Role of Blood Retinal Barrier in Drug Absorption

Tyagi A, Sharma PK and Malviya R

Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Yamuna Expressway, Greater Noida, U.P., India

Corresponding author: Anchal Tyagi, Department of Pharmacy, School of Medical and Allied Sciences, Galgotias University, Yamuna Expressway, Greater Noida, U.P., India, Tel: +91-8273544416; E-mail: tyagianchal1234@gmail.com

Received date: April 25, 2018; Accepted date: May 10, 2018; Published date: May 16, 2018

Abstract

The blood-retinal barrier is the one of the earliest retinal changes in diabetes. The blood retinal barrier is a physiological barrier that regulates ion, protein and water flux in inner and outer retina. In blood-retinal barrier function vitreous fluorophotometry technique is an excellent technique to quantitate. The two most relevant retinal diseases are diabetic retinopathy and age related macular degeneration (AMD), are directly associated with alterations of the Blood retinal barrier (BRB). In this review, the authors also mentioned tracer molecules for evaluating the blood retinal barrier integrity.

Keywords: Blood-retinal barrier; Blood-brain barrier; Retinal pigment epithelial; Blood aqueous barrier

Introduction

The blood ocular barrier is formed by two main barriers- 1) The blood aqueous barrier (BAB) and 2) The blood retinal barrier (BRB). The blood aqueous barrier composed of the uveal capillary endothelial and ciliary epithelia which avoid to the drugs from entering the anterior chamber. The blood retinal barrier which inhibits the drugs from entering into the extravascular space of the retina and vitreous body [1]. The blood retinal barrier is tight and restrictive barrier and it is also a physiologic barrier and that regulates the water flux, protein, and ion in outer and inner of the retina. The blood retinal barrier consists of two components: Outer components and Inner components. The outer blood retinal barrier is formed a tight junctions between retinal pigment epithelial cells (RPE). The inner blood retinal barrier is formed by tight junctions between retinal epithelial cells (REC). Its principle can be accepted by tight junctions between these cells with metabolic gradients that comprise the barrier. The fraction, distribution to the inside of the eye is further prevented by the blood retinal barrier. Retinal drug delivery might be achieved using other methods, such as topical, periccular (sub-conjunctival, posterior juxtascleral, systemic, peribulbar and retrobulbar injections), sub-retinal, sub-Tenon’s and suprachoroidal drug administration, but these approaches may not be satisfactory drug concentrations in the retina with currently available technologies [2]. Systemic administration has also been used to deliver beneficial agents to the posterior segment of the eye. The route of administration desire large drug administration because of the inner and outer blood retinal barriers that separate the retina and the glassy humor from the systemic circulation [3]. The blood retinal barrier is composed of two cells in the posterior segment of the eye: Retinal pigment epithelial (RPE) and Retinal capillary endothelial (RCP). The retinal pigment epithelial and the retinal capillary epithelial barriers are provided due to their tight junctions and non-fenestrated capillaries [4-7]. In the eye, the retina is responsible for converting light into the electrochemical signal elucidated by the brain as vision. The epithelial and vascular both components of the blood retinal barrier are maintaining the specific environment of the neural retina. The molecular structure of the tight junction that provide the unique properties of the blood retinal barrier. Ocular drug absorption is delayed by static, metabolic and dynamic barriers. The Static ocular barriers contain blood aqueous barrier, sclera, corneal epithelium, blood capillary endothelial cells and retinal pigment epithelium. The dynamic ocular barriers comprise tear drainage, conjunctival blood and choroidal blood and lymphatic circulations. These three barriers are separated and described the anterior and posterior segment barriers. The maintenance of the inner blood retinal barrier appears to be under the control of perivascula astrocytes. Astrocytes migrate into the retina from the optic nerve and their migration across the retina coincides with the spread of patent vessels.

Pharmacokinetics of Ocular Route

Lachrymal fluid barrier: Drug absorption of lachrymal fluid in the eye gets restricted due to the presence of corneal epithelium [8]. Hydrophobic drugs have huge affinity across this barrier than hydrophilic drugs [9].

Blood ocular barriers: This barrier implement the protection from xenobiotics to the blood. Blood ocular barrier constitutes two types of barriers: Blood aqueous barrier (BAB) and Blood-retina barrier (BRB) [10]. After passing this barrier, drug can be easily arrive to the choroid and retina. For this specific targeting is required.

Loss of drug through ocular surfaces: The lachrymal fluid attempt to remove installed drug rapidly within a minute from ocular surface after instillation [11]. The elimination due to lachrymal flow decreases the concentration of the drug in the blood. For that reason, ocular bioavailability of the drug in tear fluid becomes only 10% [12].

