Autoantibodies to the NMDA Receptor in Schizophrenia: a literature review

Liam Kennedy

M.Sc. Neuroscience

Abstract

Schizophrenia is a chronic mental illness characterised by positive and negative symptoms, and cognitive dysfunction. The aetiology of the condition is poorly understood; among the various proposed hypotheses are theories involving glutamate transmission and autoimmunity. The N-methyl-D-aspartate receptor (NMDAR) is an ionotropic glutamate receptor expressed widely in the CNS, it is involved in long-term potentiation, memory and learning, and regulation of glutamatergic transmission via GABA-ergic interneurons. Pharmacological blockade of NMDARs induces positive and negative symptoms of schizophrenia in healthy subjects, and exacerbates symptoms in patients. NMDA hypo-function has been demonstrated to cause localised glutamate excito-toxicity in schizophrenia. Anti-NMDAR auto-encephalitis is a recently described neuro-immune condition, which often presents with acute psychosis. Due to the behavioural symptoms caused by the condition, 65% of those who develop anti-NMDAR auto-encephalitis are initially seen by psychiatric services. Studies of anti-NMDAR antibody prevalence in schizophrenic patients and the general population have found conflicting results. Analysis is complicated by variance between studies in terms of antibody specificity and assays used. Further work in this expanding field will help delineate the exact relevance of antibody seropositivity to the development of schizophrenia or psychosis. Anti-NMDAR auto-encephalitis represents an important aetiological factor of psychosis to be considered in the clinical assessment of acute psychosis.

Introduction

Schizophrenia is a severe, chronic, and debilitating mental illness characterised primarily by negative symptoms such as hallucination, delusion, and thought disorder[1]. Despite major research efforts spanning decades, no clear picture of a precise aetiology underpinning the disorder has emerged[1]. However, hypotheses implicating dopamine, glutamate, serotonin, neurodevelopment, and neuro-immune interactions have been proposed[2]. Factors that appear to be associated with the development of schizophrenia include genetic variance, maternal or perinatal infection, urban upbringing, lower socioeconomic status, and regular cannabis use[1]. A diagnosis of schizophrenia carries with it a significantly lowered life expectancy with major causes of death including suicide, cardiovascular disease, respiratory disease, and infection[1].

For decades, the immune system has been investigated as a potential causal factor in the aetiology of schizophrenia[2]. A correlation between immunity and schizophrenia has long been established. Specifically, those with a diagnosis of schizophrenia have a significantly higher rate of autoimmune diseases[3]. The recent descriptions of a spontaneous organic form of psychosis seen in anti-NMDAR auto-encephalitis have sparked fresh interest in the field, birthing the concept of an antibody-mediated treatable form of "schizophrenia"[4-7].

This report aims to review:

- The NMDA hypofunction hypothesis of schizophrenia
- Recent descriptions of the psychiatric and behavioural symptoms commonly seen in anti-NMDAR auto-encephalitis

- The prevalence of IgG anti-NR1 NMDAR autoantibodies in the general population, and those diagnosed with schizophrenia and first episode psychosis (FEP)

NMDA hypofunction in schizophrenia

For decades, altered dopamine transmission has been considered the key neurochemical driving force in schizophrenia. Although dopaminergic blockade has been the primary mode of pharmacological treatment, antipsychotic therapies remain limited and imperfect. More recently, interest has grown in the role of glutamate transmission as an aetiological defect and therapeutic target in schizophrenia with some suggesting it may even be primary to dopaminergic dysfunction[8].In contrast to the dopamine hypothesis, the positive and negative symptoms of schizophrenia, as well as cognitive deficits, are plausible for a glutamatergic theory[9].

