Could anti-inflammatory medicines treat viral eye diseases?

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New research has shown that non-steroidal anti-inflammatory drugs (NSAIDs) can prevent reactivation of ocular herpes in mice. Presented to the *Association for Research in Vision and Ophthalmology* (ARVO)[1] by Herbert E. Kaufman, the work also shows a link between viral reactivation and the induction of a cellular gene.

Ocular herpes is the most common cause of infectious blindness in the developed world. There are about 50,000 cases per year in the US alone, of which >90% are recurrences of the initial infection. It is caused by herpes simplex virus type-1 (HSV-1), a common virus that also causes cold sores or fever blisters. It is present in 50–80% of the adult population, but most remain asymptomatic. After infecting the eye, the virus migrates down the optic nerve and establishes a life-long latent infection in the trigeminal ganglia. Some people then experience periodic reactivation of the virus, resulting in painful sores on the eyelid, the corneal surface or, most seriously, in the deeper stromal layer of the cornea. Known as stromal keratitis, this condition accounts for ~25% of ocular herpes cases and causes progressive corneal scarring, deterioration of vision and sometimes blindness.

Like other herpes infections, ocular herpes is currently incurable. Recurrences are treated with a combination of antiviral drops (e.g. trifluridine) and corticosteroids. Oral acyclovir reduces the incidence of recurrence, but only by 40%. It is ineffective in treating or preventing stromal disease[2], leaving a significant burden of progressive corneal damage requiring laser surgery or corneal transplant.

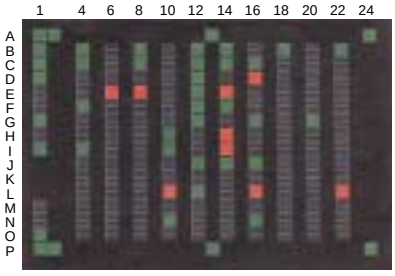

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Figure 1. Gene expression microarray of mouse trigeminal ganglia probed with PolyA + RNA/[^{32}P-ATP-cDNA] showing nine upregulated genes in latently HSV-infected BALB/c mice 1 h after hyperthermia stress. 10L = heat shock protein 60; >16L = cyclooxygenase 2.

The role of prostaglandins

There has been extensive research into the lifecycle and molecular biology of HSV, focusing on how it evades the immune system and how reactivations are triggered at the molecular level. Much of the work has centred on therapeutic vaccines, but none has yet prevented recurrence completely. In 1999, new reports suggested that ocular herpes was reactivated and made more severe by the anti-glaucoma drug latanoprost, a topical prostaglandin analogue[3]. Kaufman and colleagues at the Louisiana State University Eye Center (New Orleans, LA, USA) confirmed, in controlled animal experiments, that latanoprost increased both the frequency of recurrence and the severity of attacks[4,5]. However, there was no effect from unoprostone, a docosanoid prostaglandin-derivative with low affinity for prostaglandin receptors. This suggested that the prostaglandin system might play a role in viral reactivation and multiplication, a hypothesis first advanced in the 1980s and recently supported by studies with vesicular stomatitis virus in the mouse CNS[6]. The likely candidate was COX-2, the inducible cyclooxygenase enzyme involved in the production of inflammatory prostaglandins.

Latent ocular herpes in mice is known to be reactivated when the animals are subjected to heat stress. Kaufman and coworkers found that heat stress increased the transcription of the COX-2 gene in the ganglia of these mice. Furthermore, treating them with cyclooxygenase inhibitors in the form of NSAIDs such as aspirin, DFU (a tetrasubstituted furanone) and celecoxib reduced recurrence of HSV by 70–80%[1] – a clear improvement on the 40–60% reduction achieved with antiviral drugs such as acyclovir. NSAIDs also reduced the quantity of viral DNA detected in the mouse ganglia.

Wider applications

Preventing virus activation through inhibition of a host gene is a new line of attack, because existing antiviral drugs work on the virus itself. Although work on the use of NSAIDs for the treatment of viral eye diseases is preliminary, it could have far-reaching implications. 'This host reactivation mechanism may be important for other latent herpes viruses – HSV-2 (genital herpes), herpes zoster and perhaps even cytomegalovirus and Epstein–Barr virus,' says Kaufman, who pioneered the use of antiviral drugs in the 1960s. Genital herpes is a common and distressing infection that can be only partially controlled, so

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an improved treatment would be highly significant. Cytomegalovirus is a common cause of retinal damage and blindness in patients with AIDS, and COX-2 inhibitors have been shown to slow its replication *in vitro*[7].

