Latent infection by bovine herpesvirus type-5 in experimentally infected rabbits: virus reactivation, shedding and recrudescence of neurological disease


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Abstract

Latent infection with bovine herpesvirus type-5 (BHV-5) was established in rabbits inoculated with two South American isolates (EVI-88 and 613) by intranasal or conjunctival routes. Nine rabbits (613, 8/27; EVI-88, 1/34) developed neurological disease and died during acute infection and other three (613, n = 2; EVI-88, n = 1) developed a delayed neurological disease, at days 34, 41 and 56 post-inoculation (p.i.). Between days 56 and 62 p.i., the remaining rabbits were submitted to five daily administrations of dexamethasone (Dx) to reactivate the infection. Twenty-five out of 44 rabbits (56.8%) shed virus in nasal or ocular secretions after Dx treatment. Virus shedding was first detected at day two post-Dx and lasted from one to 11 days. The highest frequencies of virus reactivation were observed in rabbits inoculated conjunctivally (10/15 versus 15/29); and among rabbits infected with isolate 613 (12/16 versus 13/28). Virus reactivation upon Dx treatment was accompanied by neurological disease in nine rabbits (20.4%), resulting in six deaths (13.6%). Virus in moderate titers and mild to moderate non-suppurative inflammatory changes in the brain characterized the neurological infection. Three other rabbits showed severe neurological signs followed by death after 31 to 54 days of Dx treatment. Virus, viral nucleic acids and inflammatory changes were detected in their brains. The late-onset neurological disease, after acute infection or...
Dx treatment, was probably a consequence of spontaneous virus reactivation. These results demonstrate that BHV-5 does establish a latent infection in rabbits and that clinical recrudescence may occur upon reactivation. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Bovine herpesvirus type-5; Latent infection; Rabbit

1. Introduction

The establishment of latent infection in neurons of sensory and autonomic nerve ganglia is the hallmark of the infection by viruses belonging to the subfamily Alphaherpesvirinae (Roizman, 1992). Viral reactivation and shedding may occur under certain induced or naturally occurring stimuli and provide adequate means for viral transmission and spread (Davies and Duncan, 1974; Pastoret and Thiry, 1985). Recrudescence of clinical disease, transmission of the virus to the newborn and encephalitis in adults are important consequences of reactivation of latent infection by herpes simplex virus (HSV) in humans (Whitley and Gnann, 1993).

Bovine herpesvirus type-5 (BHV-5) is an alphaherpesvirus associated with meningoencephalitis in cattle (Roizman, 1992). Natural and experimental BHV-5 infections of young cattle are often followed by viral invasion and massive replication in the central nervous system (CNS), leading to a severe and usually fatal meningoencephalitis (Bagust and Clark, 1972; Carrillo et al., 1983; Schudel et al., 1986). Animals that do not develop acute disease upon infection may become latently infected (Belknap et al., 1994; Cascio et al., 1999) and similarly to other alphaherpesvirus infections, BHV-5 latency can be experimentally reactivated by means of corticosteroid administration (Belknap et al., 1994; Silva et al., 1999a).

The pathogenesis of acute and latent BHV-5 infection in cattle is poorly understood. This is due, in part, to the unprecise taxonomic classification of the virus, traditionally classified as a subtype of bovine herpesvirus type-1 (BHV-1). The lack of a suitable animal model has also hampered in depth studies of BHV-5 neuropathogenesis. Only recently, the acute BHV-5 infection and disease have been successfully reproduced in other animal species, namely rabbits (Meyer et al., 1996; Chowdhury et al., 1997; Silva et al., 1999b) and sheep (Silva et al., 1999a). In addition, lambs were shown to be susceptible to latent BHV-5 infection and reactivate latency upon dexamethasone (Dx) administration (Silva et al., 1999a).

