Review Article

Experimental animal models for retinal and choroidal diseases

Abstract

Experimental animal models have critical importance for the recognition and the management of various retinal and choroidal diseases. To date, they were described for the induction of melanoma and neovascularization of choroid, degenerations, and detachment in the retina, proliferative vitreoretinopathy, diabetic and hypertensive retinopathy, pre–retinal neovascularization, central serous chorioretinopathy, retinopathy of prematurity (ROP) or O_2 induced retinopathy (OIR) and retinoblastoma. The aim of this review is to provide an overview of experimental animal models for retinal and choroidal diseases. To know the most favorite models and animals for these diseases will provide many utilities to the researchers in their experimental studies and thesis.

Keywords: experimental, animal models, retinal, choroidal, diseases

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Introduction

Experimental animal models have an important place in medical research for the development of new therapeutic strategies in the treatment of the ocular diseases in humans. The aim of using animal models in ocular experiments is to achieve the easiness in the understanding of the pathophysiology of the diseases and to determine the specific treatment protocols for the diseases. Currently, a number of animal models are available for various choroidal and retinal diseases.[1–6] The researchers should be the choice to use the adequate animal model having the closest homology with human anatomy and pathology at the setting stage of their studies. The aim of this review is to give the general information on experimental animal models for various retinal and choroidal diseases and to provide the methods and techniques for researchers regarding experimental procedures in animals.

Choroidal malign melanoma

Choroidal melanoma is the most common primary malignant intraocular tumor and the second most common primary malignant melanoma in adults. It has been considered that the mouse model is the best in the immunologic studies while as rabbit model is more useful in the therapeutic studies for experimental choroidal melanoma. B16F10 melanoma cell lines originally isolated from melanotic tumors are used to establish choroidal melanomas. Tumor cells are implanted transclerally into the choroid. B16F10 melanoma cell line has also the more metastasis compared the other melanoma cell lines.[4–13]

Choroidal neovascularization (CNV) and neovascular age related macular degeneration (n–AMD)

Age–related macular degeneration (AMD) is a leading cause of irreversible visual loss in over 65 years old. Neovascular AMD is responsible for 90% of cases with severe vision loss from hemorrhage and fibrosis and it is characterized by CNV that is developed due to a rupture in the Bruch membrane. The induction of the neovascular AMD in an animal model is not easy. The animals having a macula are only the primates. Although the mechanical rupture of Bruch's membrane with laser photocoagulation (LFC) can stimulate CNV in primates, rabbits, and rodents, these usually improve spontaneously. Additionally, the recent studies in transgenic mice demonstrated that the neovascularization (NV) originated from the inner side of the retina but not from the outer side.[14–24] However, it has been recently developed an Ad vector encoding human VEGF to induce CNV. In this model used the Long–Evans rats, CNV developed two weeks following the subretinal injection of the viral vector (Table 1).[25]

Table I Experimental disease and most favorite animal for experimental retinal and choroidal diseases

Experimental ocular disease	Favorite animal for experimental model
Choroidal melanoma	Rabbit, Mouse
CNV and neovascular AMD	Primates, Rodents
Retinal detachment	Mouse
PVR	Rodents
Diabetic Retinopathy	Rat, Mice, Zebrafish
Preretinal neovascularization	Rabbit
CSCR	Monkey
Hypertensive retinopathy	Dog, Monkey
ROP or OIR	Mouse, Rat
Retinoblastoma	Mice, Murine
Retinal degeneration	Mice, Rat, Zebrafish
RIR	Rodent
CRVO	Rat
CRAO	Rat

CNV, choroidal neovascularization; AMD, age related macular degeneration; PVR, proliferative vitreoretinopathy; CSCR, central serous chorioretinopathy; ROP, retinopathy of prematurity; OIR, oxygene induced retinopathy; CRVO, central retinal vein occlusion; CRAO, central retinal artery occlusion; RIR, retinal ischemia-reperfusion

