Genetics of Natural Resistance to Herpes Simplex Virus Type 1 Latent Infection of the Peripheral Nervous System in Mice

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SUMMARY

The genetics of natural resistance to the development of latent infection in the trigeminal ganglia of mice inoculated in the lip with herpes simplex virus type 1 (HSV-1) was examined. Based on coefficients of a logistic regression relating latency to strain and HSV-1 concentration, inbred strains of mice formed a continuum of resistance ranging from most resistant (C57BL/6J) to most susceptible (PL/J). When these results were analysed along with latency data derived from studies employing a non-fatal concentration of HSV-1, three subpopulations were identified among these strains: resistant (C57BL/10J, BALB/cByJ, C57BL/6J), moderately resistant (DBA/2J, SWR/J, A/J, AKR/J, DBA/1J) and susceptible (PL/J, LP/J, CBA/J). Results from F1 hybrids between resistant and moderately resistant strains (B6D2F1/J, B6AF1/J) and between resistant and susceptible strains [(C57BL/6J × CBA/J)F1, (C57BL/6J × LP/J)F1] indicated that resistance is dominant. Data from both inbred and congenic strains failed to show an association between H-2 and resistance to the development of a latent infection. Studies of mortality also indicated that a continuum was present, with C57BL/10J, C57BL/6J and DBA/1J being most resistant and PL/J mice most susceptible. When inbred strains were categorized on the basis of resistance to the development of latent infection and mortality, five groups could be identified. Group A are strains resistant to both mortality and latency (C57BL/6J, C57BL/10J, DBA/1J) while group B consists of one strain (BALB/cByJ) intermediate in resistance to mortality but resistant to latency. Group C are strains intermediate in resistance to mortality and susceptible to latency (LP/J, CBA/J) while Group D are strains susceptible to mortality and intermediate in susceptibility to latency (AKR/J, SWR/J, DBA/2J). Group E consists of one strain (PL/J) susceptible to both mortality and latency. These results indicate that host factors play an important role in the establishment of latent infection in vivo.

INTRODUCTION

Herpes simplex virus type 1 (HSV-1) is a double-stranded DNA-containing member of the family Herpesviridae. Peripheral inoculation of virus in mice gives rise to an acute, followed by a latent infection of the peripheral nervous system (PNS) (Stevens & Cook, 1971; Cook & Stevens, 1973; Kastrukoff et al., 1982). The acute stage of the infection in the trigeminal ganglia (TG) is defined by the ability to isolate infectious virus from tissue homogenates and is present for 10 to 12 days post-inoculation. The latent stage is defined by the ability to isolate virus by explantation and co-cultivation methods and follows the acute phase of the infection. Following peripheral inoculation, HSV-1 spreads centripetally to the ganglia, probably by retrograde intraxonal transport (Cook & Stevens, 1973). Central nervous system (CNS) involvement follows,
probably as an extension of the infection from the PNS (Kastrukoff et al., 1981), with mortality the result of an acute encephalitis (Stevens & Cook, 1971; Cook & Stevens, 1973).

Host genetic factors often play a major role in resistance to virus infections (Fenner, 1972; Bang, 1978; Brinton & Nathanson, 1981). Most studies of the genetics of natural resistance to HSV-1 have involved the investigation of acute and lethal infections rather than latent virus infection (Armerding et al., 1981; Caspary et al., 1980; Kirchner et al., 1978a, b, c; Lopez, 1975, 1980a). The results of these studies indicate that resistance to mortality is dominant (Lopez, 1975) and that two loci are the major determinants although other loci may play a role in some strains (Lopez, 1980a). H-2, the major histocompatibility complex of the mouse, does not appear to play a role in influencing resistance (Lopez, 1980a). These results have been interpreted as indicating a role for the immune system (Lopez, 1980b).

