Autoimmunity and NMDA receptor in brain disorders: Where do we stand?

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ABSTRACT

Over the past decades, the identification of autoimmune encephalitis in which patients express autoantibodies directed against neurotransmitter receptors has generated great hope to shed new light on the molecular mechanisms underpinning neurological and psychiatric conditions. Among these autoimmune encephalitides, the discovery of autoantibodies directed against the glutamatergic NMDA receptor (NMDAR-Ab), in the anti-NMDAR encephalitis, has provided some key information on how complex neuropsychiatric symptoms can be caused by a deficit in NMDAR signalling. Yet, NMDAR-Abs have also been detected in several neurological and psychiatric conditions, as well as in healthy individuals. In addition, these various NMDAR-Abs appear to have different molecular properties and pathogenicities onto receptors and synaptic functions. Here, we discuss the current view on the variety of NMDAR-Abs and, in particular, how these autoantibodies can lead to receptor dysfunction in neuronal networks. Since our mechanistic understanding on patients’ NMDAR-Abs is still in its infancy, several complementary processes can be proposed and further in-depth molecular and cellular investigations will surely reveal key insights. Autoantibodies represent a great opportunity to gain knowledge on the etiology of neuropsychiatric disorders and pave the way for innovative therapeutic strategies.

One sentence summary: Current view on patients’ autoantibody against NMDAR.

1. Introduction

In the vertebrate central nervous system, excitatory glutamatergic neurotransmission constitutes the vast majority of intercellular communication (Traynelis et al., 2010). Among the glutamatergic receptors underpinning fast transmission, NMDA receptors (NMDARs) play a key role in synaptic adaptation processes (Lau and Zukin, 2007; Paoletti et al., 2013). Furthermore, dysfunctions of NMDAR signalling have been involved in the etiology of several major neurological and psychiatric disorders. NMDARs are heterotetramers composed of a combination of GluN1, GluN2, and GluN3 subunits. These subunit families contain several variants: the single GluN1 subunit with eight splice isoforms, four distinct GluN2 subunits (A-D), and two GluN3 subunits (Paoletti et al., 2013). The assembled NMDAR has a large extracellular domain, transmembrane loops, and an intracellular tail. The agonist, i.e. glutamate, binds to GluN2 subunits whereas the co-agonist, i.e. glycine or D-serine, binds to GluN1 subunits. The GluN2 subunits provide specific biophysical and pharmacological properties to the receptor. In addition to their biophysical specificities, NMDAR subtypes exhibit different trafficking properties that have been thoroughly reviewed (Horak et al., 2014; Lau and Zukin, 2007; Luusier et al., 2015; Paoletti et al., 2013). Schematically, there is a large pool of GluN1 subunits in the endoplasmic reticulum that await assembly with GluN2 subunits. The correctly assembled receptors are intracellularly trafficked through the dendrite, carried along microtubules by molecular motor kinesins. After insertion into the plasma membrane, NMDARs laterally diffuse and explore large domains of neuronal dendrites (Ladepeche et al., 2014). Upon entry into postsynaptic compartment, the NMDAR becomes anchored and stabilized by protein-protein interactions with various scaffold partners. In the extrasynaptic compartment NMDAR are endocytosed and eventually recycle to the plasma membrane through exocytosis, keeping the membrane pool rather constant. The surface dynamics of NMDAR is not only important to regulate the synaptic pool, it also plays a key role in the establishment of long-term synaptic plasticity in an unconventional process (Groc and Choquet, 2020).

Understanding the dysfunction of the NMDAR signalling in various brain disorders has captured a lot of attention over the past decades (Hardingham, 2019; Myers et al., 2019; Nakazawa et al., 2017). From genetic mutations observed in patients with neurological and

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psychiatric conditions to drugs that target the NMDAR and trigger neuropsychiatric symptoms, several putative mechanisms underpinning NMDAR signalling dysfunction have been proposed. The direct role of NMDAR dysfunction in human brain disorders has recently gained strong support with the discovery of autoantibodies directed against the NMDAR (NMDAR-Abs). Dalmau et al. (2007) identified a patient cohort who presented initially with a viral-like prodromal phase. This condition was followed sharply by psychotic symptoms baring a striking resemblance to that of a first psychotic episode. It is then concurrent with subtle indicators of underlying neurologic pathology including dyskinesia (Dalmau et al., 2010; Dalmau et al., 2007). Later stages of the disease progression comprise a seizure phenotype and a worsening autonomic dysfunction often leading to fatality if untreated. It was later identified that the root of this disorder was by the pathogenic action of patient-generated NMDAR-Abs directed against the extracellular domain of the receptor (Dalmau et al., 2008; Gleichman et al., 2012; Hughes et al., 2010). The initial psychiatric phase is considerably heterogeneous between patients, experiencing symptoms of psychosis (auditory and visual hallucination), depression, mania, eating disorder and addiction (Graus et al., 2016). Alarming, a large fraction of these patients were initially admitted to psychiatric institutions as opposed to neurological wards (Graus et al., 2016; Lejuste et al., 2016; Pollak et al., 2020). The question of whether different clinical expression of anti-NMDAR encephalitis exists is a current debate. For instance, NMDAR-Abs have been found in up to 20% of patients diagnosed with schizophrenia (Jezequel et al., 2018), suggesting that these autoantibodies can be expressed in patients with psychosis and/or in patients with anti-NMDAR encephalitis with prominent psychiatric features. Ongoing investigations will surely shed light on this debate. Today, less than twenty different autoimmune encephalitic disorders had been identified in which autoantibodies are directed against synaptic receptors (i.e NMDAR, GABA receptor) or neuronal cell surface proteins (i.e LGI1, CASPR2) (Crisp et al., 2016). Brain-targeting antibodies have also been identified in non-encephalitic disorders. It is estimated that up to 70% of patients with autism spectrum disorder have systemic circulation of autoantibodies against brain targets. Also, in patients with systemic lupus erythematosus and a concurrent neuropsychiatric component (NPSLE), it has been shown that anti-double-stranded DNA antibodies (dsDNA-Abs) have cross-reactivity with NMDARs (Brimberg et al., 2015). Adding still further complexity, brain-targeting autoantibodies...
have also been identified in the systemic circulation of healthy individuals, suggesting that - in a least some cases - such autoantibodies lack any observable pathogenicity. Given the association of NMDAR-reactive autoantibodies across many neuropsychiatric disorders, and its high prevalence in autoimmune encephalitis and NPSLE, we will dedicate our focus to the actions of two mechanistically opposing NMDAR-Abs, those found in encephalitis and NPSLE. As there is considerable heterogeneity in the mechanism of action for these NMDAR-Abs within different neurological conditions, we will discuss these various mechanisms of action and propose emerging working models.