NMDARs

The NMDAR is an ionotropic glutamate receptor, widely expressed both pre- and post-synaptically on the cell surface of brain neurons. It has a role in regulating glutamatergic transmission and is involved in synaptic plasticity, memory, and learning[10]. The NMDAR is composed of one or more NR1 subunits in addition to a combination of NR2 and/or NR3 subunits. Different formations of these subunits give rise to several structurally and functionally distinct NMDARs[11].The natural ligand for the receptor is glutamate, but it also requires co-stimulation from glycine. At resting membrane potential, the ion channel is blocked by a magnesium ion. Depolarisation unblocks the channel and allows influx of calcium and sodium ions, and efflux of potassium (figure 1). Calcium ion influx plays an important role in long-term potentiation and, thus, in learning and memory[10]

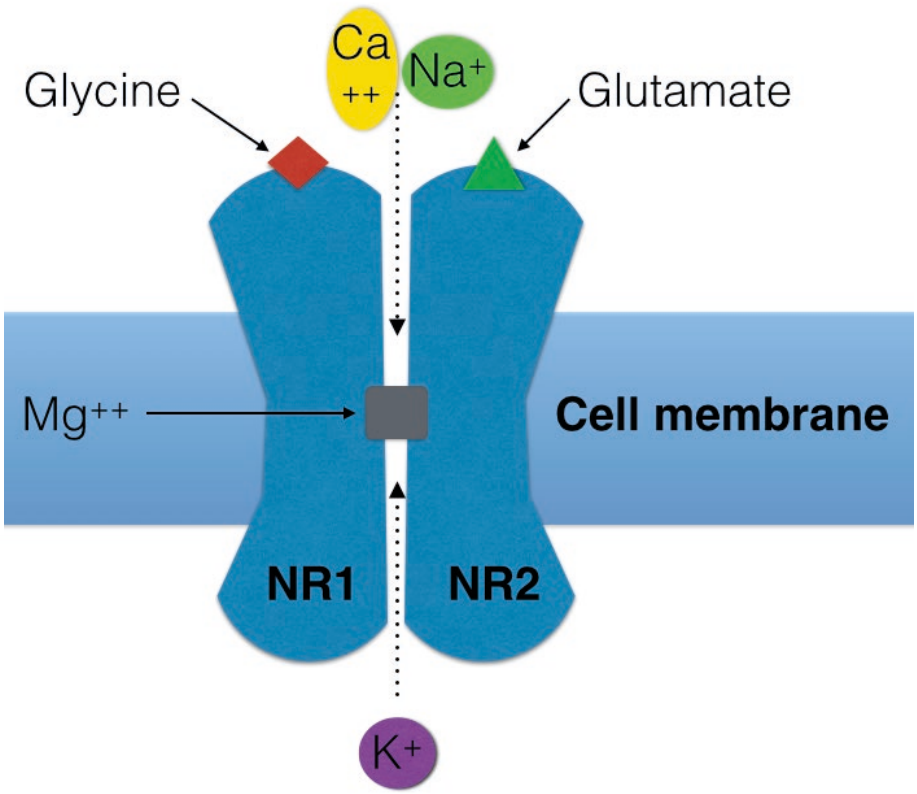

figure 1 Structure of NMDAR

Glutamate in schizophrenia

The core observations underlying the glutamatergic model of schizophrenia have resulted from pharmacological studies. Blockade of NMDARs using dissociative anaesthetics (e.g. phencyclidine or ketamine) cause schizophrenia-like behavioural and cognitive symptoms in healthy subjects, and the exacerbation of psychotic symptoms in subjects with schizophrenia[12, 13]. Rodent models demonstrate schizophrenia-like behaviours, such as catatonia and stereotyped movements in response to administration of NMDA antagonists[14].

Initial hypotheses involving glutamate transmission speculated that overall glutamate deficiency might play a role in the development of schizophrenia. It is now thought that hypofunction of

the NMDAR on GABAergic inhibitory interneurons causes an overall excitotoxic effect with glutamate levels increased rather than deficient[15]. Administration of NMDA antagonists have been shown to cause extracellular glutamate levels to be increased specifically in the anterior cingulate cortex, part of the limbic system[16].

Post-mortem studies examining the levels of expression of the NMDAR have found conflicting results with various studies showing increased, normal, or decreased levels of NMDAR mRNA or protein expression[17, 18, 19]. Without definitive evidence that receptor expression is significantly altered in schizophrenia, researchers have looked to modulatory and downstream factors that may affect receptor function. A number of genes which have been linked to schizophrenia are important in glutamatergic signalling via the NMDAR[20].