The genetics of natural resistance to the development of latent HSV infection is less well defined. Several studies have identified differences among inbred murine strains in their ability to support a latent infection, suggesting host genetic factors may play a role; however, the limited number of strains studied would preclude a detailed analysis of these factors (Price & Schnitz, 1979; Harbour et al., 1981; Clements & Subak-Sharpe, 1983; Subak-Sharpe et al., 1984). Mechanisms mediating the establishment and maintenance of a latent infection in the PNS are not yet clearly defined. Emphasis has been placed on examining relevant molecular aspects of the virus and on virus-cell interaction in the establishment of a restrictive infection (Becker, 1981) while the development of a latent infection in vivo along with a possible role for the host immune system remains unclear.

The purpose of this study was to define the genetic control of resistance to the establishment of a latent infection in the TG and to determine from these results whether mechanisms mediating such resistance can be identified.

METHODS

Animals and animal inoculations. Twelve strains of inbred mice (A/J, AKR/J, BALB/cByJ, CBA/J, C57BL/10J, C57BL/6J, C3H/HeJ, DBA/1J, DBA/2J, LP/J, PL/J, SWR/J), six congenic strains (A. BY/SnJ, B6. C-H-2d/ByJ, B10.A/SgSnJ, B10.BR/SgSnJ, B10.D2/nSnJ, C3H.SW/SnJ) and four F1 hybrids [B6AF1/J, B6D2F1/J, (C57BL/6J × CBA/J)F1, (C57BL/6J × LP/J)F1] were obtained from Jackson Laboratories, Bar Harbor, Me., U.S.A. They were maintained for 2 weeks prior to use at 10 to 12 weeks of age. Adult male mice were lip-inoculated as previously described (Kastrukoff et al., 1982). Groups of 10 mice were inoculated with 25 μl of tenfold dilutions of HSV-1 stock (10⁰ to 10⁻⁴) (sample 1). Additional groups of 20 mice were inoculated with 25 μl of a 10⁻⁵ dilution of HSV-1 stock (sample 2).

Virus and cells. HSV-1 laboratory strain 2 was used throughout these studies. Virus was propagated on BHK-21 cells and plaque-assayed on CV-1 cells as previously described (Kastrukoff et al., 1982). The titre was 1.5 × 10¹¹ p.f.u./ml.

Virus isolation. The presence of latent virus in the TG was identified as previously described (Kastrukoff et al., 1982). Briefly, TG were removed after animals had been bled by sectioning the axillary artery. Tissue was minced and added to T-25 tissue culture flasks 75 to 80% confluent with CV-1 cells. The flasks were maintained in a 37 °C incubator at 5% CO₂, 100% humidity. Tissue was considered positive for virus if a typical c.p.e. was observed and if virus could be passed in subsequent cultures. Cultures were maintained and examined for 6 weeks before being scored as negative.

Statistics. Data from the two samples of mice were analysed independently. In the first sample, strain effects on latency and survival were compared using analysis of covariance based on a logistic regression model (Cox, 1970). The viral dose was chosen as covariate. Tests for strain differences were based on the asymptotic normality of the logistic regression coefficient estimates using the Bonferroni simultaneous comparison approach (Miller, 1981). The LD₁₀ for survival data was estimated using both the Spearman–Karber method and a logistic model. Logistic regression was performed using the BMD PLR computer program.

RESULTS

Genetics of natural resistance to the development of latent infection in the PNS

Animals surviving the acute infection were sacrificed 21 days after lip inoculation and their TG examined for latent HSV-1 infection. Cytopathic effect was first observed 3 days after explantation of ganglia in several strains. The average delay was 6 days with a range of 3 to 12 days. Of the 20 strains of mice studied, 12 showed a relationship between the dose of virus
Natural resistance to HSV-1 latent infection

