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Prevention by Gamma Interferon of Fatal Infection with *Listeria monocytogenes* in Mice Treated with Cyclosporin A

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The significance of interferons (IFNs) induced by *Listeria monocytogenes* in the antilisterial defense mechanism was studied in mice. Cyclosporin A (CsA) had no effect on IFN-α production that was induced in the bloodstream after intravenous infection of mice with *L. monocytogenes*, whereas IFN-γ that was induced in the bloodstreams of control mice 6 h after stimulation with specific antigen in the late phase of infection was suppressed in CsA-treated mice, depending on the dose of the drug injected. The decrease in IFN-γ production caused an increase in bacterial growth in the spleens and livers of CsA-treated mice. Furthermore, administration of a daily dose of CsA at 80 or 100 mg/kg of body weight resulted in fatal listeriosis, even though the dose was nonlethal for normal mice. The administration of recombinant murine IFN-γ on day 0 of *L. monocytogenes* infection prevented CsA-treated mice from developing fatal listeriosis and restored their ability to produce IFN-γ in the bloodstream, in response to specific antigen in the late phase of infection.

Elimination of *Listeria monocytogenes*, a facultative intracellular pathogen, from the tissues of infected animals is performed by two steps involving T-cell-independent mechanisms in the early phase of infection and T-cell-dependent mechanisms in the late phase of infection (14–16, 23). Results of our studies (20, 22) have demonstrated that either alpha/beta interferon (IFN-α/β; this is referred to as IFN-α in this report) or IFN-γ is produced in the bloodstreams of mice during infection with *L. monocytogenes*, depending on the immunological status of the host. We reported that IFN-α produced in the early phase of infection might play a key role as a messenger to generate antigen-specific T cells involving IFN-γ production and acquired resistance to the infection. We also reported that IFN-γ production and elimination of the bacterium from the organs in the late phase of infection were suppressed when IFN-α produced in the early phase was neutralized by injection of anti-murine IFN-α/β antibody (20). On the other hand, IFN-γ produced in the late phase of infection might be essential for the generation of activated macrophages, which are responsible for the complete elimination of bacteria from the tissues. Buchmeier and Schreiber (5) have reported that inhibition of clearance of *L. monocytogenes* cells and a higher mortality rate were found in mice treated with monoclonal anti-murine IFN-γ antibody.

The administration of cyclosporin A (CsA) to animals results in the inhibition of many T-cell-dependent functions, such as allograft rejection (6), delayed-type hypersensitivity reactions (30), contact sensitization (25), and T-cell-dependent antibody production (13). An important effect of CsA is its ability to inhibit production of mRNA for cytokines, including IFN-γ, interleukin-1 (IL-1), IL-2, and IL-3 (7, 26). Although decreased resistance of CsA-treated mice to infection with *L. monocytogenes* has been reported (10, 27, 31), investigation of the mechanism of the effect of CsA on resistance to the bacterium has not been carried out from the standpoint of the regulation of cytokine production. In this report, we provide evidence that CsA suppresses production of IFN-γ but not of IFN-α in the bloodstream of *L. monocytogenes*-infected mice, in parallel with a decrease in acquired resistance to the infection, and that both IFN-γ production and acquired resistance can be restored in CsA-treated mice by the administration of recombinant murine IFN-γ (rMuIFN-γ) in vivo.

MATERIALS AND METHODS

Mice. Female mice (age, 5 to 7 weeks) of the ddY strain (obtained from the Shizuoka Agricultural Cooperative Association for Laboratory Animals, Hamamatsu, Shizuoka, Japan) were used in this study.

Bacteria and bacterial antigen. *L. monocytogenes* 1b1684 cells were prepared as described previously (21). The concentration of the washed cells was adjusted spectrophotometrically at 550 nm. Mice were infected intravenously with 0.2 ml of a solution containing 10^4 CFU of viable *L. monocytogenes* cells in 0.01 M phosphate-buffered saline (PBS; pH 7.4). *Listeria* cell wall fraction (LCWF) was prepared as described previously (17). Mice were injected intravenously with 50 μg of LCWF suspended in PBS on day 6 of infection with *L. monocytogenes*.

