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Review

Autoimmune channelopathies in paraneoplastic neurological syndromes☆

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ABSTRACT

Paraneoplastic neurological syndromes and autoimmune encephalitides are immune neurological disorders occurring or not in association with a cancer. They are thought to be due to an autoimmune reaction against neuronal antigens ectopically expressed by the underlying tumour or by cross-reaction with an unknown infectious agent. In some instances, paraneoplastic neurological syndromes and autoimmune encephalitides are related to an antibody-induced dysfunction of ion channels, a situation that can be labelled as autoimmune channelopathies. Such functional alterations of ion channels are caused by the specific fixation of an autoantibody upon its target, implying that autoimmune channelopathies are usually highly responsive to immuno-modulatory treatments. Over the recent years, numerous autoantibodies corresponding to various neurological syndromes have been discovered and their mechanisms of action partially deciphered. Autoantibodies in neurological autoimmune channelopathies may target either directly ion channels or proteins associated to ion channels and induce channel dysfunction by various mechanisms generally leading to the reduction of synaptic expression of the considered channel. The discovery of those mechanisms of action has provided insights on the regulation of the synaptic expression of the altered channels as well as the putative roles of some of their functional subdomains. Interestingly, patients' autoantibodies themselves can be used as specific tools in order to study the functions of ion channels. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

1. Introduction

Paraneoplastic neurological syndromes (PNS) are disorders of the nervous system occurring in association with a cancer that are not related to any metabolic, infectious, degenerative, metastatic or iatrogenic cause [1]. PNS are thought to be secondary to an autoimmune reaction

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against neuronal antigens ectopically expressed by the underlying tumour (Fig. 1) [2]. The discovery of autoantibodies targeting such antigens has greatly improved our knowledge of these syndromes as they proved to be useful diagnostic and prognostic tools. In particular, autoantibodies targeting neuron membrane proteins such as ion channels, but not intracellular antigens, were associated to better outcomes and can improve with immunotherapy [3]. The standardization of antigen characterization techniques such as immunoprecipitation coupled to mass spectrometry has allowed the identification of numerous specific antigens involved in antibody-mediated neurologic syndromes, including ion channels or proteins modulating the functions of ion channels [4–7]. Ion channels expressed at the cell membrane are distributed throughout the nervous system and play an essential role in its homeostasis by tuning the polarization of neural cells. Ions traffic through resting membrane channels keeps the basal polarization of neural cells steady while activation of voltage or ligand-gated ion channels regulate excitation and inhibition of neurons by inducing either a depolarized or a hyperpolarized state, respectively [8]. In several autoimmune neurological syndromes, including PNS, patients' autoantibodies targeting ion channels or their associated proteins were shown to alter *in vitro* and *in vivo* the function of their targets, leading to the concept of neurological autoimmune channelopathies (NACs), that is, a group of various autoimmune neurological diseases sharing antibody-mediated ion channel dysfunction as a common pathogenesis. In this chapter, we will systematically review the autoimmune neurological syndromes related to antibodies against neuronal ion channels (Table 1), with a particular focus on the molecular mechanisms of ion channels dysfunction and the immunological mechanisms of autoantibody generation.

2. Anti-NMDA receptor encephalitis

N-methyl-D-aspartate receptors (NMDAR) are major ionotropic glutamate receptors of the central nervous system (CNS). NMDAR are mainly post-synaptic, and when activated they mediate an input of calcium and sodium that generates excitatory post-synaptic currents [9]. NMDAR activation requires the binding of glutamate and a co-agonist, either D-serine or glycine, and prior depolarization of the post-synaptic neuron [10,11]. Due to those characteristics, NMDAR act as molecular coincidence detectors and are involved in two major mechanisms of synaptic plasticity: long-term potentiation (LTP) and depression (LTD), which consist in respectively long-lasting enhancement and reduction of the synaptic transmission between two neurons after repetitive stimulation [9]. Those properties underlie the involvement of NMDAR in physiological and pathological processes such as memory [12], executive functions [13], excitotoxicity [14] and psychiatric disorders including schizophrenia [15]. NMDAR forms a heterotetrameric cation channel composed of a mix of an obligatory subunit, GluN1, with a variable composition of auxiliary subunits, GluN2 (A-D) and/or GluN3 (A-B) [16].

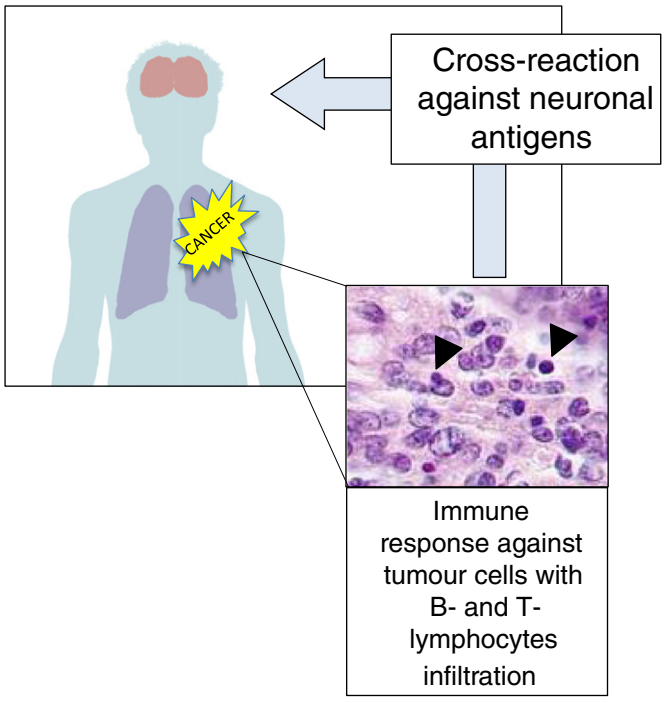

Fig. 1. Pathogenesis of the paraneoplastic neurological syndromes. Ectopic neuronal antigens expressed by some tumours are presented to the lymphocytes present within inflammatory infiltrates (arrowheads), leading to a cross-reaction against the same antigens normally expressed by neurons. As a result, an autoimmune reaction against the nervous system can develop and progress independently of the triggering cancer.

Autoimmune encephalitis with antibodies against the GluN1 subunit of NMDAR (NMDAR encephalitis) was described in 2007 and turned out to be one of the most frequent acute autoimmune encephalitis [7,17,18], even outnumbering infectious aetiologies in young patients [19]. NMDAR encephalitis mostly involves women less than 45 years [20]. A paraneoplastic origin is documented in 38-58% of the patients and involves an ovarian teratoma in 94% of the cases [17,20]. The disease follows a stereotyped course [17]. Seventy percent of patients experience prodromal symptoms such as fever, nausea, diarrhoea and upper respiratory tract disorders. The neurologic presentation usually begins with acute psychiatric symptoms and cognitive impairment, followed in days to weeks by a loss of consciousness alternating with periods of agitation and/or catatonia associated with oro-lingual and limbs dyskinesias. Dysautonomic symptoms and central hypoventilation are frequent and severe. During the comatose phase, dissociated responses to stimuli, similar to the effect of NMDAR antagonists such as ketamine, may be observed. Seizures can occur at any point of the disease course. Although the disease progression is approximately similar, initial presentation is slightly different in children who tend to experience more movement disorders and atypical neurological signs [20,21], and in men who are more subject to seizures [22]. More importantly, cancers are much less frequent in men and children [20,22], rending the diagnostic strategy less clear. Outcome is good in 81 % of the patients, but the recovering phase may last more than two years [20]. Relapses occur in 12-22% of the patients [20,23]. Prognosis seems to depend on the precocity of immunotherapy initiation, while immunotherapy after the first event is associated with a lower frequency of relapses [20,24]. Considering NMDAR encephalitis as a primarily antibody-mediated disease, the utility of B-cell depleting treatments, such as the monoclonal anti-CD20 antibody rituximab, has been emphasized [25,26].

