INTERFERON PRODUCTION BY DIFFERENT INDUCERS

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Interferon formation is a multistate process which can be divided into two principal phases: induction and production. During the first phase the inducer is attached to the cells and derepression of the interferon gene(s) takes place; the production phase includes transcription and translation of interferon messenger RNAs followed by processing and secretion of interferon [3]. The duration of each of these stages and the amount of interferon produced are largely determined by the nature of the inducers and also, as the writers showed previously, by their mode of administration.

In this paper we describe determination of the levels and time course of interferon production in mice following administration of a single dose of various inducers. Attention was concentrated on preparations of Soviet origin, some of which (polyguacil and GSN) have already been used in clinical practice, and the rest have passed through all stages of preclinical experimental trials [2].

EXPERIMENTAL METHOD

Noninbred albino mice weighing 10-12 g were used. Ten animals were tested for each experimental condition. The unit of interferon activity was taken to be the reciprocal of the dilution of serum causing 50% protection of cells against the cytopathic action of vesicular stomatitis virus.

Poly(I) · poly(C) was obtained from the Special Design and Technology Bureau for Biologically Active Substances (Novosibirsk), polyguacil from the Leningrad Institute of Nuclear Physics, Academy of Sciences of the USSR (Leningrad), RFf_2 from the Institute of Molecular Genetics, Czechoslovak Academy of Sciences (Prague), dsRNA* from the A. Kirkhenshtein Institute of Microbiology, Academy of Sciences of the Latvian SSR (Riga), levamisole from Gedeon Richter (Hungary), tilorone from the Institute of Physical Chemistry, Academy of Sciences of the Ukrainian SSR (Odessa), and the GSN, Tash-3 and Tash-4 from the Institute of Bioorganic Chemistry, Academy of Sciences of the Uzbek SSR (Tashkent). All preparations except levamisole and tilorone were injected intraperitoneally.

EXPERIMENTAL RESULTS

In preliminary experiments the concentrations of inducers yielding maximal interferon titers in mice were determined.

As Table 1 shows, the interferon titers when all the preparations chosen were used reached 250-500 units/ml, so that all these inducers can be classed as highly active. The strongest interferon-inducing ability was exhibited by synthetic and natural polymers, which are characterized by a short induction phase and by early interferon formation with a production peak after 4-6 h. Low-molecular-weight preparations except tilorone induced "late" interferon (peak after 24-48 h). Effective concentrations of these inducers were 5-10 times higher than the corresponding concentrations of the polymers.

If the results of the study of the time course of interferon formation in response to

*Double-stranded RNA.

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TABLE 1. Parameters of Interferon Production in Mice when Using Different Inducers

Nature of inducer	Preparation	Mode of administration	Dose, mg/kg	Times of interferon production peaks, h	Interferon titers at peak, units/ml
High-molecular-weight synthetic	Poly(I)·poly(C)	Intraperitoneally	6	2—4	2560
	Polyguacil	"	5	4—8	1280
natural	RFf_2	"	1	6	1280
		"	2	6	1280
Low-molecular-weight synthetic	Levamisole	Perorally	20	4—6	320
	Tilorone	"	200	24	1280
	GSN	Intraperitoneally	50	24	320
natural	Tash-3	"	100	48—72	256—512
	Tash-4	"	25	24—48	512—1024

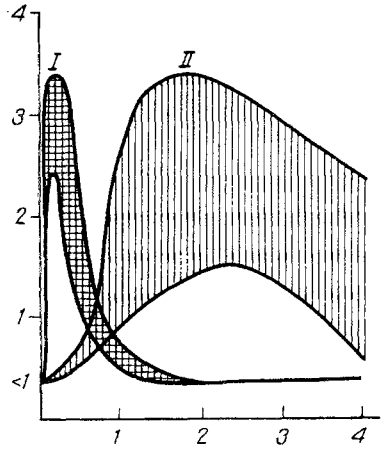

Fig. 1. "Early" type of interferon production observed with the use of poly(I)·poly(C), polyguacil, RFf_2, dsRNA, and levamisole (I) and "late" type of interferon production when tilorone, GSN, and PKhL-6 were used (II). Shaded zones show scatter of interferon titers in different experiments. Abscissa, days of experiments; ordinate, interferon titers (in units/ml).

different inducers are pooled, the general principles of production of "early" and "late" interferon can be clearly traced (Fig. 1). Early interferon formation is characterized by a comparatively short lag period (1-3 h), during which the interferon production system is "switched on." This is followed by a rapid rise and an equally rapid fall of interferon yield. By 24 h after administration of the inducer the quantity of circulating interferon falls to a minimum and it ceases to be detectable. The scatter of interferon titers with the early type of production (the shaded zone in Fig. 1) was narrow. When inducers of "late" interferon were used the lag-period extended to 1-2 days and maximal interferon production did not occur as a strictly delineated peak. Circulation of interferon correspondingly was more prolonged and the scatter of interferon titers was very wide (from tens to thousands of units in 1 ml serum).

Interferon inducers can be subdivided into natural and synthetic and into high- and low-molecular-weight types. Of the vast number of interferon inducers known at present only a few are promising for clinical use [1]. In the present investigation, in order to study the principles governing interferon production, nine of the most promising inducers, representing groups of different nature, were selected (Table 1).

These experiments showed that the polymers poly(I)·poly(C), polyguacil, RFf_2, dsRNA, and levamisole are characterized by early interferon formation with a production peak after 4-6 h and by rapid disappearance of serum interferon thereafter (Fig. 1). The low-molecular-weight synthetic and natural preparations tested (tilorone, GSN, Tash-3 and Tash-4) induce late interferon formation with a peak after 24-48 h, and with prolonged circulation in the blood (time of observation upto 4 days) and a wide scatter of titers. The practical conclusion can be drawn from these results that if interferon is to be obtained rapidly synthetic and natural polymers must be used, whereas if more prolonged production and circulation of interferon are required, the use of low-molecular-weight inducers can be recommended.

LITERATURE CITED

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