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Invited Review

Current knowledge of dystrophin and dystrophin-associated proteins in the retina

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Summary. Dramatical development of molecular genetics has been disclosing the molecular mechanism of Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (RMD). DMD gene product, dystrophin, is a submembranous cytoskeletal protein and many dystrophin-associated proteins (DAPs) have been identified, such as utrophin, dystroglycans, sarcoglycans, syntrophins and dystrobrevins. Dystrophin and DAPs are very important proteins not only for skeletal, cardiac, or smooth muscles but also for peripheral and central nervous systems including the retina. The retina has been extensively examined to demonstrate that dystrophin and ß-dystroglycan localize at the photoreceptor terminal, and their deficiency produces the abnormal neurotransmission between photoreceptor cells and ON-bipolar cells. Dystrophin has seven isoforms in variable tissues, and the retina contains full-length dystrophin (Dp427), Dp260, and Dp71. Recent studies have demonstrated that Dp71 localizes in the inner limiting membrane (INL) and around the blood vessel, and Dp260 is expressed in the outer plexiform layer (OPL). B-dystroglycan is also expressed in the same regions as well as dystrophin, but it remains unclear whether other DAPs are expressed in the retina or not. It is generally assumed that dystrophin functions to stabilize muscle fibers with DAPs by linking the sarcolemma to the basement membrane, but its function in the retina is totally unknown so far.

Key words: Retina, Dystrophin, Dystrophin-associated proteins, Photoreceptor cells, Müller cells

Introduction

Both DMD and BMD are X-linked recessive lethal disorders with a worldwide incidence of 1 in 3500 male births (Moser, 1984). The most striking clinical feature is skeletal muscle weakness, and usually DMD patients die with respiratory insufficiency by around 20 years old. Another prominent symptom is a non-progressive cognitive impairment, which approximately 30% of patients with DMD have. In addition, although no visual disturbance had been reported in the past several decades, recent physiological studies using electroretinograms (ERGs) have clarified that abnormal ERGs develop in some DMD/BMD patients (Cibis et al., 1993; Pillers et al., 1993; Fitzgerald et al., 1994; Sigesmund et al., 1994). Dystrophin, a lacking protein in DMD patients, is localized not only under the sarcolemma of skeletal, cardiac, or smooth muscle fibers (Arahata et al., 1988; Watkins et al., 1988; Zubrzycka-Gaarn et al., 1988) but also in the central nervous system (Lidov et al., 1990, 1993; Jung et al., 1991), peripheral nerves (Byers et al., 1993), and retinas (Miike et al., 1989; Zhao et al., 1991; Schmitz et al., 1993; Ueda et al., 1995, 1997a,b). Most of our current knowledge about dystrophin in synaptic regions is based on the studies of neuromuscular junctions (NMJs), which have no neuronal postsynaptic components. So it does not seem precisely to apply the knowledge obtained from the NMJ to other synapses. The retina is one of relatively easily-handled tissues for examination of the synaptic function and structure in the central nervous system. Since some excellent reviews have been published on the biochemical aspects of dystrophin and DAPs (Ahn and Kunkel, 1993; Ozawa et al., 1995, 1998; Henry and Campbell, 1996; Ohlendieck, 1996; Durbeej et al., 1998) and on the retinal dystrophin (Schmitz and Drenckhahn, 1997b), in this review we summarize recent knowledge about dystrophin and DAPs in the retina.

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Dystrophin and utrophin

Dystrophin has several spliced variants which are transformed from the large dystrophin gene, Xp21. Full-length dystrophin in muscle tissues such as skeletal, cardiac, or smooth muscles has a 427kDa molecular weight (M-dystrophin; Dp427), consisting of α-actinin-like domain, ß-spectrin-like domain, cysteine-rich domain, and carboxyl-terminal domain (Ahn and Kunkel, 1993). In the brain, the full-length dystrophin is

controlled by two different promotors; one is responsible for C-dystrophin expressed in cortex or hippocampus and the other is for P-dystrophin specifically expressed in Purkinje cells in cerebellum (Ahn and Kunkel, 1993). Several promotors which encode truncated dystrophin isoforms have been identified. Dp71, lacking a α-actinin-like or ß-spectrin-like domain, is widely expressed in nonmuscle tissues, but not in muscle tissues (Bar et al., 1990; Ahn and Kunkel, 1993). Dp116, Dp140, and Dp260 lack the α-actinin-like domain but retain ß-spectrin-like and cysteine-rich domains. The Dp116 is specifically expressed in Schwann cells of the peripheral nerves (Byers et al., 1993; Saito et al., 1999), the Dp140 is detected in the central nervous system and kidney (Lidov et al., 1995; Lidov and Kunkel, 1997), and the Dp260 is expressed in the brain, cardiac muscle, and retina (D'Souza et al., 1995).

