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Review

Apoptosis: Current therapeutic approach in retinitis pigmentosa

Marianne L. Shahsuvaryan

Yerevan State Medical University, Armenia. E-mail: mar_shah@hotmail.com. Tel: (374 10) 52 34 68.

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Apoptosis is a genetically programmed mechanism of cell death in which the cell activates a specific set of instructions that lead to the deconstruction of the cell from within. Retinitis pigmentosa (RP) represents a group of hereditary retinal degenerations principally characterized by progressive rod-dominant photoreceptor degeneration in the initial stage and eventual cone photoreceptor degeneration in later stages. RP has been known to be initiated by photoreceptor apoptosis as a final common pathway at the cellular level, irrespective of gene mutations, and apoptosis can thus be considered as a therapeutic target. The goal of this review is to discuss the rationale behind the recent suggestions that calcium channel blockers may be useful in the treatment of retinitis pigmentosa. The National Center for Biotechnology Information (NCBI) at the US National Library of Medicine (NLM) was searched using the terms "Calcium channel blockers in retinitis pigmentosa". It is time to conduct a randomized controlled trial to provide direct evidence of the effectiveness of specific type calcium channel blockers in lowering progression of RP. New intervention as calcium channel blockers usage to prevent retinitis pigmentosa progression remains an important strategy to limit the morbidity of this significant health problem.

Key words: Apoptosis, retinitis pigmentosa, photoreceptors degeneration, calcium channel blockers, therapeutic effect.

INTRODUCTION

Apoptosis is a genetically programmed mechanism of cell death in which the cell activates a specific set of instructions that lead to the deconstruction of the cell from within. Retinitis pigmentosa represents a group of hereditary retinal degenerations principally characterized by progressive rod-dominant photoreceptor degeneration in the initial stage and eventual cone photoreceptor degeneration in later stages. Patients with retinitis pigmentosa (RP) mainly complain of night blindness and photophobia in the early stage, followed by gradual constriction of the visual field, decreased visual acuity, and color blindness in later stages. The prevalence of RP is roughly 1 in 4,000 people, and the condition is common in both Asian and Western countries (Liesegang et al., 2002). Significant features of RP include heterogeneity in both clinical and genetic characteristics. The severity and progression of RP vary from patient to patient even in the same family, despite affected members presumably sharing the same causative gene mutation.

Molecular genetic studies have also demonstrated that a primary lesion in RP involves photoreceptor and/or retinal pigment epithelial cells in which many causative genes are specifically expressed under physiological conditions. Photoreceptor or retinal pigment epithelial cells are known to degenerate mostly through apoptosis (Chang et al., 1993), which is now understood as a final common pathway for RP at the cellular level. Apoptosis can thus be considered as a therapeutic target as it plays many roles in retinitis pigmentosa (Doonan and Gotter, 2004; Cottet and Schorderet, 2009).

The general consensus is that intracellular concentrations of calcium ion are increased in apoptosis (Nicotera and Orrenius, 1998; Fox et al., 1999; Delyfer et al., 2004; Doonan et al., 2005; Sanges et al., 2006; Paquet-Durand et al., 2007). Intracellular calcium ions are provided through several types of calcium channels and transporters located on cell membranes, endoplasmic reticulum, and mitochondria. Cyclic-nucleotide-gated cation channels (CNGCs) are located in the outer segment and closed by depletion of cGMP as a result of the

phototransduction reaction triggering hyperpolarization. L-type voltage-gated calcium channels (VGCCs) are located in the cell body and synaptic terminal and are closed by hyperpolarization of the cell membrane induced by phototransduction. Steele. et al., (2005) suggested that the average concentration of calcium in the terminal ranges from 350 nM in hyperpolarized light-adapted cells to more than 39 µM in cells depolarized to dark potentials in salamander rods and cones. In addition to CNGC and VGCC, intracellular concentrations of calcium ions are regulated by many other factors, such as plasma membrane calcium ATPase, store-operated calcium entry, calcium stores in the endoplasmic reticulum, and mitochondria. Under pathological conditions, like those in rd1 mice, intracellular calcium levels significantly increase in rods, even before the detection of apoptotic cells (Doonan et al., 2005). The marked elevation of intracellular concentrations of calcium ions activates down stream reactions, including hydrolytic enzymes like calpains, and eventually leads to cell death (Nicotera and Orrenius, 1998). Excessive calcium influx is initiated in the cytosol and subsequently in mitochondria in rd1mouse (Doonan et al., 2005), suggesting that increased calcium ions may affect many biochemical cascades and reactions not only in the cytosol but also in the mitochondria (Szikra and Krizaj, 2009; Barabas et al., 2010).

