudin elements, such as claudin-1,3 and claudin-11, are also associated with the BBB, although their levels are much lower than that of claudin-5 (67).

3.1.1.2 Occludin

Occludin is the first confirmed TJ protein, with a molecular weight of 65 kDa (53). The expression level of occludin in ECs is higher than that in non-nerve tissues (68). Similar to claudin-5, it regulates the BBB through the paracellular pathway (53). However, it does not participate in the developmental regulation of the BBB and only maintains its integrity (69). Previous studies have shown that the downregulation of occludin can significantly reduce transcutaneous/transendothelial resistance (TEER) and

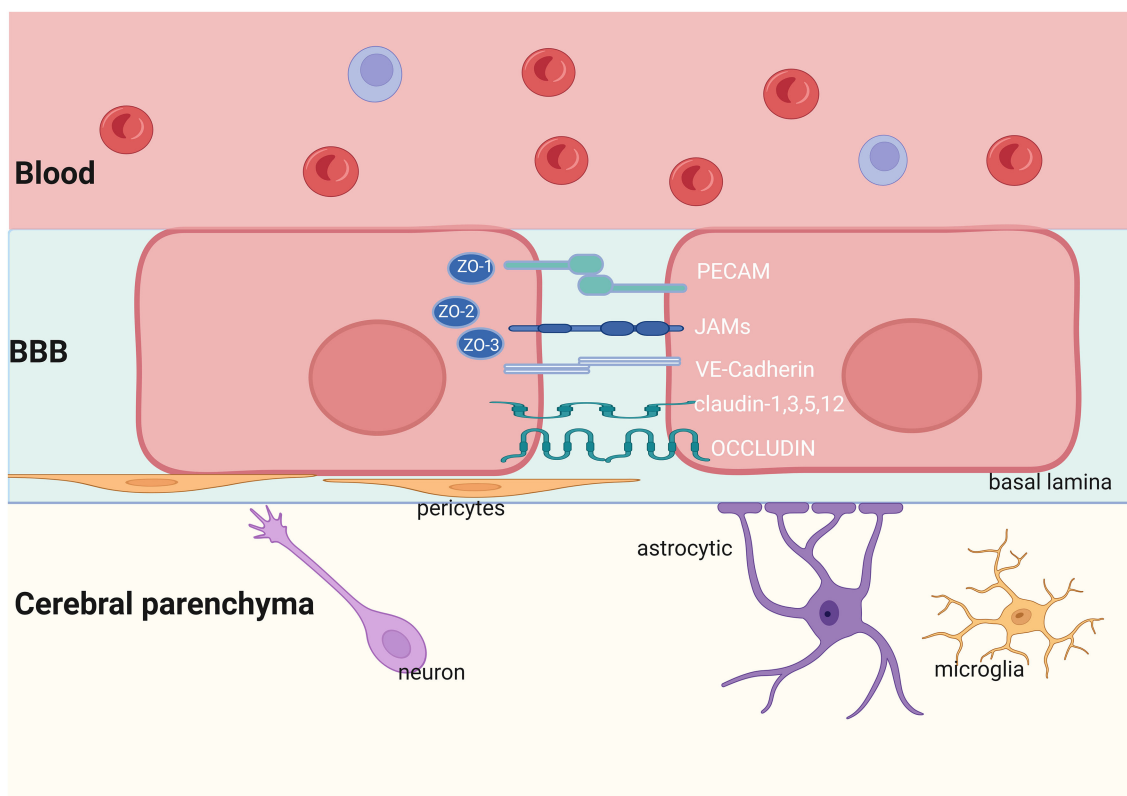


FIGURE 1

Structure of the BBB. The NVU is made up of neurons, astrocytes, microglia, pericytes, and endothelial cells. The TJs and AJs in the brain endothelial cells limit the transportation of proteins and other nutrients. JAMs, Junctional Adhesion Molecules; PECAM, Platelet Endothelial Cell Adhesion Molecule; VE-Cadherin, Vascular Endothelial Cadherin; ZO, Zonula Occludens. Created with [BioRender.com](https://www.biorender.com).

increase paracellular diffusion (70). Compared to wild-type mice, the permeability of the BBB significantly increases in occludin-deficient mice after stroke (71). Many factors, such as matrix metalloproteinase-9 (MMP-9), ubiquitination, phosphorylation, tumor necrosis factor, IL-1 β , and IFN- γ , participate in regulating the expression of occludin (69). Various signaling pathways are involved in the regulation of occludin, including the NF- κ B, MAPK, PKC, RhoK, and ERK1/2 (72, 73). Vascular endothelial growth factor (VEGF) mediates MMP-9 activation to damage the BBB, leading to a decrease in the expression of occludin (74, 75). Autophagy also participates in BBB disruption by regulating occludin (70).

