# THE INITIATING STIMULI FOR UVEITIS

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Uveitis is an inflammation of the choroid, ciliary body or iris. The term, however, is commonly used to describe intraocular inflammation not only involving the uveal tract, but also the retina, vitreous and sclera. Uveitis is not a specific disease; it can be caused by a multitude of conditions. In the early part of this century infection was felt to be the cause of most forms of uveitis.[1] Specifically, syphilis and tuberculosis accounted for the majority of diagnosable cases of the disease. More recently, researchers have shown that an immune response against ocular antigens may play a pathogenic role in the development of some forms of uveitis. Although the specific cause of uveitis remains unknown in many patients with this disease, the initiating stimuli for intraocular inflammation can be divided into two major pathways: an antigen-specific immune-mediated inflammatory response and a non-specific inflammatory response (Fig. 1). Each of these major pathways will be discussed here.

## NON-SPECIFIC OCULAR IMMUNE RESPONSE

There are a number of causes of intraocular inflammation that are not antigen specific, including infection, trauma and surgery. Endotoxin-induced uveitis is an animal model useful for studying the mechanisms by which non-antigen-specific stimuli induce ocular inflammation. Endotoxins elicit a plethora of biological effects such as fever and hypotension, and the lipid A moiety of bacterial endotoxins is responsible for the biological activity.[2] In 1943 Corrado Ayo showed that a single intravenous injection of endotoxin could induce ocular inflammation in large laboratory animals including dogs, cats and rabbits.[3] This endotoxin-induced uveitis (EIU) was later demonstrated in Lewis rats following intravenous, intraperitoneal or intrafootpad endotoxin injection,[4] and in Columbia-Sherman rats following intraocular endotoxin injection.[5] More recently, EIU has been elicited in C3H/Hen mice.[6]

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EIU is characterised by miosis, iris hyperaemia, increased aqueous humour protein, and inflammatory cell infiltration into the anterior uvea, anterior chamber (Fig. 2a) and the vitreous in the area of the optic nerve head (Fig. 2b). Kinetic studies show that inflammatory cells first migrate into the eye about 6 hours after endotoxin injection, and ocular inflammation peaks approximately 18 hours later. Analysis of eyes with EIU shows that inflammation is related to the release of cytokines from activated cells. Tumour necrosis factor-alpha (TNF-$\alpha$), interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-8 (IL-8) are other inflammatory mediators that appear to be stimulated by endotoxins.[7–9] Endotoxins also prime neutrophils for enhanced release of oxygen metabolites and leukotriene $B_4$.[10,11]

Recent studies have shown that endotoxin directly increases surface expression of Mac-1 on leucocytes, including neutrophils.[12,13] We have demonstrated that upregulated expression of specific cell adhesion molecules (CAM) is important for initiating inflammation in the eye. There are three structural groups of CAM: selectins, integrins and the immunoglobulin gene superfamily. Selectins mediate the initial contact of leucocytes and the vascular endothelium. Firmer adhesions are promoted by the interaction of integrins expressed on inflammatory cells and members of the immunoglobulin gene superfamily expressed on the vascular endothelium. Leucocytes are then able to migrate out of the vasculature and into the tissue. We have shown that E-selectin is expressed on the vascular endothelium of the ciliary body before substantial numbers of inflammatory cells infiltrate the eye.[14] Intercellular adhesion molecule-1 (ICAM-1) also appears to be expressed on the ciliary body epithelium, vascular endothelium of the iris and ciliary body, and cornea prior to the development of acute inflammation.[15] Importantly, monoclonal antibodies against adhesion molecules including ICAM-1, lymphocyte function-associated molecule-1 (LFA-1), Mac-1, and E-selectin and P-selectin, inhibit the development of EIU.[15–17] Once a critical number of inflammatory cells migrate

