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Inner Blood-Retinal Barrier Transporters: Relevance to Diabetic Retinopathy

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1. Introduction

Diabetic retinopathy is a frequent complication of diabetes, and leads to acquired blindness. A variety of gene and molecules have been studied to clarify its pathophysiological mechanism. The retina is involved in the vision process and contains neuronal cells that are the most sensitive to changes in the retinal environment, and the physiological barrier structure is important for maintaining optimal retinal homeostasis. The blood-retinal barrier (BRB) is composed of two cellular barriers, the tight junction of the retinal capillary endothelial cells (inner BRB) and the retinal pigment epithelial cells (outer BRB), restricting nonspecific material transport between the circulating blood and the retina. However, the specific transport of low molecular weight compounds, that is the supply of nutrients and elimination of undesired toxic compounds, is carried out by membrane transporter molecules at the BRB, suggesting that they are closely related to diabetic retinopathy. Since it is also known that two thirds of the human retina is nourished by the inner BRB (Cunha-Vaz, 2004; Hosoya & Tomi, 2005), in this chapter, we will describe the relationship between diabetic retinopathy and the membrane transporter molecules expressed at the inner BRB.

2. Structure and function of the inner BRB

In 1913, Schnaudigel was the first to propose the concept of the BRB. In his experiment, the retina showed similarity to the blood-brain barrier (BBB), that is, the retina was not stained with dye injected intravenously although peripheral tissues were stained (Schnaudigel, 1913). The tight junctions of retinal pigment epithelial (RPE) cells form the outer BRB, and the choriocapillaries are fenestrated while the inner BRB consists of multiple cells, retinal endothelial cells, pericytes and glial cells, and Müller cells are representative retinal glial cells. The inner BRB is formed by tight junctions of the retinal endothelial cells that are covered by pericytes and glial cells (Figure 1). Since the endothelial barrier is formed by a network complex including neurons, Müller cells/astrocytes and endothelial cells which control the function of retinal capillaries, the inner BRB can be thought of as a 'glio-vascular unit' (Kim et al., 2006).

2.1 Cellular interaction

The functional properties of the inner BRB are inducible by paracrine interactions with pericytes and glial cells. For example, in the endothelial cells, several barrier properties and

host-derived angiogenesis are induced by injection of type I astrocytes into the anterior eye chamber of rats (Janzer & Raff, 1987; Janzer, 1997), and the barrier properties of bovine-derived retinal endothelial cells are increased by co-culture with rat brain-derived astrocytes (Gardner et al., 1997). These pieces of evidence suggest that retinal glial cells (Müller cells and astrocytes) acts in a similar manner to astrocytes in the brain, and imply that the barrier function of the inner BRB is modified by several factors secreted from astrocytes. It is known that Müller cells produce several factors to enhance the barrier function of blood vessels in the retina (Tout et al., 1993). In experiments with TR-MUL cells, conditionally immortalized rat Müller cells, TR-MUL cells produce transforming growth factor-beta (TGF-β) to increase the activity of barrier marker proteins expressed in the TR-iBRB cells, conditionally immortalized rat retinal capillary endothelial cells, suggesting that Müller cells contribute to the regulation of barrier function (Abukawa et al., 2009). In addition, it has been reported that there is involvement of glia cell-derived neurotropic growth factors in the TGF-β family, interleukin-6, and basic fibroblast growth factor (bFGF), in barrier regulation (Abbott, 2002). Pericytes produce angiopoietin-1 to modify the barrier function of endothelial cells (Hori et al., 2004). The gap junction-mediated interaction between pericytes, endothelial cells and contractile cells is involved in the regulation of blood flow (Bandopadhyay et al., 2001). It is also known that pericytes exhibit contraction in the presence of endothelin-1, angiotensin II, ATP and hypoxia, and relaxation in the presence of CO_2, NO, and adenosine (Matsugi et al,. 1997a; Matsugi et al., 1997b; Chen & Anderson, 1997).

