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Antiviral Research 71 (2006) 127–133
Antiviral Research
www.elsevier.com/locate/antiviral

Mini-review

Herpesvirus latency and therapy—From a veterinary perspective

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Received 7 February 2006; accepted 1 March 2006

Dedicated to Prof. Erik De Clercq on the occasion of reaching the status of Emeritus-Professor at the Katholieke Universiteit Leuven in September 2006.

Abstract

This short review considers how the human herpesviruses were among the first viruses to be effectively treated by means of antiviral therapy although the ability of alphaherpsviruses to establish neuronal latency with reactivation remains the major obstacle to achieving a cure. Laboratory animals played an essential role in the development of herpes antivirals including our understanding of the complexity of the neurological infection in relation to chemotherapy. The existence of natural herpesvirus infections in domestic species also contributes to our understanding of latency and reactivation relevant to antiviral therapy although the use of antivirals to treat or prevent virus infections in veterinary species has been minimal, to date. The review briefly focuses on herpes infections in the horse and cat where some progress has already been achieved in the veterinary antiviral field.

Keywords: HSV; EHV-1; FHV-1; Veterinary; Antiviral nucleosides; Latency

Contents

1. The Herpesviridae

Herpesviruses comprise a large, ancient family of viruses that infect most if not all vertebrates and even lower organisms (Davison et al., 2005). These viruses have characteristic morphology with an icosahedral capsid comprising 162 capsomers (150 pentons and 12 hexons) and a structured tegument (Zhou et al., 1994); the nucleocapsid is enveloped with morphologically indistinct glycoprotein spikes. Members of the Herpesviridae were among the very first viruses to be completely sequenced (the EBV, VZV, HSV-1 and CMV, HSV-2 DNA genome sequences were reported in 1983, 1986, 1990, 1997, respectively). The double stranded DNA genome which ranges in size from 130 to over 230 kb encodes from 70 to more than 100 genes. As well as coding for the structural elements of the complex capsid other protein functions include the external glycoproteins, several enzymes and many gene products that interact with the host adaptive immune responses, innate immune mechanism and inflammatory processes. The hall-mark of herpesvirus infection in the natu-

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doi:10.1016/j.antiviral.2006.03.018

Table 1
Human herpesviruses to date

Virinae	Common abbreviation	Common name	Common manifestations	Antiviral therapy
Alpha	HSV-1	Herpes simplex virus type 1	Cold sores, keratitis, encephalitis	+++
Alpha	HSV-2	Herpes simplex virus type 2	Genital sores	+++
Alpha	VZV	Varicella-zoster virus	Chicken pox; shingles	+++
Beta	CMV	Cytomegalovirus	Severe disease in immunocompromised	++
Beta	HHV-6	Human herpesvirus-6	Roseola infantum; rash and fever	–
Beta	HHV-7	Human herpesvirus-7	Roseola infantum; rash and fever	–
Gamma	EBV	Epstein Barr virus	Infectious mononucleosis, B-cell tumours, etc.	+
Gamma	HHV-8	Human herpesvirus-8	Kaposi's sarcoma	–

(+++) widely used and successful; (++) widely used and quite successful; (+) occasionally used with limited success; (−) rarely used with uncertain outcome.

ral host and in experimental models is the ability to establish a lifelong infection usually achieved by a state of latency from which virus may reactivate from time to time with recurrence of infection leading to transmission to susceptible hosts.