The objective of this review is to evaluate the evidence and discuss the rationale behind the recent suggestions that calcium channel blockers may be useful in the treatment of retinitis pigmentosa. The National Center for Biotechnology Information (NCBI) at the US National Library of Medicine (NLM) was searched using the terms “Calcium channel blockers in retinitis pigmentosa”.

CALCIUM CHANNEL BLOCKERS IN THE TREATMENT OF RETINITIS PIGMENTOSA

Calcium channel blockers, which alter the intracellular calcium concentration by modifying calcium flux across cell membranes and affect various intracellular signaling processes, have been long and widely used to treat essential hypertension and certain types of cardiac diseases such as angina pectoris. Among five subtypes of calcium channels, only specific agents for L-type calcium channels have been used as therapeutics. Calcium channel blockers generally dilate isolated ocular vessels and increase ocular blood flow in experimental animals, normal humans, and patients with open-angle glaucoma (Luksch et al., 2005; Koseki et al., 2008; Araie and Yamaya, 2011). Frasson et al., (1999) first reported the effects of D-cis-diltiazem, a benzothiazepin calcium channel antagonist which blocks both CNGC and VGCC, on photoreceptor protection in rd1 mice, several investigators have reported positive and negative effects of calcium channel blockers on animal models of RP (Bush et al., 2000; Pearce-Kelling et al., 2001; Pawlyk et al., 2002; Yamazaki et al., 2002; Hart et al., 2003; Sato et al., 2003; Takano et al., 2004; Vallazza-Deschamps et al., 2005; Sanges et al., 2006; Takeuchi et al., 2008).

Since rd1 is caused by a mutation in the gene encoding the β-subunit of rod cGMP-phosphodiesterase, one of the key enzymes in the phototransduction pathway, CNGCs located in the outer segment cannot be closed despite light stimulation in the rod receptor cells. Inhibition of light-induced hyperpolarization, caused by a mutation in the rod cGMP-phosphodiesterase gene, also does not close VGCC. These phenomena increase calcium influx in both outer and inner segment in rd1 mice. The intracellular concentration of calcium ions is subsequently elevated, leading to photoreceptor apoptosis (Frasson et al., 1999), possibly by upregulation of calpains and other proteins (Paquet-Durand et al., 2007). Sanges et al. (2006) demonstrated that systemic administration of D-cis-diltiazem reduced intracellular concentrations of calcium, downregulating calpains and photoreceptor apoptosis in rd1 mice. Direct inhibitory effects of D-cis-diltiazem on L-type VGCC have been reported by Hart et al. (2003), and D-cis-diltiazem effectively blocks photoreceptor light damage in mouse models by inhibiting photoreceptor apoptosis (Vallazza-Deschamps et al., 2005). In contrast, L-cis isomer inhibits L-type VGCC similarly to D-cis isomer (Cia et al., 2005). The difference in action between D-cis- and L-cis-diltiazems on photoreceptor neuroprotection suggests that CNGC might also be important for photoreceptor neuroprotection (Frasson et al., 1999). Read et al. (2002) also reported that the β-subunit of VGCC knock-out rd1 mice showed retardation of photoreceptor degeneration, suggesting that blockage of calcium influx may partially contribute to photoreceptor rescue in these animal models although it did not prevent photoreceptor degeneration. Despite these studies, however, Pawlyk et al. (2002) and Takano et al. (2004) found no rescue effects of D-cis-diltiazem on retinal degeneration in rd1 mice, and Bush et al. (2000) also reported that D-cis-diltiazem was ineffective for photoreceptor rescue in rhodopsin p23Htransgenic rats. While the effects of diltiazem on animal models of retinal degeneration remain controversial, another type of calcium channel blockers, nilvadipine a member of the dihydropyridine derivatives, is another candidate therapeutic agent for RP. Nilvadipine has low-voltage-activated calcium blocking actions in addition to L-type high-voltage calcium blocking actions. The hydrophobic nature induced by the chemical structure of nilvadipine allows high permeability to the central nervous system, including the retina (Tokuma et al., 1987). Systemic administration of nilvadipine has been shown to be effective for protecting photoreceptors in RCS rats (Yamazaki et al., 2002; Sato et al., 2003), rd1 mice (Takano et al., 2004), and heterozygous rd2 (rds) mice (Takeuchi et al., 2008).

