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# Does autoimmunity of endogenous vasoactive neuropeptides cause retinopathy in humans?

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**Summary** Immune privilege is a physiologic mechanism within the eye which protects it against pathogens, while also protecting it from inflammation. Immunological mechanisms in the eye must be tightly regulated to ensure externally mediated injury and infection or internally mediated autoimmunity do not exceed self-defence tolerance. Vasoactive neuropeptides (VNs) including vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase polypeptide (PACAP) and their receptors exist in the mammalian eye including the sclera, iris, ciliary body, ciliary process and the retina and may have a role in protecting these normally immune privileged sites. VN receptors are class II G protein-coupled receptors (GPCRs) which couple primarily to the adenylate cyclase (AC)-cyclic AMP pathway.

A sound blood supply is essential for retinal survival hence vascular compromise will have serious consequences. Retinal vasculitis is a potentially blinding condition with a strong association with systemic inflammatory diseases. Compromise of the endothelial barriers and the blood retina barrier (BRB) may instigate inflammatory responses setting up a chain of events involving VNs in a manner which provokes autoimmunity to them. Protection from BRB breakdown may be linked to nitric oxide (NO) effects and actions of phosphodiesterase inhibitors and cAMP production. Induced NO expressed under influences of inflammatory mediators evokes neurodegeneration and cell apoptosis and may lead to serious ocular disease including retinal injury. Other inflammatory mediators also play a role in retinal pathology.

PACAP and glutamate are co-stored in the retinohypothalamic tract and PACAP attenuates glutamate induced neurotoxicity in cultured retinal neurons suggesting that compromise of this VN would have significant detrimental impact on retinal viability though glutamate toxicity. Additional effects of VN compromise would possibly occur through unopposed vasoconstriction and inflammation. Proof of this hypothesis has important implications for treatment and prevention of autoimmune retinopathy and blindness as a number of therapeutic pathways may be opened. Importantly for therapeutic contexts cAMP effects are maintained by phosphodiesterase (PDE) inhibitors which could be used in VN autoimmune disorders. A compelling case may exist to undertake a therapeutic trial of VN replacement, PDE inhibitors and other agents in autoimmune retinopathies resulting from possible VN autoimmunity. Crown Copyright © 2007 Published by Elsevier Ltd. All rights reserved.

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## Background

Vasoactive neuropeptides (VNs) including vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase polypeptide (PACAP) and their receptors exist in the mammalian eye including the sclera,

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cornea, iris, ciliary body, ciliary process and the retina [1,2]. VNs influence regulatory T cells and are important in maintaining immunological homeostasis [3]. They have significant anti-inflammatory and anti-apoptotic roles particularly in immune privileged sites including the eye. They are potent vasodilators and are essential for the maintenance of blood supply. VN receptors are class II G protein-coupled receptors (GPCRs) which couple primarily to the adenylate cyclase (AC)-cyclic AMP (cAMP) pathway [4] and are present in the retina of different mammalian species [5]. VNs activate AC and have a key role in converting ATP to cAMP, hence setting balance levels for ATP and cAMP. Importantly, ATP is critical for cell survival and cAMP has a central role in neurological metabolism including influencing blood–brain barrier permeability, coordination of neuroregulatory pathways, and protecting against neuronal apoptosis.

Autoimmunity affecting VNs has been postulated as contributing to certain fatigue-related conditions in humans [6]. This hypothesis was suggested to account for the multi-faceted and confusing symptomatology of some fatigue-related conditions e.g. chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) and fibromyalgia (FM). The constellation of symptoms associated with these conditions is consistent with compromise of receptors associated with VIP and PACAP. This present paper examines the hypothesis that these VNs may also have a role in autoimmune retinal disease.

## Autoimmunity and retinal pathology

Immune privilege of the internal compartments of the eye is a physiologic mechanism which protects the eye against pathogens, while protecting the visual axis from the sight destroying potential of immunogenic inflammation [7]. Immunological mechanisms in the eye must be tightly regulated to ensure externally mediated injury and infection or internally mediated autoimmunity do not exceed self-defence tolerance. Autoimmunity as a cause of retinal pathology has been postulated in patients with peripheral vitreo-chorioretinal dystrophies (PVCRD). Self-antibodies were detected in 70% of these cases, although in no cases were circulating immune complexes detected in the blood suggesting that pathology was due to local effects only [8].

Retinal pathology may be mediated through autoantibody-induced apoptosis associated with retinal proteins [9]. Anti-recoverin antibodies are cytotoxic to retinal cells and induce apoptotic death of retinal

photoreceptor cells which leads to the degeneration of the photoreceptor layer and cell death. Antibodies with other retinal specificities induce their target retinal cell death by activating a caspase 3-dependent apoptotic pathway. Thus autoantibody-induced apoptosis may be a common pathway that leads to retinal death and blindness. Autoimmunity to recoverin has also been suggested in some cases with systemic malignancy [10].