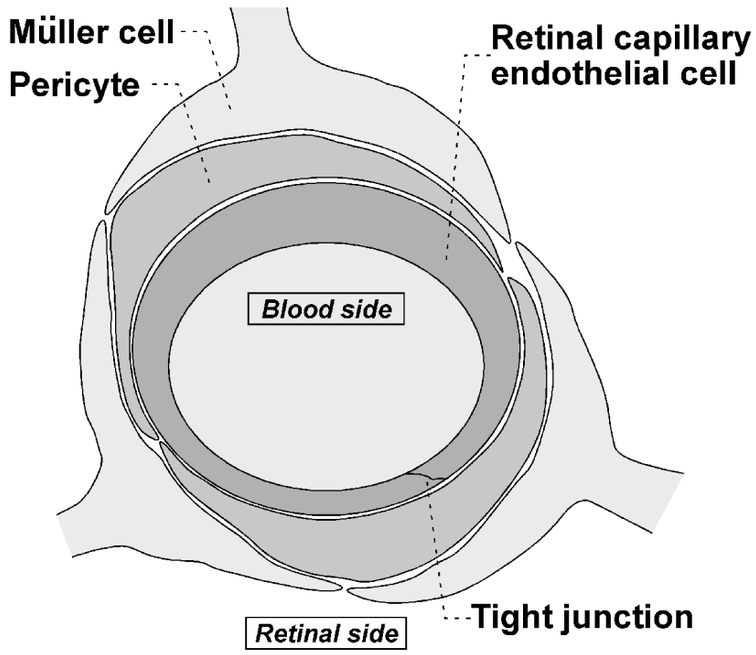

Fig. 1. Structure of inner Blood-Retinal Barrier (BRB)

2.2 Molecular aspects of the barrier structure

At the inner BRB, the retinal endothelial cells form a tightly sealed monolayer, separating the abluminal (retina side) and luminal (blood side) domains of the retinal endothelium, and prevent paracellular transport of materials across endothelial cells between the retina and

circulating blood (Wolburg et al., 2009). In particular, D-mannitol, a representative non-permeable paracellular marker, exhibits very low blood-to-retina influx permeability while D-glucose and amino acids, the substrates of membrane transporter molecules, exhibit over a 300-fold higher permeability than that of D-mannitol (Puchowicz et al., 2004; Hosoya & Tachikawa, 2009). These pieces of evidence strongly suggest that the inner BRB is a selective barrier for the retina. In order to maintain the tightly sealed monolayer, it is important for the retinal endothelial cells to be connected via a junctional complex including adherens junctions and tight junctions. Tight junctions are formed by signaling, scaffolding and transmembrane proteins, and it is known that the junctional adhesion molecules (JAM), occuludin and claudin play a role in the tight junctions (Hirase et al., 1997; Furuse et al., 1998; Bazzoni et al, 2005). The quantitative transcript analysis of rodent retinal endothelial cells shows markedly higher expressions of claudin-5, occludin, and JAM-1 than non-retinal endothelial cells (Tomi & Hosoya, 2004; Tachikawa et al., 2008). ZO-1, ZO-2 and ZO-3, accessory proteins, belong to the zonula occludens family, and are involved in linking the actin cytoskeleton and the cytoplasmic tails of the occludin and claudin complex (Anderson et al., 1995; Haskins et al., 1998). In addition, the seal between the retinal endothelial cells is enhanced by catenins and vascular endothelial cadherin (VE-cadherin) (Bazzoni & Dejana, 2004). An anti-sense nucleotide study has suggested that occludin plays an important role in the functional regulation of the inner BRB since the barrier permeability is increased by a reduction in occludin expression (Kevil et al., 1998). In addition, the expression of occludin is reduced in experimentally conditioned-diabetes, suggesting a change in retinal barrier function in patients with diabetic retinopathy (Antonetti et al., 1998). Other reports have suggested that vascular endothelial growth factor (VEGF) and nitric oxide (NO) have an effect on the increase in retinal barrier permeability. In the presence of vascular endothelial growth factor (VEGF), the cultured endothelial cells exhibit reduced occludin expression and increased barrier permeability across the endothelial cell monolayers (Yaccino et al., 1997), and the NO synthesis or release has been reported to increase the vascular permeability (Mark et al., 2004). Thus, it is thought that VEGF and NO are closely involved in retinal barrier function in diabetic retinopathy since the retina exhibits enhanced production of these factors in hypoxia (Kaur et al., 2006). In addition, hypoxia-ischemia leads to the production of reactive oxygen species (ROS) that cause oxidative stress and affect neovascularization in the diabetic eyes and retinopathy of prematurity (ROP) (Augustin et al., 1993; Saugstad & Rognum, 1988). Therefore, the physiological and pathological roles of VEGF, NO and ROS are important in retinal barrier function, and the suppression of their production or function will help in the clinical treatment of diabetic retinopathy, retinal hypoxia, ischemic central retinal vein occlusion, and other conditions (Kaur et al., 2008).

