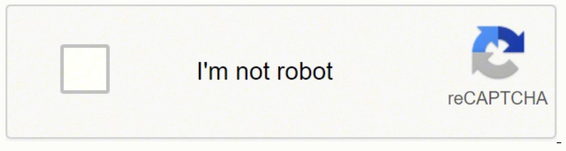
Herpes simplex ganglion



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Herpes simplex ganglion

Herpes simplex trigeminal ganglion. Can you get herpes simplex on your hands. Can i get herpes on my wrist. Dorsal root ganglion herpes simplex. Herpes simplex virus infection ganglion. Can herpes simplex cause nerve damage. Herpes simplex virus ganglion. Does herpes simplex cause nerve pain.

[Skip to Navigation] JVI Volume 89, Number 1615 August 2015 Herpes simplex virus 1 (HSV-1) and HSV-2 establish latency in sensory and autonomic neurons after ocular or genital infection, but their patterns of recurrence differ. HSV-1 reacts by latency to cause recurrent orofacial disease, and while HSV-1 also causes genital lesions, HSV-2 occurs most effectively in the genital region and rarely causes eye disease. The mechanisms governing these anatomical preferences are unclear. To determine whether differences in latent infection and reactivation in autonomous ganglia contribute to differences in HSV-1 and HSV-2 anatomical preferences for recurrent disease, we compared clinical disease HSV-1 and HSV-2, acute and latent viral loads, and viral gene expression in cervical and ciliary ganglia upper sensory and autonomic organs in a guinea pig eye infection model. HSV-2 produced a more severe acute disease, related to higher viral DNA loads in the sensory and autonomic ganglia, as well as higher levels of expression of thymidine kinase, a marker of productive infection, in autonomic ganglia. HSV-1 reactivated in ciliary ganglia, independently of trigeminal ganglia, to cause more frequent recurrent symptoms, while HSV-2 replicated simultaneously in autonomic and sensory ganglia to cause more persistent disease. While both HSV-1 and HSV-2 expressed latency-associated transcription (LAT) in trigeminal and upper cervical ganglia, only HSV-1 expressed LAT in ciliary ganglia, suggesting that HSV-2 is not competent reactivation or does not fully establish latency in ciliary ganglia. Thus, differences in replication and viral gene expression in autonomic ganglia may contribute to differences in HSV-1 and HSV-2 acute and recurrent clinical disease. IMPORTIONS Herpes simplex virus 1 (HSV-1) and HSV-2 establish latent infections, from which the viruses reactivate to cause recurrent disease throughout the host's lifetime. However, viruses show different manifestations and frequencies of recurrent disease. HSV-1 and HSV-2 determine latency in both sensory and autonomic ganglia. Autonomous ganglia are more responsive than sensory ganglia to stimuli associated with recurrent disease in humans, such as stress and hormonal fluctuations, suggesting that autonomous ganglia may play an important role in recurrent disease. We show that HSV-1 can reactivate from autonomous nodes, independently of sensory nodes, to cause recurrent eye disease. We found no evidence that HSV-2 could reactivate from autonomous ganglia regardless of the sensory ganglia after eye infection, but HSV-2 replicated in both ganglia simultaneously to cause persistent disease. Thus, viral replication and reactivation in ganglia contribute to several manifestations of clinical disease of HSV-1 and HSV-2 after eye infection. Herpes simplex virus 1 (HSV-1) and HSV-2 infect and establish latency in peripheral sensory nodes, including trigeminal trigeminal (TG) after orofacial infection and dorsal ganglia (DRG) after genital infection. While both viruses can reactivate from latency to cause recurrent lesions throughout the life of the host, HSV-1 and HSV-2 demonstrate different patterns of recurrent disease. HSV-1 is more likely to occur recurrent lesions in the orofacial region, whereas HSV-2 rarely, if ever, acts in the oofacial region, even if the primary infection occurs in the mouth, nose or eyes. HSV-1 is becoming more common as a cause of genital herpes, but HSV-2 reproduces much more effectively after genital infection. Although 60-90% of people with HSV-2 genitals show symptomatic recurrences, only 25% with HSV-1 genital infections experience symptomatic recurrences (1, 2), demonstrating that HSV-1 and HSV-2 the characteristic patterns of recurrent disease are not simply the result of differences in the site of initial infection. After reaching the sensory nodes after peripheral inoculation, viruses replicate in some neurons, while establishing latent infection in others. Sensory neuronal populations that are permissive for productive infection differ between HSV-1 and HSV-2. Sensory neurons recognized by the Fe-A5 monoclonal antibody (A5+) limit the productive HSV-1 infection (3, 4). In contrast, sensory neurons bound by