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

Donald R Staines 1,2
Ekua W Brenu 2
Sonya Marshall-Gradisnik 2

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.
As PACAP has a role in the relaxation of pericytes, this may form the basis for a diagnostic procedure for diabetic retinopathy. 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. VIP and PACAP are likely to have an important role in retinal development. PACAP and VIP autoimmunity has been hypothesized previously as a causal agent in retinopathy. 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 vitre-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. 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. Additionally the presence of anti-recoverin immunoreactivity may be a possible causal factor in some patients with retinal pathologies.

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. 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. 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) and cAMP regulation. 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. 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.

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. Microglial activation might be exacerbated under conditions of trauma and hypoxia 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. 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. Importantly, PDEIs are effective in regulating cAMP. Interestingly, PDEIs also enhance tyrosine hydroxylase phenotypes of dopaminergic cells, which are important during retinal development. 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, although care should be taken with the use of PDE5 inhibitors. 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 way occurs with the resultant effect of retinal photoreceptor cell death, degeneration of the photoreceptor layer, and loss of sight. Additionally the presence of anti-recoverin immunoreactivity may be a possible causal factor in some patients with retinal pathologies.

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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**
