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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

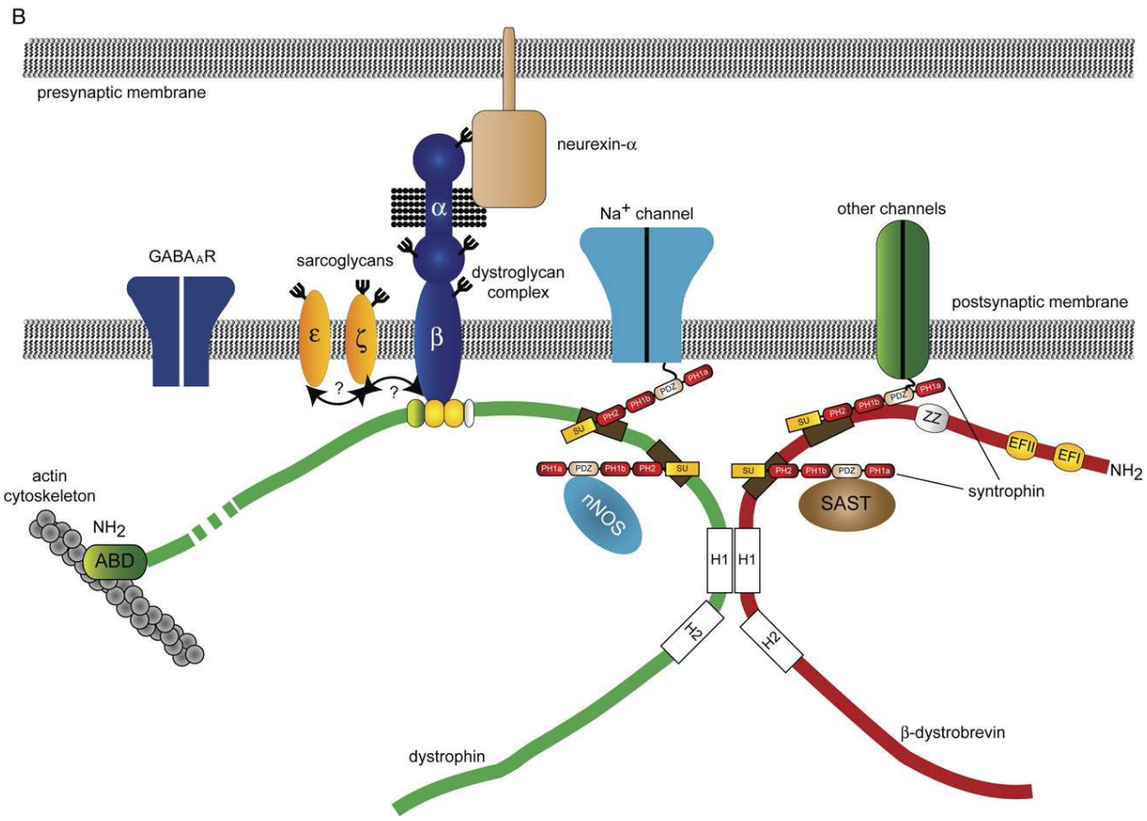


Fig. 1. The molecular organization of the "DGC-like" complexes and associated proteins in neurons (Modified from Waite et al. 2009).

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 α2, 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, cingulated cortex) and hippocampus (pyramidal layer , layer II of infrahinal 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).

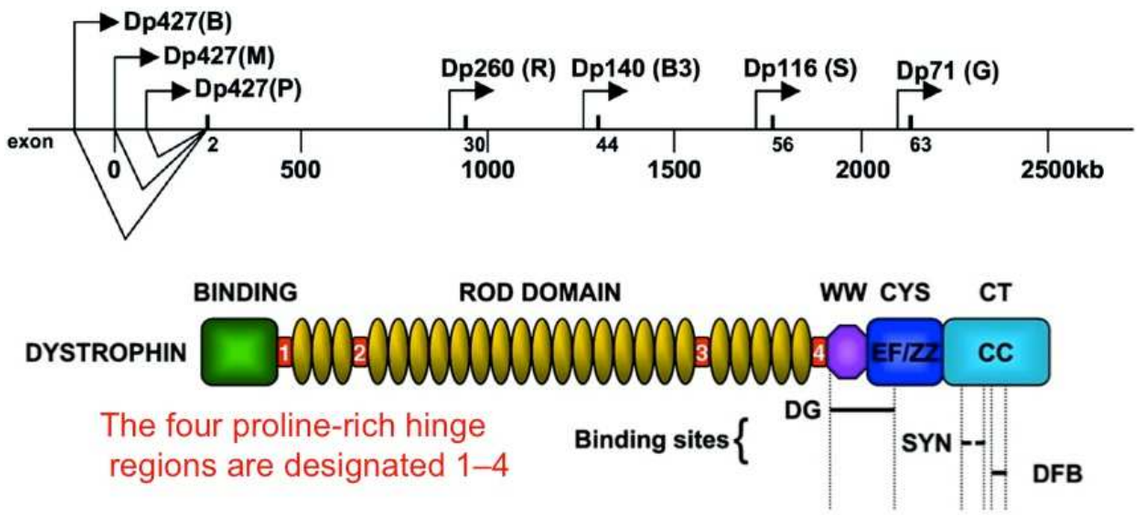


Fig. 2. Schematic showing the organization of the human Duchenne muscular dystrophy (DMD) gene and the dystrophin-related protein family (Modified from Blake et al. 2002).

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 (Cyrulnik & 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 dystrophinopthies, 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 (*m*uscular *d*ystrophy *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 & Duchen 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, α1 and α2 $GABA_A$ 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 $GABA_A$ α1 subunit in β-dystrobrevin knockout mice, they found a decrease in the number of $GABA_A$ α1-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 α2 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 synpatogenesis it may be important in maintenance and stabilisation of postsynaptic $GABA_A$ receptors. They note that dystrophin is co-localised with α2-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 α1 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-acetylaspartate 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 ^{13}C 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-^{13}C] 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 extrasynpatic $GABA_A$ receptors is increased.

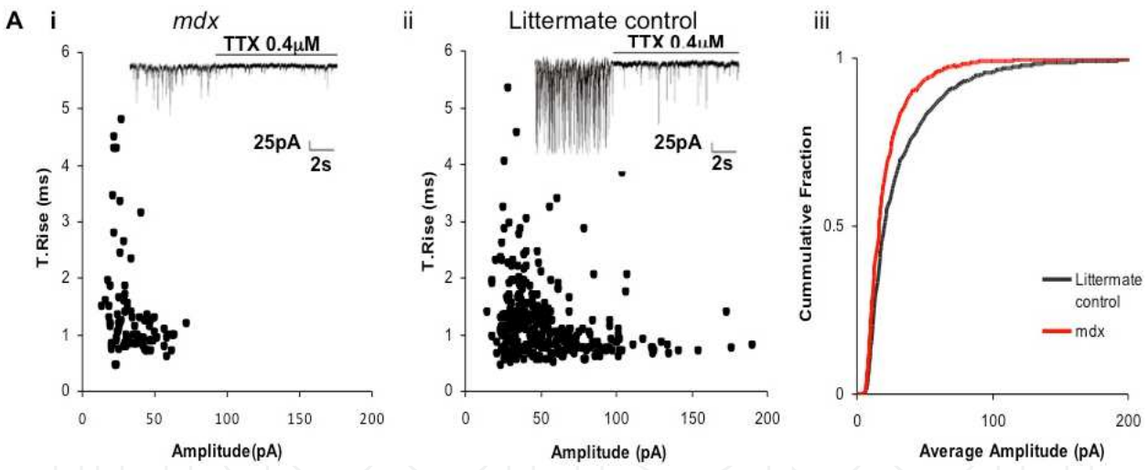


Fig. 3. A scatter plot of rise time versus peak amplitude, showing the distribution of mIPSCs in a (i) *mdx* and a (ii) littermate control mouse. The inserts show a section of the recording in aCSF and when TTX was added to the bath. iii) Cumulative probability of mIPSC amplitudes (average) in *mdx* and littermate control cells. There was a significant difference between mIPSC amplitudes between *mdx* and litermate 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

