

Review Article

Immune dysregulation and self-reactivity in schizophrenia: Do some cases of schizophrenia have an autoimmune basis?

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Summary Schizophrenia affects 1% of the world's population, but its cause remains obscure. Numerous theories have been proposed regarding the cause of schizophrenia, ranging from developmental or neurodegenerative processes or neurotransmitter abnormalities to infectious or autoimmune processes. In this review, findings suggestive of immune dysregulation and reactivity to self in patients with schizophrenia are examined with reference to criteria for defining whether or not a human disease is autoimmune in origin. Associations with other autoimmune diseases and particular MHC haplotypes, increased serum levels of autoantibodies, and *in vivo* and *in vitro* replication of some of the functional and ultrastructural abnormalities of schizophrenia by transfer of autoantibodies from the sera of patients with schizophrenia suggest that, in some patients at least, autoimmune mechanisms could play a role in the development of disease. Recent findings regarding specific autoimmune responses directed against neurotransmitter receptors in the brain in patients with schizophrenia will also be reviewed.

Key words: antibodies, autoimmunity, neurotransmitter receptors, schizophrenia.

Introduction

Schizophrenia is a severe, disabling psychiatric disorder that affects approximately 1% of the world's population. Written accounts of the symptoms that are now associated with schizophrenia can be found throughout history. However, it was not until the late 19th century that a formal diagnosis of a distinct form of psychosis separate from those caused by diseases such as syphilis was formed. Termed dementia praecox (dementia of the young) by Emil Kraepelin, the disorder was differentiated from manic-depressive disorder by its classic poor long-term prognosis compared to the relatively non-deteriorating course of manic-depressive illness.¹ In 1911 Eugene Bleuler proposed the term schizophrenia (splitting of the mind) for the disorder that was characterized by abnormalities in thought processes, perception and content of thought and by withdrawal of interest in other people, rather than by dementia.²

The exact cause of schizophrenia is not known, and patients are diagnosed based on the presence of several distinct symptoms and the absence of any detectable organic cause for these features. The characteristic symptoms of schizophrenia can vary in both type and severity, and many attempts have been made to classify 'schizophrenic subtypes' according to the predominant symptoms. The most general classification

currently used is of positive and negative symptoms. Positive symptoms occur in most people with schizophrenia and are generally associated with a good response to classical antipsychotic drugs; they are characterized by an excess of normal function and include hallucinations, delusions and disorganized thoughts. Negative symptoms such as loss of function, impaired concentration, diminished social engagement, diminished emotional expression and anhedonia are associated with a poor response to antipsychotic treatment and predominate in approximately one third of all people with schizophrenia. Disorganized symptoms of formal thought disorder and disorganized behaviour may be considered to comprise a third group of symptoms.³

Several aetiological theories have been proposed for schizophrenia, including developmental⁴ or neurodegenerative processes,⁵ neurotransmitter abnormalities,^{6–8} viral infection^{9,10} and immune dysfunction or autoimmune mechanisms.^{11–22} In addition, there is substantial evidence for a genetic predisposition to schizophrenia.^{23,24} However, none of the current aetiological theories can fully explain the varied presentations observed in different patients. The mechanism of action of antipsychotic drugs suggests, however, that schizophrenia results from either blocking or over stimulation of normal neurotransmission (Fig. 1). With recent advances in technology and an increased understanding of the immune system, autoimmune theories of schizophrenia have once again become a major focus of research. This paper will review the literature regarding altered immunological findings in schizophrenia and will examine whether the criteria for defining schizophrenia as an autoimmune disease are met.

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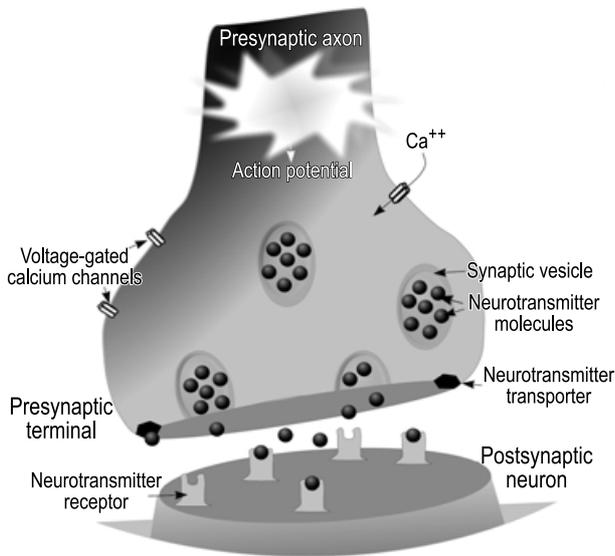