CLINICAL POINTS

Anti-NMDA autoencephalitis is a recently described neuro-immune condition which often presents with acute psychosis

While first described exclusively in those with ovarian teratoma, the condition has since been seen in males, and in females without malignancy

65% of those who develop anti-NMDA autoencephalitis are initially seen by psychiatry services

NMDAR autoencephalitis therefore represents an important organic aetiology to be considered in first episode psychosis

Interest lies in the prevalence of anti-NMDAR antibodies in those already diagnosed with schizophrenia, as seropositivity may represent an organic cause for previously diagnosed psychiatric disease

NMDAR autoencephalitis and psychosis

Anti-NMDA receptor autoencephalitis is a recently described autoimmune condition. Initially described in 2005 as a paraneoplastic phenomenon in young women with ovarian teratomas[4], anti-NMDAR autoencephalitis has more recently been shown to occur in males and females with no underlying malignancy[21]. Clinical expression consists of a prodromal phase of nausea, headache, fever, vomiting, and diarrhoea which develop within days into a variable presentation of psychiatric symptoms such as delusions, mania, anxiety, catatonia and insomnia[6]. Motor dysfunction such as choreiform movements and ataxia may also manifest. Approximately 65% of adults first present with psychiatric symptoms and the majority are initially assessed by psychiatric services making anti-NMDA autoencephalitis a valid differential diagnosis to be considered in presentations of acute psychosis[20].

According to Dalmau and associates, IgG antibodies targeting the extracellular domain of the NR1 subunit of the NMDAR are pathognomic of the condition[5]. This pathology is consistent with the clinical course of the autoencephalitis, with many symptoms similar to those observed in pharmacological NMDA blockade and NMDAR knockout in animal studies[22, 23]. In vitro and in vivo studies have demonstrated that anti-NMDAR autoantibodies act pathogenically by causing a reduction in the number of expressed neuronal surface NMDARs leading to a selective functional attenuation of the excitatory post-synaptic potential (EPSP)[24]. The synaptic and clinical effects of this process have been demonstrated to be titre-dependent: cerebral spinal fluid (CSF) and serum samples taken at symptom presentation or symptom worsening displayed higher anti-NR1 antibody titres than samples taken during symptomatic improvement. High-titre samples had a greater observed effect on reducing in vitro post-synaptic receptor cluster concentrations than relatively low-titre samples[24]. The pathological reduction in post-synaptic receptor density has been shown to reverse with removal of antibody, providing a basic mechanistic explanation for the symptom relief observed once patients receive therapeutic intervention[5].

Prevalence of anti-NMDAR autoantibodies

Several studies have investigated the prevalence of anti-NMDA autoantibodies in populations with schizophrenia, but found conflicting results. Initial studies discovered minor or zero prevalence of antibody in case populations, with many of these studies having small sample size and failed to compare with control populations (figure 2)[25, 26, 27].

The first substantial comparison of seroprevalence rates between cases and matched controls came in the form of a prospective study by Steiner and colleagues in 2013 (n=459). The authors found non-specific antibodies against NMDA in 9.9% of acutely ill patients with an initial diagnosis of schizophrenia, contrasting strongly with a seropositivity rate of only 0.4% (1/230) of controls[28]. Studying a significantly larger cohort population (n=2817) and controls, Hammer and co-workers found anti-NMDAR autoantibodies in 10.5% of all subjects, with no significant difference in seropositivity between cases and controls[29].