Treatment with CsA. CsA was donated by Sandoz AG (Basel, Switzerland). It was dissolved in pharmaceutical grade olive oil with sonication before use. Different doses of the drug in 0.1-ml quantities were injected intraperitoneally. This treatment was started 1 day before infection with *L. monocytogenes* and was continued for 3 days. Control mice were injected with drug-free olive oil.

rMuIFN-γ treatment. rMuIFN-γ was produced and purified by Genentech, Inc. (San Francisco, Calif.) (8). The IFN-γ preparation was donated by M. Moriyama, Torey Industries, Inc. (Tokyo, Japan). A stock solution of rMuIFN-γ (4.3×10^6 IU/ml) dissolved in 0.02 M Tris hydrochloride buffer (pH 7.5) containing 0.9% NaCl was diluted with PBS, and 4×10^6 IU/kg in 0.2 ml was injected intravenously.

Assay and characterization of IFN. The IFN samples were pooled sera obtained from at least four mice for each group of samples. The IFN assay was carried out by the dye-binding method (1) by using mouse L-929 cells and vesicular stomatitis virus (Indiana strain), as reported previously (18). Neutralization tests with monoclonal anti-mouse IFN-α antibody, monoclonal anti-mouse IFN-β antibody, and mono-

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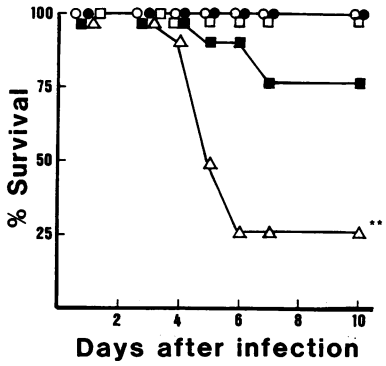

FIG. 1. Effect of CsA on antilisterial resistance in mice after intravenous inoculation of 10^4 CFU of *L. monocytogenes* cells. Mice received, intraperitoneally, 60 mg (□), 80 mg (■), or 100 mg (△) of CsA per kg per day from day −1 to day 1 of infection. The controls received olive oil only (●) or were untreated (○). **, $P < 0.01$.

clonal anti-mouse IFN-γ antibody were carried out as reported elsewhere (19). Monoclonal antibodies against murine IFN-α and IFN-β were donated by Y. Watanabe and Y. Kawade (Institute for Virus Research, Kyoto University, Kyoto, Japan). Monoclonal anti-murine IFN-γ antibody was produced by Genentech, Inc., and was donated by Torey Industries.

Determination of viable *L. monocytogenes* cells in the organs. The numbers of viable *L. monocytogenes* cells in the spleens and livers of the infected animals were established by plating serial 10-fold dilutions of organ homogenate in PBS on Trypticase soy agar (BBL Microbiology Systems, Cockeysville, Md.). Colonies were routinely counted 18 to 24 h later.

Statistical evaluation of the data. Data were expressed as means ± standard deviations, and the Wilcoxon rank sum test was used to determine the significance of the differences between control and experimental groups. The χ^2 test was used to determine the significance of differences in survival rate.

RESULTS

Effect of CsA on survival of mice infected with *L. monocytogenes*. Mice were infected intravenously with 10^4 CFU of *L. monocytogenes* cells, which was equivalent to a 0.05 50% lethal dose. These animals were also treated intraperitoneally with 60, 80, or 100 mg of CsA dissolved in olive oil per kg per mouse per day or with drug-free olive oil. The treatment was started the day before infection and continued for 3 successive days. The survival rate for each group is shown in Fig. 1. Administration of drug-free olive oil or 60 mg of CsA per kg per mouse caused no deaths from infection. In contrast, some of the mice treated with 80 mg of the drug per kg per day died, and the survival rate for the animals injected with 100 mg/kg per day was markedly lower. In all cases, death occurred during the late stage of *L. monocytogenes* infection.

Effect of CsA on IFN-α production in the bloodstream and bacterial growth in the organs of mice in the early stage of *L. monocytogenes* infection. IFN production in the serum and the number of *L. monocytogenes* cells in the spleens and livers were determined on day 2 of the infection (Table 1). No significant effect of CsA treatment on the number of bacterial cells in the spleens and livers was observed. Likewise, the IFN titers in the bloodstreams of CsA-treated mice were comparable to the antiviral activities in the untreated animals. In our previous report (20), the antigenic type of IFN in the sera obtained from mice in the early stage of *L. monocytogenes* infection was expressed as the α/β type. In this study the antiviral substance was identified as IFN-α by using monoclonal antibodies against murine IFN-α and murine IFN-β (Table 2).

