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Duchenne Muscular Dystrophy and Brain Function

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1. Introduction

Muscular dystrophies have historically been characterised according to clinical criteria, however in the genomic age the muscular dystrophies are now subdivided into groups according to the primary gene defect. Currently identified are 29 different loci and encoded proteins, giving rise to 34 distinct forms of muscular dystrophy (Dalkilic & Kunkel 2003; Hsu 2004). The majority of these types of muscular dystrophy are caused by perturbations of different components of the dystrophin-glycoprotein complex (DGC) an integral component of the cellular cytoskeleton (see below). Dystrophin is the largest component of the DGC and is absent in Duchenne muscular dystrophy (DMD), and severely truncated with decreased levels in Becker muscular dystrophy (BMD) (Hoffman & Kunkel 1989). DMD and the allelic BMD are the most common forms of muscular dystrophy in humans and together they are termed dystrophinopathies (Kingston et al. 1984; Shaw & Dreifuss 1969). DMD alone accounts for approximately 80% of all the myopathies in the muscular dystrophy group (Culligan et al. 1998). The dystrophin gene is the second largest described to date, totalling 1.5% of the X chromosome, 0.1% of the entire genome. The DMD gene is 99% introns, with a coding sequence of 86 exons (including the promoters) and remains the only known human metagene (Blake et al. 2002; Burmeister et al. 1988; Hamed & Hoffmann 2006; Kenwrick et al. 1987; Koenig et al. 1987; Kunkel et al. 1986; Muntoni et al. 2003; Roberts et al. 1993; Smith et al. 2006; Van Ommen et al. 1987; Wallis et al. 2004). Dystrophin was demonstrated to be localised at the sarcolemma in human skeletal muscle after its' genetic characterisation (Arahata et al. 1988; Sugita et al. 1988; Zubrzycka-Gaarn et al. 1988). This discovery was followed by a report of dystrophin messenger RNA in brain, with the protein being specifically localised at postsynaptic densities (PSD) in the CNS, in particular in the hippocampus, cerebral cortex and in cerebellar Purkinje cells (PC) (Chamberlain et al. 1988; Chelly et al. 1988, 1989; Lidov et al. 1990, Nudel et al. 1988).

From the earliest reports authors have noted a preponderance of cognitive impairment in the Duchenne population and it has been well established that the average IQ of the boys with DMD is 85, one standard deviation below the normal of 100 (Cotton et al. 2005). With a greater understanding of the underlying molecular biology i.e. genotype, the recognised phenotype of dystrophinopathies is expanding (Beggs 1997; Emery 2002, 2002a; Ferlini et al. 1999; Muntoni et al. 1993). More recently investigations into the role of these proteins in the

CNS have commenced. In contrast to skeletal muscle, the function of dystrophin in brain is less well understood in part due to its more recent discovery in the CNS as well as the greater complexity of the dystrophin gene products and DGCs in this location (Culligan et al. 2001). It has been suggested that dystrophin may play a role in anchoring the postsynaptic apparatus, receptor channel clustering and membrane organization (Lidov et al. 1993). This anchoring of molecules, critical for neuronal function, may be achieved by dystrophin/DGC acting as adaptors between the actin cytoskeleton and membrane bound receptors (Yoshihara et al. 2003). It may also play a critical role in the formation and maintenance of macromolecular signalling complexes (Tokarz et al. 1998; Yoshihara et al. 2003). Dystrophin has also been suggested to play a role in stabilizing the postsynaptic apparatus to maintain a certain status of the network after brain maturation and/or episodes of synaptic plasticity (Brunig et al. 2002). Calcium levels have been found to be abnormal in neurons from an animal model of DMD (*mdx* mouse), and in a situation analogous to muscle, this could make these cells more susceptible to necrosis (Culligan et al. 2001). In summary, dystrophin deficiency may significantly alter membrane integrity, ion channel physiology, calcium homeostasis, regional cellular signal integration and structural reorganisation at the synapse (Mehler 2000; Vaillend & Billard 2002; Vaillend et al. 2004). The majority of recent studies support a role for dystrophin in organisation of the mature synapse – particularly GABA-ergic synapses under dynamic conditions. Below is a brief summary of the localisation of dystrophin/DGC in the CNS and a synthesis of the current literature investigating the role of dystrophin in human and murine CNS at the behavioural, morphological, biochemical and electrophysiological level.

1.1 The dystrophin-glycoprotein complex in CNS

Individual members of the DGC show a variety of site-specific specializations leading to many different DGCs (differentiated by binding-partner profile, localization and composition) existing in the CNS. Differences exist between the DGC in muscle and neuromuscular junction and also between both of these DGCs and brain DGCs. Additionally, individual members of the DGC play different roles at different sites. In the brain, unlike in muscle, the association of syntrophin with dystrophin is not crucial for DGC formation (Moukhles & Carbonetto 2001; Waite et al. 2009). Furthermore, Culligan & Ohlendieck (2002) have suggested that the brain DGC consists of four main components, the dystroglycan subcomplex, a dystrophin or utrophin gene product, a dystrobrevin isoform and a syntrophin subcomplex (Fig.1). Complexes including short dystrophin gene products together with syntrophin may also be expressed in both neurons and glia.

A role for the DGC in CNS has been suggested by many investigators, yet unequivocal evidence has yet to emerge. One theory suggests a role for the DGC in cellular communication by acting as a transmembrane signalling complex (Muntoni et al. 2003; Petrof 2002; Rando 2001). Supportive evidence for this theory is seen when mutations of the DGC component genes leads to cell death, thought to be due to a disruption of cell survival pathways and cellular defence mechanisms, both of which are regulated by signalling cascades (Muntoni et al. 2003; Rando 2001). The DGC in CNS may also play a dual function: incorporating both membrane stabilization as well as transmembrane signalling, as has been demonstrated at the neuromuscular junction (Albrecht & Froehner 2002). Additionally, the DGC has been suggested to play a role in the structural/functional organisation and/or stabilization of synapses (Albrecht & Froehner 2002). Dystroglycan and dystrophin, as