Anti-NMDAR antibodies' epitope is thought to be located on a small region of the GluN1 amino-terminal domain (Fig. 2) and may depend on post-translational modifications, hence the peculiar pattern of patients' anti-NMDAR antibodies observed on rat brain immunohistochemistry [27,28]. The biological effects of anti-NMDAR antibodies have been extensively studied over the recent years (Fig. 3). Patients' antibodies applied on cultured hippocampal neurons alter NMDAR synaptic currents [29,30] while AMPAR currents are preserved [31]. NMDAR deregulation is likely not mediated by direct receptor inhibition [30] but rather by a decrease in surface receptor density [31]. Indeed, NMDAR capping by the autoantibodies results in receptor cross-linking [31] and disruption of its interaction with EphB2R [32]. As a consequence, the surface trafficking of the receptor is altered [32], leading to a time and dose dependant NMDAR internalization through recycling endosomes and lysosomes [27,30,31]. Intracerebro-ventricular infusion of mice with patients' CSF induce memory deficits and a depressive-like behaviour [33]. In rats infused with CSF from NMDAR-E patients, excessive extracellular glutamate concentrations are observed, likely due to an imbalance between NMDA and AMPA receptors [34]. Alternatively, down-regulation of pre-synaptic NMDAR on the GABAergic neurons may

Table 1
Characteristics of the autoantibodies involved in neurologic autoimmune channelopathies.
ATD: amino-terminal domain; LTP: long-term potentiation; SPS: stiff person syndrome; PERM: progressive encephalomyelitis with rigidity and myoclonus; LRR: leucin rich region; FBDS: facio-brachial dystonic seizures; NMT: neuromyotonia; MoS: Morvan' syndrome; Ach: acetylcholine; LEMS: Lambert-Eaton myasthenic syndrome; CA: cerebellar ataxia.

Antigen	Epitope	Modulatory mechanisms	Functional consequences	Cancer (frequency, histology)	Associated Syndromes	references
NMDAR	GluN1(ATD)	Cross-linking and disruption of its interaction with EphB2R resulting in: 1) Alteration of surface mobility; 2) increased internalization	Abrogation of NMDAR currents & LTP Increased extracellular levels of glutamate	38-58%; teratomas	Encephalitis (limbic, dysautonomic, movement disorders)	[17,20,30–32,34,35]
AMPAR	GluA1/GluA2 (ATD)	Decreased of synaptic surface AMPAR	Non evaluated	70%; thymus, lung or breast cancer	Encephalitis	[5,51–54]
$GABA_AR$	α1 and/or β3 subunits	Decreased surface density and mobility of $GABA_AR$	Decreased inhibitory post-synaptic currents' amplitude	40%; thymoma	High titres: encephalitis Low titres:Seizures, SPS, OM	[61,62]
α1-AchR	α1 subunit	Internalization of muscle-type AchR	Impaired neuromuscular transmission	10%; thymoma	AMG	[68,71,81]
α3-AchR	α3 subunit	unknown	Decreased ganglion-type AchR currents	6-60%; various	AAG	[70,94,98,99]
GlyR	α1 subunit	Increased internalization	Non evaluated	9%; thymoma, lymphoma	SPS, PERM	[105]
Lgi1	EPTP repeats and LRR domains	Disruption of the interaction between Lgi1 and ADAM23 resulting in a decrease in surface AMPAR	Non evaluated	15%; highly variable	Encephalitis, FBDS	[4,125,132,133]
Caspr2	Extracellular domain	Non evaluated	Non evaluated	25%; thymomas	Encephalitis, NMT, MoS	[6,122,123]
VGCC	α1 subunit of the P/Q type VGCC	VGCC cross-linking and internalization	Reduction of P/Q type VGCC Decrease of Ach release	LEMS: 50-60% CA: ≈100%	LEMS, CA	[149,150,153,160]

hamper inhibitory inputs on glutamategic neurons and therefore contribute to a hyperexcitatory state [30,34]. This hyperglutamatergic state explains the cortical hyperexcitability observed in rats infused with the patients' antibodies [35] and may account for the epileptic seizures frequently observed in the patients. Besides, anti-NMDAR antibodies applied on an *in vitro* model of neural network decreased the spontaneous burst and spike rates while the rhythmic activity was preserved [36]. Such preserved rhythmic activity within a hypo-functional network have been suggested to promote seizures [36]. On the other hand, anti-NMDAR antibodies abrogate glutamatergic LTP in hippocampal neurons [29,37]. Hippocampal LTP being thought to constitute the biological basis for memory encoding, such effect is likely to account for the anterograde amnesia presented by anti-NMDAR encephalitic patients. Patient's brain histopathological studies have comforted the idea of a mainly antibody-mediated CNS disorder by revealing prominent perivascular B-cell infiltrates, microglial activation and immunoglobulin deposits, without complement accumulation or neuronal damages [27, 38–40]. Accordingly, increased production of the B-cell attracting chemokine CXCL-13 [41], B-cell expansion [42] and intrathecal synthesis of anti-NMDAR antibodies [17] have been demonstrated in the CSF of NMDAR encephalitis patients. Interestingly, poor outcomes are correlated to elevated serum and CSF anti-NMDAR antibodies titres, while relapses significantly associate with increased CSF NMDAR Ab titres [17, 43]. Pathologic studies on patients' teratomas have brought insights on the immunological pathogenesis of paraneoplastic NMDAR encephalitis. Ovarian teratomas contain neural tissues expressing GluN1 and GluN2 subunits of NMDAR [44]. In NMDAR encephalitis patients, this neural component can present as foci of dysplastic neurons resembling cells from neuroblastic tumours of the CNS [45] and are in close contact with lympho-plasmocytic infiltrates often organized as ectopic reactive germinal centres [44,46]. Therefore, in paraneoplastic cases intratumorous inflammatory processes are likely to directly trigger anti-NMDAR autoimmune reaction, particularly when dysplastic neural tissue is present in the tumour. Conversely, non-paraneoplastic cases

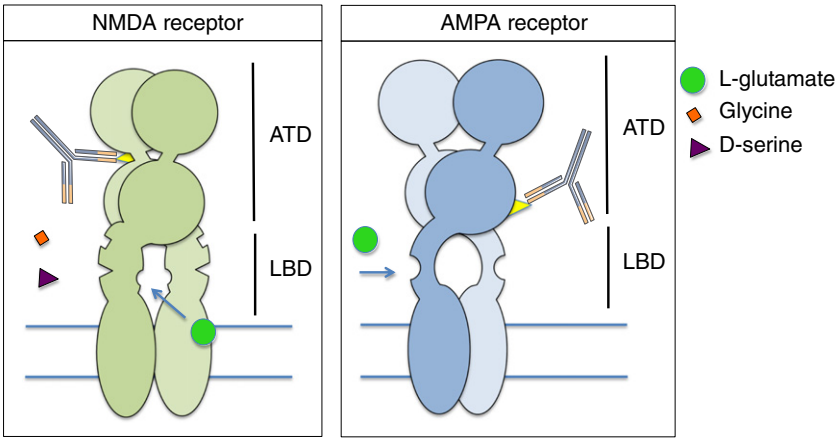

Fig. 2. NMDA and AMPA receptors structure and epitope localization. NMDA and AMPA receptors extracellular regions are composed of an amino-terminal domain (ATD) with two lobes and a ligand-binding domain (LBD). The epitope (yellow) recognized by autoantibodies from NMDAR encephalitis patients has been localized in a small region between the two lobes of the NMDAR ATD. On the other hand, autoantibodies form patients with AMPAR encephalitis target an epitope in the bottom lobe of the AMPAR ATD. So far the functional roles of those regions are unknown.

