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The role of the Dystrophin Glycoprotein Complex on the Neuromuscular System

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Abstract

The Dystrophin Glycoprotein Complex (DGC) is a large multi-protein complex that links cytoskeleton actin to the extracellular matrix. This complex is critical in maintaining the structural integrity of muscle fibers and the stability of the neuromuscular synapse. The DGC consists of dystrophin and its utrophin homolog, as well as dystroglycans, sarcoglycans, sarcospan, syntrophins, and dystrobrevins. Deficiencies in DGC proteins result in several forms of muscular dystrophy with varying symptoms and degrees of severity in addition to structurally abnormal neuromuscular junctions (NMJs). This mini-review highlights current knowledge regarding the role of the DGC on the molecular dynamics of acetylcholine receptors (AChRs) as it relates to the formation and maintenance of the mammalian NMJ.

INTRODUCTION

High density clustering of AChRs at the postsynaptic membrane is a major hallmark of the neuromuscular junction [1–3]. During embryonic development, acetylcholine receptors (AChRs) are diffusely and evenly distributed (pre-patterned) on the cell surface in the absence of primary myotube innervation and subsequently form clusters where growing nerves form contacts [1, 4–6]. This initial clustering of AChRs is a multi-step process that involves a variety of molecules and signaling pathways [1, 4, 6]. One of these is the agrin-LRP4-MuSK pathway, of which several core molecules have been identified including agrin, LRP4, Musk, Dock7, and rapsyn; mice deficient in any of these fail to form synapses [7–14]. Numerous key alterations occur over the course of synaptic development, including a transformation from plaque-like AChR clusters to complex pretzel-shaped aggregates, a molecular transition from embryonic AChR gamma subunits to adult epsilon subunits, and an increase in the concentration, size, and metabolic stability of AChR clusters [15–18]. In mature NMJs, AChRs accumulate at a density estimated to be >10,000/μm^2 at the crests of

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postsynaptic folds and drops to <10/μm^2 within a few microns of the NMJ boundary in the extrasynaptic zone [2, 3, 19, 20]. This high density of AChRs at the postsynaptic membrane is required for efficient impulse transmission between the nerve and the muscle.

Several auxiliary proteins, including the DGC, play important roles in the maturation and maintenance of high density of AChR clusters at the NMJ. Over the past decades, the role of DGC intracellular proteins (dystrophin/utrophin, syntrophins, and dystrobrevins) and transmembrane and extracellular proteins (dystroglycan α and β subunits, sarcoglycans α, β, γ, and δ subunits) on the maintenance of muscle cell function have been extensively studied [1, 14, 21–25]. Genetically engineered animal models for these proteins have substantially contributed to current understanding of the mechanisms underlying the molecular pathogenesis of muscular dystrophy. However, not all mutations that disrupt DGC proteins lead to muscular dystrophy. For instance, while muscles deficient in dystrophin, dystroglycans, sarcoglycans, or α-dystrobrevin all exhibit muscular dystrophies, those deficient in α1-syntrophin or utrophin display no muscular dystrophy or alterations in muscle contractile properties [23, 26–32]. However, the neuromuscular systems in all of these mutants were affected to varying degrees. Moreover, biochemical, immunocytochemical, and bimolecular fluorescence complementation (BiFC) approaches have provided useful information about DGC protein distribution at the synapse. DGC proteins have been found to be present at both synaptic and non-synaptic areas throughout the muscle cell. At the NMJ, α-syntrophin and α-dystrobrevin1 form complexes with utrophin, rapsyn and AChRs at the crests of the post-junctional folds [24, 33–36], while dystrophin and dystroglycans are concentrated in the depths of post-junctional folds and throughout the muscle fiber surface [20, 37, 38].

