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Commentary

The Eyes Have it! Protective Role of Prolactin in the Retina

David R. Grattan

Centre for Neuroendocrinology and Department of Anatomy, University of Otago, Dunedin, New Zealand

To most biomedical scientists, the anterior pituitary hormone, prolactin, will rightly be thought of as the hormone responsible for lactation. However, this is just one of this remarkable molecule's functions. Prolactin might better be thought of as a pleiotropic cytokine with diverse functions in different tissues (Bole-Feysot et al., 1998; Grattan and LeTissier, 2015). In the May issue of *EBioMedicine*, Garcia et al. add a new function to this already long list (Garcia et al., 2016): an anti-apoptotic protective role maintaining the function of the retinal pigment epithelium (RPE). While prolactin receptor expression had previously been identified in the retina, prolactin's functional role in the RPE has, until the present study, been poorly understood.

The RPE forms an integral part of the structure and function of the retina. Apart from absorption of light, it also forms a blood/retinal fluid barrier to maintain appropriate electrolyte balance in the subretinal space and to control nutrient supply to photoreceptors. The RPE plays a critical role in recycling retinal to maintain photoreceptor excitability (the so-called "visual cycle"), and it secretes a number of growth factors to help maintain the function of the local tissues, including the photoreceptor cells (Strauss, 2005). Dysregulation of the RPE is implicated in a number of retinal diseases, including age-related decline in visual function. Further understanding of the regulation of RPE function is clearly important for development of therapies for degenerative diseases of the retina that lead to impaired vision or even blindness. Hence, the discovery by Garcia et al. of a protective role of prolactin in the RPE, along with insight into the anti-apoptotic mechanisms, is significant because it may provide opportunities for developing novel therapeutics targeting this system.

While an effect of this "lactation hormone" on the RPE might seem surprising, it is perhaps not so dissimilar from other recognised functions of prolactin throughout phylogeny, where regulation of ion transport and secretion from integument and other epithelial cells has been shown from fish to birds to mammals (Bole-Feysot et al., 1998). In addition to integument epithelial tissue, like the mammary gland, prolactin has actions in a wide range of epithelia, including kidney, intestine and the prostate gland (Bole-Feysot et al., 1998). Similar to the nervous system role now identified in the RPE (Garcia et al., 2016), prolactin receptors are also highly expressed in the choroid plexus, a structure found within the cerebral ventricles that synthesizes and secretes cerebrospinal fluid (CSF). Here, prolactin seems to act to regulate the composition of the CSF, perhaps helping to maintain the blood/CSF barrier (Grattan, 2015). The protective function of prolactin seen in the RPE is also consistent with known actions of prolactin in a number of other tissues, ranging from stem cells to the brain, where it promotes cell division and cell survival. Indeed, growth and survival of rat NB2 lymphoma cells has long been utilised as a highly sensitive bioassay for prolactin (Lawson et al., 1982). The anti-apoptotic actions of prolactin are likely to have important physiological roles, but may also underlie the oncogenic potential of this hormone in mammary, prostate and other cancers (Goffin and Touraine, 2015).

Using a combination of human and rodent cell lines, as well as in vivo studies using age-related decline in retinal function in mice lacking the prolactin receptor gene, Garcia et al. have demonstrated a protective role for prolactin in RPE homeostasis (Garcia et al., 2016). They have also demonstrated that this is mediated by suppression of apoptosis, driven by reduced oxidative stress, consequent inhibition of expression of sirtuin 2, and reduced signalling through TRPM2 channels. Thus, they have identified a mechanism that might enable development of novel therapies for retinal disorders. However, a number of questions remain. Antagonist studies revealed that endogenous prolactin mediates the anti-apoptotic effect, but it is still unclear to what extent this is through prolactin synthesised locally, within the retina, or pituitary prolactin arriving via the systemic circulation. While Garcia et al. present some data suggestive of limited local synthesis (for example in RPE cell lines), it is difficult to determine what levels might be produced from this source, and it seems highly likely that circulating prolactin would also contribute to this effect. If this is correct, the obvious question is whether there are endogenous adaptive changes in RPE function during times when circulating prolactin is elevated, such as during pregnancy or lactation. Another question is the relationship of the protective function of prolactin with similar actions of the related vasoinhibin molecules. In previous studies, this group demonstrated that vasoinhibins protected the retina from diabetic retinopathy (Arnold et al., 2010). Vasoinhibins are produced as proteolytically-cleaved fragments of prolactin and act by inhibiting vascular permeability, but do not act through the prolactin receptor (Triebel et al., 2015). Hence, the balance between prolactin and vasoinhibin signalling in a particular tissue might be critical to the overall outcome. In many

