ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1975, p. 793-800
Vol. 7, No. 6
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Herpesvirus hominis Infection in Newborn Mice: Treatment with Interferon Inducer Polyinosinic-Polycytidylic Acid[1]

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Received for publication 6 February 1975

Intranasal inoculation of newborn mice with *Herpesvirus hominis* (HVH) type 2 provides a model for disseminated herpesvirus infections of human newborn infants. Treatment of this experimental infection with polyinosinic-polycytidylic acid [poly(I:C)] significantly increased the mean survival time and markedly altered the pathogenesis of the infection. No significant protection against final mortality was observed. Poly(I:C) therapy completely inhibited detectable viral replication in all target organs tested except the brain. In the brain there was a 2-day delay in the onset of viral replication in treated animals, which correlated with the 1- to 2-day increase in mean survival time. In general, the control of HVH replication occurred in those target organs in which poly(I:C)-induced interferon was detectable. The failure of poly(I:C) to alter the final mortality of newborn mice infected with HVH appears to be primarily due to the lack of sufficient levels of interferon induced in brain tissue and the failure to prevent viral replication in this critical target organ.

Interferon is thought to be an important component of host resistance to viral infections. Results from a number of laboratories suggest that it may be successful in the prevention or treatment of certain viral infections in vitro as well as in infections of animals and humans (11, 12, 14, 17, 20). Although members of the herpesvirus group are relatively insensitive to the action of interferon (5, 11, 13), evidence suggests that interferon or interferon inducers may be efficacious in certain experimental herpetic infections. The synthetic double-stranded ribonucleic acid inducer of interferon, polyinosinic-polycytidylic acid [poly(I:C)], has been reported to be effective against *Herpesvirus hominis* (HVH) encephalitis in mice (6, 7, 15) and HVH keratoconjunctivitis in rabbits (15, 26).

The type 2 (genital) strains of HVH have been shown to cause generalized infections and severe disease in human neonates. It has been estimated that greater than 50% of cases may either terminate fatally or result in serious sequelae (23). Although 5-iodo-2'-deoxyuridine, cytosine arabinoside, and adenine arabinoside have been utilized in treatment of individual cases, there are no controlled studies documenting the efficacy of any of these modes of therapy.

The purpose of this study was to determine the activity of the interferon inducer poly(I:C) in an experimental HVH infection of newborn mice which simulates disseminated herpesvirus infections seen in human neonates (21). Therapeutic efficacy was evaluated by determining the effects of treatment on mortality, mean survival time (MST), and the pathogenesis of the infection.

(This paper is taken in part from a dissertation submitted by E. R. K. to the University of Utah in partial fulfillment of the requirements for the Ph.D degree.)

MATERIALS AND METHODS

Animal model. Newborn mice (5 to 7 days old) from pregnant Swiss Webster females (Simonson Laboratories, Gilroy, Calif.) were inoculated intranasally by allowing each mouse to inhale 6 drops (approximately 0.01 ml) of the MS strain of HVH type 2 from a 26-gauge needle. Each animal received approximately 1,000 plaque-forming units (PFU) (8 mean lethal doses [LD_{50}]) of virus, resulting in a 90 to 100% mortality. When lower mortality rates were desired, appropriate dilutions of the inoculum were utilized.

Viruses. The MS strain of HVH type 2 was obtained from Andre Nahmias, Emory University,

[1] Publication no. 17 from the Cooperative Antiviral Testing Group of the National Institute of Allergy and Infectious Diseases, National Institutes of Health.

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Atlanta, Ga. The virus was propagated in primary rabbit kidney cells, and the stock pool titered 10^6 PFU/ml. Other type 2 strains, Alabama, Curtis, Ellison, and Lovelace, and three type 1 strains, Shealey, Tyler, and VR_3, were also obtained from A. Nahmias. Herpesvirus strains isolated in our own laboratory from genital lesions include Holt, Turner, and Jensen. Although these isolates have not been fully characterized, they are probably type 2.