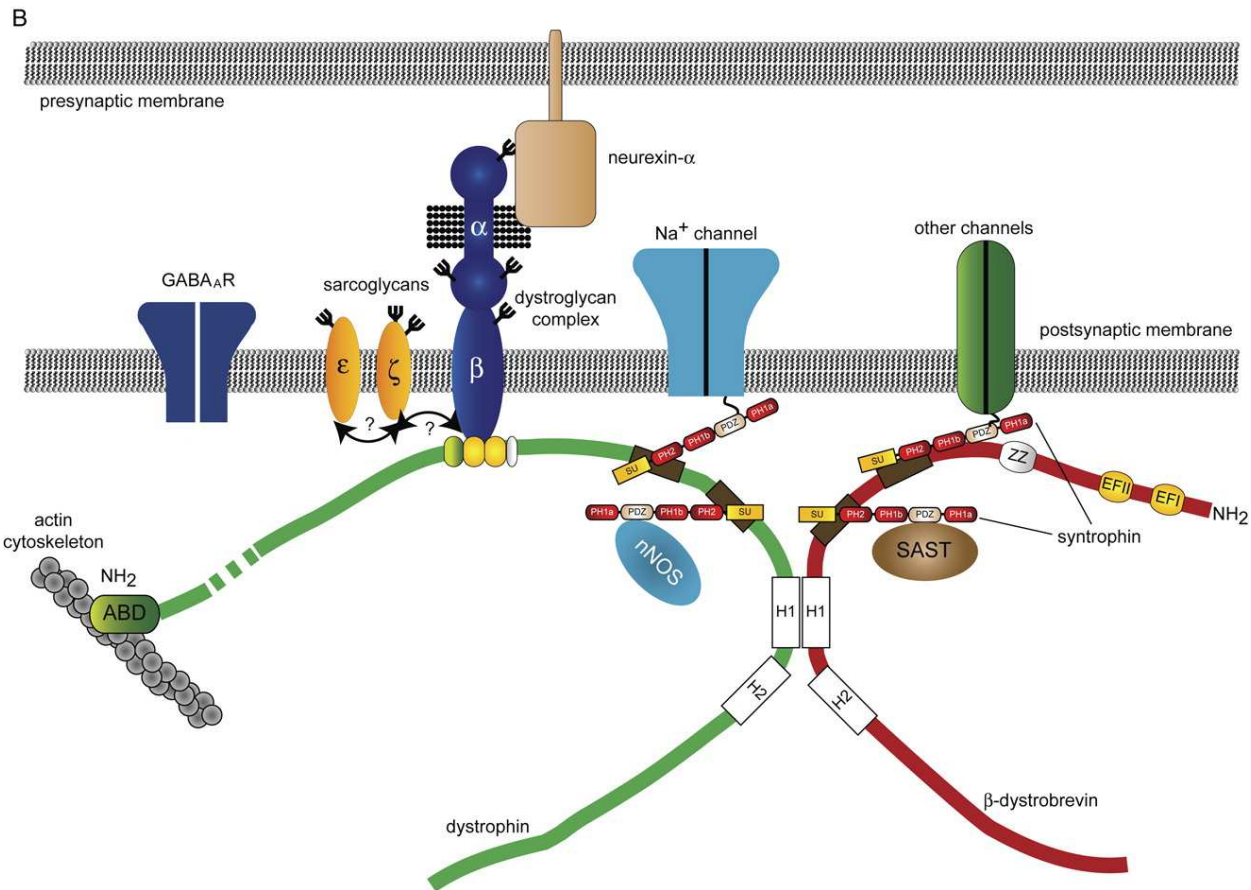


Fig. 1. The molecular organization of the “DGC-like” complexes and associated proteins in neurons (Modified from Waite et al. 2009).

central components of DGCs, have been implicated in the stabilisation of neurotransmitter receptor clusters e.g. GABAergic and cholinergic afferents (Knuesel et al. 1999; Zaccaria et al. 2001). It has been suggested that the DGC may act as a cytoskeletal scaffold on which signalling complexes as well as transmembrane proteins can be assembled and clustered, largely mediated by the syntrophins and dystrobrevins (Albrecht & Froehner 2002; Cavaldesi et al. 1999; Connors et al. 2004; Gee et al. 1998; Hashida-Okumura et al. 1999). Culligan and Ohlendieck (2002) propose that the extracellular component of neuronal DGCs mediates cellular signalling through interactions of specific proteins such as laminin, laminin $\alpha 2$, perlecan, agrin and biglycan. These interactions are believed to play a role in terminal consolidation, integrity and maintenance. Ceccarini et al. (2002) postulate that the DGC may play a role in the neuronal maturation process i.e. in morphological and functional modifications such as neurite outgrowth and synapse formation. Levi et al. (2002) suggest that the DGC may act as a trans-synaptic signal for some aspects of signalling involved in central neuron synaptic differentiation (Levi et al. 2002).

2. Dystrophin and the CNS

2.1 Localization

Dystrophin expression in the CNS is significantly more complicated compared to muscle due to the site specificity, developmental expression and diversity of gene products in this

tissue. Levels of dystrophin in the brain are approximately 10% of those found in muscle. However, the CNS has the highest number of different dystrophin gene products of any other organ/tissue in the body (Abdulrazzak et al. 2001; Gorecki et al. 1991, 1992; Gorecki & Barnard 1995; Tokarz et al. 1998). Early studies indicated that in the CNS dystrophin localises primarily to the vascular endothelium, postsynaptic regions, pia and choroid plexus (Kamakura et al. 1994; Lidov et al. 1990; Uchino et al. 1994). Later studies demonstrated that Dp71 a smaller gene product of the dystrophin gene, is present in the wall of blood vessels, but is actually expressed in perivascular astrocyte endfeet (Ueda et al. 2000). Nudel et al. 1998, Chelly et al. (1988 and 1989) and Chamberlain et al. (1988) found dystrophin messenger RNA in brain and suggested that the lack of dystrophin in DMD may be the cause of cognitive impairment known to exist in this population. Lidov et al. (1990) demonstrated that dystrophin was specifically localised at postsynaptic densities (PSD) in the CNS, in particular in the hippocampus, cerebral cortex and in cerebellar Purkinje cells (PC) in rodents. This is in agreement with others who also found Dp427 as well as Dp71 enriched at the PSD (Blake et al. 1999; Jung et al. 1993; Kim et al. 1992; Moukhles & Carbonetto 2001). Uchino et al. (1994) confirmed these findings of PSD localisation in humans in agreement with Kim et al. (1995) and Jancsik & Hajos (1998). This latter group found that dystrophin was in the spines of neurons, with particularly heavy labelling at the PSD (Jancsik & Hajos 1998). There are now known to be three full-length dystrophin gene-products found in the CNS: M-dystrophin has been found in cerebral cortex and hippocampus (CA1, CA2 and CA3), C-dystrophin has also been localised to the cortex (grey matter, parietal layers II-IV, cingulate cortex) and hippocampus (pyramidal layer, layer II of infralimbic cortex, striatum radiatum and striatum oriens). C-dystrophin has also been demonstrated to be present in brainstem (inferior olive and trigeminal complex) and the midbrain (Caudate putamen). The third full-length dystrophin gene product P-dystrophin has been found in foetal cerebral cortex and Purkinje cells from early in the developmental process. Full-length dystrophin gene products are expressed almost exclusively in neurons (Lidov et al. 1990; Waite et al. 2009). The shorter dystrophin-gene products have a nomenclature of 'Dp' followed by their molecular weight: Dp 260 (D'Souza et al. 1995) Dp 140 (Lidov et al. 1995), Dp 116 (Byers et al. 1993; Schofield et al. 1994) and Dp71 (Blake et al. 1992; Iannello et al. 1991; formerly named apo-dystrophin 1 or G-dystrophin). Dp260 is found predominately in the retina (also brain and cardiac tissue) (Cibis et al. 1993; Costa et al. 2007; D'Souza et al. 1995; Pillers et al. 1993). Dp140 is predominately expressed in brain during foetal development and at very low levels in the adult brain, localised to astro-glial processes, vascular endothelium and leptomeningeal surfaces (Bardoni et al. 2000; Lidov et al. 1995). Dp 116 has been localised to adult peripheral nerves, along the Schwann cell membrane and fibroblasts (Byers et al. 1993; Labarque et al. 2008). Dp71 is expressed in a variety of tissues, predominately the CNS (where it is the most abundant dystrophin gene product), it has multiple isoforms each with specific subcellular localisations (Austin et al. 1995, 2000; Bar et al. 1990; Blake & Kroger 2000; Ceccarini et al. 2002; Chamberlain et al. 1988; Greenberg et al. 1996; Holder et al. 1996; Huard et al. 1992; Ilarraza-Lomeli et al. 2007; Lederfein et al. 1992; Miyatake et al. 1991; Rapaport et al. 1992). Dp71 has been localised to hippocampus (CA1 and dentate gyrus), olfactory bulb as well as perivascular astrocyte feet (Daoud et al. 2009). Figure 2 (modified from Blake et al. 2002) is a schematic diagram of the structure of dystrophin gene products. The basic structure consists of four main domains:

- i. the N terminal which shares similarities to α -actin and has an actin-binding domain (Byers 1989; Fabbrizio et al. 1995; Koenig et al. 1988).
- ii. a central rod domain with 24 spectrin-like triple helical repeats conferring an extended rod shape interrupted by four proline-rich spacer domains thought to act as hinges and conferring flexibility (Arahata et al. 1988; Cross et al. 1990; Koenig & Kunkel 1990, Michalak & Opas et al. 2001; O'Brien & Kunkel 2001; Roberts 2001).
- iii. Cysteine-rich domain, separated from the rod domain by a WW domain (a protein-binding module found in several signalling and regulatory molecules). The cysteine-rich domain encompasses the EF1, EF2 and ZZ domains which together are termed the dystroglycan-binding domain. Following the ZZ domain is an α -helical domain important in mediating interactions with syntrophin (Bork & Sudol 1994; Huang et al. 2000; Ishikawa-Sakurai et al. 2004; Jung et al. 1995; Ponting et al. 1996; Rentschler et al. 1999; Suzuki et al. 1994; Winder et al. 1995).
- iv. The C-terminal domain which contains binding sites for some dystrophin-associated glycoproteins, as well as putative sites for endogenous protein kinases to act upon (Lederfein et al. 1993; Michalak & Opas et al. 2001; Milner et al. 1993; Zubrzycka-Gaarn et al. 1988).