Table 1. Latent TG infection in mice previously lip-inoculated with HSV-1

<table>
<thead>
<tr>
<th>Inbred strain</th>
<th>H-2</th>
<th>Strain effect coefficient* (± s.E.) (sample 1)</th>
<th>Latent infection in TG† (sample 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6J</td>
<td>b</td>
<td>-0.98 ± 0.42</td>
<td>0/20</td>
</tr>
<tr>
<td>BALB/cByJ</td>
<td>d</td>
<td>-0.02 ± 0.45</td>
<td>0/20</td>
</tr>
<tr>
<td>C57BL/10J</td>
<td>b</td>
<td>0.28 ± 0.44</td>
<td>2/20</td>
</tr>
<tr>
<td>AKR/J</td>
<td>k</td>
<td>1.17 ± 0.58</td>
<td>6/20</td>
</tr>
<tr>
<td>DBA/1J</td>
<td>q</td>
<td>1.17 ± 0.52</td>
<td>5/20</td>
</tr>
<tr>
<td>A/J</td>
<td>a</td>
<td>1.20 ± 0.65</td>
<td>8/20</td>
</tr>
<tr>
<td>SWR/J</td>
<td>q</td>
<td>1.24 ± 0.58</td>
<td>8/20</td>
</tr>
<tr>
<td>DBA/2J</td>
<td>d</td>
<td>1.52 ± 0.65</td>
<td>11/20</td>
</tr>
<tr>
<td>CBA/J</td>
<td>k</td>
<td>2.99 ± 0.99</td>
<td>16/20</td>
</tr>
<tr>
<td>LP/J</td>
<td>b</td>
<td>3.02 ± 0.99</td>
<td>18/20</td>
</tr>
<tr>
<td>PL/J</td>
<td>u</td>
<td>&gt; 3.02‡</td>
<td>19/20</td>
</tr>
<tr>
<td>F1 hybrids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B6AF1/J</td>
<td>b × a</td>
<td>-2.09 ± 0.46</td>
<td>0/20</td>
</tr>
<tr>
<td>B6D2F1/J</td>
<td>b × d</td>
<td>-1.33 ± 0.43</td>
<td>0/20</td>
</tr>
<tr>
<td>(C57BL/6J × LP/J)F1</td>
<td>b × b</td>
<td>-0.98 ± 0.42</td>
<td>0/20</td>
</tr>
<tr>
<td>(C57BL/6J × CBA/J)F1</td>
<td>b × k</td>
<td>-0.28 ± 0.42</td>
<td>0/20</td>
</tr>
<tr>
<td>Congenic strains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B10.A/SgSnJ</td>
<td>a → b</td>
<td>-2.53 ± 0.50</td>
<td>0/20</td>
</tr>
<tr>
<td>B6.C-H-24/BByJ</td>
<td>d → b</td>
<td>-1.98 ± 0.46</td>
<td>0/20</td>
</tr>
<tr>
<td>B10.D2/nSnJ</td>
<td>d → b</td>
<td>-1.51 ± 0.43</td>
<td>0/20</td>
</tr>
<tr>
<td>B10.BR/SgSnJ</td>
<td>k → b</td>
<td>-1.51 ± 0.43</td>
<td>0/20</td>
</tr>
<tr>
<td>A.BY/SnJ</td>
<td>b → a</td>
<td>0.61 ± 0.57</td>
<td>0/20</td>
</tr>
</tbody>
</table>

* Strain effect coefficient from logistic regression analysis (conditional on survival of acute infection).
† All mice lip-inoculated with 4 × 10^4 p.f.u. All survived acute infection and were analysed for latent infection independent of mortality.
‡ All mice infected; regression coefficient and s.E. could not be estimated.

Inoculated and the first appearance of c.p.e. while in eight strains no such relationship was observed. In the former case, the appearance of c.p.e. occurred earlier in mice given a larger dose of virus. The relationship between latency and concentration of HSV-1 was analysed using analysis of covariance based on a logistic model. Results are given in Table 1. Based on formal statistical tests for differences in strain effects based on regression coefficients at an overall significance level of 0.05, PL/J, LP/J and CBA/J mice had a greater probability for latency than C57BL/6J. No other strain differences were statistically significant. No clear association between H-2 and resistance to the development of latent infection in the PNS could be identified.

