Interferon and Interferon Inducers
in Protozoal Infections

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ABSTRACT Several interferon inducers (Newcastle disease virus, statolon, and poly rI:poly rC) as well as exogenous mouse interferon protect mice from sporozoite-induced *Plasmodium berghei* malaria, as long as they are administered before the end of the preerythrocytic phase of development of the parasite. The protective effect of the interferon inducers was related to their interferon-inducing effect; the protective effect of the interferon preparations was related to the interferon titer of the preparations, and it exhibited other attributes of interferon such as species specificity. In contrast to sporozoite-induced infection, blood forms-induced *P. berghei* malaria was only weakly susceptible to the protective effect of interferon inducers. This difference may provide an approach to study the mechanism of protection. The growth in cell cultures of another intracellular protozoon, *Toxoplasma gondii*, is also inhibited by interferon (22). The fact that *P. berghei* and *T. gondii* (as well as another group of intracellular parasites susceptible to interferon, the *Chlamydia*) have their own ribosomes raises questions, concerning the role of host cell ribosomes in the host cell-parasite relationship of these intracellular parasites and in the mechanism of interferon action against them, that can be approached experimentally. The possibility of therapeutic or prophylactic application of interferon or of its inducers to certain protozoal diseases of man and of other animals is still remote, but it has to be considered for long range planning.

The activity of interferon was initially thought to be limited to viral infections (14). Interference phenomena between viruses and Protozoa (31), between *Chlamydia* and Protozoa (8), and between *Eperythrozoon* and Protozoa (18, 19, 29) have been reported, but the possibility that they could have been caused by interferons was not considered. Indeed, it may be significant that the first instance in which interferon was found to be effective against an agent other than a virus occurred with an organism that was at the time believed to be a virus. In 1963, Sueltenfuss and Pollard (27) reported that psittacosis “virus” was susceptible to interferon. Just about that time, a consensus was forming among microbiologists that organisms of the psittacosis-lymphogranuloma...
venereum-trachoma group had many properties that set them aside from viruses, notably in their mode of reproduction, and that they should be included into a different genus, the *Chlamydia* (16). This made the behavior of the agent of psittacosis anomalous with respect to its susceptibility to interferon and, soon, it was found that other chlamydiae such as the agents of trachoma and of inclusion conjunctivities were also susceptible to interferon (4, 12, 15, 21).

By that time, it had also been found that several agents other than viruses, such as rickettsiae (6, 13), certain bacteria (5, 26), and some protozoa (1, 7, 24) were capable of inducing interferon, thus raising the question of the possible role of interferon in the natural history of diseases caused by these agents. These two sets of findings led to independent studies of the effects of interferons and interferon inducers on other nonviral infections. Two intracellular protozoal infections, due respectively to *Toxoplasma gondii* (22) and *Plasmodium berghei*, were found to be susceptible to interferon. Several protozoal infections (11, 25) and bacterial infections (20, 30) were affected by interferon inducers. Thus, the spectrum of action of interferons as well as that of interferon inducers appear to be broader than was formerly thought.

I shall first describe the main features of the effects of interferon and interferon inducers on *P. berghei* malaria in mice and then discuss the implications of these findings and of studies from other laboratories on the mechanism of action of interferon inducers and interferon against protozoa and on potential prophylactic and therapeutic applications.

**EFFECTS OF INTERFERON INDUCERS AND OF INTERFERON ON P. BERGHEI MALARIA IN MICE**

The system has been described in detail elsewhere (10), and only its main features will be outlined. *P. berghei* can be maintained cyclically in the laboratory (32) so that infection of mice can be initiated either with sporozoites or with blood forms. Following sporozoite inoculation, the preerythrocytic development takes place in the liver in hepatocytes (32). This phase of development is completed from 42 to 48 hr after inoculation (28, 32) when tissue merozoites are released from infected hepatocytes. Following their release from hepatocytes, the merozoites enter red blood cells (RBC), and the erythrocytic cycles start. Detectable parasitemia (patent infection) usually develops between 4 and 6 days after sporozoite inoculation (28). Mice with detectable parasitemia almost invariably die of the infection, death occurring