2. Diversity in NMDAR autoantibody types and pathogenicity

The concept that autoantibodies contribute to the etiology of specific neurological and psychiatric conditions is almost a century old (Jezequel et al., 2018). Yet, since the identification of NMDAR-Abs in anti-NMDAR encephalitis more than a decade ago, the number of studies reporting NMDAR-autoimmunity in brain disorders has been exponentially growing (Dalmau et al., 2019; Ehrenreich, 2018; Jezequel et al., 2018). The study of NMDAR-Abs has primarily focussed on neuropsychiatric diseases, since they were initially found in the serum and CSF of women suffering from immune psychosis, NPSLE, and autoimmune encephalitis (Dalmau et al., 2019; Ehrenreich, 2018; Jezequel et al., 2018). In 2001, NMDAR-Abs were reported in patients with NPSLE. This presentation of NMDAR-Abs has primarily focussed on neuropsychiatric diseases, since they were initially found in the serum and CSF of women suffering from immune psychosis, NPSLE, and autoimmune encephalitis (Dalmau et al., 2019; Ehrenreich, 2018; Jezequel et al., 2018).

The presence of NMDAR-Abs in a number of patients with variable dementia has also been reported; including progressive supranuclear palsy, corticobasal syndrome, Parkinson’s disease-related dementia, primary progressive aphasia, ischemic stroke and amyotrophic lateral sclerosis (Dalmau et al., 2019; Ehrenreich, 2018; Jezequel et al., 2018). In 2001, NMDAR-Abs were reported in patients with NPSLE. This autoimmune disease is first characterised by the presence of dsDNA-Abs. It has been proposed that a pentapeptide sequence in the extracellular portion of the NMDAR GluN2A/2B subunits is a molecular mimic of double-stranded DNA. This cross-reactivity between dsDNA-Abs and NMDAR GluN2A/2B subunits have been associated with cognitive defects in NPSLE patients, with approximately 30% of patients showing seropositivity for NMDAR-Abs against these GluN2 subunits (DeGiogetti et al., 2001) (Fig. 1A). It should be noted that the presence of NMDAR-Abs in NPSLE has been questioned (Varley et al., 2020), calling for further in-depth investigations.

To add another layer of complexity, NMDAR-Abs have also been found in healthy individuals (Dahm et al., 2014; Doss et al., 2014; Hammer et al., 2014; Jezequel et al., 2017a; Pan et al., 2019), with a seroprevalence that has been proposed to increase with age and is slightly higher in male compared to female populations (Hammer et al., 2014).

This extensive diversity in NMDAR-Ab subtypes and disease prevalence raises, among many others, two key questions: (i) whether currently-available techniques are reliable and reproducible measures of antibody prevalence, and (ii) whether all NMDAR-Abs have similar effects on their targets. Considering the former, various assays are used worldwide (Simmaz et al., 2015). Recently, it has been shown that identical samples tested in different centres with different assays (e.g. live versus fixed heterologous cells) produced opposite outcomes (Jezequel et al., 2017b). It thus remains urgent to develop sensitive and reproducible methods to detect the presence, or absence, of NMDAR-Abs in the circulation of patients with different conditions. Secondly, considering the heterogeneity of antibody actions, the best characterised pathogenic mechanism comes from studies of anti-NMDAR encephalitis. Schematically, anti-NMDAR IgGs induce a massive hyperfunction of synaptic NMDARs, leading to a decrease in NMDAR signalling (Dalmau et al., 2017) (Fig. 1B). This antibody effect is achieved by an alteration of the lateral displacement of synaptic NMDARs. Similarly, NMDAR-Abs from patients with psychotic disorders, induce an NMDAR hyperfunction with comparably aberrant surface dynamics (Jezequel et al., 2017a). These major alterations of NMDAR signalling prevent NMDAR-dependent long-term synaptic plasticity and induce deficits in memory and cognitive functions (Jezequel et al., 2018; Planaguma et al., 2016; Planaguma et al., 2015). NMDAR-Abs (IgG) from NPSLE patients induce a positive allosteric modulation of the NMDAR, leading to a NMDAR hyperfunction, and subsequent cell death (Chan et al., 2020) (Fig. 1B).