F1 hybrids between resistant and moderately resistant strains (B6D2F1/J, B6AF1/J) as well as between resistant and susceptible strains [(C57BL/6J × CBA/J)F1, (C57BL/6J × LP/J)F1] were resistant to the development of a latent state. B6AF1/J and B6D2F1/J were more resistant than the parent C57BL/6J strain (although not significantly so at the 0.05 level) while (C57BL/6J × CBA/J)F1 was less so. The (C57BL/6J × LP/J)F1 hybrid had an identical latency pattern to the C57BL/6J strain.

Limited studies with congenic strains did not identify any association between H-2 type and susceptibility to developing a latent infection of the PNS. Susceptibility could not be conferred on resistant strains (B10.D2/nSnJ, B10.BR/SgSnJ, B10.A/SgSnJ, B6.C-H-24/BByJ) nor resistance on susceptible strains (A.BY/SnJ). Based on the regression coefficients, B10.A/SgSnJ was significantly more resistant to latent infection than C57BL/10J (P < 0.001) while B10.D2/nSnJ and B10.BR/SgSnJ were more resistant than C57BL/10J (P = 0.004). The probabilities of developing a latent infection were similar for B6.C-H-24/BByJ and C57BL/6J mice (P = 0.11). The probabilities of A.BY/SnJ and A/J mice developing latency also did not differ (P = 0.51).

When additional hybrids, inbred and congenic strains of mice were lip-inoculated with 4 × 10^4 p.f.u. of HSV-1, all animals survived the acute infection and were sacrificed 21 days after inoculation. The results appear in Table 1. When the regression coefficients (derived from
Fig. 1. Distribution of inbred strains of mice according to resistance to HSV-1 latency in the trigeminal ganglia. Based on regression coefficients (sample 1) and percent latency (sample 2), a continuum of resistance exists from most resistant (C57BL/6J) to most susceptible (PL/J). Three subpopulations occur within this continuum: resistant (A), moderately resistant (B) and susceptible (C).

Fig. 2. Dose–response curves relating HSV-1 dose to resulting mortality for murine strains C3H/HeJ (●) and SWR/J (△). The estimated response curve for strain SWR/J is plotted.

sample 1) are plotted against the independent latency data (derived from sample 2) (Fig. 1), a continuum of resistance to latency is observed, with strain C57BL/6J being most resistant and PL/J being most susceptible.

Furthermore, three groups of strains are suggested by this figure. C57BL/6J, BALB/cByJ and C57BL/10J form one group (resistant), AKR/J, DBA/1J, A/J, SWR/J and DBA/2J a second (moderately resistant) and CBA/J, LP/J and PL/J form a third group (susceptible).

Genetics of natural resistance to mortality

Following inoculation with HSV-1, mice were observed for 21 days. Mortality, when it occurred, was associated with clinical evidence of encephalitis in all cases. Mortality was observed to develop at different times in different strains, but the earliest time at which it was observed was 6 days (range 6 to 11). A relationship between the viral dose inoculated and mortality was observed with mice given a higher dilution of virus dying later than mice inoculated with a higher dose of virus. None of the strains inoculated with 25 μl of a 10⁻⁵ dilution of HSV-1 stock developed mortality. The Spearman–Karber (LD₅₀) estimates for inbred strains, F1 hybrids and congenic strains are given in Table 2. Logistic estimates of LD₅₀ paralleled these results closely. Using the analysis of covariance method, we observed (at an overall significance level of 0.05) that C57BL/10J, C57BL/6J and DBA/1J had significantly lower probabilities of death than all strains except LP/J; LP/J had a significantly lower probability of death than SWR/J, AKR/J, DBA/2J, A/J or PL/J; CBA/J had a significantly
Natural resistance to HSV-1 latent infection

Table 2. Resistance to mortality of inbred strains, F1 hybrids and congenic strains lip-inoculated with HSV-1