DYSTROPHIN AND THE NEUROMUSCULAR JUNCTION

Dystrophin is a large 427 kDa molecule that is distributed uniformly throughout the inner side of the skeletal muscle sarcolemma and is enriched in the depths of post-synaptic folds [20, 38]. In primary muscle cultures, dystrophin is highly expressed at AChR clusters where it co-localizes with rapsyn and other cytoskeletal components [39, 40]. During development, dystrophin is found to localize at the postsynaptic apparatus after postnatal day 7 [37]. Much of what we know about the structural and functional consequences of the absence of dystrophin on the maturation and stability of NMJs comes from studies on the mdx (X-chromosome-linked muscular dystrophy) mouse, a model for muscular dystrophy in which myopathy varies with age [23, 41–43]. Affected muscles manifest abnormal morphology in the form NMJ fragmentation and decreased sarcolemma and cytoskeleton stability [15]. In adult mdx mice, AChR fragmentation was observed exclusively in regenerating muscle fibers, indicating that dystrophin is necessary for the maintenance of NMJs in regenerating muscle fibers but does not seem to affect general postnatal NMJ maturation in non-regenerating fibers [44–46]. Furthermore, mdx mice also manifest a reduction in the density and depth of post-junctional folds accompanied by altered AChR distribution, but no apparent decreases in total number of AChRs at NMJ [45, 47]. Studies by Xu et al. have shown that the degradation rate of AChRs in innervated adult mdx muscle is significantly increased, suggesting that neuronal stabilization of adult AChRs may require the presence of dystrophin or its associated glycoprotein complex [48]. However, by following the same

fluorescently labeled AChRs at NMJs overtime, it was determined that the loss of AChRs in mice deficient in dystrophin was not different from normal [49]. Other studies have further have shown significant reductions in the quantity of large AChR clusters in cultured myotubes lacking dystrophin, suggesting that dystrophin may also play a role in organizing small clusters into larger ones [45]. While some early studies attributed abnormalities in AChR clustering to be a likely secondary effect of high rates of muscle degeneration and necrosis [45, 47], more recent research has demonstrated that changes in AChR clustering are indeed a consequence of dystrophin deficiency [15]. Moreover, abnormalities in neuromuscular transmission have been observed in dystrophic mdx mice, including decreases in amplitude of miniature end-plate potentials (mEPP) with age accompanied by increases in the quantal content [50]. Such quantal content increases likely occur to counteract the mEEP decreases which result from the morphological changes observed at the NMJ [50].

UTROPHIN AND THE NEUROMUSCULAR JUNCTION

Initially called dystrophin-related protein, utrophin is a dystrophin homologue selectively concentrated at the crests of post-junctional folds in NMJs [24, 36, 51]. Studies have reported that utrophin is associated with large AChR clusters on cultured muscle cells, and that it is already found concentrated at synaptic sites at birth along with AChRs [7, 52]. Studies in utrophin-deficient mice in which the utrophin gene is targeted at the C-terminal or at the N-terminal showed that loss of utrophin had subtle effects on NMJ morphology, but no effects on function [28, 51, 53, 54]. The distribution, size, and shape of synaptic AChR clusters appear normal and are indistinguishable from NMJs in wild-type mice; muscle fibers also show no sign of dystrophy [28, 51, 53, 54]. However, fluorescence analysis revealed a ~30% decrease in the density/number of AChRs in deficient targeted C-terminal utrophin [28] and a ~40% decrease in deficient targeted N-terminal utrophin accompanied by a reduction in junctional folds [53]. Overall, however, synapses in utrn $^{-/-}$ mice form and mature normally and essential synaptic components remain concentrated at both developing and mature synapses [28, 53]. It was also reported that the number of junctional folds was apparent in the second week after birth and continued into adulthood [28]. It is also worth mentioning that in utrn $^{-/-}$ mice, the localization of most synaptic specific proteins (rapsyn, β2-syntrophin, laminin β2, agrin, and MuSK) remain intact and associated DGC proteins (β-dystroglycan, dystrobrevin, α-sarcoglycan, and dystrophin) are unaffected [28, 51]. In addition, the turnover rate of AChRs was not affected by the loss of utrophin [49]. These observations indicate that utrophin is not necessary for either the development of functional NMJs nor the localization, clustering, and the metabolic stability of AChRs and associated proteins. However, studies in mice lacking both dystrophin and utrophin (mdx/utrn $^{-/-}$) indicate that utrophin may play a compensatory role for dystrophin in mdx mice [54]. Unlike in human DMD patients, utrophin is greatly upregulated in mdx mice which leads to far less severe pathology than human DMD [54–56]. The mdx/utrn$^{-/-}$ mice, on the other hand, demonstrate phenotypes more similar to human DMD, including significantly shortened lifespan and movement difficulties [54, 56].