Paradoxically, at the behavioural level, NMDAR-Abs from NPSLE patients also impair memory, promote psychotic symptoms and epileptic phenotypes, similarly to the antibody pathogenicity observed in anti-NMDAR encephalitis (Chan et al., 2020; Koval et al., 2006). NMDAR-Abs from healthy individuals lack most of the molecular pathogenicity reported in anti-NMDAR encephalitis, NPSLE or any other NMDAR-autoimmune disorder (Jezequel et al., 2018). In addition, NMDAR-Abs from an autism spectrum disorder patient also failed to alter NMDAR synaptic trafficking (Grea et al., 2017). Still, the diversity of NMDAR-Ab pathogenicity goes even further. The production and isolation of monoclonal NMDAR-Abs from encephalitic patients unveiled that affinity is heterogeneous, with 2-order of magnitude difference in binding constants between monoclonal autoantibody groups (Kreye et al., 2016; Ly et al., 2018; Wenke et al., 2019). Furthermore, several distinct epitopes may be targeted by different NMDAR-Abs. The NMDAR-Abs of encephalitic patients were initially proposed to target the specific N368/G369 region in the ATD domain of GluN1 subunit (Gleichman et al., 2012; Gresa-Arribas et al., 2014) (Fig. 1C). Immunization of mice with a short GluN1 peptide around the N368/G369 produce NMDAR-Abs and cognitive deficits associated to rodent models of anti-NMDAR encephalitis (Wagnon et al., 2020). However, this site appears to be recognised by only half of patient NMDAR-Abs (Castillo-Gomez et al., 2016; Gresa-Arribas et al., 2014), strongly suggesting the presence of additional epitopes. In this line, an extracellular peptide sequence (RNPSDK) located on the S2 domain of the GluN1 subunit have been proposed to be targeted by a monoclonal NMDAR-Ab from anti-NMDAR encephalitis (Amrutarik et al., 2012). Using competition assays, it has also been shown that there is no epitope overlap on native NMDAR expressed in live neurons, between NMDAR-Abs isolated from patients with anti-NMDAR encephalitis versus psychotic disorder (Jezequel et al., 2017a). For NPSLE, the epitope targeted by NMDAR-Ab is the D/E,W,D/E,Y,S/G motif (DWES for short) located at the cleft of the amino-terminal domain (ATD) clamsheles of GluN2A (sequence WDWSYS) and GluN2B (sequence EWDY) subunit (Faust et al., 2010), although only GluN2A-NMDARs appear to be functionally affected by antibody binding (Chan et al., 2020) (Fig. 1C). It could be mentioned here that antibodies raised against the extracellular GluN1 subunit region (amino acids 654–800; contributes to the glycine binding domain) were found to be seizure-protective and neuroprotective against excitotoxic challenge in rodent models (Young, 2020). Finally, antibodies raised against the extracellular GluN1 subunit region (amino acids 168–187) do not produce brain cell and behavioural alterations (Wagnon et al., 2020). Altogether, it is evident that NMDAR-Abs are significantly heterogeneous in their pathogenic (e.g. anti-NMDAR encephalitis, autoimmune psychosis, NPSLE), protective, or neutral (e.g. healthy individuals) capacity and binding properties, supporting the view that anti-NMDAR antibody diversity is accompanied by a corresponding variety in their mechanisms of action.
3. NMDAR-Ab-induced NMDAR signalling deficit: through which cellular pathway?

The synaptic signalling through the NMDAR population can be altered by changes in the ionotropic function of the receptor or its trafficking to/from the synapse. The development of single nanoparticle tracking unveiled that the synaptic NMDAR pool is dynamic and that NMDARs laterally exchange between synaptic and extrasynaptic compartments. Within the postsynaptic compartment, NMDARs are stabilized and anchored through protein-protein interactions; for instance, by the interaction with EphB2Rs due to negative charge on GluN1 extracellular domain and positive charge on EphB2R (Washburn et al., 2020). In anti-NMDAR encephalitis, autoantibodies target the GluN1 subunit in surface NMDARs, causing a selective and reversible decrease in receptor surface density and synaptic localization (Dalmau et al., 2008; Hughes et al., 2010; Mikasova et al., 2012). The mechanism of this surface loss requires fully intact IgG and is observed in presence of an NMDAR antagonist (Hughes et al., 2010). Using a single nanoparticle tracking approach in hippocampal neurons, it was further shown that NMDAR-Abs, from encephalitic patients, impact the surface dynamics of synaptic and extrasynaptic NMDARs in opposing directions (Mikasova et al., 2012). For synaptic NMDARs, NMDAR-Abs destabilize NMDARs