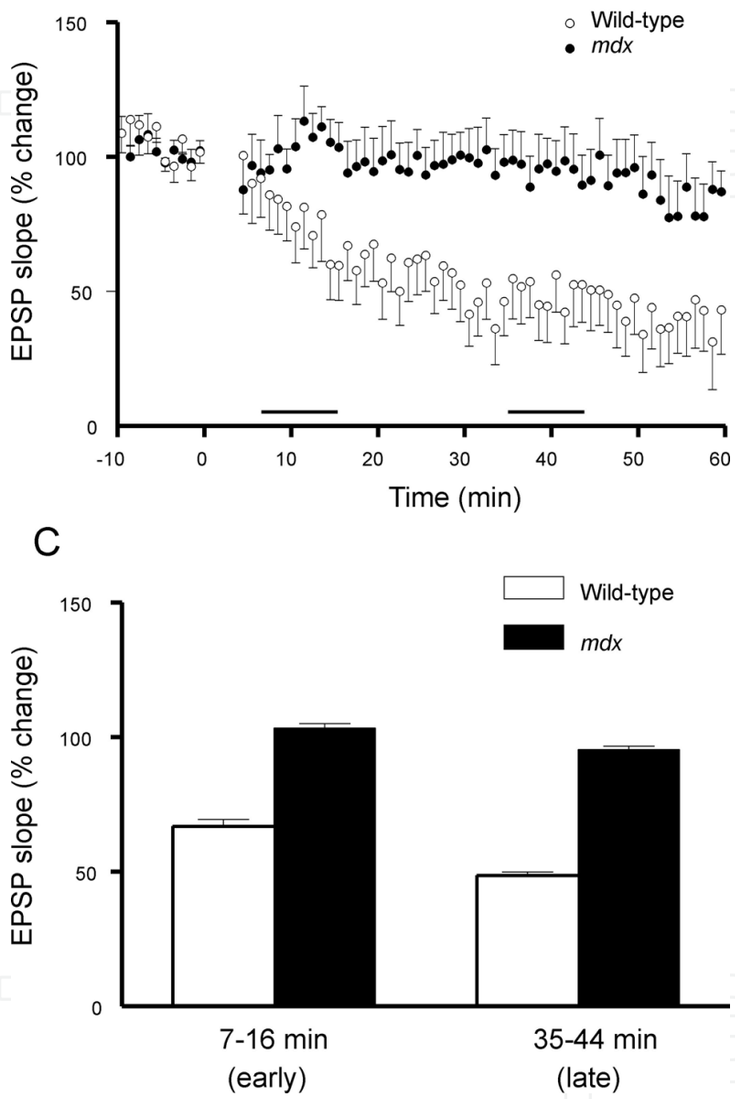


Fig. 4. Long-term depression (LTD) in cerebellar Purkinje cells of wild-type and *mdx* mice. Upper graph shows the average slope of evoked EPSPs in wild-type and *mdx* Purkinje cells before and after LTD induction. Open circles are wildtype Purkinje cells (n=11) and closed circles are *mdx* Purkinje 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

ABDULRAZZAK, H., NORO, N., SIMONS, J. P., GOLDSPINK, G., BARNARD, E. A. & GORECKI, D. C. (2001). Structural diversity despite strong evolutionary conservation in the 5'-untranslated region of the P-type dystrophin transcript. *Molecular & Cellular Neursciences,* 17, 500-13.

ALBRECHT, D. E. & FROEHNER, S. C. (2002). Syntrophins and dystrobrevins: defining the dystrophin scaffold at synapses. *Neurosignals,* 11, 123-9.

AL-QUDAH, A. A., KOBAYASHI, J., CHUANG, S., DENNIS, M. & RAY, P. (1990). Etiology of intellectual impairment in Duchenne muscular dystrophy. *Pediatr Neurol,* 6, 57-9.

ALTER, J., LOU, F., RABINOWITZ, A., YIN, H., ROSENFELD, J., WILTON, S.D., PARTRIDGE, T.A. & LU Q.L. (2006). Systemic delivery of morpholino oligonucleotide restores dystrophin expression bodywide and improves dystrophic pathology. *Nature Medicine* 12, 175-77.

AMIRY-MOGHADDAM, M., XUE, R., FINN-MOGENS, H., NEELY, J.D., BHARDWAJ, A., AGRE, P., ADAMS, M.E., FROEHNER, S.C., MORI, S. & OTTERSEN, O.P. (2004). Alpha-syntrophin deletion removes the perivascular but not the endothelial pool of aquaporin-4 at the blood-brain barrier and delays the development of brain edema in an experimental model of acute hyponatraemia. *The FASEB Journal* 18 542-44.

ANDERSON, J.L. (2009) Cerebellar synaptic plasticity in two animal models of muscular dystrophy. PhD dissertation. University of New South Wales, Sydney Australia.

ANDERSON, J.L., HEAD, S.I., RAE, C. & MORLEY, J.W. (2002). Brain function in Duchenne muscular dystrophy. *Brain* 125: 4-13.

ANDERSON, J.L., HEAD, S.I. & MORLEY, J.W. (2003). Altered inhibitory input to Purkinje cells of dystrophin-deficient mice. *Brain Res* 982: 280-283.

ANDERSON, J.L., HEAD, S.I. & MORLEY, J.W. (2004). Long-term depression is reduced in cerebellar Purkinje cells of dystrophin-deficient mdx mice. *Brain Res* 1019: 289-92.

ANDERSON, J.L., MORLEY, J.W. & HEAD, S.I. (2010). Enhanced homosynaptic LTD in cerebellar Purkinje cells of the dystrophic mdx mouse. *Muscle & Nerve* 41 (3) 329-34.

ANDERSON, S. W., ROUTH, D. K. & IONASESCU, V. V. (1988). Serial position memory of boys with Duchenne muscular dystrophy. *Dev Med Child Neurol,* 30, 328-33.

ARAHATA, K., ISHIURA, S., ISHIGURO, T., TSUKAHARA, T., SUHARA, Y., EGUCHI, C., ISHIHARA, T., NONAKA, I., OZAWA, E. & SUGITA, H. (1988). Immunostaining of skeletal and cardiac muscle surface membrane with antibody against Duchenne muscular dystrophy peptide. *Nature,* 333, 861-3.

AUSTIN, R. C., HOWARD, P. L., D'SOUZA, V. N., KLAMUT, H. J. & RAY, P. N. (1995). Cloning and characterization of alternatively spliced isoforms of Dp71. *Hum Mol Genet,* 4, 1475-83.

AUSTIN, R. C., MORRIS, G. E., HOWARD, P. L., KLAMUT, H. J. & RAY, P. N. (2000). Expression and synthesis of alternatively spliced variants of Dp71 in adult human brain. *Neuromuscul Disord,* 10, 187-93.

BANDOH, T., KAWAI, H., ADACHI, K. & II, K. (1987). [Clinical and pathological studies on intellectual impairment in Duchenne muscular dystrophy, with special reference to patients with severe intellectual impairment]. *Rinsho Shinkeigaku,* 27, 692-701.

BAR, S., BARNEA, E., LEVY, Z., NEUMAN, S., YAFFE, D. & NUDEL, U. (1990). A novel product of the Duchenne muscular dystrophy gene which greatly differs from the known isoforms in its structure and tissue distribution. *Biochem J,* 272, 557-60.

BARDONI, A., FELISARI, G., SIRONI, M., COMI, G., LAI, M., ROBOTTI, M. & BRESOLIN, N. (2000). Loss of Dp140 regulatory sequences is associated with cognitive impairment in the dystrophinopathies. *Neuromuscul Disord* 10(3) 194-199.

BARWICK, D. D., OSSELTON, J. W. & WALTON, J. N. (1965). Electroencephalographic Studies in Hereditary Myopathy. *J Neurol Neurosurg Psychiatry,* 28, 109-14.

BEGGS, A. H. (1997). Dystrophinopathy, the expanding phenotype. Dystrophin abnormalities in X-linked dilated cardiomyopathy. *Circulation,* 95, 2344-7.

BILLARD, C., GILLET, P., SIGNORET, J. L., UICAUT, E., BERTRAND, P., FARDEAU, M., BARTHEZ-CARPENTIER, M. A. & SANTINI, J. J. (1992). Cognitive functions in Duchenne muscular dystrophy: a reappraisal and comparison with spinal muscular atrophy. *Neuromuscul Disord,* 2, 371-8.

BILLARD, C., GILLET, P., BARTHEZ, M., HOMMET, C. & BERTRAND, P. (1998). Reading ability and processing in Duchenne muscular dystrophy and spinal muscular atrophy. *Dev Med Child Neurol,* 40, 12-20.

BLAKE, D. J., LOVE, D. R., TINSLEY, J., MORRIS, G. E., TURLEY, H., GATTER, K., DICKSON, G., EDWARDS, Y. H. & DAVIES, K. E. (1992). Characterization of a 4.8kb transcript from the Duchenne muscular dystrophy locus expressed in Schwannoma cells. *Hum Mol Genet,* 1, 103-9

BLAKE, D. J., HAWKES, R., BENSON, M. A. & BEESLEY, P. W. (1999). Different dystrophin-like complexes are expressed in neurons and glia. *J Cell Biol,* 147, 645-58.

BLAKE, D. J. & KROGER, S. (2000). The neurobiology of duchenne muscular dystrophy: learning lessons from muscle? *Trends Neurosci,* 23, 92-9.

BLAKE, D.J., WEIR, A., NEWEY, S.E. & DAVIES, K.E. (2002). Function and genetics of dystrophin and dystrophin-related proteins in muscle. *Physiol Rev* 82 (2) 291-329.

BORK, P. & SUDOL, M. (1994). The WW domain: a signalling site in dystrophin? *Trends Biochem Sci,* 19, 531-3.

BRESOLIN, N., CASTELLI, E., COMI, G. P., FELISARI, G., BARDONI, A., PERANI, D., GRASSI, F., TURCONI, A., MAZZUCCHELLI, F., GALLOTTI, D. & ET AL. (1994). Cognitive impairment in Duchenne muscular dystrophy. *Neuromuscul Disord,* 4, 359-69.

BRUNIG, I., SUTER, A., KNUESEL, I., LUSCHER, B. & FRITSCHY, J. M. (2002). GABAergic terminals are required for postsynaptic clustering of dystrophin but not of GABA(A) receptors and gephyrin. *J Neurosci,* 22, 4805-13.

