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Interferon Crosses Blood-Cerebrospinal Fluid Barrier in Monkeys[1] (38790)

D. V. HABIF, RITA LIPTON, AND K. CANTELL

Department of Surgery, Columbia University, New York, N.Y. 10032; and Department of Virology, Central Public Health Laboratory, Helsinki 28, Finland

The methodology for the production and purification of human leukocyte interferon has been developed during the past 10 yr (1) and sufficient amounts are now available for small-scale clinical trials against viral infections and malignancies (2–5). Many severe diseases of the central nervous system (CNS) would seem to lend themselves to interferon trials, but little information is available about the pharmacokinetics of interferon in CNS. It appears from experiments in animals (6) and man (5) that there is a considerable barrier to the penetration of interferon from the blood into CSF and the brain. Since the interferon detected in CNS in the animal experiments with interferon inducers could have been formed locally it is not clear how much interferon actually passed from the blood to CSF and the brain. Recently, Ho *et al.* (7) reported that exogenous interferon injected in the CSF space of rabbits disappeared from CSF with a longer half-life than the corresponding one in the bloodstream. We now present data about the penetration of human leukocyte interferon from the circulation of monkeys into CSF and *vice versa*. We used similar preparations of potent human leukocyte interferon to those employed in current clinical trials (2–5). The monkey seemed a suitable experimental animal for these studies, because there is a complete crossreaction between human and monkey interferons (8).

Materials and Methods. The concentrated interferon (C-IF) and the partially purified interferon (P-IF) were prepared in human leukocyte suspensions as described previously (1, 9). The C-IF preparation contained 1.2 million reference units per ml and had a specific activity of 2×10^4 units/mg protein. The P-IF preparation contained 13 million units per ml and its specific activity was 7×10^5 units/mg protein.

The weight of the stump-tailed monkeys (Macaca arctoides) ranged between 4.25 and 12.5 kg. They received periodically 1–2 mg/kg Sernylan (Phencyclidine HCl 20 mg/ml) intramuscularly (im) to maintain desired state of sedation during the experiments. Five per cent dextrose in 0.5 strength saline was infused intravenously (iv) at a rate of about 0.5 ml/min throughout the experiment. The iv injections were given into a forearm vein, and the im injections into the thigh. The cisterna magna was tapped with a 2.5 in., 22 gauge needle to give injections into the CSF space or to collect CSF samples of 0.5 ml. After the interferon injections the syringe was washed back and forth several times with CSF. There was no visible contamination of the CSF samples with blood. Blood samples were collected from the external saphenous vein. In general, the monkeys tolerated the interferon quite well even when it was administered directly into the CSF space. A febrile response peaking at 5–8 hr after injection was seen, but it varied considerably (100.2–105.2°F) in individual monkeys.

Results. Figure 1 shows the results of an experiment in which two monkeys were injected with 30 million units of C-IF iv or im. The early clearance rate of the iv administered interferon (A) was similar to that obtained in previous animal studies (9, 10). However, the persistence of interferon at measurable levels was much more pronounced than in the earlier studies probably due to the fact that a considerably higher interferon dose was used than previously. A detectable level of interferon in the serum was maintained for, at least, 24 hr, and during the period from 6 to 24 hr after injection the half-time of the circulating interferon was 7.1 hr. Small amounts of inter-

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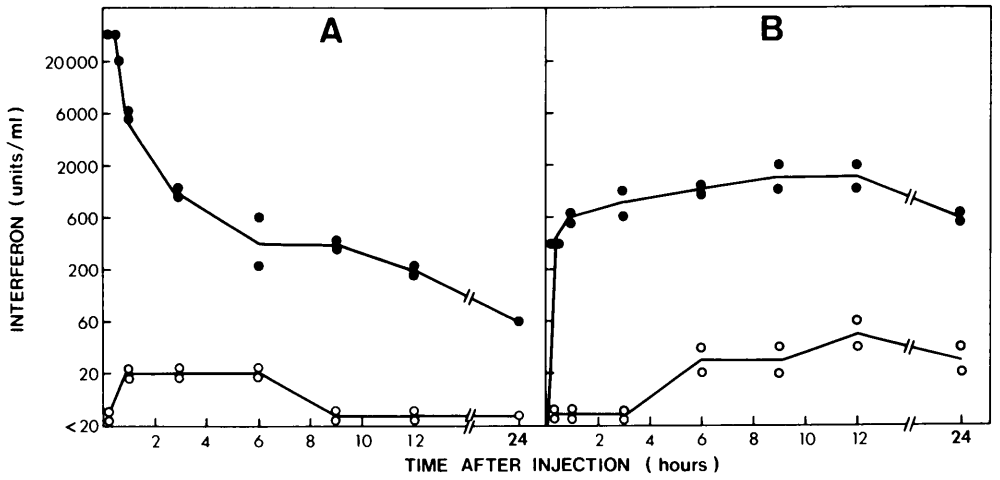

FIG. 1. Interferon levels in serum (●) and cerebrospinal fluid (○) of monkeys at different times after intravenous (A) or intramuscular (B) injection of 30 million units of concentrated human leukocyte interferon (C-IF).

feron were detected in CSF during the period from 1 to 6 hr after injection.

