RADIOPROTECTIVE ACTION OF ATP IN EXPERIMENTS ON MICE

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ATP administered to mice before irradiation increases the survival rate of the animals. The hemopoietic system is depressed to a lesser degree and recovers sooner.

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Death of cells in an irradiated animal is due to changes in the biochemical mechanisms of the cell nuclei. An important link in the chain of these changes is the metabolic disorder associated with disturbance of the formation and utilization of high-energy phosphorus compounds, a leading member of which is ATP.

The decrease in content of high-energy phosphorus compounds in the tissues of irradiated animals has been confirmed repeatedly [1, 5, 7], and attention has been drawn to the greater depth and duration of this process in radiosensitive organs [2]. Other work has shown that in most tissues the ability of the cells to accumulate energy liberated during vital metabolism processes in the form of high-energy phosphate bonds is undisturbed after exposure to ionizing radiation [4]. Accordingly attempts have previously been made to use ATP as a radioprotective substance. Some investigators [10-12] gave ATP to mice and rats before irradiation and observed an increase in survival rate and in the value of LD_{50} of x-rays of more than 30%. When ATP was given in conjunction with other radioprotectors, the dose reduction factor (DRF) was also increased [6-10]. Meanwhile the absence of effect of ATP administration before irradiation has also been reported [4, 8, 9, 13]. When ATP was used in the early treatment of irradiated animals, a stimulant effect on the blood system was observed [3]. In the investigations cited above, it will be noted, animals of different species, different doses and methods of administration of ATP, and also different doses of irradiation were used.

Because of the conflicting nature of data in the literature, the present investigation was carried out to study the radioprotective action of ATP on the basis of analysis of peripheral blood indices.

EXPERIMENTAL METHOD

Experiments were carried out on 538 male albino mice weighing 18-20 g. The animals were subjected to whole-body irradiation by a single dose of Co^{60} γ-rays from a type ÉGO-2 apparatus, dose 650 R, dose rate 690 R/min ($LD_{80-85/30}$). ATP was given to the animals of the experimental group as a 1% solution (packed in ampules at the Ivanovo Meat Combine). The doses and method and times of administration are given in Table 1. The efficacy of action of ATP was estimated from the survival rate, the mean duration of survival of the dying animals, and changes in peripheral blood indices. Observations were kept on the animals for 30 days after irradiation. A full blood count on blood taken from the mice after decapitation was carried out on the experimental animals receiving ATP by intraperitoneal injection in a dose of 350 mg/kg before irradiation and on control mice on the 1st, 3rd, 7th, 10th, 15th, 20th, 25th, and 30th days of the experiment. At each time 5 mice from each group were sacrificed. As original data peripheral blood indices of 15 intact mice were used.

EXPERIMENTAL RESULTS

The results of these experiments demonstrated the protective effect of ATP on mice irradiated with high-power γ-rays. Intraperiotoneal injection of ATP into mice in a dose of 350 mg/kg 15-20 min before irradiation increased the survival rate to 41% but had no significant effect on the mean life span (Table 1).

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TABLE 1. Effect of ATP on Survival Rate and Mean Life Span of Mice Irradiated with Co^{60} γ-Rays in a Dose of 650 R

Time of administration of ATP	Mode of injection	Dose of ATP (in mg/kg)	No. of animals	No. surviving		t Compared with control	Mean life span of dying animals
				abs.	%		
15-20 min before irradiation	Intraperitoneally	350	180	106	59	9.8	15.5
	Intramuscularly	500	20	15	75	5.7	12.0
	Intramuscularly	350	196	91	46.4	6.8	15.8
		200	20	4	20	–	17.5
Control	Intramuscularly	–	342	61	17.8	–	14.2

Note. Value of t calculated by alternative variation method. Results considered significant if $t \geq 3$.

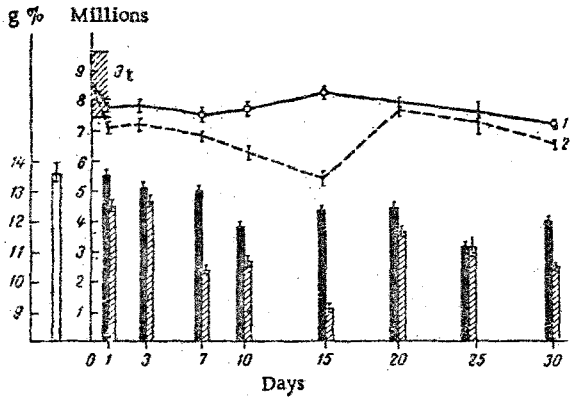

Fig. 1. Changes in erythrocyte count and hemoglobin concentration in ATP-protected and control mice. Curves show erythrocyte count in experimental (1) and control (2) mice; clear circles on curves indicate significant differences. Hemoglobin concentration shown by black (experimental) and shaded (control) columns. Unshaded column shows normal level.