CNV induction can be performed with a slit lamp delivery system using Argon green LFC (100µm spot size, 180–300mW power, and 0.1 second duration) or Diode LFC (100µm spot size, 150–180mW power and 0.1 second duration) at the localization such as 8 regions between the major blood vessels in each eye or four LFC burns in each eye at the positions of 3, 6, 9, and 12 o'clock, almost two discs diameters from the optic nerve head. The observation of an acute vaporization or cavitation bubble indicates the rupture of Bruch's membrane. A spot size of 50 mm and duration of 100 ms has been most widely used in nonhuman primates.[19,20,22] Although LFC power may show a variation as a range between 240mW and 1500mW, the LFC power of 300–700 mW are most commonly used.[18,22,26] However, it has been choiced multiple and repeated LFC applications at the same spot or an immediately adjacent one to provide Bruch's membrane rupture. The indicator of the perforation of Bruch's membrane is a heard of a voice of "pop" and the observation of a sub retinal bubble. Although, early studies showed that laser–induced CNV in non–human primates is low incidence, recent studies demonstrated that CNV incidence following LFC of the macula increased.[18–20,22,27] The physiology and anatomy of human and nonhuman primate eyes are so similar. Thus, the primate laser–induced CNV models in rhesus and cynomolgus monkeys have been choiced for preclinical evaluation of n–AMD treatment options.[19,21,22,26] Except for the LFC induced CNV, the sub–retinal NV has been formed in transgenic mice through the increased expression of vascular endothelial growth factor in the retina.[23]

Retinal detachment (RD)

The animal RD models are important in the evaluation of the pathogenesis of the disease and new treatment methods in RD.[28–40] Many studies have used the mouse as a model to study retinal detachment/reattachment. Mouse eye is a good model for the experimental eye diseases because its manupilation is easy.[41–44] In animal RD models, manual peeling off the neuroretina from the retina pigment epithelium (RPE) and the subretinal injection of saline, balanced salt solution, phosphate–buffered saline (PBS), hyaluronate or RPE cells have been used to establish an experimental RD in rodent eyes and provide the pathologic features of human RD.[45–54] The subretinal injection of sodium hyaluronate has some advantages such as no known ocular toxicity and the long duration of RD compared to others. The subretinal injection of sodium hyaluronate may performed with a trans vitreal or a trans scleral way with the observation of the fundus.[28,29,32–34,40] In the trans–vitreal method, a sub retinal injector is introduced into the vitreous cavity, a peripheral retinotomy is created, and the sodium hyaluronate is injected into the subretinal space. In this method, two retinal tears are created to increase the risk of retinal hemorrhage. Subretinal hemorrhage or hemorrhage entered underneath the retina is toxic for photoreceptor cells through retinal hypoxia and metabolic impairment due toits diffusion barrier effect, and toxicity due to iron in blood in the detached retina. This induces retinal degeneration and RD.[28,29,32–34,40]

In trans–scleral method, a 30 G needle with a syringe containing sodium hyaluronate is inserted into the subretinal space through the conjunctiva, sclera, choroid, and RPE following reduction of intraocular pressure (IOP) with an anterior chamber parasenthesis. The sodium hyaluronate is then injected into the subretinal space.[32,33,37] The incidence of retinal tear and lens injury in transscleral method is less compared to that in the trans–vitreal method. As the sclera puncture by a 30 G needle may be large for mouse eyes, the reflux from scleral hole of sodium hyaluronate injected into the subretinal space may easily occur. Thus, this may cause to establish a lower and less persistent RD.[45–54]

Proliferative vitreoretinopathy (PVR)

Proliferative vitreoretinopathy is one of the most important complications experienced by vitreoretinal surgeons and one of the most important causes for serious vision loss worldwide. It is an abnormal tissue response characterized by the proliferation of non–neoplastic cells within the vitreous gel and on retinal surfaces, resulting in contractile membrane formation and the retinal traction.[55,56] Currently, the most widely used models of PVR in animals are the intravitreal injection of RPE cells or dispase. PVR induction by the injection of RPE cells cultured from healthy, homologous eyes or tissue in balanced salt solution is performed using with a 30–gauge needle, 4 mm posterior to the limbus into the vitreous cavity.[55–58] The PVR model formed by intravitreal injection of dispase, a proteolytic enzyme derived from Bacillus polymyxa, is an easy and cheap method.[58] Dispase selectively disrupts type 4 collagen and fibronectin in the structure of the basement membrane which plays acritical role in the continuity of RPE cell layer. In recent studies, it was shown that an effective dose of dispase is $0.05 - 0.07$ U and that average duration is 8-10 weeks for PVR development.[58,59]

