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The role of cGMP-signalling and calcium-signalling in photoreceptor cell death: perspectives for therapy development.

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The second messengers, cGMP and Ca²⁺, have both been implicated in retinal degeneration; however, it is still unclear which of the two is most relevant for photoreceptor cell death. This problem is exacerbated by the close connections and crosstalk between cGMP-signalling and calcium (Ca²⁺)-signalling in photoreceptors. In this review, we summarize key aspects of cGMP-signalling and Ca²⁺-signalling relevant for hereditary photoreceptor degeneration. The topics covered include cGMP-signalling targets, the role of Ca²⁺ permeable channels, relation to energy metabolism, calpain-type proteases, and how the related metabolic processes may trigger and execute photoreceptor cell death. A focus is then put on cGMP-dependent mechanisms and how exceedingly high photoreceptor cGMP levels set in motion cascades of Ca²⁺-dependent and independent processes that eventually bring about photoreceptor cell death. Finally, an outlook is given into mutation-independent therapeutic approaches that exploit specific features of cGMP-signalling. Such approaches might be combined with suitable drug delivery systems for translation into clinical applications.

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