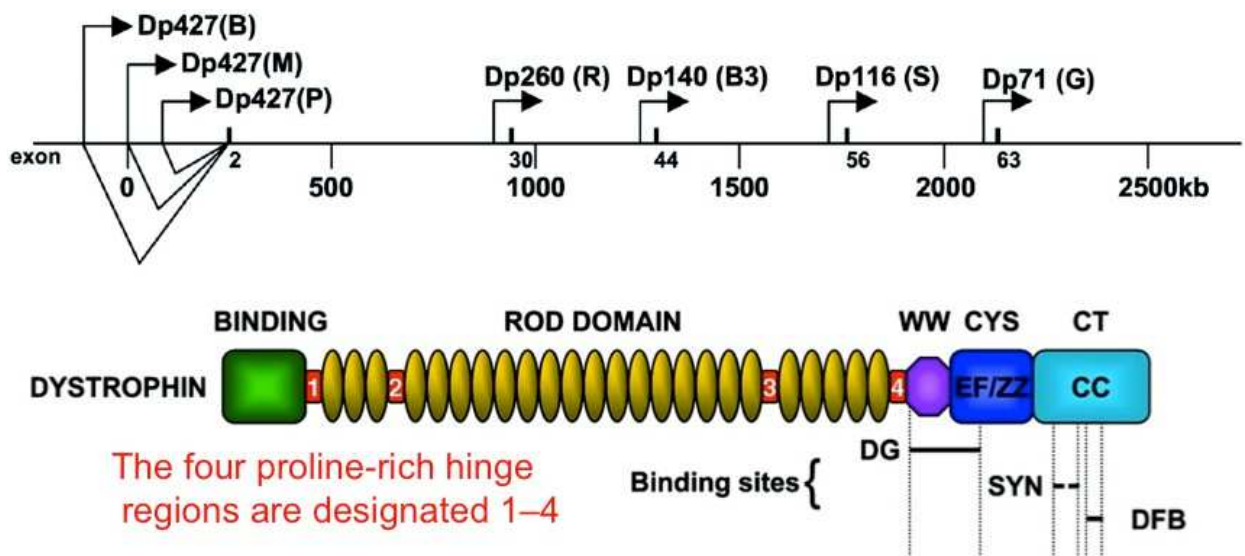


Fig. 2. Schematic showing the organization of the human Duchenne muscular dystrophy (DMD) gene and the dystrophin-related protein family (Modified from Blake et al. 2002).

3. Functional evidence of CNS aberrations in dystrophinopathy

Since the original description of the disease by Duchenne (1868) in which he reported five patients with some degree of cognitive impairment there has been debate as to whether there is a cognitive deficit associated with DMD. A meta-analysis of 32 studies comprising of 1224 patients with DMD with full-scale IQ data available for 1146 DMD patients reported an average IQ of 80.6 (SD 19.3), which was statistically different from the normal population average (Cotton et al. 2001). In this sample 35% of boys had an IQ lower than 70. Of these 79% were characterized as mild, 19% moderate, 1% severe and 0.3% profound (Cotton et al. 2001).

The importance of cognitive impairment in DMD has been demonstrated by a number of reports detailing developmental delay as the first presentation of disease (Essex & Roper 2001;

Kaplan et al. 1986; Mohamed et al. 2000; Smith et al. 1989). Specific subsets in cognitive ability which have been found to be affected in DMD/BMD include: memory/attention/recall (for patterns, numbers and verbal labels, serial position), verbal learning, language/verbal skills/confrontational naming, phonological and graphophonological production, reading, visuospatial organization skills, writing/spelling, comprehension/receptive language, mathematics, locomotor areas, verbal expression/fluency and conceptual ability (Anderson et al. 1988; Billard et al. 1992, 1998; Bresolin et al. 1994; Cotton et al. 1998; D'Angelo & Bresolin 2003; Dorman et al. 1988; Hendriksen & Vles 2006; Hinton et al. 2000, 2001; Karagan et al. 1980; Ogasawara 1989; Palumbo et al. 1996; Savage & Adams 1979; Smith et al. 1989, 1990; Sollee et al. 1985; Whelan 1987). Recent evidence suggests that children with DMD may have a distinct language-based learning deficit, similar to that seen in developmental dysphonetic-dyseidetic dyslexia i.e. problems with phonic analysis and synthesis of words as well as perception of the visual shape of words (Billard et al. 1992, 1998; Cotton et al. 2001). A number of investigators have hypothesized that the cerebellum plays an important role in the manifestation of cognitive deficits in dystrophinopathies (Cyrułnik & Hinton 2008; D'Angelo & Bresolin 2003; Hendriksen & Vles 2006).

Individual studies finding a difference between verbal and performance IQ include Karagan & Zellweger (1976), Karagan & Zellweger (1978), Karagan (1979), Glaub & Mechler (1987), Bresolin et al. (1994), Roccella et al. (2003), and Ogasawara (1989a). In a more recent meta-analysis VIQ and PIQ data was available for >800 children with VIQ = 80.4 +/- 18.8 (SD, n=881) and PIQ 85.4 +/- 16.9 (SD, n=878), both significantly different from the normal population. The discrepancy in VIQ and PIQ was -5.1 +/- 14.4 (SD, n=877). The mean was significantly different from zero but the distribution did not differ significantly from normal and was less than 10, the figure thought to establish clinical significance (Cotton et al. 2001, Wechsler 1997). Although there is a statistical difference between these IQ scores the functional significance is negligible.

Gauld et al. (2005) investigated the influence of IQ on the ability of children with DMD to perform spirometry, as well as assessing the impact of specific interventions for improvement. They found that the mean IQ was 84.7, PIQ 90.6 and VIQ 85.6 in 47 boys tested (mean age 12.6 years). The mean parent reported oppositional behaviour score was 56.3 (range 39 - 87) and mean teacher reported oppositional behaviour score was 56.9 (range 45 - 90) (higher scores on the scale correlate to children more likely to break rules, have problems with authority and who are easily annoyed) (Conners 2000). The oppositional behavioural scores remained stable over a 2.3 year period with a test-retest reliability of $r = 0.54$ (parent-rated) and $r = 0.6$ (teacher-rated), $P < 0.001$ for both (Gauld et al. 2005). They found that the results of spirometry testing were related to the individuals' performance IQ and can be explained by difficulties in understanding or learning to perform the technique required. The use of computer visualised incentives led to an improvement in function of spirometry testing in those shown to have a moderate intellectual or behavioural disturbance (Gauld et al. 2005). Additionally, Uchikawa et al. (2004) found in a group of 7 - 14 year old boys with DMD living in the community, that motor scores were higher in those with good cognitive functioning compared to those with impaired cognitive functioning, even though muscle strength was not significantly different. The authors note that poor cognitive functioning has an adverse effect on activities of daily living in DMD and that this impacts training and performance of these activities. These studies demonstrate the importance of paying attention to the cognitive functioning of individual patients with

DMD, as specific interventions can lead to improved symptom management and quality of life.