BULFIELD, G., SILLER, W. G., WIGHT, P. A. & MOORE, K. J. (1984). X chromosome-linked muscular dystrophy (mdx) in the mouse. *Proc Natl Acad Sci U S A,* 81, 1189-92.

BURMEISTER, M., MONACO, A. P., GILLARD, E. F., VAN OMMEN, G. J., AFFARA, N. A., FERGUSON-SMITH, M. A., KUNKEL, L. M. & LEHRACH, H. (1988). A 10-megabase physical map of human Xp21, including the Duchenne muscular dystrophy gene. *Genomics,* 2, 189-202.

BYERS, T. J., HUSAIN-CHISHTI, A., DUBREUIL, R. R., BRANTON, D. & GOLDSTEIN, L. S. (1989). Sequence similarity of the amino-terminal domain of Drosophila beta spectrin to alpha actinin and dystrophin. *J Cell Biol,* 109, 1633-41.

BYERS, T.J., LIDOV, H.G. & KUNKEL, L.M. (1993). An alternative dystrophin transcript specific to peripheral nerve. *Nat Genet* 4 (1) 77-81.

CARRETTA, D., SANTARELLI, M., VANNI, D., CARRAI, R., SBRICCOLI, A., PINTO, F. & MINCIACCHI, D. (2001). The organisation of spinal projecting brainstem neurons in an animal model of muscular dystrophy. A retrograde tracing study on mdx mutant mice. *Brain Res,* 895, 213-22.

CARRETTA, D., SANTARELLI, M., VANNI, D., CIABATTI, S., SBRICCOLI, A., PINTO, F. & MINCIACCHI, D. (2003). Cortical and brainstem neurons containing calcium-binding proteins in a murine model of Duchenne's muscular dystrophy: selective changes in the sensorimotor cortex. *J Comp Neurol,* 456, 48-59.

CARRETTA, D., SANTARELLI, M., SBRICCOLI, A., PINTO, F., CATINI, C. & MINCIACCHI, D. (2004). Spatial analysis reveals alterations of parvalbumin- and calbindin-positive local circuit neurons in the cerebral cortex of mutant mdx mice. *Brain Res,* 1016, 1-11.

CASTLES, A. & COLTHEART, M. (1993). Varieties of developmental dyslexia. *Cognition,* 47, 149-80.

CAVALDESI, M., MACCHIA, G., BARCA, S., DEFILIPPI, P., TARONE, G. & PETRUCCI, T. C. (1999). Association of the dystroglycan complex isolated from bovine brain synaptosomes with proteins involved in signal transduction. *J Neurochem,* 72, 1648-55.

CECCARINI, M., MACIOCE, P., PANETTA, B. & PETRUCCI, T. C. (2002). Expression of dystrophin-associated proteins during neuronal differentiation of P19 embryonal carcinoma cells. *Neuromuscul Disord,* 12, 36-48.

CHAMBERLAIN, J. S., GRANT, S. G., REEVES, A. A., MULLINS, L. J., STEPHENSON, D. A., HOFFMAN, E. P., MONACO, A. P., KUNKEL, L. M., CASKEY, C. T. & CHAPMAN, V. M. (1987). Regional localization of the murine Duchenne muscular dystrophy gene on the mouse X chromosome. *Somat Cell Mol Genet,* 13, 671-8.

CHAMBERLAIN, J. S., PEARLMAN, J. A., MUZNY, D. M., GIBBS, R. A., RANIER, J. E., CASKEY, C. T. & REEVES, A. A. (1988). Expression of the murine Duchenne muscular dystrophy gene in muscle and brain. *Science,* 239, 1416-8.

CHELLY, J., KAPLAN, J-C., MAIRE, P., GAUTRON, S. & KAHN, A. (1988). Transcription of the dystrophin gene in human muscle and non-muscle tissues. *Nature* 333, 858-60.

CHELLY, J., CONCORDET, J. P., KAPLAN, J. C. & KAHN, A. (1989). Illegitimate transcription: transcription of any gene in any cell type. *Proc Natl Acad Sci U S A,* 86, 2617-21.

CIBIS, G.W., FITZGERALD, K.W., HARRIS, D.J., ROTHBERG, P.G. & RUPANI, M. (1993). The effect of dystrophin gene mutations on the ERG in mice and humans. *Invest Ophthalmol Vis Sci* 34 (13) 3646-52.

COLLINS, C. A. & MORGAN, J. E. (2003). Duchenne's muscular dystrophy: animal models used to investigate pathogenesis and develop therapeutic strategies. *Int J Exp Pathol,* 84, 165-72.

CONNERS, K. (2000). *Technical manual for the Conners rating scales - revised,* North Tonawanda, Multi-Health Systems Inc.

CONNORS, N. C., ADAMS, M. E., FROEHNER, S. C. & KOFUJI, P. (2004). The potassium channel Kir4.1 associates with the dystrophin-glycoprotein complex via alpha-syntrophin in glia. *J Biol Chem,* 279, 28387-92.

COSTA, M.F., OLIVEIRA, A.G., FEITOSA-SANTANA, C., ZATZ, M. & VENTURA, D.F. (2007). Red-green colour vision impairment in Duchenne muscular dystrophy. *Am J Hum Genet* 80 (6) 1064-75.

COTTON, S., CROWE, S. & VOUDOURIS, N. (1998). Neuropsychological Profile of Duchenne Muscular Dystrophy. *Child Neuropsychology,* 4, 110-17.

COTTON, S., VOUDOURIS, N. J. & GREENWOOD, K. M. (2001). Intelligence and Duchenne muscular dystrophy: full-scale, verbal, and performance intelligence quotients. *Dev Med Child Neurol,* 43, 497-501.

COTTON, S. M., VOUDOURIS, N. J. & GREENWOOD, K. M. (2005). Association between intellectual functioning and age in children and young adults with Duchenne muscular dystrophy: further results from a meta-analysis. *Dev Med Child Neurol,* 47, 257-65.

CROSS, R. A., STEWART, M. & KENDRICK-JONES, J. (1990). Structural predictions for the central domain of dystrophin. *FEBS Lett,* 262, 87-92.

CULLIGAN, K. G., MACKEY, A. J., FINN, D. M., MAGUIRE, P. B. & OHLENDIECK, K. (1998). Role of dystrophin isoforms and associated proteins in muscular dystrophy (review). *Int J Mol Med,* 2, 639-48.

CULLIGAN, K., GLOVER, L., DOWLING, P. & OHLENDIECK, K. (2001). Brain dystrophin-glycoprotein complex: persistent expression of beta-dystroglycan, impaired oligomerization of Dp71 and up-regulation of utrophins in animal models of muscular dystrophy. *BMC Cell Biol,* 2, 2.

CULLIGAN, K. & OHLENDIECK, K. (2002). Diversity of the Brain Dystrophin-Glycoprotein Complex. *J Biomed Biotechnol,* 2, 31-36.

CYRULNIK, S. E. & HINTON, V. J. (2008). Duchenne muscular dystrophy: A cerebellar disorder? *Neurosci Biobehav Rev,* 32, 486-96.

D'ANGELO, M. G. & BRESOLIN, N. (2003). Report of the 95th European Neuromuscular Centre (ENMC) sponsored international workshop cognitive impairment in neuromuscular disorders, Naarden, The Netherlands, 13-15 July 2001. *Neuromuscul Disord,* 13, 72-9.

D'SOUZA, V. N., NGUYEN, T. M., MORRIS, G. E., KARGES, W., PILLERS, D. A. & RAY, P. N. (1995). A novel dystrophin isoform is required for normal retinal electrophysiology. *Hum Mol Genet,* 4, 837-42.

DALKILIC, I. & KUNKEL, L. M. (2003). Muscular dystrophies: genes to pathogenesis. *Curr Opin Genet Dev,* 13, 231-8.

DALLERAC, G., PERRONNET, C., CHAGNEAU, C., LEBLANC-VEYRAC, P., SAMSON-DESVIGNES, N., PELTEKIAN, E., DANOS, O., GARCIA LAROCHE, S., BILLARD, J.M. & VAILLEND, C. (2011). Rescue of a dystrophin-like protein by exon skipping normalizes synaptic plasticity in the hippocampus of the mdx mouse. *Neurobiol Dis* 43(3) 635-41.

DAOUD, F., ANGEARD, N., DEMERRE, B., MARTIE, I., BENYAOU, R., LETURCQ, F., COSSÉE, M., DEBURGRAVE, N., SAILLOUR, Y., TUFFERY, S., URTIZBEREA, A., TOUTAIN, A., ECHENNE, B., FRISCHMAN, M., MAYER, M., DESGUERRE, I., ESTOURNET, B., RÉVEILLÈRE, C., PENISSON-BESNIER, CUISSET, J.M., KAPLAN, J.C., HÉRON, D., RIVIER, F. & CHELLY, J. (2009). Analysis of Dp71 contribution in the severity of mental retardation through comparison of Duchenne and Becker patients differing by mutation consequences on Dp71 expression. *Hum Mol Genet* 18 (20) 3779-94.

DE SARRO, G., IBBADU, G. F., MARRA, R., ROTIROTI, D., LOIACONO, A., DONATO DI PAOLA, E. & RUSSO, E. (2004). Seizure susceptibility to various convulsant stimuli in dystrophin-deficient mdx mice. *Neurosci Res,* 50, 37-44.