2. Human herpesviruses and antiviral therapy

Eight distinct herpesivures are known, to date, to infect humans (Table 1). The table also indicates the human herpesviruses for which most success with antiviral chemotherapy has been obtained. The classification of the Herpesviridae recognizes three sub-families: Alpha-, Beta- and Gamma-herpesvirinae. For this minireview, only the members of the Alphaherpesvirinae will be considered, i.e. HSV-1 and HSV-2 and varicella-zoster virus (VZV). The human members of this group and many of their animal counterparts have a predilection for ganglionic neurons and have evolved the particular strategy of neuronal latency and reactivation (Field and Borchers, 2001). HSV, the prototype, has played an extremely prominent historical role in the development of antiviral chemotherapy being among the very first infections to prove the principle that a virus disease could be successfully treated using antiviral compounds. The first of these was the nucleoside analogue 5-iodo-2′-deoxyuridine (idoxuridine; IDU) (Prusoff, 1959) soon to be followed by further nucleosides: adenosine arabinoside (Ara-A) and trifluorothymidine (TFT). These compounds were of relatively low selective toxicity and came to be known, collectively as "first generation" nucleosides. Together with the pyrophosphate analogue, phosponoformate (foscarnet, PFA), the efficacies of all these compounds (reviewed Field and Whitley, 2005) were validated in tissue culture and using relevant animal infection models prior to their use in man. Acyclovir (ACV) (Elion et al., 1997) was one of the first of the "second generation" nucleoside analogues to show very high selective toxicity for virus-infected cells and remarkable safety for oral administration. The efficacy of ACV was established in a variety of infection models for the various syndromes of HSV (Field et al., 1979; Klein et al., 1979), during preclinical development prior to its use in man (Table 2).

With the concept of safe antiviral therapy firmly established, in the 1980s the research focus switched to other virus infections notably HIV, hepatitis viruses and respiratory viruses; thus herpesviruses are no longer dominant in the field although many interesting developments have continued. These include further nucleosides, e.g. brivudine; penciclovir (PCV); the nucleoside phosphonates (e.g. cidofovir); nucleoside prodrugs valaciclovir (yielding ACV *in vivo*) and famciclovir (yielding PCV *in vivo*). All these compounds ultimately target herpesvirus DNA-pol (reviewed by De Clercq, 2005; Field and Whitley, 2005). Novel herpes drug targets have been explored (reviewed by Coen and Schaffer, 2003) notably the enzymes ribonucleotide reductase (Paradis et al., 1988) and proteases (Waxman and Darke, 2000). Currently, there is much interest in extremely potent inhibitors of HSV helicase/primase that have been shown to be highly efficacious in various animal infection models (Betz et al., 2002; Kleymann et al., 2002; S. Biswas and H.J. Field, unpublished observations).

Table 2
Veterinary alphaherpesviruses that are potential targets for therapy

Virus	Alternative names	Species affected	Chemotherapy	Reference
Cercopithecus virus-1	Herpesvirus simae; herpesvirus B	Man	ACV	Boulter et al. (1980)
Simian varicella virus		Monkey	ACV	Fyfe et al. (1982)
EHV-1 and -4	Equine abortion and equine rhinopneumonitis	Horse	PCV, HPMPC	Awan and Field (1993), Field and Awan (1990), Fuente et al. (1992) and Gibson et al. (1992)
BHV-1	Infectious bovine rhinotracheitis, red nose, infectious pustular vulovaginitis	Cow	HPMPC	Gilliam and Field (1993)
BHV-2	Bovine mammilitis	Cow		
FHV-1	Feline rhinotracheitis	Cat	ACV, PCV, TFT IDU, HPMPC	Maggs (2005), Maggs and Clarke (2004), Nasisse et al. (1989, 1997), Owens et al. (1996), Sandmeyer et al. (2005) and Weiss (1989)
SHV-1	Aujeszky's disease; pseudorabies	Pig	GCV	Field (1985)
CHV-1	Canine herpes	Dog	None	