Figure 1 Neurotransmission. The nerve impulse (action potential) travels down the presynaptic axon towards the synapse, where it activates voltage-gated calcium channels leading to calcium influx, which triggers the simultaneous release of neurotransmitter molecules from many synaptic vesicles by fusing the membranes of the vesicles to that of the nerve terminal. The neurotransmitter molecules are expelled into, and diffuse across, the synaptic cleft, bind briefly to receptors on the postsynaptic neurone to activate them, causing physiological responses that may be excitatory or inhibitory depending on the receptor. The neurotransmitter molecules are then either quickly pumped back into the presynaptic nerve terminal via transporters (e.g. dopamine, GABA), are destroyed by enzymes near the receptors (e.g. breakdown of acetylcholine by cholinesterase) or diffuse into the surrounding area. Researchers believe that schizophrenia results from blocking or over stimulation of normal neurotransmission. Known sites of attack by autoantibodies in other diseases of the nervous system include the voltage-gated calcium channels (in Lambert–Eaton myasthenic syndrome) and the neurotransmitter receptors (in myasthenia gravis and Rasmussen’s encephalitis).

Immune dysregulation in schizophrenia

The question of whether some or all cases of schizophrenia have an immune or autoimmune aetiology has been asked now for nearly 100 years. Many general immune abnormalities have been reported over this time. These include morphological changes in lymphocytes, altered levels of CD4⁺CD45RA⁺ T cells, CD8⁺ T cells, CD5⁺ B cells and $\gamma\delta$ T cells, increased or decreased levels of γ -globulin in serum, increased levels of circulating cytokines, particularly IL-2, IFN- γ and IL-6, and increased levels of antiviral antibodies. These aspects of altered immune reactivity in schizophrenia have recently been thoroughly reviewed,²⁵ and are therefore not discussed in detail here.

Despite the numerous reports of immune abnormalities in schizophrenia, the hypothesis that these abnormalities are related to the pathogenesis of the disease continues to be viewed with much scepticism. This has largely been because many studies have failed to control for extraneous factors

such as antipsychotic medication, the duration and current clinical status of schizophrenia, nutritional status, substance abuse or concurrent illness, any of which may alter immune responses and lead to the apparent abnormalities. Recent studies, however, suggest that a functional adaptive immune system is necessary for cognitive function because mice deprived of mature T cells have been found to manifest cognitive deficits and behavioural abnormalities that can be ameliorated by T-cell restoration.²⁶

Some of the altered immunological factors identified in schizophrenia could promote the development or maintenance of autoimmunity. For example, increased levels of IL-6 have been found consistently in the sera of people with schizophrenia.^{27–32} Interleukin-6 is released from various cell types in the blood and, as one of its main functions is to activate B cells to synthesize antibodies,³³ elevated serum IL-6 levels could result in an increased humoral immune response. It has also been suggested that IL-6 may mediate the exacerbation of autoimmune disorders in the central nervous system (CNS) by supporting local IgG synthesis in the CNS³⁴ and promoting disturbances of the blood–brain barrier (BBB).³⁵

Furthermore, in a study from Korea, the genotype and allele distribution of an A/G single nucleotide polymorphism (SNP) at position 49 in exon 1 of the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) gene, which has previously been proposed to regulate CTLA-4 function, was found to be significantly different between patients with schizophrenia and healthy controls.³⁶ CTLA-4 is a CD28 homologue that plays an important role in the negative regulation of T-cell responses; its transient expression on the surface of activated T cells antagonizes the activating signals and terminates the T-cell response. Differences between patients and controls at this SNP have also been described in a variety of autoimmune diseases including systemic lupus erythematosus (SLE), multiple sclerosis, Hashimoto’s thyroiditis, Graves’ disease and type 1 diabetes mellitus.^{37,38} Thus, such polymorphisms might increase susceptibility to development of immune reactivity to self.