Laboratory animal models have been notably useful for addressing key questions on the biology of latent infections by human and animal alphaherpesviruses, e.g. HSV (reviewed by Fawl and Roizman, 1994) and BHV-1 (Rock and Reed, 1982; Brown and Field, 1990; Rock et al., 1992). Therefore, the availability of an adequate animal model for BHV-5 latent infection will be important for investigation of the biological and molecular basis of BHV-5 latency. Likewise, understanding the pathogenesis of BHV-5 latent infections may shed light on the pathogenesis of other neuropathogenic alphaherpesvirus infections. In this study, we investigated whether BHV-5 can establish and reactivate latent infection in the rabbit model previously described for acute BHV-5 neurological infection (Silva et al., 1999b).
2. Material and methods

2.1. Cell culture and viruses

A bovine cell line named CRIB (Flores and Donis, 1995), derived from Madin–Darby bovine kidney cells (MDBK; American Type Culture Collection, CCL-22) was used for virus multiplication, quantification and isolation from nasal, ocular swabs and tissues. Cells were routinely maintained in Eagle’s minimal essential medium (MEM) containing penicillin (1.6 mg/l), streptomycin (0.4 mg/l), and 5% of fetal calf serum (Gibco, BRL). The BHV-5 isolate EVI-88 (used at passage # 7) has been isolated from an outbreak of meningoencephalitis in Brazil and partially characterized by Roehe et al. (1997). The BHV-5 isolate 613 (used at passage #6) was obtained from cases of neurological disease in calves in Argentina and was partially characterized (Odeon, unpublished, Perez et al., 2001). The virus doses used in each inoculation are listed in Table 1.

2.2. Rabbits, virus inoculation and dexamethasone (Dx) treatment

New Zealand rabbits (3 to 4 or 5 to 6-months-old, weighing an average of 2.5 and 3 kg, respectively) were used for virus inoculation. Rabbits were maintained in shared cages (two animals each) and given food and water ad libitum. Groups of rabbits were inoculated either by the intranasal or intraconjugunctival route (Table 1). For intranasal inoculation, rabbits were previously anesthetized by intramuscular administration of 2 mg of Tiletamine/Zolazepan (Zoletil, Virbac). The virus suspension was inoculated into the paranasal sinuses through trephine openings, according to a protocol adapted from Brown and Field (1990). Rabbits were inoculated with 0.5 ml of viral suspension in each nostril or conjunctival sac. Control rabbits were inoculated with the same volume of MEM. Beginning at days 56 to 62 post-inoculation (pi), rabbits were submitted to daily five administrations of Dx (Decadronal, Merck & Co. Inc.). The Dx doses used in each group are presented in Table 1. In each experiment, three MEM-inoculated rabbits were submitted to the same Dex treatment. All procedures of animal handling and experimentation were performed under veterinary supervision and according to recommendations by the Brazilian Committee on Animal Experimentation (COBEA; law # 6.638 of 8 May, 1979).

2.3. Animal monitoring, sample collection and processing

Rabbits were monitored clinically on a daily basis; nasal or ocular swabs (according to the route of inoculation) for viral isolation were collected every 3 days up to day 15 p.i.. Subsequently, swabs were obtained at weekly intervals up to the day of first Dx administration. Thereafter, swabs were collected daily up to day 20 post-Dx (pDx). Swab specimens (0.5 ml) were inoculated onto CRIB cells grown in 24 well plates and monitored for cytopathic effect (CPE) for 5 days. Negative samples were further inoculated onto fresh CRIB cell monolayers and monitored for 5 additional days. Blood for serology was collected from all inoculated rabbits before virus inoculation, at days 30 p.i.; at the day of the first Dx administration and 15 days pDx. Serum samples were submitted to a standard
Table 1
Acute and latent infection in rabbits inoculated with bovine herpesvirus type-5 (BHV-5)