3. Herpesvirus latency—the greatest obstacle for effective chemotherapy

As mentioned above, the key protein target for all the successful compounds that are active against alphaherpesviruses, to date, is the virus encoded DNA-polymerase (DNA-pol). Second generation nucleosides, depend for their selectivity on their phosphorylation by the herpesvirus thymidine kinase (TK). Because, during the latent phase, the virus does not generally express the genes coding for virus proteins, including TK and DNA-pol, latent virus is unaffected by any of the conventional nucleoside analogues or drugs that rely on viral protein targets. Experimental infection in animal models (see below) suggests that latency is established early, and foci of latently infected neurons are detected a few hours after the first round of virus replication at the mucosal site of infection (Field and Thackray, 2000). Notwithstanding, in experimental models, when early therapy using valaciclovir or famciclovir is applied under ideal conditions it appears that latency can be markedly reduced as evidenced by subsequent reactivation from explanted neural tissue and famciclovir appeared to be superior under these conditions (Thackray and Field, 1996, 2000). In man, the process of establishing latency may take a little longer, but the implication is that chemotherapy is unlikely to be started early enough to prevent the establishment of latency during a primary infection. Even if chemotherapy is successful in limiting the clinical signs of disease, the virus will persist, to reactivate later (Darby and Field, 1984). However, ACV and more recently famciclovir or valaciclovir suppress recurrent infections and patients have taken suppressive therapy for this purpose over periods up to 10 years (Douglas et al., 1984; Straus et al., 1984; Goldberg et al., 1993; Mertz et al., 1984). Furthermore, prophylaxis can prevent episodes of herpes resulting from reactivation in immunosuppressed patients. The problem of eradicating herpesvirus DNA harboured in latently infected cells is one for which there remains no obvious solution. On the plus side, antiviral drug resistance to ACV and similar nucleosides has not proved to be problem. It may be that the early establishment of latency (and the subsequent role of the nervous system in the reactivation and recurrence of infection) may underlie the very low incidence of HSV drug resistance. In patients with a normal immune system, the incidence of antiviral drug resistance remains extremely low and there is no evidence that it is increasing (Field, 2001).

4. Comparative virology plays an essential role in the development of herpes antivirals

Animals have played a vital role in the development of herpes chemotherapy from the outset (reviewed by Field and Brown,