the monoclonal antibody KH10 or isolectin IB4 (IB4+) limit the productive infection of HSV-2 (3-5). Similar percentages of these non-overlapping populations of sensory neurons are found in TG (10-12%) and DRG (13-15%). HSV-1 and HSV-2 demonstrate the neuronal specificity of A5+ and IB4+ neurons, respectively, regardless of the path of infection. Half of the reservoir of latent LAT-positive HSV-1 is in the A5+ neurons, and half of the reservoir of latent LAT-positive HSV-2 is in the IB4+ neurons, in the TG after eye infection, or in the DRG after genital infection (5â9). Therefore, different patterns of HSV-1 and HSV-2 recurrence cannot be adequately explained by the preferential institution of latency in different types of sensory neurons. Also the orofacial and genital regions, which are located within the sensory TG and DRG, are largely innervated by the autonomic nerve endings. Sympathetic neurons of the upper cervical ganglia (SCG) and parasympathetic neurons in the ciliary ganglia (CG) innervate the conjunctival epithelium and stroma (6), and mixed autonomic neurons in the main pelvic ganglia (MPG) innervate the genitourinary tract. In both humans and animal models, HSV-1 and HSV-2 latent viral DNA was detected in autonomic ganglia, including SCG, CG, pterygopalatine ganglia (PTG), and MPG (also called as paracervical ganglia) (7-12). Autonomous pathways are intimately involved in physiological activities associated with symptomatic recurrences in humans, including stress, febrile response and hormone regulation. Although the sensory nodes are considered the site of reactivating HSV, reactivation of the dormant virus residing in autonomous autonomous may contribute to recurring symptoms. To determine whether differences between HSV-1 and HSV-2 in autonomic ganglia may contribute to different patterns of recurrent virus disease, we used a guinea pig eye infection model to evaluate clinical signs and to analyse viral DNA load and gene expression in sensory and autonomic ganglia at various post-noculation sites. After eye infection, reactivation of HSV-1 occurred from autonomic ganglia to cause recurrent disease symptoms, but there was no evidence that HSV-2 could reactivate independently from autonomic ganglia to cause recurrent disease. We also provide evidence that differences in viral gene expression in sympathetic and parasympathetic ganglia are probably responsible for differences between virulence and HSV-1 and HSV-2 reactivation. HSV-1 strain 17+ was originally transferred by John Hay (SUNY Buffalo, Buffalo, NY) and HSV-2 strain 333 by Gary Hayward (Johns Hopkins, MD) to Krause Laboratory (FDA, Bethesda, MD.) Viruses were propagated in Vero cells (ATCC,) and first pass actions were transferred to Margolis Laboratory (UCSF, San Francisco, CA.) Viruses were propagated in Vero cells, and first pass stocks were transferred to the Bertke lab (Virginia Tech, Blacksburg, VA.) Viruses were propagated in Vero cells and titrated into duplicates by plaque analysis in Vero cells. The viruses were diluted in Dulbecco Modified Eagle Medium (DMEM) for guinea pig and mouse inoculations. Female 3-week-old Hartley guinea pigs (HillTop Laboratories) were infected with 5 105 PFU of HSV-1 or HSV-2 by corneal inoculation after scarification. Guinea pigs were observed every day for 60 days of post-infection (dpi). The severity of acute infection was plotted as the mean injury score for each group of animals up to day 14, based on a scale of 0 to 4 (0, no symptoms; 1, inflammation or redness; 2, one or two lesions; 3, three to five lesions; 4, more than five lesions, lesion charonscence, or deep stromal involvement.) Frequencies of recurrence were graphite as cumulative recurs for guinea pigs from 15 to 60 days postinfection (p.i) At various time points (days 1, 2, 3, 4, 7, 10, 14, 30 and 60), guinea pigs were slaughtered, and SCG, CG and TG were collected in homogenised RLT (Qiagen,) buffers and frozen until further treatment by quantitative PCR or reverse transcription (RT) -PCR. The experiments were carried out twice, and the data from the two experiments were combined. The severity of the acute was statistically analyzed by the Mann-Whitney test (SPSS) using the area under the guinea pig curve. Cumulative recurrences were statistically analysed by the Mann-Whitney test (SPSS) using cumulative recurrences per animal. All studies are approved and conducted in accordance with the Virginia Tech Institutional Care and Use Committee (IACUC# 13-008-CVM). Viral DNA and RNA were extracted from homogenized tissues with Qiagen AllPrep DNA/RNA minikit (Qiagen) according to the instructions of After the extraction of the RNA, the