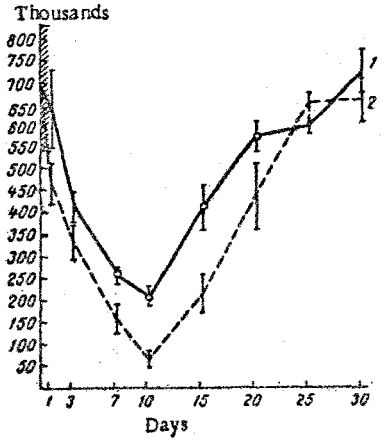

Fig. 3. Changes in platelet count in blood of ATP-protected and control mice. Legend as in Fig. 1.

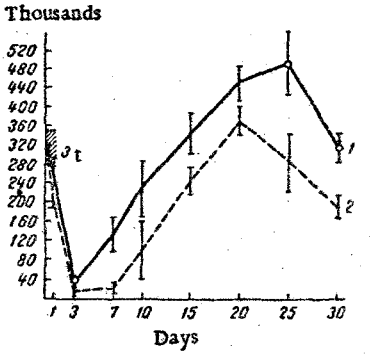

Fig. 2. Changes in reticulocyte count in blood of ATP-protected and control mice. Legend as in Fig. 1.

Intramuscular injection of ATP in a dose of 200 mg/kg gave no significant increase in the survival rate of the animals and prolonged the mean life span only slightly.

An increase in the dose to 350 and 500 mg/kg, using the same method of administration, increased the survival rate of the irradiated mice by 28.6 and 57% respectively, but after administration of the latter dose the life span was shortened.

The peripheral blood picture of the control mice was typical of acute radiation sickness. The erythrocyte count, after a period of slight oscillation at a lower level than normal, began to fall progressively from the 7th day to reach 5,400,000 by the 15th day compared with a normal count of 9,800,000 (Fig. 1). The hemoglobin concentration correlated fully with these changes and by the 15th day had fallen to 9 g% (normal 13.6 g%). Later an increase in the erythrocyte count was observed.

In the group of animals receiving ATP intraperitoneally in a dose of 350 mg/kg 15-20 min before irradiation the erythrocyte count fluctuated throughout the period of observation within the limits

of scatter of normal values, and differed significantly from the control on the 7th, 10th, 15th, and 30th days ($P = 0.05$). The hemoglobin concentration corresponded to the level of the erythrocyte count. The reticulocyte count fell simultaneously in both groups to a minimum on the 3rd day (Fig. 2). Later it rose, and by the 20th day was above its original level. The platelet count in the control mice fell progressively to reach 69,000/mm^3 by the 10th day (Fig. 3). In the animals receiving ATP the changes in the platelet count were in the same direction, but until the 20th day inclusive the platelet count was higher than in the control series, the difference being significant on the 7th, 10th, 15th, and 20th days. The dynamics of the leukocyte count in mice of the experimental groups was the same as in the control, although the difference between them was significant on the 7th, 10th, and 15th days.

It follows from the results of these experiments that administration of ATP to mice before irradiation increases the survival rate and reduces the disturbances in the hemopoietic system. A significant difference between the control and experimental groups was obtained with respect to indices such as the erythrocyte and reticulocyte counts and the hemoglobin concentration. These may indicate that ATP can reduce the depression of erythropoiesis and lead to its earlier recovery. A similar relationship was observed also in relation to the platelet count. So far as the changes in the leukocyte count are concerned, all that could be observed here was an earlier onset of recovery (7th, 10th, and 15th days), but the severity of the leukopenia was identical in the animals of the two groups.

In assessing the radioprotective action of ATP, attention must be paid to its participation in various biosynthetic reactions. In particular, it participates in the synthesis of 5-hydroxytryptamine (serotonin), as is confirmed by the increase in amount of liberated serotonin associated with lowering of the blood ATP level [12]. Evidence has also been found [11, 12] that ATP, if injected into animals before irradiation, promotes recovery of disturbed serotonin synthesis. Serotonin in known to have marked radioprotective action. On the other hand, the protective action of ATP may be due to hypoxia and to a fall in the oxygen tension in radiosensitive tissues, caused by circulatory disorders characteristically found after parenteral injection of this preparation.

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