In addition to direct effects of calcium channel blockers

on intracellular concentrations of calcium ion in photoreceptor cells, other indirect effects are expected such as increased expression of fibroblast growth factor (FGF)2 (Sato et al., 2003; Takano et al., 2004) and ciliary neurotrophic factor (CNTF) (Takeuchi et al., 2008) in the retina, and increased choroidal blood flow (Koseki et al., 2008). Since FGF2 and CNTF are known to exert photoreceptor-protective effects (Bok et al., 2002; Tao et al., 2002; Schlichtenbrede et al., 2003; Wen et al., 2006), upregulating such intrinsic neurotropic factors by nilvadipine may demonstrate beneficial effects against RP. CNTF has also been applied as a clinical trial for RP by Sieving et al. (2006). Oxidative stress as have been shown in multiple studies (Carmody and Cotter, 2000; Yu et al., 2004; Shen et al., 2005; Komeima et al., 2006; Tuson et al., 2009; Usi et al., 2009) may be involved in photoreceptor death in RP, and nilvadipine has the highest antioxidant potency among calcium channel blockers (Sugawara et al., 1996). The beneficial effect of calcium channel blockers on photoreceptor degeneration achieved in animal models of RP, have encouraged researches to conduct the human trials.

Pasantes-Morales et al. (2002) reported that a combination of D-cis-diltiazem, taurin, and vitamin E has beneficial effects on the visual field progression, although the study did not clarify whether diltiazem alone demonstrated beneficial effects. Ohguro (2008) reported the photoreceptor rescue effects of nilvadipine in a small patient group. Nakazawa et al. (2010; 2011) expanded his nilvadipine study for RP patients to confirm the results. Although both treated and control groups are still small, authors results have shown significant retardation of the mean deviation (MD) slope as calculated by the central visual field (Humphry Visual Field Analyzer, 10-2 Program) after a mean of 48 months of observation.

CONCLUSION

In conclusion, there are potentially multiple biological bases such as decreasing the elevated intracellular concentrations of calcium ion in photoreceptor or retinal pigment epithelial cells, preventing their apoptotic degeneration; dilatation of ocular vessels and increase of ocular blood flow; photoreceptor neuroprotection through increased expression of fibroblast growth factor (FGF)2 and ciliary neurotrophic factor (CNTF) in the retina, and increased choroidal blood flow and antioxidant potency for the protective effect of calcium channel blockers on photoreceptors apoptosis in retinitis pigmentosa. Taking into account that not all calcium channel blockers are equally effective, the challenge for future laboratory research will be to determine the best type and dosage of specific crossing the blood-brain barrier calcium channel blocker and also to determine which processes are modulated by calcium channel blockers *in vivo* and therefore are primarily responsible for the apparent beneficial effects observed in the previous studies. Clearly, further observational studies cannot adequately address many unanswered questions. It is time to conduct a randomized controlled trial to provide direct evidence of the effectiveness of specific type of calcium channel blockers in lowering the progression of RP.

REFERENCES

Araie M and Yamaya C (2011). Use of calcium channel blockers for glaucoma. Prog Ret Eye Res. 30:54-71.

Barabas P, Peck CC, Krizaj D (2010). Do calcium channel blockers rescue dying photoreceptors in the Pde6b^{rd1} mouse? Advances in Experimental Medicine and Biology. 664:491-499.

Bok D, Yasumura D, Matthes MT (2002). Effects of adeno-associated virus-vectored ciliary neurotrophic factor on retinal structure and function in mice with a P216L rds/peripherin mutation. Exper. Eye Res. 74(6): 719-735.

Bush RA, Kononen L, Machida S, Sieving PA (2000). The effect of calcium channel blocker diltiazem on photoreceptor degeneration in the rhodopsin Pro23His rat. Investigative Ophthalmology and Visual Science.41(9):2697-2701.

Carmody RA, Cotter TG (2000). Oxidative stress induces caspase-independent retinal apoptosis in vitro. Cell Death and Differentiation.7(3):282-291.

Chang GO, Hao Y, Wong F (1993). Apoptosis: final common pathway of photoreceptor death in rd, rds, and rhodopsin mutant mice. Neuron.11(4):595-605.

Cia D, Bordais A, Varela C, Forster V, Sahel JA, Rendon A, Picaud S (2005).Voltage-gated channels and calcium homeostasis in mammalian rod photoreceptors. Journal of Neurophysiology. 93(3):1468-1475.

Cottet S, Schorderet DF (2009). Mechanisms of Apoptosis in retinitis pigmentosa. Current Molecular Medicine. 9(3):375-383.