An autoimmune hypothesis of schizophrenia

The argument in favour of an autoimmune basis for schizophrenia was popularized by Burch in the early 1960s.³⁹ After analysing the age-specific and sex-specific incidence rates and prevalence of several conditions presumed to be autoimmune in origin, he concluded that schizophrenia also had an autoimmune basis because the age of onset, sex differences and relapsing clinical course matched well with diseases such as rheumatoid arthritis. Many subsequent studies have noted similarities between schizophrenia and other autoimmune diseases. However, this alone is not sufficient evidence for establishing schizophrenia as an autoimmune disease. In the 1950s, Witebsky and colleagues⁴⁰ proposed criteria that could be used to determine whether a disease is actually autoimmune in origin, and these criteria were more recently refined by Rose and Bona.⁴¹ The criteria propose several levels of evidence: direct evidence (i.e. transmissibility by lymphoid cells or antibody of the characteristic lesions of the disease from human to human or human to animal, or reproduction of the functional defects characteristic of the disease *in vitro*), indirect evidence (i.e. reproduction of the autoimmune disease in experimental animals or isolation of autoantibodies

or autoreactive T cells from the target organ), and circumstantial evidence (i.e. the presence of markers that are descriptive of autoimmune disease). The evidence provided in the schizophrenia literature for each level of the criteria is summarized below.

Circumstantial evidence of autoimmunity

Several features are common to many autoimmune diseases, namely, association with other autoimmune diseases in the same individual or the same family, the presence of immune cells in the affected organ, association with particular MHC haplotypes, high serum levels of autoantibodies, deposition of antigen-antibody complexes in the affected organ and improvement of disease symptoms with immunosuppression.

Association with other autoimmune diseases

Epidemiological studies have shown that relatives of people with schizophrenia have an increased risk of developing several other autoimmune diseases, particularly type 1 diabetes mellitus and thyrotoxicosis.^{42,43} In patients with schizophrenia, there is a strong negative correlation with rheumatoid arthritis.⁴⁴ Patients with coexistent schizophrenia and other autoimmune diseases have been reported in individual case studies, but no large-scale epidemiological studies have been done that specifically address whether patients with schizophrenia have a higher incidence of other autoimmune diseases than do the general population. One study, however, found that the prevalence of antithyroid antibodies was almost doubled in both male and female schizophrenic patients compared to controls.⁴⁵

Systemic lupus erythematosus has an interesting association with schizophrenia because it arises relatively frequently in patients with schizophrenia, particularly as a result of treatment with phenothiazine or dibenzodiazepine antipsychotic agents.⁴⁶⁻⁴⁸ The reasons for development of drug-induced SLE remain poorly understood, but it may indicate that some patients with schizophrenia have an underlying susceptibility to the development of autoimmunity. In addition, a number of SLE patients develop a schizophrenia-like psychosis resulting from cerebral lupus. This is discussed in more detail under 'Indirect evidence'.

Presence of immune cells in the target organ

There is no overt inflammatory infiltrate of mononuclear cells in the brains of the majority of patients with schizophrenia. There are, however, reports of an increased frequency of activated lymphocytes in the cerebrospinal fluid (CSF), the fluid that bathes the brain and spinal cord, of patients with acute schizophrenia.^{49,50} Only one study has investigated whether immunoglobulin can be detected in the brains of people with schizophrenia: Heath and Krupp⁵¹ found that a fluorescein-tagged antihuman antibody labelled the nuclei of some neural cells in the brain tissues from 12 of 14 patients with schizophrenia, but not in the tissues from any of 19 non-schizophrenic controls.

Association with particular MHC haplotypes

Several MHC associations have been reported for schizophrenia. Because of the negative correlation between schizophrenia and rheumatoid arthritis, a disease that exhibits association with the HLA-DRB1*04 gene, several studies have

investigated the frequency of carriage of DRB1*04 in patients with schizophrenia and found that only half the expected number of schizophrenic patients carried this gene compared with controls.⁵² In addition, preferential non-transmission of DRB1*04 alleles from heterozygous parents to their schizophrenic offspring also occurs.⁵³ One study has linked certain schizophrenia subtypes with the carriage of DQB1*0602,⁵⁴ but this association has not been found by other researchers,⁵² and in African American schizophrenic patients there appears to be a negative correlation with this allele.⁵⁵ In Japanese populations, a higher incidence of DRB1*0101 is found compared to healthy controls.⁵⁶ Recently, a chip-based mass spectrometry analysis for SNP within a 25 Mb region on human chromosome 6p21 (which covers the MHC) found a significant increase in schizophrenia, compared to other diseases and healthy controls, in the frequency of a SNP in HLA-DOA, a molecule found inside the cell that modulates MHC class II-restricted antigen presentation by interacting with HLA-DM, and a significant decrease in the frequency of a SNP in HLA-DRB1.⁵⁷