Vesicular stomatitis virus (VSV), Indiana strain, was obtained from the American Type Culture Collection (Rockville, Md.), and stock pools were prepared in primary chicken embryo cells. The strain of encephalomyocarditis (EMC) virus used in these studies was a large-plaque variant originally obtained from K. K. Takemoto (National Institutes of Health, Bethesda, Md.). Virus pools were prepared in suckling mouse brains. Sindbis virus was obtained from Philip K. Russell at Walter Reed Army Medical Center, Washington, D.C., and was grown in human foreskin fibroblasts. Vaccinia virus was originally obtained from Karl Habel, National Institutes of Health, Bethesda, Md., and was propagated in primary chicken embryo cells.

Media, cell cultures, and virus assays. The media utilized and the preparation of mouse embryo fibroblast and fetal lamb kidney cells have been described previously (21). A continuous line of mouse L-cell fibroblasts (L-929) was obtained from the Amercian Type Culture Collection. Assays for HVH were performed in fetal lamb kidney cells by a plaque assay technique as described previously (21).

Interferon induction and assay. Poly(I:C) was prepared by P-L Biochemicals, Inc., Milwaukee, Wis., and was furnished through the Antiviral Substances Program, National Institute of Allergy and Infectious Diseases, Bethesda, Md. The solution had a concentration of 1 mg/ml and was stored at −20 C until used. It was administered intraperitoneally (i.p.) in a volume of 0.05 ml.

All samples to be assayed for interferon were maintained at pH 2.0 for 48 h to inactivate any HVH present. Assays for interferon activity were performed on L cells in plastic petri dishes (10 by 30 mm). The medium was removed from confluent cell monolayers, and 1.0 ml of the appropriate dilution of the interferon-containing sample was added to the cells. After incubation at 37 C for 18 to 24 h, the samples were aspirated from the plates and the cells were washed once with 2.0 ml of phosphate-buffered saline. The cells were then challenged with a dilution of VSV resulting in approximately 50 PFU per 0.2 ml of inoculum. The virus was allowed to adsorb for 60 min, and an overlay medium of 0.5% agarose in minimal essential medium was added. After the overlay had solidified, the cultures were incubated for 24 h and stained with neutral red, and plaques were counted 12 to 24 h later. Interferon titers were expressed as the reciprocal of the highest dilution inhibiting 50% of the number of VSV plaques found on control plates. An interferon standard was included in all assays in order to compare the relative sensitivities of different assays.

Statistical evaluation. To statistically evaluate the differences in the MST between drug-treated and untreated animals, the data were compared by use of Student's t test. To compare the final mortalities of drug-treated and untreated mice, the data were evaluated by chi-square analysis. A P value of <0.05 was considered to be significant.

RESULTS

Sensitivity of HVH to interferon. To determine whether the MS strain of HVH used in our mouse experiments was representative of other HVH strains, we compared its sensitivity with four other type 2 strains and three type 1 strains to two interferon preparations. In addition, the HVH strains were compared with EMC virus, Sindbis virus, vaccinia virus, and VSV to determine their relative sensitivity to interferon in relation to other viruses. The poly(I:C)-induced interferon preparation used was our laboratory standard prepared by injecting 8-week-old mice with 100 μg of poly(I:C) and pooling serum collected 3 h after injection. The second preparation consisted of supernatant fluid from L cells induced by Newcastle disease virus. In this experiment, mouse embryo fibroblasts were treated with dilutions of each of the two interferon preparations and 24 h later challenged with an appropriate inoculum of each of the viruses (approximately 50 PFU/plate). The 50% inhibitory level for each interferon preparation against each of the viruses was calculated (Table 1). The sensitivity patterns for all of the viruses were similar with both of the interferon preparations. The type 2 strains of HVH appeared to be slightly more sensitive to both interferon preparations than the type 1 strains. The herpesviruses were relatively insensitive to interferon when compared with the other viruses (VSV > Sindbis > EMC > HVH type 2 > vaccinia > HVH type 1).

