Biochimica et Biophysica Acta xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbadis

Review

Myasthenia gravis and related disorders: Pathology and molecular pathogenesis ☆

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ARTICLE INFO

Article history:
Received 1 July 2014
Received in revised form 20 November 2014
Accepted 29 November 2014
Available online xxxx

Keywords:
Neuromuscular junction
Myasthenia gravis
Lambert–Eaton myasthenic syndrome
Botulism
Organophosphate poisoning
Congenital myasthenic syndrome

ABSTRACT

Disorders affecting the presynaptic, synaptic, and postsynaptic portions of the neuromuscular junction arise from various mechanisms in children and adults, including acquired autoimmune or toxic processes as well as genetic mutations. Disorders include autoimmune myasthenia gravis associated with acetylcholine receptor, muscle specific kinase or Lrp4 antibodies, Lambert–Eaton myasthenic syndrome, nerve terminal hyperexcitability syndromes, Guillain Barré syndrome, botulism, organophosphate poisoning and a number of congenital myasthenic syndromes. This review focuses on the various molecular and pathophysiological mechanisms of these disorders, characterization of which has been crucial to the development of treatment strategies specific for each pathogenic mechanism. In the future, further understanding of the underlying processes may lead to more effective and targeted therapies of these disorders. This article is part of a Special Issue entitled: Neuromuscular Diseases: Pathology and Molecular Pathogenesis.

1. Introduction

Diseases of the neuromuscular junction (NMJ) (Table 1) produce weakness which generally varies with repeated synaptic firing, i.e. sustained or repeated muscle contraction [1–3]. The "true" myasthenias are NMJ disorders in which weakness worsens with sustained muscle contraction or work and improves with rest. Analysis of these diseases has determined that they primarily involve components of the postsynaptic portion of the NMJ. The other disorders of the NMJ result in weakness that either improves or remains unchanged with exercise. The latter group is associated with dysfunction of the presynaptic apparatus or of the components of the synaptic cleft. The clinical characteristics of the "fatiguing" weakness in an individual patient with one of the "true" myasthenias can be confirmed electrophysiologically by decrementing compound muscle action potentials (CMAPs) in response to slow rates of motor nerve stimulation (2–3 Hz), in association with normal amplitudes of the responses to single nerve stimuli. In contrast, most of the presynaptic NMJ disorders are associated with reduced amplitudes of the CMAPs in response to single motor nerve stimuli but with increased amplitudes following rapid stimulation of the nerve.

The majority of patients with NMJ dysfunction have either myasthenia gravis (MG) or Lambert–Eaton myasthenic syndrome (LEMS) [4,5]. Remarkably, both diseases are autoimmune in nature and, moreover, each results from a T cell-directed antibody (Ab)-mediated attack on ion channels that are crucial for neuromuscular transmission (NMTx) via the NMJ. For MG, the target of the auto-Ab attack is the nicotinic acetylcholine receptor (AChR) in the postsynaptic membrane, whereas for LEMS the target is the P/Q-type voltage-gated calcium channel (VGCC) located in the presynaptic motor nerve terminal membrane. In a third disorder, autoimmune neuromyotonia, Ab-mediated attack on the nerve terminal (rectifying) voltage-gated potassium channel results in spontaneous firing of the synapse [6]. In Guillain Barré syndrome Abs directed against gangliosides GM1 and GQ1b have been shown to affect NMTx at the NMJ in addition to demyelinating and axonal nerve damage. The reasons for the particular susceptibility of the NMJ to autoimmune attack have not yet been elucidated. Nonimmune diseases also lead to disordered NMTx. Organophosphate poisoning results in blockade of the muscle acetylcholinesterase, leading to NMJ dysfunction from excessive neurotransmitter activity. In botulism, the various toxins bind to and hydrolyze individual intracellular presynaptic proteins involved in docking and release of (acetylcholine (ACh)-containing vesicles. In addition, over the last twenty years or so, a group of genetically determined congenital myasthenias have been identified and studied. Each congenital myasthenic syndrome (CMS) results from a mutation in a protein important to NMTx. The mutations have been classified as to whether they involve presynaptic, synaptic cleft or postsynaptic proteins [7].

2. Review of NMJ structure and function

The NMJ is the most highly studied neural synapse—primarily because of its location in the peripheral nervous system isolated from

☆ This article is part of a Special Issue entitled: Neuromuscular Diseases: Pathology and Molecular Pathogenesis.

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http://dx.doi.org/10.1016/j.bbadis.2014.11.022
0925-4439/

Table 1
Features of various neuromuscular junction disorders. NMJ = neuromuscular junction, AChR = acetylcholine receptor, MuSK = muscle specific receptor tyrosine kinase, Lrp4 = lipoprotein receptor-related protein 4, LEMS = Lambert-Eaton myasthenic syndrome, VGCC = voltage gated calcium channel, VGKC = voltage gated potassium channel, CMS = congenital myasthenic syndrome.