3.1.1.3 ZO-1

Zonula occludens proteins (ZO-1, ZO-2, and ZO-3) share sequence similarities. ZO-1 and ZO-3 are cytoplasmic tight junctional accessory proteins that provide structural support to ECs (76) and are related to BBB dysfunction in many neurological diseases, such as stroke, subarachnoid hemorrhage, and Parkinson's disease (77–82). ZO-1 redistribution and reduction, mediated by autophagy and MMP-2/9, participate in BBB leakage in stroke. Endophilin-1 participates in regulating BBB permeability by controlling ZO-1 and occludin expression (83).

3.1.2 Transcellular transport

In addition to paracellular transport, intercellular transport is another important way for substances to pass through the

BBB. This approach is influenced by specific transport proteins, endocytosis, and diffusion movements in the endothelial cell membrane (84). Endocytosis includes internalization, sorting, and exocytosis. EC internalization may occur through vesicles, grid protein-dependent endocytosis, or grid protein-independent endocytosis pathways (85). Vesicles in brain endothelial cells (BECs) play an important role in the endocytosis of the BBB, although the number of vesicles in BECs is lower than that in peripheral endothelial cells (86). The vesicles contain the vesicle protein caveolin-1, which participates in the transcytosis of the BBB. The upregulation of caveolin-1 and caveolin-2 expression was found in BECs in the EAE model and stroke (87, 88).

3.2 Other cell elements of the BBB

Although ECs are thought to be the primary element of the BBB, they require contact with various NVU elements to establish BBB characteristics (89). Pericytes are blood vessel wall cells wrapped around the basement membrane of microvessels (see Figure 1). PCs make close contact with ECs through “peg-and-socket” junctions within a common basal lamina (90, 91). Pericytes can regulate BBB permeability by controlling the expression of TJs and adhesive junction proteins in the BBB and influencing vesicles (92). Mice with low pericyte coverage around endothelial cells have a disrupted BBB (93–95). PC dysfunction leads to a decrease in TJs, increasing BBB permeability, and a loss of basement

membrane proteins (92, 93, 96). In response to inflammatory mediators, pericytes may secrete key molecules that influence the BBB. Pericyte-derived vitronectin is an extracellular matrix (ECM) protein. It regulates BBB integrity by binding to integrin $\alpha 5$ on endothelial cells to inhibit endocytosis (97). The downregulation of pericytes can lead to BBB dysfunction via transcellular transport, leading to leakage of a large amount of polymer substances, including IgG and albumin (90, 92).

The end feet of astrocytes ensheath the microvasculature. Astrocytes may secrete several factors that have dual effects on maintaining BBB function. Various factors, including VEGF (98), MMPs, nitric oxide (NO), glutamate, and endothelin-1, may exacerbate the disruption of the BBB by regulating TJs. Other factors secreted by astrocytes may decrease BBB permeability, such as angiopoietin-1 (Ang-1), sonic hedgehog (Shh), GDNF, transforming growth factor- β (TGF- β), retinoic acid (RA), insulin-like growth factor-1, and apolipoprotein E (99, 100). Astrocyte-secreted Shhs have been shown to protect the BBB (101), which reinforce BBB junctional tightness by increasing TJ expression in ECs (102) and delaying BBB breakdown under pathological conditions. Induced by albumin extravasation, astrocytes also release MMP to degrade the basement membrane, resulting in BBB dysfunction (103).

Microglia are resident CNS macrophages (104). Microglia are widely distributed in the brain tissue, including the basal ganglia, hippocampus, substantia nigra, and olfactory brain (105). They exist at vascular junctions and bridge endothelial tip cells, monitoring BBB integrity and the inflow of agents into the brain (106). It can synthesize many proinflammatory cytokines, directly affecting the permeability of the BBB (107). Microglia also have a dual effect on the BBB. M1-type microglia may damage BBB function, while M2 anti-inflammatory microglia play a protective role in the BBB (108, 109).