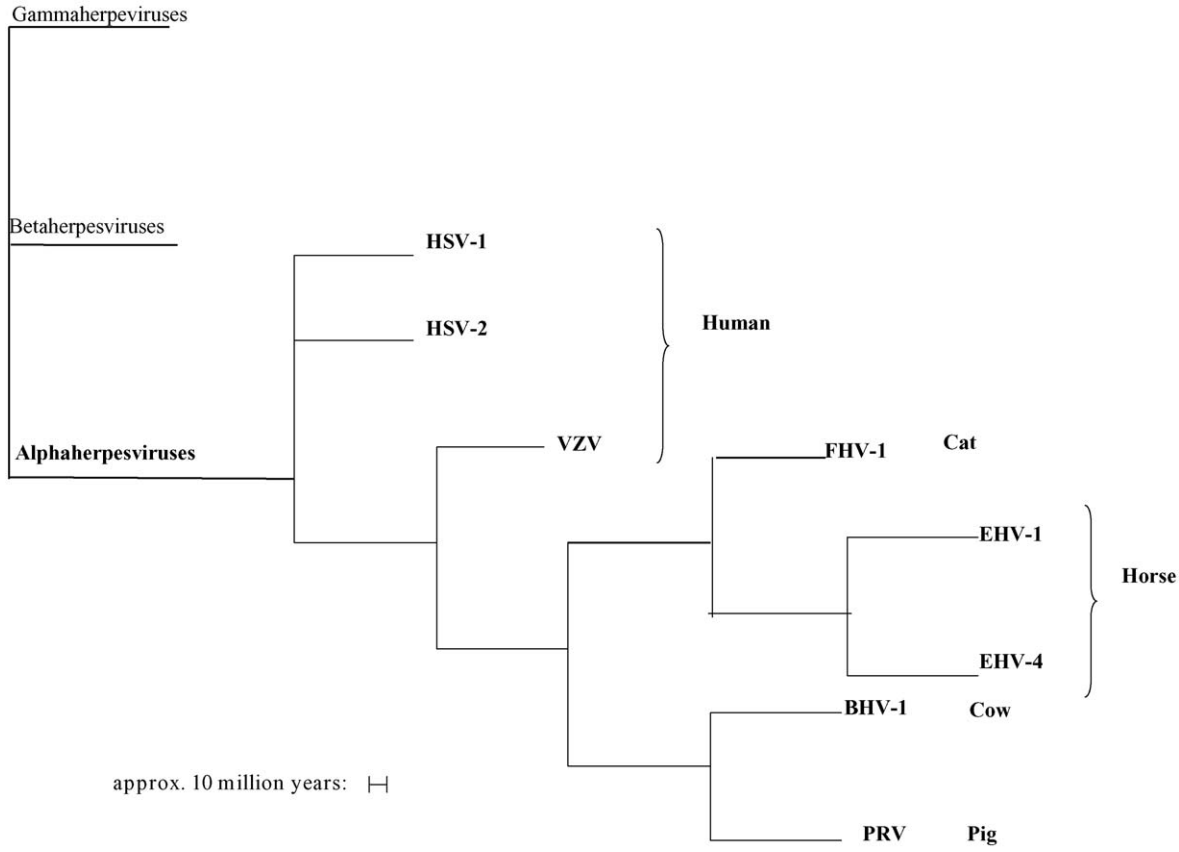

Fig. 1. A phylogenetic tree showing the relationship between the human alphaherpesviruses and several important alphaherperpesviruses of domestic animals. The figure is adapted from Willoughby et al. (1999) and Davison (2002) and shows how the viruses have diverged over a time-span of tens of millions of years. The relatively close relationships between the veterinary viruses and VZV compared with HSV should be noted. The original analysis was based on comparison of the DNA-pol gene whose product also happens to be the critical target for many active antiviral compounds.

1989). Human herpesviruses have evolved with their hosts for tens of millions of years (Fig. 1). Herpesvirus infections were present prior to the divergence of the modern species and naturally they have established extremely complex relationships with their hosts. HSV and many related animal herpesviruses are highly adapted to their natural hosts and lifelong infection is achieved by a neuronal latency with reactivation upon diverse stimuli including parturition. Notwithstanding, it was shown as early as the 1920s (Goodpasture and Teague, 1923) that guinea pigs and rabbits were susceptible to HSV producing characteristic lesions. This enabled the therapeutic potential of the first antiviral compounds (IDU, TFT and ara-A) to be tested in animals for example by means of topical application to experimental ocular infections (Kaufman and Maloney, 1962; Kaufman et al., 1962). In 1972 a major advance occurred with the report (Stevens and Cook, 1971) that ganglionic latency with reactivation could be established in mice (and subsequently rats) infected with the human viruses (HSV-1 and HSV-2). Thus, from this time, it was possible to study the effects of antiviral agents on virus infections in the nervous system which is impossible in the human host.

Conclusions drawn from these early studies were later confirmed following many years of clinical use in man. The predictions were: (i) late therapy can ameliorate advanced disease; (ii) reversal of established herpes encephalitis is possible; (iii) an intact immune system is not essential for clinical benefit; antiviral agents are effective in the immunocompromised host; (iv) the establishment of latency cannot be completely prevented even with very early therapy; (v) recurrences are suppressible with chronic therapy whilst latency is not eradicated; (vi) circumstances arise where antiviral resistance develops *in vivo*; (vii) many resistant mutants have altered pathogenicity (reviewed by Field, 1988).

Animal infection models continue to play a vital role in the development of new and refinement of classical therapeutic regimens. A good example of this is the use of topical antiviral and anti-inflammatory compounds in combination. This strategy was first introduced in the 1960s to control severe eye disease following recurrent herpes keratitis by means of topical steroids combined with antiviral therapy (Kaufman and Maloney, 1962). The problem was, while the steroid was successful in modulating the damaging inflammatory response to infection, there was a tendency for the anti-inflammatory drugs to prolong and increase virus replication—hence the need for combination with an effective antiviral compound. A programme was pursued in which many combinations of steroidal and non-steroidal anti-inflammatory drugs or local anaesthetic creams were administered together with nucleoside analogue or pyrophosphate analogue antivirals. These were systematically tested *in vitro* and in animal infection models until the desired outcome was achieved (Awan et al., 1998). The optimum formulation, a cream containing 5% ACV mixed with 1% hydrocortisone given the name ME-609 underwent clinical trials including a study of therapy initiated subsequent to UV-induced experimental reactivation in human patients (Harmenberg et al., 2002; Evans et al., 2002). The US FDA have recently approved proposals for the clinical trials to allow drug registration of labial (oral) herpes project ME-609 and a phase-II clinical trial is scheduled to commence during the autumn of 2006.

