Vasoactive neuropeptides in clinical ophthalmology: An association with autoimmune retinopathy?

Donald R Staines^{1,2}

Ekua W Brenu²

Sonya Marshall-Gradisnik²

¹Queensland Health, Gold Coast Population Health Unit, Southport, Gold Coast, Queensland, Australia;

²Faculty of Health Science and Medicine, Population Health and Neuroimmunology Unit, Bond University, Robina, Queensland, Australia

Abstract: The mammalian eye is protected against pathogens and inflammation in a relatively immune-privileged environment. Stringent mechanisms are activated that regulate external injury, infection, and autoimmunity. The eye contains a variety of cells expressing vasoactive neuropeptides (VNs), and their receptors, located in the sclera, cornea, iris, ciliary body, ciliary process, and the retina. VNs are important activators of adenylate cyclase, deriving cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). Impairment of VN function would arguably impede cAMP production and impede utilization of ATP. Thus VN autoimmunity may be an etiological factor in retinopathy involving perturbations of purinergic signaling. A sound blood supply is necessary for the existence and functional properties of the retina. This paper postulates that impairments in the endothelial barriers and the blood–retinal barrier, as well as certain inflammatory responses, may arise from disruption to VN function. Phosphodiesterase inhibitors and purinergic modulators may have a role in the treatment of postulated VN autoimmune retinopathy.

Keywords: retinopathy, autoimmune, vasoactive neuropeptides, phosphodiesterase inhibitors

Background

Vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP) are vasoactive neuropeptides (VNs) that have been shown to exist in the mammalian eye in areas such as the sclera, cornea, iris, ciliary body, ciliary process, and the retina.^{1,2} An important feature of VN receptors is their ability to activate adenylate cyclase (AC) to produce cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP) in the retina of mammals.³ VN receptors are class II G protein-coupled receptors (GPCRs) and are important for regulating levels of ATP and cAMP.⁴ Additionally, ATP is a vasoactive signal in the microvasculature of the rat retina⁵ and cAMP regulates neurological metabolism by influencing blood–brain (BBB) and blood–retinal (BRB) barrier permeability, coordination of neuroregulatory pathways, and inducing protection against neuronal apoptosis. However failure to metabolize ATP adequately may result in elevated extracellular ATP levels and set in train perturbations of purinergic signaling initiating significant neuro- and retino-toxicity.^{6,7}

PACAP also acts as a neurotransmitter in the retinohypothalamic tract mediating photic regulation of the brain's biological clock⁸ and, along with other neuropeptides, is likely to be of significance in other parts of the eye⁹ in addition to the retina. Moreover PACAP has protective effects on monosodium glutamate (MSG)-induced retinal degeneration¹⁰ and kainic acid retinal degeneration.¹¹ PACAP and glutamate are co-stored in the retinohypothalamic tract¹² and PACAP attenuates glutamate-induced neurotoxicity in cultured retinal neurons,¹³ which suggests that compromise of this VN would have significant detrimental impact on retinal viability and function.

Correspondence: Donald R Staines
Associate Professor and Public Health
Physician, Gold Coast Population Health
Unit, 10–12 Young Street, Southport 4215,
Queensland, Australia
Tel +61 7 5509 7222
Fax +61 7 5561 1851
Email don_staines@health.qld.gov.au

As PACAP has a role in the relaxation of pericytes, this may form the basis for a diagnostic procedure for diabetic retinopathy.¹⁴ In view of the vasodilatory roles of these VNs along with hypoxia protection, they may have a place in the prevention of ischemic retinal degeneration.¹⁵ VIP and PACAP are likely to have an important role in retinal development.¹⁶ PACAP and VIP autoimmunity has been hypothesized previously as a causal agent in retinopathy.¹⁷ VN function and postulated autoimmunity is an emerging field and may be relevant to clinical ophthalmologists because of the opportunity to develop novel treatments.