Histopathological assessment of the sections from Labrador Retriever revealed a fibro–cellular membrane formation containing RPE cells, ciliary epithelial cells and glial cells on detached retina.[60] It is considered that this PVR model is unique spontaneous PVR model similar to the human PVR. In the past, formation of retinal hole with endodiathermy in the inferior retinal quadrants at equatorial line with following lensectomy and vitrectomy has been commonly used to establish an experimental PVR.[61] A combination of retinotomy, incomplete vitrectomy, and retinal criopexy or only the intravitreal injection of fibroblast or thrombocyte on optic nerve head have been also used for the same purpose in rabbits and porcine.[62–65] In a recent study, it has been reported that PVR might also be induced in domestic swine by creation of a posterior vitreous detachment, creation of a retinal detachment by the injection of subretinal fluid, and intravitreal injection of green fluorescent protein–positive RPE cells.[57]

Diabetic retinopathy (DR)

Diabetic retinopathy is currently one of the leading causes of blindness over the world. The use of animal models of DR is very important for understanding the pathogenesis of disease and for the development of specific and effective treatment modalities for DR. Currently, there are various animal models of DR and the earliest retinal pathologies could be developed in these. However, none of these models has been the success to mimic fully human DR. The animal models of DR which were used most commonly are rats and mice. However, currently, the zebrafish DR model is a promising option. Nonhuman primates and humans have similar eye structures, and both can develop spontaneous diabetes mellitus (DM).[66–68] There are four options using for the induction of DM in rodents: injection of streptozotocin (STZ) or alloxan, pancreatectomy, genetic modification and galactose diet. Streptozotocin or alloxan induces hyperglycemia and causes the destruction of pancreatic beta cells and subsequently insulin deficiency and Type 1 DM. This is the main diabetic retinopathy model in the rats. However, pre–retinal neovascularization, microaneurysms, and intraretinal vascular abnormalities are not detected in these rat models. On the other hand, vascular events in non–proliferative diabetic retinopathy (NPDR)

such as loss in the capillaries and their cells such as pericyte in the capillary, and thickening at the basement membrane can be developed in rats with STZ or alloxan induced diabetes after six months from the onset of diabetes.[66–69]

In rats, it has been used to provide experimental DR formation via the administration of STZ–all–oxane, supplementation with hypercaloric diet (for seven months), leptin receptor gene mutation (spontaneously). In mice, the administration of STZ, supplementation with hypercaloric diet (for 21–26 months), gene mutation (spontaneously) may be a choice for the same purpose.[66–69] Zebrafish (Danio rerio), a small freshwater fish species which originated in the Ganges River, are currently commonly used as an adequate experimental model to study the genetic, cellular, and molecular mechanisms of various human diseases.[70] They have similar blood glucose and pancreatic islet cells with human. Thus, intraperitoneal STZ injection and water with glucose 2% may be used to induce DR.[66–70] Additionally, experimental DR has been formed with pancreatectomy, administration of STZ–all–oxane, 30% galactose diet (over 36 months) in dogs, administration of STZ–alloxane in porcine, pancreatectomy in cats and administration of STZ (15 years) in primates.[65,67]

Preretinal/retinal neovascularization (NV)

Severe retinal NV is responsible for severe visual loss in various retinal diseases such as DR, retinal vein occlusion (RVO), and ROP. Many investigators have attempted to induce retinal NV experimentally by intravitreal injection of dermal fibroblasts, intravitreal implants impregnated with Interleukin–1, laser photocoagulation of retinal veins, and hyperoxygenation, intravitreal tumor cell implantation and intravitreal preparation of cultured fibroblasts on rats also develop retino–vitreal NV.[71–85]

Central serous chorioretinopathy (CSCR)