The search for a clear genotype-phenotype correlation with the degree of cognitive impairment has been confusing with conflicting reports. A recent study has brought some clarity to this issue. Taylor et al. (2010) have demonstrated that there is a quasi dose-response i.e. the cognitive impairment increases with cumulative loss of dystrophin gene products. A number of studies have suggested a higher incidence of a variety of neuropsychiatric deficits in boys with DMD compared to normal including dysthmic and major depressive disorders, anxiety, attention deficit hyperactivity disorder, obsessive-compulsive disorder and autism spectrum disorder (Fitzpatrick et al. 1986; Hendriksen & Vles 2008; Komoto et al. 1984; Melo et al. 1995; Poysky 2007; Reid & Renwick 2001; Roccella et al. 2003; Sekiguchi 2005; Wu et al. 2005; Young et al. 2008; Zwaigenbaum & Tarnopolsky 2003). As yet Reid & Renwick (2001) have been the only investigators to demonstrate an effect of decreased IQ on mental health in the dystrophinopathies, with no reports to investigate if the converse is true.

3.1 Morphological evidence of a CNS deformity in dystrophinopathy

Morphological studies of the CNS in dystrophinopathy have been inconsistent with some investigators reporting no or minimal changes (Bresolin et al. 1994; Dubowitz and Crome 1969; Rae et al. 1998), cerebral atrophy in later stages of disease (Al-Qudah et al. 1990; Yoshioka et al. 1980), abnormalities in dendritic development and arborisation in visual cortical neurons with extensive Purkinje cell loss (Jagadha & Becker 1988) and pachygyria (Bandoh et al. 1987; Rosman & Kakulas 1966; Wibawa et al. 2000). Some investigators have found a link between morphological abnormalities and impaired cognitive function (Bandoh et al. 1987; Bresolin et al. 1994; Rosman & Kakulas 1966; Septien et al. 1991; Wibawa et al. 2000; Yoshioka et al. 1980), whilst others have not (Al-Qudah et al. 1990).

Sogos et al. (1997) disrupted the expression of dystrophin in human neuronal cultures using *in vitro* techniques. They found a disruption of the morphology of synaptic boutons with alteration of the neuronal cytoskeleton in these cells. This also assessed whether a lack of dystrophin would lead to any perturbations of neuronal NOS (*n*NOS) using similar techniques (Sogos et al. 2003). They found that *n*NOS messenger RNA was significantly decreased (~ 35%) in neurones treated with B-dystrophin antisense. These authors postulated that decreased *n*NOS in neurons deficient for dystrophin may be responsible for alterations in synaptic plasticity (due to known association between *n*NOS and the NMDA receptor). Alternatively, the involvement of *n*NOS in CNS development may mean any perturbation could lead to altered neuronal maturation and abnormal synaptogenesis in developing neurons (Sogos et al. 2003).

3.2 Biochemical evidence of a CNS abnormality in dystrophinopathy

The search for the biochemical mechanisms underlying the cognitive deficit associated with lack of dystrophin in humans has been necessarily limited, however, new technologies allowing *in vivo* analysis has enabled some investigations. Not surprisingly oxygen and carbon dioxide levels have been found to be abnormal (especially during sleep), thought to be due to weakened respiratory function secondary to underlying muscle weakness and rib

cage deformation (Khan & Heckmatt 1994; Manni et al. 1991; Misuri et al. 2000; Smith et al. 1988). Glucose hypometabolism has been studied by a number of groups as it is a common feature of disorders with associated cognitive deficits, and is generally indicative of lowered synaptic activity (Jueptner & Weiller 1995). Bresolin et al. (1994) found decreased glucose uptake in the cerebellum in DMD boys using PET imaging. Lee et al. (2002) using PET and MRI found four clusters of decreased glucose metabolism in DMD: medial temporal structures and cerebellum bilaterally, the sensorimotor and lateral temporal cortex on the right side (compared to an adult control group). The authors suggest that these findings may reflect local cytoarchitectural changes and abnormalities associated with altered neural development. Tracey et al. (1995), Kato et al. (1997) and Rae et al. (1998) using magnetic resonance spectroscopy and autopsy studies (Kato et al. 1997) focussed on choline-containing compounds which are seen to be elevated in a number of brain disorders and interpreted as symptomatic of increased membrane turnover or decreased membrane stability (Rae et al. 1998). MRI demonstrated significantly increased choline-containing compounds in the cerebellum, but not the cortex of boys < 13 years (Rae et al. 1998). The ratio of choline-containing compounds to N-acetylaspartyl-containing compounds (Cho/NA) was shown to correlate significantly with scores on the Matrix Analogies Test (MAT). The cerebellar and hippocampal focus of the biochemical lesions in DMD are of interest, due to the normally high expression of dystrophin in neurons found in these regions (Bresolin et al. 1994; Lee et al. 2002; Rae et al. 1998). Both Dorman et al. (1988) and Billard et al. (1998) noted that the reading deficits seen in DMD patients are similar to those seen in phonological dyslexia (Castles & Coltheart, 1993). Persons with phonological dyslexia, either developmental (Nicolson et al. 1999; Rae et al. 1998) or acquired (Levisohn et al. 2000), have been shown to have abnormalities in the right cerebellum. Similarly, deficits in verbal working memory, a large component of the DMD cognitive deficit (Hinton et al. 2001) are known to have a cerebellar focus (Desmond et al. 1997).

3.3 Electrophysiological evidence of a CNS abnormality in dystrophinopathy

EEG abnormalities have been reported in DMD although the only large study with appropriate controls (Barwick et al. 1965) found no association between abnormal EEG and dystrophinopathy. To date no studies have examined genotypically confirmed DMD and EEG abnormalities although an increased incidence of epilepsy has been noted in boys with dystrophinopathies compared to the general population (Etemadifar & Molaei 2004; Goodwin et al. 1997). Motor cortex excitability has also been demonstrated to be affected in DMD with reduced excitability thought to be due to aberrant synaptic functioning (Bresolin et al. 1994; Di Lazzaro et al. 1998; Jueptner & Weiller 1995).

4. Evidence from animal models of dystrophinopathy: the *mdx* mouse

The *mdx* mouse (*muscular dystrophy X-linked*) is the most widely studied animal model of dystrophinopathy (Collins & Morgan 2003; Durbeej & Campbell 2002; Partridge 1991). Although its discovery predated the genotyping of this disorder it has since been proven to be an appropriate model with identification of a premature stop codon terminating translation of murine dystrophin resulting in an absence of all full-length dystrophin-gene products (Bulfield et al. 1984; Chamberlain et al. 1987; Hoffman et al. 1987; Sicinski et al. 1989). This mouse model has aided in investigations of the function of dystrophin,

particularly in the CNS as invasive functional investigations can be carried out on these animals. The majority of current knowledge of the role of dystrophin in the CNS comes from this animal model.

4.1 Cognitive functioning

Impairments in passive avoidance learning, long-term recognition memory and procedural learning have all been shown to be adversely affected in *mdx* mice compared to controls. Task acquisition, procedural memory spatial discrimination tasks, novelty-seeking behaviour and exploration in an elevated plus maze have all been shown to be unaffected in the *mdx* mouse (Mehler et al. 1992; Muntoni et al. 1991; Perronnet & Vaillend 2010; Sesay et al. 1996; Vaillend et al. 1995, 1998, 1999, 2004). Most recently Sekiguchi et al. (2009) have demonstrated an enhanced defensive freezing response to a brief restraint as well as enhanced unconditioned and conditioned defensive responses to electrical footshock in *mdx* mice compared to wildtype. This abnormal behaviour was ameliorated with intracerebroventricular administration of antisense morpholino oligonucleotide (which induces skipping of the premature stop codon located at exon 23 in the *mdx* mouse and produces a truncated dystrophin with a 71 amino acid deletion in the mid-rod domain) (Alter et al. 2006; Sekiguchi et al. 2009).

