Failure to Modify Scrapie in Mice by Administration of Interferon or Anti-interferon Globulin

By I. GRESSER,* C. MAURY AND R. L. CHANDLER 1

Laboratory of Viral Oncology, Institut de Recherches Scientifiques sur le Cancer, BP 8, 94802 Villejuif, France and 1Agricultural Research Council, Institute for Research on Animal Diseases, Compton, Nr Newbury, Berkshire, U.K.

(Accepted 19 January 1983)

SUMMARY

Administration of potent mouse interferon preparations or anti-mouse interferon globulin did not influence the evolution of scrapie in mice after intraperitoneal injection of the agent. We conclude that the interferon system is probably not involved in scrapie.

The scrapie agent has been considered by many investigators to be a small virus but its nature is still unknown (Kimberlin, 1982; Prusiner, 1982). It is known that the evolution of most acute virus diseases can be inhibited by interferon (Stewart, 1979) and we have previously attempted to modify the course of scrapie in mice by daily administration of interferon for 3 months (Gresser & Pattison, 1968). In these experiments the scrapie agent was inoculated intracerebrally (i.c.). Although we noted no effect on the evolution of scrapie, it seemed worthwhile repeating these experiments with the following modifications: injection of the agent intraperitoneally (i.p.) which results in a longer period of multiplication of the agent outside the CNS (central nervous system) (Kimberlin & Walker, 1979), and administration of 20- to 100-fold more potent interferon preparations than had been available for our previous experiments. Furthermore, potent anti-mouse interferon antibody has provided a useful means of demonstrating the role of interferon in the pathogenesis of several acute viral diseases of mice (Fauconnier, 1970; Gresser et al., 1976a, b; Inglot & Oleszak, 1978). Even the genetically determined resistance of various strains of mice to several different viruses can be overcome by treating them with anti-interferon antibody (Virelizier & Gresser, 1978; Haller et al., 1979). We have therefore also determined the effect of potent sheep anti-mouse interferon antibody on scrapie.

Mice in the different groups in experiments 1 and 2 (Table 1) were injected with either $10^{-2}$, $10^{-3}$ or $10^{-4}$ dilutions of a scrapie-affected brain suspension. There were two cages per scrapie agent dilution per group. The techniques used in the production, purification and assay of mouse C-243 cell interferon (Tovey et al., 1974) or sheep anti-mouse interferon globulin have been previously described (Gresser et al., 1976a, b). In experiment 1 all mice died, with characteristic signs of scrapie disease. There was no significant difference between the survival times of mice in any of the different groups (Table 1) whether comparing the survival times per cage, per treatment, or per dilution of agent injected. Ten representative mice from the different groups injected with the scrapie brain extract were sacrificed between the 224th and 280th day. All showed advanced CNS lesions characteristic of scrapie. None of 20 mice injected with a $10^{-2}$ suspension of 'normal' brain died (either left untreated or treated with anti-interferon globulin), and no lesions were seen in the brains of two of these mice sacrificed at 274 days. Likewise, in experiment 2 (Table 1), there was no significant difference in the survival times of mice in any of the groups. Five mice with scrapie disease from the different groups were sacrificed between the 263rd and 270th days, and four mice injected with normal brain extract (with or without treatment with anti-interferon globulin) were sacrificed at 328 days (at which time experiment 2 was
Table 1. *Attempt to modify scrapie in mice with either mouse interferon or anti-mouse interferon antibody*  