Central serous chorioretinopathy is characterized by serous detachment of the neurosensory retina and/or RPE frequently in the macular region. Recurrent or chronic detachment is often associated with more diffuse retina pigment epitheliopathy, which is resulted in RPE atrophy, macular degeneration, foveal atrophy and secondary sub–retinal NV.[86] The pathogenesis of CSCR is unknown. However, it has been considered that the CSCR may be due to focal RPE defect or choroidal lobular ischemia and choroidal venous congestion. Although there are various risk factors for the development of CSCR, psychosomatic factors and the increased levels of serum catecholamine or both have been thought to have important role in the pathogenesis of CSCR. Yannuzzi considered that type A personality might be strongly associated with the sympathetic release in CSCR and that macula was the target tissue for this pathology. In the previous studies, it has been suggested that CSCR could be created by intravenous epinephrine in the experimental monkey model. It has been observed disciform retinal detachment after 2 months following administration IV epinephrine and prednisolone.It was postulated that elevated catecholamine levels in patients with CSCR might cause choroidal vasoconstriction by activating the sympathetic nervous system. It was also considered that the elevation of choroidal hydrostatic pressure caused by choroidal vasoconstriction leads to the breakdown of tight junctions among RPE cells, allowing fluid to pass from the choroid to the subretinal space.[87–93]

Hypertensive retinopathy

Hypertensive retinopathy refers to changes in the retina in response to elevated blood pressure (BP). Hypertensive retinopathy is broadly divided into different stages, including vasoconstrictive, sclerotic, exudative, and malignant hypertension phases.[94] In fact, hypertensive retinopathy signs are detected frequently in persons without a known history of hypertension.[94] Experimental studies on hypertensive retinopathy have been performed on rodents, dogs, and monkeys. Experimental hypertension in dogs and monkeys has been created surgically to form the renal ischemia. Spontaneous hypertension has been frequently reported in dogs and cats. The hypertension model with complete or partial renal artery occlusion has established acute hypertension model in humans.[95–98] Animal models, in vitro experiments, and clinical studies have demonstrated that microcirculatory changes such as arteriolar narrowing, enhanced vasoconstriction, reduced vasodilator responses and arteriolar or capillary diminishing are the earliest changes in the pathogenesis of hypertension. It has been considered that the microcirculation plays a critical role in the pathogenesis of hypertension.[99–104]

Retinopathy of prematurity (ROP)/O2 induced retinopathy (OIR)

Retinopathy of prematurity is one of the most common causes of visual loss which could lead to blindness from fibrovascular RD in childhood. Recent studies in OIR animal models have been demonstrated that high oxygen levels, oxidative stress, and inflammation cause ROP via dysregulation in hypoxia inducible factors and angiogenic factors, neuroprotective growth factors and oxidative molecules.[105] Most OIR models provide some features of human ROP because healthy newborns but not premature animals were used in these models. The most commonly used animals for OIR model are mouse and rat.[105–107] However, various animal species, including rat, mouse, beagle puppy, and zebrafish have been used as animal models of OIR.[106–110] Human and animal models have some differences regarding the stages of OIR. Human ROP phases include "early phase" (stages 1 and 2 ROP with delayed physiologic retinal vascular development and partial vaso–obliteration), "vascular phase" (intravitreal NV, stage 3 ROP with plus disease) or ''fibrovascular phase" (stages 4 and 5 ROP with RD). OIR Phase 1 in the rat and mouse conform the "early phase" of ROP in human (delayed physiologic retinal vascular development and vaso–obliteration, respectively). OIR Phase 2 in the rat and mouse models conform the vaso–proliferative intravitreal NV like "vascular phase" of stage 3 ROP with plus disease in humans. The beagle OIR model can show some features such as retinal folds and dragging of retinal vessels seen in stage 4 human ROP.[111–116]