![Fig. 2. Facts and models for the molecular mechanism behind NMDAR signalling in health and disease. A) In basal conditions, NMDARs are linked to anchor proteins, such as EphB2. The pool of NMDARs is dynamic, displaying surface trafficking between synaptic and extrasynaptic compartment, providing an equilibrium between the two pools of NMDARs. NMDARs go through endocytosis and exocytosis. B) The facts known in pathological conditions with NMDAR-Ab from AE patients are represented in this figure. It starts with the observation of a massive loss of synaptic and extrasynaptic NMDAR, while the intracellular pool remains the same. The surface trafficking of NMDAR is altered: NMDARs are more dynamic at the synapse and less dynamic at the extrasynaptic compartment where crosslinking events of extrasynaptic NMDARs leads to receptor internalisation. At the synapse, a disruption between NMDAR and EphB2 interaction is observed. These facts lead to global NMDAR hypofunction with decrease of synaptic NMDAR current and LTP as well as impact on the behaviour in rodent such as memory impairment. C) Two models can be built to explain these facts. If NMDAR-Ab can massively target the synapse, the key point (1) in NMDAR-Ab mechanism of action in the synaptocentric model is the disruption of interaction between NMDAR and EphB2. NMDAR is no longer anchored to the synapse, leading to its delocalization in the extrasynaptic part where it’s crosslinked (2) and internalized (3). In the extrasynaptocentric model, it is considered that NMDAR-Ab mainly targets extrasynaptic NMDAR due to a better access than within the synaptic cleft. The key point is the crosslinking of extrasynaptic NMDAR by NMDAR-Ab (1). To refill the extrasynaptic pool, there is a massive NMDAR surface trafficking of NMDAR from the synapse to the extrasynaptic compartment (2). Then, the NMDAR that translocates to the extrasynaptic compartment is trapped and internalized (3). NMDAR-EphB2 disruption still occurs but its effect is minimal compared to the synaptocentric model.](https://example.com/fig2.png)
by preventing their association with EphB2 receptor, increasing their lateral diffusion and dispersion towards the extrasynaptic compartment. Whereas, for extrasynaptic NMDARs, diffusion was massively reduced in the presence of patient IgGs, consistent with previously described antibody-induced cross linking of surface receptors (Fig. 2B) (Dupuis et al., 2014; Groc et al., 2008; Heine et al., 2008).

In anti-NMDAR encephalitis, it has been proposed that NMDAR synaptic hypofunction is primarily due to a deficit in anchoring of the receptor at postsynaptic sites (Hughes et al., 2010; Mikasova et al., 2012). Indeed, it has been observed that synaptic expression of NMDARs decreases in the presence of NMDAR-Abs, and that this process is associated with the disruption of the NMDA-EphB2R interaction, an increase of synaptic NMDAR dynamics and altered nanoscale organization within the synapse. A similar phenotype has been reported with NMDAR-Abs from patients diagnosed with psychotic disorders (Jezequel et al., 2017a). In mice infused with CSF from patients with anti-NMDAR encephalitis, administration of ephrin-B2 (ligand of EphB2R) prevents the pathogenic effect of NMDAR-Ab (Planaguma et al., 2016). A positive allosteric modulator of the NMDAR has also been shown to prevent the pathogenic effect of NMDAR-Abs on the synaptic NMDAR content in rodents (Mannara et al., 2020). Furthermore, rodents immunized with NMDAR extracellular domain or amino acid sequences consistently develop NMDAR-dependent cellular and behavioural dysfunctions (Jones et al., 2019; Wagner et al., 2020). The conventional approach, where focus is dedicated principally to the synaptic component of antibody action, has thus developed an expectantly “synaptocentric” model of the disease (Fig. 2C). However, such a deficit in synaptic NMDAR expression can also feasibly originate from a primarily extrasynaptic antibody action. Indeed, NMDARs traffic through the extrasynaptic compartment to reach the synapse and maintain a stable pool of synaptic receptors. Hence, a robust deficit in NMDAR trafficking outside the synapse would inevitably decrease the synaptic pool over time and also lead to a hypofunction of synaptic NMDAR transmission. Given that NMDAR-Abs demonstrate NMDAR cross-linking competence at extrasynaptic sites, the possibility that antibody-induced synaptic hypofunction instead originates from the disturbance at the extrasynaptic compartment should not be discarded. While not necessarily the exclusive mechanism of action, this hypothesis would constitute an alternative “extrasynaptocentric” model of pathogenesis (Fig. 2C). Compellingly, considering that the synaptic cleft is close in size to NMDAR-Abs (around 20 nm and 12 nm, respectively) and the substantially enriched molecular density, one could assume that NMDAR-Abs can more efficiently target extrasynaptic NMDARs, as compared to the synaptic population. This is further supported by studies showing that different monoclonal NMDAR-Abs can target preferentially extrasynaptic or presynaptic NMDARs rather than postsynaptic ones (Sharma et al., 2018; Wagner et al., 2020). In this scenario, NMDAR-Abs will primarily cross-link extrasynaptic NMDARs, leading to a deficit in diffusion and synaptic incorporation, which by extension reduces the pool of synaptic NMDARs. Some NMDAR-Abs may also penetrate the synapse and destabilize the synaptic pool directly, but in this model such action would represent a simple a confounding effect, insufficient by itself of causing the behavioural pathology seen in encephalitic patients (Fig. 2C). Importantly, the interest to localise predominant antibody action to either synaptic or non-synaptic sites, is not a trivial one. Since NMDAR synaptic hypofunction constitutes the core etiology in major psychotic disorders, understanding the precise locus of NMDAR disorganization is of major translational interest. Following the synaptocentric dogma, the optimal therapeutic design strategy will consist of stabilizing NMDARs, favouring their retention at the synapse. However, in the exact contrary direction, the extrasynaptocentric model would promote the concept of NMDAR destabilisation as a therapeutic route, to negate the influence of croslinking and favour their trafficking towards synaptic compartments. Ultimately, two molecular hypotheses suggesting two opposing therapeutic solutions. As such, defining the locus of origin for antibody-induced synaptic deficit is of prime importance for the future development of molecular interventions for neuropsychiatric conditions. Similarly, comparing the effect of NMDAR-Abs from patients with anti-NMDAR encephalitis or psychotic disorders provide further insights to the heterogeneity of antibody actions. As in encephalitis, NMDAR-Abs from patients with psychotic disorders also destabilize the synaptic NMDAR content, through a disruption of EphB2R interactions (Jezequel et al., 2017a). While the psychiatric component of anti-NMDAR encephalitis bears a striking resemblance to that of other psychiatric disorders, the additional symptomology of encephalitis, namely cognitive deficits, dyskinesia and seizure phenotypes, may be explained by differences in the principal subcellular site of antibody action. Conversely to encephalitic autoantibodies, NMDAR-Abs from patients with psychosis do not alter the extrasynaptic NMDAR content (Jezequel et al., 2017a, 2017b), further demonstrating that a refined focus on the extrasynaptic compartment could yield some important insights on the pathogenesis of NMDAR-Abs from different brain disorders. It is conceivable that the main mechanism of action of NMDAR-Abs, a least in the case of anti-NMDAR encephalitis, deviate from the currently accepted model of this disease, and instead follow this novel extra-synaptocentric model.