2.3 Transport system across the barrier

The paracellular impermeability of hydrophilic molecules is governed by the tight junctions in the retinal capillary endothelium. However, it is essential that retinal neural cells, such as photoreceptor cells, are able to take up sources of energy and eliminate undesired materials. Thus, transcellular transport by retinal capillary endothelial cells is needed for a variety of low molecular weight compounds, such as D-glucose, amino acids and their metabolites (Niemeyer, 1997; Tachikawa et al., 2007). Regarding the mechanisms of transcellualr

transport, there are three transport systems at the inner BRB, namely, passive diffusion, receptor-mediated transport and carrier-mediated transport (Figure 2). In particular, carrier-mediated transport is the most important for the uptake of essential nutrients and elimination of discarded metabolites, and this can be subdivided into facilitated transport, primary active efflux transport and secondary active influx and efflux transport (Hosoya & Tachikawa, 2009). In general, the membrane transporter is the 12 membrane-spanning membrane protein widely found in a variety of species ranging from bacteria to humans (Kubo et al., 2000; Kubo et al., 2005), and it is protein responsible for carrier-mediated transport. ATP-binding cassette (ABC) transporter and Solute carrier (SLC) transporter are involved in primary active efflux transport and secondary influx and efflux transport, respectively (Figure 3). It has been shown that a variety of influx membrane transporters, such as GLUT1 for D-glucose, are expressed in retinal capillary endothelial cells (Table 1), and they contribute to the retinal uptake of essential nutrients. It is also important to eliminate unwanted metabolites and toxic compounds from the retina. While facilitative and secondary active influx transport systems mediated by influx membrane transporters contribute to the influx of nutrients at the inner BRB, the elimination involves primary active and secondary active efflux transport systems. The efflux transport systems are mediated by ABC transporters, such as MDR1 (P-gp), and SLC transporters, such as OAT3 (Table 1). Research of membrane transporters uses a variety of analytical methods (Kubo et al., 2007). In particular, in the study of the inner BRB, integration plot and retinal uptake index analyses are available to study the *in vivo* blood-to-retina transport (Hosoya & Tomi, 2008), and TR-iBRB cells, the model cell line of retinal capillary endothelial cells, are useful for studying *in vitro* transport mechanisms (Hosoya & Tomi, 2005; Hosoya et al., 2001a).