In mouse OIR model, C57BL/6J mice with 1–week–old are exposed to 75% oxygen for 5 days and then they are returned to room air.[106] Significantly retinal NV occurs between postnatal days 17 and 21. The rats have been also used for this purpose.[107,108,117,118] The transgenic mice may also be used in the mouse OIR model. These may be more helpful to study vaso–attenuation caused by hyperoxia and vascular regrowth into the retina or vitreous following the return to relative hypoxia.[106] The most favorite OIR model is the rat OIR model because it has features of both central retinal vaso–attenuation and delayed physiologic peripheral retinal vascularization.[107,108,117] In another OIR model, newly born pups and dams are placed into

a controlled oxygen environment and exposed oxygen levels from 50% to 100% every 24 hours for 14 days. This hyperoxia provides the increase of arterial oxygen similar to that in a human preterm infant with severe ROP.[119,120] The appearance of first delayed physiologic retinal vascular development followed by intravitreal NV at the junction of the vascular and avascular retina at day 18 is similar to type 1 severe ROP.[121] Thus, the rat OIR model closely represents human preterm infants with severe ROP. The beagle OIR modelhas more similarity to the human preterm infant eye than the newborn rodent regarding the sizes of the eyes. The retina of a newborn beagle initially vascularizes via vasculogenesis and then angiogenesis like that occurs in premature human infant retina. However, the model uses very high oxygen to cause OIR, which differs from the pathogenesis of ROP in most premature infants. In the beagle model, newborn pups are placed into 100% oxygen in day 1 postnatal for 4 days and then returned to room air for recreating the phases of OIR.[111,112–118]

Retinoblastoma (RB)

Retinoblastoma is the most common ocular tumor of malignant childhood and it is fatal if left untreated. Great majority of RB cases are diagnosed by 3 years of age. It has been reported that in RB, the development of tumor is caused by mutations in the retinoblastoma gene (pRb) in some animals such as primates and fishes.[4,122–132] Additionally, the mice RB model has been developed with on cogenesis induced by the usage of nickel and viruses.[133] The RB animal models in murine and mice are genetic mutation (gene knockout) models and xenograft models. Transgenic models of RB include LH–beta T–Ag models an RB knockout model.[129] The histopathological phenotypic changes in RB gene knockouts with an additional loss of p107, p130, p53 and using promoters of Nestin, Chx10, and Pax6 genes are very similar to those of human RB.[129–133]

Retinal degeneration

In the animal models of retinal cell degeneration, degeneration includes transient ischemia–induced retinal cell degeneration; degeneration of retinal ganglion cells (RGC), photoreceptor cells and amacrine cells; glutamate release and N–methyl–D–aspartate (NMDA)/non–NMDAreceptor activation, activation of TNF/TNF–R system.[134–136] In inherited retinal degeneration model, a gene mutation or the expression of a transgene is used to provide retinal degeneration. Gene mutations can appear spontaneously as those in the rd1 (retinal degeneration 1) mouse. The RCS (Royal College of Surgeon) rat may also be used for same purpose. This one shows a functional deficiency in the MerTK gene. Additionally, dogs and cats have been used for inherited model generally.[134] Currently, Zebrafish model is a more popular option for the establishment of the animal retinal degeneration because this fish species can be efficiently and easily mutagenized by the addition of the alkylating agent ethyl nitrosourea (ENU) to the water. Additionally, the cloning of the disrupted gene via viral insertion mutagenesis of a mutating agent such as a pseudo typed virus is an option for this purpose.[137,138]

Alternatively, the transient knockdown of a protein of choice by morpholino antisense technology, modified (morpholino) antisense nucleotides can be used for same purpose. In this model, these nucleotides interfere the blockage of translation initiation, or with splice sites, and cause aberrant splicing and hence nonfunctional mRNA.[139,140] In *in vivo* retina ischemia models, degeneration of retinal ganglion cells (RGC), photoreceptor cells and amacrine cells, retinal degeneration is established by the induction and progression of photoreceptor cell death via the exposure of wild–type or genetically

engineered animals such as mice and rats to light or N–methyl–N–nitrosourea (MNU).[134] NMDA–induced retinal cell degeneration causes RGC loss via NMDAR, (GlunN2B and Glun2D) and activation glutamate transporter deficit.[141–145] Cobalt chloride (CoCl2)–induced retinal cell degeneration has been provided by the use of CoCl2 which was reported as hypoxia–mimicking agent in both in vivo and in vitro studies. It causes photoreceptor cell loss via HIF–1alpha.[146–148] Light–induced retinal damage and related degeneration provides most of the essential features of human AMD. The exact pathogenetic mechanism of light–induced retinal degeneration and photoreceptor and RGC damage is not well–known. However, there are several pathogenetic mechanisms such as the induction of apoptosis in photoreceptors and RGCs, upregulation of pyruvate kinase isozyme type M2 (PKM2) for RGC loss and increased expression of some proton–sensing G protein–coupled receptors.[149–154]