The Structure and function of the inner Blood Retinal Barrier: The retina is showing the similarity to the blood brain barrier (BBB). The inner blood-retinal barrier (inner BRB) procedures tight junctions of retinal capillary endothelial cells and to prevent the free diffusion of substances between the neural retina and the circulating blood [13]. The inner blood retinal barrier is formed by tight junctions of the retinal endothelial cells that are covered by glial cells and pericytes cells. The choriocapillaries are fenestrated while the inner blood retinal...
barrier is consisting of such cells pericytes cell, glial cells, muller cells and retinal endothelial cells. The inner blood retinal barrier, the retinal endothelial cells a form tight junction separate the blood side and the retinal side of the retinal endothelium and prevents paracellular transport of materials. The tight junction between endothelial cells, pericytes cells and contractile cells is involved in regulation of blood flow [14].

**Transport system across the barrier:** The inner Blood retinal barrier, like the Blood brain barrier, has secondary components. The impermeability of hydrophilic molecules is conducted by the tight junction in the retinal capillary endothelium (RCE). Transcellular transport by retinal capillary endothelial cells is required for a variety of low molecular weight compounds, such as amino acids and D-glucose [15,16]. In the mechanisms of the transcellular transport three transport systems at the inner blood retinal barrier such as passive diffusion, carrier mediated transport and receptor mediated transport (Figure 1). The inner blood retinal barrier, carrier mediated transport is the important for the uptake of essential elimination and nutrients of discarded metabolites and it is divided into four parts such as facilitated transport, secondary active influx, secondary active efflux, and primary active efflux transport [17,18]. Secondary and facilitated active influx transport system mediated by influx membrane transporters provides to the nutrients at the inner BRB and the elimination involves primary active efflux and secondary active efflux system. It is also required for elimination of toxic compounds and unwanted metabolites form the retina (Figure 2).

**Blood retinal barrier and retinal diseases:** The inner BRB, from endothelial dysfunction are the alteration in diabetic retinal disease. In the alteration of the inner blood retinal barrier are leads to diabetic macular oedema are cause of loss of vision in diabetes [19]. In the outer blood retinal barrier is cause age-related macular degeneration (AMD). AMD is the integrity of the outer BRB that keeps the choroidal vascular response in the retina and converted the dry AMD into wet AMD. In both the Inner blood retinal barrier (iBRB) and the outer blood retinal barrier (oBRB), the tight cell junctions inhibit paracellular movement of fluids and molecules between blood and
retina, and the endothelial cells and retinal pigment epithelial (RPE) cells actively balance inward and outward movement [20]. The oBRB is stable by the tight junctions between nearby retinal pigment epithelial (RPE) cells [21,22]. The RPE is composed of a single layer of retinal pigment epithelial cells that are merged parallel towards their apices by tight junctions between neighboring lateral cell walls.

**The blood retinal barrier to treatment of retinal diseases:** When a drug is administered systemically and pass the blood retinal barrier to reach the therapeutic levels in the retina. When the drug enters into the retina are depends upon a number of factors such as the relative permeability of the BRB, plasma protein binding, the plasma concentration profile of the drug and the volume of its distribution. The therapeutic concentration of retina new strategies is considered, including chemical modification of drugs to increase blood retinal barrier transport, coupling of the drug to vectors and delivery of nanoparticles. The new strategy has not only enhanced the permeation into the tissue other than the retina, but also decreases the bioavailability of oral administration. The treatment of the posterior segment disease eye drops is considered to be limited benefit. Intravitreal injections are required for high concentration of the drug in the retina and the vitreous humor for preserving crucial protective function and blood retinal barrier integrity. Then decreases the concentration of intravitreal injections in case of anti-vascular endothelial growth factor (anti-VEGF) treatment, are given every six weeks to maintain efficacy.

**Clinical application:** Ocular diseases are increasing the function of the blood ocular barrier.

**Diabetic retinopathy:** Diabetic retinopathy is a major cause of loss of vision in adults [23]. It enhances the permeability of the blood ocular barrier. In some case of vitreous fluorophotometry are detecting the abnormality in blood retinal barrier function before ophthalmoscopy can determine the any abnormalities [24]. Laser flare photometry are determining the abnormality of blood aqueous barrier function is comparable with the clinical grade of retinopathy. There was no difference between diabetic patients and healthy patients without retinopathy [25,26]. The vitreous fluorophotometry value is normal in diabetic patients or minimal retinopathy and it is higher in advanced retinopathy [27,28]. The exacerbating factors of diabetic retinopathy are oxidative stress.

**Ocular inflammation:** In various types of uveitis in blood aqueous barrier function laser flare photometry has been used. Laser flare photometry has also been studying of post-surgical inflammation of the eye. Aqueous flare values have been described to increase after cataract surgery [29].

