Activity of protein kinase G (PKG) causes photoreceptor degeneration in two mouse models for Retinitis Pigmentosa

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Abstract

Purpose: Photoreceptor degeneration in retinitis pigmentosa (RP) is one of the leading causes of hereditary blindness in the developed world. Although causative genetic mutations are often known, the underlying neuronal degeneration mechanisms still remain to be elucidated. Gene mutations affecting the levels of cyclic guanosine-monophosphate (cGMP) are often associated with rapid photoreceptor cell death. We asked the question whether activity of cGMP-dependent protein kinase (PKG) was involved in retinal degeneration mechanisms.

Methods: We used custom-made antibodies directed against different PKG isoforms to investigate expression in wild-type (wt) and rd retina. We then employed organotypic retinal explant cultures derived from wt, rd, and rd mutant animals to test compounds affecting the activity of either phosphodiesterase 6 (PDE6) and/or PKG. To confirm the effects observed in vivo, we obtained three different in vitro assay systems (topical application, intravitreal injection, subretinal injection). For evaluation of the treatment outcomes, histological staining, immunofluorescence, immunoblot, and TUNEL techniques were used.

Results: We found expression of PKG 1 to be restricted mostly to the photoreceptor layer, whereas PKG 2 was expressed in the inner nuclear layer and in ganglion cells. More importantly, we showed that activation of PKG hallmark photoreceptor degeneration in rd and rd2 human homologous mouse models. When induced in wt retina, PKG activity was both necessary and sufficient to trigger cGMP-mediated photoreceptor cell death. Target specific, pharmacological inhibition of PKG activity in both rd and rd2 retina strongly reduced photoreceptor cell death in organotypic retinal explants and increased long-term photoreceptor survival. Likewise, inhibition of PKG in vivo, using three different application paradigms, resulted in photoreceptor protection in the rd retina.

Conclusions: These findings suggest a pivotal role for PKG activity in cGMP-mediated photoreceptor degeneration mechanisms and highlight the importance of PKG as a novel target for the pharmacological intervention in RP.

Summary and Conclusions

1) cGMP accumulation and PKG activation hallmark rd and rd2 mouse retinal degeneration
2) PKG activation selectively killed wt photoreceptors, while PKG inhibition rescued rd and rd2 photoreceptors in vitro
3) PKG inhibition in vivo strongly and significantly protected rd photoreceptors
4) PKG may constitute a novel and highly promising target for the treatment of Retinitis Pigmentosa and related diseases.


Selected References


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