Leber's congenital amaurosis

Leber congenital amaurosis (LCA) is an inherited retinal disease that causes severe vision loss in infants. Leber congenital amaurosis is caused by a defect in rods and cones. Although LCA may be related to 18 gene mutations, great majority of the patients with LCA have an RPE65 deficiency. Currently, there are two animal models of RPE65 deficiency for LCA. The first one is the Swedish Briard dog model with a spontaneous mutation.[155,156] Affected Briard dogs have a homozygous 4–bp deletion (485delAAGA) in canine RPE65 gene. In this model, severe visual impairment is similar to that in human LCA.[157,158] The other is the mice model, a knockout of RPE65. The progressive retinal degeneration, severe visual loss, lackness of the rhodopsin photopigment, and accumulation of all–trans were detected in the both animals.[155–158]

Retinal ischemia–reperfusion (RIR)

Retinal ischemia, a common cause of irreversible visual impairment, is associated with various retinal diseases such as ischemic optic neuropathies, obstructive retinopathies, carotid occlusive disorders, diabetic retinopathy and glaucoma.[159–164] Retinal ischemia occurs when there is an imbalance between the blood supply and the metabolic requirements of the retina and it results in cellular death. As the blood supply to retina and choroid is too similar to that in humans, the rats are frequently used for the studies in RIR models. The main methods of the induction of retinal ischemia in the animal include the raising the IOP, middle cerebral artery (MCA) occlusion, chronic carotid ligation, photo–thrombosis or photocoagulation of retinal vessels, central retinal artery (CRA) occlusion, and intravitreal or intravenous endothelin administration.[159–164] Filamentous MCA occlusion is one of most commonly used method both focal cerebral and retinal ischemia models in rodents because the ophthalmic artery and is proximal to the origin of the MCA.[162,163] As the ophthalmic artery arises from the internal carotid artery and it is located at the proximal region to the origin of MCA and predominantly supplies the inner retina, the MCA occlusion causes interruption of the vascular supply to the retina and allocular structures, consequently it results in retinal ischemia.[164]

Central retinal artery occlusion (CRAO)

In humans, CRAO causes severe retinal ischemia and consequently irreversible retinal damage in a few hours. CRAO model for transient retinal ischemia may be formed with photo–thrombosis of CRA using an intravenous injection of Rose Bengal and the irradiation of CRA with green laser or CRA ligation in rats.[165] If Rose Bengal, a

photosensitive dye, is irradiated by the laser; it causes oxygen free radicals and consequently the intraluminal thrombus formation and CRAO. In CRA ligation model, CRAO is created through placing a suture on the CRA and ciliary artery behind the eye globe, the passion of suture ends through a small plastic tube and pressing the tube against the CRA for induction for ischemia.[166] Central retinal artery occlusion can also be obtained by injection of Endothelin–1 (ET–1) which is a potent vasoconstrictive drug. The injection of ET–1 is less invasive and has no need to any special equipment. Recent studies demonstrated that ET–1 showed similar effects on rabbit and cat eyes following the intravenous, intravitreal or subconjunctival administration, respectively.[167–169]

Retinal vein occlusion

Retinal vein occlusion is the second most common retinal vascular disease following diabetic retinopathy.[170] Some methods including mechanical ligation, endothelin–1 injection and light coagulation for RVO animal models in rats, cats, or rabbits have been defined. However, laser photocoagulation with a photo sensitizer is currently the most common method to induce RVO in rats.[171–174] Recently, another reproducible and reliable animal RVO model has been developed in rats and miniature pigs. In this model, RVO was induced by photo chemically–induced ischemia with erythrosin B, and the main manifestations of human RVO were obtained.[175,176] It has been well–known that that glutamate release and activation of NMDA and non–NMDA receptors play a significant role in retinal ischemic injury.[135,170,177–182]

Conflicts of interest

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