INCREASED THYMIDINE EXCRETION INDUCED BY POLYANIONS

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UDC 612.461:577.113.3].014.46:54-128.2

Marked thymidinuria, as is usually observed in rats and mice following exposure to high doses of ionizing radiation, develops in these animals during the first day after injection of polyanions (dextran sulfate and polyI—polyC). It is postulated that the thymidinuria is connected with the ability of the polyanions to induce migration of lymphocytes into the blood stream.

KEY WORDS: dextran sulfate; double-stranded polynucleotides (polyI—polyC); thymidinuria.

It was shown previously that the thymidine excretion in irradiated animals characterizes the state of their lymphoid tissue [3]. Administration of polyanions has a marked effect on hematopoiesis and increases the resistance of the organism to the action of ionizing radiation [5, 6].

On the assumption that polyanions act through their effect on lymphoid tissue, which participates in hematopoiesis [9], it was decided to study the excretion of thymidine in irradiated animals after treatment with dextran sulfate and the double-stranded polyribonucleotide polyI—polyC.

EXPERIMENTAL METHOD

Noninbred albino mice aged about 3 months and male Wistar rats weighing 155-160 g were used. Dextran sulfate (Ferak, Berlin) was given to the rats in a dose of 62.5 mg/kg, and polyI—polyC (Calbiochem, USA) was injected intraperitoneally into rats in a dose of 0.5 mg/kg and into mice in a dose of 2.5 mg/kg.

The animals were irradiated with Co^{60} γ rays on the Gamma-Cell 220 apparatus in a dose of 300 rad (dose rate 1084 R/min) 2 h after administration of the polyanions. The daily sample of urine was collected before administration of the preparations, and immediately before and after irradiation. Thymidine was isolated from the urine by means of the anionic-exchange resin Dowex-1 in a formate cycle and by chromatography on paper. Quantitative estimation of thymidine was carried out spectrophotometrically [2]. Parallel with the collection of urine, to determine the DNA content in the organs animals were sacrificed five at a time. The thymus and spleen were quickly removed, homogenized, and processed [10] for DNA determination [1].

EXPERIMENTAL RESULTS AND DISCUSSION

The thymidine excretion of the irradiated rats previously treated with polyanions is shown in Fig. 1. During the first day dextran sulfate increased the excretion of thymidine almost to the level characteristic of the control animals after irradiation. On the second day after administration of dextran sulfate the thymidine excretion returned to normal. After irradiation the thymidine excretion of these animals was increased by a much lesser degree than in the control. Injection of polyI—polyC into the rats had virtually no effect on thymidine excretion, but subsequent irradiation caused the same increase in the excretion of

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(Presented by Academician of the Academy of Medical Sciences of the USSR A. D. Ado.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 81, No. 6, pp. 655-656, June, 1976. Original article submitted November 14, 1975.

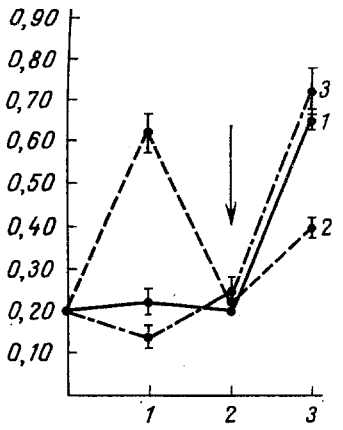

Fig. 1

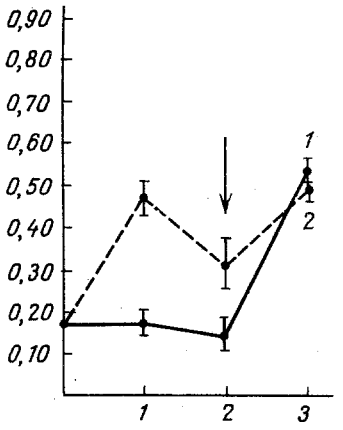

Fig. 2

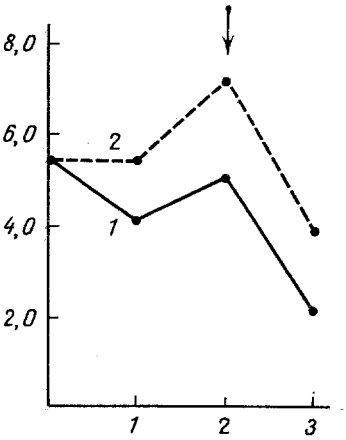

Fig. 3

Fig. 1. Effect of polyanions on thymidine excretion in rats irradiated in a dose of 300 rad: 1) control (administration of 0.15 M NaCl); 2) administration of dextran sulfate; 3) injection of polyI—polyC. Arrow indicates moment of irradiation. Abscissa, days after administration of substances; ordinate, thymidine excretion (in μmoles/day).

Fig. 2. Thymidine excretion in mice irradiated in a dose of 300 rad, after injection of polyI—polyC: 1) control (0.15 M NaCl given); 2) injection of polyI—polyC. Remainder of legend as in Fig. 1.

Fig. 3. DNA content in spleen of rats irradiated in a dose of 300 rad, after administration of dextran sulfate: 1) control; 2) administration of dextran sulfate. Ordinate, DNA content (in mg). Remainder of legend as in Fig. 1.

thymidine with the urine as in the control. However, in mice receiving a much larger dose of polyI—polyC, a marked increase in thymidine excretion was observed on the first day (Fig. 2). Since an increase in the urinary thymidine excretion reflects stimulation of catabolism [4] it can be postulated that the polyanions used had a cytotoxic action and blocked the reutilization of the breakdown products.

After administration of dextran sulfate to the rats the DNA content in their thymus fell a little (3.8 ± 0.03 mg compared with 4.4 ± 0.05 mg in the control). However, in the spleen, another radiosensitive organ, which after irradiation is responsible for up to 40% of excretion of nucleosides, the DNA content rose (Fig. 3). Similar results were obtained after injection of polyI—polyC into mice.

The increase in thymidine excretion can tentatively be ascribed to the ability of polyanions to cause migration of lymphocytes [8]. In this case, some of the cells may perhaps die or, at least, become incapable of synthesizing DNA for a certain time. The increase in the DNA content in the spleen was probably due to migration of lymphocytes into that organ. The thymidinuria may also be connected with the ability of certain polyanions to induce interferon, which blocks cell division [7].

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