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3. Herman, R., and S. Baron. 1969. The effects of interferon inducers upon the intracellular growth of the protozoan parasite *Leishmania donovani*. Personal communication.
within a range of 7–35 days after inoculation (28). The studies on the effects on interferon inducers and interferon, performed with this system in my laboratory, were done in collaboration with Doctors Jan Vilček, Ruth Nussenzweig, and Jerome Vanderberg, and Mr. Steve Levine, a medical student. All experiments were performed with 4-wk-old female CF1 mice (Carworth Farms, New City, N.Y.), each weighing 12–15 g. The interferon inducers were Newcastle disease virus (NDV), statolon (S), and the double-stranded complex of polyriboinosinic and polyribocytidylic acids (poly rI:poly C). To produce mouse serum interferon, mice were injected with NDV and bled 6–8 hr later; the serum was dialyzed for 5 days against a pH 2 buffer. Interferon levels were measured with a plaque reduction technique, using vesicular stomatitis virus and mouse L-cell cultures (10). The titer of interferon was expressed as the reciprocal of the highest dilution of the interferon preparation that caused at least 50% inhibition of the control plaque count.

**Sporozoite-Induced Infection**

The time in relation to sporozoite inoculation when interferon or interferon inducers were given was critical (9). The maximum protective effect (Fig. 1) occurred when interferon inducers were given about 20 hr after sporozoite inoculation. The protective effect (measured by the survival rate, an index of strong protection) decreased markedly when interferon inducers were given later than 36 hr after inoculation. The protective effect of mouse serum interferon was significant when it was given during the first 24 hr after inoculation or just before it; the protective effect (measured by the survival rate) decreased when interferon was given later than 36 hr after inoculation. When the mean number of parasitized RBC on the 6th day after inoculation (an index which records moderate protection) was used, the protective effect of interferon inducers and of interferon was found to decrease markedly when they were given later than 42–48 hr after inoculation.

The most likely explanation for these findings is that the parasite is either more susceptible or more accessible to the effect of interferon and its inducers during its intrahepatic, preerythrocytic phase of development than during its erythrocytic phase. A less likely alternative is that interferon or its inducers interfere (possibly through a stimulation of the reticuloendothelial system) with the release of the parasite from the liver cell and the subsequent invasion of erythrocytes.

**Role of Interferon in Protection Against Sporozoite-Induced Infection**

Evidence suggesting that interferon is the agent in the interferon-containing serum which is responsible for protection includes the following: (a) the relation of the protective effect of the serum to its interferon titer (Table I); (b) the demonstration that a similarly prepared rabbit serum interferon of
interferon and interferon inducers

Figure 1. Antimalarial effect of interferon inducers and of interferon at different stages of development of P. berghei. Inoculation of 5000 sporozoites was performed intravenously at zero time. A single injection of NDV (10⁹ p.f.u.), statolon (8 mg), poly rI-poly rC (100 μg; indicated as poly I-poly C), or exogenous mouse serum interferon (about 4000 U) was given to each mouse. The control range refers to the mortality in mice inoculated with sporozoites and injected with diluent or with normal mouse serum. The stage of development reached by the parasite at various times after inoculation is shown at the top of the figure.

comparable titer in rabbit cells is without protective effect against infection of the mouse; (c) the demonstration that an interferon induced in mouse L-cell cultures by poly rI-poly rC has a protective effect of the same magnitude as that of a NDV-induced mouse serum interferon of comparable titer; and (d) the resistance of the protective agent to prolonged pH 2 dialysis. These findings suggest strongly that interferon is the agent in mouse serum that protected mice against P. berghei malaria, but this point will not be completely established until this effect is demonstrated with purified preparations of interferon. Such studies are now in progress.