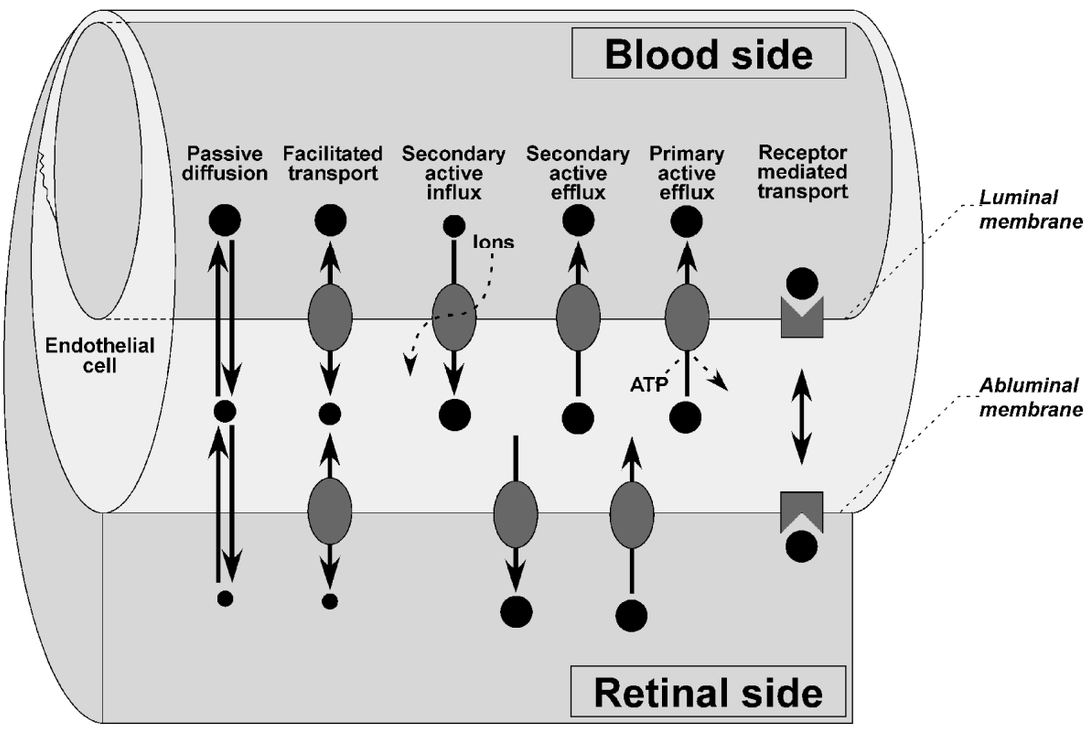

Fig. 2. Transport Systems in the inner BRB

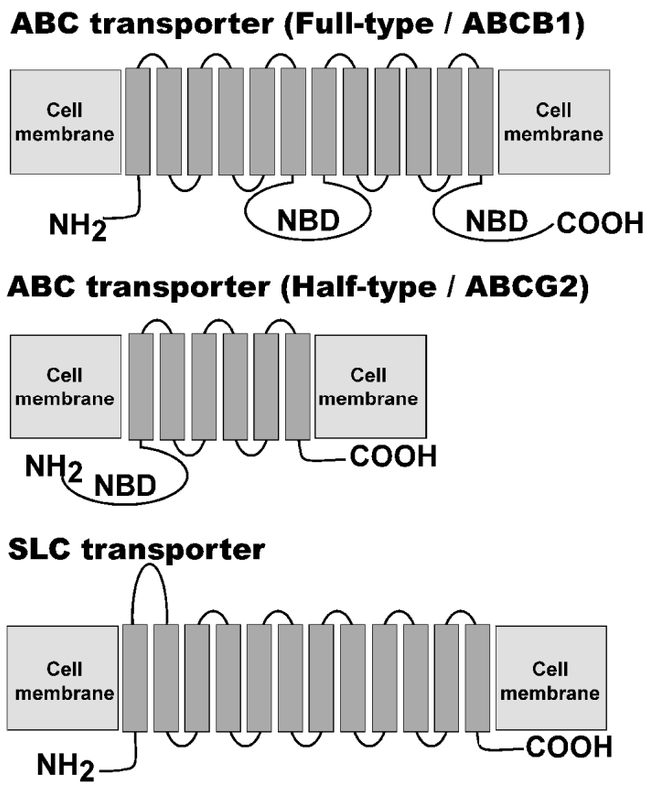

Fig. 3. Structure of Membrane Transporter

3. Hyperglycemia and glucose transporter (GLUT1)

Hyperglycemia (an increased blood D-glucose concentration) is the most important symptom exhibited by diabetic patients, and this has severe effects on the development of diabetic retinopathy (Cai & Boulton, 2002). At the inner BRB, the retinal endothelial cells express facilitative glucose transporter, GLUT1 that recognizes hexoses and dehydroascorbic acid (DHA) as substrates (Vera et al., 1993). GLUT1 mainly mediates the influx transport of D-glucose across the inner BRB. GLUT1 exhibits an asymmetrical localization at the inner BRB, and the abluminal expression of GLUT1 protein is 2- and 3-times higher than that on the luminal membrane (Takata K et al., 1992; Fernandes et al., 2003), suggesting that GLUT1 suppresses glucose accumulation in the retinal interstinal fluid. Regarding the influx permeability rate, the blood-to-retina transport is 544 and 2440 microL/(min · g retina) for D-glucose and DHA, respectively (Puchowicz et al., 2004; Hosoya et al., 2004). DHA is the oxidized form of ascorbic acid (vitamin C), one of the representative antioxidants, and rapidly undergoes cellular reduction to ascorbic acid, resulting in the higher permeability rate of DHA (Hosoya et al., 2008b). According to the K_m values of GLUT1 for D-glucose (5 mM) and DHA (93 microM) and the physiological plasma concentration of D-glucose (~5 mM) and DHA (~10 microM) (Hosoya et al., 2004; Ennis et al., 1982), GLUT1-mediated DHA influx transport across the inner BRB is not inhibited completely under normal and healthy conditions. However, under diabetic conditions, the elevated plasma concentration of D-glucose (>20 mM, hyperglycemia) causes a reduction in GLUT1-mediated DHA transport from the blood to the retina (Minamizono et al., 2006), showing that the retina of diabetic patients is subject to increased oxidative stress.