**Age related macular degeneration (AMD):** Age related macular degeneration is a common disorder of the retina and it affects the central vision. It is divided into two types: 1) Exudative and 2) Non exudative. Exudative age related macular degeneration are classified in the presence of choroidal neovascularization which may lead to lipid exudation and hemorrhage. To determine the various stages of age related macular degeneration, laser flare photometry are used. Vitreous fluorophotometry are showing the alteration in blood retinal barrier [30].

**Central serous chorioretinopathy:** The central serous chorioretinopathy mainly affects the outer blood retinal barrier. The abnormal blood retinal barrier function is shown vitreous fluorophotometry. The central serous chorioretinopathy are associated serous detachment of the retinal pigment epithelium may occur.

**Specific proteins of blood retinal barrier:** Some proteins can be used as an immunohistochemical to reveal functional blood retinal sites. It is divided into two categories. 1) Proteins associated with tight junctional complexes and 2) Proteins responsible for maintaining metabolic or ionic gradients. Retinal capillaries mainly share the same molecular component as brain capillaries with the barring of the y-gluamyl transpeptidase is not present from retinal capillaries but convey in brain capillaries [31]. A 140 kDa membrane protein combines with pericytes in the peripheral and central nervous system; it has been limited only in regions of blood nerve barrier (BNB) or blood brain barrier (BBB). The glucose transporter is another molecule that is reduced from interepithelial or interendothelial junctions are comprising blood tissue barrier such as blood retinal barrier (BRB) and blood brain barrier (BBB). It has been determined the capillary endothelial cells of the retina, iris and optic nerve on the ciliary body epithelium and the posterior epithelium of the iris. The glucose transporter (GLUTI) is bounded on cells by preventing the ocular tissue junction there is no pursuit of the transporter with the tight junction itself. GLUTI is no create on the capillary endothelium of vessels in the sclera, ciliary body, choroid or other retro orbital tissues that do not form a functional barrier.

**Blood retinal barrier (BRB) integrity of tracer molecules:** A number of molecules have been described with a radioactive isotope and used as a tracer molecule (Table 1) to determine the blood retinal barrier (BRB) function.

| S.No. | Tracer molecules | Molecular weight | Limitation | Application |
|-------|-----------------|------------------|------------|-------------|
| 1.    | Albumin         | 66, 120          | It is not useful clinically, but established and experimental sample can examine immunohistochemically. | The help of radiolabeled blood retinal barrier leakage can be measured, but not bounded sites of blood retinal barrier breakdown can be immunolocalized by electron microscopy. It is readily soluble in water and can only be precipitated by high concentrations of neutral salts such as ammonium sulphate. |
| 2.    | 14C-Sucrose     | 344              | Cannot localize sites of drainage, impossible for clinical studies | Quantification of blood retinal barrier leakage in experimental animals. It is photosynthesizing leaf, then visualization of the path of the radioactive tracer through photographing cross section of the plant stem |
3. Lanthanum 139 Requires perfusion or fixed tissue not useful clinically Localization of blood retinal barrier breakdown sites at the electron microscopic level.

4. Micro peroxidase 1,900 Requires tissue fixation and sectioning, not useful clinically may be cost prohibitive Localization of blood retinal barrier breakdown sites in experimental animals, can be used for electron microscopic evaluation.

5. Fibrinogen 34,000 Large molecular weight limits sensitivity, only determine the areas of substantial drainage, use limited to pathological sample Immunohistochimical localization of blood retinal barrier disruption sites.

6. Fluorescein 376 General can show the areas of leakage, but not specific sites at the cellular level Experimental or clinical it can be visually in-vivo by fluorescein angiography, vitreous fluorophotometry can be used for measurable leakage.

7. Horseradish peroxidase 40,000 Requires tissue fixation and sectioning; may induce artifactual BRB breakdown; not useful clinically Localization of BRB breakdown sites in experimental animals. It can be used for electron microscopic evaluation.

8. Evans blue dye 961 Only useful with gross pathological specimens Gross visualization of areas with BRB compromise

Table 1: Tracer molecules for evaluating the blood retinal barrier integrity [32].

Conclusion

Blood-ocular barriers play important roles in the maintenance and function of the eye. Laser flare photometry has also been studying of post-surgical inflammation of the eye. It can be concluded from the manuscript that the Structure and function of the inner blood retinal barrier and tracer molecules for evaluating the blood retinal barrier integrity.