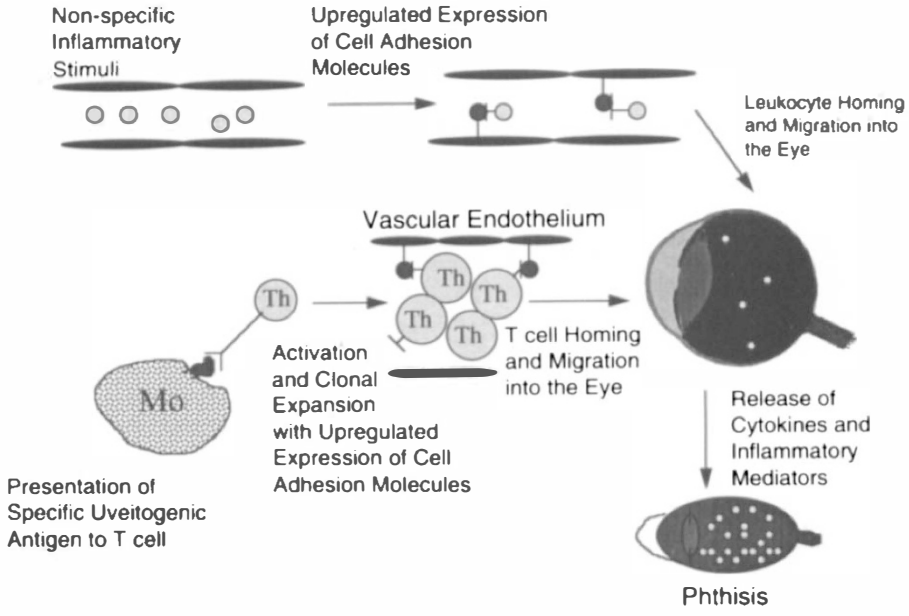


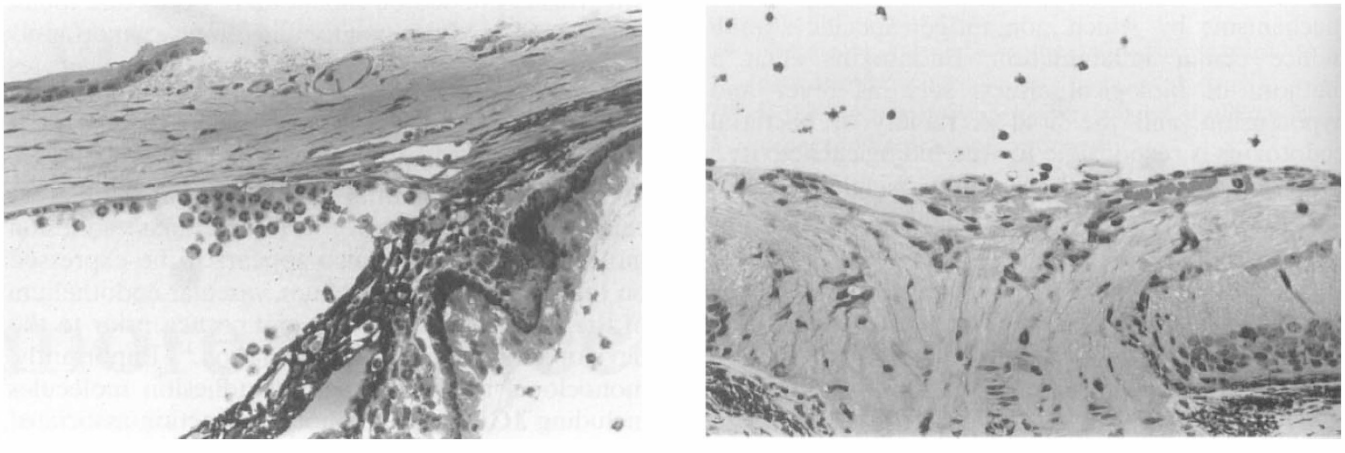

**Fig. 1.** *Initiating stimuli for uveitis. Intraocular inflammation can result from an immune response against a specific ocular antigen. This is the presumed mechanism for autoimmunity in the eye.*

into the eye, release of cytokines and other inflammatory molecules can start the inflammatory cascade with breakdown of the blood–aqueous and blood–retinal barriers, leading to additional cellular infiltration of the eye.

## ANTIGEN-SPECIFIC OCULAR IMMUNE RESPONSE

Whereas non-specific stimuli such as endotoxin can incite an inflammatory response in the eye, many causes of uveitis are thought to involve a specific immune response against retinal antigens. Antigen-specific immune responses are divided into a cell-mediated and a humoral response. Both of these require processing of the antigen by specialised antigen-presenting cells (APC). Some ocular tissues, including the retinal pigment epithelium, can also process and present antigens.[18] A humoral response then occurs when an APC presenting the appropriate antigen and a helper T lymphocyte cause a B lymphocyte to proliferate and develop into an antibody-forming cell. Cell-mediated immunity occurs when APC process and present antigen to helper T cells (Fig. 1). These T cells are then stimulated, proliferate, and are able to modulate a number of other effector cells in the immune response such as macrophages, cytotoxic T cells and natural killer cells.

Importantly, activated T helper cells are able to home to organs containing the specific antigen to



(a) (b)

**Fig. 2.** *Photomicrographs of the histopathology of endotoxin-induced uveitis in a C3H/HeN mouse. (a) Numerous inflammatory cells, predominantly neutrophils, and exudate are seen in the anterior chamber of the eye. (b) Inflammatory cells are also seen in the vitreous in the area of the optic nerve head. Haematoxylin and eosin; original magnification* ×400.

which they are sensitised. Once enough of these activated, antigen-specific T cells enter a target organ such as the eye, they release cytokines which then start an inflammatory cascade by breaking down the blood–ocular barriers and allowing additional leucocytes into the area. Production of other inflammatory mediators such as free radicals, cyclo-oxygenase and lipoxygenase derivatives, and cellular enzymes and neuropeptides then further the inflammatory response.