<table>
<thead>
<tr>
<th>Expt. no.</th>
<th>Dilution of scrapie</th>
<th>Interferon 1 week</th>
<th>Interferon preparation 6 months 3× per week</th>
<th>Control preparation 6 months 3× per week</th>
<th>Sheep anti-interferon globulin +1, +21 days</th>
<th>Sheep normal globulin +1, +21 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10⁻²</td>
<td>10</td>
<td>271.4 ± 2.7</td>
<td>267.1 ± 3.9</td>
<td>271.2 ± 4.2</td>
<td>267.3 ± 3.4</td>
</tr>
<tr>
<td></td>
<td>10⁻³</td>
<td>11</td>
<td>271.0 ± 2.1</td>
<td>263.0 ± 7.6</td>
<td>279.2 ± 3.5</td>
<td>267.9 ± 2.1</td>
</tr>
<tr>
<td></td>
<td>10⁻⁴</td>
<td>12</td>
<td>275.9 ± 2.3</td>
<td>269.4 ± 3.5</td>
<td>277.5 ± 2.3</td>
<td>277.5 ± 2.8</td>
</tr>
<tr>
<td>2</td>
<td>10⁻²</td>
<td>12/14§</td>
<td>13/15</td>
<td>271.0</td>
<td>267.0</td>
<td>278.2</td>
</tr>
<tr>
<td></td>
<td>10⁻³</td>
<td>(250-1–269-4)</td>
<td>NT</td>
<td></td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td></td>
<td>10⁻⁴</td>
<td>12/14</td>
<td>13/15</td>
<td>273.5</td>
<td>265</td>
<td>(266-1–281-3)</td>
</tr>
</tbody>
</table>

* For both experiments scrapie brain was prepared as follows. Two scrapie brains derived from B.S.V.S. mice stored at −20 °C at Compton since 20-975 [38th passage in mice since original isolation (Chandler, 1961)] were thawed and a suspension 10% (w/v) in PBS was prepared. This suspension was centrifuged at 3000 rev/min at 4 °C for 10 min. The supernatant was considered to represent a dilution of 10⁻¹ of scrapie brain. Mice were injected i.p. with 0.25 ml of 10-fold dilutions of this suspension of the original brain suspension. Expt. 1. Over the course of 6 months Swiss mice (Compton strain) were injected with 0.2 ml i.p. of four different interferon preparations having titres between 6.4 × 10⁻³ and 3.2 × 10⁻⁶ (expressed in terms of the mouse interferon reference). They were injected daily for the first week (beginning 24 h after injection of scrapie) and then either received no further treatment or treatment was continued (three injections i.p. per week for 6 months). The control preparation had no interferon activity at a 1:10 dilution. Twenty-four h after inoculation of scrapie brain extract, other groups of mice were injected i.p. with 0-2 ml of sheep anti-mouse interferon globulin diluted 1:5 in PBS or normal sheep globulin. The neutralizing titre of the anti-interferon globulin was 6 × 10⁻³ against 8 units of mouse interferon. Mice received a second injection 20 days later of 0.2 ml i.p. of anti-interferon globulin (titre 1 × 10⁻⁵) or normal sheep globulin. In addition 10 mice were injected with a 10⁻² suspension of normal mouse brain extract and another 10 mice were injected with this extract and with anti-interferon globulin. Expt. 2. Swiss mice (IRSC strain, Villejuif) were injected with the same dose of anti-interferon globulin or normal sheep globulin as in expt. 1. As in the latter, other mice (not listed) were injected with normal brain extract (10⁻²) with or without treatment with anti-interferon globulin.

† Number of mice.
‡ Mean day of survival ± standard error.
§ Number of mice dead/total number injected.
|| Harmonic mean survival (days ± standard error).
¶ NT, Not tested.

Characteristic lesions were seen only in the CNS of mice inoculated with scrapie brain. There is no evidence from the literature that the interferon system plays any role in the pathogenesis of scrapie in mice: interferon has not been found in the tissues of mice with scrapie, and scrapie infection does not alter the interferon response to a variety of interferon inducers (Gresser & Pattison, 1968 and unpublished observations; Katz & Koprowski, 1968) and the evolution of the disease is not altered by either exogenous interferon (Gresser & Pattison, 1968) or by weekly injections of Statolon, an interferon inducer (Field et al., 1969). The failure of potent interferon preparations and potent anti-interferon globulin to influence the evolution of scrapie in mice further indicates that the interferon system is probably not involved in scrapie disease.

This work was supported in part by grants from D.R.E.T. (contract 80-34-522); I.N.S.E.R.M. (PRC 12 90 26; PRC 12 70 12); I.N.S.E.R.M. (CRL 81 20 08); C.N.R.S. (ATP USA), and the Richard Lounsbery Foundation.
REFERENCES


(Received 29 November 1982)