<table>
<thead>
<tr>
<th>Inbred strain</th>
<th>H-2</th>
<th>( \log_{10} LD_{50} ) (HSV-1)*</th>
<th>Strain effect coefficient and s.e. (sample 1)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/10J</td>
<td>b</td>
<td>&gt;9.59</td>
<td>(&lt; -2.33^+)</td>
</tr>
<tr>
<td>C57BL/6J</td>
<td>b</td>
<td>&gt;9.59</td>
<td>(&lt; -2.33^+)</td>
</tr>
<tr>
<td>DBA/1J</td>
<td>q</td>
<td>&gt;9.59</td>
<td>(&lt; -2.33^+)</td>
</tr>
<tr>
<td>LP/J</td>
<td>b</td>
<td>8.77</td>
<td>(-2.33 \pm 0.42)</td>
</tr>
<tr>
<td>CBA/J</td>
<td>k</td>
<td>8.12</td>
<td>(-1.36 \pm 0.39)</td>
</tr>
<tr>
<td>BALB/cByJ</td>
<td>d</td>
<td>7.80</td>
<td>(-0.89 \pm 0.38)</td>
</tr>
<tr>
<td>SWR/J</td>
<td>q</td>
<td>7.06</td>
<td>(0.20 \pm 0.38)</td>
</tr>
<tr>
<td>AKR/J</td>
<td>k</td>
<td>6.96</td>
<td>(0.35 \pm 0.38)</td>
</tr>
<tr>
<td>DBA/2J</td>
<td>d</td>
<td>6.85</td>
<td>(0.51 \pm 0.38)</td>
</tr>
<tr>
<td>A/J</td>
<td>a</td>
<td>6.52</td>
<td>(1.00 \pm 0.39)</td>
</tr>
<tr>
<td>PL/J</td>
<td>u</td>
<td>6.06</td>
<td>(1.69 \pm 0.42)</td>
</tr>
<tr>
<td>C3H/HeJ</td>
<td>k</td>
<td>NR§</td>
<td>NR§</td>
</tr>
<tr>
<td>F1 hybrids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B6AF1/J</td>
<td>b \times a</td>
<td>9.59</td>
<td>(&lt; -2.33^+)</td>
</tr>
<tr>
<td>B6D2F1/J</td>
<td>b \times d</td>
<td>9.59</td>
<td>(&lt; -2.33^+)</td>
</tr>
<tr>
<td>(C57BL/6J \times CBA/J)FI</td>
<td>b \times k</td>
<td>9.59</td>
<td>(&lt; -2.33^+)</td>
</tr>
<tr>
<td>(C57BL/6J \times LP/J)FI</td>
<td>b \times b</td>
<td>9.59</td>
<td>(&lt; -2.33^+)</td>
</tr>
</tbody>
</table>

| Congenic strains         |     |                                  |                                               |
| B10. A/SgSnJ             | a \rightarrow b | >9.59                         | \(< -2.33^+\)                                |
| B6. C-H-2^d/ByJ          | d \rightarrow b | >9.59                         | \(< -2.33^+\)                                |
| B10. D2/nSnJ             | d \rightarrow b | >9.59                         | \(< -2.33^+\)                                |
| B10. BR/SgSnJ            | k \rightarrow b | >9.59                         | \(< -2.33^+\)                                |
| A .BY/SnJ                | b \rightarrow a | 6.69                          | \(0.84 \pm 0.39\)                            |
| C3H .SW/SnJ              | b \rightarrow k | NR§                           | NR§                                           |

* Spearman-Karber estimate.
† Strain effect coefficient from logistic regression analysis of mortality.
‡ All mice survived at all dilutions. Coefficient less than smallest estimated coefficient; no s.e. available.
§ NR, Dose-response pattern could not be adequately summarized by LD50 or the logistic model.

lower probability of death than AKR/J, DBA/2J, A/J or PL/J; BALB/cByJ had a significantly lower probability of death than A/J or PL/J. C3H/HeJ had a dose-response relationship that could not be adequately summarized by LD50 or the logistic model. The dose-response curve is presented in Fig. 2 and is compared with the curve for strain SWR/J. The difficulty with the former strain was previously recognized by Lopez (1975).

The 11 inbred strains of mice represent a continuum of resistance to mortality with C57BL/10J, C57BL/6J and DBA/1J being most resistant and PL/J most susceptible. Furthermore, if Lopez’s classification is applied (Lopez, 1975), the strains can be roughly separated into three categories of resistance on the basis of regression coefficients. This includes C57BL/10J, C57BL/6J, DBA/1J, LP/J and CBA/J as resistant, BALB/cByJ, SWR/J, AKR/J and DBA/2J as moderately resistant, and A/J and PL/J as susceptible.