Evidence suggesting that interferon plays a role in the protection granted by interferon inducers includes (10): (a) the fact that three different inducers (NDV, S, and poly rI-poly rC) protect mice; (b) the fact that sensitivity to the protective effect of exogenous mouse serum interferon and to that of interferon inducers decreases at about the same time² (10); (c) demonstration
TABLE I
PROTECTION AGAINST SPOROZOITE-INDUCED *PLASMODIUM BERGHEI*
MALARIA WITH EXOGENOUS INTERFERON

| Number of interferon units injected per mouse | Interferon-injected group | Control group | Δapp* (days) | Interferon-injected group | Control group |
|---------------------------------------------|---------------------------|---------------|-------------|---------------------------|---------------|
| 10 \times 10^8                              | 5/8                       | 8/8           | +1.5‡       | 14                        | 348           |
| 7 \times 10^8                               | 3/8                       | 8/8           | +1.1‡       | 9                         | 166           |
| 2 \times 10^8                               | 6/8                       | 7/8           | +1.0‡       | 45                        | 485           |
| 9 \times 10^2                               | 8/8                       | 8/8           | +0.6        | 156                       | 348           |
| 6 \times 10^2                               | 10/10                     | 8/10          | −0.1        | 90                        | 97            |

Results of four experiments from Jahiel, Víšek, and Nussenzweig.1 Mice were injected with 5000 sporozoites intravenously. 20-28 hr later, groups of mice were injected with interferon-containing mouse serum or with normal mouse serum (control groups).

* Δapp, mean prepatent period of interferon-injected group minus mean prepatent period of control group.
‡ P < 0.01 with the t test.

that procedures which decreased the interferon-inducing effect of statolon (such as heating) or of NDV (centrifugation at 100,000 g) also decreased their protective effect and that there was a constant relationship in various experimental conditions between the last dilution of statolon or of NDV which could induce interferon and the last dilution of these agents which had a protective effect (Table II) (10).

While this evidence suggests that at least part of the protection granted by interferon inducers is mediated through interferons, it does not preclude the possibility that additional mechanisms of protection may also be involved.

**Blood Forms-Induced Infection**

Inoculation of mice with infected RBC bypasses the preerythrocytic phase of the infection, and the erythrocytic cycles start right away. Various results have been obtained in different laboratories using different experimental conditions. We have shown (9, 10) that treatment of mice with interferon inducers before or after inoculation with blood forms causes a slight but significant delay in occurrence of detectable parasitemia and a decrease in the number of infected RBC on the 6th day after inoculation. (Table III). We have not yet performed studies of blood forms-induced infections in mice treated with exogenous interferon. Schultz, Huang, and Gordon (25) exposed *P. berghei*-infected RBC to normal serum or to interferon-containing serum for periods of several hours in vitro and found that the cells exposed to interferon were no longer able to infect mice. However purified interferon was not used, and it is possible that the observed effect was due to another constituent of the serum. Geiman and Merigan (T. C. Merigan, personal
### TABLE II

**SPOROZOITE-INDUCED PLASMODIUM BERGHEI MALARIA: PROTECTIVE EFFECT AND SERUM INTERFERON-INDUCING EFFECT OF NDV AND STATOLON**

| Amount injected | % dead | \( P \) | Range of serum IF* titers |
|-----------------|--------|---------|--------------------------|
| **NDV**         |        |         |                          |
| None§           | 77.5   | <40     |                          |
| 2.0 \times 10^4 - 2.2 \times 10^4 | 80.0 | <40 |
| 9.0 \times 10^4 - 2.2 \times 10^6 | 77.5|| <40 |
| 9.0 \times 10^4 - 2.2 \times 10^6 | 43.3 | <0.01 | <40 |
| 5.6 \times 10^4 - 2.2 \times 10^6 | 21.7 | <0.001 | <40-40 |
| 1.0 \times 10^8 - 1.0 \times 10^9 | 10.0 | <0.001 | 320-10,240 |
| **Statolon**    |        |         |                          |
| None¶          | 93.3   | <40     |                          |
| 0.08           | 80.0** | <40     |                          |
| 0.8            | 35.0   | <0.01   | 80                       |
| 15.0           | <0.001 | 160-320 |                          |