High serum levels of autoantibodies

As early as the 1930s, circulating antibodies specific for antigens found in post-mortem brains from people with schizophrenia were reported to occur in sera from people with schizophrenia.⁵⁸ However, around this time the popularity of psychoanalytical psychiatry was growing substantially and that, coupled with the limited knowledge of the immune system at the time, meant that investigations into specific immune responses in schizophrenia were largely forgotten until the 1960s, by which time the concept of autoimmunity had developed significantly.

In the early 1960s several investigators described a variety of antibrain antibodies in the sera of patients with schizophrenia.^{51,59,60} In an attempt to replicate these results many studies have been conducted searching for the presence of autoantibodies in the sera of people with schizophrenia, but consistency in the findings between different research groups has not been high (Table 1). Several groups have reported the increased occurrence of autoantibodies in people with schizophrenia, when compared to controls, against the brain or specific areas of the brain (including the cerebrum,⁶¹ septum⁶² and amygdala, frontal cortex, cingulate gyrus and septal area⁶³), or against brain constituents such as gangliosides.⁶⁴ However, other research groups have found no significant differences between people with schizophrenia and controls in the levels of antibodies directed against brain,¹⁸ brain septal regions,⁶⁵ hippocampus,⁶⁶ brain lipids⁶⁷ or gangliosides.⁶⁸

Antibodies against several neurotransmitter receptors have also been investigated in schizophrenia, with numerous research groups proposing that the presence of such autoantibodies could block or stimulate neurotransmitter receptors and could be the cause of the diverse symptoms observed in patients with schizophrenia.^{22,69-71} Several groups have reported significantly higher levels of antibodies to cerebral M₁ cholinergic muscarinic receptors,^{70,72,73} nicotinic acetylcholine receptors,⁷⁴ dopamine D₂ receptors,^{73,75} astrocyte M₁ and M₂ muscarinic cholinergic receptors,⁷² mu-opioid and serotonin (5-HT_{1A}) receptors⁷³ in sera from people with schizophrenia when compared to sera from healthy controls. Despite the relatively small numbers of patients in most of these studies

Table 1 Autoantibodies detected in people with schizophrenia compared with controls

Autoantibody to	Finding	Reference
Brain	Significantly higher	51,63,64,112,113
	None detected	18,114,115
	No difference	116–118
Brain septal region	No difference	65
	Significantly higher	62
Brain lipids	No difference	67
Cerebellum	Significantly higher	61
Gangliosides	No difference	68
Hippocampus	No difference	66
Cell nuclei	Significantly higher	76,78
	No difference	79,80
	Present in sera	119
Lymphocyte nuclei	Significantly higher	120
DNA	Significantly higher	77
	None detected	78
	Significantly higher	121
Anticardiolipin	Significantly higher	122,123
Heat shock proteins	Higher frequency	79
Gastric parietal cells	Present in sera	119
	Significantly higher	124
Platelets	Significantly higher	70,72–75

and a lack of disease specificity for some of these antibodies to schizophrenia alone (one group found antibodies to several neurotransmitter receptors in serum samples from people with psychiatric diseases other than schizophrenia⁷³), the results are nevertheless suggestive of an autoimmune response directed against neurotransmitter receptors in at least some patients with schizophrenia. Recent direct evidence of a functional role for some of the neurotransmitter receptor antibodies will be discussed below.

