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Review

A possible role of dystrophin in neuronal excitability: A review of the current literature☆

Ruben G.F. Hendriksen[a,*], Govert Hoogland[b,c], Sandra Schipper[c], Jos G.M. Hendriksen[d,a], Johan S.H. Vles[a,d,1], Marlien W. Aalbers[a,c,1]

[a] Department of Neurology, Maastricht University Medical Centre, P. Debyelaan 25, P.O. Box 5800, 6202 AZ Maastricht, The Netherlands
[b] Department of Neurosurgery, Maastricht University Medical Centre, P. Debyelaan 25, 6202 AZ Maastricht, The Netherlands
[c] School for Mental Health & Neuroscience, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands
[d] Kempenhaeghe, Centre of Neurological Learning Disabilities, Sterkselseweg 65, 5591 VE Heeze, The Netherlands

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ABSTRACT

Duchenne muscular dystrophy (DMD) is a recessive hereditary form of muscular dystrophy caused by a mutation in the dystrophin gene on the X chromosome. Clinical observations show that in addition to progressive muscular degeneration, DMD is more often accompanied by neurocognitive symptoms and learning disabilities, especially in automatisation of reading, attention processes, and expressive language skills. Additionally, three studies reported a higher prevalence of epilepsy in DMD, suggesting that the absence of dystrophin might be related to increased CNS excitability. In this article, we aim to review current clinical and experimental evidence for a potential role of brain dystrophin in seizure generation.

Contents

Abbreviations: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AQP4, aquaporin 4; BBB, blood brain barrier; BMD, Becker muscular dystrophy; CNS, central nervous system; DGC, dystrophin-associated glycoprotein complex; DMD, Duchenne muscular dystrophy; GABAA, γ-aminobutyric acid type A; Kir4.1, inwardly-rectifying potassium; nAchR, nicotinic acetylcholine receptor; NMDA, N-methyl-D-aspartate receptor; PSD, postsynaptic densities; SE, status epilepticus.

☆ The research was conducted at School for Mental Health & Neuroscience, Maastricht University, Maastricht, The Netherlands.

* Corresponding author. Tel.: +31 43 387 50 58; fax: +31 43 387 70 55.
E-mail addresses: hendriksen.ruben@gmail.com (R.G.F. Hendriksen), g.hoogland@maastrichtuniversity.nl (G. Hoogland), s.schipper@maastrichtuniversity.nl (S. Schipper), hendriksenj@kempenhaeghe.nl (J.G.M. Hendriksen), jsh.vles@mumc.nl (J.S.H. Vles), mwaalbers@gmail.com (M.W. Aalbers).

[1] These authors contributed equally to this work.

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1. Introduction

Dystrophin is a cytoplasmic protein linking cytoskeletal actin filaments to membrane proteins. A mutation in the X chromosomal dystrophin gene causes muscular degeneration known as Duchenne muscular dystrophy (DMD). This is the most common form of muscular dystrophy and the second most common genetically inherited disease, affecting approximately 1 in 3500 live male births (Anderson et al., 2002; Emery, 2002). Degeneration occurs progressively in skeletal musculature and ultimately in the heart and respiration muscles, thereby causing premature death (Melacini et al., 1996; Sussman, 2002).

In addition to muscular tissue, dystrophin is also expressed in the retina, kidney, and central nervous system (CNS) (Ahn and Kunkel, 1993). Consequently, DMD patients do not exhibit brain dystrophin (Boyce et al., 1991; Kim et al., 1995) thereby potentially affecting brain function (Chamberlain et al., 1988). Duchenne De Boulogne already described cognitive limitations in boys with DMD (Duchenne, 1868). General intelligence among boys with DMD is one standard deviation below the normal population mean IQ and mental retardation has been reported in approximately one third (34.8%) of patients with DMD (Cotton et al., 2001). Moreover, boys with DMD more often have ADHD (present in 11.7%), autism spectrum disorder (3.1%) and reading problems (20% moderate, 20% severe reading problems) (Cotton et al., 2001; Hendriksen and Vles, 2006, 2008; Snow et al., 2013). Dystrophin mutations can even cause intellectual disability in the absence of muscular dystrophy (de Brouwer et al., 2014). These cognitive deficits do not seem to depend on the location of the gene mutation; hence a clear genotype-phenotype correlation for cognitive impairment has yet to be established (Anderson et al., 2002, 2012; Waite et al., 2012). The gene encodes several dystrophin isoforms and therefore the number of affected gene products or cell-type specific isoforms may correlate with the occurrence and severity of cognitive impairment (Perronnet and Vaillend, 2010; Taylor et al., 2010; Waite et al., 2012).

In addition to cognitive dysfunction, epilepsy is more often reported in patients with DMD (Etemadifar and Molaei, 2004; Goodwin et al., 1997; Pane et al., 2013). This observation suggests that reduced brain dystrophin levels facilitate neuronal excitability. In the current paper we discuss the role of dystrophin in normal CNS functioning and the molecular mechanisms that may underlie the possible association between DMD and epilepsy.

