Review Article

Aquaporin Expression in Normal and Pathological Skeletal Muscles: A Brief Review with Focus on AQP4

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Freeze-fracture electron microscopy enabled us to observe the molecular architecture of the biological membranes. We were studying the myofiber plasma membranes of health and disease by using this technique and were interested in the special assembly called orthogonal arrays (OAs). OAs were present in normal myofiber plasma membranes and were especially numerous in fast twitch type 2 myofibers; while OAs were lost from sarcolemmal plasma membranes of severely affected muscles with dystrophinopathy and dysferlinopathy but not with caveolinopathy. In the mid nineties of the last century, the OAs turned out to be a water channel named aquaporin 4 (AQP4). Since this discovery, several groups of investigators have been studying AQP4 expression in diseased muscles. This review summarizes the papers which describe the expression of OAs, AQP4, and other AQPs at the sarcolemma of healthy and diseased muscle and discusses the possible role of AQPs, especially that of AQP4, in normal and pathological skeletal muscles.

1. Introduction

Water is an essential substance for mammals, invertebrates, plants, and microorganisms. Water channel proteins named aquaporins (AQPs) have been found in the cell membranes of these organisms. In mammals, they have been identified in cell membranes such as in epithelial and endothelial cells. The first cloned water channel, AQP1, was purified from human erythrocytes by Agre and his associates [1] and its cDNA sequence was reported by Preston and Agre [2]. Then its water transporting capacity was demonstrated by cDNA expression studies in Xenopus oocytes [3]. So far 13 AQPs (AQP0–AQP12) have been cloned and sequenced in mammalian tissues. Each is a small intrinsic membrane protein of molecular weight ~30 kDa. These AQPs are classified into two groups: one is water selective channel (orthodox AQPs) and another is water, glycerol, and urea channel (aquaglyceroporins). Among 13 AQPs, AQP4 has a characteristic ultrastructural feature, since AQP4 can be identified by freeze-fracture (F-F) electron microscopy and can be seen as orthogonal arrays (OAs) in this method [4, 5]. We have so far been studying the pathophysiology of dystrophic muscles at RNA and protein levels including F-F electron microscopy. We found that the densities of both OAs and their subunit particles were reduced in Duchenne muscular dystrophy (DMD) muscles [6, 7]. So I would like to begin this review from F-F aspect of biological membrane especially focusing on OAs.

2. Tissue Distribution of Orthogonal Arrays (OAs)

The cleavage line of F-F goes into hydrophobic interior of biological membrane and F-F technique yields two leaflets of biological membrane: one is protoplasmic (P) face and another is extracellular (E) face [8]. The presence of OAs in cytoplasmic half (P face) of frozen cleaved biological plasma membranes has been described in different cell types of different species and different organs and tissues. Those containing OAs in their membranes include epithelial cells of the small intestine [9], brain astrocytes [10, 11], skeletal muscle cells [12–14], cardiac muscle cells [15], light cells of the kidney collecting tubules [16], tracheal epithelial
cells [17], satellite cells of developing spinal ganglia [18], sympathetic ganglia [19], gastric parietal cells [20], olfactory receptor cells of the newt [21], and tanycytes of the organum vasculosum of the lamina terminalis in dog [22]. The functional significance of this specific assembly (OAs) was unknown until Verkman and his coworkers discovered its function as water channel [4, 23–25]. Possible functions thought before the discovery included (1) regulation of membrane permeability [10, 16], (2) membrane transport of ions and so on [10, 14, 19–22, 26], (3) regulation of osmotic pressure [21], (4) conduction of activities of epithelial cells [17], (5) cell-to-cell communication [27], (6) adhesive properties [19], and (7) cellular junction [9, 22]. Before the discovery of OAs function as water channel, it was unknown whether the OAs acted as a monofunctional apparatus or one with several functions that differed in different organs and/or tissues.