<table>
<thead>
<tr>
<th>Group</th>
<th>Rabbits (n)</th>
<th>Age (month)</th>
<th>Isolate</th>
<th>Virus inoculum (TCID_{50})</th>
<th>Via^{a}</th>
<th>Acute disease (dpi)</th>
<th>Late-onset disease (dpi)</th>
<th>Dx^{b} treatment (days), dose/kg</th>
<th>Virus shedding after Dx (n/total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19</td>
<td>5–6</td>
<td>EVI-88</td>
<td>10^{7.8}</td>
<td>in</td>
<td>1/19</td>
<td>0/18</td>
<td>60, 18</td>
<td>0.5 mg, 7/18</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>5–6</td>
<td>613</td>
<td>10^{6.6}</td>
<td>in</td>
<td>6/12</td>
<td>0/12</td>
<td>60, 6</td>
<td>0.5 mg, 5/6</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>5–6</td>
<td>EVI-88</td>
<td>10^{7.3}</td>
<td>ic</td>
<td>0/10</td>
<td>1/10^{f}</td>
<td>62, 5</td>
<td>2.6 mg, 3/5</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>5–6</td>
<td>613</td>
<td>10^{6.6}</td>
<td>ic</td>
<td>2/10</td>
<td>2/10^{f}</td>
<td>62, 5</td>
<td>2.6 mg, 4/5</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>3–4</td>
<td>EVI-88</td>
<td>10^{7.3}</td>
<td>in</td>
<td>0/5</td>
<td>0/5</td>
<td>56, 5</td>
<td>1.6 mg, 3/5</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>3–4</td>
<td>613</td>
<td>10^{6.3}</td>
<td>ic</td>
<td>0/5</td>
<td>0/5</td>
<td>56, 5</td>
<td>1.6 mg, 3/5</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9/61</td>
<td>44</td>
<td>25 (58.6%)</td>
<td></td>
</tr>
</tbody>
</table>

^{a} Route of inoculation: in: intranasal; ic: intraconjunctival.

^{b} Dexamethasone.

^{c} Days post virus inoculation.

^{d} Dosis of Dx/kg per day (total: five daily administrations).

^{e} One rabbit developed neurological disease and died 58 dpi (not during acute infection). Other four rabbits were slaughtered with other purposes before Dx treatment.

^{f} In addition to two rabbits developing neurological disease during acute infection, other two rabbits showed neurological signs and died 37 and 41 dpi. One rabbit slaughtered for other purposes before Dx treatment.
microtiter virus-neutralizing (VN) assay, using two-fold dilutions of serum against a fixed dose of virus (100–200TCID$_{50}$ per well). Tissue samples for viral isolation and histological examination were collected at necropsy. Brain sections aseptically collected for virus isolation were processed by preparing a 10% (wt./vol.) homogenized suspension, which was inoculated onto CRIB monolayers. Monitoring of virus replication was performed as described above. The positive samples (original homogenates) were subsequently submitted to virus quantification by limiting dilution and the virus titers were calculated according to Reed and Muench (1938) and expressed as TCID$_{50}$/g of tissue. Tissues for histological examination were fixed in 10% formalin, embedded in paraffin, sectioned at 5 μm and stained with hematoxylin-eosin (HE). In situ hybridization (ISH) for BHV-5 nucleic acids was performed in brain sections of two rabbits that developed neurological disease and died at days 34 and 54 pDx (rabbits 30 and 31). ISH was performed in formalin-fixed tissue sections, according to a protocol described by Chowdhury et al. (1997). Briefly, sections were deparaffinized, rehydrated, treated with proteinase K (Sigma, Inc.; 20 mg/ml in PBS) and hybridized with a 1.7 kb DNA probe corresponding to the BHV-5 gC coding region (Dr. S. Chowdhury, Kansas State University). The probe was labeled by nick translation with digoxigenin-dUTP (DIG; Boehringer Mannheim Inc.). The hybridized DNA probe was detected with the DIG-alkaline phosphatase conjugate and color substrate nitroblue tetrazolium salt (Boehringer Mannheim).

3. Results

3.1. Acute infection

The summary of acute infection and virus shedding after Dx treatment is shown in Table 1. During acute infection, most rabbits (58/61) shed virus in nasal (up to day 3, n = 8; day 6, n = 18; day 9, n = 8) or ocular secretions (day 3, n = 14; day 6, n = 9; day 9, n = 1). Virus was not detected in nasal or ocular secretions after day 9 p.i., nor in swabs collected at weekly intervals up to the first day of Dx administration. Out of 44 rabbits used for latency studies, 38 (86.4%) seroconverted to BHV-5 by day 30 p.i., developing VN titers from 2 to 8.