4. Cellular targets of NMDA-Abs

To date, the majority of antibody pathogenesis has been hypothesised solely on pyramidal cell populations. However, the inhibitory interneuron networks remain an underexploited area of investigation that we expect to be strikingly relevant to the disease mechanisms of NMDAR-Abs action. Although the possibility that interneuron dysfunction may contribute to NMDAR-Ab pathogenesis has been proposed (Masdeu et al., 2016), direct experimental investigations into this possibility are simply lacking. The interneuron population represents a relative minority in the hippocampus, yet the local inhibitory drive provided by this network forms a major contribution to the larger scale circuit behaviour of hippocampal networks and beyond (Pelkey et al., 2017). Particularly, hippocampal interneurons have been implicated in both psychotic disorder, where their ability to successfully regulate network oscillatory behaviour is compromised (Heckers and Konradi, 2015; Marin, 2012) and in epilepsy, where a loss of inhibitory drive renders hippocampal networks susceptible to hyper-activation states and seizure generation (Marx et al., 2013). These findings, combined with our understanding of anti-NMDAR encephalitis and NPSLE presenting with major symptoms of psychosis and seizure, suggest that a substantial contribution to disease pathogenesis, may originate with a perturbation of hippocampal interneuron function. Recent investigations in the field of psychiatric disorders have suggested that NMDAR hypofunction, specifically on interneuron populations, may be a key driver of psychosis phenotypes. Certain NMDAR antagonists are long-since known to acutely replicate poly-symptomatic psychiatric disorders in humans, including hallucination, affect flattening and paranoia (Javitt, 2004; Nakazawa et al., 2017). Beyond this behavioural homology, antagonist administration also reproduces the rise in extracellular glutamate of the medial prefrontal cortex seen in psychosis patients, and increases the activity of cortical principal cells in rodents (Moghaddam and Javitt, 2012). Given that the application of antagonists, instead, promotes excitatory cell action and glutamate release, it is hypothesised that a principal route of psychotic disorders is mediated by a disinhibition across brain structures including the frontal cortex and limbic system. Further research has aimed to identify the source of this disinhibition, after the observation that local interneuron action is not a viable route to antagonist-induced activity increase in cortical structures (Amat-Foraster et al., 2019). However, local disinhibition has been demonstrated in the CA1 subfield of the hippocampus, and to effectively inhibit the prefrontal cortex through disruption of downstream signalling (Jodo et al., 2005). Applying this reasoning to the study of anti-NMDAR encephalitis, we might speculate that antibody-induced receptor hypofunction on interneurons is a principal mechanism for the...
generation of psychotic symptoms observed in the initial presentation of this disorder (Fig. 3). These findings are also congruent with the proposition that autoantibody actions are specific on hippocampal and limbic regions in encephalitic patients, albeit through an as yet unidentified mechanism (Dalmau et al., 2008). Conversely, the positive allosteric modulation of GluN2A-NMDARs by NMDAR-Abs in NPSLE, generates a similar phenotype, despite the directly opposing functional consequence of antibody binding (Chan et al., 2020). In this case, we expect that the pathogenesis is mediated by direct hyperactivation of the GluN2A-enriched principal cell populations (Fig. 3). These divergent autoimmune diseases, with paradoxically similar phenotypic disturbance, only demonstrate the need to further elucidate and expand our current models of anti-NMDAR antibody action, both at cellular and circuit levels.

