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Review Article

Retinitis Pigmentosa: WHAT ELSE WE CAN DO?

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ABSTRACT

Retinitis pigmentosa (RP) represents a group of progressive hereditary diseases of the retina that lead to incurable blindness and affect two million people worldwide and 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 intracellular concentrations of calcium ion are increased in apoptosis.

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.

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.

Key words: *Retinitis pigmentosa, photoreceptors degeneration, calcium channel blockers, therapeutic effect.*

Retinitis pigmentosa represents a group of progressive hereditary diseases of the retina that lead to incurable blindness and affect two million people worldwide [1] , and 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 4,000-5,000 people, and the condition is common in both Asian and Western countries [2]. 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 [3], 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 [4, 5].

The general consensus is that intracellular concentrations of calcium ion are increased in apoptosis [6-10]. Continuous signaling of photoreceptors appears to be prone to malfunction, disturbances of Ca 2+ and cGMP-mediated signaling in photoreceptors can lead to visual defects, retinal degeneration, and even blindness [11]. The intracellular concentration of calcium ions is subsequently elevated, leading to photoreceptor apoptosis [12], possibly by upregulation of calpains and other proteins [10, 13].

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 [14-16].

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.

Frasson *et al* [12] first reported the effects of D-cis-diltiazem, a benzothiazepin calcium channel antagonist, on photoreceptor protection in rd1 mice, several investigators have reported positive and negative effects of calcium channel blockers on animal models of RP [9, 17-25].

Sanges *et al.* [9] demonstrated that systemic administration of D-cis-diltiazem reduced intracellular concentrations of calcium, downregulating calpains and photoreceptor apoptosis in rd1 mice. D-cis-diltiazem effectively blocks photoreceptor light damage in mouse models by inhibiting photoreceptor apoptosis [24]. Despite these studies, however, Pawlyk et al. [19] and Takano et al. [23] found no rescue effects of D-cis-diltiazem on retinal degeneration in rd1 mice, and Bush et al. [17] 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 [26] .Systemic administration of nilvadipine has been shown to be effective for protecting photoreceptors in RCS rats [20, 22], rd1 mice [23], and heterozygous rd2(rds) mice [25].

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 [22,23] and ciliary neurotrophic factor (CNTF) [25] in the retina, and increased choroidal blood flow [15]. Since FGF2 and CNTF are known to exert photoreceptor-protective effects [27-30], 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. [31].

Oxidative stress as have been shown in multiple studies [32-35] may be involved in photoreceptor death in RP, and nilvadipine has the highest antioxidant potency among calcium channel blockers [36].

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. [37] 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 [38] reported the photoreceptor rescue effects of nilvadipine in a small patient group. Nakazawa et al. [39,40] 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 for the protective effect of calcium channel blockers on photoreceptors apoptosis in retinitis pigmentosa.

Taken 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

1. Busskamp V , Picaud S, Sahel JA , Roska B (2012). Optogenetic therapy for retinitis pigmentosa. *Gene Therapy*. 19 (**2**):169-175.
2. Liesegang TJ, Deutsch TA, Grand MG (2002). Basic and Clinical Science Course. American Academy of Ophthalmology. Section 12, p.190.