Utrophin, a chromosome 6q24 gene product in human, is an 80% sequence homology of dystrophin, and its calculated molecular weight is 395kDa (Love et al., 1989; Lidov et al., 1990). Utrophin is expressed under the sarcolemma of skeletal muscle fibers during normal development by birth and then replaced by dystrophin, but in mature muscles it is only present at NMJs and myotendinous junctions (Bewick et al., 1992; Law et al., 1994). Utrophin expression often increases in muscles, in which dystrophin is decreased or lacks; accordingly it is assumed that utrophin functions to compensate dystrophin deficiency. Utrophin-dystrophin-deficient mice have skeletal and cardiac myopathies (Deconinck et al., 1997b; Grady et al., 1997b), but utrophin null mutants display no overt phenotypic abnormalities such as muscle weakness (Deconinck et al., 1997a; Grady et al., 1997a). Utrophin is also detected in brains (Khurana et al., 1992) and retinas (Montanaro et al., 1995), but it remains unclear whether utrophin mutant mice have abnormally ocular phenotypes.

Dystrophin-associated proteins (DAPs)

DAPs can be classified into three major groups; the dystroglycan complex, the sarcoglycan complex, and the syntrophin complex (Brown, 1996). Dystroglycans provide a crucial linkage between basement membrane and dystrophin with its cysteine-rich domain in the skeletal muscle, and which are widely expressed in many tissues (Henry and Campbell, 1996; Ohlendieck, 1996; Durbeej et al., 1998). The dystroglycan complex is the chromosome 3p21 gene product in human and is posttranslationally cleaved into α-dystroglycan and ß-dystroglycan (Ibraghimov-Beskrovnaya et al., 1992). α-dystroglycan is a glycosylated protein with 156 kDa molecular weight and its N-terminus binds to extracellular matrix components such as laminin 1, laminin 2, or agrin (Durbeej et al., 1998). Interestingly, recent studies have demonstrated that α-dystroglycan in Schwann cells may serve as a receptor for Mycobacterium leprae (Rambukkana et al., 1998), Lymphocytic choriomeningitis virus, or Lassa fever virus (Cao et al., 1998). ß-dystroglycan, a transmembrane protein with 43 kDa molecular weight, binds to cysteine-rich domains of dystrophin or utrophin via its C-terminus and to α-dystroglycan via its N-terminus (Henry and Campbell, 1996). In the central nervous system, ß-dystroglycan localizes at the basement membrane around blood vessels and in the astrocytic processes attaching to Purkinje cell bodies (Tian et al., 1996). In the retina α-dystroglycan is recognized in the outer plexiform layer (OPL), inner limiting membrane (ILM), and around blood vessels (Montanaro et al., 1995), but this has not yet been confirmed by electron microscopy. ß-dystroglycan is expressed in the astrocytic endfeet in the brain (Tian et al., 1996), Müller cell processes and photoreceptor cell terminals in the retina (Blank et al., 1997, 1999; Koulen et al., 1998; Schmitz and Drenckhahn, 1997a; Ueda et al., 1998).

The sarcoglycan complex is comprised of five different transmembrane proteins which are encoded by different genes in human, respectively, such as α-sarcoglycan (50 kDa; 17q21),ß-sarcoglycan (43 kDa; 4q12), γ-sarcoglycan (35 kDa; 13q12), δ-sarcoglycan (35 kDa; 5q33) and sarcospan (25 kDa; 12p11.2). Severe childhood autosomal recessive muscular dystrophy (SCRAMD) is clinically very similar to DMD but genetically heterogeneous; that is, a mutation in any one gene encoding any one of the components of the sarcoglycan complex may be responsible for SCRAMD (Ozawa et al., 1998). So far, to our knowledge, there has been neither a report on ocular phenotype in patients with SCRAMD nor on the sarcoglycan complex localization in the retina.