A large number of studies have investigated organ non-specific autoantibodies, such as those against DNA, heat shock proteins and the nucleus, because these are often increased in patients with an autoimmune disease even if organ-specific autoantibodies are not. A significantly higher frequency of circulating antinuclear antibodies in people with schizophrenia compared to controls has been found in a number of studies,^{76–78} whereas others^{79,80} have found no significant increase in antinuclear antibodies in never-medicated people with schizophrenia compared to controls. Autoantibodies to both single and double-stranded DNA have also been found to be significantly more common in people with schizophrenia compared to controls by one group⁷⁷ and not present at all by another research group.⁷⁸

Several possible reasons could account for the discrepancies in findings from different research groups. The heterogeneity of the disease and the diagnostic criteria used to classify patients could influence results, in that patients with drastically different presentations (that could be indicative of different disease processes or causes) are being compared against one another. The medication status of patients could also influence results, with patients who are neuroleptic naïve being compared with patients who are merely currently unmedicated but who have had previous exposure to antipsychotic medication. The techniques used by different research groups have also varied markedly over the 40-year timespan in which the tests have been done, with some studies using much more sensitive techniques than others.

Deposition of antigen–antibody complexes in the affected organ

It has been proposed that schizophrenia may be caused by a covert immune complex-driven basal lamina disease of the choroid plexus.⁸¹ This proposal was largely based on findings from patients with SLE and associated schizophreniform psychoses, in which immune complexes are deposited in the choroid plexus. In schizophrenia itself, however, no studies have investigated whether or not such immune complex deposition occurs. One research group has reported that concentrations of circulating immune complexes are elevated in the blood of many patients with schizophrenia compared to chronic alcoholics;⁸² however, another group found no increased incidence of circulating immune complexes.¹²

Improvement of disease symptoms with immunosuppression

Despite the popularity of the autoimmune hypothesis for schizophrenia, few studies have reported results of trials of immunosuppressive agents in schizophrenia. Plasma exchange was not found to affect the course of schizophrenia in one small trial of 10 patients;⁸³ however, it has been noted that most autoimmune diseases (with the exception of acute Guillain–Barré syndrome) appear to require the combined use of immunosuppressive drugs and/or lymphocytapheresis for successful outcomes with plasmapheresis.⁸⁴ Levine and colleagues⁸⁵ showed that short-term treatment with azathioprine improved the psychiatric symptomatology in a subgroup of patients with schizophrenia. Few other studies have set out to test well-defined immunosuppressive agents in schizophrenia. However, it is known that some of the anti-psychotic drugs such as haloperidol and clozapine are highly immunosuppressive.⁸⁶ If autoimmune responses are playing a role in the development of schizophrenia, then treatment with some of the common antipsychotic drugs may act synergistically as direct antagonists of brain neurotransmitter receptors and also as inhibitors of autoimmune responses, thus leading to amelioration of psychotic behaviour.

Indirect evidence of autoimmunity

In general, indirect evidence of autoimmunity includes such observations as the induction of autoimmunity in an animal model or the finding of autoimmune cells or antibodies in the target organ. No appropriate experiments to investigate these aspects of autoimmunity have been carried out for schizophrenia. Probably the best indirect evidence for an autoimmune basis for schizophrenia comes from studies examining SLE, a known autoimmune disease characterized by the presence of autoantibodies against double-stranded DNA. Between 14% and 75% of patients with SLE are estimated to experience neuropsychiatric symptoms, including mood and behavioural disturbances and psychotic symptoms.^{87,88} Recently it has been shown that a subset of anti-DNA antibodies can cross-react with the NR2 subunit of the N-methyl-D-aspartate (NMDA) glutamate receptor.⁸⁹ If the psychotic symptoms in SLE patients are the result of anti-DNA antibodies cross-reacting with the glutamate receptor, then it is possible that the psychotic symptoms in some schizophrenic patients could be caused by similar reactions of antibodies with neurotransmitter receptors.

Direct evidence of autoimmunity

The most direct evidence for an autoimmune aetiology of a disease is that direct transfer of T cells or antibody from a diseased to a healthy individual can induce the characteristic lesions of the disease. In the 1960s Heath *et al.*⁵⁹ isolated a protein that they termed ‘taraxein’ from the sera of actively psychotic people with schizophrenia. Taraxein was later identified as an immunoglobulin, but its specificity was not determined. When administered intravenously into monkeys, taraxein caused electroencephalographic (EEG) changes in the monkeys similar to those observed in people with schizophrenia. In addition, when taraxein was injected intravenously into healthy human volunteers it resulted in similar EEG changes and the induction of psychotic symptoms comparable to those observed in the active psychosis stage of schizophrenia. Later studies from the same group using antibodies induced in rabbits with specificity for the septum pellucidum of the brain showed that these antibodies could produce focal EEG changes when injected into cats.⁹⁰