Abstracted from Tables 7 and 8, Jahiel, Nussenzweig, Vilcek, and Vanderberg (10). Mice were inoculated with 5000 sporozoites intravenously, and they were injected 20 hr later with NDV-infected allantoic fluid or with statolon, diluted in physiological saline, or in 1% sodium bicarbonate, respectively. All mice which died had previously developed parasitemia, and none of the mice which developed parasitemia survived. \( P \) was determined with the chi square test. The serum interferon titer was measured in blood samples withdrawn 6 hr after injection of NDV or 16 hr after injection of statolon, since it had been shown (see Table 6 in reference 10) that these were the times for peak interferon titers after injection of NDV or statolon, respectively.

* IF, interferon.

† p.f.u., plaque-forming units.

‡ Injected with normal allantoic fluid or with physiological saline.

§ Prepatent period not significantly prolonged.

¶ Injected with 1% sodium bicarbonate.

** Significant prolongation of mean prepatent period; excess of mean prepatent period over that of the control group was 1.8 days (\( P, 0.001 \) with the \( t \) test).

communication), working with infected RBC in vitro, found no difference in the increase in number of malarial parasites in the presence or absence of interferon. In this system, however, multiplication of the parasite occurs only for a period of several hours at a relatively slow rate, i.e., it is not clear to what extent the multiplication of the parasite in this system can be equated to its multiplication in vivo.

Thus, there is no substantial evidence that interferon has any protective effect against a blood forms-induced infection or any inhibitory effect on the development of the parasite in red blood cells. The slight protective effect observed with interferon inducers could very well be mediated by something other than interferon. On the other hand, the possibility that interferon exerts
TABLE I

| Exp. No. | Material Injected* | Mean Prepatent Period in Days† | Mean No. of Parasitized RBC on Day § |
|----------|-------------------|-------------------------------|-----------------------------------|
| 1        | NAF               | 4.2                           | 155.0                             |
|          | NDV               | 5.0 <0.1                      | 70.0 <0.05                        |
|          | Statolon          | 5.2 <0.05                     | 116.5 <0.1                        |
| 2        | None              | 5.2                           | 41.0                              |
|          | NDV               | 5.7 <0.1                      | 4.3 <0.001                        |
|          | Statolon          | 6.0 <0.05                     | 17.5 <0.01                        |

Results from Jahiel, Nussenzweig, Vilcek, and Vanderberg (10). Mice were inoculated intravenously with 1000 P. berghei infected RBC. The number of mice per group was 10. All mice in each group developed detectable parasitemia and died.

* The injections were made 17-18 hr after inoculation. NAF, normal allantoic fluid.
† ppp, mean prepatent period; P, significance with the t test.
‡ x, mean number of parasitized RBC; P, significance with the t test.

A slight protective effect against blood forms-induced infection has not been ruled out either.

EFFECTS OF INTERFERON AND INTERFERON INDUCERS ON OTHER PROTOZOAL INFECTIONS

Remington and Merigan showed in 1968 (22) that interferon inhibits the cytopathic effect and formation of plaques in mouse and chick cell systems. Inhibition was species-specific; the activity of the preparations was retained after pH 2 dialysis but lost after heating at 80°C or treatment with trypsin. Several purified preparations were tested for their antitoxoplasmic and antiviral effect, and there was consistently a direct relation between the activities of the preparations in the viral assay and that in the toxoplasma assay.

The effect of interferon inducers on Leishmania donovani infection in mice has been studied by Actor et al.2 and by Herman and Baron.3 The parasitic load of various cells in liver and spleen was measured. The results were extremely complex.3 This suggested that several mechanisms may have been acting at different times and in different organs. Furthermore when there was a protective effect, there was no correlation with the interferon titer of the serum. Thus, as the authors pointed out,3 there is at present no evidence that interferon is active against L. donovani. Cell culture studies with L. donovani also failed to yield such evidence.3

POSSIBLE MECHANISMS

In view of the lack of direct experimental data bearing on the mechanism in experiments with protozoa, the still rather uncertain status of proposed
mechanisms for the antiviral action of interferon (2), and the risk inherent in applying to protozoal infections concepts based on studies done with viral infection, this section must necessarily be highly speculative. Its function is not to promote hypothetical mechanisms but merely to suggest some experimental approaches with protozoa.