Retinal degeneration is associated with coronavirus infection in murine models and is accompanied by retinal vasculitis and antiretinal antibodies [11] suggesting a role for autoimmunity in the pathogenesis of murine coronavirus induced retinal degeneration. This murine model of retinal degeneration is associated with autoimmune reactivity and breakdown of the blood–retinal barrier [12]. This finding may be a cardinal feature of postulated VN autoimmune disorders in humans because of the critical role of cyclic AMP in maintaining endothelial integrity in blood–brain barrier (BBB) and blood–retinal barrier (BRB) settings. A sound blood supply is essential for retinal survival and its compromise will have serious consequences [13]. Retinal vasculitis is a potentially blinding condition with a strong association with systemic inflammatory diseases. Noninfective retinal vasculitis is likely to be an autoimmune condition although preceding infection and cross reaction to putative autoantigens is suggested [14]. Compromise of the endothelial barriers and the BRB may instigate inflammatory responses setting up a chain of events involving VNs in a manner which provokes autoimmunity to them.

Protection from BRB and BBB breakdown may be linked to nitric oxide (NO) effects and actions of phosphodiesterase inhibitors [15] and cAMP production. However, contradictory findings have been reported [16]. Ocular blood flow is regulated by NO derived from the endothelium and efferent nitrergic neurons. However, induced NO expressed under influences of inflammatory mediators evokes neurodegeneration and cell apoptosis and may lead to serious ocular disease including retinal injury [17]. Other inflammatory mediators also play a role in retinal pathology [18]. Moreover, PACAP and glutamate are co-stored in the retinohypothalamic tract [19] and PACAP attenuates glutamate induced neurotoxicity in cultured retinal neurons [20] suggesting that compromise of this VN would have significant detrimental impact on retinal viability though glutamate toxicity. Additional effects of VN compromise would possibly occur through unopposed vasoconstriction and inflammation.

Research data exist on experimental autoimmune conditions such as experimental autoimmune

encephalomyelitis (EAE) and experimental autoimmune uveoretinitis (EAU) as models for human autoimmune disorders [21,22]. Importantly, regulatory T cells suppress EAU [23] and VIP generates regulatory T cells in EAE [24] suggesting that VNs may have an important role in therapies. While a role for VIP in the treatment of EAU has not been established [25] some supportive evidence is encouraging [26,27]. Nevertheless, the question to be posed is could autoimmune or other dysfunction of VNs contribute to retinal disease by failing to provide proper immune regulation?

### Postulated vasoactive neuropeptide autoimmunity in retinal disease

Why VNs should participate in induction of autoimmunity, not just protecting from it, is unclear given their key role usually in protecting physiological systems from infection and inflammatory responses. Promoter regions of some VN receptor genes have CpG fragments which might promote autoimmunity if exposed to apoptotic or necrotic circumstances and become recognised by the immune system as foreign immune complexes [28]. Also as their receptors are members of the GPCR family they may be susceptible to autoimmunity as are other members of the GPCR family [29].

The hypothesis that VN autoimmunity causes retinal disease requires definitive evidence. However, there may be an association between retinal pathology and postulated VN fatigue-related conditions. Some limited evidence exists that retinal disease occurs in patients with CFS/ME [30]. Evidence is now also available that abnormalities in VN receptor genes cause immunological disturbance in T cells of patients with multiple sclerosis MS resulting in Th1 skewed profiles and consequent pathology [31]. This latter finding provides support for the case that VN disturbance does have demonstrable effects on downstream immunological function.

Proof of this hypothesis has important implications for treatment and prevention of autoimmune retinopathy and blindness as a number of therapeutic pathways may be opened. Importantly for therapeutic contexts cAMP effects are maintained by phosphodiesterase (PDE) inhibitors which could be used in VN autoimmune disorders. PDE inhibitors have subsets which are highly specific and may constitute appropriately targeted interventions in cAMP disorders [32–34]. A case may exist to undertake a therapeutic trial of VN replacement, PDE inhibitors and other agents in autoimmune retinopathies resulting from possible VN autoimmunity.

### Conclusion

Autoimmunity of VNs is not yet proven although evidence now exists implicating VNs in human autoimmune disorders such as MS. VNs not only protect against retinal pathology, but may themselves undergo autoimmune disruption to affect normally immune privileged regions of the eye. An association of VN autoimmunity with retinopathy in humans should be investigated as preventive and treatment opportunities may already exist. Clinical trials for VN replacement, PDE inhibitors and other interventions may then be considered for the treatment of autoimmune eye conditions and potentially the prevention of blindness in them.

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