4. Hyperosmolality mediated by GLUT1

For all cells in the body, it is important to maintain a physiologically optimal osmolality. Sorbitol, a popular sweetener, works as a common organic osmolyte in cells. In the retinal cells, it is known that the cellular polyol pathway is responsible for sorbitol production from D-glucose (Vinores et al., 1993). The rate-limiting enzyme involved in sorbitol production is aldose reductase encoded by the *AR2* gene located on 7q35 which is thought to be a possible susceptible region for diabetic retinopathy (Patel et al., 1996). Under diabetic conditions, hyperglycemia enhances the intracellular accumulation of sorbitol because of the increased GLUT1-mediated facilitative D-glucose transport to the retina and stimulated cellular aldose reductase activity (Iannello et al., 1999). The elevated concentration of sorbitol causes hyperosmolality which stimulates lactate production and intracellular water and reduces the uptake of O_2 (Stevens et al., 1993; Lim et al., 2001). Therefore, GLUT1 is closely involved in the dysfunction and loss of retinal cells, including the capillary endothelial cells in diabetes. Although the change in GLUT1 expression also needs to be considered for a better understanding of the pathological and therapeutic aspects of diabetic retinopathy, both up- and down-regulation of GLUT1 have been reported in the retina with diabetes (Kumagai et al., 1996; Badr et al., 2000), and this remains controversial.

5. Advanced glycation end products (AGEs)

Advanced glycation end products (AGEs) are the result of a chemical chain reaction (non-enzymatic reaction). During normal aging and metabolism, glucose binds to the amino groups of proteins, through the Maillard reaction, Schiff base, and Amadori rearrangement, to produce Amadori products such as glycolhemoglobin (HbA1c) and glycolalbumin that are used to diagnose diabetes. The Amadori products undergo dehydration, hydrolysis and cleavage to form alpha-dicarbonyl compounds, such as glyoxal, methylglyoxal and 3-deoxyglucosone, that have a much greater ability than glucose to accelerate protein glycation. After further reactions, such as oxidation and degradation, irreversible AGEs are produced finally (Brownlee et al., 1988; Takeuchi & Makita Z, 2001).

5.1 AGE effects on the inner BRB

AGEs is the generic term that includes a number of compounds such as pentosidine, pyrraline, crossline, and N (epsilon)-(carboxymethyl) lysine. Interestingly, there are reports of the expression of receptors for AGEs, such as RAGE, on the cellular surface (Schmidt at al. 1992; Neeper et al., 1992). Under diabetic conditions, hyperglycemia promotes the production and accumulation of AGEs, and it is suggested that AGEs are closely related to the pericytes loss in diabetic retinopathy (Brownlee et al., 1988). As described previously, the retinal capillary is composed of endothelial cells, pericytes and glial cells, and it has been reported that the pericytes interacts with the endothelial cells to suppress the undesirable proliferation and prostacyclin production of endothelial cells and to protect these endothelial cells from harmful events (Yamagishi et al., 1993a; Yamagishi et al., 1993b). Therefore, the loss of pericytes, observed during the early stage of diabetic retinopathy, can be an exacerbating factor leading to the induction of neoangiogenesis via VEGF production, thrombus and hypoxia via prostacylin suppression in the retinal capillary endothelial cells. According to a recent report, the loss of pericytes is caused by AGEs and their receptors that inhibit the proliferation of pericytes and induce their apoptosis (Yamagishi et al., 1995; Yamagishi et al., 2002).