In an attempt to reproduce the results of Heath *et al.*'s studies, Bergen and colleagues⁹¹ used IgG purified from the blood of acutely ill schizophrenic patients and injected it into the CSF of rhesus monkeys. They found that 22% of sera from patients with schizophrenia compared with 7% of sera from healthy controls were able to induce EEG abnormalities in the monkeys. The results obtained using IgG from patients with schizophrenia were similar to the results recorded by Heath *et al.*; however, the previous work had reported that no abnormalities occurred using sera from healthy controls.

Purified IgG from the blood of patients with schizophrenia has also been injected intracisternally into the CSF of rats, and subsequent electron microscopic and biochemical studies used to investigate changes in the brains of the rats. It was found that ultrastructural abnormalities of the sensorimotor cortex and activation of lipid peroxidation occurred; these changes were similar to the alterations that can be detected in the brains of patients with schizophrenia.⁹²

These early experiments support the hypothesis that autoantibodies from some patients with schizophrenia have the potential to transmit disease from one individual to another. However, they provide little explanation of how such an effect might occur. Recently, it has been shown that autoantibodies purified from the blood of patients with schizophrenia that are specific for the M1 muscarinic acetylcholine receptor (mAChR), one of several neurotransmitter receptors implicated in schizophrenia, can exert functionally relevant effects in *in vitro* assays.⁷² These antibodies have been shown to inhibit the binding of natural ligands to the receptors and to display agonistic-like activity leading to M1 mAChR activation.

Does schizophrenia in some patients result from an autoantibody-mediated autoimmune disease?

The findings presented in the preceding section give many hints that, in some patients at least, autoantibodies could play a role in the development of schizophrenia. The finding of neurotransmitter-receptor-specific antibodies that appear to have functional properties⁷² represents a substantial step forward in our understanding of how such autoimmune responses might lead to schizophrenia; however, the mechanisms are

not entirely unexpected. Functional autoantibodies that inhibit or stimulate receptor-mediated neurotransmission have been reported for several different diseases. For example, IgG in the sera of children with congenital heart block can bind and activate β -adrenoceptors and mAChR receptors of the neonatal heart.⁹³ Similarly in patients with Chagas' disease, a cardiomyopathy induced by infection with *Trypanosoma cruzi*, antibodies specific for a ribosomal protein of *T. cruzi* cross-react with β 1 adrenergic receptors of the human heart, activating the receptor excessively and leading to receptor desensitization and internalization.⁹⁴ In addition, functional autoantibodies against M3 mAChR can be found in patients with scleroderma and Sjögren's syndrome.⁹⁵ Neurotransmitter-receptor-specific autoantibodies have been found in patients with several autoimmune diseases affecting the peripheral nervous system and are believed to be responsible for the symptoms of those diseases. In some cases, the autoantibodies bind to the neurotransmitter receptor and prevent the normal ligand from binding, resulting in a reduction in the number of functional neurotransmitter receptors by increasing the receptor internalization. One example of this type of antibody-mediated disruption of neurotransmission is observed in myasthenia gravis in which autoantibodies bind to post-synaptic nicotinic acetylcholine receptors in the neuromuscular junction, with a resultant increase in internalization of the neurotransmitter receptors and a decrease in the number of functional receptors. In CNS disorders, several autoantibodies against known neurotransmitter autoantigens have been reported that are pathogenic either *in vitro* or *in vivo* (reviewed recently by Lang *et al.*⁹⁶). For example, in Rasmussen's encephalitis, a rare cause of epilepsy, autoantibodies bind selectively to ionotropic glutamate receptors and destroy neuronal cells via activation of the complement pathway.⁹⁷

Other structures in and around the synaptic junction could also be targeted by autoantibodies, leading to functional effects similar to those observed with the neurotransmitter-receptor-specific autoantibodies (Fig. 1). For example, in Lambert-Eaton myasthenic syndrome, binding of antibodies specific for L-, N- or P/Q-type voltage-gated calcium channels (VGCC) leads to morphological changes (cross-linking) in the active zone particles at the nerve terminals and inhibits the release of the neurotransmitter from the nerve terminals. Synaptotagmin, one of the functionally VGCC-associated synaptic proteins, is also targeted by autoantibodies in this syndrome.^{98,99}