The syntrophin complex directly binds to the last half of the C-terminal domain of dystrophin and consists of cytoplasmic proteins encoded by different genes, respectively, such as α-syntrophin (60 kDa; 20q11.2), ß1-syntrophin (60 kDa; 8q23-24), and ß2-syntrophin (60 kDa; 16q22-23). However, the function of these proteins remains unclear even in striated muscles, and it has not been determined whether the syntrophin complex is expressed in the retina. Recently, dystrobrevin, a new dystrophin-associated protein, was cloned and localized at the postsynaptic membrane in mice and Torpedo (Blake et al., 1996; Sadoulet-Puccio et al., 1996). Subsequently, a couple of isoforms have been identified as α-dystrobrevin-1 (87kDa; 18q12.1-12.2),α-dystrobrevin-2 (65kDa; 18q12.1-12.2), and ß-dystrobrevin (71kDa; 2p22-23). There is no report on dystrobrevin expression in the retina yet, but recently our data demonstrate that dystrobrevin is expressed at the paravitreous and perivascular regions, in the ILM, OPL and retinal pigment epithelium (RPE) of the retina (manuscript in submission). Dystrophin and DAPs expression in the retina is summarized in Table 1.

ERG abnormality in patients with DMD and dystrophin mutant mice

There had been no reports on visual disturbance and

Table 1. Dystrophin and dystrophin-associated proteins in the retina. Their subcellular localization is described in parenthesis.

	kDa	GENE IN HUMAN	LOCALIZATION IN THE RETINA
Dystrophin		Xp2l	
Dp427	427		
DP260	260		OPL (photoreceptor cells)
DP 140	140		
DP116	116		
Dp71	71		ILM, Blood vessels
Utrophin	395	6q24	OPL
Dystroglycan (DG)		3p21	
α-DG	156		OPL
ß-DG	43		OPL (photoreceptor cells), ILM (Müller cells), blood vessels (Müller cells)
Sarcoglycan (SG)			
α-SG	50	17q21	
ß-SG	43	4q12	
γ-SG	35	13q12	
δ-SG	35	5q33	
Sarcospan	25	12p11.2	
Syntrophin (SP)			
α-SP	60	20q11.2	
ß1-SP	60	8q23-24	
ß2-SP	60	16q22-23	
Dystrobevin (DB)		18q12.1-12.2	
α-DB-1	87		
α-DB-2	65		
ß-DB	71	2p22-23	

ILM: inner limiting membrane; OPL: outer plexiform layer.

morphological abnormality in retinas of DMD or BMD patients. However, several recent studies have demonstrated that some DMD/BMD patients show abnormal ERG patterns with a reduced amplitude of b-wave under conditions of dark adaptation (Cibis et al., 1993; Pillers et al., 1993; Sigesmund et al., 1994; Fitzgerald et al., 1994; Lenk et al., 1996). Pillers et al. (1993) examined many DMD/BMD patients with ERGs and demonstrated that most of them had abnormal responses of rod cells. Neither had there been reports on color vision disturbance nor abnormal responses of cone cells in the ERGs in DMD/BMD patients (Sigesmund et al., 1994), but Fitzgerald et al. (1994) concluded that some of them had depolarizing bipolar cell dysfunction in cone cells as well.

The mdx mouse has a point mutation in exon 23 (Sicinski et al., 1989), resulting in lack of full-length dystrophin, but there is no abnormal ERG (Cibis et al., 1993). Novel genetic techniques have additionally produced four new mutant mice, $mdx^{Cv2\text{-}5}$, which lack some dystrophin isoforms (Champman et al., 1989; Cox et al., 1993; Im et al., 1996). mdx^{Cv3} mice, lacking all dystrophin isoforms, show prominent abnormal ERGs with reduced scotopic b-wave amplitude and increased b-wave oscillatory potential implicit times (Pillers et al., 1995, 1999). mdxCv2 mice are deficient in Dp427 and Dp260, and mdxCv4 mice run short of Dp 427, Dp260, and Dp140. Both mutant mice have increased ß-wave and oscillatory potential implicit times, but not significantly reduced b-wave amplitude (Pillers et al., 1999). Kameya et al. (1997) produced dystrophin gene exon 52 knock-out mice lacking Dp427 and Dp260, which showed the similar abnormal ERG patterns. mdx^{Cv5} mice retain all dystrophin isoforms except for Dp 427 and show normal ERGs (Pillers et al., 1999).