DESMOND, J. E., GABRIELI, J. D., WAGNER, A. D., GINIER, B. L. & GLOVER, G. H. (1997) Lobular patterns of cerebellar activation in verbal working-memory and finger-tapping tasks as revealed by functiona*l MRI. J Neurosci, 17, 9675-85.*

DI LAZZARO, V., RESTUCCIA, D., SERVIDEI, S., NARDONE, R., OLIVIERO, A., PROFICE, P., MANGIOLA, F., TONALI, P. & ROTHWELL, J. C. (1998). Functional involvement of cerebral cortex in Duchenne muscular dystrophy. *Muscle Nerve,* 21, 662-4.

DORMAN, C., HURLEY, A. D. & D'AVIGNON, J. (1988). Language and learning disorders of older boys with Duchenne muscular dystrophy. *Dev Med Child Neurol,* 30, 316-27.

DUBOWITZ, V. & CROME, L. (1969). The central nervous system in Duchenne muscular dystrophy. *Brain,* 92, 805-808.

DUCHENNE, G. (1868). Recherche sur la paralysie musculaire pseudo-hypertrophique ou paralysie myosclerosique. *Archives of General Medicine,* 2, 5.

DUNN, J. F. & ZAIM-WADGHIRI, Y. (1999). Quantitative magnetic resonance imaging of the mdx mouse model of Duchenne muscular dystrophy. *Muscle Nerve,* 22, 1367-71.

DURBEEJ, M. & CAMPBELL, K. P. (2002). Muscular dystrophies involving the dystrophin-glycoprotein complex: an overview of current mouse models. *Curr Opin Genet Dev,* 12, 349-61.

EMERY, A. E. (2002). Muscular dystrophy into the new millennium. *Neuromuscul Disord,* 12, 343-9.

EMERY, A. E. (2002a). The muscular dystrophies. *Lancet,* 359, 687-95.

ESSEX, C. & ROPER, H. (2001). Lesson of the week: late diagnosis of Duchenne's muscular dystrophy presenting as global developmental delay. *BMJ,* 323, 37-38.

ETEMADIFAR, M. & MOLAEI, S. (2004). Epilepsy in Boys with Duchenne Muscular Dystrophy. *Journal of Research in Medical Sciences,* 3, 14-17.

FABBRIZIO, E., BONET-KERRACHE, A., LIMAS, F., HUGON, G. & MORNET, D. (1995). Dystrophin, the protein that promotes membrane resistance. *Biochem Biophys Res Commun,* 213, 295-301.

FERLINI, A., SEWRY, C., MELIS, M. A., MATEDDU, A. & MUNTONI, F. (1999). X-linked dilated cardiomyopathy and the dystrophin gene. *Neuromuscul Disord,* 9, 339-46.

FITZPATRICK, C., BARRY, C. & GARVEY, C. (1986). Psychiatric disorder among boys with Duchenne muscular dystrophy. *Dev Med Child Neurol* 28(5):589-95.

FRIGERI, A., NICCHIA, G. P., NICO, B., QUONDAMATTEO, F., HERKEN, R., RONCALI, L. & SVELTO, M. (2001). Aquaporin-4 deficiency in skeletal muscle and brain of dystrophic mdx mice. *Faseb J,* 15, 90-98.

GAULD, L. M., BOYNTON, A., BETTS, G. A. & JOHNSTON, H. (2005). Spirometry is affected by intelligence and behavior in Duchenne muscular dystrophy. *Pediatr Pulmonol,* 40, 408-13.

GEE, S. H., MADHAVAN, R., LEVINSON, S. R., CALDWELL, J. H., SEALOCK, R. & FROEHNER, S. C. (1998). Interaction of muscle and brain sodium channels with multiple members of the syntrophin family of dystrophin-associated proteins. *J Neurosci,* 18, 128-37.

GLAUB, T. & MECHLER, F. (1987). Intellectual function in muscular dystrophies. *Eur Arch Psychiatry Neurol Sci,* 236, 379-82.

GODFRAIND, J.-M., TEKKOK, S. B. & KRNJEVIC, K. (1998). Hypoxia on hippocampal slices from mice deficient in dystrophin (mdx) and dystrophin isoforms (mdx3cv). *Soc Neurosci Abst*

GODFRAIND, J.-M., TEKKOK, S. B. & KRNJEVIC, K. (2000). Hypoxia on Hippocampal Slices From Mice Deficient in Dystrophin (mdx) and Isoforms (mdx3cv). *J Cereb Blood Flow Metab,* 20, 145-152.

GOODWIN, F., MUNTONI, F. & DUBOWITZ, V. (1997). Epilepsy in Duchenne and Becker muscular dystrophies. *Eur J Paediatr Neurol,* 1, 115-9.

GORECKI, D., GENG, Y., THOMAS, K., HUNT, S. P., BARNARD, E. A. & BARNARD, P. J. (1991). Expression of the dystrophin gene in mouse and rat brain. *Neuroreport,* 2, 773-6.

GORECKI, D. C., MONACO, A. P., DERRY, J. M., WALKER, A. P., BARNARD, E. A. & BARNARD, P. J. (1992). Expression of four alternative dystrophin transcripts in brain regions regulated by different promoters. *Hum Mol Genet,* 1, 505-10.

GORECKI, D. C. & BARNARD, E. A. (1995). Specific expression of G-dystrophin (Dp71) in the brain. *Neuroreport,* 6, 893-6.

GORECKI, D. C., ABDULRAZZAK, H., LUKASIUK, K. & BARNARD, E. A. (1997). Differential expression of syntrophins and analysis of alternatively spliced dystrophin transcripts in the mouse brain. *Eur J Neurosci,* 9, 965-76.

GORECKI, D. C., LUKASIUK, K., SZKLARCZYK, A. & KACZMAREK, L. (1998). Kainate-evoked changes in dystrophin messenger RNA levels in the rat hippocampus. *Neuroscience,* 84, 467-77.

GRACIOTTI, L., MINELLI, A., MINCIACCHI, D., PROCOPIO, A. & FULGENZI, G. (2008). GABAergic miniature spontaneous activity is increased in the CA1 hippocampal region of dystrophic mdx mice. *Neuromuscul Disord* 18(3) 220-26.

GRADY, R.M., WOZNIAK, D.F., OHLEMILLER, K.K. & SANES, J.R. (2006). Cerebellar synaptic defects and abnormal motor behavior in mice lacking alpha- and beta-dystrobrevin. *J Neurosci* 26(11) 2841-51.

GREENBERG, D. S., SCHATZ, Y., LEVY, Z., PIZZO, P., YAFFE, D. & NUDEL, U. (1996). Reduced levels of dystrophin associated proteins in the brains of mice deficient for Dp71. *Hum Mol Genet,* 5, 1299-303.

GRIFFIN, J., NICHOLLS, A., MORTSHIRE-SMITH, R., RAE, C. & NICHOLSON, J. (1999). High resolution magic angle spinning ^{1}H NMR of cerebral tissue as applied to a mouse model of Duchenne muscular dystrophy [abstract]. *International Society Magnetic Resonance Medicine*. British Chapter.

GRIFFIN, J. L., WILLIAMS, H. J., SANG, E., CLARKE, K., RAE, C. & NICHOLSON, J. K. (2001). Metabolic profiling of genetic disorders: a multitissue (1)H nuclear magnetic resonance spectroscopic and pattern recognition study into dystrophic tissue. *Anal Biochem,* 293, 16-21.

HAMED, S. A. & HOFFMAN, E. P. (2006). Automated sequence screening of the entire dystrophin cDNA in Duchenne dystrophy: point mutation detection. *Am J Med Genet B Neuropsychiatr Genet,* 141, 44-50.

HASHIDA-OKUMURA, A., OKUMURA, N., IWAMATSU, A., BUIJS, R. M., ROMIJN, H. J. & NAGAI, K. (1999). Interaction of neuronal nitric-oxide synthase with alpha1-syntrophin in rat brain. *J Biol Chem,* 274, 11736-41.

HENDRIKSEN, J. G. & VLES, J. S. (2006). Are males with Duchenne muscular dystrophy at risk for reading disabilities? *Pediatr Neurol,* 34, 296-300.

HENDRIKSEN, J.G. & VLES, J.S. (2008). Neuropsychiatric disorders in males with duchenne muscular dystrophy: frequency rate of attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder, and obsessive--compulsive disorder. *J Child Neurol* 23(5) 477-81.

HINTON, V. J., DE VIVO, D. C., NEREO, N. E., GOLDSTEIN, E. & STERN, Y. (2000). Poor verbal working memory across intellectual level in boys with Duchenne dystrophy. *Neurology,* 54, 2127-32.

HINTON, V. J., DE VIVO, D. C., NEREO, N. E., GOLDSTEIN, E. & STERN, Y. (2001). Selective deficits in verbal working memory associated with a known genetic etiology: the neuropsychological profile of duchenne muscular dystrophy. *J Int Neuropsychol Soc,* 7, 45-54.

HOFFMAN, E. P., BROWN, R. H., JR. & KUNKEL, L. M. (1987). Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell,* 51, 919-28.

HOFFMAN, E. P. & KUNKEL, L. M. (1989). Dystrophin abnormalities in Duchenne/Becker muscular dystrophy. *Neuron,* 2, 1019-29.