ECs may lose their BBB properties when cultured alone. They may show enhanced TEER and begin to express many TJs in coculture with astrocytes and pericytes (109). Endothelial cells cocultured with resting microglia or astrocytes express more occludin and ZO-1 (85). Endothelial TJs are also tighter in the presence of pericytes. A recent study demonstrated that PCs may transfer signals to ECs through ligand–receptor interactions, which is an important mechanism for regulating BBB permeability (97). Astrocytic end feet are important for the establishment and maintenance of the BBB (91). They play an important role in preventing excessive immune cells from entering the space around blood vessels.

3.3 BBB and disease

The BBB exists widely in the brain and is involved in CNS diseases, including epilepsy, cerebrovascular accidents, and mental disorders. It provides immune preservation of the CNS. Any damage to the BBB will result in adverse consequences, leading to diseases, or aggravation of illness. The role of the BBB in stroke has been widely researched. A large amount of evidence suggests that inflammation after ischemia is associated with BBB disruption, vascular edema, hemorrhagic transformation, and a

poorer neurological prognosis. Occludin is mediated by MMPs (110), nitric oxide synthase (111), reactive oxygen species (112), and rho kinase (113). VEGF may affect the permeability of the BBB after cerebral ischemia and reperfusion. BBB dysfunction is closely associated with the onset of Alzheimer's disease (AD). Glucose transporter1 (GLUT1) in the ECs of AD patients is lower than in the control group (114). The deficiency of GLUT1 in AD mice may lead to BBB dysfunction and a decrease in TJ protein (115). Multiple sclerosis (MS) is a CNS disease associated with immunity. BBB destruction and immune cell infiltration into the CNS are characteristics of MS. Reduced or interrupted staining of occludin, claudin-5, and VE cadherin has been observed in the brain tissues of MS patients on autopsy (116–118). Brain microvascular endothelial cell-like cells derived from MS showed increased BBB permeability and decreased TJ integrity (119). Immune cell migration across the endothelial barrier is generally mediated by the coordinated binding of adhesion molecules and the interaction of chemokines/chemokine receptors, as well as the action of MMPs and their tissue inhibitors (TIMPs) (120). ECs alter their immune phenotype by upregulating intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and atypical chemokine receptor 1 (ACKR1), allowing more immune cells to infiltrate the CNS (121–124). T cells infiltrate the CNS mainly by transcellular transport (125). B-cell migration across ECs is faster than that of T cells. It may be regulated by the adhesion molecules VLA-4 and ICAM-1, the chemokines monocyte chemoattractant protein-1 and IL-8, and TIMP-1 (126).

The BBB exists widely in the brain and is involved in neural microenvironmental homeostasis. It provides immune preservation of the CNS. On the other hand, it is the main obstacle to the treatment of most CNS diseases (127). Only a few CNS disorders may be treated by small-molecule drugs, which cross the BBB (128). The human immunodeficiency virus in the periphery may be significantly reduced by antiretroviral therapy (129). However, owing to the presence of the BBB, antiretroviral drugs cannot be used in the brain (130). How to overcome the BBB is a challenge in the therapeutic development of CNS diseases (131). New strategies and medicines are currently being developed to resolve this problem.

4 BBB, NMDARs, and anti-NMDAR encephalitis

4.1 NMDARs and BBB

NMDARs may be activated to induce a breakdown of the BBB (132). Overactivation of NMDARs can alter the expression of TJs, affecting BBB permeability (133). Circulating tPA can activate endothelial NMDARs and increase BBB permeability via the Rho signaling pathway (133, 134). In addition, the activation of NMDARs can disrupt the BBB by activating the MEK1/2-ERK1/2 signaling pathway and upregulating MMP2/9 expression (135, 136).