A stable and long-lasting level of circulating interferon was obtained after im injection of 30 million units of C-IF (Fig. 1B). Interferon was detectable in CSF during the period from 6 to 24 hr. During this steadystate the levels of interferon in CSF ranged between 2 and 4.5% of the corresponding levels in the serum. In other words, there was about a 30-fold difference between the interferon concentration in the serum and in CSF.

In the following experiments the interferon was injected directly into the CSF space and the clearance rate was followed. Figure 2A shows that interferon was cleared from CSF at a similar rate as it was cleared from the blood after iv injection of a massive dose. The early disappearance rate from CSF was slower than the corresponding rate in the bloodstream, but this could be due to a less effective distribution of the injected interferon in CSF than in the blood.

There was no essential difference in the clearance rates of C-IF and P-IF from CSF. Similarly, the clearance rates of C-IF and P-IF from the blood after iv administration are indistinguishable (9, 11). Interferon was readily detected in the blood after administration of 10 million units of P-IF into the CSF space (Fig. 2B). The pattern of the circulating interferon resembled closely that obtained after im injection of interferon (9, 12) except that the appearance in the blood was slower after administration into CSF space than after im injection. During the period from 12 to 24 hr there appeared to be a roughly constant ratio between serum and CSF interferon at about 4–5%.

Discussion. Our results agree with those of Ho *et al.* (6) concerning the slow disappearance of intrathecally injected rabbit interferon from CSF in the homologous host. They found a much faster clearance of interferon from the blood after iv injection than in the present study, but our interferon dose per kg of body weight was about 50 times as great as the dose used by them.

The present findings clearly demonstrate that there is a barrier to the penetration of interferon from plasma to CSF and *vice versa*, but that some interferon can pass the barrier in both directions. The finding that a long lasting plateau of interferon in CSF can be maintained by administering a sufficient im dose may be of clinical importance, although it is not known how much interferon penetrated into the brain. The im route of administration is used in the current clinical trials with human leukocyte interferon and the blood levels obtained in man (12, 5) tally well with previous animal findings (9–12).

Summary. Interferon was detected in the cerebrospinal fluid (CSF) of monkeys in-

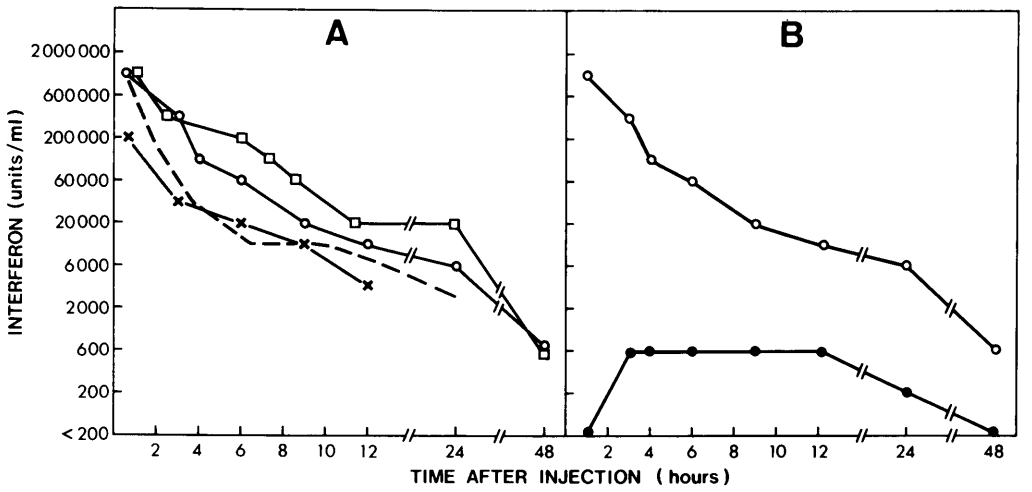

FIG. 2. Interferon levels in cerebrospinal fluid (CSF) and serum of monkeys at different times after injection of human leukocyte interferon into cerebrospinal canal. (A) Interferon in CSF after injection of 3 million units of C-IF (□), 10 million units of P-IF (○) or 1 million units of P-IF (×). The blood clearance rate (- - -) after intravenous injection of interferon is inserted for comparison of slopes only. The curve is taken from Fig. 1A which gives the actual interferon titers. (B) Interferon in CSF (○) and serum (●) after injection of 10 million units of P-IF.

jected iv or im with 30 million units of human leukocyte interferon. The im injection maintained a long-lasting plateau at about 1/30th of the corresponding level of interferon in the serum. Interferon injected into the cerebrospinal canal was cleared from CSF at a similar rate as it disappeared from blood after iv administration of a high dose. A relatively stable serum level was maintained for 12–24 hr after the injection of interferon into the CSF space.

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