4.2 Morphology

No gross abnormalities in brain or spinal cord in the *mdx* mouse have been found (Bulfield et al. 1984; Dunn & Zaim-Wadghiri 1999; Torres & Duchenne 1987; Yoshihara et al. 2003). This was most recently confirmed using MRI by Miranda et al. (2009) who found no major alteration of brain anatomy in *mdx* mice, reporting no significant changes in the cortex, hippocampus or cerebellum (normally dystrophin-positive). At the cellular/axonal level dystrophin has been found to localise to the cell membrane, predominately the soma and postsynaptic densities particularly in hippocampus, neocortex, cerebellum and amygdale (Anderson et al. 2002; Lidov 1996; Perronnet & Vaillend 2010). Anatomical alterations have been found in the *mdx* mouse in various brain regions including decreased cell number, altered cell packing density and changes in cell morphology (Carretta et al. 2001; Sbriccoli et al. 1995). It should be noted that these changes were not demonstrated when investigated in the hippocampus. CA1 pyramidal cell packing density, mean nuclear area and circularity has been found to be unaltered in *mdx* mice (Miranda et al. 2009). PSD length of axospinous perforated excitatory synapses has been found to be larger in *mdx* proximal radiatum of the hippocampus (Miranda et al. 2009). These authors note that perforated synapses are the hallmarks of activity dependent synaptic plasticity (Miranda et al. 2009). A more recent report by this group has demonstrated that the presynaptic ultrastructure of excitatory hippocampal synapses is altered in both *mdx* and Dp71-null mice (Miranda et al. 2011). Again examining the proximal radiatum glutaminergic synapses (normally dystrophin-positive) they report an increased number of docked vesicles, with the number and size of vesicles similar in *mdx* mice compared to controls. They also found a decrease in the number of vesicles in the 'reserve pool' i.e. > 300nm away from the synapse) in *mdx* mice compared to controls. In the Dp71-null mice they found that the number and spatial distribution of vesicles was no different from control (Miranda et al. 2011). In contrast to Dp427-null (*mdx*) mice the number of vesicles in the active zone was decreased and the number of vesicles in

the reserve pool was increased compared to controls, whilst the number of docked vesicles remained the same. Alterations in parvalbumin-positive and calbindin-positive interneurons (both calcium binding proteins) have been demonstrated to be significantly increased in particular brain regions of *mdx* compared to wildtype (Carretta et al. 2003, 2004). At the receptor level the glucose transporters GLUT1 and GLUT4, $\alpha 1$ and $\alpha 2$ GABA_A receptor subunit and nicotinic ACh receptor gene expression is decreased in specific brain regions of *mdx* mouse (Wallis et al. 2004). Of particular interest is the strong association of dystrophin with the GABA_A receptor. Knuesel et al. (1999) found co-localization of the GABA_A channel with dystrophin in the mouse cerebellum and hippocampus. In these areas of the *mdx* mouse there was a marked reduction of GABA_A clusters. This decrease in clustering was particularly striking around the soma of cerebellar Purkinje cells. In both the cerebellum and hippocampus the number (but not size) of GABA_A clusters was reduced by ~ 50%. Brunig et al. (2002) found that the DGC and GABA_A-gephyrin complexes undergo different clustering mechanisms and that the DGC is unchanged by the absence of gephyrin/GABA_A. They suggested that selective signalling from presynaptic GABAergic terminals contributes to DGC clustering (Brunig et al. 2002). The authors postulated that the DGC may stabilise GABA_A clusters, in a developmentally regulated manner. They also suggested functions for the DGC at the synapse: i) by stabilizing the postsynaptic apparatus, the DGC may “freeze” GABAergic synapses in order to maintain a certain status of the network once learning processes have been primarily completed or ii) DGC may provide a scaffold enabling changes in clusters of GABA_A receptor without incurring the loss of the postsynaptic apparatus, as may be required in circuits with a high degree of synaptic plasticity.

Grady et al. (2006) generated α -dystrobrevin, β -dystrobrevin (both members of the DGC) and double mutant α - and β -dystrobrevin knockout mice. They examined the localisation of α and β -dystrobrevin, finding both proteins in the hippocampus and cerebral cortex. They found that all larger β -dystrobrevin-positive puncta on the dendrites (but not somata) of PC were colocalised with gephyrin staining (gephyrin is associated with inhibitory synapses in the CNS). When staining for the GABA_A $\alpha 1$ subunit in β -dystrobrevin knockout mice, they found a decrease in the number of GABA_A $\alpha 1$ -positive clusters of 33% and reduction in size by approx 50% in cerebellar PC. This finding is comparable with Knuesel et al. (1999) (no such association in the cerebellum of α -dystrobrevin knockout mice was found). They further demonstrated that, in *mdx* mice, a loss of dystrophin led to a loss of dystrobrevin at these sites and in dystrobrevin knockout mice, a loss of dystrobrevin led to a loss of dystrophin at these sites. This interrelationship between dystrobrevin and dystrophin was not demonstrated in the hippocampus. Another member of the DGC - dystroglycan has also been demonstrated to be clustered at GABAergic synapses. Dystroglycan deficient mice have GABAergic clusters lacking dystrophin, however dystrophin-deficient mice (i.e. *mdx*) as well as gephyrin-deficient mice do not lose colocalisation of dystroglycan and GABAergic synapses (Brunig et al. 2002; Levi et al. 2002; Waite et al. 2009). As will be described below Kueh et al. (2011) demonstrated that there is a reduction in the number of functional receptors localised at the GABAergic synapses in the cerebellar PCs of *mdx* mice and an increase in extrasynaptic GABA_A receptors. Vaillend et al. (2010) have demonstrated a re-expression of a truncated dystrophin in the hippocampus after intra-hippocampal injection of adenovirus-associated vector expressing antisense sequences linked to a modified U7 small nuclear RNA that re-directed the splicing of dystrophin pre-mRNA allowing omission

of exon 23 of the dystrophin gene in the *mdx* mouse. This allows restoration of the reading frame and a functional dystrophin protein to be expressed. The levels of expression of the truncated dystrophin reached 15-25% of wildtype. They further investigated whether this 'rescue' of dystrophin expression had an impact on GABA_A receptor clustering. They found that the number of clusters and the area of the $\alpha 2$ subunit of the GABA_A receptor was significantly larger in the treated *mdx* mice compared to untreated *mdx* mice, and was actually no longer significantly different from wildtype (Vaillend et al. 2010) suggesting complete recovery of GABA_A receptor clustering after partial dystrophin-rescue. They conclude that although dystrophin is not involved in synaptogenesis it may be important in maintenance and stabilisation of postsynaptic GABA_A receptors. They note that dystrophin is co-localised with $\alpha 2$ -containing GABA_A receptors at a relatively low rate and postulate that the remaining dystrophin may be involved in trafficking/targeting processes, expressed in empty synapses transiently devoid of GABA_A receptors (Vaillend et al. 2010).

The overall protein expression levels of GABA_A receptors containing $\alpha 1$ subunits in a whole membrane preparation of murine cerebellum was investigated by our group and found to be no different from littermate controls (Kueh et al. 2008). This finding supports the theory that it is the organisation of the GABA_A receptor (i.e. altered clustering) rather than the expression (i.e. quantity) that is adversely affected by a lack of dystrophin.