Eight rabbits inoculated with isolate 613 (intranasal, n = 6; conjunctival, n = 2) and one rabbit inoculated with EVI-88 (intranasal) developed acute neurological disease and died between days 9 and 18 p.i. (Table 1). The disease was characterized by excitation/depression, seizures, tremors, bruxism, opisthotonus, rear limb paralysis and severe depression and the sick animals died or were euthanized in extremis within 24–48 h of clinical signs. Infectious virus (titers between $10^{2.3}$ and $10^{3.8}$ TCID$_{50}$/g) and mild to moderate non-suppurative inflammatory changes were detected in the brain of these rabbits. The histological changes consisted of mononuclear perivascular cuffing, focal gliosis (close to meninges), and meningeal congestion (not shown). Three rabbits presented neurological signs at days 34, 41 and 56 p.i.. Rabbit 128 (group 4) showed neurological signs from day 34 and died 3 days later. Rabbit 113 (group 4) developed a fulminant neurological disease (4 to 6 h of clinical signs) and died at day 41. Rabbit 146 (group 3) died at day 58, after 2 days of neurological signs. Infectious virus (titers of $10^{1.8}$ to $10^{2.5}$
TCID_{50}/g) and mild to moderate inflammatory changes, as described above, were detected in the brain of these animals.

### 3.2. Latent infection

Rabbits surviving acute infection were submitted to Dx administration at days 56–62 p.i. (exceptions were the rabbits mentioned above and 5 rabbits (group 3, n = 4; group 4, n = 1) that were culled for other purposes). The virological and clinical findings in rabbits that shed virus after Dx treatment are summarized in Table 2. Virus shedding (according to the route of inoculation) was detected in 56.8 % (25/44) of the rabbits treated with Dx, being more frequently detected among rabbits inoculated with isolate 613 (12/16 or 76.8%) than with isolate EVI-88 (13/28 or 46.4%). In 16 rabbits (64%), virus shedding was detected in only one swab collection. Virus excretion was detected as early as at day 2 pDx and lasted up to 11 days (two rabbits, groups 2 and 3). In rabbits shedding virus during 9 or 11 days (groups 1, 2 and 3), the shedding was intermittent. Virus was not detected in nasal or ocular specimens collected after day 15 pDx. In addition to the 25 rabbits that shed virus, six rabbits (31.6%) showed an increase (four-fold) in BHV-5 VN titers in serum collected at day 15 pDx. In addition to the 25 rabbits that shed virus, six rabbits (31.6%) showed an increase (four-fold) in BHV-5 VN titers in serum collected at day 15 pDx. No virus shedding or seroconversion were detected in control, MEM-inoculated rabbits submitted to Dx treatment. Nine rabbits (20.4%) showed neurological signs within a few days after Dx treatment and six (13.6%) died or were sacrificed in extremis. The clinical signs were similar to those of the acute disease; started as early as at day 3 pDx and lasted from a few hours (8–12 h in one rabbit) to 12 days (one rabbit). In most animals (7/9), the neurological signs lasted from 2 to 4 days. Three rabbits recovered from neurological disease after 2–4 days of clinical signs. The virus was isolated from the brain of all rabbits that developed neurological signs upon Dx treatment. The cerebral cortex was consistently positive for virus (6/6) and yielded titers of 10^{1.8} to 10^{3.1} TCID_{50}/g. The olfactory bulb was positive in only one rabbit (titer below 10^{1.8} TCID_{50}/g). Further distribution of the virus within the different areas of the brain was not studied in these animals.