HOLDER, E., MAEDA, M. & BIES, R. D. (1996). Expression and regulation of the dystrophin Purkinje promoter in human skeletal muscle, heart, and brain. *Hum Genet,* 97, 232-9.

HOPF, F. W. & STEINHARDT, R. A. (1992). Regulation of intracellular free calcium in normal and dystrophic mouse cerebellar neurons. *Brain Res,* 578, 49-54.

HSU, Y. D. (2004). Muscular dystrophy: from pathogenesis to strategy. *Acta Neurol Taiwan,* 13, 50-8.

HUANG, X., POY, F., ZHANG, R., JOACHIMIAK, A., SUDOL, M. & ECK, M. J. (2000). Structure of a WW domain containing fragment of dystrophin in complex with beta-dystroglycan. *Nat Struct Biol,* 7, 634-8.

HUARD, J. & TREMBLAY, J. P. (1992) Localization of dystrophin in the Purkinje cells of normal mice. *Neurosci Lett,* 137**,** 105-8.

IANNELLO, R. C., MAR, J. H. & ORDAHL, C. P. (1991). Characterization of a promoter element required for transcription in myocardial cells. *J Biol Chem,* 266, 3309-16.

ILARRAZA-LOMELI, R., CISNEROS-VEGA, B., CERVANTES-GOMEZ, M.D.E. L., MORNET, D. & MONTAÑEZ, C. (2007). Dp71, utrophin and beta-dystroglycan expression and distribution in PC12/L6 cell cocultures. *NEUROREPORT* 18(16):1657-61.

ISHIKAWA-SAKURAI, M., YOSHIDA, M., IMAMURA, M., DAVIES, K. E. & OZAWA, E. (2004). ZZ domain is essentially required for the physiological binding of dystrophin and utrophin to beta-dystroglycan. *Hum Mol Genet,* 13, 693-702.

ITO, K., SAWADA, Y., SUGIYAMA, Y., SUZUKI, H., HANANO, M. & IGA, T. (1994). Linear relationship between GABAA receptor occupancy of muscimol and glucose metabolic response in the conscious mouse brain. Clinical implication based on comparison with benzodiazepine receptor agonist. *Drug Metab Dispos,* 22, 50-4.

IVES, J. H., DREWERY, D. L. & THOMPSON, C. L. (2002). Neuronal activity and its influence on developmentally regulated GABA(A) receptor expression in cultured mouse cerebellar granule cells. *Neuropharmacology,* 43, 715-25.

JAGADHA, V. & BECKER, L. E. (1988). Brain morphology in Duchenne muscular dystrophy: a Golgi study. *Pediatr Neurol,* 4, 87-92.

JANCSIK, V. & HAJOS, F. (1998). Differential distribution of dystrophin in postsynaptic densities of spine synapses. *Neuroreport,* 9, 2249-51.

JUEPTNER, M. & WEILLER, C. (1995). Review: does measurement of regional cerebral blood flow reflect synaptic activity? Implications for PET and fMRI. *Neuroimage,* 2, 148-56.

JUNG, D., FILLIOL, D., METZ-BOUTIGUE, M. H. & RENDON, A. (1993). Characterization and subcellular localization of the dystrophin-protein 71 (Dp71) from brain. *Neuromuscul Disord,* 3, 515-8.

JUNG, D., YANG, B., MEYER, J., CHAMBERLAIN, J. S. & CAMPBELL, K. P. (1995). Identification and characterization of the dystrophin anchoring site on beta-dystroglycan. *J Biol Chem,* 270, 27305-10.

KAMAKURA, K., TADANO, Y., KAWAI, M., ISHIURA, S., NAKAMURA, R., MIYAMOTO, K., NAGATA, N. & SUGITA, H. (1994). Dystrophin-related protein is found in the central nervous system of mice at various developmental stages, especially at the postsynaptic membrane. *J Neurosci Res,* 37, 728-34.

KAPLAN, L. C., OSBORNE, P. & ELIAS, E. (1986). The diagnosis of muscular dystrophy in patients referred for language delay. *J Child Psychol Psychiatry,* 27, 545-9.

KARAGAN, N. J. & ZELLWEGER, H. U. (1976). IQ studies in Duchenne muscular dystrophy II: test-retest performance. *Developmental Medicine and Child Neurology,* 18, 251.

KARAGAN, N. J. & ZELLWEGER, H. U. (1978). Early verbal disability in children with Duchenne muscular dystrophy. *Dev Med Child Neurol,* 20, 435-41.

KARAGAN, N. J. (1979). Intellectual functioning in Duchenne muscular dystrophy: a review. *Psychol Bull,* 86, 250-9.

KARAGAN, N. J., RICHMAN, L. C. & SORENSEN, J. P. (1980). Analysis of verbal disability in Duchenne muscular dystrophy. *J Nerv Ment Dis,* 168, 419-23.

KATO, T., NISHINA, M., MATSUSHITA, K., HORI, E., AKABOSHI, S. & TAKASHIMA, S. (1997). Increased cerebral choline-compounds in Duchenne muscular dystrophy. *Neuroreport,* 8, 1435-7.

KENWRICK, S., PATTERSON, M., SPEER, A., FISCHBECK, K. & DAVIES, K. (1987). Molecular analysis of the Duchenne muscular dystrophy region using pulsed field gel electrophoresis. *Cell,* 48, 351-7.

KHAN, Y. & HECKMATT, J. Z. (1994). Obstructive apnoeas in Duchenne muscular dystrophy. *Thorax,* 49, 157-61.

KIM, T. W., WU, K., XU, J. L. & BLACK, I. B. (1992). Detection of dystrophin in the postsynaptic density of rat brain and deficiency in a mouse model of Duchenne muscular dystrophy. *Proc Natl Acad Sci U S A,* 89, 11642-4.

KIM, T. W., WU, K. & BLACK, I. B. (1995). Deficiency of brain synaptic dystrophin in human Duchenne muscular dystrophy. *Ann Neurol,* 38, 446-9.

KINGSTON, H. M., SARFARAZI, M., THOMAS, N. S. & HARPER, P. S. (1984). Localisation of the Becker muscular dystrophy gene on the short arm of the X chromosome by linkage to cloned DNA sequences. *Hum Genet,* 67, 6-17.

KNUESEL, I., MASTROCOLA, M., ZUELLIG, R. A., BORNHAUSER, B., SCHAUB, M. C. & FRITSCHY, J. M. (1999). Short communication: altered synaptic clustering of GABAA receptors in mice lacking dystrophin (mdx mice). *Eur J Neurosci,* 11, 4457-62.

KNUESEL, I., ZUELLIG, R. A., SCHAUB, M. C. & FRITSCHY, J. M. (2001). Alterations in dystrophin and utrophin expression parallel the reorganization of GABAergic synapses in a mouse model of temporal lobe epilepsy. *Eur J Neurosci,* 13, 1113-24.

KOENIG, M., HOFFMAN, E. P., BERTELSON, C. J., MONACO, A. P., FEENER, C. & KUNKEL, L. M. (1987). Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. *Cell,* 50, 509-17.

KOENIG, M., MONACO, A. P. & KUNKEL, L. M. (1988). The complete sequence of dystrophin predicts a rod-shaped cytoskeletal protein. *Cell,* 53, 219-26

KOENIG, M. & KUNKEL, L. M. (1990). Detailed analysis of the repeat domain of dystrophin reveals four potential hinge segments that may confer flexibility. *J Biol Chem,* 265, 4560-6.

KOMOTO, J., USUI, S., OTSUKI, S. & TERAO, A. (1984). Infantile autism and Duchenne muscular dystrophy. *J Autism Dev Disord,* 14, 191-5.

KUEH, S.L., HEAD, S.I. & MORLEY, J.W. (2008). GABA(A) receptor expression and inhibitory post-synaptic currents in cerebellar Purkinje cells in dystrophin-deficient mdx mice. *Clin Exp Pharmacol Physiol* 35(2):207-10.

KUEH, S.L., DEMPSTER, J., HEAD, S.I. & MORLEY, J.W. (2011). Reduced postsynaptic GABAA receptor number and enhanced gaboxadol induced change in holding currents in Purkinje cells of the dystrophin-deficient mdx mouse. *Neurobiol Dis* 43(3):558-64.

KUNKEL, L. M., MONACO, A. P., BERTELSON, C. J. & COLLETTI, C. A. (1986). Molecular genetics of Duchenne muscular dystrophy. *Cold Spring Harb Symp Quant Biol,* 51 Pt 1, 349-51.

LABARQUE, V., FRESON, K., THYS, C., WITTEVRONGEL, C., HOYLAERTS, M.F., DE VOS, R., GOEMANS, N. & VAN GEET, C. (2008). Increased Gs signalling in platelets and impaired collagen activation, due to a defect in the dystrophin gene, result in increased blood loss during spinal surgery. *Hum Mol Genet* 17(3):357-66.

LEDERFEIN, D., LEVY, Z., AUGIER, N., MORNET, D., MORRIS, G., FUCHS, O., YAFFE, D. & NUDEL, U. (1992). A 71-kilodalton protein is a major product of the Duchenne muscular dystrophy gene in brain and other nonmuscle tissues. *Proc Natl Acad Sci U S A,* 89, 5346-50.