No mortality occurred among the F1 hybrids (Table 2). Hybrids of resistant and susceptible (B6AF1/J), resistant and moderately resistant (B6D2F1/J), and resistant mice [(C57BL/6J × CBA/J)F1, (C57BL/6J × LP/J)F1] were all resistant to HSV-1, suggesting that resistance is dominant.

Although a preliminary evaluation of inbred strains suggested an association between H-2 type and resistance to mortality, formal statistical evaluation did not clearly separate strains on the basis of H-2 type. H-2b, k or d strains had significantly lower probabilities of mortality than strains with H-2a or u, whereas strains with H-2q had lower probabilities of mortality than H-2u but H-2b, k and d could not be separated from each other.

Estimates of LD50 and regression coefficients for congenic strains are given in Table 2. There was no mortality in any strain except A.BY/SnJ. Susceptibility could not be conferred on resistant mice (B10. A/SgSnJ, B6. C-H-2^d/ByJ, B10. D2/nSnJ, B10. BR/SgSnJ) and resistance
could not be conferred on susceptible mice (A. BY/SnJ). Strains A. BY/SnJ and A/J did not differ significantly \( (P = 0.78) \) in resistance. C3H. SW/SnJ had a dose–response relationship which could not be appropriately summarized using the logistic model or LD\(_{50}\). Based on the results of inbred and congenic strains, a clear association between H-2 and resistance to mortality cannot be established.

**Classification of inbred strains of mice based on resistance to mortality and latency**

The 11 inbred strains of mice were classified on the basis of mortality and latency. Based on a scatter plot of LD\(_{50}\) (derived from sample 1) and the percentage of latency in an independent sample (sample 2), five different groups of strains can be identified (Fig. 3). Group A consists of strains that are resistant to mortality and latency (C57BL/6J, C57BL/10J, DBA/1J). Group B consists of strain BALB/cByJ which is intermediate in resistance to mortality but resistant to latency. Group C consists of strains that are intermediate in resistance to mortality and susceptible to latency (LP/J, CBA/J). Group D consists of strains that are susceptible to mortality and intermediate in susceptibility to latency (AKR/J, SWR/J, A/J, DBA/2J). Group E consists of strain PL/J which is susceptible to both mortality and latency.

**DISCUSSION**

The results of this study indicate that following lip inoculation with HSV-1, inbred and congenic strains as well as F1 hybrids vary in their natural resistance to the development of latent infection in the TG. These results confirm the observation of a number of investigators (Harbour *et al.*, 1981; Clements & Subak-Sharpe, 1983; Subak-Sharpe *et al.*, 1984) that different
murine strains vary in their ability to resist the development of latent HSV infection in peripheral ganglia. These observations were made in a limited number of murine strains and have been extended to include a large series of strains in this study. The results of this study indicate that a continuum of resistance exists ranging from very resistant to very susceptible. Further evaluation of the inbred strains alone and based on regression coefficients derived from one sampling versus latency data derived from a second sampling, suggests that three subpopulations (resistant, moderately resistant and susceptible) may exist within this continuum (Fig. 1). All murine strains examined in this study were capable of supporting a latent TG infection. Furthermore, the dose-response curves for all strains examined (excluding C3H/HeJ) showed a steady increase in the percentage of mice harbouring latent infection as the viral dose was increased, including strain BALB/cByJ. These results differ from those reported by Price & Schmitz (1979) for BALB/c mice where the highest frequency of latent infection developed at a relatively low concentration of inoculated virus and higher concentrations led to progressively lower rates of latency. The reason for this is unclear but probably reflects differences in the mode of inoculation, site of inoculation, and possibly the age and sex of mice used. The results do emphasize the potential difficulties in comparing results of studies where the methodology differs. Results from studies of F1 hybrids indicate that resistance is dominant while those from both inbred and congenic strains fail to identify a clear association between H-2 and the development of a latent infection. Studies to determine the number of genes involved are in progress.