DYSTROGLYCANS AND THE NEUROMUSCULAR JUNCTION

The dystroglycan (DG) complex plays a central role within the DGC by linking the extracellular matrix to the cytoskeleton in skeletal muscle [22]. It includes both the transmembrane β and extracellular α isoforms, derived from a single gene [57, 58]. The β component primarily binds to utrophin/dystrophin and rapsyn [25, 59–61], while the highly glycosylated α-dystroglycan binds directly to agrin and laminins in the basal lamina, both of which play important roles in the clustering of AChRs in cultured myotubes and the formation and maturation of NMJs in vivo [7–11, 62–66]. The α-dystroglycan isoform has also been reported to mediate the assembly of basement membranes [67, 68]. Due to the unviability of complete dystroglycan knockout, in-vivo research has largely been performed on chimeric mice lacking DG in muscle cells. Studies from the Carbonetto lab have shown that DG deficient muscle cells in these mice display aberrant NMJ morphological phenotype [29]. DG-null cultured myotubes also display disorganized, unstable, and highly dispersed AChR clusters [69]. These aberrant AChR clusters were similar in appearance to clusters on myotubes treated with a monoclonal antibody to inhibit α-DG function [7]. Interestingly, in α-DG-deficient muscle cell lines, both spontaneous and agrin-induced AChR aggregates were reduced in an independent agrin-MuSK signaling mechanism, with laminins no longer accumulating at AChR clusters [70]. This suggests that dystroglycan plays a critical role in organizing and stabilizing AChR clusters with the mediation of laminin rather that agrin [29, 67, 68]. Indeed, several groups have reported that the formation of large AChR clusters can be directly stimulated by laminin [10, 71–74] via dystroglycans aggregation [72], indicating that the binding of laminin to dystroglycan is an essential aspect of synapse formation.

SARCOGLYCANS AND THE NEUROMUSCULAR JUNCTION

The sarcoglycan complex is composed of various isoforms of sarcoglycan, all of which are transmembrane glycoproteins [22]. Mutations in the sarcoglycan genes (α, β, γ, and δ) result in several versions of autosomal recessive Limb-girdle Muscular Dystrophy along with reduced expression and stability of associated DGC proteins, notably α-dystroglycan and other sarcoglycans isoforms, [30, 75, 76]. For instance, hamsters deficient in δ-sarcoglycan exhibit a reduction in α-dystroglycan expression and a complete loss of other sarcoglycan isoforms [76–78]. In contrast to the aberrant NMJs observed in muscle lacking other DGC proteins, deficiencies in γ-sarcoglycan muscles show no detectable defects in NMJ structure, including the density of AChR [21, 30, 79]. However, a recent study by Mei's group suggests that a reduction in α-sarcoglycan expression levels is associated with age-related structural alterations in the NMJ. Specifically, they found that the interaction of α-sarcoglycan with agrin receptor LRP4 is critical for LRP4 stability, and thus, overexpressing α-sarcoglycan in muscle cells mitigates age-related NMJ abnormalities by preventing the degradation of LRP4 which normally occurs in aging mice [13, 80]. The mechanism by which α-sarcoglycan acts to promote the stability of LRP4 is still unclear.

SYNTROPHINS AND THE NEUROMUSCULAR JUNCTION

Syntrophins are a family of five adapter protein isoforms encoded by separate genes (α, β1, β2, γ1, γ2) that are associated with utrophin and dystrobrevin [81]. The muscles of

mice lacking syntrophins do not display any significant histological changes or muscular dystrophy [31, 82]. Interestingly, syntrophins differ in their localization and expression profiles during the various stages of muscle development, indicating that each isoform plays a distinct role in NMJ development and maintenance [34, 83]. For instance, β2-syntrophin is found primarily in adult post-synaptic junctional fold troughs, β1-syntrophin is found mostly in the sarcolemma until 6 weeks of age [34], and α-syntrophin accumulates at the postsynaptic membrane at birth after which it clusters at junctional fold troughs alongside dystrophin and at crests with utrophin and AChRs during synaptic development [34, 81]. The observation that α-syntrophin is the only isoform that is enriched at the postsynaptic membrane at birth suggests that it may be of particular significance in the maturation and maintenance of the NMJ [34, 81].