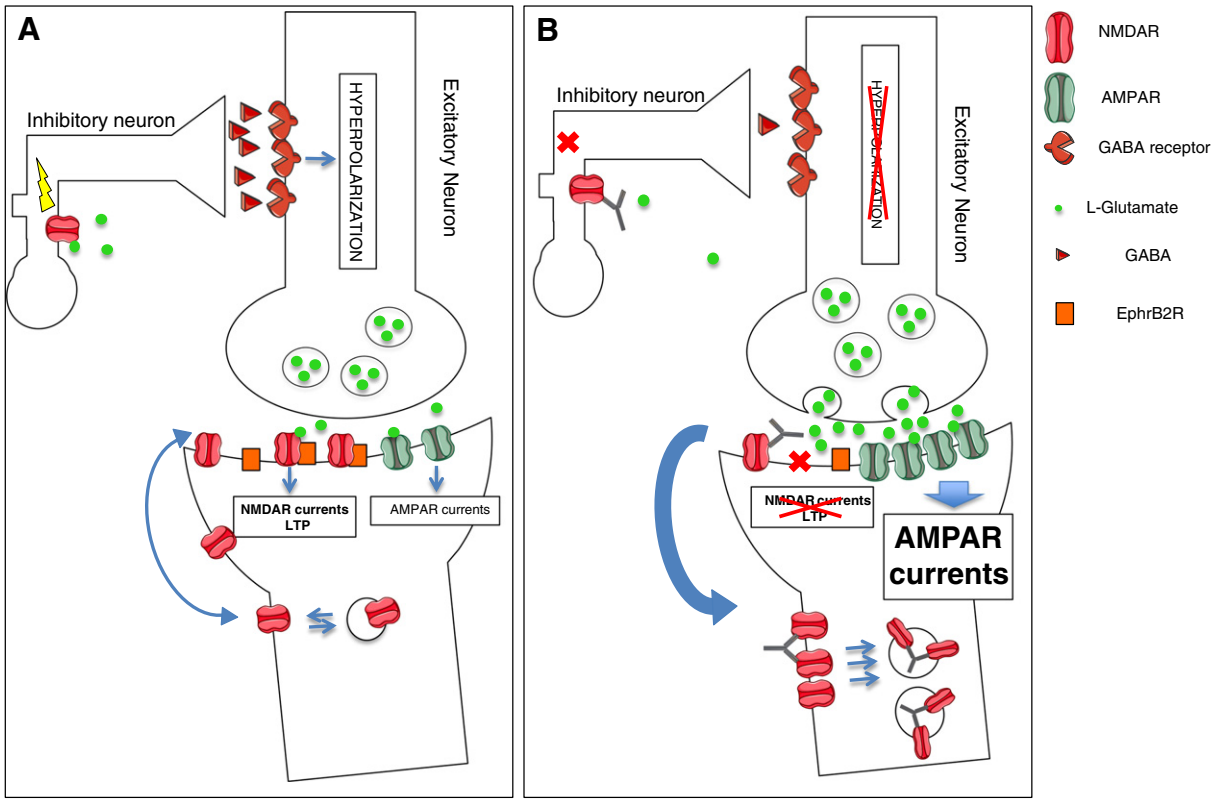

Fig. 3. Functional effects of anti-NMDAR antibodies. A. Basal state. AMPAR and NMDAR are both expressed at the post-synaptic surface of glutamatergic synapses. NMDAR diffuse laterally to and from synaptic areas. Recycling of NMDAR occurs in the extra-synaptic regions, while they are retained at the synapse by the interaction with the EphrinB2 receptor (EphB2R). Furthermore, NMDAR present on inhibitory GABAergic neurons enhance GABA release to lower the excitability of glutamatergic neurons. B. NMDAR encephalitis. NMDAR Ab disrupt the interaction between EphB2R and NMDAR, thus impairing NMDAR synaptic retention, and cross-link NMDAR, therefore reducing lateral diffusion and increasing the internalization of the receptor. As a result, post-synaptic NMDAR are decreased, leading to the abrogation of NMDAR currents and LTP, an important mechanism of synaptic plasticity. Impairment of NMDAR on GABAergic neurons may result in a lack of the inhibitory tone upon glutamatergic transmission, while post-synaptic AMPAR are overexpressed compared to NMDAR. Those two phenomenons result in an increased excitatory glutamatergic transmission.

may result from diverse environmental and endogenous factors in predisposed individuals. For instance, NR2B expression was found in normal ovary tissue [47], and some authors suggested that local inflammation or mild viral infection could be sufficient to induce the presentation of ovarian NMDAR subunits to the immune system and trigger NMDAR encephalitis, explaining why viral-like prodromas are frequent. Similarly, the increased occurrence of NMDAR encephalitis in patients with a history of recent HSV encephalitis is now well described [48]. Brain inflammation and breakage of the blood-brain barrier during HSV encephalitis course is likely to lead to the exposure of many CNS antigens to the immune system, including NMDAR subunits, thus favouring the development of NMDAR encephalitis later on.

3. Anti- AMPA receptor encephalitis

A-amino-3-hydroxy-5-methyl-4-isoxazolepropion acid receptors (AMPAR) are ionotropic glutamate receptors permeable to cations that mediate most of the excitatory neurotransmission in the mammalian brain. AMPAR play a fundamental role in major neurophysiological processes including learning, memory and cognition [49]. Four different AMPAR subunits are known, labelled GLuA1 to GluA4, that assemble in variable heterotetrameric compositions, mostly GluA1/2 and GluA2/3 [50]. AMPAR are notably involved in synaptic plasticity processes such as LTP and LTD, that are characterized respectively by an increase and a decrease in surface synaptic AMPAR density in response to neuron repetitive stimulation [49].

Autoantibodies directed against the GluA1 and/or GluA2 subunits of the AMPAR were described recently in a series of ten patients [5] (Fig. 4). The patients were mostly middle-aged women and had experienced typical symptoms of a limbic encephalopathy, such as anterograde amnesia, seizures and behavioural problems [5]. Sixty percent of the patients also had diverse extra-limbic symptoms, such as dysexecutive signs, cerebellar syndrome (cinetic, static, nystagmus), visual hallucinations and sleep disorders. Fourty percent experienced seizure and 50% had 1 to 3 relapses after the first episode. By contrast with anti-NMDAR encephalitis, no movement disorder or sign of dysautonomia were observed. Paraneoplastic aetiology with thymus, lung or breast cancer was found in 70% of the patients. Additional case reports further illustrated the variability of the clinical features, such as pseudo-dementia presentations with isolated confusion or isolated dysexecutive symptoms [51]. A case of dramatic fulminant encephalitis in a young woman has also been described [52]. In most patients, brain MRI shows mesiotemporal hyperintensities, although involvement of extra-limbic regions is possible [5,52]. EEG is altered in 60% of the patients and can be useful in the absence of CSF and MRI abnormalities [51]. Outcome is marked by poor cognitive recovery, 50% of the reported cases remaining significantly disabled [5,51–53]. Prognosis seems to depend on the number of relapses and the association with other autoantibodies [5].