Several problems could influence the results of this study. As the results are based on dose-response curves and regression coefficients, and therefore dependent on animals surviving the acute infection, a potential source of error could result from the degree of mortality that occurred among some strains. This is unlikely, however, as similar results for latency were obtained when the inoculum of HSV-1 was adjusted to ensure that all mice would survive the acute infection (Fig. 1). Indeed, the similarity of the results derived from the two experiments indicates that incidence values derived from studies where latency was conditional on survival of a potentially fatal dose of HSV-1 are similar to those derived from studies where latency was determined following non-fatal doses of HSV. This would suggest that future studies of mortality and latency can be performed simultaneously. A second problem involves the injection of a 10% saline solution into the lip several hours prior to scarification with virus. This could conceivably alter the natural resistance at the site of inoculation and introduce error. As the study was designed to compare different murine strains and as all strains were treated in a similar fashion, it is unlikely that this comparison will be affected provided the effect of a saline injection on natural resistance is the same in all strains.

The results of this study also indicate that following lip inoculation with HSV-1, inbred and congenic strains as well as F1 hybrids vary in their natural resistance to mortality. When these results were compared to Lopez’s study (1975), nine inbred strains of mice were found to be common to both studies. The results obtained by Lopez following intraperitoneal (i.p.) inoculation of HSV-1 closely paralleled those obtained following lip inoculation. The results of studies using F1 hybrids and congenic strains would support his conclusion that resistance to mortality is dominant and not linked to H-2. Only strain CBA/J was observed to be more resistant following lip inoculation than i.p. inoculation. The results obtained with DBA/1J and DBA/2J mice could not be directly compared with strain DBA used in Lopez’s study.

The mechanisms mediating resistance to the development of latent infection in the PNS remain undefined. Although the immune system plays an important role in the elimination of the acute ganglionic infection (Openshaw et al., 1979b; Price & Schmitz, 1979), its role in establishing and maintaining a latent infection is less clear (Stevens & Cook, 1974). Immune modulation and immune elimination are two hypotheses which have been proposed as mechanisms by which the immune system could mediate the development of a latent state (Openshaw et al., 1979a). Our previous studies have identified an association between mortality, viral involvement of the CNS and viral involvement of the TG during the acute phase of the infection which would allow mortality to be used as an index of viral involvement of the TG (Kastrukoff et al., 1981). Recent studies with C57BL/6J, BALB/cByJ and A/J mice in which
mortality was correlated with viral titres of HSV-1 in the CNS and the TG confirm this impression (L. F. Kastrukoff, S. U. Kim, A. S. Lau & D. W. Paty, unpublished results). If this correlation is valid when extrapolated to the other strains, mortality may be used as an index of viral titres achieved in the TG during the acute phase of the infection and of the effectiveness of the immune system in eliminating the acute ganglionic infection. When inbred strains were classified on the basis of resistance to latency and mortality (Fig. 3), only four strains were equally resistant or susceptible to both mortality and latency while seven strains differed in their resistance to both. If the assumptions made are correct, the differences observed in these seven strains would suggest that different mechanisms play a role in eliminating the acute infection and in establishing the latent infection. It is not known whether the mechanisms mediating the establishment of latent infection are immune or non-immune in nature.

The results of this study indicate that host factors play an important role in determining mortality and the development of latent infection following peripheral inoculation with HSV-1. Furthermore, the results confirm Lopez’s observations that resistance to mortality is genetically determined and are a step towards identification of the genetics of natural resistance to the development of latency in the PNS. Although the mechanisms remain unclear, these results can be interpreted as indicating that the mechanisms mediating resistance to acute ganglionic infection differ from those mediating resistance to latency in at least some strains of mice. Finally, several strains of mice (LP/J, CBA/J) have been identified which are resistant to mortality but susceptible to latency in the PNS and may represent useful models for the further study of latency in vivo.

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Natural resistance to HSV-1 latent infection


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