PHASIC CHANGES IN PERMEABILITY OF THE BLOOD-BRAIN BARRIER AFTER SELECTIVE γ-IRRADIATION OF MICE

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The interest of research workers in changes in the blood-brain barrier (BBB) after irradiation is due to the established role of this anatomophysiological system in radiation damage [2, 4 11 12]. There is extremely little information on early changes in the BBB, but gross disturbances of BBB are found at the beginning of radiation sickness [4]. It has been suggested that changes in the vascular endothelium of the brain play a leading and triggering role in the pathogenesis of radiation damage to the CNS.

The aim of this investigation was to determine early changes in permeability of the BBB in mice after irradiation of the head or trunk.

METHODS

Experiments were carried out on 200 male (C57 × CBA)F_1 mice weighing on average 25.1 ± 0.8 g and irradiated to the head or trunk with a dose of 2.58 Ci/kg body weight. Unilateral (from the side) irradiation with ^{60}Co γ-quanta, with a dose rate of 1.43 mA/kg on the midline of the animal's body was given in transparent plastic constraining cages, virtually preventing movement of the animals relative to the source of irradiation and the screen (the edge of a collimator). The line of screening passed along the upper part of the chest (the first and second ribs). The weight of the anterior part of the animal (head) was 25-30% of the total body weight of the mouse, and the weight of its posterior part (trunk) was 70-75% of the total.

Permeability of the BBB was studied by the method in [10]. The essence of the method, in the modification used, was as follows. An intraperitoneal injection of label (0.8 ml of a 10% aqueous solution of acid fuchsine) which penetrates the difficulty into brain tissue, was given to the animals. At the moment of its penetration into the brain, the animals develop generalized convulsions. Observations on the animals after the injection continued for 2 h. The time of appearance of the first convulsions was determined, and is inversely proportional to the permeability of BBB. In the present experiments acid fuchsine was injected 5 min (observation 0-2 h), 2 h (2-4 h), 4 h (4-6 h), and 24, 48, 72, and 120 h after irradiation. Acid fuchsine was injected simultaneously into the experimental mice and control mice undergoing mock irradiation. Each group contained 10 animals. Permeability was expressed as a percentage of the corresponding control. The significance of differences between the groups was determined by the Wilcoxon–Mann–Whitney nonparametric U test [3].

RESULTS

The results are given in Table 1. They show that permeability of BBB was increased immediately (0-2 h) after irradiation as applied in both versions.

Later the picture changed considerably. In the early stages (2-6 h) the reduction of permeability of the BBB increased: toward 2-4 h after irradiation of the head and toward 4-6 h after irradiation of the trunk. The coefficients of variation, incidentally, changed in different ways: They decreased after irradiation of the head but increased after irradiation of the trunk.

The absence of an increase in permeability of the BBB at these times (2-6 h) after irradiation of the head with similar doses (300 Gy) was described in [8], in which a disturbance

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TABLE 1. Changes in Permeability of Mouse BBB for Acid Fuchsine (in % of control) after Selective Irradiation in a Dose of 2.58 Ci/mg Body Weight (M ± m)

Experimental condition	Time after irradiation, h						
	0—2	2—4	4—6	24	48	72	120
Irradiation of head	137,1±16,8* (36,8)	73,7±4,7* (19,3)	74,7±3,5* (14,2)	172,4±18,6* (32,3)	388,1±12,5* (9,7)	246,1±19,4* (23,6)	491,4±18,7* (11,4)
Irradiation of trunk	144,2±18,5* (38,4)	96,8±10,0 (31,0)	73,0±10,5* (43,3)	96,8±13,0 (40,2)	103,8±19,7 (57,0)	89,5±13,2 (44,4)	—

Legend. Coefficient of variation of parameters shown in parentheses. *P < 0.05 compared with control.

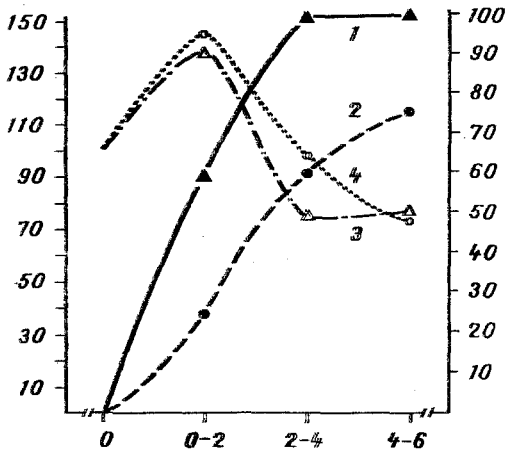

Fig. 1. Comparison of permeability of BBB and frequency of appearance of tremor and ataxia after irradiation of head and trunk of mice in a dose of 2.58 Ci/kg. Abscissa, time after irradiation (in h); ordinate: on left, permeability of BBB (in %); on right, frequency of tremor and ataxia (in %). 1) Frequency of appearance of neurological symptoms after irradiation of head; 2) the same, after irradiation of trunk; 3) permeability of BBB after irradiation of head; 4) the same after irradiation of trunk.

(increase) of permeability of the BBB was not observed until 10-20 h after irradiation. The authors cited concluded that marked changes in the BBB do not develop until 24 h after irradiation. In that investigation the first phase (increased permeability) was evidently simply not recorded because the estimates were made later (after 4-6 h), when, according to our own data, permeability of BBB was actually reduced.

In the early stages after irradiation at least two phases of change of BBB permeability are thus observed: an increase (0-2 h) followed by a decrease of permeability (2-6 h). The second phase possibly developed because of redistribution of fluid and electrolytes between the vascular bed and the tissues, and also, probably, between the intracellular and extracellular spaces [7]. This redistribution, as morphological investigations have shown [1, 4, 6, 9], leads most frequently to edema; under these circumstances permeability may be sharply reduced, as has been shown after local irradiation of different parts of the body [5].

Changes in BBB in the later stages (24-120 h) also were marked. Permeability of BBB after irradiation of the trunk did not differ from the control values, even though the animals developed a very severe intestinal syndrome and they all died in the course of 100 h. Permeability of the BBB increased progressively after irradiation of the head. This phenomenon evidently indicates generalization of the disturbance of vascular permeability (mainly in the brain), which leads to total dysfunction of BBB and loss of the ability of this anatomo-physiological formation to perform its characteristic defensive function.

A study of correlation between BBB permeability and the frequency of appearance of neurological symptoms (tremor and ataxia — convulsions do not arise with this dose of irradiation), which was determined in parallel experiments (Fig. 1: 1, 2) shows that, beginning with the first time of observation, correlation between these parameters was negative. This indicates that the time factor plays an important role in the development of changes in BBB. There is evidently an association between the redistribution of fluid between the blood and the internal medium of the brain (increased edema) and the development of clinical manifestations of CNS damage.

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