The hypothesis that an immune response against autoantigens could cause uveitis was proposed by Elschnig in 1910.[19] Researchers later showed that injection of retinal extracts into experimental animals could induce uveitis.[20] The uveitogenic antigen was identified as retinal S-antigen (S-Ag), also known as arrestin. S-Ag is found in photoreceptor outer segments and in the pineal gland of some species. Further studies showed that immunisation with S-Ag, interphotoreceptor retinoid-binding protein (IRBP), rhodopsin or recoverin at sites far from the eye can induce uveitis.[21] This animal model of ocular inflammatory disease is called experimental autoimmune uveitis (EAU), and has been useful for studying the pathogenesis and therapy of uveitis in humans. Clinical signs of inflammation develop about 10–14 days after immunisation. Histologically, there is destruction of the photoreceptor layer of the retina, choroidal and retinal infiltration with inflammatory cells, retinal haemorrhage, and vasculitis (Fig. 3). Immunostaining shows that T lymphocytes are the predominant inflammatory cell in these eyes, although infiltrating macrophages can also be found.[22]

This animal model of uveitis has clinical and histological similarities to certain forms of uveitis in humans. Sympathetic ophthalmia is a bilateral granulomatous uveitis that follows a penetrating injury in one (exciting) eye, followed in days to years by uveitis in the contralateral (sympathising) eye. The disease is characterised clinically by a granulomatous uveal inflammation in the anterior chamber of the eye, vitritis, and choroidal infiltrates. Histological examination shows diffuse granulomatous uveal inflammation, epithelioid cells that contain phagocytosed uveal pigment, and Dalen–Fuchs' nodules composed of collections of epithelioid cells lying between Bruch's membrane and the retinal pigment epithelium.[23–25] Interestingly, similar findings have been described in EAU.[26]

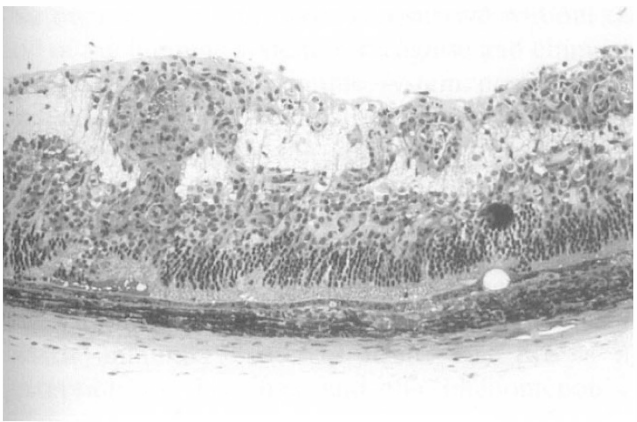


**Fig. 3.** *Photomicrograph of the histopathology of experimental autoimmune uveitis in a B10/A mouse immunised with interphotoreceptor retinoid-binding protein. There is destruction of photoreceptors and inflammatory cell infiltration into the retina resulting in retinal oedema and loss of the retinal architecture. Haematoxylin and eosin; original magnification* ×200.

In most forms of human uveitis the initiating stimuli are unknown. In sympathetic ophthalmia it is felt that penetrating trauma causes the release of previously sequestered ocular antigens into the circulation leading to an immune response against these specific antigens. Trauma, infectious agents or toxic substances that can enter the eye at the time of the initial injury may stimulate upregulation of CAM. This may guide activated T cells to migrate into the eye where they can release cytokines and amplify the inflammatory response.

T cells active against ocular antigens may develop by other mechanisms. The immune response presumably developed to fight infection. An immune response against infectious agents may cross-react against ocular antigens and induce uveitis. Researchers have noted homology between a yeast histone and S-Ag.[27] A number of forms of uveitis follow an infectious disease, but do not seem to be caused by direct infection. Reiter's syndrome, a form of uveitis characterised by arthritis, conjunctivitis and urethritis, may occur after Gram-negative dysentery or after non-gonococcal urethritis as a result of *Chlamydia trachomatis* and *Ureaplasma urealyticum.*[28]

In summary, there are probably multiple initiating stimuli for inflammation in the uvea. Unfortunately, the exact causes of most cases of uveitis in humans remain an enigma. It is hoped that experimental models and immunological studies in patients will allow us to better define the pathogenesis of intraocular inflammatory disease and lead to the development of better therapy for this disorder.

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