cDNA was synthesized using the cDNA synthesis kit (Bio-Rad). Quantitative PCR was performed on a Viia7 (Applied Biosystems) real-time PCR machine, using the iTaq (Bio-Rad) universal probe mix and ZEN (IDT) primer/probe sets specific for genes encoding HSV-1 or HSV-2 thymidine kinase (TK) and transcribed associated with laten (LAT) and immediate (IE).) genes encoding ICP0 (infected cell protein 0), ICP27 and ICP4, as follows: HSV-1 TK forward, 5Â¢Â¬2-AAAACCACCACGCAACT-3Â¢Â¬2, inverse, 5Â¢Â¬2-TCATCGCTCGGGTACGTA-3 Â¬2, and probe, 5Â¬2-TGGTTC GCGCGACGATCG-3Â”2; HSV-1 LAT forward, 5Â”2-ACCCACGTACTCCAAGAAGGC-3Â”2, inverse, 5Â”2-TAAGACCCAAGAGAGAGAGCCA-3Â”2, and probe, 5Â”2-TCCCCCCCCCCGCCTGTGTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTTT-3Â”2; HSV-1 ICP0 forward, 5Â”2-GATGCAATTGCAC-3Â”2, reverse, 5Â”2-GCGTCACGCCCACTATCAG-3Â”2 and probe, 5Â”2-GCTGTGCAACGCCAAGCTGGTGTA-3Â”2; HSV-1 ICP27 forward, 5 Â”2-GCGGCTGCTGATAA-3Â”2, inverse, 5Â”2-GCGAACAGTTCGTCCA-3Â”2, and probe, 5Â”2-TTTCTCCAGTGCTACCTGAAGGCGA-3Â”2; HSV-1 ICP4 forward, 5Â”2-CATGGCGTAGCCC AGGT-3Â”2, reverse, 5Â”2-GGCCTGCTTCCGGATCT-3Â”2, and probe, 5Â”2-CCGGTGATGAAGGAGCTGCTGTT-3Â”2; HSV-2 TK forward, 5Â”2-TAATGACCAGCGCCCAGAT-3Â”2, reverse, 5Â”2-CG ATATGAGGCCAAAACG-3Â”2, and probe, 5Â”2-ACAATGAGCACGCCTTATGCGC-3Â”2; HSV-2 LAT forward, 5Â”2-GTCAACACGGACACTCTTT-3Â”2, reverse, 5Â”2-CGAGGCCTGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGGG ACCAAGACGGAGCCA-3”2; HSV-2 ICP0 forward, 5Â”2-GGTCACGCCCACTATCAGGTA-3Â”2, reverse, 5Â”2-CCTGCACCCCTTCTGCAT-3Â”2, and probe, 5Â” Â§2-CAACGGAATCCAGGTCTTCATGCACG-3Â”2; HSV-2 ICP27 forward, 5Â”2-CTTTCTGCAGTGCTACCTGAA-3Â”2, reverse, 5Â”2-CAGGATGACCAACAAAGGA-3Â”2, and probe, 5Â”2-CGACGCCTGGGG ACATTAAGGAT-3Â”2; and HSV-2 ICP4 forward, 5Â”2-GTC GTCGTCGTCAG-3Â”2, inverse, 5Â”2-CCGCCCCTCTGACTCATCAAA-3Â”2, and probe, 5Â”2-ATGCAGGAGGAGGAGGAGGAG-3Â”2. Viral DNA load was determined by quantifying viral DNA by quantitative PCR (qPCR) using primers and gene-specific probes HSV-1 and HSV-2 TK (13, 14). All tests were normalized to 18-year-old rRNA (Applied Biosystems) and reported as 200 ng of DNA or RNA. Trigeminal ganglia (TG), upper cervical ganglia (SCG) and ciliary ganglia (CG) were removed from 6-week-old Swiss Webster mice and cultured on 8-well. Lab-Tek coated with Matrigel. Chamber II slides (Thermo Scientific), as described above (3). Briefly, the ganglia were digested into papain, collagenase and dispase (Worthington), followed by mechanical shredding with a pipette. The TGs were passed through an OptiPrep gradient (BD Biosciences) to enrich the neurons; SCG and CG were plated without the gradient gradient, as they contain minimal axonal residues in the cell suspension. Cells were washed and plated in Neurobasal A medium supplemented with 2% B27, 1% penicillin-streptomycin, l-glutamine, neurotrophic factors and mitotic inhibitors (Life) Four days after plating 3,000 neurons for cockpit, removal of the medium, neurons were inoculated with HSV-1 (Cert 17+) or HSV-2 HSV-2333), viruses were allowed to absorb for 1 hour, and a complete Neuro medium (Neurobasal A, B27, l-glutamine, and neurotrophic factors, without mythical inhibitors). Neurons have been fixed with 2% paraformaldehyde and immunostained for HSV antigens with polychlonal anti-siers (Dako). The neurons were counted to determine the percentage of HSV-positive neurons. Six-week Swiss Webster mice have been infected with HSV-1 VP26-GFP or HSV-2 VP26-GFP (where GFP is a green fluorescent protein). The mice were euthanasia 21 days after inoculation, and TG, SCG and CG were collected in Neurobasal A substrate integrated with B27 and penicillin-streptomicin. The Ganglia have been dissociated as described above and plated on 24 well-coated plates with Matrigel (BD Biosciences). Human immunoglobulin (hIgG) has been included in the medium to prevent the viral spread of the infectious virus released in the middle by the reactivation of neurons. Reactivation was determined by the daily observation of the expression of GFP in neurons for the first 3 days after plating. The positions of reactivation neurons, as detected by the expression of GFP, have been carefully recorded and the overlapping signals have been excluded in the following days to ensure that reactivation neurons were counted only once. The data represent the average results of three different infection experiments, using 10 mice per virus for each experiment. All studies were approved and conducted in accordance with the Virginia Tech Institutional Care and Use Committee (IACUC# 13-003-CVM). In order to characterize the HSV-1 and HSV-2 eye disease in a caviar model, female cavies were inoculated by the topic