Description of the experimental infection. Intranasal inoculation of 5- to 7-day-old mice with approximately 1,000 PFU (8 LD_{50}) of HVH type 2 resulted in a generalized infection, followed by paralysis and death by day 5 in approximately 90% of the animals. The pathogenesis of HVH infection in suckling mice after intranasal inoculation has been previously described (21) and is characterized by initial replication of virus in the lung, followed by a viremia with subsequent seeding of the liver, spleen, and brain. Virus is also transmitted to the central nervous system (CNS) by way of the olfactory and trigeminal nerves. Interferon levels in blood and tissues induced by HVH replication were determined throughout the course of infection. Low levels of interferon (50 to 200 U) were found in blood, and titers of 200

TABLE 1. *Sensitivity of HVH types 1 and 2, EMC, VSV, Sindbis, and vaccinia viruses in mouse embryo fibroblast cells to poly(I:C)-induced mouse serum interferon and Newcastle disease virus (NDV)-induced L-cell interferon*

Virus	IF titer[a] (U/ml)	
	Poly(I:C)-induced IF	NDV-induced IF
HVH type 2		
Alabama	425	350
Curtis	850	1,675
Ellison	550	1,175
Lovelace	350	225
MS	525	400
HVH type 1		
Shealey	225	150
Tyler	325	200
VR_3	200	100
Other		
EMC	800	1,100
Sindbis	7,750	4,475
Vaccinia	200	575
VSV	6,250	5,300

[a] Reciprocal of the dilution of interferon (IF) which reduced the control virus plaque count by 50%.

to 500 U of interferon were detected in lung, liver, and spleen. No detectable interferon was found in brain tissue.

Kinetics of the interferon response in newborn mice injected with poly(I:C). To determine the capability of newborn mice to produce interferon in response to daily injections of poly(I:C), the following experiments were conducted. Groups of 10 animals each were given 50 or 25 μg of poly(I:C) i.p. daily for 4 consecutive days. No toxicity was observed with these concentrations. After each daily injection, groups of animals were bled at 3, 6, 10, and 24 h, and serum was collected and assayed for interferon activity (Table 2). Animals that received 50 μg of poly(I:C) had a peak interferon response of 5,350 U/ml after the first injection of the inducer. After each consecutive injection of poly(I:C), the animals exhibited a decreased capacity to produce interferon, the well-described phenomenon of hyporeactivity (4). Animals receiving multiple injections of 25 μg of the inducer produced less interferon than those receiving the higher dose; however, a similar pattern of hyporeactivity was observed.

Since serum interferon levels may not reflect the amount of interferon present in target organs, a second experiment was initiated to determine the interferon response in various tissues of newborn mice after daily administration of poly(I:C). Groups of animals were each injected daily with 50 μg of poly(I:C) i.p. Four hours after each daily injection, a time when interferon levels in tissues should be maximal, 10 animals were bled and the lungs, liver, spleen, and brain were removed. Blood and tissues from 10 animals were pooled together by organ group. Blood was homogenized undiluted, whereas other tissues were homogenized as 10% suspensions in minimal essential medium. The tissue homogenates were centrifuged and the supernatants were collected. All samples were stored at −20 C until assayed for interferon activity. The results from one of two experiments are tabulated in Table 3. High levels of interferon were detected in the blood, lungs, and spleen on the first 2 days of poly(I:C) inoculation, but markedly lower levels were detected on days 3 and 4. No detectable interferon was present in either liver or brain tissue at any time during the experiment. It is possible that levels of interferon below the sensitivity of the assay may have been present in these tissues. The pattern of hyporeactivity of interferon production previously demonstrated in serum was also manifested in tissues after multiple injections of the inducer. These data suggest that during the first few days of therapy, moderate to high levels of interferon may be induced in the lung and spleen. The absence of detectable levels in the brain, however,

TABLE 2. *Interferon titers in serum from newborn mice given daily i.p. injections of 50 to 25 μg of poly(I:C)*

Day of poly(I:C) administration	Time of bleeding (h)	Interferon (U/ml)[a]	
		50 μg	25 μg
0	3	950	950
	6	5,350	3,150
	10	3,050	2,200
	24	290	230
0, 1	3	920	850
	6	3,300	1,060
	10	830	1,040
	24	<50	135
0, 1, 2	3	215	165
	6	490	195
	24	90	<50
0, 1, 2, 3	3	185	100

[a] Reciprocal of the dilution of interferon which inhibited 50% of VSV plaque count when compared with control plates.