Much research has characterized NMJs phenotype in mice deficient in single syntrophin isoforms (αKO or β2KO) and double mutants (α/β2KO). Such studies have shown that α-syn$^{-/-}$ adult mice exhibit morphologically aberrant NMJs with significant reductions in AChR density (~30% of wild type), abnormal patterning of AChR, and increased AChR turnover rate [61, 84]. Intriguingly, the absence of α-syntrophin also causes the loss of utrophin from NMJs and a significant reduction in α-dystrobrevin, particularly in its phosphorylated form [82]. Other studies have also shown that α-syntrophin is necessary for proper development of the postsynaptic apparatus [85]. Analysis of α-syntrophin deficient NMJs during muscle development revealed that synapses formed normally but matured abnormally, having a low AChR density, high turnover rate, and a reduced number of recycled AChRs, while AChRs transcript levels remained unchanged [85]. However, mice deficient in either β1 or β2 syntrophin isoforms showed normal NMJs, indicating that these isoforms play a less important role than α-syntrophin [86]. Moreover, NMJs of mice deficient in both α- and β2-syntrophin showed more structural alterations with fewer junctional folds and a significant reduction in AChR density compared with mice lacking α-syntrophin alone [83]. While abnormalities of NMJs in triple mutant mice deficient in α-, β1- and β2-syntrophins were not investigated, the levels of dystrophin and utrophin were significantly reduced suggesting that all three syntrophins are required for the insertion and stability of these proteins at the sarcolemma [86]. Furthermore, experiments involving genetic mutation of various syntrophin domains have indicated that the PH1 and PDZ domains are necessary for its proper functioning, as mutations in these domains prevent proper AChR distribution [81, 87].

DYSTROBREVINS AND THE NEUROMUSCULAR JUNCTION

Dystrobrevin is a DGC component that binds to dystrophin/utrophin and α-syntrophin [88] [89]. In muscle fibers, there are at least three forms of α-dystrobrevin (α-dbn1, α-dbn2 and α-dbn3) produced by the alternative splicing of a single gene [90]. The α-dbn3 isoform is the least studied and its function remains unclear. The α-dbn1 isoform, which is highly concentrated at the post-synaptic membrane, has a 188 amino acid C-terminus which is a substrate for tyrosine kinases, while α-dbn2 lacks these 188 residues and is instead present at high levels in extrasynaptic regions [89, 91].

The absence of α-dystrobrevin causes partial muscle dystrophy (~50%) [32] and has a dramatic effect on AChR mobility and turnover (half-life of 3 days at NMJs compared to 9–14 days in wild type) [49]. This indicates that α-dystrobrevin plays an integral role in tethering AChRs to the postsynaptic membrane. Similar to α-syntrophin, NMJs deficient in α-dystrobrevin display abnormal distributions of AChRs with frequent extensions of receptors beyond synaptic gutters, decreased density of AChRs (~30% of wild type), and small irregular receptor clusters dispersed over synaptic branches without being specifically concentrated at post-junctional crests [32, 92]. Dystrobrevin has also been demonstrated to be necessary for the stabilization of agrin-induced AChR clusters in cultured myotubes [32]. In α-dbn$^{-/-}$ mouse models, the postsynaptic membrane forms properly but matures aberrantly with postsynaptic abnormalities appearing in the first week after birth, thus suggesting that α-dystrobrevin is not essential for the initial steps of synapse formation, but rather for proper maturation later on [32]. Although both α-dbn1 and α-dbn2 accumulate at NMJs, it appears that the tyrosine phosphorylated α-dbn1 is the version involved in the maturation process of the NMJ. Expression of α-dbn1 that lacks proper tyrosine phosphorylation sites is unable to restore impaired postsynaptic structure in dystrobrevin deficient mouse muscles, while expression of the phosphorylated isoform has been shown to completely rescue abnormal synaptic phenotype [92, 93]. The phosphorylation of α-dbn1 is important for the stabilization of the postsynaptic apparatus, and anchoring of the AChRs in the synaptic membrane [94].