application of viruses (5 ¥ 105 PFU of viruses) and observed for 60 days to detect clinical signs. During the acute phase of the infection (from 1 to 14 dpi), HSV-2 produced a significantly more severe eye disease than the HSV-1 infection (Fig. 1A) (P = 0.002 according to the Mann-Whitney test). Both viruses have caused corneal and periorbital lesions, corneal, conjunctivitis and blepharite (Fig. 1C). However, HSV-2 has caused deep stromal ulcerations in 18 guinea pigs of 42 (42.9%), of which 12 bilateral, while similar deep lesions were observed only in 1 guinea pig out of 40 (2.5%) infected by HSV-1. Between 5 and 9 days, the inclination of the head, the rotational movement of the head and the postural instability compatible with dizziness were observed in 13 cavies infected by HSV-2; These symptoms have been resolved in 2-4 days, while similar signs have not been observed in cavies infected by HSV-1.FIG 1 Acute and relapse cumulative in the eye pattern of cavies. (A) Gravity of acute infection from 1 to 14 dpi, expressed as an average lesion score for each groupguinea pigs for each day of observation, on a scale of 0 to 4 (0, no symptoms; 1, inflammation or redness; 2, 1 or 2 lesions; 3, 3-5 lesions; 4, > 5 lesions or coalescence of lesions); HSV-1, n = 40; HSV-2, n = 42; P = 0.002 of di Try it. (B) Cumulative recidivism per guinea pig for each group during latent infection 15 to 60 dpi; HSV-1, n = 11; HSV-2, n = 9; P = 0.020 from Mann-Whitney test. (C) Representative images of acute (day 7) and recurrent (HSV-1, day 22; HSV-2, day 39) HSV-2, eye disease. HSV-1 produced recurrent corneal and periocular lesions at a significantly higher frequency from days 15 to 60 p.i. compared to HSV-2 (Fig. 1B) (P = 0.020 from Mann-Whitney test). HSV-1 produced asymptomatic latent infection with definite episodes of symptomatic recurrent recurrences consisting of 1 or 2 corneal and/or periocular lesions which were erased within 2 to 4 days (Fig. 1C). However, HSV-2 produced a more persistent form of symptomatic disease, characterized by continuous eruption of lesions and corneal cloud over a period of 5 to 18 days with minimal clearance between episodes. In addition, all nine HSV-2 infected guinea pigs observed during the 60-day period developed vesicular lesions on the nose, while none of the HSV-1 infected pigs developed nasal lesions, suggesting a more widespread zosteriform with HSV-2 than with HSV-1. To determine whether differences in viral DNA load were responsible for differences in injury severity and frequency of recurrence, viral DNA levels were assessed at various time points in sensory and autonomic ganglia, including sensory trigeminal ganglia (TG), sympathetic superior cervical ganglia (SCG), and ciliary ganglia parasympathetic (CG). Both HSV-1 and HSV-2 effectively infected sensory neurons in the TG after ocular infection, as expected (Fig. 2A). Viral DNA increased during the first 4 days of infection, correlated with increased clinical severity of infections. By day 14 p.i., a reservoir of latent viral DNA was established, and was maintained during the 60-day experiment (Fig. 2A). Although the amount of HSV-1 DNA was consistently lower than the amount of HSV-2 (P = 0.0001), viruses produced almost identical patterns within the TG, peaking on day 4 p.i. and decreasing thereafter. FIG 2 Amount of viral DNA and gene expression of thymidine kinases of HSV-1 and HSV-2 in sensory and autonomic ganglia of guinea pigs. The viral DNA HSV-1 and HSV-2 extracted from ganglia was quantified by qPCR in sensory trigeminal ganglia (TG) (A), superior sympathetic cervical ganglia (SCG) (B), and parasympathetic ciliary ganglia (CG) (C). HSV-1 and HSV-2 viral thymidine kinase (TK) genes copy number was quantified by qRT-PCR in sensory trigeminal ganglia (D), superior sympathetic cervical ganglia (E), and parasympathetic ciliary ganglia (F). (n = 2 to 4 samples per group per time point.) In sympathetic SCG, the HSV-1 viral DNA increased transiently on day 2 postinfection and thus maintained a static amount of DNA in the ganglia, suggesting that the virus replicated briefly within the ganglia soon after infection and then established a latent reservoir in the SCG, which remained stable during the 60 daysperiod (Fig. 2B). The HSV-2 viral DNA showed a less variability between time points, but remained relatively stable during the parasympathetic GC infection period, viral DNA was detected 1 day after inoculation and both HSV-1 and HSV-2 increased on day 2 p.i.The parasympathetic GC detected viral DNA 1 day after inoculation and DNA 2.V-2 increased However, HSV-2 DNA remained elevated from day 3 to day 14 p.i., while HSV-1 