Retinal pathology and autoimmunity

Retinal pathology may arise as a consequence of autoimmunity. For example, peripheral vitreo-chorioretinal dystrophies (PVCRD) have been shown to arise from localized reactions, noting that self antibodies were detected in 70% of PVCRD cases with normal levels of immune complexes in the blood.¹⁸ Antibody-induced apoptosis is a possible mechanism for retinal pathology. Antibodies such as antirecoverin can induce retinopathy by exerting cytotoxic effects on retinal cells. Activation of the caspase 3-dependent apoptotic pathway occurs with the resultant effect of retinal photoreceptor cell death, degeneration of the photoreceptor layer, and loss of sight.¹⁹ Additionally the presence of anti-recoverin immunoreactivity may be a possible causal factor in some patients with retinal pathologies.²⁰

Importantly viruses such as coronavirus exacerbate retinal degeneration in murine models with retinal disease; this manifests as retinal vasculitis and the presence of anti-retinal antibodies.²¹ Acute inflammation and BRB compromise occur in the early stages of the disease in these mice while autoimmune reactivity and neurodegeneration are features of the later stages of retinal disease.²² These findings support some involvement of autoimmunity in the mechanism of retinal degeneration.

The significant contribution of cAMP function in the BRB suggests retinal pathologies could involve VN autoimmunity. Stabilization of BRB function may be associated with nitric oxide, phosphodiesterase enzymes (PDEs)²³ and cAMP regulation.²⁴ Failure to metabolize ATP to cAMP could result in perturbation of purinergic signaling in the retina. Indeed, other causes of ATP elevation and subsequent pathology have been demonstrated.²⁵ Purinergic activation may promote the effects of diabetes-induced increase in the vulnerability of retinal microvessels and be a previously unrecognized mechanism by which diabetic

retinopathy progresses.²⁶ Certainly ATP participates in bi-directional signaling between glial cells and the retina²⁷ and gliosis may impede recovery from repair of retinal detachment.²⁸

The present hypothesis postulates that cAMP relies extensively on PACAP/VIP activation of AC and that compromise of their function would result in impaired cAMP derivation from ATP. ATP is implicated as an endogenous trigger of microglial activation, and reactive gliosis may affect microglia, neurons, and oligodendrocytes.²⁹ Microglial activation might be exacerbated under conditions of trauma and hypoxia^{30,31} and impaired metabolism of intracellular ATP may lead to extravasation of ATP to the extracellular compartment. While ectonucleotidases are responsible for metabolizing extracellular ATP, its utilization and availability is determined by the balance of release and removal by enzymatic degradation and uptake.³² This mechanism may result in perturbation of purinergic signaling. Thus a pathomechanism involving ATP toxicity may occur with potentially serious consequences.

Implications for treatment interventions

Retinopathy may occur from VN autoimmunity which impedes cAMP production while elevating ATP levels. Theoretically phosphodiesterase inhibitor (PDEI) therapy may assist in restoring cAMP levels, however ATP toxicity may remain an issue and purinergic antagonists may act to protect retinal neurodegeneration from ATP toxicity.³³ Importantly, PDEIs are effective in regulating cAMP. Interestingly, PDEIs also enhance tyrosine hydroxylase phenotypes of dopaminergic cells, which are important during retinal development.³⁴ Inhibitors of PDE4 could be considered as a candidate for therapeutic drugs to treat diseases associated with disorders of retinal circulation without severe cardiovascular side-effects,³⁵ although care should be taken with the use of PDE5 inhibitors.³⁶ Nevertheless, a case may exist for undertaking a therapeutic trial of cAMP-specific PDE inhibitors in retinopathies resulting from VN autoimmunity should this pathology subsequently be proven.

A possible association of VN autoimmunity with retinopathy in humans seems plausible and suggests the need for further research. Specific therapeutic interventions may already be available or could be developed for the prevention and treatment of VN autoimmune retinopathy. Recent evidence suggests that VIP may be useful in the treatment of experimental autoimmune uveoretinitis (EAU). The possibility of vasoactive neuropeptides acting in a therapeutic

context may support the hypothesis of VN impairment as an etiology in retinal pathology.³⁷

Disclosure

The authors report no conflicts of interest in this work.