4.3 Biochemistry

A number of reports have examined metabolites in *mdx* CNS. Griffin et al. (2001) identified discernable changes in metabolic pathways: glycolysis, β -oxidation, the TCA cycle, phosphocreatine/ATP cycle and lipid metabolism were all altered in *mdx* cerebral cortex and cerebellum. Young *mdx* mice have been found to have normal levels of N-acetylaspate and total creatinine content, increased whole-brain levels of choline-containing compounds (glycero- and phosphocholine) and *myo*-inositol, and a decrease in the ATP synthase γ subunit in cerebellum and hippocampi (Tracey et al. 1996; Wallis et al. 2004). In older *mdx* mice a decrease in the total creatinine content, increase in inorganic phosphate to phosphocreatine ratio, increased intracellular brain pH, decreased expression of mitochondrial creatine kinase in *mdx* hippocampi, and increased choline containing compounds in cerebellum and hippocampus of *mdx* brain, but not the cortex, have all been reported (Rae et al. 2002; Tracey et al. 1996; Wallis et al. 2004). Together these results indicate that there are significant differences in *mdx* mice CNS metabolism possibly indicating increased membrane turnover or decreased membrane stability. Furthermore, there is a clear exacerbation of these biochemical abnormalities with age, although there is yet no clear explanation of how a lack of dystrophin leads to these changes and why some of these perturbations are increased and others decreased with age.

Other reports have looked at glucose utilisation in CNS of *mdx* mice. Rae et al. (2002) found significantly decreased free glucose in *mdx*, significantly increased fractional enrichment and increased flux of ¹³C into metabolites such as glutamate and GABA. These authors noted that this may indicate a faster metabolic rate in dystrophin-deficient brain due to abnormal functioning of GABA_A receptors and, therefore, decreased inhibition (as, in general, excitatory stimulation leads to increased glucose metabolism and inhibitory activation leads to decreased glucose metabolism) (Ito et al. 1994; Rae et al. 2000, 2002). In old *mdx* mice there was abnormal metabolism of [1-¹³C] glucose (Rae et al. 2002). In a follow-on study this

group found no significant difference in glucose metabolism in the young *mdx* mice compared to controls, suggesting that changes in glucose metabolism seen in the old *mdx* mice are due to other factors (i.e. not changes in expression of glucose transporters) (Wallis et al. 2004).

AQP4 and osmotic/cellular volume alterations in *mdx* mice has been reported. Increased extracellular and decreased intracellular volume in *mdx* brain as well as altered osmoregulation was reported by Tracey et al. (1996a) and Griffin et al. (2001). Frigeri et al. (2001) found that although AQP4 mRNA staining pattern was unaltered, the level of this protein was decreased in *mdx* CNS. This decrease grew with age (70% decrease at 12 months). Dp71 has been found to be the major dystrophin gene product responsible for anchoring AQP4 and the DGC at the glial endfeet (Amiry-Moghaddam et al. 2004; Neely et al. 2001; Nicchia et al. 2008; Yokota et al. 2000). Nicchia et al. (2004) reported the unpublished observation of Frigeri et al. (2001) that *mdx* mice also demonstrate a resistance to brain oedema. They postulated that the absence and/or mislocalisation of AQP4 at the perivascular endfeet is protective in induced brain oedema. Nico et al. (2003) found a profoundly altered blood-brain-barrier (BBB). Although initial reports suggested no alteration in response to osmotic stress (hypo-osmotic shock) in *mdx* CNS (Rae et al. 2002). Vajda et al. (2002, 2004) found, in osmotic stress experiments, that the *mdx-βgeo* mice had a delayed decompensation and increased survival time (66.5 min compared to 56 min) indicating that Dp71 is necessary for the polarized distribution of AQP4 in brain.

Interestingly, many of these reports propose a link between the biochemical abnormalities and underlying channel dysfunction secondary to a lack of dystrophin. Rae et al.'s (2002) report suggests that the increased glucose use demonstrated in *mdx* brain may be due to decreased inhibitory input from the subset of abnormally clustered GABA_A-receptors. Further Griffin et al. (1999) have proposed this elevation is associated with cellular membranes implying a progressive, degenerative or compensatory process (Rae et al. 2002).

Decreased bioenergetic buffering capacity would be expected to influence susceptibility to hypoxia. Mehler and coworkers (Mehler et al. 1992) reported an increase in sensitivity of hippocampal slices from *mdx* mice to loss of synaptic transmission of CA1 hippocampal pyramidal cells during hypoxia. This was partially ameliorated by blocking both sodium-dependent action potentials as well as low-threshold calcium conductances. Yoshihara et al. (2003) suggested that the increased sensitivity to hypoxia found by Mehler et al. (1992) may be due to impaired function of inhibitory synapses at this site. Another group (Godfraind et al. 1998, 2000) has shown increased susceptibility of *mdx* hippocampal tissue slices to irreversible hypoxic failure when kept in 10 mM glucose, but less susceptibility of *mdx* slices when kept in 4 mM glucose, in agreement with Wallis et al. (2004). The latter group suggest that the decrease in GLUT1 and GLUT3 expression they found is most likely related to decreased synaptic integrity, resulting in decreased activity and decreased glucose utilization. These authors noted that dystrophin may be required to maintain synaptic integrity (Knuesel et al. 2001) rather than being directly involved in anchoring/clustering of the GABA_A receptor itself. Additionally, it is known that the expression of components of the GABA_A receptor relate to synaptic activity (Ives et al. 2002). Thus, Wallis et al. (2004) proposed that the lack of dystrophin in the PSD may impede synaptic activity leading to decreased GABA_A receptor components due to decreased GABAergic demand. Wallis et al. (2004) suggested that dystrophin may be involved in the clustering of this complex of

proteins (mitochondrial creatine kinase, adenine nucleotide translocase and the gamma subunit of ATP synthase). Furthermore, Rae et al. (2002) suggested that the regulation of oxidative metabolism during hypoxia was impaired, and that this may be another manifestation of calcium overload in the neuronal mitochondria of *mdx* CNS.

4.4 Electrophysiology

The highest levels of dystrophin gene products are in areas in which neurons maintain a high degree of synaptic plasticity: olfactory bulb, hippocampus, neocortex and cerebellum (Gorecki et al. 1997, 1998; Lidov et al. 1990). Synaptic plasticity has been examined in both the hippocampus and cerebellum and found to be altered in the *mdx* mouse in both of these brain regions (Anderson et al. 2004, 2010; Vaillend et al. 1998, 1999, 2004). Vaillend's group examined the CA1 dendritic layer of the hippocampus and found that NMDA-receptor dependent short-term and long-term potentiation, and long-term depression were abnormally enhanced in *mdx* mice (Perronnet & Vaillend 2010; Vaillend et al. 1998, 1999, 2004). Both our and Vaillend's group have investigated the function of the GABA receptor in the *mdx* cerebellum and hippocampus respectively as it is known to colocalise with dystrophin (Knuesel et al. 1999). In *mdx* mice hippocampus and cerebellum there is a marked reduction of GABA_A clusters, with the number (but not size) of GABA_A clusters being reduced by ~ 50% (Knuesel et al. 1999). In both the cerebellum and hippocampus the GABA_A antagonist had a decreased effect (Anderson et al. 2003; Vaillend et al. 2002). When miniature inhibitory postsynaptic potentials were examined in the cerebellum a decrease in frequency and amplitude was found in contrast to the hippocampus where an increase in frequency was demonstrated (Anderson et al. 2003; Kueh et al. 2008; Graciotti et al. 2008). We have noted however that the reduction in amplitude may lead to a falsely lowered frequency due to lowered amplitude IPSCs being below counting threshold. These results have led to the 'dysfunctional inhibition' hypothesis being postulated as the cause of the cognitive impairment seen in DMD (Perronnet & Vaillend 2010). Dallerac et al. (2011) demonstrated that *mdx* mice treated with U7 small nuclear RNAs modified to encode antisense sequences and expressed from recombinant adeno-associated viral vectors to induce skipping of the premature stop codon at exon 23 of the dystrophin gene normalises hippocampal synaptic plasticity. The vector was injected into the hippocampus and months after two months CA1 hippocampal LTP, which is normally enhanced compared to wildtype, was no longer different from wildtype. In studies of seizure induction in mice, dystrophin deficiency has been found to alter the neuronal excitability of AMPA/kainic-type glutamate receptors suggesting a dysfunctional excitatory-inhibitory balance (De Sarro et al. 2004; Perronnet & Vaillend 2010; Yoshihara et al. 2003). Basolateral nucleus of the amygdale pyramidal neurons have also been studied in the *mdx* mouse and have been demonstrated to have decreased inductions of GABA-ergic IPSCs by noradrenalin. These authors note that in the *mdx* there were cells sensitive to noradrenalin (~40%) and a larger subset of cells insensitive to noradrenalin (~60%). Whilst the regular-spiking non-pyramidal basolateral nucleus of the amygdale neurons had similar proportions of noradrenalin-induced depolarisation and AP firing (~50%) in wildtype and *mdx* demonstrating that the mechanism by which noradrenalin depolarises interneurons beyond AP threshold is not impaired in *mdx* mice. Rather it is more likely that a decrease in the number of normal functioning GABAergic synapses between the noradrenalin-responsive interneurons and pyramidal neurons underlies their findings (Sekiguchi et al. 2009).