DNA began to decrease day 3 p.i. (P = 0,0001) (Fig. 2C). A significantly greater quantity of HSV-2 Viral DNA has been detected in all three sensory and autonomous ganglia analyzed, suggesting that the viral charge may be responsible for the different severity of the disease. HSV codifies the TK enzyme, important for replication of HSV in neurons (15). During acute infection (from 1 to 14 dpi), HSV-2 showed higher TK levels in TG, SCG and CG than HSV-1, in correlation with the most severe symptoms of acute disease observed in cavies. In TG sensory, HSV-1 and HSV-2 showed relatively similar TK expression patterns (Fig. 2D), although HSV-2 TK expression was generally higher than HSV-1 (P = 0.0001). In the sympathetic SCG, however, the expression of TK was only detected in HSV-2 infected animals in days 1 and 4 p.i. and in HSV-1 infected animals per day 2 (Fig. 2E). Considering the amount of viral DNA detected in SCG, these results indicate that adult sympathetic SCGs limit both HSV-1 and HSV-2 replication during acute cavie infection after eye infection. In the parasympathetic CG, the expression of HSV-2 TK was maintained at high levels for the first 4 days after the infection (Fig. 2F), which was significantly different from the expression of HSV-1 TK in the same time period (P = 0.025). The expression of HSV-1 TK was detected at a high level per day 2 and at reduced levels at 3 and 7 days. In combination with the amounts of DNA detected, these TK expression patterns suggest that sensory TGs and parasympathetic GCs support both HSV-1 and HSV-2 replication, determining large amounts of viral DNA in ganglion in latent times. However, CG preferably supports HSV-2 replication rather than HSV-1 during the first 4 days of acute infection. Although large amounts of HSV-1 and HSV-2 viral DNA are present in SCG, neither viruses are effectively reproduced in SCG after eye infection. During latency periods, the HSV-2 TK expression was detected in TG, SCG and CG (Fig. 2D, E, and F), which coincided with the observed recurring injuries. On the 14th day, the TK expression was found in 2 out of 4 TG; one of these guinea pigs at the same time expressed TK in the CG. Day 30, TK was detected in aPig guinea in both TG and SCG. On day 60, TK was detected in a single guinea pig in the TG only. Guinea piglets infected with HSV-2 that had lesions at the time of tissue analysis expressed TK to TG or TG and autonomic ganglia; thus, recurrent lesions could have been caused by virus replication in both TG and autonomic ganglia. HSV-1 TK was detected in TG and CG, but not SCG during latent time points. On day 14, a non-injured guinea pig expressed TK only in the TG, demonstrating that HSV-1 can replicate in the TG without producing peripheral lesions. Another pig guinea with lesions on day 14 p.i. expressed TK only in CG, demonstrating that HSV-1 can reactivate from CG independently of TG to cause recurrent eye lesions. HSV-1 TK expression was also detected on day 60 in the TG of a single animal, which had lesions but no TK expression detectable in other ganglia. Thus, HSV-1 can reactivate by TG or CG to produce recurrent eye lesions. HSV produces genes immediately early (IE), which manipulate host cell replication and antiviral mechanisms to promote early (E) and late (L) viral gene expression. Infected cell protein 0 (ICP0) is a ubiquitin ligase involved in both lytic and latent infections and has been implicated in reactivation by latency (16, 17). ICP0 expression was detected in Guinea pig TG very early after infection, on day 1 p.i. for HSV-2 and day 2 p.i. for HSV-1, but there was no significant difference in expression patterns (Fig. 3A). In sympathetic SCG, the ICP0 expression was delayed compared to the TG expression, but the expression profiles for HSV-1 and HSV-2 were similar (Fig. 3B). Expression profiles differed in CG, however; while both HSV-1 and HSV-2 ICP0 transcripts were detected on day 2, HSV-2 continued to express ICP0 at all time points, but HSV-1 expressed ICP0 at levels detectable only during acute infection, and at lower levels of HSV-2 (Figure 3C). These results suggest that ICP0 functions may differ between HSV-1 and HSV-2 in parasympathetic neurons. FIG 3 Immediate early gene expression in sensory and autonomous ganglia of guinea pigs. HSV-1 and immediate viral HSV-2 (IE) ICP0 gene expression was quantified by qRT-PCR in sensory trigeminal ganglia (A), sympathetic superior cervical ganglia (B), and parasympathetic ciliary ganglia (C). ICP27 viral HSV-1 and HSV-2 gene expression was quantified by qRT-PCR in sensory trigeminal ganglia (D), sympathetic superior cervical ganglia (E), and parasympathetic ciliary