Studies using fusion proteins constituted of subdomains of the AMPAR extracellular region suggested that the epitope recognized by the patients' autoantibodies was situated within the bottom lobe of the amino-terminal region of GluA1 or GluA2 (50, Fig. 2). A direct functional effect of the autoantibodies is suggested by the reversibility of at least part of the symptomatology after patients immunosuppression and by the correlation of antibody titres with the clinical evolution observed in one patient [52]. Moreover, *in vitro* experiments on cultured hippocampal neurons showed that patients' antibodies decrease, in a

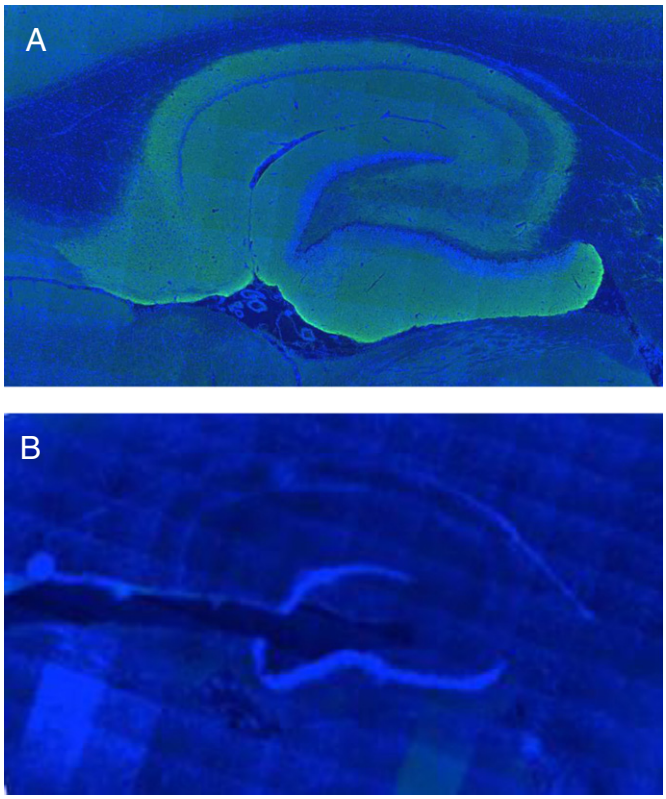

Fig. 4. Immunohistofluorescence of a rat hippocampus slice incubated with CSF from an AMPAR encephalitis patients or CSF from a control subject. Human IgGs are stained in green, cells nuclei in blue (DAPI). A. **Incubation with a patient's CSF.** Patient's IgGs staining is distributed throughout the hippocampus neuropil with a pattern characteristic of AMPAR. B. Incubation with control CSF.

specific and reversible way, surface AMPAR [5]. Application of purified IgG from AMPAR encephalitis patients reduces the spontaneous AMPAR-dependant miniature excitatory post-synaptic currents (mEPSCs) recorded at the surface of cultured neurons [54]. Considering that the functional properties of AMPAR depend on its subunit composition, notably with GluA2 [49], and that sustained LTP involves a switch between GluA1-containing and GluA2/3 AMPAR [49,55,56], one can expect that different effects on synaptic transmission and plasticity might be observed according to which subunit is targeted. However, such differences depending on antigenic specificities have not yet been assessed. Concerning the paraneoplastic cases, four tumours were examined and all expressed GluA1 and GluA2, suggesting that tumorous ectopic expression of AMPAR subunit is the trigger to develop an aberrant auto-immune reaction against those auto-antigens [5]. On the other hand, the origin of the immune deregulation in non-paraneoplastic cases remains obscure.

4. Anti-GABA$_A$ receptor encephalitis

Γ-amino butyric acid receptor A (GABA$_A$R) is a heteropentameric chloride channel activated by the binding of GABA, the main inhibitory neurotransmitter in the CNS [57]. Altogether with other members of the cys-loop pentameric ligand-gated ion channels superfamily, GABA$_A$R is constituted of a variable combination of five subunits arranged around a central pore [58]. In mammals, 19 different subunits have been described (α1-6, β1-3, γ1-3, δ, ε, π, ρ1-3 and θ), but in the adult brain, the most frequent combination associates two copies of a α1, two copies of β2 and one copy of γ2 [58]. GABA$_A$R intrinsic properties, such as ligand affinity and channel conductance, kinetics and pharmacological modulations essentially depend on the receptor subunit composition [57]. GABA$_A$R is thought to mediate most of inhibitory neurotransmission in the adult brain, and several seizure models have been developed by pharmacologically or genetically blocking GABA$_A$R [59,60].

Antibodies targeting the α1 and/or β3 subunits of the GABA$_A$ receptor were recently described in twenty patients with central and/or peripheral neurological symptoms [61,62]. High titre antibodies (>1:160) are associated with a subacute encephalopathy with refractory seizures and/or cognitive or behavioural disturbances, whereas lower titres were found in patients with a more variable symptomatology, such as atypical encephalopathy with seizures, stiff-person syndrome or opsoclonus-myoclonus syndromes. In patients with low-titres anti-GABA$_A$R antibodies where found only in serum but not in CSF and were associated in 50% of the cases with other autoantibodies such as anti-NMDAR or anti-GAD65 antibodies, putting into question whether such low-titre antibodies were actually responsible for the patients' symptoms. Brain MRI in all encephalitic patients displayed multifocal patchy cortico-subcortical FLAIR hyperintensities predominantly involving fronto-temporal areas. CSF analysis was normal in most cases. Forty per cent of the patients with high-titre antibodies had an invasive thymoma and their disease was considered as paraneoplastic, although reactivity for GABA$_A$R in tumour tissue was not evaluated. Recovery was good in most patients but devastating status epilepticus are possible.

In vitro, anti-GABA$_A$R autoantibodies applied on cultured rat hippocampal neurons target inhibitory synapses, decrease total surface GABA$_A$R density and remove them away from the synaptic areas [61,62]. In the same model, patients' antibodies decreased inhibitory post-synaptic currents' amplitude while excitatory currents remain unaltered. Though strongly advocating for a pathogenic effect of anti-GABA$_A$R antibodies, those data have yet to be correlated to *in vivo* data in animal models.

5. Autoimmunity against nicotinic acetylcholine receptors: myasthenia gravis and autoimmune autonomic ganglionopathy

Nicotinic acetylcholine receptors (AchRs) belong to the cys-loop pentameric ligand-gated ion channels superfamily that also includes GABA$_A$, glycine, serotonine and chloride permeable glutamate receptors [63]. AchR are allosteric membrane receptors composed of five subunits symmetrically arranged around a central pore [64] and were reported in both neural and non-neural cells [65]. Twelve AchR subunits have been described so far (α2-10 and β2-4) [63] but muscle-type AchR also include a γ- (fetal form) or an ε- (adult form) subunit [64]. AchR subunits assemble into different homo- and heteromeric combinations that determine AchR electrophysiological and kinetic properties [65]. Subunit combination varies according to the cell-type, adult muscle AchRs following an $(\alpha1)_2\beta\delta\varepsilon$ stoichiometry [63] and vegetative ganglionic receptors combine α3 and β4 subunits [66] while brain-type AchR consist of heteromeric combinations of α4-10 and β2-10 subunits and homopentamers of α7 subunits [67]. Muscle-type AchR are expressed at the post-synaptic level of the neuromuscular junction (NMJ) and play a fundamental role in the transmission of motor signalling [68]. On the other hand, ganglionic AchR are expressed at the post-synaptic level of the vegetative ganglion neurons that control the autonomic functions of the body, such as eye pupil constriction, heart beat frequency, bladder functions and digestive motility [8]. CNS cholinergic transmission is involved in a broad spectrum of brain functions, and has been suggested to play a pivotal role in various cognitive and psychiatric disorders [67]. So far, autoimmunity against AchR subunits has been documented in patients with two distinct PNS autoimmune conditions, namely myasthenia gravis and autoimmune autonomic ganglionopathy [69,70].

