EFFECT OF IRRADIATION ON METABOLISM OF DESOXYNUCLEOSIDES AND ROLE OF HORMONAL FACTORS IN CHANGES IN THEIR TISSUE AND URINE LEVELS

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From 4-6 h after whole-body x-ray irradiation (650 R) the thymidine level in the organs (spleen, kidneys, liver) rises and this is followed by an increase in its excretion in the urine. Experiments on adrenalectomized animals showed that adrenal cortical hormones reduce the postradiational nucleosiduria.

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Irradiation causes definite disturbances of DNA metabolism manifested by a considerable increase in the excretion of nucleosides [1, 5-7, 9], especially thymidine [2-4], in the urine. This can be used as an early diagnostic test of radiation injury.

The object of this investigation was to examine the mechanisms causing an increase in thymidine excretion in the urine. The hypothesis that the main cause of it is breakdown of DNA in rapidly regenerating tissues, and that some contribution is made by inhibition of DNA synthesis, leading to the accumulation on unused precursors of DNA in the tissues, was tested. An attempt was also made to investigate the role of hormonal factors, notably adrenal hormones, in changes in the nucleoside level in the tissues and urine after irradiation.

EXPERIMENTAL METHOD AND RESULTS

It was shown by chromatography on paper and on ion-exchange resins that 4-6 h after whole-body x-ray irradiation of rats in a dose of 650 R a maximal increase in the thymidine level takes place: in the spleen, liver, and kidneys up to 52.1 ± 6.3, 2.2 ± 0.9, and 14.5 ± 6.3 μmoles/g tissue respectively. Immediately after this increase in the thymidine concentration in the tissues, its excretion in the urine increased, reaching a maximum 6-12 h after irradiation (Fig. 1). In samples of urine collected during the period of most severe block of DNA synthesis (in the first 6 h after irradiation), the increase in thymidine concentration was not so marked and was due to an additional factor – disturbance of the conversion of thymidine into β-aminoisobutyric acid. The results obtained demonstrate the leading role of DNA catabolism in the production of postradional thymidinuria. This is confirmed by results obtained during investigation of the activity of enzymes responsible for the synthesis (thymidylate synthetase) and breakdown (5-nucleotidase) of thymidine monophosphate (TMP) in the body. Inhibition of thymidylate synthetase activity was found in the liver of rats irradiated in doses of 850, 600, and 300 R (dose rate 165 R/min) 5 h after hepatectomy (Fig. 2).

After irradiation in a dose of 300 R the thymidylate synthetase activity was lowered by 57%, and in doses of 600 and 850 R, by 64 and 66% respectively compared with the normal level. Blocking of TMP formation and, consequently, of the formation of thymidine de novo may indicate that the increase in thymidine concentration in the tissues and urine after irradiation is more particularly the result of increased DNA breakdown. A statistically significant increase in 5-nucleotidase activity was found in extracts of the spleen and small intestine 24 and 72 h after irradiation of rats in a dose of 850 R, i.e., in the nucleosides in the tissues and urine. However, the 5-nucleotidase activity of the tissues is extremely high under normal conditions also [8]. For this reason, even without marked activation, these enzymes bring about intensive

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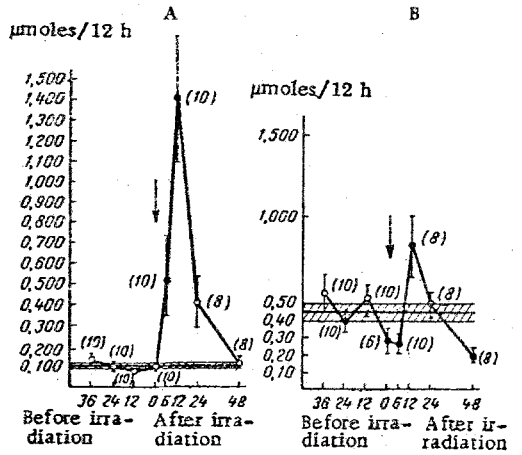

Fig. 1. Dynamics of excretion of thymidine (A) and β-aminoisobutyric acid (B) in the urine (in μmoles/12 h) of rats under normal conditions and after whole-body x-ray irradiation in a minimal absolutely lethal dose (650 R). White circles represent $M_{mean} \pm m$ for each time of observation; dark circles, $M_{mean} \pm m$ for its differences from normal, are statistically significant. Shaded areas give normal values of $M_{mean} \pm m$. Arrow indicates moment of irradiation. Excretion at the point 6 h after irradiation given in μmoles over a period of 6 h. Level of excretion at the point 48 h after irradiation was obtained by dividing excretion over the period from 24 to 48 h by 2.

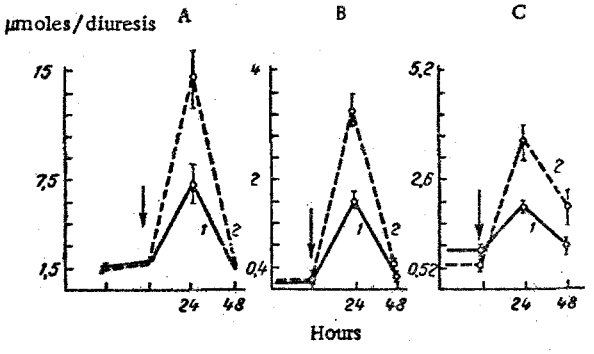

Fig. 3. Excretion of the nucleosides desoxycytidine (A), thymidine (B), and desoxyuridine (C), (in μmoles/diuresis) in the urine of intact (1) and adrenalectomized (2) rats before and after γ-ray irradiation (Co^{60}) in a minimal absolutely lethal dose (800 R).

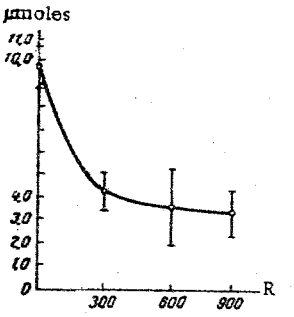

Fig. 2. Thymidylate synthetase activity of regenerating liver of rats (in μmoles) before and after γ-ray irradiation (Co^{60}) in doses of 300, 600, and 850 R.

breakdown of nucleotides appearing as a result of increased DNA breakdown, leading to an increase in the concentration of desoxynucleosides in the tissue and urine of irradiated animals.

Adrenal hormones definitely reduce the postradiational nucleosiduria effect: in adrenalectomized (4 days before irradiation) animals the levels of desoxycytidine, thymidine, and desoxyuridine in the urine increased during the first day after irradiation by 100% compared with their levels in control irradiated rats (Fig. 3).

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