ganglia (F). (n = 2 to 4 samples per group per time point.) Another viral IE gene encodes a multifunctional protein, ICP27, which helps block host cells, regulates the interferon response, and promotes viral transcription and (18). In guinea pig TG, HSV-1 and HSV-2 expressed both ICP27 during acute infection (days 1 to 14 p.i.), but expression was also detected in HSV-2-infected ganglia analyzed in latent time, suggestive suggestive a persistent infection (Fig. 3D). No ICP27 was detected in SCG by either virus (Fig. 3E), and expression was sporadically detected in CG (Fig. 3F), suggesting that ICP27 expression is not required for lytic infection in autonomic neurons. Latency-associated transcription (LAT) is the most abundant gene expressed during HSV latency. Although not required for latency establishment, exon LAT 1 is required for the specificity of specific HSV-type neurons and characteristic reactivation patterns (4, 13, 19). To determine whether differences in LAT expression play a role in differences between HSV-1 and HSV-2, LAT expression was analyzed in sensory and autonomic ganglia. In TG, LAT expression was detected on day 1 p.i. and subsequently increased, as expected, demonstrating the establishment of latent infection in TG (Fig. 4A). A similar pattern of LAT expression was detected in the sympathetic SCG, although LAT expression was detected for the first time after infection on day 3 for HSV-1 and day 4 for HSV-2 (Fig. 4B). The constant presence of viral DNA and LAT expression in the SCG demonstrates that both HSV-1 and HSV-2 established latency in sympathetic ganglia as effectively as in sensory TG, and there were no significant differences between HSV-1 and HSV-2 LAT expression in the TG or SCG (P = 0.231 and 0.200, respectively). FIG 4 LAT gene expression in sensory and autonomous ganglia of guinea pigs. HSV-1 and HSV-2 viral gene The LAT copy number was quantified by qRT-PCR in sensory trigeminal ganglia (A), sympathetic superior cervical ganglia (B), and parasympathetic ciliary ganglia (C). (n = 2 or 3 samples per group per time point.) A different pattern of LAT expression has been identified in parasympathetic GC (Fig. 4C). HSV-1 LAT expression was detected at a high level on day 2 p.i. and persisted during the 60-day period of analysis. Since both viral DNA and LAT expression persist, these data show that HSV-1 established a latent LAT-positive infection in the guinea pig's GC after ocular infection. However, the expression HSV-2 LAT was not detected in GC at any time (P = 0.0001), suggesting that HSV-2 is not able to reactivate from ciliary ganglia neurons or that LAT is not required for reactivation from ciliary ganglia. Animal models of HSV infection are needed to identify differences in the severity of disease and recurrence frequencies of HSV-1 and HSV-2. In an animal model, however, hormone levels and immune response are involved in regulating the severity of the disease and also contribute to viral reactivation either to limit or promote recurrent symptoms. To identify any differences in the ability of HSV-1 and HSV-2 to productively infect sensory and autonomic neurons the influence of adaptive immune response or exogenous hormone induction, primary adult ganglinic neurons cultured by TG, SCG and CG were infected with HSV-1 or HSV-2 at a multiple infection rate (MOI) of 10. No. No. After infection, the percentages of cultured neurons that were infected with HSV-1 or HSV-2 were determined using polyclonal antisera to visualize HSV production cycle antigens. HSV-1 and HSV-2 were detected in similar percentages of neurons in TG and CG culture (Fig. 5A). In cultured SCG, however, HSV-1 productively infected a significantly higher percentage of cultured neurons (18.8%) than HSV-2 (8.7%). In guinea pigs, neither HSV-1 nor HSV-2 effectively infected SCGs, suggesting that extracellular factors limit productive HSV-1 infection of SCG neurons in vivo in the guinea pig model. Further studies are needed to determine whether these extracellular factors are immune- or hormone-related factors or a host-specific restriction mechanism.FIG 5 HSV-1 and HSV-2 in cultured mouse primary neurons. (A) Percentage of cultured adult murine neurons productively infected in vitro with HSV-1 or HSV-2 at a 10-hour MAI, immunostained for HSV antigens with polyclonal antisera, in trigeminal ganglia (TG, P = 0.045, n = 30 cultures/virus), in upper cervical ganglia (SC) G, P = 0.01 5, n = 8 cultures/viruses) and ciliary ganglia (CG, P = 0.880, n = 4 cultures/viruses). (B) Cumulative number of neurons reactivating in 3 days ex vivo from ganglia harvested and cultured by adult mice latently infected with HSV-1 