4.1. Cell intrinsic properties of hippocampal interneurons

Parvalbumin expressing (PV+) interneurons exhibit local control over hippocampal excitation through a rapid and repetitive firing pattern. This interneuron population has gained significant traction in the field of psychosis, as this uniquely fast-spiking phenotype is known to exert control over high frequency gamma oscillations, that are also disrupted in psychotic patient electroencephalographs (Marin, 2012). This suggests PV+ interneurons as a good candidate for the disinhibition model of psychosis in anti-NMDAR encephalitis. However, the question remains how encephalitic NMDAR-Abs, which presumably bind indiscriminately to NMDARs may demonstrate a targeted effect on interneurons, without a brain-wide activity depression by an equivalent effect on principal cells. One possibility is that the NMDAR itself serves a different functional purpose when expressed in interneurons or principal cells. Notably, interneuron populations demonstrate more depolarised resting membrane potentials than the surrounding pyramidal cell populations (Lacaille et al., 1987), and it has been further elucidated that the PV+ interneuron population is among the most depolarised of all cell types in the hippocampal structure, usually remaining around ~55 mV (Tricoire et al., 2011). Despite this more depolarised resting potential, all interneuron families have an approximately equivalent threshold for action potential generation as pyramidal cells, at around ~35 mV (Tricoire et al., 2011), setting apart the PV+ interneuron subtype as they normally rest relatively close to spike threshold. It has been shown that PV+ interneurons display a significant enrichment of the magnesium-insensitive GluN2D-containing NMDAR (Akgul and McBain, 2016). The expression of this receptor subtype is known to contribute to resting membrane potential in early developmental stages in the cortex (Hanson et al., 2019). It is possible that a similar tonic current on PV+ interneurons, may represent a unique pathological avenue for encephalitis, whereby the internalisation of NMDARs on interneurons drives down the resting potential away from threshold, ablating the fast-spiking phenotype and inhibitory drive. This remains to be examined in the context of exposure to encephalitic NMDAR-Abs, however it has encouragingly been demonstrated that genetic ablation of NMDARs on PV+ fast-spiking interneurons does significantly disrupt the characteristic firing pattern of this interneuron family (Carlen et al., 2012). This differential subunit enrichment on interneurons is also consistent with the opposing action of NMDAR-Abs in NPSLE. These antibodies bind both GluN2A and GluN2B subunits, however the increased open probability via positive allosteric modulation is selective for the GluN2A-containing receptor (Chan et al., 2020). While GluN2A-NMDARs are also expressed on hippocampal interneurons, the expression is significantly lower as compared to that on principal cells in the hippocampal structure (Akgul and McBain, 2016). Hence, the relative reduction of GluN2A subunit expression on interneuron populations renders inhibitory activity unchanged in response to antibody exposure in NPSLE. However, the high GluN2A-NMDAR expression at pyramidal cell synapses is likely to shift the overall network behaviour in favour of direct hyperexcitation (Fig. 3). This is certainly interesting considering that the phenotype of NPSLE is similar to that observed in anti-NMDAR encephalitis. Demonstrating that even directly opposing action of antibody pathogenesis, hypo- versus hyper-function, can result in a comparable phenotypic outcome through discrete mechanisms, further highlighting the necessity to characterise the possible effects on NMDAR function on both excitatory principal cells and the concurrent balancing effect on local inhibitory networks.

4.2. Differential glutamatergic neurotransmission on hippocampal interneurons

Alongside the variable functional roles of NMDARs expressed on principal and interneuron cell types, glutamatergic transmission is itself mediated differently between these neural populations (Pelkey et al., 2017). Interneurons in the CA1 area of the hippocampus which receive Schaffer collateral inputs, maintain a GluN2B-NMDAR predominance at the synapse across all stages of development, differing from the pyramidal cell population which upregulates synaptic incorporation of GluN2A-NMDARs after early postnatal development (Matta et al., 2013). Interestingly, the relative contributions of NMDA and AMPA receptor populations at these synapses is approximately equal, again differing from the pyramidal cell, where the AMPA receptor number greatly exceeds the NMDAR population (Matta et al., 2013). Taken together, the maintenance of the GluN2B-NMDAR, with an endogenously increased current transfer and prolonged decay constant when compared to GluN2A-NMDARs, and higher ratio of NMDA-to-AMPA expression at interneuron synapses, indicates an increased reliance on NMDAR pools for hippocampal interneurons. It is therefore possible that a homogenous action of NMDAR-Abs in encephalitis, might induce a greater disruption to synaptic (tonic) function on interneurons over principal cells (Fig. 3). Considering this, in addition to the increased vulnerability of interneurons by the presence of tonic NMDAR currents, yields a significantly heightened susceptibility to perturbation by NMDAR-Abs. Genetic ablation of GluN2B subunits from interneurons in the CA1 subfield of the hippocampus causes a localised decrease in AMPA-mediated miniature excitatory postsynaptic currents in interneuron populations in the stratum oriens (Kelsch et al., 2014). It was further demonstrated that this loss of excitatory drive onto inhibitory networks, not only developed into a local disinhibition of the CA1, but induced epileptiform activity (Kelsch et al., 2014). Given this specific role of GluN2B-NMDARs on the hippocampal interneuron population, we might consider a route to seizure pathology in anti-NMDAR encephalitis, may be mediated by surface loss of GluN2B from interneuron synapses.

Regarding NPSLE, this disparity between the synaptic composition of NMDAR subtypes on principal cells and interneurons again suggests a selective shielding of interneurons from the hyperexcitation elicited by antibody binding; further shifting the overall balance towards hyperexcitation that is mediated by a relatively isolated impact at the pyramidal cell synapse (Fig. 3). We may further consider that this unbalancing of physiological excitatory-inhibitory action will develop into epileptogenic seizure generation in NPSLE, and prevent the correct level of interneuron control over network oscillations caused by the mismatch in cell perturbations which may contribute to the psychotic elements in this disease. However, one must note that this hypothesis is based on knowledge from antibody binding to NMDARs expressed in a heterologous system (Chan et al., 2020). It is therefore possible that while antibody binding to GluN2B-NMDARs does not induce any functional consequence to the channel, alterations to surface expression level or surface diffusion may well introduce a possible impact on this receptor population. This point is recapitulated by our knowledge that NMDARs in encephalitis do not produce a direct modulation of channel function, but instead elicit their effect via indirect perturbations to channel internalisation and altered stabilisation states in the cell membrane (Jezquel et al., 2018).