TABLE 3. *Interferon titers in blood and tissues from newborn mice given daily i.p. injections of 50 μg of poly(I:C)*

Day of poly(I:C) administration	Interferon (U/g or ml)[a] in:				
	Blood[b]	Lung[c]	Liver	Spleen	Brain
0	3,000	1,000	<500[d]	3,000	<200[d]
0, 1	3,450	1,650	<500	6,850	<200
0, 1, 2	180	<200[d]	<500	300	<200
0, 1, 2, 3	150	250	<500	850	<200
0, 1, 2, 3, 4	50	<200	<500	<200[d]	<200
Control	<20	<200	<500	<200	<200

[a] Reciprocal of the dilution of interferon which inhibited 50% of VSV plaque count when compared with control plates.

[b] Animals were bled 4 h after poly(I:C) injection.

[c] Tissues were removed about 5 h after poly(I:C) injection and prepared as 10% homogenates.

[d] Lowest concentration that could be assayed without cell monolayer toxicity.

suggests a potential limitation in the use of poly(I:C) for therapy of HVH infections involving the CNS.

Treatment of HVH-infected mice with poly(I:C). To determine the effectiveness of poly(I:C) in altering the mortality of mice infected with HVH type 2, animals were inoculated with 8 LD_{50} of virus and then treated i.p. with poly(I:C). Although a single injection of poly(I:C) resulted in the highest levels of interferon in serum, previous data from our laboratory indicate that treatment of mice infected with EMC virus with multiple doses of poly(I:C) is more effective than a single dose (29). The treatment regimens used and the results obtained in groups of 40 mice are summarized in Table 4. The animals were observed for 21 days in all experiments. In the first experiment, the untreated control animals had a final mortality of 68% with an MST of 5.4 days. Animals treated twice daily for 3 days with 50 μg of poly(I:C) beginning immediately after infection had a final mortality of 58% with an MST of 6.1 days. Mice that received the same treatment once a day had a mortality rate of 48% with an MST of 6.0 days. Although the mortality of control mice was not significantly different from the treated groups, the differences in the MST were significant ($P < 0.05$). Similar results were obtained when the mice were treated with 25 μg of poly(I:C). The data indicate that poly(I:C) administered twice daily was no more effective than treatment once daily and that both treatment regimens increased the MST without altering final mortality.

Since interferon inducers have generally been shown to be more effective when administered prophylactically, the second experiment was designed to compare the effectiveness of the inducer when given before infection with HVH with treatment initiated immediately after infection. The control group of mice had a final mortality of 88% with an MST of 5.6 days. Mice given poly(I:C) 6 h before infection and then once daily for 3 days after inoculation had a final mortality of 73% with an MST of 7.3 days. Animals that received poly(I:C) immediately after infection and were treated once daily for a total of 4 days had a final mortality of 92% with an MST of 7.1 days. There was no significant difference in the mortality of the treated animals when compared with the controls; however, the increase in the MST of both groups receiving therapy was highly significant ($P < 0.001$).

Effect of poly(I:C) therapy on HVH pathogenesis. The increase in MST suggested

TABLE 4. *Effect of poly(I:C) treatment on mortality of newborn mice infected intranasally with HVH type 2*

Expt no.	Treatment[a]	Mortality			MST	
		No.	Percent	P[b]	Days	P
1	None	27/40	68		5.4	
	50 μg 2×/day for 3 days	23/40	58	NS	6.1	<0.05
	50 μg 1×/day for 3 days	19/40	48	NS	6.0	<0.05
	25 μg 2×/day for 3 days	20/38	53	NS	5.8	NS
	25 μg 1×/day for 3 days	19/38	50	NS	6.0	<0.05
2	None	35/40	88		5.6	
	50 μg at −6 h, then 1×/day for 3 days	27/37	73	NS	7.3	<0.001
	50 μg 1×/day for 4 days	35/39	90	NS	7.2	<0.001

[a] Treatment was initiated i.p. immediately after infection except where pretreatment is indicated.