Could autoantibody-mediated damage at the synapse in schizophrenia cause a similar clinical phenotype to that which would be caused by some of the other putative pathogenic processes in schizophrenia, such as genetic mutations or neurodevelopmental abnormalities? This is not yet known for schizophrenia; however, it is known that such widely variant pathological processes can result in a very similar end-stage clinical phenotype. For example, a similar clinical phenotype is observed in myasthenia gravis (mediated by anti-acetylcholine receptor antibodies) and in several different congenital myasthenic syndromes caused by mutations in genes encoding the acetylcholine receptor ϵ chain or the acetylcholinesterase collagen anchor. Thus, while some cases of schizophrenia may result from genetic or neurodevelopmental disruption to one or more components of the synapse, it is possible that, in other cases, autoantibodies directed against the same components could lead to very similar clinical manifestations.

How do the autoantibodies get into the nervous system?

One difficulty in accepting the idea of an autoantibody-mediated disease of the CNS is the widely held belief that the BBB limits the access of circulating antibody to the normal nervous system; however, at least one antibody has been reported to cross the intact BBB.¹⁰⁰ In addition, there is evidence that activated B cells can cross the intact BBB and enter the CNS, clonally expand and produce antibody.^{101,102} However, for most circulating antibodies against the brain to play a role in disease, the BBB probably needs to be impaired in some way. For example, in multiple sclerosis, an autoimmune CNS disorder, damage to the BBB allows antibodies and complement access to the brain. In schizophrenia, however, there is no clear evidence of T-cell infiltration of the CNS or disruption of the BBB. One study has suggested that there may be an underlying inflammatory process occurring in the brains of people with schizophrenia based on the presence of fibrin degradation products in the CNS,¹⁰³ whereas another group have found no evidence of CNS inflammation based on two indicators of inflammation, neopterin and macrophage inflammatory protein-1 α (MIP-1 α).¹⁰⁴ It has also been suggested that increased levels of soluble circulating intercellular adhesion molecule-1 (ICAM-1) in some people with schizophrenia are indicative of damage to, or increased permeability of, the BBB^{105,106} and that both typical and atypical antipsychotic drugs may induce alterations in the BBB.¹⁰⁷ Several groups have used the ratio of CSF/serum albumin as a measure of the permeability of the BBB and have found increased permeability in 15–30% of people with schizophrenia.^{105,108–111}

Thus, several possibilities exist: many patients with schizophrenia may produce autoantibodies against neurotransmitters or other brain structures that have the potential to be functionally relevant, but these antibodies may play a role in disease pathogenesis only in those patients whose BBB is impaired or who produce such antibodies locally in the CNS. Alternatively, non-immune-mediated damage to the CNS in schizophrenia may allow the release of autoantigens and the production of autoantibodies, which may contribute to the symptoms of the disease.

Conclusions

Schizophrenia is a devastating mental illness, the symptoms of which affect the normal functioning of an individual by causing a loss of contact with reality and by disturbing the capacity for work and social interactions. The exact cause of schizophrenia remains undetermined, although the clinical symptoms and signs appear to result from either blocking or over stimulation of normal neurotransmission. There is a large volume of circumstantial evidence for an autoimmune aetiology of at least some cases of schizophrenia. This evidence includes the occurrence of other autoimmune diseases in the relatives of people with schizophrenia, the association of schizophrenia with particular HLA haplotypes and the presence of circulating autoantibodies. Because neurotransmission is abnormal in schizophrenia, the finding of increased levels of antibodies specific for several neurotransmitter receptors and the demonstration that such antibodies can exert functional effects *in vitro* constitute compelling evidence in

support of the hypothesis that autoantibodies may play a role in the development of schizophrenia.

Further research is warranted to confirm the presence of autoantibodies in people with schizophrenia and to ascertain the targets of an antibody-mediated autoimmune response. If autoantibodies directed against neurotransmitter receptors play a functional role, as suggested by current evidence, then more effective treatments based on the specific receptor systems targeted by antibodies could be investigated, as could new strategies for immunotherapeutic intervention in schizophrenia.

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