Autoimmune Myasthenia Gravis (AMG) is a chronic disease characterized by a fluctuating weakness of the voluntary muscles that typically worsens after exercise. A specific electromyography (EMG) feature is the decrement of the compound muscle action potentials (CMAP) after low-frequency repetitive stimulation of the motor nerves [71]. AMG is rather heterogeneous and patients can be classified according

to their age of onset (juvenile, early-onset or late-onset MG), to their clinical presentation (ocular, oro-pharyngeal or generalized), to the status of their thymus (normal/atrophic, hyperplasia or thymoma) and to the presence of specific autoantibodies [71]. Eighty to ninety per cent of AMG patients have detectable antibodies targeting an extracellular portion of the muscle-specific α1 subunit (α1-AchR Ab) [68]. Antibodies directed against other proteins interacting with the AchR at the NMJ, such as Musk and Lrp4, can be found in a subset of α1-AchR Ab negative AMG patients [72,73].

A body of evidence has suggested a direct role of α1-AchR Ab antibodies in the pathogenesis of AMG. Active immunization with the muscle-type AchR as well as passive transfer of patients' antibodies to rodents induce an experimental AMG that is clinically and electrophysiologically similar to AMG [68,74]. Moreover, clinical evolution seems to correlate with serum antibody titres [75]. In AMG patients as well as in animals passively immunized with anti-AchR Ab, disruption of the postsynaptic membrane structure and decrease of AchR cluster density is observed [68,76]. Muscle AchR Ab are likely to impair NMJ functions through several mechanisms. For instance, autoantibodies from a subset of patients are able to exert a direct blockade of the binding of Ach upon its receptor [77]. More importantly, α1-AchR Ab are able to cross-link muscle-type AchR through binding of the α1-subunit of two adjacent AchR, resulting in an increase of AchR endocytosis and lysosomal degradation [78]. Moreover, patients' α1-AchR Ab antibodies are of the IgG1 and IgG3 isotypes and are therefore able to recruit complement [79]. Accordingly, activation of the membrane attack complex and complement-mediated damage of the muscle EP have been demonstrated in animal studies and in neuromuscular biopsies from AMG patients [80].

Around 10% of AMG patients have a thymoma, and 38% of all thymoma patients display AMG features, suggesting a causal relationship between thymoma and AMG [81,82]. Compared to other subtypes of AMG, thymoma-associated AMG (TAMG) usually involves older patients and is more frequently generalized [71]. Several evidences point towards a role of the thymoma in the autoimmune process. The vast majority of TAMG patients have detectable α1-AchR Ab [83]. Thymoma resection can be followed by clinical improvement and decreased titres of α1-AchR Ab [75]. Furthermore, a growing body of evidence suggest impaired thymocyte maturation in TAMG patients. In the normal thymus, immature thymocytes from bone marrow progenitors are processed in order to undergo positive selection of competent, self-tolerant T-cells and negative selection of autoreactive T-cells [84]. During normal thymopoiesis, the induction of tolerance depends on the expression, under the control of the autoimmune regulator (AIRE) transcription factor, of a large repertoire of self-antigens bound to MHC-II molecules at the surface of medullary thymic epithelial cells [84]. Importantly, muscle-type AchR are furthermore expressed by thymic myoid cells [78]. In contrast, expression of AIRE is usually defective in thymomas [85] and MHC-II molecules expression is down regulated [86] while the medulla is often disorganized [83]. Besides, thymomas are able to produce large amounts of long-lived T-cells despite the fact they contain more immature T-cells than the normal thymus [87–89]. Moreover, decreased production of thymic regulatory T-cells has been observed in thymoma patients [90]. Different but non-mutually exclusive mechanisms have therefore been proposed to explain the development of autoimmunity in TAMG patients. On the one hand, impaired thymocyte maturation is likely to result in the escape of immature and potentially autoreactive thymocytes from thymomas, while T-cells might also undergo autoimmunization against self antigens present within the thymus, such as the AchR expressed by thymic myoid cells [91]. On the other hand, the defective production of regulatory T-cells could facilitate the development of autoimmune diseases such as AMG [90]. AMG has thus turned out to be a useful physiopathological model for antibody-mediated neurological diseases as well as for autoimmune conditions related to thymus dysfunction [68,71].

Autoimmune autonomic ganglionopathy (AAG) is a rare cause of autonomic failure [92]. Patients present with symptoms of sympathetic (orthostatic hypotension, anhidrosis) and parasympathetic failure (fixed heart rate, sicca syndrome, impaired pupil constriction, genito-urinary dysfunction and gastro-intestinal dysmotility). Mean age is around 60 years [93,94]. The course is usually subacute and monophasic, followed by a slow and often incomplete recovery [92]. Autonomic dysfunction can be demonstrated by standardized tests for autonomic function such as the quantitative sudomotor axon reflex test or the heart rate response to deep breathing [92]. An immune-mediated mechanism has been suspected in many patients due to the subacute installation of the symptoms, the association with cancer and autoimmune diseases, and the frequent improvement after immunotherapy [93]. Antibodies directed against the α3-subunit of the ganglionic AchR (α3-AchR Ab) have been identified in 1998 in a subset of AAG patients but revealed to be non specific for AAG as only 21-22% of the patients with α3-AchR Ab present with AAG criteria [70,93,94]. Indeed, α3-AchR Ab are also found, although at lower levels, in patients with neurodegenerative or non neurological autoimmune conditions [93,94]. Coexisting autoantibodies, including α1-AchR Ab with MG, are present in 26% of the patients [93]. α3-AchR Ab have been suggested to be associated to cancer, notably lung cancers and adenocarcinomas from various tissues, but the association with a cancer greatly varies from a study to another and the expression of the α3-subunit by tumour tissue has not been studied [70,92–94]. Despite those limitations, a pathogenic role of α3-AchR Ab in AAG patients is supported by clinical and experimental data. Elevated α3-AchR Ab levels correlate with AAG while low-levels of serum autoantibodies are more frequent in non-AAG patients [93,94]. Furthermore, fluctuations of serum α3-AchR Ab levels seems to follow clinical evolution and to correlate with the severity of the dysautonomy [92,93,95]. In animal models, active immunization against the α3-AchR subunit and passive transfer of patients' antibodies lead to severe autonomic dysfunction [96,97] and to impair autonomic ganglionic synaptic transmission [98]. *In vitro*, application of serum IgG from AAG patients and rabbits immunized against the α3 AchR subunits on cultured neuroblastoma cells constitutively expressing AchR results in an inhibition of the ganglion-type AchR current [99]. This effect required cross-linking of the AchR by divalent IgG and was time- and dose-dependant [99]. It can be therefore assumed that, similarly to α1-AchR Ab, α3-AchR Ab may cross-link ganglionic AchR at the surface of ganglionic neurons, leading to its internalization and reduction of its surface density, hence the impairment of the ganglion-type cholinergic transmission.