Delyfer MN, Leveillard T, Mohand-Said S, Hicks D, Picaud S, Sahel A (2004). Inherited retinal degenerations: therapeutic prospects. Biology of the Cell. 96(4):261-269.

Doonan F, Cotter TG (2004). Apoptosis: a potential therapeutic target for retinal degenerations. Current Neurovascular Research. 1(1):41-53.

Doonan F, Donovan M, Cotter TG (2005). Activation of multiple pathways during photoreceptor apoptosis in the rd mouse. Investigative Ophthalmology and Visual Science. 46(10):3530-3538.

Fox DA, Poblenz AT, He L (1999). Calcium overload triggers rod photoreceptor apoptotic cell death in chemical-induced and inherited retinal degenerations. Annals of the New York Academy of Science. 893:282-285.

Frasson M, Sahel JA, Fabre M, Simonutti M, Dreyfus H, Picaud S (1999). Retinitis pigmentosa: rod photoreceptor rescue by a calcium-channel blocker in the rd mouse. Nature Medicine. 5(10):1183-1187.

Hart J, Wilkinson MF, Kelly MEM, Barnes S (2003). Inhibitory action of diltiazem on voltage-gated calcium channels in cone photoreceptors. Experimental Eye Research. 76(5):597-604.

Komeima K, Rogers BS, Lu L, Campochiaro PA (2006). Antioxidants reduce cone cell death in a model of retinitis pigmentosa. Proceedings of the National Academy of Sciences of the United States of America. 103(30):11300-11305.

Koseki N, Araie M, Tomidokoro A (2008). A placebo-controlled 3-year study of a calcium blocker on visual field and ocular circulation in glaucoma with low-normal pressure. Ophthalmology. 115(11):2049-2057.

Liesegang TJ, Deutsch TA, Grand MG (2002). Basic and Clinical science Course. American Academy of ophthalmology. Section 12, p.190.

Luksch A, Rainer G, Koyuncu D, Ehrlich P, Maca T, Gschwandtner ME, Vass C, Schmetterer L (2005). Effect of nimodipine on ocular blood flow and color contrast sensitivity in patients with normal tension glaucoma. Br. J. Ophthalmol., 89:21-25.