Dystrophin and ß-dystroglycan expression in rod spherules and cone pedicles

Synapses in the OPL, named as "photoreceptor ribbon synapses", have been known to have unique structures and functions. Photoreceptor cells function as sensors for light and are morphologically classified into rod cells and cone cells. In general, it is assumed that a rod spherule has a "triad" structure with a single bipolar cell process and two horizontal cell processes. However, a recent study with morphological reconstruction analyses reported that the rod spherule of the cat retina had two bipolar cell processes and two horizontal cell processes (Rao-Mirotznik et al., 1995). Cone cells have two kinds of synapses, invaginated and flat synapses. While invaginated synapses consist of two horizontal cell processes and only one bipolar process with synaptic ribbon(s), flat synapses have neither horizontal cell processes nor synaptic ribbons. A presynapse, i.e. photoreceptor cell terminal, is characterized by many synaptic clear vesicles and synaptic ribbons, and submembranous dense regions were always recognized under the photoreceptor cell membrane facing bipolar cells, but not horizontal cells (Ueda et al., 1997a). Moreover, photoreceptor cells have some biochemical features such as the lack of MAP-2 (De Camilli et al., 1984), neurofilament proteins (Shaw and Weber, 1984) and synapsins (Mandell et al., 1990) which are thought to connect synaptic vesicles with actin filaments and to be responsible for exocytosis at other synapses (Landis et al., 1988; Hirokawa et al., 1989). Therefore, vesicle clustering and mobilization in ribbon synapses probably differ from those in other synapses. Additionally the photoreceptor ribbon synapses have unique functions.

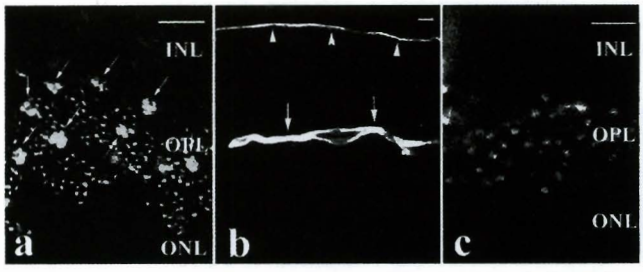

Fig. 1. Dystrophin **(a)** or ß-dystroglycan **(b)** expression in the retina. Dystrophin is expressed in cones (**a**, arrows) and rods at the outer plexiform layer of the rabbit retina. ß-dystroglycan expression is detected in the inner limiting membrane (**b**, arrowheads), around the blood vessels (**b**, arrows), and in the outer plexiform layer **(c)** of the rat retina. INL: inner nuclear layer; ONL: outer nuclear layer; OPL: outer plexiform layer. Bar: 10 μm.

The photoreceptor cells continuously release neurotransmitter, L-glutamate, to bipolar cells under dark conditions, and inhibit it under light stimulation (Massey, 1982). They respond to such stimuli with slow and graded potential changes, which are quite lower than those in other synapses, and generate no action potentials in vivo (Katz and Miledi, 1967).

Dystrophin is expressed in the OPL (Fig. 1a) and its subcellular localization has been demonstrated in the retina. Our immunoelectron microscopic studies showed that dystrophin was localized at projections and submembranous dense regions of rod spherules (Fig. 2; Ueda et al., 1995, 1997a). The interspace between two bipolar cell processes was always filled by the projections of rod spherules, whose tips showed the submembranous density and rarely had synaptic vesicles. The projections have been reported to be significant structures in lower vertebrates, because they are often recipients of the feedback synaptic input from horizontal cell processes (Linberg and Fisher, 1988). Similar projections were detected in the rat retina and were much more prominent in dark-adapted eyes (Brandon and Lam, 1983). Accordingly, it has been assumed that the projections are also important structures for physiological functions in mammalian retinas, although no feedback from horizontal cells to rod cells has been demonstrated in mammalian retinas (Linberg and Fisher, 1988). Dystrophin is also detected at the electron dense regions under the cone cell membrane as well as in rod cells (Fig. 3; Ueda et al., 1997b). Until now three different promotors of dystrophin have been identified in the retina and encode Dp427, Dp260, and Dp71, respectively. Recent studies have clarified that Dp260 localizes in the OPL (D'Souza et al., 1995; Kameya et al., 1997; Howard et al., 1998) and Dp71 in the ILM (Howard et al., 1998). However, it is not yet confirmed at an electron microscopic level whether Dp260 is expressed at the same submembranous regions in the photoreceptor cell terminal as shown in previous studies (Ueda et al., 1995, 1997a,b). Taken together with electrophysiological findings in the dystrophin-mutant mice, both Dp260 and Dp71, but not Dp427, are necessary for normal ERGs. However, little is known as to how Dp71 and/or Dp260 are implicated in neurotransmission in the retina.