[b] Probability that difference between the virus-infected control groups and the virus-infected treatment groups was due to chance; NS, not significant.

that therapy with poly(I:C) altered the pathogenesis of the HVH infection. To define the effect of poly(I:C) therapy on pathogenesis, groups of animals were each inoculated intranasally with HVH type 2 and treated daily for 4 days with 50 μg of poly(I:C) i.p. beginning immediately after virus inoculation. At 24 h after each injection of poly(I:C), 10 animals from an untreated control group and 10 animals from a poly(I:C)-treated group were sacrificed. The animals were bled, organs were removed and homogenized, and all samples were assayed for HVH (Fig. 1). In untreated animals, virus was first detected in all tissues by 48 h after HVH inoculation but not in the blood until 72 h. It is probable that low levels of virus not detected by our assay system were present in the blood at the earlier time periods and resulted in seeding of the target organs. Titers of virus in the lung reached 10^5 to 10^6 PFU/g and in the liver and spleen 10^3 to 10^4 PFU/g throughout the remainder of the infection. Titers of HVH in brain tissue increased to greater than 10^6 PFU/g by 96 h. In animals treated with poly(I:C) there was a marked alteration in the course of the infection. Complete inhibition of viral replication in the lungs, liver, and spleen and prevention of a detectable viremia were observed through the 5-day course of infection. Viral replication in the CNS was inhibited until 96 h, a 2-day delay when compared with control animals. These data suggest that viral replication in the CNS, although delayed and/or suppressed, still occurred in spite of continued treatment.

DISCUSSION

Herpesvirus hominis infections of human newborn infants often result in disseminated, frequently fatal disease. Although these infections have received a high priority in the search for an effective means of treatment, a suitable chemotherapeutic agent for disseminated herpesvirus infections has not, as yet, been developed. Treatment of HVH infections of newborn infants and herpesvirus encephalitis in children and adults has been primarily with 5-iodo-2′-deoxyuridine and, more recently, cytosine arabinoside or adenine arabinoside. The effectiveness of these drugs, however, has not been proven in controlled clinical trials. There has been only one reported case of the use of an interferon inducer for the treatment of HVH infection in humans. Bellanti and co-workers (3) treated a 4-month-old infant suffering from herpesvirus encephalitis with poly(I:C). Although the patient appeared to improve clinically shortly after treatment, a therapeutic effect due to the poly(I:C) was not definitely established.

For these studies we chose newborn mice infected with HVH type 2 by the intranasal route as an experimental infection that simulates the disseminated infection of human neonates. Pathological and virological studies of tissues from infants that have died of herpesvirus infections have established that the organs most commonly involved were the brain, lungs, liver, spleen, kidneys, and adrenal glands (2, 8, 30, 31). After intranasal inoculation of newborn mice with HVH type 2, virus initially replicated in cells of the respiratory tract. A viremia followed, with subsequent seeding of liver, spleen, and brain. Virus was also transmitted to the CNS by neural pathways. This experimental infection in mice, therefore, appears to be quite similar to the disseminated infection of human neonates.