NMJ disorder	Synaptic location	Autoantibody	Protein(s) involved	Thymic abnormalities	Age at onset (years)	Female : male ratio
Autoimmune MG						
AChR MG	Postsynaptic	Nicotinic AChR	–	Lymphoid hyperplasia and thymoma	20–30 (women) and > 50 (men)	1:2 (3:1 in juvenile MG)
MuSK-MG	Postsynaptic	MuSK	–	–	Variable	8.5:1
Lrp4-MG	Postsynaptic	Lrp4	–	Unknown	> 40 (limited data)	2.5:1
LEMS	Presynaptic	P/Q type VGCC	–	–	40–60 (usually related to lung carcinoma)	1:1
Acquired peripheral nerve Hyper excitability syndromes	Presynaptic	VGKC	–	–	Unknown	Unknown
Guillain–Barre syndrome	Presynaptic	GM1, GQ1b	–	–	Bimodal (adult and childhood)	1:1.25
Botulism	Presynaptic	–	BoNT toxin and SNARE proteins	–	Neonates and all other ages affected	–
Organophosphate Poisoning	Synaptic deft	–	Acetylcholinesterase	–	–	–
CMS	Presynaptic, synaptic deft or postsynaptic	–	Various mutated proteins	–	Predominanantly in childhood	–

other synapses and because of the availability of a highly abundant source of its close analog within the electric organs of electric fish. The information on the biology of the NMJ has assisted in the analysis of a series of diseases that affect its function resulting in motor weakness. The NMJ begins to form when the axon growth cone of a developing motor neuron, or a sprouting motor axon, encounters a developing myotube, or a denervated muscle fiber, and begins to secrete agrin, a glycoprotein with a laminin-binding domain that anchors it to the extracellular matrix [8–11]. Agrin can initiate the formation of the NMJ but requires the presence of the postsynaptic transmembrane kinase, muscle-specific kinase (MuSK). The latter is a receptor tyrosine kinase that, when activated by agrin, self-phosphorylates and phosphorylates a number of other proteins important to the formation of the NMJ, mediated through various downstream signal transduction pathways. The agrin/MuSK interaction requires mutual binding to a third transmembrane muscle protein, the low density lipoprotein receptor-related protein 4 (Lrp4) [12–15]. This process induces dense clustering of the AChRs in the postsynaptic membrane and marked folding and specialization of that membrane [8–11,16,17]. A number of less well understood processes also occur in the postsynaptic region, referred to as the muscle endplate (EP), that lead to: 1) secretion of acetylcholinesterase into the extracellular matrix, 2) concentration of sodium channels in the membrane of the valleys of the postsynaptic folds and 3) retrograde release of factors that induce the axon terminal to develop the specializations involved in activity-induced release of neurotransmitter (ACh)-containing synaptic vesicles. The mature NMJ (Fig. 1) consists of the specialized nerve terminal of the motor axon, which, when depolarized by an action potential, releases the ACh into the synaptic cleft. The released ACh diffuses across the cleft to bind to the very tightly packed AChRs located on the peaks of the highly folded EP membrane. The AChR is a multi-subunit transmembrane ligand-gated ion channel that opens upon binding of two molecules of ACh, resulting in cation influx and depolarization of the muscle membrane. When the depolarization reaches threshold, an action potential is initiated in the sodium channel-rich valleys of the synaptic folds leading to muscle contraction.

3. MG subgroups

Several subgroups of MG have been identified on the basis of clinical presentation, autoAb profile and thymic pathology including: early-onset (before age 40) MG, late-onset MG and thymoma associated-MG. Early-onset MG generally begins with ocular muscle weakness followed by generalized weakness and occurs more often in female patients. There is an association with HLA-B8DR3 and thymic hyperplasia [18]. In contrast, late-onset MG is more common in males over 60 years of age without thymoma [19]. There is no apparent gender predilection; however, compared to early-onset MG without thymoma, weakness including oropharyngeal involvement appears to be more severe and associated with additional autoAbs, including titin Abs [20], paraneoplastic Abs, voltage-gated K+ and Ca2+ channel Abs, Hu Abs, DHP related protein 5 and GAD Abs [21].

4. Role of the thymus in MG

Although the factors involved in the induction of autoimmune MG have not been fully elucidated, the association of MG with abnormalities of the thymus was described by Weingart as early as 1901. Approximately 10% of patients with autoimmune MG have a thymoma, which may possibly play a role in disease initiation through multiple mechanisms including the expression of self-antigens by thymoma cells and impaired negative selection of autoreactive T lymphocytes. Another 60% of patients have thymic hyperplasia, defined by the presence of medullary lymphoid follicles and germinal centers. While a body of evidence exists [22] that thymectomy produces long-term benefit in MG, the first randomized controlled clinical trial of this treatment is currently in progress.

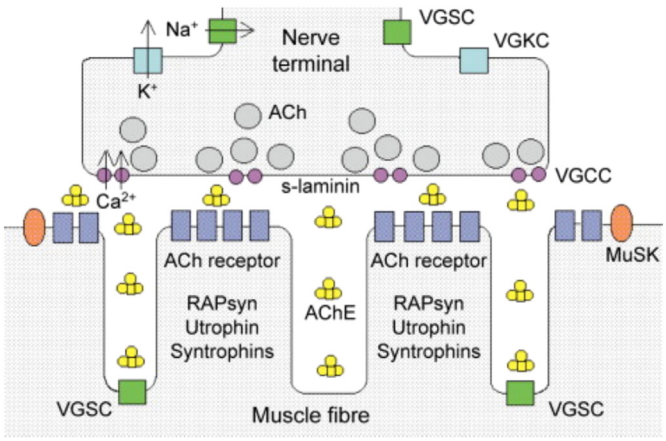

Fig. 1. Schematic of the neuromuscular Junction. VGSC = voltage-gated Na channel, VGKC = voltage-gated potassium channel, VGCC = voltage-gated calcium channel, AChE = acetylcholinesterase. Adapted from Vincent A, Newland C, Croxen R, Beeson D. Genes at the junction—candidates for congenital myasthenic syndromes. Trends Neurosci 1997; 20(1):15–22. Adapted with permission.

Please cite this article as: J.C. Ha, D.P. Richman, Myasthenia gravis and related disorders: Pathology and molecular pathogenesis, Biochim. Biophys. Acta (2014), http://dx.doi.org/10.1016/j.bbadis.2014.11.022