ß-dystroglycan is expressed not only in OPL but also in ILM and around blood vessels (Fig. 1b,c). ß-dystroglycan is localized at the electron dense regions of the photoreceptor cell membrane including projections as well as dystrophin (Figs. 2, 3), and in Müller cell processes apposing to paravitreous or perivascular basement membranes discontinuously (Fig. 4; Blank et al., 1997; Koulen et al., 1998; Ueda et al., 1998). Interestingly, ß-dystroglycan expression was decreased

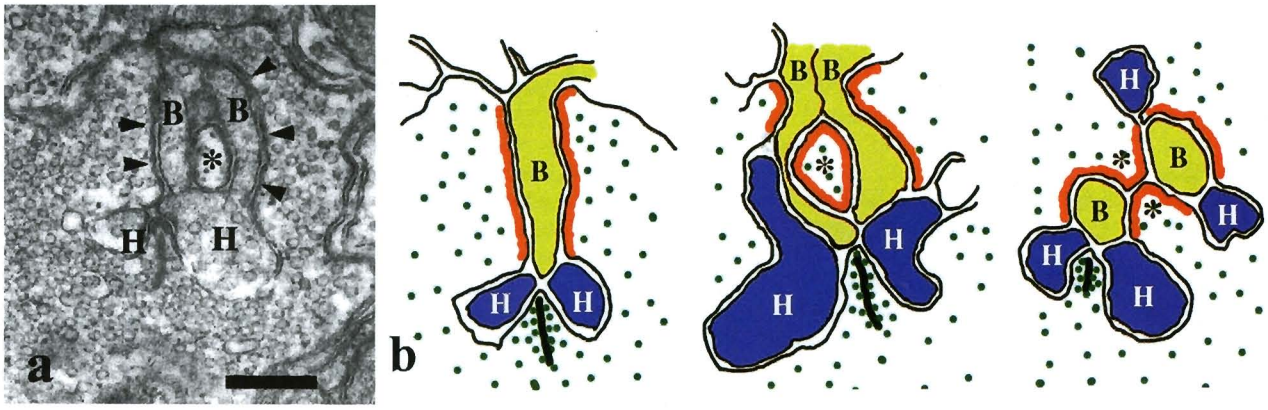

Fig. 2. Subcellular localization of dystrophin and ß-dystroglycan in the rod spherule. The rod cell membrane apposing to bipolar dendrites has electron dense regions (**a**, arrowheads) including projections (**a** and **b**, asterisks) where dystrophin and ß-dystroglycan are expressed (**b**, red lines). B: bipolar cell dendrite; H: horizontal cell process. Bar: 500 nm.

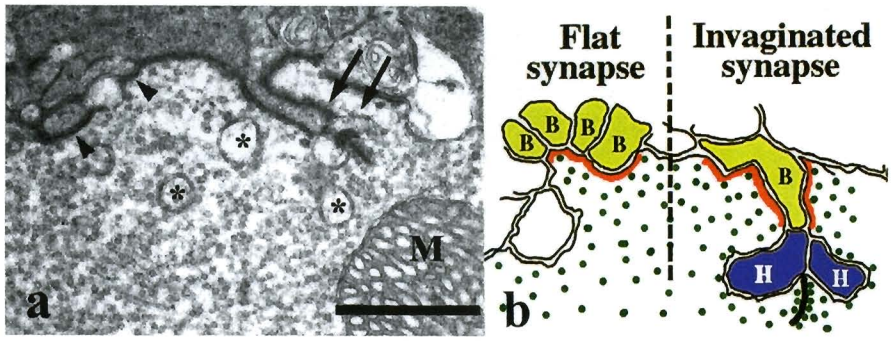

Fig. 3. Subcellular localization of dystrophin and ß-dystroglycan in the cone pedicle. The cone cell membrane facing bipolar dendrites has electron-dense regions as well as rod cell membrane **(a)**, where dystrophin and ß-dystroglycan are expressed (**b**, red lines). Arrowheads indicate a flat synapse, and arrows indicate an invaginated synapse **(a)**. Asterisks show endosomes. B: bipolar cell dendrite; H: horizontal cell process; M: mitochondria. Bar: 1μm.