5. Veterinary herpesvirus targets for chemotherapy

Animals, both wild and domesticated, are widely infected with members of the Herpesviridae from each of the three subfamilies. Furthermore, several of our domestic animals suffer disease problems caused by herpesvirus infections related to the human alphaherpeviruses; like their human counterparts, these viruses also establish ganglionic latency (Field and Borchers, 2001). The extent of these relationships is shown (Fig. 1) thus, these viruses diverged from the human viruses prior to speciation. It may also be seen (Fig. 1) that several of the common diseases of domestic animals: bovine herpesvirus-1, equine herpesvirus-1 and -4; feline herpesvirus-1 and suid herpesvirus-1 (pseudorabies) are more closely related to VZV than they are to HSV-1 or -2 and have thus been placed in the genus Varicellovirus. For a recent review on the molecular biology and impact on neurovirology and veterinary medicine of pseudorabies, see Pomeranz et al. (2005). The importance of this can be considered from two angles. (i) The human virus, VZV is one for which there are no satisfactory rodent models, to date. Thus, the animal herpesviruses represent surrogate models which can provide data relevant to man. (ii) The infections represent problems in companion and domestic species themselves for which there is both a commercial and welfare need for prevention and control. Particularly relevant examples of veterinary Varicelloviruses that are realistic candidates for antiviral therapy are FHV-1 and EHV-1. For both there are well established and well characterized cell lines derived from equine and feline cells, respectively, in which preliminary antiviral studies may be carried out.

6. Feline herpesvirus-1

Feline herpesvirus-1 (FHV-1) is the most common viral pathogen of domestic cats worldwide, with up to 97% of cats having serologic evidence of exposure. It causes an upper respiratory tract and ocular disease in cats known as “feline viral rhinotracheitis” characterized by conjunctivitis, profuse ocular and nasal discharges, and in some cases, severe keratitis and corneal ulceration. In kittens, the infection can generalize resulting in mortality rates of up to 50% (reviewed by Andrew, 2001; Stiles, 2003; Maggs, 2005). Despite routine vaccination of cats, FHV-1 disease remains a common problem as a consequence of lifelong neuronal latency. Furthermore, vaccination may not always prevent infection although it may lessen clinical signs of disease and FHV-1 shedding (Lappin et al., 2006). Long-term protection for >7 years following administration of an inactivated trivalent vaccine to specific pathogen-free cats has been claimed (Scott and Geissinger, 1999). However, under some circumstances, vaccinated cats can still develop latent FHV-1 infections with consequent periodic reactivations which allow the virus to transmit (Gaskell and Willoughby, 1999). Furthermore, there is incomplete vaccination coverage of the feline population as a whole and it is in the unvaccinated population

where the majority of carriers reside. Cats are not routinely tested for FHV-1 prior to being vaccinated and so this makes it difficult sometimes to determine (without PCR testing for vaccine markers) if an animal was already naturally infected with FHV-1 prior to being vaccinated. Also, vaccination does not confer lifelong protection and must be boosted periodically.