References

1. Tervo T, Tervo K, Eranko L. Ocular neuropeptides. *Med Biol.* 1982;60(2):53–60.
2. Nillson SF, De Neef P, Robberecht P, Christophe J. Characterization of ocular receptors for pituitary adenylate cyclase activating polypeptide (PACAP) and their coupling to adenylate cyclase. *Exp Eye Res.* 1994;58(4):459–467.
3. Onali P, Orianas MC. PACAP is a potent and highly effective stimulator of adenylyl cyclase activity in the retinas of different mammalian species. *Brain Res.* 1994;641(1):132–134.
4. Martin B, Lopez de Maturana R, Breneman R, Walent T, Mattson MP, Maudsley S. Class II G protein-coupled receptors and their ligands in neuronal function and protection. *Neuromolecular Med.* 2005; 7(1–2):3–36.
5. Kawamura H, Sugiyama T, Wu DM, et al. ATP: a vasoactive signal in the pericyte-containing microvasculature of the rat retina. *J Physiol.* 2003;551(Pt 3):787–799.
6. Sugiyama T, Kawamura H, Yamanishi S, Kobayashi M, Katsumura K, Puro DG. Regulation of P2X7-induced pore formation and cell death in pericyte-containing retinal microvessels. *Am J Physiol Cell Physiol.* 2005;288(3):C568–C576.
7. Zhang X, Zhang M, Laties AM, Mitchell CH. Stimulation of P2X7 receptors elevates Ca²⁺ and kills retinal ganglion cells. *Invest Ophthalmol Vis Sci.* 2005;46(6):2183–2191.
8. Fahrenkrug J. PACAP – a multifaceted neuropeptide. *Chronobiol Int.* 2006;23(1–2):53–61.
9. Troger J, Kieselbach G, Teuchner B, et al. Peptidergic nerves in the eye, their source and potential pathophysiological relevance. *Brain Res Rev.* 2007;53(1):39–62.
10. Rácz B, Gallyas F Jr, Kiss P, et al. Effects of pituitary adenylate cyclase activating polypeptide (PACAP) on the PKA-Bad-14-3-3 signaling pathway in glutamate-induced retinal injury in neonatal rats. *Neurotox Res.* 2007;12(2):95–104.
11. Seki T, Nakatani M, Taki C, et al. Neuroprotective effect of PACAP against kainic acid-induced neurotoxicity in rat retina. *Ann N Y Acad Sci.* 2006;1070:531–534.
12. Hannibal J, Møller M, Ottersen OP, Fahrenkrug J. PACAP and glutamate are co-stored in the retinohypothalamic tract. *J Comp Neurol.* 2000;418(2):147–155.
13. Shoge K, Mishima HK, Saitoh T, et al. Attenuation by PACAP of glutamate-induced neurotoxicity in cultured retinal neurons. *Brain Res.* 1999;839(1):66–73.
14. Markhotina N, Liu GJ, Martin DK. Contractility of retinal pericytes grown on silicone elastomer substrates is through a protein kinase A-mediated intracellular pathway in response to vasoactive peptides. *IET Nanobiotechnol.* 2007;1(3):44–51.
15. Atlasz T, Babai N, Kiss P, et al. Pituitary adenylate cyclase activating polypeptide is protective in bilateral carotid occlusion-induced retinal lesion in rats. *Gen Comp Endocrinol.* 2007;153(1–3):108–114.
16. Casini G. Neuropeptides and retinal development. *Arch Ital Biol.* 2005;143(3–4):191–198.
17. Staines DR. 2006. Does autoimmunity of endogenous vasoactive neuropeptides cause retinopathy in humans? *Med Hypotheses.* 2008;70(1):137–140.
18. Balashova LM, Saskonova EO, Zaitseva NS, et al. [Role of immunological factors in peripheral vitreo-chorioretinal dystrophies and macular ruptures of the retina.] *Vestn Oftalmol.* 1995;111(1):16–18 [in Russian].
19. Adamus G. Autoantibody-induced apoptosis as a possible mechanism of autoimmune retinopathy. *Autoimmun Rev.* 2003;2(2):63–68.