Any NSAID-based treatment would probably be used in addition to antiviral therapy. 'The reduction in recurrences is likely to be additive to antiviral drugs', Kaufman says, 'but the work is early and much more needs to be done before we use these drugs for this purpose in humans.'

The Louisiana State University team will now focus on determining which COX-2 inhibitors are most effective against herpes reactivation, and on the efficacy of topical NSAID preparations. They will also attempt to repeat the results in other species; to date, all the work has been done in mice.

References

1 Kaufman, H.E. (2001) Can we prevent recurrence of herpes infections without antiviral drugs? Weisenfeld Award Lecture, *Association for Research in Vision and Ophthalmology Annual Meeting*, 1 May 2001, Fort Lauderdale, FL, USA

2 The Herpetic Eye Disease Study Group (1997) A controlled trial of oral acyclovir for the prevention of stromal keratitis or iritis in patients with herpes simplex viral epithelial keratitis. The epithelial keratitis trial. *Arch. Ophthalmol.* 115, 703–712

3 Wand, M. *et al.* (1999) Latanoprost and herpes simplex keratitis. *Am. J. Ophthalmol.* 127, 602–604

4 Kaufman, H.E. *et al.* (1999) Latanoprost increases the severity and recurrence of herpetic keratitis in the rabbit. *Am. J. Ophthalmol.* 127, 531–536

5 Kaufman, H.E. *et al.* (2001) Effects of topical unoprostone and latanoprost on acute and recurrent herpetic keratitis in the rabbit. *Am. J. Ophthalmol.* 131, 643–646

6 Chen, N. *et al.* (2000) NSAID treatment suppresses VSV propagation in mouse CNS. *Virology* 276, 44–51

7 Shenk, T. (2000) Use of microarrays to probe the replication and pathogenesis of human cytomegalovirus. *25th International Herpesvirus Workshop*, 3 August 2000, Portland, OR, USA

The rise and fall of Viagra

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New drugs for male erectile dysfunction (ED) are set to challenge the market dominance currently enjoyed by sildenafil citrate (Viagra™, Pfizer, Sandwich, UK). The new drugs, vardenafil (Bayer, Leverkusen, Germany) and Cialis™ (IC351; Eli Lilly, Indianapolis, IN, USA), both of which are phosphodiesterase-5 (PDE5) inhibitors, are currently in Phase III clinical trials and could prove more potent, and produce fewer side effects, than sildenafil.

ED is defined as the consistent inability to attain and maintain a penile erection adequate for satisfactory sexual activity. Vascular disease, diabetes, prostate surgery, psychiatric disorders and concomitant drug therapy can predispose to ED, which can be exacerbated by psychological factors. ED is widespread: in a large community-based epidemiology survey (Massachusetts Male Aging Study; MMAS), one-third of 1290 men aged 40–70 years reported having moderate or complete ED[1]. Other studies have found that ~50% of men in this age group have some degree of ED, and 30% report moderate-to-severe impotence[2].

Sildenafil

Sildenafil citrate, introduced in 1998, was considered to be a major breakthrough as the first effective oral treatment for ED. Sildenafil is an active inhibitor of cGMP-specific PDE5 – the enzyme responsible for degrading cGMP in the corpus cavernosum of the penis. This inhibition, combined with nitric oxide-mediated increased formation of cGMP resulting from sexual arousal, leads to more pronounced relaxation of the corpus cavernosum smooth muscle, leading to accumulation of blood in the sinusoids and, therefore, improved penile rigidity.

Sildenafil also exerts a significant effect on PDE6, an isoform important for phototransduction in the retina. Although sildenafil is about 4,000–10,000-fold more selective for PDE5 over PDE1–4 and PDE7, it is only approximately tenfold more selective for PDE5 over PDE6. Therefore, at clinically effective doses, sildenafil is likely to inhibit PDE6, accounting for the transient colour change in vision reported by 1 in 12 patients taking sildenafil[3].

'Genetic defects in PDE6 are the cause of autosomal recessive retinitis pigmentosa and autosomal dominant night blindness,' says Patrick Vallance, Professor of Clinical Pharmacology at University College London (London, UK). In addition, experimental lesions in PDE6 cause retinal degeneration in mice[4]. 'There is no doubt that complete loss of PDE6 is bad news for the retina. The question remains whether 10% inhibition will do any longer-term damage apart from reversible changes in colour vision. Sildenafil has just not been used for long enough to tell,' adds Vallance.

The more frequent side effects of sildenafil, such as facial flushing, headache, nasal congestion and dyspepsia[3], have

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