For an interferon inducer to be effective against a virus infection in humans, the particular virus must be sensitive to the action of interferon. Members of the herpesvirus group

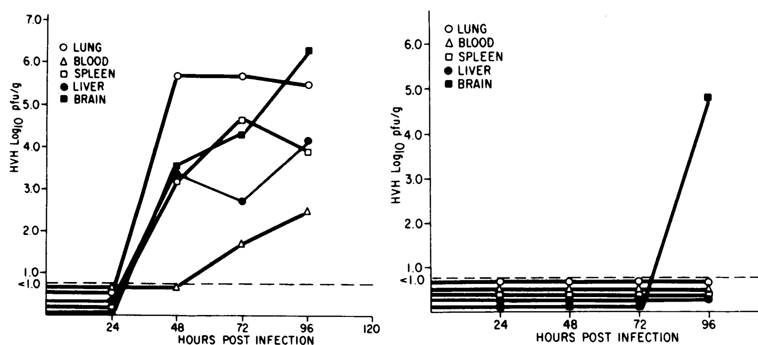

FIG. 1. *Effect of poly(I:C) (50 µg/day i.p. for 4 days) treatment on the pathogenesis of HVH type 2 infection in newborn mice. (Left) Untreated control group; (right) poly(I:C)-treated group.*

are generally regarded as relatively insensitive to the effects of interferon (5, 11, 13). The type 2 strains of HVH have been reported to be more sensitive than type 1 strains to poly(I:C) (24). In our assay system, type 2 strains were about twofold more sensitive than type 1 strains to both poly(I:C)-induced mouse serum interferon and Newcastle disease virus-induced L-cell interferon. Due to the fact that poly(I:C) did not induce detectable interferon or antiviral activity in the mouse embryo fibroblast cells used, we could not directly determine the sensitivity of the two antigenic types of HVH to the action of poly(I:C) in mouse cells. Our results indicate that although both strains of HVH are less sensitive than VSV or Sindbis virus to mouse interferon, there are similar levels of sensitivity with HVH as compared with EMC and vaccinia viruses. Previous reports (29) have indicated that either interferon or interferon inducer therapy is highly successful in EMC infections of mice if treatment is initiated within the first few days of viral infection. These data indicate that the level of sensitivity of a given virus to interferon in vitro may not be the only determinant of whether inferferon or interferon inducer therapy will be successful in the treatment of the same viral infection in vivo.

In the results reported here, poly(I:C) therapy did not reduce final mortality rates in newborn mice infected intranasally with HVH type 2. Treatment twice daily failed to improve results over those obtained with once daily injections. Even the initiation of poly(I:C) therapy 6 h before inoculation of virus did not reduce mortality rates. All treatment regimens, however, did result in a significant increase in the MST and in a marked alteration of the pathogenesis of the infection. Viremia and viral replication in the lungs, liver, and spleen of treated animals were completely inhibited throughout the course of infection. In contrast, replication of HVH in the CNS was suppressed for a period of only 2 days, after which time virus titers in the brain increased rapidly and the animals died. This transient suppression of viral replication in the brain appears to be directly correlated with the 1- to 2-day increase in the MST. These results indicate that the failure of poly(I:C) therapy to reduce mortality in newborn mice with disseminated HVH type 2 infection is due to the inability to completely control viral replication in the CNS.

Other workers have reported success in the treatment of herpesvirus infections in experimental animals with poly(I:C). Park and Baron (26) demonstrated that administration of poly(I:C) resulted in recovery from severe herpesvirus keratoconjunctivitis in rabbits, even when treatment was begun as late as 3 days after virus inoculation. Similar results have been reported by Hamilton and co-workers (15), who indicated that poly(I:C) therapy, initiated at either 2 or 24 h postinfection, was successful in both reducing mortality and prolonging the MST of adult mice infected i.p. with 60 LD_{50} of HVH. If treatment was initiated at 48 h after infection, no decrease in mortality was noted, but there was an increase in MST. Catalano and Baron (6) reported that pretreatment with poly(I:C) of HVH encephalitis in adult mice was effective in reducing mortality only with a low intracerebral challenge dose of virus (1 but not 10 or 100 mean tissue culture infective doses). A delay in time of death was noted in those animals that did not survive. Subsequent experiments (7) demonstrated that a complex of poly(I:C) and poly-D-lysine enhanced the levels of interferon induced in mice and afforded greater protection than poly(I:C) alone against herpesvirus encephalitis. This enhanced protection was still observed in mice inoculated subcutaneously with HVH even when treatment was begun as late as four days after viral infection at a time when some mice were showing early signs of CNS infection.