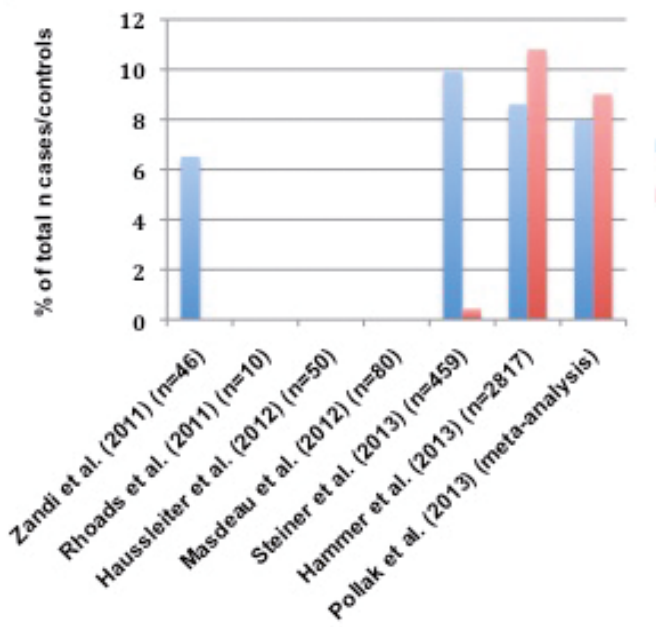

figure 2 Prevalence rates of anti-NMDA autoantibodies as repored in recent literature

Pollak and colleagues carried out a systematic review and meta-analysis, including data from seven studies comprising 1,441 patients and 1,598 healthy controls[30]. Meta-analysis gave figures of 7.98% prevalence of anti-NMDAR autoantibodies in patients and 9.01% prevalence in controls. Studies were noted to be inconsistent in assaying for specific classes of immunoglobulin and receptor subunit epitope. Notably, while 7.98% of patients tested positive for anti-NMDAR antibody, only 1.46% of patients were found to carry IgG antibodies specifically, with the remainder testing positive for IgA and IgM anti-NMDAR antibodies. If IgA and IgM antibodies were excluded from analysis, antibody prevalence was significantly greater in cases than in controls.

Blood-brain barrier integrity

The cited study by Hammer and colleagues stands in stark contrast to others included in the systematic review of Pollak and co-authors in that it found anti-NMDAR autoantibodies to be prevalent in a significant proportion of the general population. One possible reason for this discrepancy is the slightly higher average age of the control population studied as autoantibody prevalence is correlated with age. Interpreting this finding, the authors propose that in light of equal seroprevalence rates across cases and controls, impaired blood-barrier function may confer susceptibility to autoantibody-mediated impairment of function in seropositive populations. Supporting this hypothesis is their finding of a significant correlation, within seropositive individuals between proxy indicators of temporary blood-brain barrier damage (past neurological trauma/birth complication) and schizophrenia. Future approaches to this hypothesis might investigate a correlation between anti-NMDA autoantibody seropositivity, psychosis and blood-brain barrier damage in relation to more sensitive indicators of blood-brain barrier function, e.g. serum/CSF markers or imaging studies.

Implications for practice

The relatively recent discovery of anti-NMDA autoencephalitis and subsequent research on its underlying pathology, course, and treatment raise important considerations among physicians and psychiatrists. Given the large proportion of those eventually diagnosed with anti-NMDA autoencephalitis who initially present to psychiatric services, psychiatrists must be fully aware of the presentation and clinical course of the condition and keep it in mind as an important organic cause of psychosis. Maneta and associates propose a list of features which should raise the index of suspicion of anti-NMDA autoencephalitis in anyone presenting with first episode psychosis: these include a flu-like prodrome, rapid onset of symptoms, seizures, and catatonia, among other features[31].

Another important consideration is screening in the existing population of diagnosed schizophrenics. A finding of seropositivity for anti-NMDAR autoantibodies in a treatment-resistant schizophrenic may provide a novel approach for therapeutic intervention in the form of immune therapies.

Conclusion

The discovery of antibodies targeting the NMDAR as a cause of organic psychosis has interesting ramifications for future management and treatment in mental healthcare. It underlines the strong link between the medical and psychiatric fields and strongly reinforces the NMDA hypofunction model of schizophrenia as a biological basis for mental illness. The clinical course of anti-NMDA autoencephalitis is in agreement with pharmacological and genetic knockout studies of NMDA hypofunction and serves as another direct link between NMDA hypofunction and psychotic symptoms. Future clarification of the currently inconclusive evidence regarding the prevalence of anti-NMDA autoantibodies in schizophrenic and general populations will help further delineate the relevance of antibody seropositivity to the development of psychotic disease.

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Liam Kennedy