or HSV-2 expressing GFP. The graph represents three separate experiments, including 10 mice/group for each experiment.Studies of eye infection in guinea pigs have shown that HSV-1 can reactivate GC independently of TG causing symptomatic recurrences. However, studies in guinea pigs did not provide evidence that relapses of HSV-2 could be caused by viral reactivation in autonomous ganglia independently of TGs. To determine whether HSV-1 and HSV-2 could reactivate from individual autonomous neurons, mice were infected with HSV-1 or HSV-2 viruses that express a VP26-GFP fusion protein during replication. VP26, expressed by a late gene, is a small capsidic protein that decorates the outer surface of mature capsids, linked to VP5 (20â22); previous studies have shown that HSV VP26-GFP reporter viruses are indeed a productive infection (3, 5). Twenty-one days after infection, when viruses had established latency, TG, SCG and CG were removed from infected mice, cultured and observed for viral reactivation, as shown by GFP expression in individual neurons. Cumulatively for 3 days after culture, HSV-1 and HSV-2 were both reactivated in more autonomous neurons than TG neurons (Fig. 5B), demonstrating that autonomous neurons effectively support viral reactivation. HSV-1 also reactivated much more efficiently by CG neurons, with an average of 160 cumulative, than HSV-2, with a mean of 61 cumulative reactivations in individual neurons, demonstrating the selectivity of the viral type of reactivation of HSV. HSV. and cause lesions with similar characteristics, there are significant differences in patterns of recurrent disease between HSV-1 and HSV-2. HSV-1 is most commonly associated with recurrent orolabial lesions and keratitis, while HSV-2 is most commonly associated with recurrent genital lesions. Eye infections caused by herpesvirus are a serious clinical problem worldwide, and about 500,000 people have recurrent eye infections with HSV in the United States alone. While HSV-1 and HSV-2 can cause eye diseases, HSV-1 is much more likely to spread to the eyes and cause recurrent diseases, causing herpes simplex keratitis characterized by dendritic lesions and inflammation of the cornea, leading to irreversible blindness. While HSV-1 orolabial lesions and herpes keratitis are commonly seen in healthy adults, reports of recurrence of oral or ocular HSV-2 are rare and typically associated with immunocompromised status (23, 24). HSV-2 ocular disease occurs more often as acute retinal necrosis than as recurrent keratitis characteristic of HSV-1 (24, 25). While the incidence of genital HSV-1 disease is increasing due to changes in sexual behavior, HSV-2 is more likely to cause recurrent genital lesions, and the anatomical specificity of the recurrent disease is not simply due to the site of infection; 60-90% of people with genital HSV-2 recurrence, while only about 25% of people with genital HSV-1 develop recurrent lesions (1, 2). It is not clear why these viruses preferably reactivate in a site-specific anatomical way, causing different patterns of recurrent disease.In our guinea pig model, HSV-1 produced acute symptoms, which in most animals resolved by day 14 and then recurred periodically as corneal and/or periocular lesions. The corneas became opaque during these episodic recurrences, indicative of inflammation. Thus, guinea pig eye disease caused by HSV-1 was clinically similar to human disease, characterised by recurrent corneal and/or periocular lesions along with inflammation and corneal blurring. After HSV-2 ocular infection, the guinea pigs experienced a more persistent form of symptomatic infection with deep stromal involvement, rather than definite episodic recurrences. The rare cases of human HSV-2 ocular disease typically take the form of persistent retinal necrosis. Although we did not evaluate the retinas of our guinea pigs, the persistent necrotic characteristics observed in our guinea pigs were consistent with the eye disease HSV-2 in humans. In guinea piglets, HSV-1 reactivated spontaneously to cause episodic symptomatic relapses, while HSV-2 seldom reactivated after the 30th day p.i., consistent with disease relapse rates Therefore, the guinea pig eye model is a valid model to study the differences between HSV-1 and HSV-2 of ocular disease. and the HSV-2 viral DNA is regularly found in the autonomous ganglia of humans and also in animal models after eye or genital infection (7, 10, 12, 26–32). Although many researchers have reported the results of HSV activity in the sympathetic and parasympathetic autonomic ganglia, it is not yet clear whether the virus in the autonomic ganglia contributes to the