LEDERFEIN, D., YAFFE, D. & NUDEL, U. (1993). A housekeeping type promoter, located in the 3' region of the Duchenne muscular dystrophy gene, controls the expression of Dp71, a major product of the gene. *Hum Mol Genet,* 2, 1883-8.

LEE, J. S., PFUND, Z., JUHASZ, C., BEHEN, M. E., MUZIK, O., CHUGANI, D. C., NIGRO, M. A. & CHUGANI, H. T. (2002). Altered regional brain glucose metabolism in Duchenne muscular dystrophy: a pet study. *Muscle Nerve,* 26, 506-12.

LEVI, S., GRADY, R. M., HENRY, M. D., CAMPBELL, K. P., SANES, J. R. & CRAIG, A. M. (2002). Dystroglycan is selectively associated with inhibitory GABAergic synapses but is dispensable for their differentiation. *J Neurosci,* 22, 4274-85.

LEVISOHN, L., CRONIN-GOLOMB, A. & SCHMAHMANN, J. D. (2000). Neuropsychological consequences of cerebellar tumour resection in children: cerebellar cognitive affective syndrome in a paediatric population. *Brain,* 123 (Pt 5), 1041-50.

LIDOV, H. G., BYERS, T. J., WATKINS, S. C. & KUNKEL, L. M. (1990). Localization of dystrophin to postsynaptic regions of central nervous system cortical neurons. *Nature,* 348, 725-8.

LIDOV, H. G., BYERS, T. J. & KUNKEL, L. M. (1993). The distribution of dystrophin in the murine central nervous system: an immunocytochemical study. *Neuroscience,* 54, 167-87.

LIDOV, H. G., SELIG, S. & KUNKEL, L. M. (1995). Dp140: a novel 140 kDa CNS transcript from the dystrophin locus. *Hum Mol Genet,* 4, 329-35.

LIDOV, H. G. (1996). Dystrophin in the nervous system. *Brain Pathol,* 6, 63-77.

MANNI, R., ZUCCA, C., GALIMBERTI, C. A., OTTOLINI, A., CERVERI, I., BRUSCHI, C., ZOIA, M. C., LANZI, G. & TARTARA, A. (1991). Nocturnal sleep and oxygen balance in Duchenne muscular dystrophy. A clinical and polygraphic 2-year follow-up study. *Eur Arch Psychiatry Clin Neurosci,* 240, 255-7.

MEHLER, M. F., HAAS, K. Z., KESSLER, J. A. & STANTON, P. K. (1992). Enhanced sensitivity of hippocampal pyramidal neurons from mdx mice to hypoxia-induced loss of synaptic transmission. *Proc Natl Acad Sci U S A,* 89, 2461-5.

MEHLER, M. F. (2000). Brain dystrophin, neurogenetics and mental retardation. *Brain Res Brain Res Rev,* 32, 277-307.

MELO, M., LAURIANO, V., GENTIL, V., EGGERS, S., DEL BIANCO, S. S., GIMENEZ, P. R., AKIYAMA, J., OKABAIASHI, H., FROTA-PESSOA, O., PASSOS-BUENO, M. R. & ET AL. (1995). Becker and limb-girdle muscular dystrophies: a psychiatric and intellectual level comparative study. *Am J Med Genet,* 60, 33-8.

MICHALAK, M. & OPAS, M. (2001). *Duchenne muscular dystrophy,* Chichester, John Wiley & Sons LTD.

MILNER, R. E., BUSAAN, J. L., HOLMES, C. F., WANG, J. H. & MICHALAK, M. (1993). Phosphorylation of dystrophin. The carboxyl-terminal region of dystrophin is a substrate for in vitro phosphorylation by p34cdc2 protein kinase. *J Biol Chem,* 268, 21901-5.

MIRANDA, R., SÉBRIÉ, C., DEGROUARD, J., GILLET, B., JAILLARD, D., LAROCHE, S., VAILLEND, C. (2009). Reorganization of inhibitory synapses and increased PSD length of perforated excitatory synapses in hippocampal area CA1 of dystrophin-deficient mdx mice. *Cereb Cortex* 19(4):876-88.

MIRANDA, R., NUDEL, U., LAROCHE, S. & VAILLEND, C. (2011). Altered presynaptic ultrastructure in excitatory hippocampal synapses of mice lacking dystrophins Dp427 or Dp71. *Neurobiol Dis* 43(1):134-41,

MISURI, G., LANINI, B., GIGLIOTTI, F., IANDELLI, I., PIZZI, A., BERTOLINI, M. G. & SCANO, G. (2000). Mechanism of CO(2) retention in patients with neuromuscular disease. *Chest,* 117, 447-53.

MIYATAKE, M., MIIKE, T., ZHAO, J. E., YOSHIOKA, K., UCHINO, M. & USUKU, G. (1991). Dystrophin: localization and presumed function. *Muscle Nerve,* 14, 113-9.

MOHAMED, K., APPLETON, R. & NICOLAIDES, P. (2000). Delayed diagnosis of Duchenne muscular dystrophy. *Eur J Paediatr Neurol,* 4, 219-23.

MOUKHLES, H. & CARBONETTO, S. (2001). Dystroglycan contributes to the formation of multiple dystrophin-like complexes in brain. *J Neurochem,* 78, 824-34.

MUNTONI, F., MATEDDU, A. & SERRA, G. (1991). Passive avoidance behaviour deficit in the mdx mouse. *Neuromuscul Disord,* 1, 121-3.

MUNTONI, F., CAU, M., GANAU, A., CONGIU, R., ARVEDI, G., MATEDDU, A., MARROSU, M. G., CIANCHETTI, C., REALDI, G., CAO, A. & ET AL. (1993). Brief report: deletion of the dystrophin muscle-promoter region associated with X-linked dilated cardiomyopathy. *N Engl J Med,* 329, 921-5.

MUNTONI, F., TORELLI, S. & FERLINI, A. (2003). Dystrophin and mutations: one gene, several proteins, multiple phenotypes. *Lancet Neurol,* 2, 731-40.

NEELY, J. D., AMIRY-MOGHADDAM, M., OTTERSEN, O. P., FROEHNER, S. C., AGRE, P. & ADAMS, M. E. (2001). Syntrophin-dependent expression and localization of Aquaporin-4 water channel protein. *Proc Natl Acad Sci U S A,* 98, 14108-13.

NICCHIA, G.P., NICO, B., CAMASSA, L.M., MOLA, M.G., LOH, N., DERMIETZEL, R., SPRAY, D.C., SVELTO, M. & FRIGERI, A. (2004). The role of aquaporin-4 in the blood-brain barrier development and integrity: studies in animal and cell culture models. *Neuroscience* 129(4):935-45.

NICCHIA, G.P., ROSSI, A., NUDEL, U., SVELTO, M. & FRIGERI, A. (2008). Dystrophin-dependent and -independent AQP4 pools are expressed in the mouse brain. *Glia* 56(8):869-76.

NICO, B., FRIGERI, A., NICCHIA, G. P., CORSI, P., RIBATTI, D., QUONDAMATTEO, F., HERKEN, R., GIROLAMO, F., MARZULLO, A., SVELTO, M. & RONCALI, L. (2003). Severe alterations of endothelial and glial cells in the blood-brain barrier of dystrophic mdx mice. *Glia,* 42, 235-51.

NICOLSON, R. I., FAWCETT, A. J., BERRY, E. L., JENKINS, I. H., DEAN, P. & BROOKS, D. J. (1999). Association of abnormal cerebellar activation with motor learning difficulties in dyslexic adults. *Lancet,* 353, 1662-7.

NUDEL, U., ROBZYK, K. & YAFFE, D. (1988). Expression of the putative Duchenne muscular dystrophy gene in differentiated myogenic cell cultures and in the brain. *Nature,* 331, 635-8.

NUSSER, Z., CULL-CANDY, S. & FARRANT, M. (1997) Differences in synaptic GABA(A) receptor number underlie variation in GABA mini amplitude. *Neuron,* 19**,** 697-709.

O'BRIEN, K. F. & KUNKEL, L. M. (2001). Dystrophin and muscular dystrophy: past, present, and future. *Mol Genet Metab,* 74, 75-88.

OGASAWARA, A. (1989). Similarity of IQs of siblings with Duchenne progressive muscular dystrophy. *Am J Ment Retard,* 93, 548-50.

OGASAWARA, A. (1989a). Downward shift in IQ in persons with Duchenne muscular dystrophy compared to those with spinal muscular atrophy. *Am J Ment Retard,* 93, 544-7.

PALUMBO, D., PANDYA, S., MOXLEY, R. & SILVERSTEIN, S. (1996). Cognitive Dysfunction in Boys with Duchenne Muscular Dystrophy. *Archives of Clinical Neuropsychology,* 11, 431.

PARTRIDGE, T. (1991). Animal models of muscular dystrophy--what can they teach us? *Neuropathol Appl Neurobiol,* 17, 353-63.

PERRONNET, C. & VAILLEND, C. (2010). Dystrophins, utrophins, and associated scaffolding complexes: role in mammalian brain and implications for therapeutic strategies. J *Biomed Biotechnol* 2010:849426.

PETROF, B. J. (2002). Molecular pathophysiology of myofiber injury in deficiencies of the dystrophin-glycoprotein complex. *Am J Phys Med Rehabil,* 81, S162-74.