<table>
<thead>
<tr>
<th>Group</th>
<th>Virus shedding</th>
<th>Neurological disease</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Frequency</td>
<td>Start (dpDx)^a</td>
<td>Duration (days)</td>
</tr>
<tr>
<td>1</td>
<td>7/18</td>
<td>6 (2–11)</td>
<td>3 (1–9)</td>
</tr>
<tr>
<td>2</td>
<td>5/6</td>
<td>7.2 (4–11)</td>
<td>6 (1–11)</td>
</tr>
<tr>
<td>3</td>
<td>3/5</td>
<td>4.2 (4–5)</td>
<td>5 (1–11)</td>
</tr>
<tr>
<td>4</td>
<td>4/5</td>
<td>7.2 (2–15)</td>
<td>4 (1–7)</td>
</tr>
<tr>
<td>5</td>
<td>3/5</td>
<td>6 (4–9)</td>
<td>1.5 (1–3)</td>
</tr>
<tr>
<td>6</td>
<td>3/5</td>
<td>7.6 (4–11)</td>
<td>2 (1–4)</td>
</tr>
<tr>
<td>Total</td>
<td>25/44</td>
<td>9/44 (20.4%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>Start (dpDx)</th>
<th>Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>a Days post-Dx treatment.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b One additional rabbit showed neurological signs and died at day 31 pDx.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c Two additional rabbits presented neurological signs and died at day 30 and 54 dpDx.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Three other rabbits developed a late-onset neurological disease following Dx administration. Rabbits 30 (group 2) and 20 (group 1) died at day 30 and 31 pDx, respectively, after 2 to 3 days of neurological signs. Rabbit 31 (group 2) showed neurological signs from day 51 and died 3 days later. Infectious virus (titers from \( \leq 10^{1.8} \) to \( 10^{2.5} \) TCID \(_{50} / g \)) and moderate inflammatory changes (mononuclear perivascular cuffing, gliosis) were detected in the brain of these animals. In rabbits 30 and 31, infectious virus was detected in the cerebral cortex (\( 10^{2.3} \) to \( 10^{2.5} \) TCID \(_{50} / g \)) and thalamus (\( 10^{2.1} \) TCID \(_{50} / g \)). Virus was not detected in the olfactory bulbs and further distribution of virus in the SNC was not examined. In situ hybridization using a BHV-5 gC probe evidenced abundant neurons (and glial cells) harboring BHV-5 nucleic acids in the cerebral cortex and thalamus of rabbits 30 and 31 (Fig. 1). BHV-5 nucleic acids were also detected in sensory neurons of the trigeminal ganglia of these two rabbits (not shown).

4. Discussion

In this study we demonstrated that BHV-5 does establish a latent infection in rabbits upon experimental inoculation. The main findings of a series of inoculations of two South American BHV-5 isolates were: (1) rabbits not developing fatal neurological disease during acute infection became latently infected; (2) latent infection could be reactivated experimentally by means of Dx administration; (3) Dx-induced reactivation coursed with virus shedding and frequently with recrudescence of clinical disease; (4) neurological
disease developed upon Dx-induced viral reactivation was frequently non-fatal and some animals recovered; (5) spontaneous virus reactivation occasionally occurred and coursed with clinical recrudescence; (6) both intranasal and conjunctival routes of virus inoculation resulted in the establishment of reactivatable latent infection.

In addition to the ability of BHV-5 to establish latent infection in rabbits, the most relevant finding was that virus reactivation may course with recrudescence of neurological disease. Corticosteroid-induced BHV-1 reactivation in cattle is usually subclinical, but it may be accompanied by mild to moderate clinical signs (Sheffy and Davies, 1972; Davies and Duncan, 1974). Recurrent ocular lesions have also been associated with Dx-induced reactivation of BHV-1 latent infection in experimentally infected rabbits (Rock and Reed, 1982). Data on BHV-5 latent infection are scarce and only recently began to emerge. Previous studies showed that Dx-induced BHV-5 reactivation in experimentally infected calves usually courses without evident clinical signs (Belknap et al., 1994; Cascio et al., 1999; Flores, unpublished data). Nevertheless, recent data demonstrated clinical recrudescence of neurological disease upon Dx-induced BHV-5 reactivation in experimentally infected calves (Perez et al., 2001). One calf was found shedding virus in the day of the first Dx administration and developed a fatal meningo-encephalitis after Dx treatment. Upon Dx treatment, three other calves developed mild and intermittent neurological signs associated with meningoencephalitis (Perez et al., 2001). In our study, in addition to 6 rabbits developing severe neurological disease upon Dx treatment, three rabbits showed mild and transient neurological signs. It should be mentioned that the isolate used by the authors (BHV-5 613) was the same virus used in our experiments.