Ultimately, there is a current challenge posed by directly opposing
Fig. 3. Schematic model of network disturbance by discreet NMDA receptor autoantibodies. The centre panel denotes a simple schematic network comprised of two pyramidal cells (green) and an interneuron (purple); the left on this panel demonstrates a model of disinhibition hypothesised to underpin network dysfunction in anti-NMDAR encephalitic patients (AE, red), the right describing a model of hyperexcitation in lupus patients (NPSLE, blue). The phasic action on interneuron synapses is shown in (A), where AE antibodies (red) induce a GluN2B-NMDA receptor hypofunction and lupus antibodies (blue) bind but elicit no change in these receptors. B) The impact of antibody exposure on the tonic current of interneurons, where AE antibodies again induce further hypofunction of the GluN2D-NMDARs but lupus antibodies show no action or binding on this receptor subtype. C) The action at a glutamate synapse onto a pyramidal cell dendrite enriched in GluN2A-NMDAR expression, where the action of antibodies from AE induce a synaptic hypofunction; and NPSLE antibodies promote an opposing hyperfunction of synaptic NMDAR signalling. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
actions of autoantibodies in anti-NMDAR encephalitis and NPSLE, whereby the respective receptor hypofunction and hyperfunction generates a paradoxically similar phenotype between these two conditions. We would argue that the inclusion of inhibitory interneuron networks into the current disease models, not only forms a more comprehensive hypothetical model for NMDAR-Ab action, but is required to address this current challenge. In this case, exposure to NMDAR-Abs in encephalitis will result in divergent degrees of reduction in NMDAR signalling and perturbation of both principal cell and inhibitory interneuron action. Such a mismatch in the functional output between principal and interneuron networks will cause a synergistic disruption to the homeostatic excitatory-inhibitory balance. This reframing of encephalitic antibody action suggests that we should consider disinhibition as a major possible component to pathology of anti-NMDAR encephalitis, whereby relative network hyperfunction is a resulting feature of targeted- or dominant- NMDAR hypofunction on inhibitory interneuron networks. Such a hypothesis is in line with the observed increased action of cortical principal cells of rodent models of psychosis (Moghadam and Javitt, 2012). Moreover, this disinhibition hypothesis of encephalitis is also more intuitively consistent with the proposed action of NMDAR-Abs in NPSLE. Here, we propose that antibodies act directly and exclusively on principal cell populations to drive a hyperexcitation and a similar unbalancing of the excitatory inhibitory drive as observed in encephalitis. Hence, while these NMDAR-Abs act through two distinct routes, we propose that the overall network perturbation and altered ratio of excitatory and inhibitory action is the driving factor for the observed phenotypic similarity of these two conditions.

5. Do NMDAR-Ab similarly hit different brain structures?

Since the identification of anti-NMDAR encephalitis, it has been noted that the binding of patient NMDAR-Abs appears substantially enriched in hippocampal and limbic structures as compared to cortical regions (Dalmau et al., 2017). This apparent hippocampal targeting has been corroborated by the observation that encephalitic patients display a marked reduction in NMDAR expression in hippocampus and memory impairments present as a primary symptom of disease in many cases (Dalmau et al., 2017). It has also been shown that hippocampal structures display a significant reduction in volume as a result of encephalitic disease and that such a reduction in volume and structural integrity across hippocampal subfields was predictive of the degree to memory impairment, cognitive deficit and disease severity in these patients (Finke et al., 2016). As such, it has remained an open question to validate the supposed targeting of patient autoantibodies to hippocampal NMDAR populations and to further elucidate a mechanism by which such a specificity in binding may arise. As previously discussed, GluN2 subunit expression is regionally and temporally controlled, such that principal cell expression of GluN2A and GluN2B forms the major fraction of channels throughout the brain, while the relative ratio is altered during an early postnatal switch, and potentially into adulthood (Paolelli et al., 2013). The less numerous interneuron populations are enriched in GluN2D-NMDARs and many show a reduction in expression of GluN2A as compared to the principal cell population (Matta et al., 2013; Persyk et al., 2016). GluN2C expression is confined mostly to cerebellar structures, however there is also evidence for enriched expression also on interneuron populations throughout the thalamus (Alsaad et al., 2019). While early work on anti-NMDAR encephalitis speculated a possible targeting of GluN2B-NMDARs, such expression profiles do not seem to bare any clear relationship to antibody specificity to the hippocampus. Moreover, the antigenic GluN1 subunit is also known to exist in eight distinct splice variants, determined by two possible deletions to the intracellular domain of the receptor and further by the exclusion or inclusion of a 21 amino acid sequence (N1 cassette) in the ATD, termed GluN1a and GluN1b, respectively (Paolelli et al., 2013). While the functional behaviour of these splice variants and their regional expression at the broad structural level during development has been well characterised (e.g. (Liu et al., 2019; Sengar et al., 2019), there is comparatively less known regarding the endogenous subcellular organization and neuron subtype-specific expression profiles of these variants (Paolelli et al., 2013). Encouragingly however ho however, it has recently been demonstrated that excitatory cells and interneuron populations within the mouse cortex demonstrate differing levels of exon inclusion, such that interneurons are enriched for GluN1b relative to their principal cell counterparts, this difference was most striking in the PV+ interneuron population (Huntley et al., 2020). We recognise that it is unlikely that variation within the intracellular C-terminal domain will have any effect on antibody action. However, we note that the localisation of the N1 cassette is of particular interest: at the interface between the GluN1-ATD and the GluN1/GluN2B ligand binding domains, and with relative proximity to a proposed epitope within the N368/G369 region of the GluN1 ATD (Gleichman et al., 2012; Regan et al., 2018). The inclusion of this sequence may therefore provide some subtle conformational differences between GluN1a and GluN1b splice variants in combination with GluN2 subunits that will shift binding efficacy for the antibody in favour of particular splice variants that are regionally targeted to hippocampal populations. Additionally, while we often consider channel function to be conferred solely by the inclusion of particular GluN2 subunits, it is important to consider that channel function can also be modulated reciprocally by the GluN1 subunit splice variant present in the channel (Rumbaugh et al., 2000). Such factors may underpin the preferential effect of patient NMDAR-Abs for hippocampal and limbic regions in the brain. In addition to potential differences in subunit and splice variant expression, differing mechanisms for receptor turnover, internalisation and anchoring in hippocampal neurons may represent further mechanisms for the observed impact on hippocampal populations, but these remain to be further explored. While the imaging studies from encephalitic patients showing hippocampal degeneration is compelling for the hippocampal selectivity of NMDAR-Abs, it is however worth considering that reduced hippocampal volumes are not uncommon in epileptic pathologies where the hippocampus is expected to be the source of seizure generation (Finke et al., 2016). We might argue that antibody function across the brain will perturb local networks and neuronal functioning, while the microarchitecture of the hippocampus – being rich in inhibitory interneurons and recurrent CA3 microcircuits – yields a propensity for sustained hyper-activation and epileptogenesis. In this case, the underlying cause of specific loss of hippocampal volumes may not be indicative of antibody targeting to hippocampal neurons, but simply that the result of antibody action in this region is such a significant disruption to homeostasis that the increase in activation becomes neurotoxic. Depletion of hippocampal volumes in this manner would sequentially explain the memory deficits observed in patients.

