Interferon Inducers Found "Highly Toxic" to Mice

NIAID-supported scientists find in animal studies that poly I·poly C--a synthetic inducer of interferon--resembles endotoxin in toxicity as well as in interferon-stimulating mechanisms.

Poly I·poly C, a synthetic double-stranded RNA, has previously been shown to stimulate interferon production in animals. This substance has been successfully used to treat an eye infection in rabbits and there has been considerable optimism that it might also prove useful in human viral diseases.

However, evidence that poly I·poly C's interferon-inducing activity resembles that of endotoxin--a toxic substance found in cell walls of certain bacteria--has aroused concern that the synthetic RNA may resemble the bacterial substance in toxicity as well. In the present study, therefore, the investigators attempted to explore further the similarities between endotoxin and poly I·poly C, with particular regard to toxic effects.

Administration of lead acetate with endotoxin is known to increase the lethality of the latter. In order to learn whether animals may be rendered similarly hyperreactive to poly I·poly C, the investigators injected lead acetate into mice immediately before challenge with various doses of the synthetic RNA. At an intermediate dose level (100μg), 4 of 10 lead acetate-treated mice died, as compared with none of 10 mice receiving poly I·poly C alone. A higher dose level (500μg) of poly I·poly C proved fatal to all of 10 lead acetate-treated mice, but to only 5 of 10 control animals.

These results indicate that toxic effects of poly I·poly C are, like those of endotoxin, enhanced by lead acetate. In addition, this experiment showed the toxic dose of poly I·poly C to be quite similar to the known toxic dose of endotoxin.

Another phenomenon characterizing the behavior of endotoxin in animals is its ability to induce tolerance to its own effects. Animals injected with sublethal doses of endotoxin develop resistance (hyporeactivity)
to both toxic and interferon-inducing effects of this material. As part of the present study, the scientists tested to see whether poly I-poly C would induce hyporeactivity to endotoxin and vice-versa. Such cross-reactions were indeed found with respect to both lethality and interferon induction.

It is of interest to note that statolon, another interferon inducer, does not cross-react with endotoxin or with poly I-poly C. Also, the lethality of statolon is not enhanced by lead acetate. It thus appears that different interferon inducers may operate via different pathways. Endotoxin and poly I-poly C, however, seem to share a single mechanism of interferon induction which the authors suggest may depend on their toxic effects.

The investigators conclude that poly I-poly C is a highly toxic substance, sharing many of the properties of bacterial endotoxin. They also state their belief that the phenomena of hyperreactivity and hyporeactivity must be considered in the clinical use of interferon inducers of this class.

Marlene Absher and Warren R. Stinebring, of the University of Vermont College of Medicine, reported their study in Nature, where it appeared as one of a group of articles on toxic properties of poly I-poly C.

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