6. Anti-Glycine receptor antibodies associated syndromes

Glycine receptors (GlyR) are chloride pentameric channels composed of a variable arrangement of α and β subunits [100]. GlyR are mainly distributed in the spine and brainstem and have a prominent role in the inhibitory modulation of motor, visual, auditive and autonomic networks [100,101].

Brainstem and spine autoimmune disorders such as stiff-person syndrome (SPS) and its variants are seen in 85% of the reported anti-GlyR patients, including progressive encephalomyelitis with rigidity and myoclonus (PERM) in 61% of them [102–105]. SPS is a disorder characterized by axial and proximal limb rigidity along with painful muscular spasms, dysautonomic signs and exaggerated startles [106], while PERM is similar to SPS with a peculiar pathological startle known as hyperekplexia, severe autonomic disturbances, brainstem and cerebellar signs and central respiratory failure [105,106]. Anecdotally, Anti-GlyR antibodies were also observed in patients with pure encephalopathic features, optic neuritis, or isolated brainstem involvement [105]. Nine percent of the reported patients had an on-going cancer, either a thymoma or lymphoma, but a clear causality link is lacking [102–105]. Fifteen percent of GlyR Ab patients have also anti-GAD 65 antibodies, an ISA Ab also associated with SPS/PERM with poorer outcome than GlyR Ab syndromes [104,105].

The alpha 1 subunit of the Glycine receptor (GlyRα1) is the main antigenic target of anti-GlyR ab [104,105]. Interestingly, GlyRα1 mutations in humans are associated with hereditary SPS and hyperekplexia, which is thought to be due to a suppression of the glycinergic inhibition in the nucleus reticularis pontis caudalis [107]. Moreover, SPS associated with anti-amphiphysin antibodies was shown to be due to a dysregulation of spinal inhibitory network [108] therefore a similar mechanism in anti-GlyR SPS is expected. Patients' antibodies co-localize with GlyRα1 in the brainstem and spinal cord of rodent [105]. *In vitro*, GlyRα1 Ab applied on GlyRα1-expressing cells induce the internalization of the antibody-glyR complex through the lysosomal pathway [105]. This increased internalization is likely to underlie glycinergic networks dysfunction, although the possibility of a direct inhibitory effect of the antibodies on the GlyR was not evaluated. GlyRs are also expressed in regions known to regulate autonomic function as for instance the locus coeruleus, nucleus solitarius, and the rostral ventrolateral medulla [109–111]. In these sites a reduction in GlyR control of sympathetic activity by the GlyR antibodies could be responsible for the dysautonomic symptoms. Similarly, a functional effect of GlyRα1 Ab on the rostral ventrolateral medulla, which express GlyRα1 and is involved in generating the rhythmic respiratory pattern, could explain the respiratory failure observed in some patients [112]. Therefore, clinical and experimental data seem concordant to suggest that anti-GlyR antibodies impair the inhibitory glycinergic transmission in patients by inducing the internalization of GlyR, although this hypothesis has yet to be confirmed by *in vivo* studies.

7. Neurological syndromes related to anti-VGKC complex antibodies

Voltage-gated potassium channels (VGKC), or Kv channels, are membrane channels able to open selectively for potassium ions in response to changes in membrane polarity [113]. Mammalian VGKC contain four α-subunits arranged around the channel pore as homo- or hetero-tetramers and can assemble with auxiliary cytoplasmic β-subunits that modulate their functions. Twelve VGKC α-subunit isoforms (named Kv1 to Kv12) with distinct physiological and pharmacological properties have been identified so far [114]. The Kv1 VGKC, also referred as shaker-type channels, are highly expressed in the brain and cerebellum and are thought to play a major role in regulating neuronal excitability [115]. Schematically, opening of presynaptic Kv1 channels following neuronal depolarization results in a progressive output of potassium that contributes to the repolarization of the activated cell until the resting membrane potential is reached [8]. Axonal Kv1 channels regulate conduction by stabilizing the resting potential and decrease the repetitive firing of neurons [116]. Six subfamilies of Kv1 channels, classified as Kv1.1 to Kv1.6, have been described [114]. In humans, Kv1 genes mutations or deletions have been related to epilepsy, episodic ataxia and hereditary neuromyotonia [117,118].

Autoantibodies called "anti-VGKC antibodies" ("VGKC Ab") were described in 1995 in patients with neuromyotonia (NMT), an acquired peripheral nerve hyperexcitability syndrome [119]. Later, similar antibodies were found in patients with encephalopathies and called "autoimmune limbic encephalitis" and in individuals with the rarer Morvan's syndrome (MoS) [120,121]. "VGKC Ab" were detected with a radioimmunoprecipitation assay (RIA) using radiolabelled ^{125}I-α-dendrotoxin, which is able to bind and to aggregate shaker type-VGKC of the Kv1.1, Kv1.2, Kv1.4 and Kv1.6 subtypes [115]. Patient's antibodies were shown to co-localize with such shaker-type VGKC aggregates obtained from human brain extracts and it was therefore assumed that they specifically recognized Kv1 channels [119]. However, different studies based on immunoprecipitation using patients' antibodies coupled to mass spectrometry allowed to identify other proteins, namely contactin-associated protein-like 2 (Caspr2) and leucin-rich glioma inactivated 1 (Lgi1), as the main antigenic targets of the previously called "VGKC Ab", while the patients' sera exceptionally recognized the VGKC itself [4,6,122]. This discrepancy is explained by the fact that Lgi1 and Caspr2 strongly interact with Kv1 channels and are present in dendrotoxin-induced aggregates [4]. Similarly, other proteins interacting with Kv1 channels, such as transient axonal glycoprotein-1 (TAG1)/Contactin2, the Netrin receptor DCC or dipeptidyl peptidase-10 (DPP10) may represent additional antigenic targets in some patients [123–125]. Moreover, up to 75% of "VGKC Ab" positive patients lack serologic specificity, raising the possibility that other antigenic targets could be still unknown [126].

Anti-Lgi1 antibodies (Lgi1 Ab) were described in a cohort of 57 patients with "VGKC Ab" associated encephalitis [4]. Lgi1 is a secreted protein expressed in neural tissues first identified as a potential tumour suppressor protein in gliomas [127]. Dimerized Lgi1 interacts with the two synaptic receptors ADAM22 and ADAM23 to constitute a trans-synaptic complex that includes post-synaptic glutamatergic AMPA receptors and pre-synaptic Kv1.1 [128]. Interaction of Lgi1 with ADAM22 promotes the interaction between ADAM22 and scaffolding proteins that enhances surface expression of post-synaptic AMPAR [125]. Besides, Lgi1 reduces Kv1.1 inactivation by modulating the auxiliary subunit Kvβ1 [129]. Lgi1 is therefore proposed to act as a key regulator of neuronal excitability at synapses. Accordingly, Lgi1 mutations in humans are related to ADPEAF, an autosomal dominant hereditary epileptic syndrome [130] and Lgi1 knockout mice develop lethal epilepsy [128]. Lgi1 Ab are found mostly in patients with a phenotype of autoimmune encephalitis [4,125,126]. Lgi1 Ab associated encephalitis usually installs in the sixth decade but age of onset ranges from 20 to 80 years [4,131,132]. Both limbic (anterograde amnesia, behavioural/psychiatric disturbances, seizures) and extra-limbic signs (motor, cerebellar, extrapyramidal involvement) can be observed. Epilepsy is found in 80% of the patients and may represent the initiating symptom [4,126,131,132]. Insomnia, paradoxical sleep disorders and hyponatremia are other typical features [4,126,131,132]. More importantly, atypical seizures called facio-brachial dystonic seizures (FBDS) are closely associated with anti-Lgi1 encephalitis [124,133]. FDBS can occur alone, accompany or precede the complete encephalitic syndrome and are highly responsive to immunotherapy despite the poor effect of antiepileptic drugs [124,133]. Additionally, prodromal severe brady-arrythmias were described in patients with Lgi1 encephalitis, presumably due to insular lobe dysfunction [134]. In the settings of Lgi1 encephalitis, high levels of Lgi1 Ab are usually found and Lgi1 is the only antigenic target, while PNS symptoms are absent [125]. Additional or isolated peripheral nerve involvement is indeed noted in only 6.5% of patients positive only for Lgi1 Ab [126]. Lgi1 Ab encephalitis seems to be associated to a poor cognitive outcome with frequent evolution to hippocampal atrophy [131]. Relapses may occur in 10% of the patients [4,131,132]. Aggressive and prolonged immunotherapy is important to relieve symptoms and to prevent relapses but may provoke severe adverse effects [124,132,135]. The prevalence of cancers varies from a study to another but does not seem to exceed 20% [4,126,131,132,136].