Effect of CsA on IFN-γ production in the bloodstream and bacterial growth in the organs of mice in the late stage of *L. monocytogenes* infection. The number of *L. monocytogenes* cells in the spleens and livers was determined on day 5 of infection, when antigen-specific elimination of bacteria had progressed. The efficiency of the elimination of bacteria from the organs decreased in CsA-treated mice with an increase in the dose of the drug (Fig. 2). In parallel, IFN production induced by specific antigen in these animals was determined. LCWF (50 μg) was injected intravenously into mice on day 6 of infection, and IFN activity in the blood of the mice was determined 6 h later. The antiviral substance produced under these conditions was IFN-γ, because the antiviral activity was neutralized by monoclonal anti-murine IFN-γ antibody, but not by monoclonal anti-murine IFN-α or anti-murine IFN-β antibody (Table 2). IFN production was partially inhibited in mice treated with 60 mg of CsA per kg per day and was completely suppressed in mice administered higher doses of CsA (Fig. 2).

Restoration of antilisterial resistance of CsA-treated mice by injection of rMuIFN-γ. The decrease in antilisterial resistance of CsA-treated mice to *L. monocytogenes* infection was presumed to be caused by suppression of IFN-γ production (Fig. 2). Therefore, we investigated whether injection of IFN-γ exogenously would be effective in restoring the acquired resistance in these animals. Mice were given a single intravenous injection of rMuIFN-γ (4×10^6 IU/kg) on day 0 or 2 of infection, and we determined how long the rMuIFN-γ could be detected in their serum. The antiviral activity of rMuIFN-γ in the serum was 120 to 840 IU/ml at 3 h and <20 IU/ml at 6 h, and no difference in IFN-γ titers was observed among the groups of mice. The survival rate for each group is shown in Fig. 3. In spite of the CsA treatment, all mice survived when rMuIFN-γ was administered on day 0 of infection. In contrast, mice which were injected with rMuIFN-γ on day 2 of infection died at approximately the same rate as did the animals treated with CsA only. The number of bacteria in the spleens and livers on day 5 of infection and IFN-γ production induced by specific antigen

TABLE 1. Effect of CsA on IFN-α production and elimination of bacteria from the organs of mice in the early phase of *L. monocytogenes* infection

Treatment[a]	Log bacteria/organ in[b]:	
	Spleen	Liver
None	5.80 ± 0.37	4.54 ± 0.42
Olive oil	6.11 ± 0.46	5.06 ± 0.50
CsA (80 mg/kg)	6.20 ± 0.25	5.01 ± 0.28
CsA (100 mg/kg)	6.46 ± 0.24	4.73 ± 0.50

[a] Mice were injected intraperitoneally with CsA dissolved in olive oil or with drug-free olive oil from day −1 to day 1 of *L. monocytogenes* infection.

[b] Mice were infected intravenously with 10^4 CFU of *L. monocytogenes* cells, and the number of viable bacteria was determined on day 2. Serum was collected 48 h after *L. monocytogenes* infection, and IFN activity was determined. The IFN titer was determined to be 32 IU/ml in mice in all treatment groups.

TABLE 2. Antigenicity of IFNs produced in the bloodstream of mice during *L. monocytogenes* infection

Preparation	Stimulated with:	IFN titer (IU/ml) after treatment with[a]:				
		Not treated	Anti-IFN-α	Anti-IFN-β	Anti-IFN-α/β	Anti-IFN-γ
Mouse serum on day 2 of infection[b]	Nothing	128	<8	128	<8	128
Mouse serum on day 6 of infection[c]	LCWF	128	128	128	128	<8
Partially purified natural murine IFN-α/β		320	80	160	<20	320
Recombinant murine IFN-β		128	128	<8	<8	128
Recombinant murine IFN-γ		64	64	64	64	<4

[a] The neutralization test was carried out as described in the text.
[b] Mice were infected intravenously with 10^4 CFU of *L. monocytogenes* cells, and serum was collected 48 h later.
[c] Mice received 50 μg of LCWF intravenously, and serum was collected 6 h later.

in the serum of each group are shown in Fig. 4. Parallel to the survival rate, antigen-specific elimination of bacteria from the organs was significantly increased in CsA-treated mice that were injected with rMuIFN-γ on day 0 of infection, compared with the animals treated with CsA only. Furthermore, IFN-γ production in mice treated with both CsA and rMuIFN-γ (on day 0) was comparable to that in the drug-free animals, although treatment with CsA only caused marked suppression of IFN-γ production. In contrast, neither elimination of bacteria from the organs nor IFN-γ production was restored in CsA-treated mice that were given rMuIFN-γ on day 2 of infection. On the other hand, among the groups of mice receiving no drug, administration of rMuIFN-γ on either day 0 or 2 of infection did not affect either elimination of bacteria from the organs or IFN-γ production in the serum.