References

1. Raviola G (1977) The structural basis of the blood-ocular barriers. Exp Eye Res 25: 25-63.
2. Amo EMD, Rimpela AK, Heikkinen E, Kari OK, Ramsay E, et al. (2017) Pharmacokinetic aspects of retinal drug delivery. Pro Ret Eye Res 57: 134-185.
3. Vinares SA (1995) Vinares assessment of blood-retinal barrier integrity. Histology and Histopathology 10: 141-154.
4. Barar J, Jawadzadeh AR, Omidi Y (2008) Ocular novel drug delivery: impacts of membranes and barriers. Expert Opin Drug Deliv 5: 567-581.
5. Hornof M, Toropainen E, Urtti A (2005) Cell culture models of the ocular barriers. Eur J Pharm Biopharm 60: 207-225.
6. Maurice DM, Mishima S (1984) Ocular pharmacokinetics. In: Sears ML, editor. Handbook of experimental pharmacology, Berlin: Springer pp: 16-119.
7. GardnerTW, Antonetti DA, Barber AJ, Lieth E, Tarbell JA (1999) The molecular structure and function of the inner blood-retinal barrier. Doc Ophthalomol 97: 229-237.
8. Urtti A, Salminen L (1993) Minimizing systemic absorption of topicaly administered ophthalmic drugs. Surv Ophthalmol 37: 435-456.
9. Pipkin JD, Rork GS (1990) Controlled drug delivery devices for experimental ocular studies with timolol, Ocular and systemic absorption in rabbits. Int J Pharm 61: 241-249.
10. Urtti A (2006) Challenges and obstacles of ocular pharmacokinetics and drug delivery. Advan Drug Deli Rev 58: 1131-1135.
11. Maurice DM, Misaim S (1984) Ocular pharmacokinetics, in: M. L. Spears, Handbook of Experimental Pharmacology. Springer Vela 69: 16-119.
12. Huang HS, Schoenwald RD, Lach JL (1983) Corneal penetration behavior of beta-blocking agents II: Assessment of barrier contributions. J Pharm Sci 72: 1272-1279.
13. Hosoya K, Tachikawa M (2009) Inner Blood-Retinal Barrier Transporters: Role of Retinal Drug Delivery. Pharm Res 26: 2055-2065.
14. Bandopadhyay R, Orte C, Lawrenson JG, Reid AR, De Silva S, et al. (2001) Contractile proteins in pericytes at the blood-brain and blood-retinal barriers. J Neurocytology 10: 39-54.
15. Niemeyer G (1997) Glucose concentration and retinal function. Clin Neurosci 4: 327-335.
16. Tachikawa M, Hosoya K, Ohtsuki S, Terasaki T (2007) A novel relationship between creatine transport at the blood-brain and blood-retinal barriers, creatine biosynthesis, and its use for brain and retinal energy homeostasis. Subcell Biochem 46: 83-98.
17. Hosoya K, Tachikawa M (2009) Inner blood-retinal barrier transporters: role of retinal drug delivery. Pharm Res 26: 2055-2065.
18. Kubo Y, Hosoya K (2012) Inner Blood-Retinal Barrier Transporters: Relevance to Diabetic Retinopathy. Diabetic Retinopathy. Physiol Rev 85: 845-881.
24. Chen MS, Kao CS, Chang CJ, Wu TJ, Chung FC, et al. (1992) Prevalence and risk factors of diabetic retinopathy among noninsulin-dependent diabetic subjects. Am J Ophthalmol 114: 723-730.

25. Cunha-Vaz JG, Abreu JRF, Campos AJ, Figo G (1975) Early breakdown of the blood-retinal barrier in diabetes. Br J Ophthalmol 59: 649-656.

26. Chen MS, Tseng MC, Yang CH (1993) Aqueous flare intensity in patients with diabetic retinopathy. Acta Soc Ophthalmol Sin 32: 205-208.

27. KUchle M, Schönherr U, Nguyen NX (1992) Quantitative measurement of aqueous flare and aqueous "cells" in eyes with diabetic retinopathy. Ger J Ophthalmol 1: 164-169.

28. Lin CP, Yu CY, Chen MS, Ko LS (1990) Vitreous fluorophotometry in diabetic subjects. Trans Soc Ophthalmol Sin 29: 959-964.

29. Engler C, Krogsaa B, Lund-Andersen H (1991) Blood-retinal barrier permeability and its relation progression of diabetic retinopathy in type I diabetics. Graefes Arch Clin Exp Ophthalmol 229: 442-446.

30. Dick HB, Schwenn O, Krummeuauer F, Krist R, Pfeiffer N (2000) Inflammation after sclerocorneal versus clear corneal tunnel phacoemulsification. Ophthalmol 107: 241-247.

31. Ferraris U, Vannini L, Grignolo FM, Menga M, Franzone U (1987) Vitreous fluorophotometry in various macular diseases. Ocular Fluorophotometry. Amsterdam: Kugler & Ghedini Publishers 93-101.

32. Johanson CE (1989) Ontogeny and phylogeny of the blood-brain barrier. In: Implications of the blood-brain barrier and its manipulation. Plenum Press New York 1: 157-198.