Work from our laboratory has similarly demonstrated altered GABA-ergic function in the cerebellum of *mdx* mice. We found that evoked excitatory post-synaptic potentials in cerebellar Purkinje cells show a decreased response (approx 50%) to bicuculline (a GABA antagonist) compared to wildtype (Anderson et al. 2003). We also demonstrated that miniature inhibitory postsynaptic currents had a significantly decreased amplitude in *mdx* cerebellar Purkinje cells compared to wildtype. This difference in amplitude was principally due to the absence of large amplitude miniature inhibitory postsynaptic currents in *mdx* mice. We postulate that this decrease is the result of a decrease in the number of postsynaptic GABA-ergic receptors (Nusser et al. 1997). This finding was reproduced in later studies (Fig. 3; Kueh et al. 2008, 2011). We further went on to investigate the number of GABA_A channels located at the GABAergic synapse of cerebellar Purkinje cells. We found a significant reduction in the number of receptors at the PSD in *mdx* compared with littermate controls determined by non-stationary noise analysis of spontaneous miniature inhibitory postsynaptic currents. Single unitary conductance, rise and decay times of the currents were no different from littermate controls demonstrating that although there is a reduction in the number of channels at the postsynaptic membrane in *mdx* cerebellar Purkinje cells, the GABA_A channels that are present are functioning normally. Further, Gaboxadol, an extrasynaptic GABA agonist, was applied inducing an increase in the holding current of the Purkinje cell. In *mdx* mice this increase was significantly greater (~200%) compared to littermate controls (Kueh et al. 2011), indicating that in *mdx* mice the number of extrasynaptic GABA_A receptors is increased.

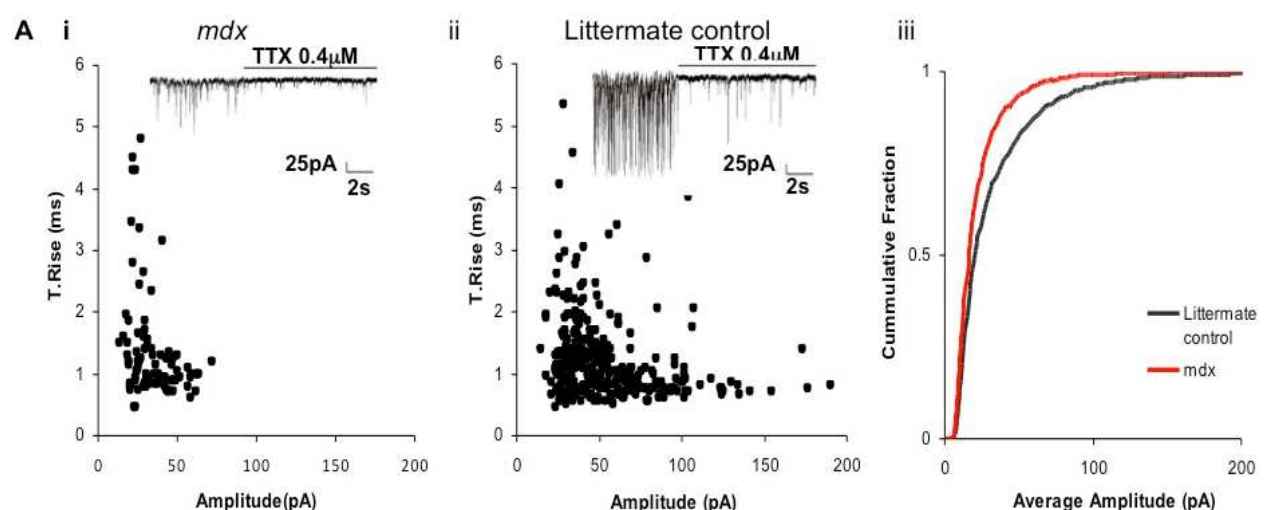


Fig. 3. A scatter plot of rise time versus peak amplitude, showing the distribution of mIPSCs in a (i) *mdx* and a (ii) littermate control mouse. The inserts show a section of the recording in aCSF and when TTX was added to the bath. iii) Cumulative probability of mIPSC amplitudes (average) in *mdx* and littermate control cells. There was a significant difference between mIPSC amplitudes between *mdx* and littermate control cells (Mann Whitney test, $p=0.0001$) (Modified from Kueh et al. 2011).

Our group has also investigated synaptic plasticity in the *mdx* cerebellum which is uniquely suited to these investigations as the Purkinje cell – the major output neuron of the cerebellum normally expresses a specific full-length dystrophin – P-dystrophin, which is absent in *mdx* mice. The major inputs to the Purkinje cells – parallel fibres and inhibitory

interneurons are normally dystrophin negative. Firstly we examined a presynaptic form of synaptic plasticity in the cerebellum – short-term synaptic plasticity mediated at the parallel-fibre to Purkinje cell synapse. We found no difference between wildtype and *mdx* mice in this form of plasticity as expected due to the post-synaptic localisation of

