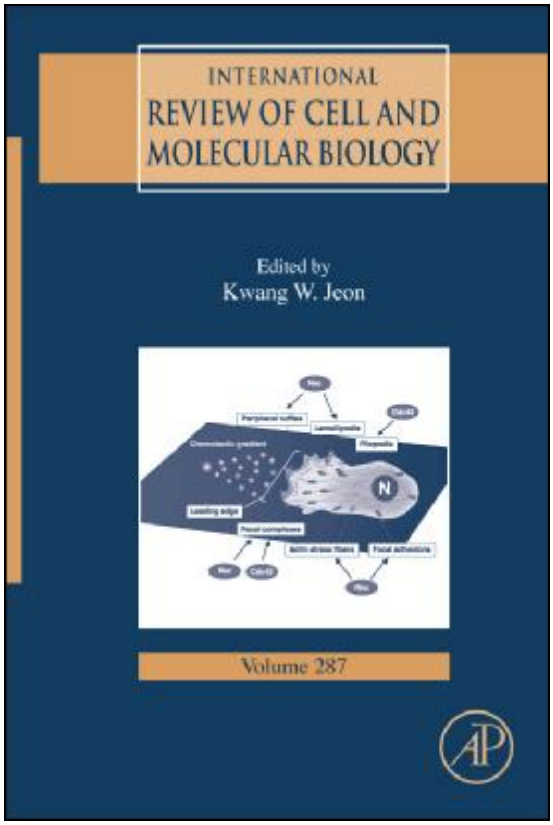

From: Hartwig Wolburg, Karen Wolburg-Buchholz, Petra Fallier-Becker, Susan Noell, and Andreas F. Mack, Structure and Functions of Aquaporin-4-Based Orthogonal Arrays of Particles. In Kwang W. Jeon, editor: *International Review of Cell and Molecular Biology*, Vol. 287, Burlington: Academic Press, 2011, pp. 1-41.
ISBN: 978-0-12-386043-9

CHAPTER ONE

Structure and Functions of Aquaporin-4-Based Orthogonal Arrays of Particles

Hartwig Wolburg,* Karen Wolburg-Buchholz,*
Petra Fallier-Becker,* Susan Noell,† and Andreas F. Mack‡

Contents

Abstract

Orthogonal arrays or assemblies of intramembranous particles (OAPs) are structures in the membrane of diverse cells which were initially discovered by means of the freeze-fracturing technique. This technique, developed in the 1960s, was important for the acceptance of the fluid mosaic model of the biological membrane. OAPs were first described in liver cells, and then in

* Institute of Pathology, University of Tübingen, Tübingen, Germany
† Clinics of Neurosurgery, Medical School, University of Tübingen, Tübingen, Germany
‡ Institute of Anatomy, University of Tübingen, Tübingen, Germany

International Review of Cell and Molecular Biology, Volume 287

ISSN 1937-6448, DOI: 10.1016/B978-0-12-386043-9.00001-3

parietal cells of the stomach, and most importantly, in the astrocytes of the brain. Since the discovery of the structure of OAPs and the identification of OAPs as the morphological equivalent of the water channel protein aquaporin-4 (AQP4) in the 1990s, a plethora of morphological work on OAPs in different cells was published. Now, we feel a need to balance new and old data on OAPs and AQP4 to elucidate the interrelationship of both structures and molecules. In this review, the identity of OAPs as AQP4-based structures in a diversity of cells will be described. At the same time, arguments are offered that under pathological or experimental circumstances, AQP4 can also be expressed in a non-OAP form. Thus, we attempt to project classical work on OAPs onto the molecular biology of AQP4. In particular, astrocytes and glioma cells will play the major part in this review, not only due to our own work but also due to the fact that most studies on structure and function of AQP4 were done in the nervous system.

Key Words: Astrocytes, Blood–brain barrier, Freeze-fracturing, Aquaporin-4, Water channel.