In addition to affecting paracellular pathways, NMDARs can also affect the BBB via transcellular transport. Treatment with NMDA can increase intercellular movement. Many bioactive molecules, including transferrin, glucose, and immunoglobulin,

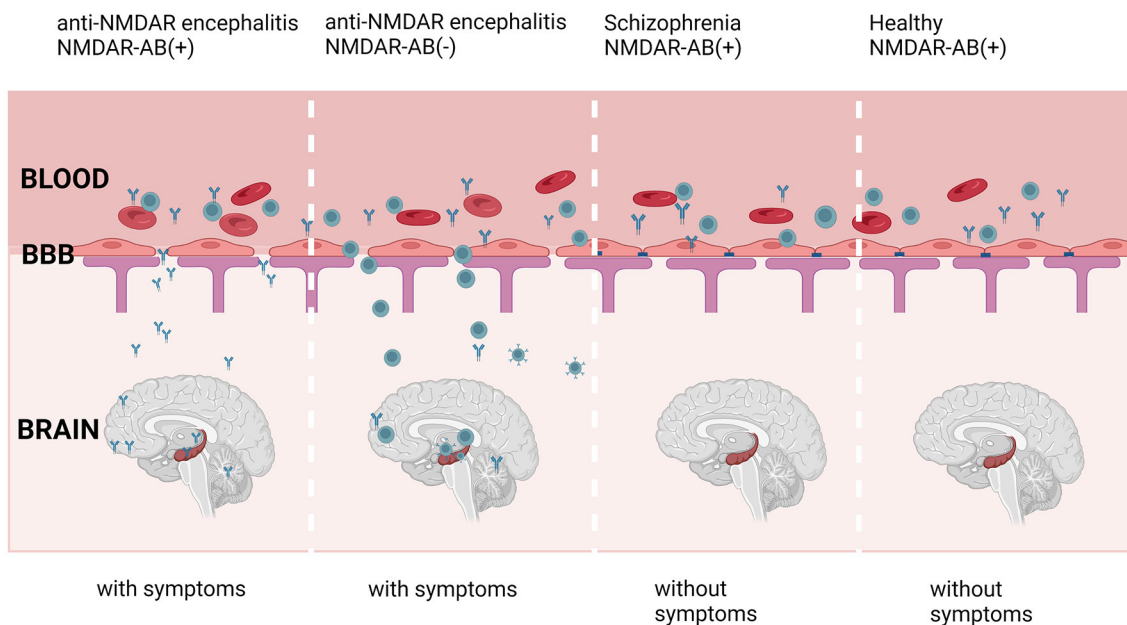


FIGURE 2

NMDAR-ab in the blood is discovered in anti-NMDAR encephalitis patients, healthy individuals, and patients with schizophrenia. However, the symptoms observed in those patients and healthy individuals are not similar to anti-NMDAR encephalitis. The symptoms may be caused by CSF antibodies, which come from blood. The impaired BBB allows the antibodies and B cells in serum to enter the brain, leading to the appearance of symptoms. Created with [BioRender.com](https://www.biorender.com).

enter the brain through the BBB. It may be achieved via clathrin and caveolin, which are inhibited by anti-NMDAR antibodies. NMDAR-deficient ECs result in decreased neuronal density and brain vasculature (137).

There is evidence indicating the existence of NMDAR in astrocytes (138). The expression of NMDARs in astrocytes may be upregulated in transient ischemic astrocytes (139). Activated astrocytic NMDARs may mediate ion currents and intracellular Ca^{2+} waves (140) and contribute to glial postsynaptic currents (141). Some studies have shown that activated NMDARs in astrocytes also stimulate the secretion of proinflammatory cytokines (142, 143).

The expression of NMDARs was also observed in oligodendrocytes and microglia. These cells are involved in the development of myelin, the regulation of glucose transporters, and glucose trafficking (144). NMDAR currents in oligodendrocytes exist in multiple brain regions and at various developmental stages, which are involved in excitotoxicity mechanisms (145, 146). The role of glucose transporters has been confirmed in anti-NMDAR encephalitis (147). Excessive activation of oligodendrocyte NMDARs may trigger excitotoxic cell death via Ca^{2+} overload and energy metabolism dysfunction (148). Microglial NMDAR may combine with NMDA, inducing microglial activation in hypertrophic and amoeboid states and the release of proinflammatory factors.

4.2 The BBB in anti-NMDAR encephalitis

The role of antibodies in anti-NMDAR encephalitis is well known. However, whether CNS NMDARs or circulating NMDARs participate in the disease is unknown. Several studies reported that the seropositive prevalence of anti-NMDAR1 antibodies is similar in both healthy individuals and psychotic patients (149, 150). All naturally occurring NMDAR1 antibodies have pathogenic potential (39). However, not all patients and healthy individuals with NMDAR antibodies show symptoms. The antibodies cause behavioral phenotypes only when they enter the CNS (see Figure 2). The antibody in CSF was more important than the serum-derived antibody. The titer change in CSF was more closely related to relapses, outcomes, and patient condition than in serum (151, 152).