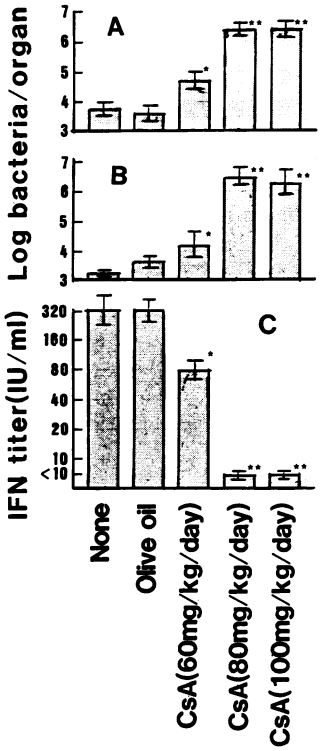

FIG. 2. Effect of CsA on growth of *L. monocytogenes* in the organs and IFN-γ production induced by specific antigen in the bloodstreams of mice in the late phase of infection. Mice were infected intravenously with 10^4 CFU of *L. monocytogenes* cells and treated with the indicated doses of CsA from day −1 to day 1 of infection. The number of *L. monocytogenes* cells in the spleens (A) and livers (B) was determined on day 5 of infection. LCWF (50 μg) was injected intravenously into mice on day 6 of infection, and IFN-γ titers of the sera collected 6 h later were determined (C). *, $P < 0.05$; **, $P < 0.01$.

DISCUSSION

We demonstrated that CsA treatment causes suppression of IFN-γ production induced by specific antigen, in parallel with the acceleration of listeriosis, and that administration of rMuIFN-γ is effective in preventing the development of severe infection with *L. monocytogenes* in mice treated with CsA. The effects of exogenous rMuIFN-γ on antilisterial resistance might be due to both activation of macrophages and restoration of endogenous IFN-γ production, which were suppressed by CsA treatment.

Endogenous production of IFN-γ without stimulation by specific antigen during *L. monocytogenes* infection is not detectable by bioassay or enzyme-linked immunosorbent assay (5, 30). However, endogenous IFN-γ production may occur at a lower level and it might play an important role in the defense against *L. monocytogenes* infection. Buchmeier and Schreiber (5) have reported that *L. monocytogenes*-infected mice injected with monoclonal anti-murine IFN-γ antibody incurred a severe infection and that some of the animals died regardless of whether they were given less than the lethal dose of bacteria. Therefore, the decreased resistance against the bacterium may be due to a defect in endogenous IFN-γ. In fact, results of the present study indicate that suppression of the elimination of bacteria from

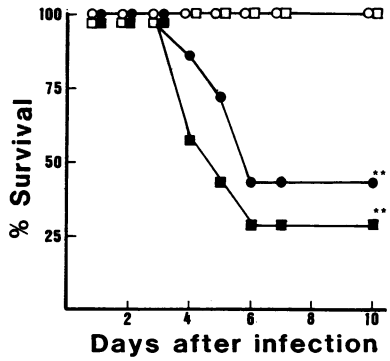

FIG. 3. Restoration of antilisterial resistance in CsA-treated mice by administration of recombinant murine IFN-γ. Mice were infected intravenously with 10^4 CFU of *L. monocytogenes* cells. They received, intraperitoneally, 100 mg of CsA per kg per day from day −1 to day 1 of infection. Some of these animals were injected intravenously with 4×10^6 IU of recombinant murine IFN-γ per kg on day 0 (□) or day 2 (■) of infection. The control groups treated with CsA only (●) or with neither CsA nor IFN-γ (○) are also shown. **, $P < 0.01$.