3. 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.
4. Doonan F and Cotter TG (2004). Apoptosis: a potential therapeutic target for retinal degenerations. *Current Neurovascular Research*. 1(**1**):41-53.
5. Cottet S and Schorderet DF(2009). Mechanisms of Apoptosis in retinitis pigmentosa. Current Molecular Medicine. 9(3):375-383.
6. Nicotera P and Orrenius S (1998). The role of calcium in apoptosis. Cell Calcium. 23(2-3):173-180.
7. Fox DA, Poblenz AT and 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.
8. 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.
9. 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. *Proceedings of the National Academy of Sciences of the United States of America*. 103(**46**):17366-17371.
10. Paquet-Durand F, Johnson L, Ekstrom P (2007). Calpain activity in retinal degeneration. *Journal of Neuroscience Research*. 85(4):693-702.
11. Schmitz f, Natarajan S, Venkatesan JK, Wahl S, Schwarz K, Grabner CP (2012). EF handed –mediated Ca 2+ and cGMP-signaling in photoreceptor synaptic terminals. Front Mol Neurosci, 5: 26.
12. 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.
13. Paquet-Durand F, Beck S, Michalakis S, Goldmann T, Huber G, Muhlfriedel R,Trifunovic D, Fisher MD, Fahl E, Duetsh G, Becirovic E, Worfrum U, van Veen T, Biel M, Tanimoto N, Seeliger MW (2011). A key role for cyclic nucleotide gated (CNG) channels in cGMP-related retinitis pigmentosa. Hum Mol Genet. 1;20(5) 941-947.
14. 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.
15. 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.
16. Araie M and Yamaya C (2011). Use of calcium channel blockers for glaucoma. Prog Ret Eye Res. 30:54-71.
17. 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.
18. 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. *Molecular Vision.* 7:42-47.
19. Pawlyk BS, Li T, Scimeca MS, Sandberg MA, Berson EL (2002). Absence of photoreceptor rescue with KD-cis-diltiazem in the rd mouse. Investigative Ophthalmology and Visual Science. 43(6):1912-1915.
20. 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. *Investigative Ophthalmology and Visual Science*. 43(4):919-926.
21. 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.
22. 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. *Biochemical and Biophysical Research Communications.* 306(**4**):826-831.
23. 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. *Biochemical and Biophysical research Communications*. 313(**4**):1015-1022.
24. Valazza-Deschamps G, Cia D, Gong J, Jellali A, Duboc A, Forster V, Sahal JA, Tessier LH, Picaud S (2005). Excessive activation of cyclic nucleotide-gated channels contributes to neuronal degeneration of photoreceptors. European journal of Neuroscience. 22(5):1013-1022.
25. Takeuchi K, Nakazawa M, Mizukoshi S (2008). Systemic administration of nilvadipine delays photoreceptor degeneration of heterozygous retinal degeneration slow (rds) mouse. Experimental *Eye Research*. 86(1):60-69
26. 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.
27. 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.
28. 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. Investigative Ophthalmology and Visual Science. 43(10):3292-3298.
29. 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 Therapy*. 10(6):523-527.
30. Wen R, Song Y, Kjellstrom S (2006). Regulation of rod phototransduction machinery by ciliary neurotrophic factor. *Journal of Neuroscience*. 26(**52**):13523-13530.
31. Sieving PA, Caruso RC, Tao W (2006). Ciliary neurotrophic factor (CNTF) for human retinal degeneration: phase I trial of CNTF delivered by encapsulated cell intraocular implants. *Proceedings of the National Academy of Sciences of the United States of America*. 103(10):3896-3901.

32. Yu DY, Cringle S, Valter K, Walsh N, Lee D, and Stone J (2004). Photoreceptor death, trophic factor expression, retinal oxygen status, and photoreceptor function in the P23H rat. Investigative Ophthalmology and Visual Science. 45(6):2013-2019.
33. Komeima K, Rogers BS, Lu L and 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.
34. 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. *Molecular Vision*. 15:168-180.
35. 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. Molecular Therapy. 17(5):778-786.
36. Suguwara H, Tobise K, and Kikuchi K (1996). Antioxidant effects of calcium antagonists on rat myocardial membrane lipid peroxidation*. Hypertension Research*. 19(**4**):223-228.
37. Pasantes-Morales H, Quiroz H and 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. *Metabolic Brain Disease*. 17(**3**):183-197.
38. Ohguro H (2008). New drug therapy for retinal degeneration . Nippon Ganka Gakkai zasshi. 112(1):7-21.
39. Nakasava M (2011). Effects of calcium ion, calpains, and calcium channel blockers on retinitis pigmentosa*. J Ophthalmol*. 43:121-127.
40. Nakazawa M, Ohguro H, Takeuchi K, Miyagawa Y, Ito T, Metoki T (2011). Effect of nilvadipine on central visual field in retinitis pigmentosa: a 30-month clinical trial. *Ophthalmologica.* 225(**2**):120-126.