PILLERS, D.A., BULMAN, D.E., WELEBER, R.G., SIGESMUND, D.A., MUSARELLA, M.A., POWELL, B.R., MURPHEY, W.H., WESTALL, C., PANTON, C., BECKER, L.E., WORTON, R.G. & RAY, P.N. (1993). Dystrophin expression in the human retina is required for normal function as defined by electroretinography. *Nat Genet* 4(1):82-6.

PONTING, C. P., BLAKE, D. J., DAVIES, K. E., KENDRICK-JONES, J. & WINDER, S. J. (1996). ZZ and TAZ: new putative zinc fingers in dystrophin and other proteins. *Trends Biochem Sci,* 21, 11-13.

POYSKY J. (2007). Behavior patterns in Duchenne muscular dystrophy: report on the Parent Project Muscular Dystrophy behavior workshop 8-9 of December 2006, Philadelphia, USA. *Neuromuscul Disord*. 17(11-12):986-94.

RAE, C., LEE, M. A., DIXON, R. M., BLAMIRE, A. M., THOMPSON, C. H., STYLES, P., TALCOTT, J., RICHARDSON, A. J. & STEIN, J. F. (1998). Metabolic abnormalities in developmental dyslexia detected by 1H magnetic resonance spectroscopy. *Lancet,* 351, 1849-52.

RAE, C., SCOTT, R. B., THOMPSON, C. H., DIXON, R. M., DUMUGHN, I., KEMP, G. J., MALE, A., PIKE, M., STYLES, P. & RADDA, G. K. (1998). Brain biochemistry in Duchenne muscular dystrophy: a 1H magnetic resonance and neuropsychological study. *J Neurol Sci,* 160, 148-57.

RAE, C., LAWRANCE, M. L., DIAS, L. S., PROVIS, T., BUBB, W. A. & BALCAR, V. J. (2000). Strategies for studies of neurotoxic mechanisms involving deficient transport of L-glutamate: antisense knockout in rat brain in vivo and changes in the neurotransmitter metabolism following inhibition of glutamate transport in guinea pig brain slices. *Brain Res Bull,* 53, 373-81.

RAE, C., GRIFFIN, J. L., BLAIR, D. H., BOTHWELL, J. H., BUBB, W. A., MAITLAND, A. & HEAD, S. (2002). Abnormalities in brain biochemistry associated with lack of dystrophin: studies of the mdx mouse. *Neuromuscul Disord,* 12, 121-9.

RANDO, T. A. (2001). The dystrophin-glycoprotein complex, cellular signaling, and the regulation of cell survival in the muscular dystrophies. *Muscle Nerve,* 24, 1575-94.

RAPAPORT, D., LEDERFEIN, D., DEN DUNNEN, J. T., GROOTSCHOLTEN, P. M., VAN OMMEN, G. J., FUCHS, O., NUDEL, U. & YAFFE, D. (1992). Characterization and cell type distribution of a novel, major transcript of the Duchenne muscular dystrophy gene. *Differentiation,* 49, 187-93.

REID, D. T. & RENWICK, R. M. (2001). Relating familial stress to the psychosocial adjustment of adolescents with Duchenne muscular dystrophy. *Int J Rehabil Res,* 24, 83-93.

RENTSCHLER, S., LINN, H., DEININGER, K., BEDFORD, M. T., ESPANEL, X. & SUDOL, M. (1999). The WW domain of dystrophin requires EF-hands region to interact with beta-dystroglycan. *Biol Chem,* 380, 431-42.

ROBERTS, R. G., COFFEY, A. J., BOBROW, M. & BENTLEY, D. R. (1993). Exon structure of the human dystrophin gene. *Genomics,* 16, 536-8.

ROBERTS, R. G. (2001). Dystrophins and dystrobrevins. *Genome Biol,* 2, REVIEWS3006.

ROCCELLA, M., PACE, R. & DE GREGORIO, M. T. (2003). Psychopathological assessment in children affected by Duchenne de Boulogne muscular dystrophy. *Minerva Pediatr,* 55, 267-73, 273-6.

ROSMAN, N. P. & KAKULAS, B. A. (1966). Mental deficiency associated with muscular dystrophy. A neuropathological study. *Brain,* 89, 769-88.

SAVAGE, R. & ADAMS, M. (1979). Cognitive Functioning and Neurological Deficit: Duchenne Muscular Dystrophy and Cerebral Palsy. *Australian Psychologist* 14, 59-75.

SBRICCOLI, A., SANTARELLI, M., CARRETTA, D., PINTO, F., GRANATO, A. & MINCIACCHI, D. (1995). Architectural changes of the cortico-spinal system in the dystrophin defective mdx mouse. *Neurosci Lett,* 200, 53-6.

SCHOFIELD, J. N., BLAKE, D. J., SIMMONS, C., MORRIS, G. E., TINSLEY, J. M., DAVIES, K. E. & EDWARDS, Y. H. (1994). Apo-dystrophin-1 and apo-dystrophin-2, products of the Duchenne muscular dystrophy locus: expression during mouse embryogenesis and in cultured cell lines. *Hum Mol Genet,* 3, 1309-16.

SEKIGUCHI, M. (2005). The role of dystrophin in the central nervous system: a mini review. *Acta Myol,* 24, 93-7.

SEKIGUCHI, M., ZUSHIDA, K., YOSHIDA, M., MAEKAWA, M., KAMICHI, S., YOSHIDA, M., SAHARA, Y., YUASA, S., TAKEDA, S. & WADA, K. (2009). A deficit of brain dystrophin impairs specific amygdala GABAergic transmission and enhances defensive behaviour in mice. *Brain* 132(Pt 1):124-35.

SEPTIEN, L., GRAS, P., BORSOTTI, J. P., GIROUD, M., NIVELON, J. L. & DUMAS, R. (1991). [Mental development in Duchenne muscular dystrophy. Correlation of data of the brain scanner]. *Pediatrie,* 46, 817-9.

SESAY, A. K., ERRINGTON, M. L., LEVITA, L. & BLISS, T. V. (1996). Spatial learning and hippocampal long-term potentiation are not impaired in mdx mice. *Neurosci Lett,* 211, 207-10.

SHAW, R. F. & DREIFUSS, F. E. (1969). Mild and severe forms of X-linked muscular dystrophy. *Arch Neurol,* 20, 451-60.

SICINSKI, P., GENG, Y., RYDER-COOK, A. S., BARNARD, E. A., DARLISON, M. G. & BARNARD, P. J. (1989). The molecular basis of muscular dystrophy in the mdx mouse: a point mutation. *Science,* 244, 1578-80.

SMITH, D. I., ZHU, Y., MCAVOY, S. & KUHN, R. (2006). Common fragile sites, extremely large genes, neural development and cancer. *Cancer Lett,* 232, 48-57.

SMITH, P. E., CALVERLEY, P. M. & EDWARDS, R. H. (1988). Hypoxemia during sleep in Duchenne muscular dystrophy. *Am Rev Respir Dis,* 137, 884-8.

SMITH, R. A., SIBERT, J. R., WALLACE, S. J. & HARPER, P. S. (1989). Early diagnosis and secondary prevention of Duchenne muscular dystrophy. *Arch Dis Child,* 64, 787-90.

SMITH, R. A., SIBERT, J. R. & HARPER, P. S. (1990). Early development of boys with Duchenne muscular dystrophy. *Dev Med Child Neurol,* 32, 519-27.

SOGOS, V., ENNAS, M. G., MUSSINI, I. & GREMO, F. (1997). Effect of dystrophin antisense oligonucleotides on cultured human neurons. *Neurochem Int,* 31, 447-57.

SOGOS, V., REALI, C., FANNI, V., CURTO, M. & GREMO, F. (2003). Dystrophin antisense oligonucleotides decrease expression of nNOS in human neurons. *Brain Res Mol Brain Res,* 118, 52-9.

SOLLEE, N. D., LATHAM, E. E., KINDLON, D. J. & BRESNAN, M. J. (1985). Neuropsychological impairment in Duchenne muscular dystrophy. *J Clin Exp Neuropsychol,* 7, 486-96.

SUGITA, H., ARAHATA, K. & ISHIGURO, T. (1988). Negative immunostaining of Duchenne muscular dystrophy (DMD) and mdx muscle surface membrane with antibody against synthetic peptide fragment predicted from DMD cDNA. *Proc Jap Acad,* 64, 37-39.

SUZUKI, A., YOSHIDA, M., HAYASHI, K., MIZUNO, Y., HAGIWARA, Y. & OZAWA, E. (1994). Molecular organization at the glycoprotein-complex-binding site of dystrophin. Three dystrophin-associated proteins bind directly to the carboxy-terminal portion of dystrophin. *Eur J Biochem,* 220, 283-92.

TAYLOR, P.J., BETTS, G.A., MAROULIS, S., GILISSEN, C., PEDERSEN, R.L., MOWAT, D.R., JOHNSTON, H.M. & BUCKLEY, M.F. (2010). Dystrophin gene mutation location and the risk of cognitive impairment in Duchenne muscular dystrophy. *PLOS ONE* 20;5(1):e8803.