In vitro, Lgi1 Ab were shown to impair Lgi1 binding to ADAM22 and to decrease surface expression of post-synaptic AMPAR in a reversible and dose-dependant manner [125]. Other putative functional roles of Lgi1 Ab, notably on Kv1 channels expression, remain to be assessed. Furthermore, appositions of complement on neuronal membranes have been demonstrated in the brain of Lgi1 encephalitis patients, suggesting the involvement of complement-dependant cytotoxicity [137]. This data might explain the more frequent occurrence of hippocampal atrophy associated with Lgi1 Ab compared to other anti-cell surface antigen antibodies associated to autoimmune encephalitis, such as anti-NMDAR or anti-Caspr2 Antibodies.

Anti-Caspr2 antibodies (Caspr2 Ab) were initially described in eight "VGKC Ab" patients with encephalitis and/or PNS symptoms [6]. Caspr2 Ab significantly correlate with the presence of PNS symptoms, mostly NMT and MoS [6,122,126]. NMT associates motor symptoms (fasciculations, myokimia, pseudomyotonia, muscular hypertrophy and gait disorders), dysautonomic features and neuropathic pain. By definition, CNS involvement is excluded in patients with pure NMT.

Electroneuromyography (ENMG) displays fasciculations, spontaneous bursts of motor neurons firing and fibrillation potentials. NMT's aetiology is mainly autoimmune and linked with Caspr2 Ab, although genetic and toxic disorders may also present some features of the disease [117]. MoS on the other hand is a rare autoimmune disorder associating neuromyotonia features along with marked dysautonomic signs (profuse sweating, tachycardia, genito-urinary dysfunction), complete disruption of sleep organization and specific encephalopathic features (visual hallucinations, delusion and impaired vigilance) [123]. MoS is thought to be a purely autoimmune disorder associated to Caspr2 Ab ((123). Caspr2 Ab is found in most of NMT/MoS, either alone or with moderately elevated anti-Lgi1 Ab [123,125]. Nevertheless, Caspr2 Ab can also be found in patients with pure limbic encephalitis, whose specific clinical pattern and prognosis remain to be precisely determined [6,131]. Differences in epitope specificities and location of the production of auto-antibodies may account for such a variety of clinical presentations (*unpublished data*). Importantly, a thymoma is found in 50% of Caspr2 positive NMT/MoS patients [123], while the prevalence of tumours is much lower in patients with CNS involvement [4,126,131, 132,136].

Caspr2 is a membrane protein first described in specific axons subdomains surrounding the nodes of Ranvier and the juxtaparanodes [138]. Caspr2 seems to be critical for the optimal progression of the nervous influx along myelinated axons [138]. In the central and peripheral nervous system, Caspr2 and TAG1/Contactin2 form a protein complex necessary for the organisation of juxtaparanodes and its enrichment in Kv1 channels [139]. Experimental findings suggest that Caspr2 may also be present in the CNS at pre-synaptic sites where it may interact with the pre-synaptic Kv1 channels [140]. Caspr2 was also suggested to play a role in synapse formation and dendritic arborisation [138]. Polymorphisms of the CASPR2 gene (CNTNAP2) have notably been described to the autistic spectrum disorders [141]. The frequent association of NMT/Mos with MG and thymomas (43% and 50%, respectively) [123] raise the possibility that Caspr2 Ab positive NMT/MoS and MG share a common etiopathogeny involving the deregulation of thymus immune functions [71]. Virtually all patients with Caspr2 NMT/MoS have concurrently multiple other auto-antibodies such as low-titre of Lgi1 Ab, anti-DCC or anti-DPP10 antibodies [125]. Some responsibility of those other antibodies in the development of the symptoms is not excluded. For instance, anti-DCC antibodies were shown to impair DCC's binding to his receptor Netrin-1, and are significantly associated to NMT/MoS features [125]. *In vitro*, Caspr2 Ab were shown to co-localize with Caspr2 at the juxtaparanodal region of mouse sciatic nerve fibers [6]. It can be therefore hypothesized that Caspr2 Ab may disrupt in some way the interaction between Caspr2 and its partners and could disorganize the juxtaparanodes as well as decrease Kv1 expression in those regions, but functional studies are lacking to assess the actual functional effects of Caspr2 Ab.

Serologic specificity for either Caspr2 or Lgi1 is lacking in 12-33% of "VGKC Ab" encephalitis patients [122,131] and in up to 75% of all "VGKC Ab" positive patients, regardless of the clinical phenotype [126]. Negativity for Caspr2/Lgi1 Ab is correlated with low "VGKC Ab" levels [131]. The clinical phenotype of "VGKC Ab" patients seronegative for both Lgi1 and Caspr2 seems to be diverse, as patients may present with features of autoimmune encephalitis, PNS symptoms, or both [4, 123,126]. One study has suggested a higher frequency of refractory epilepsy persisting despite immunotherapy in autoimmune encephalitis patients positive for "VGKC Ab" but negative for either Lgi1 or Caspr2 Ab [131]. More studies are needed to accurately decipher the clinical phenotype associated to "VGKC Ab" without Lgi1 or Caspr2 antibodies, as well as to identify the auto-antigens involved.

Lastly, autoantibodies directed against dipeptidyl-peptidase protein like-6 (DPP6 or DPPX) were recently described in seven patients with a peculiar phenotype of subacute encephalopathy, cerebellar syndrome, axial and limb stiffness and symptoms of CNS hyperexcitability such as tremor, myoclonus, seizures and hyperekplexia [142,143]. In most of the patients, prominent digestive symptoms were also observed. As DPPX is highly expressed in the vagus nerve ganglion, this could suggest an alteration of the vegetative tracts function in those patients [144]. Interestingly, DPPX was shown to co-assemble with and regulate the Kv4.2 channels in the CNS [145,146], but the precise role of this protein in the CNS and the biological effects of anti-DPPX antibodies remain unclear. Overall, the recent description of anti-DPPX antibodies further expands the spectrum of neurological autoimmune diseases to other VGKC subfamilies than Kv1 channels.

To conclude, the discovery of specific antigenic targets for the so-called "VGKC Ab" has allowed to further understand the complex clinical spectrum associated to this biological marker and the pathophysiological processes at stake. Despite the fact that clinical syndromes overlap, some symptoms specific for Lgi1 or Caspr2 sero-positivity are beginning to emerge, but further works are needed to understand the exact role of these auto-antibodies. On the other hand, other auto-antigens underlying "VGKC Ab" positivity are probably yet to discover.