There are several possible explanations for the failure of poly(I:C) administration to successfully treat disseminated HVH type 2 infections in newborn mice. First, poly(I:C) may induce lower levels of interferon in newborns as compared with the levels in adult mice. Heineberg and co-workers (16) demonstrated that newborn mice had much lower levels of interferon in tissues during the course of a Coxsackie B1 infection than adult mice even though viral titers were higher. However, the fact that poly(I:C) induced 3,000 to 5,000 U of interferon in the serum, levels that are comparable to those present in the serum of adult mice given 100 μg of poly(I:C) i.p. (29), would indicate that this is not a feasible explanation in this model infection. Second, it is possible that hyporeactivity to the induction of interferon, either as a result of multiple injections of the inducer (4, 19, 28) or caused by the herpesvirus infection itself (25, 27), could have contributed to the failure of poly(I:C) to control the later stages of the infection. Although high levels of interferon were present in the serum on the first 2 days of poly(I:C) therapy, the titers on days 3 and 4 were much lower, indicating significant hyporeactivity associated with multiple doses of poly(I:C). Hyporeactivity to interferon induction was also demonstrated in the tissues on days 3 and 4 of the poly(I:C) therapy. The

possibility that the HVH infection itself resulted in hyporeactivity was not examined as part of these studies. Third, cells and tissues in newborn animals may be less sensitive to the antiviral effects of poly(I:C)-induced interferon than cells and tissues from adult mice. Morahan and Grossberg (22) demonstrated that young chicken embryos were less sensitive to the antiviral action of interferon than older chicken embryos. Although the possibility that newborn mice are less sensitive to the protective effects of poly(I:C) than adult mice was not directly examined as part of these studies, we have demonstrated that poly(I:C) therapy does significantly reduce mortality in adult mice inoculated either intravaginally or i.p. with HVH type 2 (unpublished observations). The fact that poly(I:C) treatment resulted in complete inhibition of viral replication in the lungs, liver, and spleen, however, would seem to indicate that at least these newborn mouse organs are responsive to the antiviral effects of poly(I:C). Fourth, poly(I:C) or the interferon induced by poly(I:C) may not have reached high enough concentrations in critical target organs (e.g., the CNS) to inhibit viral replication. Interferon could never be detected in brain tissue of poly(I:C)-treated newborn mice, despite peak serum levels of 3,000 to 5,000 U/ml. Cathala and Baron (9) have reported that peak interferon levels in brain tissue are 100-fold lower than peak serum levels after intravenous inoculation with poly(I:C) in rabbits. Allen and Cochran (1) have demonstrated that intracerebral treatment of vaccinia virus encephalitis of mice with poly(I:C) successfully reduces mortality and prolongs mean survival time, whereas i.p. treatment with poly(I:C) is ineffective. In summary, although factors such as a low level of sensitivity of HVH to interferon in vitro, hyporeactivity to the induction of interferon during the later stages of the infection, and a diminished sensitivity of newborn mouse tissue to interferon may contribute to the failure of poly(I:C) therapy in this model infection, a major factor appears to be inadequate concentrations of poly(I:C) or of poly(I:C)-induced interferon in CNS tissue.

Our results do not preclude the possibility that interferon inducers may have a beneficial effect in the treatment of herpesvirus infections of humans, particularly if the CNS is not involved. Since poly(I:C) treatment in newborn mice inhibited viral replication in the lungs, liver, and spleen but not in the CNS, the results do suggest, however, that poly(I:C) therapy may not be successful in viral infections that are transmitted to the CNS by neural routes. A critical determinant of effective interferon inducer therapy in herpesvirus infections of humans involving the CNS, therefore, will be the capacity of the inducer or of interferon to reach adequate levels in CNS tissue.

ACKNOWLEDGMENTS

This investigation was supported by Public Health Service contract no. NIH 70-2133 from the Antiviral Substances Program of the National Institute of Allergy and Infectious Diseases, and by Public Health Service grant no. AI-10217 from the National Institute of Allergy and Infectious Diseases.

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