TOKARZ, S. A., DUNCAN, N. M., RASH, S. M., SADEGHI, A., DEWAN, A. K. & PILLERS, D. A. (1998). Redefinition of dystrophin isoform distribution in mouse tissue by RT-PCR implies role in nonmuscle manifestations of duchenne muscular dystrophy. *Mol Genet Metab,* 65, 272-81.

TORRES, L. F. & DUCHEN, L. W. (1987). The mutant mdx: inherited myopathy in the mouse. Morphological studies of nerves, muscles and end-plates. *Brain,* 110 (Pt 2), 269-99.

TRACEY, I., SCOTT, R. B., THOMPSON, C. H., DUNN, J. F., BARNES, P. R., STYLES, P., KEMP, G. J., RAE, C. D., PIKE, M. & RADDA, G. K. (1995). Brain abnormalities in Duchenne muscular dystrophy: phosphorus-31 magnetic resonance spectroscopy and neuropsychological study. *Lancet,* 345, 1260-4.

TRACEY, I., DUNN, J. F. & RADDA, G. K. (1996). Brain metabolism is abnormal in the mdx model of Duchenne muscular dystrophy. *Brain,* 119 (Pt 3), 1039-44.

TRACEY, I., DUNN, J. F., PARKES, H. G. & RADDA, G. K. (1996a). An in vivo and in vitro H-magnetic resonance spectroscopy study of mdx mouse brain: abnormal development or neural necrosis? *J Neurol Sci,* 141, 13-8.

UCHIKAWA, K., LIU, M., HANAYAMA, K., TSUJI, T., FUJIWARA, T. & CHINO, N. (2004). Functional staus and muscle strength in people with Duchenne muscular dystrophy living in the community. *Journal of Rehabilitation Medicine,* 36, 124-129.

UCHINO, M., YOSHIOKA, K., MIIKE, T., TOKUNAGA, M., UYAMA, E., TERAMOTO, H., NAOE, H. & ANDO, M. (1994). Dystrophin and dystrophin-related protein in the brains of normal and mdx mice. *Muscle Nerve,* 17, 533-8.

UEDA, H., BABA, T., KASHIWAGI, K., IIJIMA, H. & OHNO, S. (2000) Dystrobrevin localization in photoreceptor axon terminals and at blood-ocular barrier sites. *Invest Ophthalmol Vis Sci,* 41, 3908-14.

VAILLEND, C., RENDON, A., MISSLIN, R. & UNGERER, A. (1995). Influence of dystrophin-gene mutation on mdx mouse behavior. I. Retention deficits at long delays in spontaneous alternation and bar-pressing tasks. *Behav Genet,* 25, 569-79.

VAILLEND, C., BILLARD, J. M., CLAUDEPIERRE, T., RENDON, A., DUTAR, P. & UNGERER, A. (1998). Spatial discrimination learning and CA1 hippocampal synaptic plasticity in mdx and mdx3cv mice lacking dystrophin gene products. *Neuroscience,* 86, 53-66.

VAILLEND, C., UNGERER, A. & BILLARD, J.M. (1999). Facilitated NMDA receptor-mediated synaptic plasticity in the hippocampal CA1 area of dystrophin-deficient mice. *Synapse* 33(1):59-70.

VAILLEND, C. & BILLARD, J. M. (2002). Facilitated CA1 hippocampal synaptic plasticity in dystrophin-deficient mice: role for GABAA receptors? *Hippocampus,* 12, 713-7.

VAILLEND, C., BILLARD, J. M. & LAROCHE, S. (2004). Impaired long-term spatial and recognition memory and enhanced CA1 hippocampal LTP in the dystrophin-deficient Dmd(mdx) mouse. *Neurobiol Dis,* 17, 10-20.

VAILLEND, C., PERRONNET, C., ROS, C., GRUSZCZYNSKI, C., GOYENVALLE, A., LAROCHE, S., DANOS, O., GARCIA, L. & PELTEKIAN, E. (2010). Rescue of a dystrophin-like protein by exon skipping in vivo restores GABAA-receptor clustering in the hippocampus of the mdx mouse. *Mol Ther* 8(9):1683-8.

VAJDA, Z., PEDERSEN, M., FUCHTBAUER, E. M., WERTZ, K., STODKILDE-JORGENSEN, H., SULYOK, E., DOCZI, T., NEELY, J. D., AGRE, P., FROKIAER, J. & NIELSEN, S. (2002). Delayed onset of brain edema and mislocalization of aquaporin-4 in dystrophin-null transgenic mice. *Proc Natl Acad Sci U S A,* 99, 13131-6.

VAJDA, Z., PEDERSEN, M., DOCZI, T., SULYOK, E. & NIELSEN, S. (2004). Studies of mdx mice. *Neuroscience,* 129, 993-8.

VAN OMMEN, G. J., BERTELSON, C., GINJAAR, H. B., DEN DUNNEN, J. T., BAKKER, E., CHELLY, J., MATTON, M., VAN ESSEN, A. J., BARTLEY, J., KUNKEL, L. M. & ET AL. (1987). Long-range genomic map of the Duchenne muscular dystrophy (DMD) gene: isolation and use of J66 (DXS268), a distal intragenic marker. *Genomics,* 1, 329-36.

WAITE, A., TINSLEY, C.L., LOCKE, M. & BLAKE DJ. (2009). The neurobiology of the dystrophin-associated glycoprotein complex. *Ann Med* 1(5):344-59.

WALLIS, T., BUBB, W. A., MCQUILLAN, J. A., BALCAR, V. J. & RAE, C. (2004). For want of a nail. ramifications of a single gene deletion, dystrophin, in the brain of the mouse. *Front Biosci,* 9, 74-84.

WECHSLER, D. (1997). *WAIS-III/WMS-III Technical Manual,* San Antonio TX, Psychological Corporation.

WHELAN, T. B. (1987) Neuropsychological performance of children with Duchenne muscular dystrophy and spinal muscle atrophy. *Dev Med Child Neurol,* 29**,** 212-20.

WIBAWA, T., TAKESHIMA, Y., MITSUYOSHI, I., WADA, H., SURONO, A., NAKAMURA, H. & MATSUO, M. (2000). Complete skipping of exon 66 due to novel mutations of the dystrophin gene was identified in two Japanese families of Duchenne muscular dystrophy with severe mental retardation. *Brain Dev,* 22, 107-12.

WINDER, S. J., GIBSON, T. J. & KENDRICK-JONES, J. (1995). Dystrophin and utrophin: the missing links! *FEBS Lett,* 369, 27-33.

WU, J. W., KUBAN, K. C. K., ALLRED, E., SHAPIRO, F. & DARRAS, B. T. (2005). Association of Duchenne Muscular Dystrophy With Autism Spectrum Disorder. *Journal of Child Neurology,* 20**,** 790-795.

YOKOTA, T., MIYAGOE, Y., HOSAKA, Y., TSUKITA, K., KAMEYA, S., SHIBUYA, S., MATSUDA, R., WAKAYAMA, Y. & TAKEDA, S. (2000). Aquaporin-4 is absent at the sarcolemma and at perivascular astrocyte endfeet in .ALPHA.1-syntrophin knockout mice. *Proceedings of the Japanese Academy Series B,* 76B, 22-27.

YOSHIHARA, Y., ONODERA, H., IINUMA, K. & ITOYAMA, Y. (2003). Abnormal kainic acid receptor density and reduced seizure susceptibility in dystrophin-deficient mdx mice. *Neuroscience,* 117, 391-5.

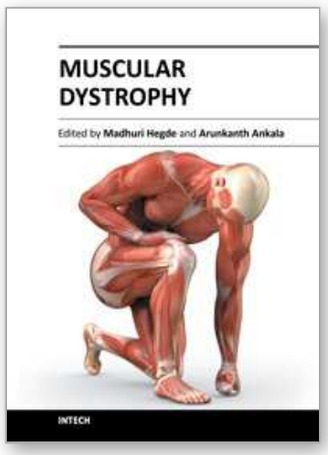
YOSHIOKA, M., OKUNO, T., HONDA, Y. & NAKANO, Y. (1980). Central nervous system involvement in progressive muscular dystrophy. *Arch Dis Child,* 55, 589-94.

YOUNG, H.K., BARTON, B.A., WAISBREN, S., PORTALES DALE, L., RYAN, M.M., WEBSTER, R.I. & NORTH, K.N. (2008). Cognitive and psychological profile in males with Becker muscular dystrophy. *J Child Neurol* 23(2):155-62.

ZACCARIA, M. L., PERRONE-CAPANO, C., MELUCCI-VIGO, G., GAETA, L., PETRUCCI, T. C. & PAGGI, P. (2001). Differential regulation of transcripts for dystrophin Isoforms, dystroglycan, and alpha3AChR subunit in mouse sympathetic ganglia following postganglionic nerve crush. *Neurobiol Dis,* 8, 513-24.

ZUBRZYCKA-GAARN, E. E., BULMAN, D. E., KARPATI, G., BURGHES, A. H., BELFALL, B., KLAMUT, H. J., TALBOT, J., HODGES, R. S., RAY, P. N. & WORTON, R. G. (1988). The Duchenne muscular dystrophy gene product is localized in sarcolemma of human skeletal muscle. *Nature,* 333, 466-9.

ZWAIGENBAUM, L. & TARNOPOLSKY, M. (2003). Two children with muscular dystrophies ascertained due to referral for diagnosis of autism. *J Autism Dev Disord,* 33, 193-9.



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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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