Nakazawa M (2011). Effects of calcium ion, calpains, and calcium channel blockersw on retinitis pygmentosa. J. Ophthalmol., 43:121-127.
Nakazawa M (2011). Effects of calcium ion, calpains, and calcium channel blockers on retinitis pigmentosa. J Ophthalmol. 43:121-127.
Nicotera P and Orrenius S (1998). The role of calcium in apoptosis. Cell Calcium. 23(2-3):173-180.
Ohguro H (2008). New drug therapy for retinal degeneration . Nippon Ganka Gakkai zasshi. 112(1):7-21.
Paquet-Durand F, Johnson L, Ekstrom P (2007). Calpain activity in retinal degeneration. J. Neurosci. Res., 85(4):693-702.
Pasantes-Morales H, Quiroz H, Quesada O (2002). Treatment with taurine, diltiazem, and vitamin E retards the progressive visual field reduction in retinitis pigmentosa: a 3-year follow-up study. Metab. Brain Dis., 17(3):183-197.
Pawlyk BS, Li T, Scimeca MS, Sandberg MA, Berson EL (2002). Absence of photoreceptor rescue with KD-cis-diltiazem in the rd mouse. Investig. Ophthalmol. Vis. Sci., 43(6):1912-1915.
Pearce-Kelling SE, Aleman TS, Nickle A (2001). Calcium channel blocker D-cis-diltiazem does not slow retinal degeneration in the PDE6B mutant rcd1 canine model of pigmentosa. Mol. Vis., 7:42-47.
Read DS, McCall MA, and Gregg RG (2002). Absence of voltage-dependent calcium channels delays photoreceptor degeneration in rd mice. Exp. Eye Res., 75(4):415-420.
Sanges D, Comitato A, Tammaro R, Marigo V (2006). Apoptosis in retinal degeneration involves cross-talk between apoptosis-inducing factor (AIF) and caspase-12 and is blocked by calpain inhibitors. Proc. Nat. Acad. Sci. USA, 103(46):17366-17371.
Sato M, Ohguro H, Ohguro I, Mamiya K, Takano Y, Yamazaki H, Metoki T, Miyagawa Y, Ishikawa F, Nakazawa M (2003). Study of pharmacological effects of nilvadipine on RCS rat retinal degeneration by microarray analysis. Biochem. Biophys. Res. Commun., 306(4):826-831.
Schlichtenbrede FC, MacNeil A, Bainbridge JWB (2003). Intraocular gene delivery of ciliary neurotrophic factor results in significant loss of retinal function in normal mice and in the Prph2 model of retinal degeneration. Gene Ther., 10(6):523-527.
Shen J, Yang X, Dong A, Petters RM, Peng YW, Wong F, Campochiaro PA (2005). Oxidative damage is a potential cause of cone cell death in retinitis pigmentosa. J. Cellular Physiol., 203(3):457-464.
Sieving PA, Caruso RC, Tao W (2006). Ciliary neurotrophic factor (CNTF) for human retinal degeneration: Phase 1 trial of CNTF delivered by encapsulated cell intraocular implants. Proc. Nat. Acad. Sci. USA, 103(10):3896-3901.
Steele Jr. EC, Chen X, Iuvone PM, MacLeish PR (2005). Imaging of Ca2+ dynamics within the presynaptic terminals of salamander rod photoreceptors. J. Neurophysiol., 94(6):4544-4553.
Suguwara H, Tobise K, and Kikuchi K (1996). Antioxidant effects of calcium antagonists on rat myocardial membrane lipid peroxidation. Hypertens. Res., 19(4):223-228.
Szikra T, Krizaj D (2009). “Calcium signals in inner-segments of photoreceptors”. In: The Visual Transduction Cascade: Basic and Clinical Principles, J Tombran-Tink and C. Barnstable (Eds.). Jumana Press, Totowa, NJ, USA, 197-223.
Takano Y, Ohguro H, Dezawa M, Ishikawa H, Yamazaki H, Ohguro I, Mamiya K, Metoki T, Ishikawa F, Nakazawa M (2004). Study of drug effects of calcium channel blockers on retinal degeneration of rd mouse. Biochem. Biophys. Res. Commun., 313(4):1015-1022.
Takeuchi K, Nakazawa M, Mizukoshi S (2008). Systemic administration of nilvadipine delays photoreceptor degeneration of heterozygous retinal degeneration slow (rds) mouse. Exp. Eye Research. 86(1):60-69.
Tao W, Wen R, Goddard MB, Sherman SD, O'Rourke PJ, Stabila PF, Bell WJ, Dean BJ, Kauper KA, Budz VA, Tsiaras WG, Acland GM, Pearce-Kelling S, Laties AM, Aguirre GD (2002). Encapsulated cell-based delivery of CNTF reduces photoreceptor degeneration in animal models of retinitis pigmentosa. Investig. Ophthalmol. Vis. Sci., 43(10):3292-3298.
Tokuma Y, Fujiwara T, Noguchi H (1987). Absorption, distribution and excretion of nilvadipine, a new dihydropyridine calcium antagonist, in rats and dogs. Xenobiotica. 17(11):1341-1349.
Tuson M, Garanto A, Gonzalez-Duarte R, Marfany G (2009). Overexpression of CERKL, a gene responsible for retinitis pigmentosa in humans, protects cells from apoptosis induces by oxidative stress. Mol. Vis., 15:168-180.
Usui S, Komeima K, Lee SY, Jo YJ, Ueno S, Rogers BS, Wu Z, Shen J, Lu L, Overson BC, Rabinovitch PS, Campochiaro PA (2009). Increased expression of catalase and superoxide dismutase 2 reduces cone cell death in retinitis pigmentosa. Mol. Ther., 17(5):778-786.
Vallazza-Deschamps G, Cia D, Gong J, Jellali A, Duboc A, Forster V, Sahel JA, Tessier LH, Picaud S (2005). Excessive activation of cyclic nucleotide-gated channels contributes to neuronal degeneration of photoreceptors. Eur. J. Neurosci.,. 22(5):1013-1022.
Wen R, Song Y, Kjellstrom S (2006). Regulation of rod phototransduction machinery by ciliary neurotrophic factor. J. Neurosci., 26(52):13523-13530.
Yamazaki H, Ohguro H, Maeda T, Maruyama I, Takano Y, Metoki T, Nakazawa M, Sawada H, Dezawa M (2002). Preservation of retinal morphology and functions in Royal College Surgeons rat by nilvadipine, a Ca2+ Antagonist. Investig. Ophthalmol. Vis. Sci., 43(4):919-926.
Yu DY, Cringle S, Valter K, Walsh N, Lee D, Stone J (2004). Photoreceptor death, trophic factor expression, retinal oxygen status, and photoreceptor function in the P23H rat. Investigative Investig. Ophthalmol. Vis. Sci., 45(6):2013-2019.