5.2 Taurine homeostasis and TAUT

It has been reported that the reactivity of AGEs can be blocked by the administration of taurine (Nandhini et al., 2004). Taurine is a non-essential amino acid which is thought to have a neuroprotective role as an osmolyte and antioxidant in the retina. In the body, taurine is synthesized from L-cysteine, and cysteine sulfinic acid decarboxylase is the rate-limiting enzyme involved in taurine biosynthesis. Interestingly, it is known that the retina is rich in taurine although the activity of cysteine sulfinic acid decarboxylase is low (Lin et al., 1985). This suggests the physiological importance of blood-to-retina taurine transport across the inner BRB for the maintenance of retina homeostasis. The taurine transport system is mediated by TAUT, which accepts taurine (K_m = 22.2 microM) for Na^+- and Cl^--dependent transport (Tomi et al., 2007). The expression of TAUT has been demonstrated in human primary retinal endothelial cells and TR-iBRB cells. Regarding the influx permeability rate, the blood-to-retinal transport is 259 microL/(min · g retina) for taurine (Tomi et al., 2007), and it has been confirmed that the substrates of TAUT have inhibitory effects on retinal taurine uptake (Törnquist et al., 1986). In a study with knockout mice, *taut*$^{-/-}$ mice exhibited an 80 to 90% reduction in taurine levels in the retina when compared with wild-type mice, showing that TAUT is responsible for the retinal homeostasis of taurine (Warskulat et al., 2007). Diabetic patients exhibit taurine deficiency, and a recent report shows that a reduced level of taurine in the retina causes the loss of cone photoreceptor and retinal ganglion cells, suggesting that retinal taurine deficiency is one of the exacerbating factors for diabetic retinopathy (Franconi et al., 1995; Jammoul et al., 2010). Reports have been published describing that taurine administration reduces the severity of the symptoms of diabetes (Barber, 2003; Moloney et al., 2010; Nakamura et al., 1999).

6. Oxidative stress

Oxidative stress is one of the exacerbating factors of diabetic retinopathy. Under normal conditions, it is important to protect the retina from light-induced oxidative stress, and the cellular uptake and synthesis of antioxidants can contribute to prevent the development of diabetic retinopathy. Catalase, superoxide dismutase (SOD) and glutathione peroxidase are representative cellular enzymatic systems that combat oxidative stress (Roginsky et al., 2001; Sozmen et al., 2001; Mates et al., 1999). Under diabetic conditions, down-regulation of SOD and glutathione peroxidase have been reported (Agardh et al., 1998; Agardh et al., 2000; Kern et al., 1994; Kowluru et al., 1997), and ROS are supposed to be generated by the production of AGE signaling via receptors for AGEs, the polyol pathway and enhanced metabolism of eicosannoid (Nourooz-Zadeh & Pereira 2000). Recently, TR-iBRB cells have been reported to show ROS-induced down-regulation of GLUT1 protein expression at the cellular plasma membrane, and proteasome and protein kinase B have been shown to be involved in this mechanism, suggesting that ROS disrupt glucose homeostasis in the retina (Fernandes et al, 2011). Regarding the enzymatic availability of NADPH, glutathione reductase, reducing the oxidized glutathione (GSSG) to glutathione (GSH), competes with aldose reductase in the polyol pathway, suggesting inhibitory effects on the retinal enzymes (Sato et al., 1999; Bravi et al., 1997). In glutathione synthesis, xCT, the membrane transporter expressed in retinal capillary endothelial cells, plays an important role in transporting L-cystine across the inner BRB from the circulating blood. xCT is the representative molecule for the system Xc^- and forms a heterodimer with 4F2hc to transport L-cystine and L-glutamate. TR-iBRB cells exhibits Na^+-independent L-cystine uptake (Km=9.2 microM), which is inhibited

by substrates of xCT. xCT is one of the important molecules involved in the biosynthesis of GSH which is a potent endogenous antioxidant. The expression and activity of xCT has been reported to be up-regulated in response to oxidative conditions (Tomi et al., 2002), and it is expected that the expressional and functional alterations of xCT will have an effect on the development of the diabetic retinopathy, regulating the retinal GSH level.