The antibody in CSF was more important than the serum-derived antibody. Where does the anti-NMDAR antibody in the CNS come from? Antibodies in serum may enter the brain through the damaged BBB (see Figure 2) (39, 41, 150). Clonally expanded plasma cells in the CNS have been suggested as another source of CSF NMDAR antibodies (153). Interestingly, these B cells are reported to originate from peripheral lymphoid organs (33, 37). BBB impairment is important for the entry of autoimmune cells into the brain. As a barrier to isolating brain tissue and the peripheral circulatory system, the BBB plays a significant role.

The clinical symptoms of anti-NMDAR encephalitis indicate that BBB impairment is a crucial step in the onset of the disease. The CSF albumin/serum albumin (QAlb) is one of the indicators of BBB damage. Yu et al. observed BBB dysfunction based on the results of QAlb in anti-NMDAR encephalitis (154). Some chemical agents related to BBB damage and CNS inflammation are observed in the CSF and serum in anti-NMDAR encephalitis (155, 156). Due to the impaired BBB, anti-NMDAR antibodies may transfer from pregnant C57BL/6J mice to fetuses, causing severe but reversible synaptic and neurodevelopmental alterations (157). A study showed that compared to wild-type mice, apoE^{-/-} mice with a disrupted BBB respond to intravenous NMDAR antibodies, showing symptoms (150, 158). It was confirmed that BBB damage was present in anti-NMDAR encephalitis mice (159).

The integrity of the BBB is related not only to the occurrence of anti-NMDAR encephalitis but also to the prognosis and severity of symptoms. According to previous reports, BBB dysfunction is associated with prognosis and mRS scores after 2 months of follow-up (154). The symptoms of anti-NMDAR encephalitis are associated with BBB dysfunction (41). Gong et al. reported that PI3K inhibition can improve neurological behavior by alleviating BBB and neuron injury (159). Interestingly, circulating antibodies, passing through the intact BBB at a low rate and titer, cannot cause obvious symptoms. The antibodies may combine tightly with the brain tissue, preventing discharge into the CSF (160). However, many antibodies enter the brain through a damaged BBB, causing clinical symptoms in anti-NMDAR encephalitis.

Although the BBB plays an important role in anti-NMDAR encephalitis, the mechanism is unclear. There are also other antibodies present in the cerebrospinal fluid of patients with anti-NMDAR encephalitis (161). These antibodies can react with different types of blood vessels. *In vitro* and *in vivo* experiments have confirmed the presence of the vascular targeting antibody mAb011-138 in the CSF of patients with NMDAR encephalitis. It can react with small blood vessels and increase BBB permeability by downregulating occludin (162).

5 Conclusion

Although anti-NMDAR encephalitis is a rare disorder, it causes a series of serious symptoms and is easily misdiagnosed as psychosis. It often affects young individuals and has attracted increasing attention. Anti-NMDAR antibodies, especially those in the CSF, play a key role in this disorder. The presence and concentration of antibodies in CSF may influence the onset and severity of this disorder. The BBB is an important physical and metabolic barrier that controls the entry of agents into the brain. BBB dysfunction is not only associated with the entry

of serum antibodies and immune cells but is also linked to the symptoms caused by antibodies. BBB breakdown has been thought to be an important event in anti-NMDAR encephalitis. However, the mechanism is unclear, and only a few studies on BBB disruption in anti-NMDAR encephalitis have been reported. The association between the elements of the BBB and NMDARs, including astrocytes, microglia, pericytes, and endothelial cells, is still unclear. The BBB has also been linked to the treatment of many CNS diseases. NMDARs are involved in BBB dysfunction in other disorders. It is still unknown whether anti-NMDAR antibodies affect the BBB in anti-NMDAR encephalitis. The repair of the BBB or the production of new medicines across the BBB for anti-NMDAR encephalitis is also important. Future studies investigating anti-NMDAR encephalitis should consider the factors that affect BBB integrity.

Author contributions

XG: Writing—original draft. NW: Writing—review & editing. HZ: Writing—review & editing. NT: Writing—review & editing. KW: Writing—review & editing. QM: Writing—review & editing.

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Conflict of interest

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