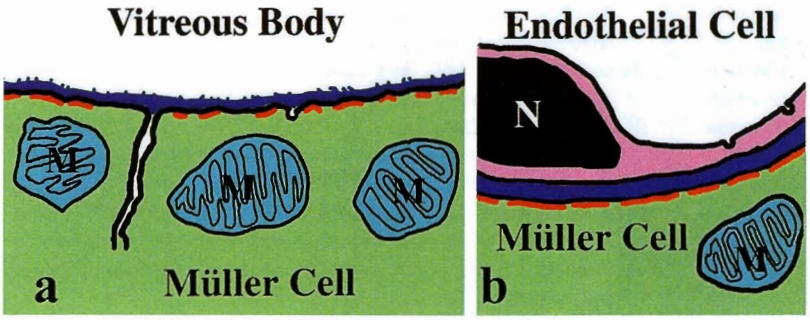

Fig. 4. Drawings of the ß-dystroglycan localization (red lines) at the paravitreous **(a)** and the pericapillary **(b)** endfeet of Müller cells. Blue lines indicate basement membranes. M: mitochondria; N: nucleus.

in the OPL of dystrophin exon 52 knock-out mouse (Kameya et al., 1997) and mdx^{Cv3} mouse retinas (Blank et al., 1999), but its expression around blood vessels or at the ILM was not affected in mdx ^{Cv3} mice (Blank et al., 1999). These data suggest that Dp260 is necessary for ß-dystroglycan localization at the photoreceptor terminal, but Dp71 is unnecessary for ß-dystroglycan positioning in the endfeet of Müller cells.

What are the functions of dystrophins or DAPs in the retina?

A function of dystrophin and DAPs has not yet been fully elucidated even in striated muscles, but there are two ideas for the function of the dystrophin complex. One is the Ca^{2+}-regulation theory and the other is the mechanical hypothesis (Ohlendieck, 1996). Some extracellular matrix proteins such as laminin, merosin and agrin are important for DAP complex (Ibraghimov-Beskrovnaya et al., 1992; Ervasti and Campbell, 1993; Gee et al., 1993, 1994; Bowe et al., 1994; Campanelli et al., 1994; Yamada et al., 1994), suggesting that the mechanical hypothesis is preferable for muscle fibers. However, recent molecular studies have shown that syntrophin PDZ domains bind the C-terminus of voltage-gated sodium channels (Gee et al., 1998; Schultz et al., 1998), suggesting that the dystrophin complex regulates intracellular homeostasis of muscle fibers. In the retina, it is assumed that characteristic exocytosis of synaptic vesicles in photoreceptor cells depends on the presynaptic Ca^{2+} channels (Augustine et al., 1988). Therefore, this idea leads us to think that retinal dystrophin may be associated with the regulation of the Ca^{2+} concentration in the photoreceptor nerve terminals, but there is no report showing direct evidence about this so far. At present, it is likely that dystrophin and DAPs play a key role in keeping the configuration between photoreceptor and bipolar cells in the retina, and its disruption induces abnormal signal transduction between them. However, another explanation can be available about abnormal neurotransmission in DMD/BMD patients and dystrophin-mutant mice. It is known that Müller cells appear to be involved in the generation of the b-wave in ERG (Newman and Odette, 1984; Wen and Oakley, 1990). Under dark-adapted conditions ON-bipolar cells depolarize, whereas OFF-bipolar cells hyperpolarize in response to light. These reactions increase extracellular potassium concentrations in the OPL (Stockton and Slaughter, 1989), and then Müller cells take in potassium and transport it through the cell body, later to release it into the vitreous humor. This potassium flux corresponds to a positive polarity when recorded as a b-wave in ERG (Newman and Odette, 1984; Wen and Oakley, 1990). The Müller cell membrane is characterized by orthogonal arrays of intramembrane particles that are revealed by the freeze-fracture replica method (Wolburg and Berg, 1988), and concentrates potassium channels at paravitreous endfeet, pericapillary endfeet, and apical endfoot-like villi (Newman and Reichenbach, 1996). ß-dystroglycan distribution at paravitreous and pericapillary endfeet of Müller cells (Schmitz and Drenckhahn, 1997a; Koulen et al., 1998; Ueda et al., 1998) seems very similar to the potassium channel distribution. In addition, Dp71 is expressed in the ILM and around blood vessels, although there is no electron microscopic examination on the Dp71 localization. Considering these electrical and immunohistochemical data in Müller cells, the relationship between dystrophins or ß-dystroglycan and potassium channels should be examined in the near future.

Conclusions

It is not doubted that dystrophins and some DAPs play a pivotal role in physiological functions in retinas, and probably in brains. However, the molecular mechanism about abnormal neurotransmission is not well known. To address this issue, extensive molecular, physiological and morphological examinations should be performed in retinas of variable dystrophin or DAP mutant mice.

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