20. Heckenlively JR, Fawzi AA, Oversier J, Jordan BL, Aptsiauri N. Autoimmune retinopathy: patients with antirecoverin immunoreactivity and panretinal degeneration. *Arch Ophthalmol.* 2000;118(11):1525–1533.
21. Hooks JJ, Percopo C, Wang Y, Detrick B. Retina and retinal pigment epithelial cell autoantibodies are produced during murine coronavirus retinopathy. *J Immunol.* 1993;151(6):3381–3389.
22. Vinorez SA, Wang Y, Vinorez MA, et al. Blood–retinal barrier breakdown in experimental coronavirus retinopathy: association with viral antigen, inflammation, and VEGF in sensitive and resistant strains. *J Neuroimmunol.* 2002;119(2):175–182.
23. Yoshikawa M, Suzumura A, Ito A, Tamaru T, Takayanagi T. Effect of phosphodiesterase inhibitors on nitric oxide production by glial cells. *Tohoku J Exp Med.* 2002;196(3):167–177.
24. Sun HA, Campochiaro PA. Stimulation of cyclic adenosine monophosphate accumulation causes breakdown of the blood–retinal barrier. *Invest Ophthalmol Vis Sci.* 1991;32(7):2006–2010.
25. Mitchell CH, Lu W, Hu H, Zhang X, Reigada D, Zhang M. The P2X(7) receptor in retinal ganglion cells: A neuronal model of pressure-induced damage and protection by a shifting purinergic balance. *Purinergic Signal.* 2008;4(4):313–321.
26. Sugiyama T, Kobayashi M, Kawamura H, Li Q, Puro DG. Enhancement of P2X (7)-induced pore formation and apoptosis: an early effect of diabetes on the retinal microvasculature. *Invest Ophthalmol Vis Sci.* 2004;45(3):1026–1032.
27. Newman EA. A dialogue between glia and neurons in the retina: modulation of neuronal excitability. *Neuron Glia Biol.* 2004;1(3):245–252.
28. Iandiev I, Uckermann O, Pannicke T, et al. Glial cell reactivity in a porcine model of retinal detachment. *Invest Ophthalmol Vis Sci.* 2006;47(5):2161–2171.
29. Abbracchio MP, Ceruti S. Roles of P2 receptors in glial cells: focus on astrocytes. *Purinergic Signal.* 2006;2(4):595–604.
30. Pedata F, Melani A, Pugliese AM, Coppi E, Cipriani S, Traini C. The role of ATP and adenosine in the brain under normoxic and ischemic conditions. *Purinergic Signal.* 2007;3(4):299–310.
31. Franke H, Schepper C, Illes P, Krügel U. Involvement of P2X and P2Y receptors in microglial activation in vivo. *Purinergic Signal.* 2007;3(4):435–445.
32. Sperlágh B, Illes P. Purinergic modulation of microglial cell activation. *Purinergic Signal.* 2007;3(1–2):117–127.
33. Puthussery T, Fletcher E. Extracellular ATP induces retinal photoreceptor apoptosis through activation of purinoceptors in rodents. *J Comp Neurol.* 2009;513(4):430–440.
34. Borba JC, Henze IP, Silveira MS, et al. Pituitary adenylate cyclase-activating polypeptide (PACAP) can act as determinant of the tyrosine hydroxylase phenotype of dopaminergic cells during retina development. *Brain Res Dev Brain Res.* 2005;156(2):193–201.
35. Miwa T, Mori A, Nakahara T, Ishii K. Intravenously administered phosphodiesterase 4 inhibitors dilate retinal blood vessels in rats. *Eur J Pharmacol.* 2009;602(1):112–116.
36. Fraunfelder FW, Fraunfelder FT. Central serous chorioretinopathy associated with sildenafil. *Retina.* 2008;28(4):606–609.
37. Camelo S, Lajavardi L, Bochet A, et al. Protective effect of intravitreal injection of vasoactive intestinal peptide (VIP)-loaded liposomes on experimental autoimmune uveoretinitis. *J Ocul Pharmacol Ther.* 2009;25(1):9–22.