2. The dystrophin gene

The dystrophin gene (DMD) is one of the largest human genes, comprising almost 0.1% of the genome (Koenig et al., 1987) and consisting of 79 exons (Roberts et al., 1993) that code for a primary transcript of 2400 kilobases. Its size causes a high mutation probability, so nearly one third of DMD cases are non-familial (Barbujani et al., 1990). The dystrophin gene is particularly complex and contains at least eight independent and tissue-specific promoters. The full-length dystrophin isoform for instance, is transcribed from three independently regulated promoters labeled as B (brain), M (striated muscle), or P (Purkinje cell), the respective letters reflecting the major sites of expression (Blake et al., 2002). Thus, independent machinery exists to regulate dystrophin transcription in the CNS (Lidov et al., 1993).

DMD can be caused by a variety of mutations in the dystophin gene, resulting in the loss of the full-length (427 kDa) dystrophin isoform (Ervasti and Campbell, 1991). Full-length dystrophin can be subdivided in a brain and a muscle isoform, differing in one alternatively spliced exon (Lidov et al., 1993). Apart from the full-length dystrophin isoforms, five additional isoforms exist due to splicing of the dystrophin RNA. These additional isoforms are named according to their respective molecular weights: Dp260 (predominantly expressed in the retina), Dp140 (expressed in CNS and kidney), Dp116 (detected in the peripheral nervous system), Dp71 (expressed in most tissues but not in muscle), and Dp40 (expressed in the brain) (Ahn and Kunkel, 1993; Austin et al., 2000; Bar et al., 1990; Goodwin et al., 1997; Tozawa et al., 2012). The Dp71 isoform can undergo several alternative splicings, resulting in different Dp71 isoforms, all with potentially different functions (Austin et al., 2000).

3. The dystrophin protein in muscle

Muscle dystrophin is localized at the cytoplasmic face of the sarcolemma membrane. Full-length dystrophin (Dp427) consists of an N-terminal actin-binding domain, a central large rod-like domain composed of spectrin-like repeats, and a cysteine rich C-terminus that is connected to the dystrophin-associated glycoprotein complex (DGC), a large protein complex that forms a critical link between the cytoskeleton and the extra-cellular matrix (Ehmsen et al., 2002). Next to dystrophin, this complex consists of dystroglycan (α and β), sarcoglycan (α, β, γ, and δ), sarcospan, syntrophin (α1, β1, β2, γ1, γ2), and α-dystrobrevin (Durbeej and Campbell, 2002). Alpha and beta dystroglycan (dystrophin-associated glycoprotein) bind laminin, a component of the basal lamina, and dystrophin respectively, thereby providing a link between the cytoskeleton and the extracellular matrix. Sarcoglycan is the second transmembrane component of the DGC. On the cytoplasmatic side, the sarcolemma DGC, through dystrophin, interacts with syntrophin and α-dystrobrevin. These latter proteins recruit scaffolding proteins onto which signaling proteins and ion channels are anchored in the membrane (Waite et al., 2009). In this way, the DGC both provides a physical and functional connection between the internal and external environment of the muscle cell. In DMD, the absence of dystrophin results in destabilization of the DGC and in secondary changes of the components of the DGC, thereby prohibiting protection against the enduring mechanical stress of muscle contraction and relaxation (Blake and Kröger, 2000).

4. The dystrophin protein in brain

In terms of quantity, brain dystrophin levels are only 10% of the levels found in muscle, yet in terms of variability brain tissue expresses many more different isoforms (Anderson et al., 2012; Gorecki and Barnard, 1995). Within the brain, dystrophin is primarily located in the hippocampus, prefrontal cortex, and cerebellum (Chamberlain et al., 1988; Lidov et al., 1993). Other major brain structures such as the thalamus, hypothalamus, basal ganglia, the majority of the brainstem, and spinal cord seem devoid of dystrophin (Lidov, 1996). Analogous to muscle tissue, dystrophin is part of the DGC in the brain where it has been shown in both neurons and glia. However, contrary to muscle DGC, several brain DGC variants exist because of the various dystrophin isoforms, alternatively spliced variants, and the presence of other DGC components, such as β-dystrobrevin, ε-sarcoglycan, and the γ-syntrophins, which are not expressed in muscle. Brain DGC is therefore often referred to as DGC-like (Waite et al., 2009, 2012).

Dystrophin isoforms are expressed in a cell-specific manner; e.g. Dp427 is localized postsynaptically in neurons, Dp140 appears to be associated with microvascular glia cells, i.e. glia cells that are part of the neurovascular unit (Blake and Kröger, 2000; Graciotti et al., 2008; Lidov et al., 1995), Dp116 is mainly present in Schwann cells of peripheral nerves, and Dp71 (a.k.a. G-dystrophin) is the most abundant dystrophin gene product in the brain that is both expressed in neurons and glia (Austin et al., 2000). The functions