CONCLUDING REMARKS

Although a large body of work exists on the role of the dystrophin glycoprotein complex on the organization and stabilization of muscle integrity, several outstanding questions remain to be resolved concerning the molecular dynamics of DGC components and their association with the metabolic stability of AChRs. For instance, what is the turnover rate of synaptic DGC components? Do synaptic and non-synaptic DGC components have similar turnover rate? Does synaptic activity effect the metabolic stability of DGC components? Understanding the functional and turnover of the DGC proteins at synaptic and non-synaptic areas along with the molecular dynamics of AChRs may provide critical insights into potential treatments and pathways in the mitigation of muscle and neuromuscular related diseases.

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Highlights

- The Dystrophin glycoprotein complex and the formation and maintenance of the NMJ
- Molecular dynamics of the acetylcholine receptors (AChRs)
- The effect of the dystrophin glycoprotein complex on the maintenance of the metabolic stability of AChRs

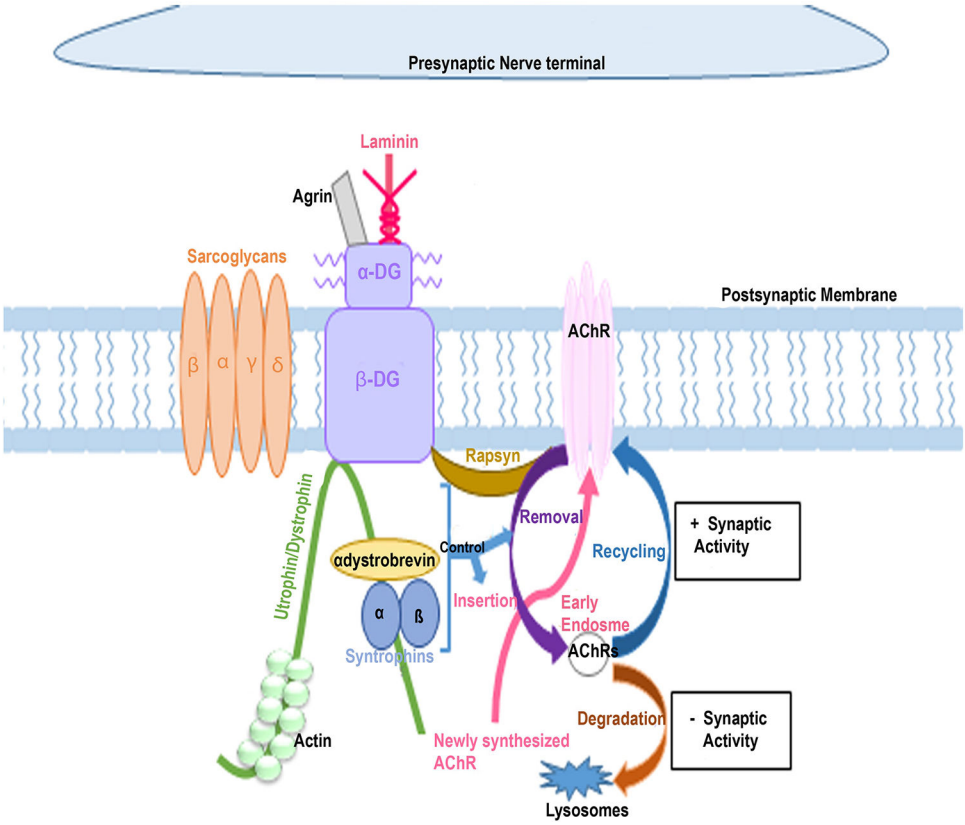

Figure:

A schematic representation of the relevant components of the dystrophin glycoprotein complex and pathways regulating the density of the nicotinic AChR at the cholinergic neuromuscular junction. The dynamics of AChR (removal, recycling, and insertion of new receptors) at synaptic sites are controlled by different events, including synaptic activity and components of the dystrophin glycoproteins complex.