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E-mail address: dave.grattan@otago.ac.nz.

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tissues, these two molecules have opposite effects, but in the retina, both seem to exert protective actions, and the relative contributions of this combination will be important to understand.

As a potential therapeutic target, the pleiotropic actions of prolactin engender both excitement and frustration. Excitement, because clear beneficial actions shown in the lab seem to have huge potential for developing new treatments. Frustration, because with so many other tissues possibly influenced by prolactin, it might be difficult to target effects specifically to the tissue of interest (Goffin and Touraine, 2015). Nevertheless, it seems inevitable that studies such as these are bringing us closer to harnessing the potential of this multifunctional molecule, and I look forward with interest to further developments coming from this group of researchers, and others stimulated by their findings.

Conflicts of interest

The author declares no conflicts of interest.

References

Arnold, E., Rivera, J.C., Thebault, S., Moreno-Paramo, D., Quiroz-Mercado, H., Quintanar-Stephano, A., Binart, N., Martinez de la Escalera, G., Clapp, C., 2010. High levels of serum prolactin protect against diabetic retinopathy by increasing ocular vasoinhibins. Diabetes 59, 3192–3197.

Bole-Feysot, C., Goffin, V., Edery, M., Binart, N., Kelly, P.A., 1998. Prolactin (PRL) and its receptor: actions, signal transduction pathways and phenotypes observed in PRL receptor knockout mice. Endocr. Rev. 19, 225–268.

Garcia, R.M., Zamarripa, D.A., Arnold, E., Ruiz-Herrera, X., Imm, R.N., Cruz, G.B., Adan, N., Binart, N., Riesgo-Escovar, J., Goffin, V., et al., 2016. Prolactin protects retinal pigment epithelium by inhibiting sirtuin 2-dependent cell death. EBioMedicine http://dx.doi.org/10.1016/j.ebiom.2016.03.048.

Goffin, V., Touraine, P., 2015. The prolactin receptor as a therapeutic target in human diseases: browsing new potential indications. Expert Opin. Ther. Targets 19, 1229–1244.

Grattan, D.R., 2015. 60 YEARS OF NEUROENDOCRINOLOGY: the hypothalamo-prolactin axis. J. Endocrinol. 226, T101–T122.

Grattan, D.R., LeTissier, P., 2015. Hypothalamic Control of Prolactin Secretion, and the Multiple Reproductive Functions of Prolactin. In: Plant, T.M., Zelesnik, A.J. (Eds.), Knobil and Neill's Physiology of Reproduction, 4th Ed. Elsevier, pp. 469–526.

Lawson, D.M., Sensui, N., Haisenleder, D.H., Gala, R.R., 1982. Rat lymphoma cell bioassay for prolactin: observations on its use and comparison with radioimmunoassay. Life Sci. 31, 3063–3070.

Strauss, O., 2005. The retinal pigment epithelium in visual function. Physiol. Rev. 85, 845–881.

Triebel, J., Bertsch, T., Bollheimer, C., Rios-Barrera, D., Pearce, C.F., Hufner, M., Martinez de la Escalera, G., Clapp, C., 2015. Principles of the prolactin/vasoinhibin axis. Am. J. Phys. Regul. Integr. Comp. Phys. 309, R1193–R1203.