3. OAs in Skeletal Muscle

In skeletal muscle, P face of muscle plasma membrane contains OAs and E face contains pits of OAs. Sirken and Fischbeck [28] reported that, in normal rat muscle, OAs were virtually absent at birth, but increased steadily from day 1 to day 27. After day 27, the number of OAs declined somewhat, then plateaued. The OA density is the highest at two months after birth in mouse skeletal muscle and, then, decreases gradually after that time [29]. The OA density is reported to be high in fast twitch type 2 myofibers; while it is almost all muscle, distribution frequency of OAs per square micron in reported to be high in fast twitch type 2 myofibers; while it is lower in slow twitch type 1 myofibers [30]. In human skeletal muscle, distribution frequency of OAs per square micron in normal muscle plasma membrane showed that almost all myofibers contained the OAs [7]. The age-related changes of OA densities were not studied in human skeletal muscles.

4. Discovery of Dystrophin and Its Associated Glycoproteins

DMD is a devastating disorder characterized by severe progressive muscle wasting and cardiac involvement both of which lead to a loss of ambulation by about 11 years of age and death by the third decade, mostly due to cardiac and/or pulmonary insufficiency [31]. Novel studies by Kunkel and his associates cloned the entire cDNA responsible for DMD [32] and determined its complete sequence [33]. The protein product of the cDNA is a large 427-kDa muscle protein that has been named dystrophin [34]. The immunofluorescent studies performed by the several groups of investigators demonstrated the localization of dystrophin at the surface membranes of the normal skeletal myofibers [35–38]. The immunoelectron microscopic investigations revealed the localization of dystrophin along the inner surface of muscle plasma membrane [39, 40]. Dystrophin constitutes 5% of membrane cytoskeletons in skeletal muscle [41]. Dystrophin is a membrane cytoskeletal protein anchored to the inner surface of the sarcolemma of normal myofibers by dystrophin-associated glycoproteins (DAGs) [42, 43]. DAGs contain extracellular α-dystroglycan, the transmembrane β-dystroglycan, α-, β-, γ-, δ-sarcoglycan and sarcospan, and cytoplasmic syntrophins and dystrobrevins [43]. The transmembrane β-dystroglycan and extracellular α-dystroglycan are encoded by a single messenger RNA and are translated in-frame from a single 97-kDa precursor protein [44, 45]. The α-dystroglycan binds to laminin of extracellular matrices in muscle and nonmuscle tissue [45]; whereas β-dystroglycan interacts directly with dystrophin [46]. α-, β-, γ-, and δ-Sarcoglycans contain one transmembranous domain; while sarcospan has four transmembranous domains [47–52]. Syntrophins and dystrobrevins are the cytoplasmic components of DAGs [43]. Syntrophins contain α, β1, β2, γ1, and γ2 isoforms which have been characterized so far [53, 54]; while dystrobrevins have α (−1 ~ −5) and β-isosforms [55–58]. Alternative splicing yields five forms of α-dystrobrevin, of which two predominate in skeletal muscle: full-length α-dystrobrevin-1 (84 kDa), and C-terminal truncated α-dystrobrevin-2 (65 kDa) [57]. α-Dystrobrevin-2, short isoform, binds dystrophin; whereas α-dystrobrevin-1 binds both dystrophin and utrophin [57]. Among five syntrophin isoforms, α1-syntrophin is present at its highest levels in skeletal muscle [59, 60] where it is located close to the inner surface of muscle plasma membrane together with β1-syntrophin. In contrast, β2-syntrophin is mainly concentrated at the neuromuscular junction [61]. AQP4 molecule turned out to be associated with α1-syntrophin as described below, although the association is not always the case.

5. Discovery of AQP4 and Its Relation to OAs

In 1995, Frigeri et al. [24] proposed that the OAs seen in F-F electron microscopy are AQP4. Then Yang et al. [25] first demonstrated that OAs are AQP4. Finally Verbavatz et al. [4] showed that OAs are absent in AQP4 knockout mouse. In central nervous tissues, astroglial endfeet membranes contain numerous OAs. Rash et al. [62] described that the direct immunogold labeling of AQP4 was observed in OAs of astrocyte and ependymocyte plasma membranes in rat brain and spinal cord. In skeletal muscle, Shibuya et al. [63] reported that anti-AQP4 antibody labeled OAs in the plasma membrane of normal rat skeletal myofiber by using fracture electron microscopy.