pathogenesis of herptic disease, both for the severity of symptoms of acute disease or for recurrent disease episodes. Since autonomic innervation and response patterns differ significantly between face and genitals, it is very likely that differences in viral behavior within autonomous ganglia account for anatomical differences in HSV-1 and HSV-2 relapse. Our results in the cavia model show that HSV-1 and HSV-2 infected and established latency in autonomous and sensory gangs after eye infection. HSV-1 and HSV-2 behave in the same way in sensory trigeminal gangl after eye infection, compared to patterns of DNA viral loads and gene expression during the time of analysis. However, viruses have behaved very differently in autonomous ganglia, which probably contributed to differences in acute disease pathogenesis and differences in reactivation. Both viruses have established latency in sympathetic SCG, with similar viral DNA loads and LAT expression. However, HSV-1 did not express TK in SCG except in a single animal on day 2 p.i., and the HSV-2 TK expression was sporadic in few animals. Moreover, neither HSV-1 nor HSV-2 have expressed ICP27 in SCG. Thus, neither virus efficiently replicated in adult SCG after eye inoculation. Although some HSV-2 viral replicas occurred in the sympathetic ganglions of three cavies during the recurring symptomatic disease, there was no evidence that the occurrence originated in the SCG, since the virus was simultaneously replicating in the TG. HSV-1 was, however, able to infect SCG viral neurons cultivated in vitro, suggesting that extracellular SCV-1 factors can act. Further studies are required to determine whether these factors are immunological or hormonal in nature or whether they represent a specific restriction by species. In the cylical ganglions, both HSV-1 and HSV-2 replicated during acute infection, shown by viral DNA increases and TK and ICP0 expression. In several animals, HSV-1 and HSV-2 TK levels were higher in CG than in TG, especially for HSV-2, suggesting that replication of the virus in the CG during acute infection was contributing to symptoms of acute disease. However, HSV-2 failed to express LAT in the CG at latent time points, suggesting that HSV-2 was able to reactivate from the CG or that LAT is not necessary for HSV-2 reactivation from theDuring the HSV-2 recursions, TK expression was detected in TG and CG simultaneously in a single animal, without providing any that the applicants came from the CG since the virus was also replicating in the TG. In contrast, HSV-1 expressed LAT in the GC during the 60-day period of analysis. At latent time points, guinea pigs showing recurrent HSV-1 lesions expressed TK as both TG and CG, but never both, demonstrating that symptomatic HSV-1 recurrent may be from TG or CG. To develop more effective antivirals that can inhibit reactivation and prevent recurrent herpes disease and viral transmission to new hosts, it is imperative to fully understand the processes involved in viral reactivation by neurons. HSV-1 and HSV-2 demonstrate preferences for infecting and establishing production latency in specific types of neurons, not only sensory neurons but also autonomous neurons. Different populations of neurons depend on, and responsive to, a wide range of neurotrophic factors and hormones, depending on the repertoire of receptors and host factors expressed. Physiological stimuli that are known to reactivate HSV-1 and/or HSV-2, in vivo or in vitro, have a greater effect on the activation and signaling of cascades in autonomic neurons than in sensory neurons, and autonomic neurons host latent viruses. Our studies show that HSV-1 is able to reactivate from autonomous ciliary ganglia, independent of sensory trigeminal ganglia, to cause recurrent lesions after ocular infection, while active HSV-2 replication was not detected in TG-independent CG. Although further studies are needed, the ability of HSV-1, but not HSV-2, to reactivate independently of ciliary ganglia to cause recurrent disease may explain the higher frequency of orofacial recurrence of HSV-1 compared to HSV-2. This work was supported by research grant K22AI097 299 from the National Institute of Allergy and Infectious Diseases. We thank Kathleen Apakupakul for the technical assistance and Leita Estes for the critical reviews of the manuscript. We declare that we have no competing financial interests in the research submitted. Lafferty WE, Coombs RW, Benedetti J, Critchlow C, Corey L. 1987. Recurrence after infection with oral and genital herpes simplex virus. Infection site and viral type. N Engl J Med 316:1444â1449. 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