Herpetic keratitis caused by HSV-1 in humans was among the very first virus targets to be successfully treated (Kaufman et al., 1962). Although the ocular disease caused by FHV-1 is similar to the one caused by HSV-1 in humans, an effective systemic therapy for treating cats with recurrent FHV-1 disease is still lacking. Two main obstacles have hindered the development of such therapy: (i) The lack of a suitable laboratory animal model due to the high species-specificity of FHV-1 (Crandell, 1973). (ii) The relative insensitivity of FHV-1 to ACV which is the widely available drug of choice for treating HSV-1 infections in man. The poor efficacy of ACV against FHV-1 was demonstrated through several *in vitro* studies (Collins, 1983; Nasisse et al., 1989; Weiss, 1989) and appears to be limited by the FHV-1 TK (I. Mohammad and H.J. Field, unpublished observations). Not only was ACV poorly bioavailable when administered to cat (Owens et al., 1996), but also cats were found to be highly sensitive to the toxic effects of valaciclovir, the oral form of ACV (Nasisse et al., 1997). Nonetheless, frequent topical administration of 0.5% ACV ophthalmic ointment five times daily was shown to be effective in resolving the ocular surface lesions associated with FHV-1 infections (Williams et al., 2005).

PCV (a nucleoside analogue structurally similar to ACV) and cidofovir (a nucleoside phosphonate analogue), both appeared to be better inhibitors of FHV-1 replication in recent *in vitro* studies (Maggs and Clarke, 2004; Sandmeyer et al., 2005). The safety and efficacy of those promising candidates in cats remain to be determined in clinical trials.

7. Equine herpesvirus-1

Equine herpesvirus-1 (EHV-1) is a major pathogen of horses which, in addition to causing respiratory disease can also result in abortion and/or neurological signs in infected animals. The infection is widespread and follows the familiar pattern of latency which has been detected in neuronal and lymphoid tissue with reactivation, shedding and transmission. Control measures are inadequate and, although vaccines are available, they are not fully protective or give protection of short duration and outbreaks of disease still occur (Allen et al., 1999). Notably, in January 2006 a serious outbreak of equine herpes has been reported at the Pimlico Race Course in Baltimore and the entire race course is currently under quarantine. Until better immunoprophylaxis is available, EHV-1 thus represents an attractive target for chemotherapy. A good murine laboratory infection exists which models the clinical signs on natural disease including the infection of the respiratory mucosa, bronchiolar epithelium, cell-associated viraemia and infection of the placenta leading to premature parturition (Field and Awan, 1990; Awan and Field, 1993). This has enabled antiviral compounds, e.g. PCV to be tested *in vivo* against the various manifestations of the infection (Fuente et al., 1992). ACV is poorly active in cell culture against EHV-1; notwithstanding it has been used to treat outbreaks of disease. Several compounds have, however been shown to be potent inhibitors of EHV-1 including PCV (Fuente et al., 1992), HPMPA and cidofovir (Gibson et al., 1993). A small trial that was carried out in experimentally infected horses using one single or two doses of cidofovir, suggested clinical benefit (Gibson et al., 1992). It is of interest that the same compound was also effective against BHV-1 (infectious bovine rhinotracheitis) which is a further veterinary member of the vesiculoviruses, in acute and reactivated experimental infections in calves (Gilliam and Field, 1993).

8. Conclusions

Antiviral therapy for human herpesviruses is now in its fifth decade and during this era much human suffering has been alleviated. These successful therapies are based on experimental work using *in vivo* infection models in laboratory animals. It is ironic, therefore that domestic animals have seen very little benefit from these developments although several of the diseases in animals caused by members of the Alphaherpesvirinae are susceptible to existing nucleoside and nucleotide analogue inhibitors (Table 2). There are genuine scientific reasons for the general lack of interest in veterinary antivirals, including concerns about residues in meat and economic constraints. These problems are less obvious in the case of companion animals such as cats and horses (although the latter may be used for human consumption). The accepted standard care for virally induced conditions such as herpetic keratitis includes the use of antivirals. However, antivirals are relatively expensive; thus, economic constraints by owners restrict their use. Patient compliance is another difficulty. In the past, veterinarians have traditionally relied on vaccination or slaughter-eradication as the primary methods for prevention of infectious disease in animals. Vaccination against herpesviruses in general has been difficult although recent developments are encouraging. Furthermore, there is growing enthusiasm to acknowledge the potential of antiviral chemotherapy in this field and it is likely that the next 50 years will see many advances in the treatment and prevention of herpesvirus infections in animals as well as man.

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