6. AQP4 Binds to α-Syntrophin

α1-Syntrophin knockout mice do not reveal any abnormal clinical phenotype and their skeletal muscles do not show pathological features in hematoxylin-eosin staining specimens. However, their muscle specimens with anti-AQP4 antibody immunostaining did not reveal any positive immunoreactivity [64, 65]. Adams et al. [66] thought that the C-terminal amino acid sequence of AQP4 is-VLSSV which is a potential class I PDZ domain interaction sequence. So they generated transgenic mice to determine whether the membrane localization of AQP4 depended on a syntrophin PDZ domain. Using their mice, they found that AQP4 was
absent from the sarcolemma and thought that the syntrophin PDZ domain is likely involved in targeting or stabilizing AQP4 [66]. Amiry-Moghaddam et al. [67] studied mice homozygous for targeted disruption of the gene encoding α-syntrophin (α-Syn−/−) and also found that these mice showed a marked loss of AQP4 from perivascular and subpial membranes but no decrease in other membrane domains [67]. In addition, Au et al. [68] described that AQP4 loss did not always correlate with loss of α-syntrophin in muscle disease. Based on these reports, it is suggested that AQP4 is associated with α-syntrophin, although this association is not always the case.

7. OAs and AQP4 Expression in Diseased Muscles and Muscles of Animal Models

The myofiber plasma membrane of DMD was thought to be fragile [69] and, in fact, the plasma membrane defect of DMD myofiber was demonstrated by electron microscopic observations [70–72]. So expression and distribution frequency of OAs in the diseased muscles were the interesting research subject at that time. Those of DMD were well analyzed [6, 73, 74]. The F-F findings of DMD muscle plasma membrane were the decreased density of individual intramembranous particles as well as OAs, or the loss of OAs [6, 33, 34] (Figure 1). The subunit particles constituting OAs were also reduced in the muscle plasma membrane of DMD [7]. Similar findings were recognized in the muscle plasma membrane of Fukuyama type congenital muscular dystrophy (FCMD) [75]. The muscle plasma membranes with Becker muscular dystrophy also showed the decrease of OA density. In the muscles of the mdx mouse, the mouse model of DMD, the muscle plasma membranes revealed the decrease of OA density but there was less conspicuous depletion of the individual intramembranous particles [76, 77]. The depletion of OAs was also seen in the muscle plasma membranes of dy/dy mice [78] and dystrophin exon 52 knockout mice [79]. In the denervated muscles, the muscle plasma membranes with early to moderate stage of amyotrophic lateral sclerosis (ALS) contained the substantial number of OAs [35]. Although the F-F study of muscle plasma membranes with advanced stage of ALS has not been reported, the muscle plasma membranes of advanced stage of ALS may have few OAs, since the rat muscles with early denervation contained no OAs [28]. DMD is a major type of human muscular dystrophy and AQP4 expression in DMD muscles has been intensively investigated. Three groups of investigators [68, 80, 81] reported the results of AQP4 expression of DMD muscles and those of mdx mouse muscles have also been described [82, 83]. All reports described that the AQP4 protein expression was reduced in the muscles of DMD boys (Figure 2) and mdx mice by immunohistochemistry. At RNA level, the results of the relative AQP4 mRNA contents of muscles with DMD boys [68, 81] and mdx mice [83] were somewhat different.
muscle. Scale bar in (a)–(c) 50 μm.

Figure 2: Immunofluorescence with anti-AQP4 antibody of normal control muscle (a) and Duchenne muscular dystrophy muscle (DMD) (b), and that with anti-spectrin antibody of serial muscle section of DMD (c). Positive immunoreactivity with anti-AQP4 antibody is seen in apparently all myofibers of normal muscle section of DMD (c). Positive immunoreactivity with anti-AQP4 antibody (b) than DMD muscle (b). DMD muscle contains less numerous myofibers with positive immunoreactivity of anti-AQP4 antibody (b) than myofibers with that of anti-spectrin antibody (c). Scattered anti-AQP4 immunonegative fibers (asterisks in (b)) are noted in DMD myofibers with that of anti-spectrin antibody (c). Scattered anti-