8. Lambert-Eaton myasthenic syndrome and cerebellar ataxia with anti-VGCC antibodies

Voltage-gated calcium channels (VGCC) are classified into 5 subfamilies (L, N, P/Q, T, R) according to voltage and time dependency, channel conductance and pharmacological properties. Most of those characteristics depend on the obligatory α1 subunit isoform. Ten α1 isoforms, distributed into the 5 subfamilies mentioned above, have been described so far. P/Q- (Cav2.1), L- (Cav1.1) and N- (Ca2.2) types VGCC are high-voltage activated calcium channels expressed at the presynaptic end of the nerve terminals and are involved in neurotransmitter release in the synaptic cleft [147]. Indeed, their opening triggered by the pre-synaptic neuron depolarization induces a calcium intra-cytosolic influx that activates neurotransmitters' exocytosis, notably acetylcholine at the neuromuscular junction (NMJ) [147]. Antibodies targeting the P/Q-type VGCC ($Ca_V2.1$) (VGCC Ab) are found in patients with Lambert-Eaton myasthenic syndrome (LEMS) or cerebellar ataxia (CA), occasionally in association with antibodies targeting the L- and N-type [148].

LEMS is a rare autoimmune disorder of the NMJ and is clinically defined by the triad of muscular weakness, dysautonomia and areflexia. The diagnosis is based on clinical features, ENMG and VGCC Ab [149]. A small-cell lung carcinoma (SCLC) with neuroendocrine features accompanies the neurological disease in 50 to 60% of cases [150]. VGCC Ab are found in 85-90% of LEMS patients, and in up to virtually 100% of the paraneoplastic cases [151,152]. Their main antigenic target is the α1 subunit of the P/Q type [153]. Concordant data suggest that VGCC Ab in LEMS patients are directly pathogenic. In rodents, genetic mutations of the $Ca_V2.1$ α1 subunit, active immunisation with VGCC peptides and passive transfer with patients' immunoglobulin all lead to a LEMS phenotype, along with a decrease of the acetylcholine release at the NMJ [149]. *In vitro*, immunoglobulin G from LEMS patients induce cross-linking of VGCC, internalization of the antibody-VGCC complexes and decrease of surface VGCC expression [154]. LEMS antibodies could therefore act by down-regulating VGCC at pre-synaptic nerve terminals, consequently decreasing acetylcholine release. A comparable effect may affect the autonomic system, as LEMS antibodies were shown *in vitro* to down-regulate VGCC at the surface of parasympathetic and sympathetic neurons [119]. P/Q type VGCC are normally expressed in both neural and endocrine tissue [109] and consistently SCLC expresses functional VGCC as well [156]. It is then widely accepted that in paraneoplastic cases the immune adapted reaction against the tumour is likely the trigger for a deregulated, autoimmune response. Interestingly, in SCLC patients with LEMS, survival appears more favourable in comparison to SCLC patients without LEMS [157], suggesting that the immune response in LEMS patients can inhibit tumour growth or even eradicate the tumour [149]. In non-paraneoplastic LEMS patients, HLA-B8-DR3-haplotype have been suggested to be a predisposing factor [158].

VGCC Ab are also found in up to 45% SCLC-associated CA [159,160]. VGCC Ab associated CA is not clinically different from other paraneoplastic CA and is usually subacute with symmetrical gait and limb ataxia, dysarthria and nystagmus. However, Anti-VGCC CA may sometimes install progressively, mimicking idiopathic sporadic late-onset ataxia [161]. Response to immunotherapy is often poor, due to the early and diffuse loss of Purkinje cells observed in these patients [162]. A few case reports have suggested that the rare VGCC Ab non-paraneoplastic CA patients may nonetheless respond well to immunotherapy [163,164]. Many observations suggest a direct pathogenic role of VGCC Ab in the developing of cerebellar ataxia. P/Q-type VGCC are prominent in the cerebellum [165], and mutations of P/Q VGCC cause ataxia in mice [166]. Post-mortem brain examination have revealed a diffuse loss of Purkinje cells along with Bergmann's gliosis, with no or slight lymphocytic perivascular infiltration [162], arguing against a prominent role of cellular immunity. Moreover, P/Q type VGCC is decreased by 70-80% in the cerebellum of VGCC Ab CA patients compared to healthy individuals or LEMS patients without CA [162]. Lastly, Intrathecal injection of antibodies from VGCC Ab CA patients have been shown to induce acute ataxia in mice, further demonstrating the prominent role of VGCC Ab in the pathogenesis of CA [167].

The association of SCLC with LEMS, CA, or both had early suggested an overlap between LEMS and CA. Indeed, clinical or electrophysiological features of LEMS are present in 43% VGCC Ab CA [160]. Conversely, CA affects 9% of LEMS patients, almost exclusively in paraneoplastic situations. Intriguingly, VGCC Ab from LEMS patients without CA were shown to reduce surface expression of VGCC in cerebellar Purkinje and granule cells *in vitro* [168]. Differences in the site of the production of VGCC Ab, but also in antibodies' epitope specificities, could account for the variable clinical presentation between patients and in particular explain why CA more frequently affects cancerous patients. For instance, antibodies targeting the DIV functional domain of VGCC are mostly found in non-paraneoplastic LEMS patients and fail to bind SCLC cells [163]. Monoclonal antibodies (mAb) designed to target a different functional domain, DIII, were shown to exert *in vitro* a direct and competitive inhibition over both N and P/Q type VGCC and to reduce pre-synaptic release of neurotransmitter quanta, while mAb against DIV had no effect [169]. Anti-DIII mAb injected into live mice *cisterna magna* induced ataxia, without evidence of neuronal loss or inflammation in post-mortem examination [169]. Further studies are needed to understand the immunological mechanisms that result in different epitope specificities and clinical phenotypes in paraneoplastic versus non-paraneoplastic cases.

9. Conclusion

Neurologic autoimmune channelopathies can be defined as neurological syndromes related to antibodies targeting ion channels or associated proteins in the nervous system. They constitute a continuously expanding entity encompassing a large spectrum of clinical symptoms. Autoimmune channelopathies reflect the functional consequences of the fixation of an autoantibody upon a protein involved in neural signalling and as such are highly responsive to immunotherapy. So far several antibodies targeting neuronal ion channels have been described and it is likely that many remain to identify. Importantly, such auto-antibodies do not systematically target ion channels themselves, but can be directed against other membrane proteins interacting with them as well. Furthermore, auto-antibodies most often do not directly modulate channel functions, but they rather decrease channel surface expression by diverse mechanisms. Those alterations may encompass the whole nervous system, hence the highly diverse clinical phenotypes observed. Moreover, such effects on channel expression result in the alteration of fast neural transmission regulation as well as of mechanisms of long-term synaptic plasticity, explaining the progressive and sometimes delayed recovery after immunotherapy. Interestingly, it is not rare that for the same apparent antigenic target different clinical syndromes can be observed from one patient to another. Important parameters seem indeed to be which functional domain is targeted by the antibody, and where auto-antibodies are produced. This ability to label and to impair specific functional subdomains of neuronal proteins has been used in the research field to identify such regions of interest [169] and alternatively as selective tools to specifically study ion channels functions within the synapse.

Finally, neurological autoimmune channelopathies encompass a wide range of treatable neurological syndromes and involve a great variety of neurophysiological processes. Further work are needed to improve our knowledge about the precise pathophysiological mechanisms at stake, while the patients' autoantibodies themselves are promising tools for functional studies of the ion channels involved in neural signalling.

Conflict of interest

The authors state that they do not have any conflict of interest.

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