The hypotheses about interferon action against viruses have had to take into account the fact that the translation of viral information takes place on host cell ribosomes. With regard to intracellular protozoal infections, this is not the case at first sight since both T. gondii and P. berghei (3) have their own ribosomes. However, the participation of host cell ribosomes in these systems is not excluded and could take place in the following two ways: either through permeability of the protozoal cell membrane to the protozoal messenger RNA and to protozoal proteins synthesized on the host cell ribosomes, or through pinocytosis or phagocytosis of host cell ribosomes by the protozoa with continued function of these ribosomes inside the protozoal cell. Pinocytosis of host cell material by some plasmodia has been demonstrated (23). Investigation of these possibilities with tracer experiments and electron microscopic studies, respectively, in the systems in which interferon has been shown to inhibit protozoal infections seems warranted.

The present emphasis on interference with translation and on ribosomal modifications in current interferon research should not deter investigations of possible other targets of action of interferon or interferon inducers, such as cell membrane, lysosomes, or mitochondrias.

Finally, the well-known stimulating effect of several interferon inducers, such as endotoxin on the reticuloendothelial system, should be kept in mind as another possible major mechanism of action of interferon inducers on protozoa in vivo. Indeed, other stimulants of the RE system, not presently known to stimulate interferon formation, such as Corynebacterium parvum (17), have a protective effect against sporozoite-induced malaria.

POSSIBLE APPLICATIONS

It is of course premature to consider applications of either interferon inducers or interferon to human or animal protozoal diseases; the toxicity of interferon inducers and the development of less toxic derivatives of the inducers requires continued investigation. Hyporeactivity and cross-hyporeactivity to the antiprotozoal effects of interferon inducers must be better defined. The mass production of human interferon appears to be feasible, but it must still be developed. The effects of interferon and of its inducers in protozoal infections require further study. So far, the only species in which antiprotozoal effects

4 Levine, S., and R. Jahiel. Antimalarial effect of poly I:poly C in the mouse. Manuscript in preparation.
of interferon inducers and of interferon have been demonstrated in vivo is the mouse.

Nevertheless, since a protective effect has been demonstrated in some systems, the potential applications of interferon and interferon inducers to human and animal protozoal diseases must be discussed. The potential applications fall into the following four classes.

(a) Prophylactic and therapeutic use in human protozoal infections, such as toxoplasmosis or malaria. There are several drugs which are effective against these infections; however, problems of toxicity and of development of resistance warrant studies of new therapeutic or prophylactic agents. The effectiveness of interferon or interferon inducers against toxoplasmosis should be studied in an in vivo system, for instance in the mouse. Next, controlled studies of the effect of interferon in humans with congenital toxoplasmosis or in immunologically deficient individuals with toxoplasmosis, designed to compare the effectiveness of human interferon to that of current therapeutic agents, would be in order. Since the protective effect against experimental malaria was most marked when interferon or its inducers were given during the preerythrocytic phase of the disease, the most promising approach to human malaria would be the use of interferon or its inducers as prophylactic agents. This would hinge upon the feasibility of devising a regimen for the administration of interferon or of interferon inducers that would be practical and effective and that would avoid the development of hyporeactivity and of chronic toxicity.

(b) Use in conjunction with another type of therapeutic or prophylactic agent. The low protective activity of interferon inducers when they are administered during the erythrocytic phase of P. berghei malaria should not deter investigators from studying the effect of administering interferon or interferon inducers together with other prophylactic or therapeutic antimalarial agents in order to detect synergistic combinations.

(c) Use in treatment of mammals and birds who are hosts for protozoa causing human diseases.

(d) Use in prophylaxis or treatment of protozoal infections of veterinary importance. The first step in these studies may be to survey the known intracellular protozoal infections of mammals and birds for their sensitivity to interferon or its inducers.

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