We [81] and Au et al. [68] reported the decreased contents of AQP4 mRNA in DMD muscles; while Frigeri et al. [83] reported the normal level of AQP4 mRNA content of mdx mouse muscles and described that the decreased total content of AQP4 protein was not transcriptional level. Au et al. [68] conducted the immunohistochemistry of AQP4 in the cultured DMD muscle cells and found the normal expression of AQP4. So they suggested that the reduced expression of AQP4 in DMD muscles was secondary to dystrophic process. Reduced AQP4 expression was also reported in severe muscular dystrophies such as FCMD [84], limb girdle muscular dystrophy (LGMD) type 2B [68, 85], sarcoglycanopathies [85], and animal models of sarcoglycanopathies [86]. However, in immunofluorescence analysis, AQP4 was reported to be expressed normally at the sarcolemma of biopsy samples from LGMD type 1C and facioscapulohumeral muscular dystrophy [80]. Many investigations revealed that the muscle contractile cycle appears to be associated with water entry into and exit out of the muscle cell [87, 88]. Muscle contraction needs energy supply which depends on anaerobic glycolysis in the fast twitch type 2 myofibers. The end product of anaerobic glycolysis is lactate and an increase of lactate by exercise prompts a rapid flux of water from the vascular compartment. The fast twitch type 2 myofibers contain many OAs (AQP4) in their sarcolemmal plasma membranes. The water molecule passes the cell membrane very rapidly through AQP4 water channel [89]. This water displacement may affect the membrane potential and thus muscle membrane excitability. Thus AQP4 is suggested to play a role in determining a rapid osmotic transfer of water from blood to muscle cell during muscle contraction. The dystrophic muscle immunohistochemistry tends to show the slow twitch type 1 fiber predominance. Slow twitch type 1 fiber contains less numerous OAs (AQP4) in the sarcolemmal plasma membrane. The decreased expression of AQP4 in the diseased muscles may relate to the slow contraction of voluntary muscles and thus, in part, may have relation to the slow motion of the myopathic patients, although the patient’s slowness mostly results from their muscle weakness. The defective expression of AQP4 in FCMD muscles may be based on the reduced expression of α1-syntrophin, which binds to AQP4, in FCMD muscles [90]. The central part of FCMD pathophysiology is the defective glycosylation of α-dystroglycan [91], however, the decreased expression of α1-syntrophin in FCMD muscles is reported to be due to the retarded maturation of FCMD muscles [91]. Reduced density of OAs was also reported in Becker muscular dystrophy (BMD) muscles and this reduction was correlated to the severity of BMD [92]. Furthermore, AQP4 expression of muscles with neurogenic muscular atrophy such as ALS was studied by Jimi et al. [93]. They reported that reduced expression of AQP4 was detected in ALS muscles. This phenomenon is confirmed by experimental studies [28, 94]. The implication of decreased AQP4 expression in the muscles of human muscular dystrophies and neurogenic atrophy is unknown. Animal models such as AQP4 knockout mice [95] and AQP4 overexpressing mice [96] showed no abnormal clinical phenotype. In dy/dy (laminin 2 deficient) mice, the reduction of OAs in the muscle plasma membrane was more marked than that of mdx mice [78].

8. Other AQPs Expressed in Sarcolemma

The presence of AQP1, 3, 4 mRNAs in skeletal muscle has been described [97–99]. Further Wang et al. [100] reported that they detected the mRNAs of AQP1, 3, 4, 7, 8, 9, and 10 in human masseter muscle and those of AQP1, 3, 4, and 10 in human infrahyoid muscle by RT-PCR. However, these AQPs mRNA expressions were considered to be the contamination of blood vessels (AQP1), adipocytes (AQP7), and leukocytes (AQP9) in skeletal muscle tissues [95]. To rule out this possibility, we and others conducted the immunocytochemical investigation of AQP1, 3, 5, 7, 9 of skeletal muscles, and confirmed the presence of these AQPs [101–105]. However, AQP1, 7 expression of normal skeletal myofiber is controversial. The negative immunostainings of AQP1 [106] and AQP7 [107] were described at the plasma membrane of skeletal myofiber, although the AQP1 and AQP7 immunoreactivities were recognized at the endothelial cells of endomysial blood vessels. We [104] and Au et al. [68] have performed the immunohistochemical study of AQP1.
in the skeletal muscle and showed the presence of AQP1 at the muscle membrane as well as the endothelial cells of endomyial blood vessels. With regard to AQP1 expression in the DMD muscles, Au et al. [68] reported that AQP1 transcript and protein expression was significantly elevated in DMD biopsies and was localized to the sarcolemma of muscle fibers and endothelia of muscle capillaries. The functional significance of aquaglyceroporins in skeletal muscle is unknown, however, these aquaglyceroporins function as a glycerol channel and may relate to the lipid metabolism in skeletal myofibers [108, 109].

