Summary of project funded by Retina Australia.

Title: ***The role of purines in photoreceptor death during retinal degeneration***

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What did we do? The main focus of our work is to examine whether there are factors that exacerbate photoreceptor death during retinal degeneration so that novel treatments can be developed. Over the last few years we have been exploring the role that ATP plays in modulating photoreceptor death. This molecule is well known for its functions in energy metabolism. However, when ATP is found outside cells, it can act as a mediator for neuronal communication. The aim of this study was to investigate whether ATP causes photoreceptor death and whether blocking the actions of ATP slows photoreceptor death in animal models of retinal degeneration.

How did we conduct our experiments?We performed three major experiments. First, we examined the effects that ATP have on photoreceptors in normal rats. Next we determined whether there are agents that block the effects of ATP on photoreceptors. Thirdly, we used the rd1 model of retinal degeneration and characterized the speed of photoreceptor death with and without treatments that block the actions of ATP.

What did we find? We confirmed that photoreceptors express receptors that bind ATP, that are called P2X7 receptors. We found that injection of ATP or a compound like ATP, caused photoreceptor death in a dose dependent and irreversible manner in normal rats. A single injection of ATP lead to complete loss of vision in normal rats within 7 days. Blocking the action of ATP with a drug called PPADS prevented 66% of photoreceptor death, suggesting that the death of photoreceptors is mediated by the receptors that bind ATP, including P2X7.We then explored how ATP might cause photoreceptor death-Does ATP act directly on photoreceptors, or id cell death caused by indirect mechanisms such as through other supporting cells in the retina? Our studies show that the actions of ATP are likely to be via direct action on the photoreceptor itself, and not via other indirect means. Finally, we examined whether agents that prevent ATP from binding to photoreceptors slow photoreceptor death in the rd1 model of retinal degeneration. Treatment of rd1mice with either PPADS or TNP-ATP, in one eye at P14 slowed photoreceptor degeneration so that around 30% more photoreceptors remained at P21.

What do our results mean for retinal degeneration: The results of our experiments suggest that when ATP is found in high concentrations around photoreceptors this promotes and accelerates their death. Moreover, application of agents that block the action of ATP slow photoreceptor death in an animal model of retinal degeneration. These findings are a first step in the development of a novel class of drug that could be useful in slowing photoreceptor death.