1. Introduction

The scientific histories of the so-called orthogonal (square) arrays (assemblies) of intramembranous particles (OAPs) on the one hand, and that of the aquaporins on the other hand, have different roots: the OAPs were first described in liver cells (Kreutziger, 1968). Staehelin (1972) described OAPs as a third type of gap junctions in intestinal epithelial cells. This characterization was refuted by Rash et al. (1974) by recognizing OAPs as a structure by its own. The following years were marked by exclusively descriptive morphological work on OAPs in different tissues without any knowledge about the molecular identity. These tissues included muscle cells, epithelial cells in the kidney, stomach, intestine, and in particular, in the nervous system, the macroglial cells such as astrocytes, retinal Müller glial cells, ependymal cells, and tanycytes. In 1986 and 1988, the independent groups of Gheorghe Benga and Peter Agre, respectively, discovered the water channel proteins which later were called aquaporins. It became not immediately clear that the family member aquaporin-4 (AQP4) is being the main constituent of the OAPs. This recognition grew gradually and was still not included in the comprehensive review of the literature on OAPs by Wolburg (1995). Since then, however, we have observed an explosion of data on OAPs and AQP4. In particular, the astrocytes were predominantly addressed as AQP4 and OAP expressing cells. More than 15 years later, we take a second look on the growing literature on OAPs and AQP4.

The detection of water-specific membrane channels in red blood cells belongs to the fundamental discoveries in biology of the twentieth century

(Benga et al., 1986a,b; Denker et al., 1988; Preston et al., 1992). The aquaporins mediate water movements between the intracellular, interstitial, vascular, and ventricular compartments which are under the strict control of osmotic and hydrostatic pressure gradients and can be regulated independently of solute transport (Nase et al., 2008; Pasantes-Morales and Cruz-Rangel, 2010). This function is conserved in animals, plants, and bacteria. At least 13 isoforms of aquaporins have been identified in mammals, designated AQP0 through AQP12 (Zelenina, 2010). Although most aquaporins, including AQP4, are selectively permeable to water, AQP3, AQP7, and AQP9 (aquaglyceroporins) are also permeable to urea and glycerol (Ma et al., 1997b). In mammals, aquaporins are involved in renal water absorption, generation of pulmonary secretions, lacrimation, secretion, and reabsorption of cerebrospinal fluid and aqueous humor, and development of edema (King et al., 2004). At the time of discovery, water channel proteins were named, such as CHIP28 (channel-forming integral membrane protein of 28 kDa; Hasegawa et al., 1994; Nielsen et al., 1993) for AQP1, GLIP (glycerol intrinsic protein; Frigeri et al., 1995) for AQP3, or MIWC (mercurial insensitive water channel; Yang et al., 1996) for AQP4. The major intrinsic protein (MIP) of the lens forms giant lattices in freeze-fracture replicas (Kistler and Bullivant, 1989). It has been identified as a water channel protein as well, now called AQP0 (King et al., 2004), and constitutes about 50% of the proteins in the fiber cells of the lens. Therefore, AQP0 and AQP4 are the only aquaporins to be visualized directly in the electron microscope. It has been pointed out that AQP0 performs not only water transport but also, probably more important, cell-to-cell adhesion in order to mediate lens transparency (Kumari and Varadaraj, 2009).

In the following sections, we will describe OAPs and AQP4 in cells outside and inside the nervous system, but it will be impossible to completely cover the literature due to the overwhelming plethora of data. In particular, many recent studies about AQP4 do not take into consideration or are not aware of the morphological aspect of this water channel as OAPs. Those studies will not be compiled preferentially in this chapter. Due to space limitation, only some selected original papers or prominent reviews will be cited considering cells of the muscle, urinary, intestinal, pulmonary, and auditory systems, before focusing on astrocytes and glioma cells in the CNS.

2. General Properties of OAPs and AQP4

It is now generally accepted that AQP4 constitutes the OAPs. This was shown by several lines of evidence, the absence of OAPs in astrocytes of AQP4-deficient mice (Verbavatz et al., 1997), the formation of OAPs in

Amiry-Moghaddam, M., Frydenlund, D.S., Ottersen, O.P., 2004. Anchoring of aquaporin-4 in brain: molecular mechanisms and implications for the physiology and pathophysiology of water transport. Neuroscience 129, 999–1010.

Anders, J.J., Brightman, M.W., 1979. Assemblies of particles in the cell membranes of developing, mature and reactive astrocytes. J. Neurocytol. 8, 777–795.