9. Triglyceride Utilization and Its Possible Aquaglyceroporin Participation in Skeletal Muscle

The intracellular triglyceride in liver and skeletal muscle has a metabolic importance [110, 111]. Fatty acids of muscle triglyceride are derived from both circulating lipoprotein-triglyceride and free fatty acid which comes at least partially from adipose tissue lipolysis [110]. Lipolysis of circulating lipoprotein-triglyceride occurs in the capillary lumen prior to cellular uptake of fatty acids [110]. This extracellular lipolysis is controlled by lipoprotein lipase which is associated with the luminal side of the capillary endothelium. Lipoprotein lipase is activated by circulating apolipoprotein CII and inhibited by apolipoprotein CIII [110]. Adipose tissue lipoprotein lipase activity is the greatest [112] and is reciprocally regulated by hormone-sensitive lipase [113]. Adipose tissue lipoprotein lipase activity has diurnal fluctuation and is most active postprandially for the aim of fatty acids uptake for storage; while its activity decreases when there is a flux of fatty acids from adipose tissue such as the case in fasting [114]. In lipogenic conditions, intracellular glucose is converted by glycerol kinase to glycerol-3-phosphate which is then esterified into triglycerides in adipocytes [115].

The discovery of AQPs has greatly influenced the medical sciences. AQP3, 7, 9, and 10 are subcategorized as aquaglyceroporins, which transport the glycerol in addition to water. Adipocytes are a major source of glycerol which is one of the substrates for hepatic gluconeogenesis [115]. AQP7 and 9 are the glycerol channels in adipocytes and hepatocytes, respectively, [115]. Recently AQP9 is reported to be expressed weakly at the surface membrane of skeletal myofibers [105]. Hepatocytes and myocytes are two major insulin-sensitizing cells [115]. Through AQP7, the hydrolyzed glycerol is efficiently released from adipocytes into the blood stream. AQP7 mRNA levels in adipose tissue are reduced by feeding and increased by fasting in opposite to the changes in plasma insulin levels. Insulin suppresses AQP7 mRNA levels through the insulin negative element located on the promoter region of the AQP7 gene [115]. Therefore, plasma glycerol levels are partly determined by the action of insulin in adipose tissue. Thus long-term regulation of AQP7 is controlled by insulin at the transcriptional level; while short-term regulation is under the control of catecholamines [115].

AQP9 is a glycerol channel in liver cells and is localized at the sinusoidal plasma membrane which faces the portal vein [115–118]. On the other hand, weakly expressed skeletal muscle AQP9 is localized at the myofiber surface membrane [105]. AQP9 mRNA levels are increased by fasting and decreased by feeding [115–117], and this pattern of changes is similar to that for glycerol kinase and for phosphoenolpyruvate carboxykinase, the latter of which is a key enzyme in gluconeogenesis [115]. In the feeding state, an elevation of plasma insulin suppresses lipolysis in adipocytes, reduces adipose AQP7 mRNA levels, and lowers the rate of glycerol release; while liver and possibly myocyte AQP9 mRNA levels are reduced, and glycerol-based gluconeogenesis seems to be suppressed [115]. The investigations of aquaglyceroporins’ expression including that of AQP9 in the pathological muscles due to endocrine disorders such as muscles with type 2 diabetes mellitus will suggest some in the functional role(s) of muscle aquaglyceroporins in these pathological conditions.

10. Closing Remarks

The expression of AQPs in normal skeletal muscles and their altered expression in the diseased muscles so far reported were summarized in this review. The research of AQPs in skeletal muscles has not been done so extensively until now and has just begun in recent years. Further studies will throw light into the functional role(s) of AQP4 and other AQPs in the normal muscle physiology as well as in the pathophysiology of diseased muscles.

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