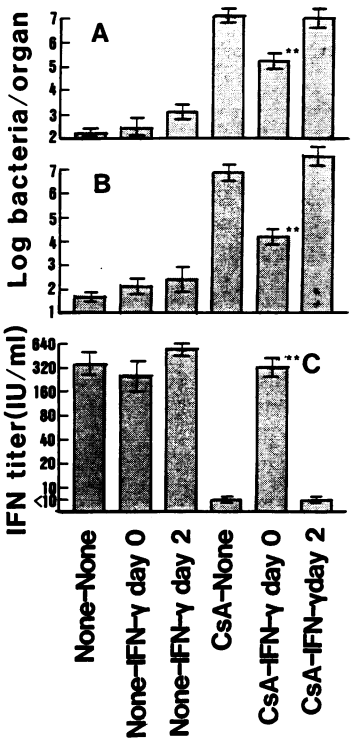

FIG. 4. Restoration of the ability to eliminate *L. monocytogenes* from the organs and of IFN-γ production induced by specific antigen in the bloodstreams of mice in the late phase of infection by administration of recombinant murine IFN-γ. Mice were infected intravenously with 10^4 CFU of *L. monocytogenes* cells and were treated with CsA (100 mg/kg per day) from day −1 to day 1 of infection. Some of these animals were injected intravenously with 4×10^6 IU of recombinant murine IFN-γ per kg on day 0 or 2 of infection. The number of *L. monocytogenes* cells in the spleens (A) and livers (B) was determined on day 5 of infection. LCWF (50 μg) was injected intravenously into mice on day 6 of infection, and IFN-γ titers of the sera collected 6 h later were determined (C). **, $P < 0.01$.

the organs and the decrease in survival rate of *L. monocytogenes*-infected mice coincided with the inhibition of IFN-γ production induced by specific antigen in the bloodstream, depending on the dose of CsA (Fig. 1 and 2). Although CsA inhibits not only IFN-γ production but also that of other cytokines, including IL-1, IL-2, and IL-3 (7, 26), the defect in IFN-γ production is presumed to result in the suppression of antilisterial resistance in the drug-treated mice, because activated macrophages are thought to be the major effector cells participating in acquired resistance to *L. monocytogenes* infection (16), and it is well known that IFN-γ acts as a macrophage-activating factor (29). Based on this consideration, we administered rMuIFN-γ exogenously to CsA-treated mice, to demonstrate the significance of IFN-γ in the antilisterial defense mechanism. It was observed that the in vivo effect of rMuIFN-γ on antilisterial resistance is dependent on the dose administered. Kiderlen et al. (12) have reported that injection of a high dose (10^6 U) of rMuIFN-γ resulted in a decrease in *L. monocytogenes* cells in spleens of normal mice on day 2 of infection. In contrast, Van Dissel et al. (32) have found that a lower dose (10^5 U) of rMuIFN-γ fails to affect antilisterial resistance in vivo. In fact, our data also indicated that 8×10^4 U of rMuIFN-γ per mouse was ineffective against antilisterial resistance in mice without CsA treatment (Fig. 4). However, we were able to demonstrate that the same dose of rMuIFN-γ was able to rescue CsA-treated mice from fatal listeriosis (Fig. 3). Hence, it is likely that mice in which endogenous IFN-γ is normally produced may be irresponsive to IFN-γ that is exogenously injected except when excess IFN-γ is administered. On the other hand, exogenous IFN-γ might induce restoration of antilisterial resistance in endogenous IFN-γ-deficient animals such as CsA-treated mice.

Administration of rMuIFN-γ affected the antigen-specific defense in the late phase of infection (Fig. 4). Restoration of antilisterial resistance in CsA-treated mice was observed when rMuIFN-γ was injected on day 0 but not on day 2 of infection, suggesting that rMuIFN-γ might act in the early phase of infection. After *L. monocytogenes* cells are injected, they are ingested and processed by Ia-bearing macrophages, and the processed antigens are presented by macrophages to T cells that share the same Ia haplotype (33); then, antigen-specific helper T cells proliferate and secrete lymphokines, including IFN-γ (9, 11), which activate macrophages to kill the bacteria more efficiently (15). It is well known that IFN-γ can induce macrophage Ia expression in vitro (4) and in vivo (28). Alternatively, CsA has been reported to inhibit macrophage-mediated antigen presentation (24) and their Ia expression (2). Based on these observations, a possible effect of rMuIFN-γ is the generation and maintenance of Ia-bearing macrophages. Furthermore, we found that IFN-γ production induced by specific antigen is also restored by injection of rMuIFN-γ into CsA-treated mice (Fig. 4). IFN-γ production is responsible for T cells in *L. monocytogenes*-immune mice in vitro (9, 11) and in vivo (20). Hence, it is possible that functions of T cells and macrophages in CsA-treated mice could be restored by the administration of rMuIFN-γ, although the possibility that IFN-γ is produced by a T-cell-independent mechanism (3) cannot be eliminated. Attempts are now being made to investigate in detail the mechanism(s) for restoration of antilisterial resistance and IFN-γ production in CsA-treated mice by the administration of rMuIFN-γ.

Finally, in other studies, administration of rMuIFN-γ rescued pregnant mice, in which the IFN system is defective (22), and CsA-treated mice from fatal listeriosis (unpublished data). The results presented here suggest that IFN-γ is very effective in preventing severe infections in immunocompromised hosts which show defective production of cytokines, including IFN-γ.

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