A further mechanism for antibody selectivity for NMDAR populations in limbic structures may reside in posttranslational modifications of the subunit proteins in these regions, however this remains to be explored. Typically, such modifications include receptor phosphorylation, ubiquitination and palmitoylation. Phosphorylation is known to occur extensively on the long intracellular tail of the GluN2B subunit, and such modification is understood to alter receptor currents, expression and diffusion in the membrane (Sanz-Clemente et al., 2013). However, it is difficult to conceptualise how such a modification, which is by nature intracellular, may impact antibody binding at the extracellular site. However, we might consider that antibody binding may work synergistically with phosphorylation processes that play a role in the lateral mobilisation of receptors and downstream internalisation mechanisms. Similarly, ubiquitination as another intracellular modification that is important for protein degradation, may not have any substantive influence over antibody action in the internalisation of receptors, however it is tempting to postulate that there may exist some differences on the degradative and receptor turnover processes that make hippocampal neuron populations intrinsically less able to compensate for antibody-mediated receptor internalisation and surface
loss. Again this would suggest however, that antibody action is not hippocampal selective per se, but instead that processes downstream of antibody action are the basis for the apparent perturbation of limbic structures. Differential glycosylation of the GluN1 extracellular domain between brain regions may constitute an additional possibility, although evidence is still lacking. Finally, the extracellular space of the brain parenchyma is a complex, tortuous and heterogeneous structure (Nicholson and Hrabotova, 2017). Since it has been shown that the diffusion of immunoglobulins within the extracellular space greatly varies between brain areas (Pizzo et al., 2018), one may propose that limbic structures favour immunoglobulin retention due to extracellular space properties. In-depth investigations, at the single immunoglobulin level, are surely needed to tackle this question.

6. Conclusions and perspectives

The link between autoantibodies directed against neurotransmitter receptors and major brain disorders is emerging as a frontrunner in the field of neurology and psychiatry. The example of NMDAR- Abs is of particular interest as the pathogenesis of the autoantibody has been well-established in anti-NMDAR encephalitis. The NMDAR-Abs impair NMDAR synaptic signalling, long-term synaptic plasticity, network activity, and associative memory. Yet, fundamental challenges remain in front of us. Defining the primary locus of action of the NMDAR-Abs, which would require us to identify whether synaptic or extrasynaptic NMDARs are the main disrupted pool, is still an open question that is often discarded. The number of B cell clones (expressing NMDAR-Abs) in each patient, the epitope(s) of the autoantibodies, their molecular pathogenicity, similarly remain exciting open questions. As most of the studies have employed the use of rodent biological substrate to unravel the mechanisms of human-generated NMDAR-Abs, exploring these questions using human-derived cells or neural tissue would also be of prime importance. Finally, when we consider the diverse array of mechanisms by which interneurons provide a local control of hippocampal network function, and the striking variety of functional roles for each patient, the epitope(s) of the autoantibodies, their molecular pathogenicity, similarly remain exciting open questions. As most of the studies have employed the use of rodent biological substrate to unravel the mechanisms of human-generated NMDAR-Abs, exploring these questions using human-derived cells or neural tissue would also be of prime importance. Finally, when we consider the diverse array of mechanisms by which interneurons provide a local control of hippocampal network function, and the striking variety of functional roles for each patient, the epitope(s) of the autoantibodies, their molecular pathogenicity, similarly remain exciting open questions. As most of the studies have employed the use of rodent biological substrate to unravel the mechanisms of human-generated NMDAR-Abs, exploring these questions using human-derived cells or neural tissue would also be of prime importance. Finally, when we consider the diverse array of mechanisms by which interneurons provide a local control of hippocampal network function, and the striking variety of functional roles for each patient, the epitope(s) of the autoantibodies, their molecular pathogenicity, similarly remain exciting open questions. As most of the studies have employed the use of rodent biological substrate to unravel the mechanisms of human-generated NMDAR-Abs, exploring these questions using human-derived cells or neural tissue would also be of prime importance. Finally, when we consider the diverse array of mechanisms by which interneurons provide a local control of hippocampal network function, and the striking variety of functional roles for each patient, the epitope(s) of the autoantibodies, their molecular pathogenicity, similarly remain exciting open questions. As most of the studies have employed the use of rodent biological substrate to unravel the mechanisms of human-generated NMDAR-Abs, exploring these questions using human-derived cells or neural tissue would also be of prime importance.
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