The development of neurological infection by rabbits 113 (group 4; 41dpi), 146 (group 3; 56 dpi) and 31 (group 2; 54 dpDx), 30 to 48 days after the end of virus shedding, was probably a consequence of spontaneous virus reactivation. Data to support this hypothesis are: (1) the clinical disease was associated with neurological infection (virus in moderate titers, viral nucleic acids and inflammatory changes in the brain); (2) these rabbits did not show clinical signs during the acute infection (rabbits 113 and 146) or after Dx administration (rabbit 31); (3) virus shedding was not detected beyond day 6 p.i. or day 9 p.i. (for rabbits 146 and 113, respectively) or after day 9 pdx (rabbit 31). In the natural host, latent infections by BHV-1 are likely associated with occasional spontaneous reactivations (Sheffy and Davies, 1972; Pastoret and Thiry, 1985), yet clinical recrudescence upon natural reactivation has been only occasionally documented (Snowdon, 1965). These findings contrast with HSV-1 and HSV-2 infection in people, in which clinical recrudescence (orolabial or genital) is a frequent consequence of spontaneous reactivation (Fawl and Roizman, 1994). Similarly, severe clinical meningoencephalitis is a rare, though well documented outcome of natural reactivation of HSV-1 infection (Whitley and Gnann, 1993). In rabbits experimentally infected with BHV-1 by the conjunctival route, a mild ocular lesion was associated with spontaneous reactivation in one rabbit (Rock and Reed, 1982). Thus, clinical recrudescence is a possible (and for some viruses, frequent) consequence of natural reactivation of latent infection by human and animal alphaherpesviruses. Recent data by Perez et al. (2001) indicated that spontaneous BHV-5 reactivation may occur in experimentally infected cattle. Whether clinical recrudescence as demonstrated herein in rabbits might also occur in naturally BHV-5 infected cattle remains an intriguing and interesting issue awaiting further investigation.
The virus titers detected in brain sections of rabbits reactivating the latent infection (10^{1.8} to 10^{2.6} TCID_{50}/g) were usually lower than the titers detected in rabbits dying during acute infection (Silva et al., 1999b; not shown). Although a more detailed distribution of virus in the brain was not studied, some observed differences might be significant: (1) the virus was not consistently detected in the olfactory bulb of rabbits reactivating the infection (two out of nine rabbits examined), in contrast with acute infection (Chowdhury et al., 1997; Lee et al., 1999; Silva et al., 1999b); (2) the thalamus was frequently virus positive (2/3) and contained abundant ISH positive neurons in two rabbits (# 30, 31) reactivating the infection a long time after Dx treatment. Differences in the nervous pathways used by the virus to access the SNC during reactivation versus acute infection (discussed below) may account for the differences in virus distribution and yield.

Both intranasal (in) and conjunctival (ic) routes of inoculation resulted in reactivatable latent infection. Although the in inoculation resulted in higher morbidity and mortality during acute infection (7/36 versus 2/25), virus reactivation and shedding was more frequently detected among rabbits inoculated by the ic route (10/15 or 66.6% versus 15/27, 51.7%). After in inoculation of rabbits, the olfactory route seems to be the major pathway used by BHV-5 to reach the SNC during acute infection (Lee et al., 1999; Silva et al., 1999b). In rabbits inoculated conjunctivally with BHV-1, latent infection was consistently demonstrated in the trigeminal ganglia (TG) and could be reactivated upon Dx treatment in nearly 100% of the animals (Rock and Reed, 1982; Rock et al., 1992). In contrast, demonstration and reactivation of BHV-1 latent infection from the TG of rabbits inoculated intranasally was far less consistent, suggesting that inoculation by the ic route leads to a higher frequency of ganglionic latency (Brown and Field, 1990). Nonetheless, the frequent infection of the trigeminal pathway after in inoculation (Chowdhury et al., 1997; Lee et al., 1999; Silva et al., 1999b) would also allow for the virus to reach and establish latent infection in the trigeminal ganglia (TG). Indeed, the demonstration of abundant sensory neurons harboring BHV-5 nucleic acids in the ganglia of rabbits reactivating the latent infection (# 30 and 31; group 2) indicates that the TG is an important site of BHV-5 latency following intranasal inoculation. Further studies are necessary to investigate the neural (and perhaps non-neural) sites of latent infection; and the role of these sites in latency and in the neurological infection that may develop upon reactivation.

In summary, the sequence of events observed in experimentally infected rabbits resembles many of the virological and clinical aspects of alphaherpesvirus (HSV, BHV-1 and BHV-5) natural and experimental infections in the natural hosts and animal models. Spontaneous and Dx-induced BHV-5 reactivation followed by clinical recrudescence has to be further characterized in cattle, yet recent experimental data indicates it may occur. As further studies on BHV-5 pathogenesis are performed, it will be possible to compare the main aspects of the infection in cattle and rabbits as to evaluate the suitability of this species as a model to study BHV-5 latent infection.

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References