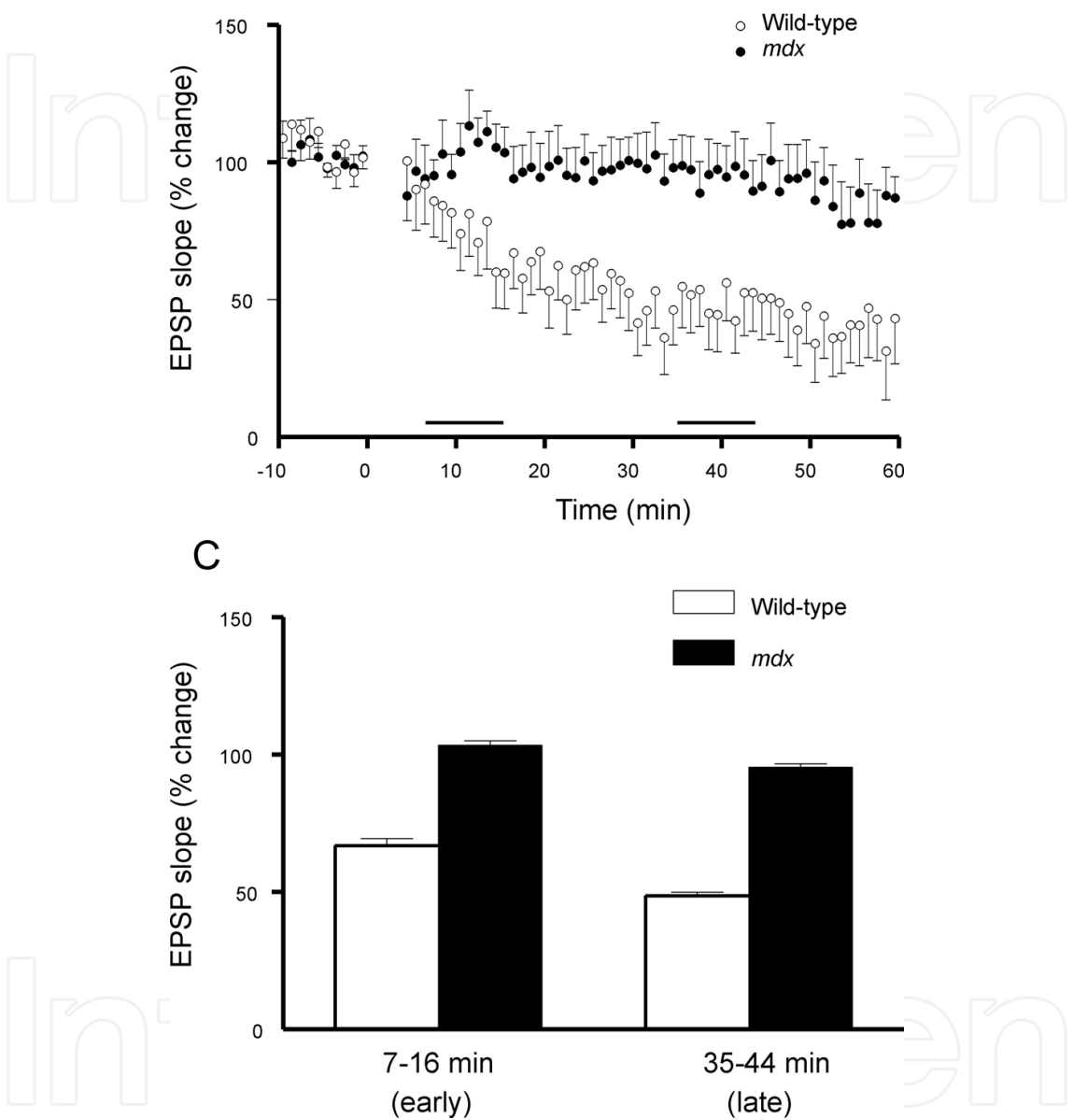


Fig. 4. Long-term depression (LTD) in cerebellar Purkinje cells of wild-type and *mdx* mice. Upper graph shows the average slope of evoked EPSPs in wild-type and *mdx* Purkinje cells before and after LTD induction. Open circles are wildtype Purkinje cells (n=11) and closed circles are *mdx* Purkinje cells (n=12). Slopes are normalised to the average slope for wild-type and *mdx* cells respectively recorded in the 10 minutes preceding LTD induction. Thin horizontal bars above the abscissa represent the two 10 minute time periods during which the EPSP slopes were averaged and represent the magnitude of early and late phases of LTD. Vertical bars are SEM and for clarity are shown on one side of the data points only. Lower bar graph displays the average slope for all wild-type and all *mdx* cells in the early and late phases following LTD induction (Modified from Anderson et al. 2004)

dystrophin. We then went on to examine a post-synaptic mediated form of synaptic plasticity – long-term depression. As postulated the extent of depression was decreased in *mdx* cerebellar Purkinje cells compared to wildtype (Fig. 4; Anderson et al. 2004). We next examined homosynaptic longterm depression at this synapse and found that there was no difference between wildtype and *mdx* cerebellar Purkinje cells in the initial observation period, however the depression was significantly greater in the latter part of the observation period in *mdx* compared to wildtype (Anderson et al. 2010). The three most compelling explanations for the differences demonstrated above are i) an alteration in calcium homeostasis, ii) an indirect effect of altered GABA_A receptor localisation and/or trafficking and iii) an alteration in putative AMPA-receptor localisation/trafficking. The most recent investigations of the multiplicity of effects of the known GABA_A receptor dysfunction on the neurophysiology of the *mdx* mouse is compelling.

Further unpublished data from our laboratory has demonstrated that that short term synaptic plasticity (inhibitory interneuron to Purkinje cell synapse) is no different between *mdx* and wildtype. However rebound potentiation – a form of longterm synaptic plasticity expressed at this synapse is significantly different. Wildtype cerebellar Purkinje cells demonstrated potentiation of the inhibitory postsynaptic potential as previously reported, however the *mdx* cerebellar Purkinje cells depressed. In a pilot study 5/12 wildtype cerebellar Purkinje cells demonstrated rebound potentiation (0 depressed) compared to 0/5 *mdx* cells demonstrating potentiation and 4/5 cells demonstrating depression. Although preliminary, these findings are the first to demonstrate a deficit in GABA-mediated synaptic plasticity. These findings also locate the problem at the post-synaptic (dystrophin-deficient Purkinje cell) locus as the presynaptically-mediated short-term synaptic plasticity of this synapse is preserved. (Anderson 2009).

5. Conclusion

The role of dystrophin in the CNS is complex and incompletely understood. It is clear that the absence of this protein leads to profound functional deficits at the macro-level (behavioural alterations and cognitive impairment) as well as the micro-level (alterations in synaptic plasticity, GABA-ergic functioning). Morphologically there are alterations in cellular architecture and organisation as well as channel localisation. The increase in investigations of the role of dystrophin in the CNS has led to a rapid appreciation of the consequence of its absence in this tissue, however a clear mechanism by which these alterations occur has yet to emerge. The majority of current evidence points convincingly to a link between a lack of dystrophin and alterations in the localisation of GABA_A receptors. Furthermore there is evidence that a lack of dystrophin is associated with abnormal functioning of GABA_A receptor-mediated cellular activity as measured by changes in amplitude of IPSCs. The well-established cognitive-impairment seen in the boys with dystrophinopathies may be due to an underlying abnormality in synaptic plasticity as demonstrated in the *mdx* animal models. However evidence linking the alteration in GABA-ergic localisation and function with alterations in synaptic plasticity is speculative. The postulated dysfunctional excitatory-inhibitory balance – perhaps mediated by chronic alteration of calcium-handling by these neurons, is the most compelling hypothesis to date linking these two major findings (alterations in GABA clustering and function with alterations in synaptic plasticity). Further how a lack of dystrophin leads to the structural

alterations seen in found in *mdx* CNS, as well as the plethora of biochemical alterations in seen in both humans and animal models of DMD has yet to emerge. The role of the smaller dystrophin gene products in the brain are now beginning to be appreciated with a recent report demonstrating that a loss of the smallest of these – Dp71, can lead to changes at the behavioural, cell membrane and synaptic levels (Daoud et al. 2009). The role of dystrophin and the dystrophin-glycoprotein complex in the CNS is slowly being elucidated. With a greater understanding of the function of this protein useful therapies may be able to ameliorate the CNS manifestations of Duchenne muscular dystrophy as well as aid in the effort to arrest the devastating muscular degeneration.

6. References

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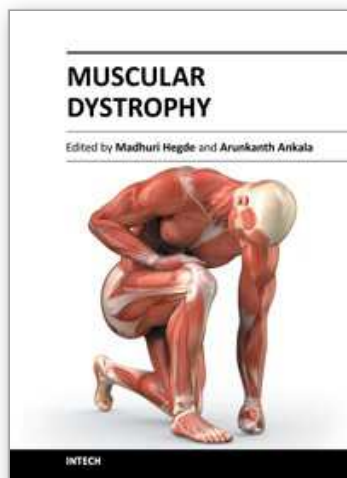
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With more than 30 different types and subtypes known and many more yet to be classified and characterized, muscular dystrophy is a highly heterogeneous group of inherited neuromuscular disorders. This book provides a comprehensive overview of the various types of muscular dystrophies, genes associated with each subtype, disease diagnosis, management as well as available treatment options. Though each different type and subtype of muscular dystrophy is associated with a different causative gene, the majority of them have overlapping clinical presentations, making molecular diagnosis inevitable for both disease diagnosis as well as patient management. This book discusses the currently available diagnostic approaches that have revolutionized clinical research. Pathophysiology of the different muscular dystrophies, multifaceted functions of the involved genes as well as efforts towards diagnosis and effective patient management, are also discussed. Adding value to the book are the included reports on ongoing studies that show a promise for future therapeutic strategies.

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