Transporter	Alias	Substrates	Transport Direction	References
SLC2A1	GLUT1	D-Glucose	Influx	Puchowicz et al., 2004
		DHA	Influx	Hosoya et al., 2004
SLC5A6	SMVT	Biotin	Influx	Ohkura et al., 2010
SLC6A6	TAUT	Taurine	Influx	Törnquist et al, 1986
		GABA	Influx	Tomi et al., 2007
SLC6A8	CRT	Creatine	Influx	Nakashima et al., 2004
SLC6A9	GlyT	Glycine	Influx	Okamoto et al., 2009
SLC7A1	CAT1	L-Arginine	Influx	Tomi et al., 2009
SLC7A5	LAT1	L-Leucine	Influx	Törnquist et al, 1986 Tomi et al., 2005
SLC7A11	xCT	L-Cystine	Influx	Tomi et al., 2002
		L-Glutamate	Influx	Hosoya et al., 2001b
SLC16A1	MCT1	L-Lactate	Influx	Gerhart et al., 1999 Alm et al., 1985 Hosoya et al., 2001c
SLC19A1	RFC1	MTF	Influx	Hosoya K et al., 2008a
SLC22A5	OCTN2	L-Carnitine	Influx	Tachikawa et al., 2010
SLC22A8	OAT3	Organic anions	Efflux	Kikuchi et al., 2003 Somervaille et al., 2003 Hosoya et al., 2009
SLC29A2	ENT2	Nucleosides	Influx	Nagase et al., 2006 Baldwin et al., 2004,
SLC38A2	ATA2	L-Proline	Efflux	Yoneyama et al., 2010
	SNAT2	L-Alanine	Efflux	LaNoue et al., 2001 Levkovitch-Verbin et al., 2002
SLCO1A4	OATP1A4 oatp2	Organic anions	Efflux	Nakakariya et al., 2008 Katayama et al., 2006 Noé et al., 1994 Gao et al., 2002 Sugiyama et al., 2001
ABCB1	MDR1 P-gp	Lipophilic drugs Organic cations	Efflux	Hosoya et al., 2001a Maines et al., 2005 Shen et al., 2003 BenEzra et al., 1990a BenEzra et al., 1990b
ABCC4	MRP4	Organic anions	Efflux	Tagami et al., 2009 Smeets et al., 2004 Uchida et al., 2007
ABCG2	BCRP MTX	Organic anions	Efflux	Asashima et al., 2006 Boulton et al., 2001

DHA dehydroascorbic acid; GABA gamma-aminobutyric acid; MTF methyltetrahydrofolate

Table 1. Membrane Transporters Identified at the inner BRB

7. Conclusion

In this chapter, we have described membrane transporters, such as GLUT1 for D-glucose and DHA, TAUT for taurine, and xCT for L-cystine and L-glutamate, which are mainly involved in the uptake of nutrients across the inner BRB under normal physiological conditions. However, under diabetic conditions, these membrane transporters have accelerating or decelerating roles in retinal capillary endothelial cells, and precise quantification of their expressional alteration in diabetes will provide information about the detailed pathological features of diabetic retinopathy. To date, although it has been shown that a variety of membrane transporters are expressed in retinal capillary endothelial cells (Table 1), there is still insufficient information about them to allow us to have a complete picture of retinal homeostasis, and further studies are needed. Therefore, there is still the possibility that several known membrane transporters play roles in diabetic retinopathy. Regarding the drug treatment of diabetic retinopathy, the membrane transporters are expected to be used in pharmacokinetic predictions and retina-specific drug delivery systems. At the inner BRB, OCTN2 and MCT1 are thought to accept drugs as their substrates (Ohashi et al., 1999; Tamai et al., 1999), and novel drug transport systems have also been suggested (Hosoya et al., 2010). Therefore, retina-specific delivery is a potential for aldose reductase inhibitors, such as sorbinil, ranirestat and epalrestat, that can suppress the cell death of the retinal capillary endothelium (Goldfarb et al., 1991; Narayanan et al., 1993). Furthermore, over 400 identified gene/protein molecules belong to the membrane transporter family, and over 100 molecules are 'orphan transporters' and their expression, localization, function, substrates and roles need to be fully identified. In addition, it is thought that there are also a number of unidentified membrane transporter genes, and new research reports on novel membrane transporters can be seen even now (Kawahara et al., 2009). Therefore, new discoveries and findings will be made as a result of the study of the membrane transporters expressed at the inner BRB, and advances in this field will contribute to our understanding of the pathological and therapeutic aspects of diabetic retinopathy.

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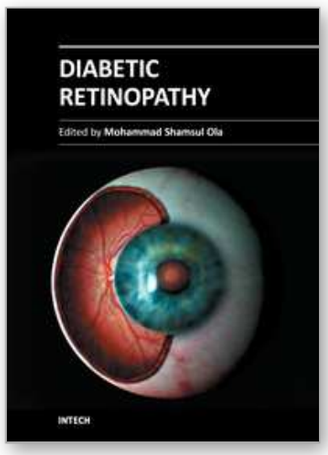

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The aim of this book is to provide a comprehensive overview of current concepts in pathogenesis, diagnosis and treatments of diabetic retinopathy. It provides a collection of topics written by excellent authors, covering discussions on advances in understanding of pathophysiology, immunological factors and emerging concepts, relating to clinical aspects and treatment strategies. The contents of the book will not only provide a resource for our knowledge but also improve diagnosis and treatment options for those patients who suffer vision loss due to diabetic retinopathy.

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