Anders, J.J., Brightman, M.W., 1982. Particle assemblies in astrocytic plasma membranes are rearranged by various agents in vitro. J. Neurocytol. 11, 1009–1029.

Anders, J.J., Pagnanelli, D.M., 1979. The protein nature and arrangement of intramembranous particle assemblies in normal and reactive astrocytes. Anat. Rec. 193, 470.

Aoki-Yoshino, K., Uchihara, T., Duyckaerts, C., Nakamura, A., Hauw, J.-J., Wakayama, Y., 2005. Enhanced expression of aquaporin 4 in human brain with inflammatory diseases. Acta Neuropathol. 110, 281–288.

Assereto, S., Mastrototaro, M., Stringara, S., Gazzerro, E., Broda, P., Nicchia, G.P., et al., 2008. Aquaporin-4 expression is severely reduced in human sarcoglycanopathies and dysferlinopathies. Cell Cycle 7, 2199–2207.

Au, C.G., Butler, T.L., Egan, J.R., Cooper, S.T., Lo, H.P., Compton, A.G., et al., 2008. Changes in skeletal muscle expression of AQP1 and AQP4 in dystrophinopathy and dysferlinopathy patients. Acta Neuropathol. 116, 235–246.

Barber, A.J., Lieth, E., 1997. Agrin accumulates in the brain microvascular basal lamina during development of the blood-brain barrier. Dev. Dyn. 208, 62–74.

Bartels, H., Miragall, F., 1986. Orthogonal arrays of particles in the plasma membrane of pneumocytes. J. Submicrosc. Cytol. 18, 637–646.

Bäuerle, C., Wolburg, H., 1993. Astrocytes in the non-myelinated lamina cribrosa of the rat are less polarized than in the optic nerve proper: a freeze-fracture study. Glia 9, 238–241.

Beitz, E., Kumagami, H., Krippeit-Drews, P., Ruppersberg, J.P., Schultz, J.E., 1999. Expression pattern of AQP water channels in the inner ear of the rat. The molecular basis for a water regulation system in the endolymphatic sac. Hear. Res. 132, 76–84.

Benfenati, V., Nicchia, G.P., Svelto, M., Rapisarda, C., Frigeri, A., Ferroni, S., 2007. Functional down-regulation of volume-regulated anion channels in AQP4 knockdown cultured rat cortical astrocytes. J. Neurochem. 1000, 87–104.

Benga, G., Popescu, O., Pop, V.I., Holmes, R.P., 1986a. p-(Chloromercuri)benzenesulfonate binding by membranes proteins and the inhibition of water transport in human erythrocytes. Biochemistry 25, 1535–1538.

Benga, G., Popescu, O., Borza, V., Pop, V.I., Muresan, A., Mocsy, I., et al., 1986b. Water permeability of human erythrocytes. Identification of membrane proteins involved in water transport. Eur. J. Cell Biol. 41, 252–262.

Berg-von der Emde, K., Wolburg, H., 1989. Müller (glial) cells but not astrocytes in the retina of the goldfish possess orthogonal arrays of particles. Glia 2, 458–469.

Berzin, T.M., Zipser, B.D., Rafii, M.S., Kuo-Leblanc, V., Yancopoulos, G.D., Glass, D.J., et al., 2000. Agrin and microvascular damage in Alzheimer's disease. Neurobiol. Aging 21, 349–355. Bezakova, G., Ruegg, M.A., 2003. New insights into the roles of agrin.

Nat. Rev. Mol. Cell Biol. 4, 295–308.

Blake, D.J., Kröger, S., 2000. The neurobiology of Duchenne muscular dystrophy: learning lessons from muscle? Trends Neurosci. 23, 92–99. 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, 645–657.

Bolz, S., Wolburg, H., 1992. First appearance of orthogonal arrays of particles in Muller cell membranes depends on retina maturation. Dev. Neurosci. 14, 203–209.

Bolz, J., Novak, N., Götz, M., Bonhoeffer, T., 1992. Formation of target-specific neuronal projections in organotypic slice cultures from rat visual cortex. Nature 346, 359–362.