IMPORTANCE OF THE PERIPHERAL INNERVATION APPARATUS IN THE GENESIS OF PERMEABILITY CHANGES IN A VASCULAR BARRIER AFTER EXPOSURE TO IONIZING RADIATION

N. I. Arlashchenko

Scientific Director, Active Member AMN SSSR A. V. Lebedinskii
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We have investigated the changes in the permeability of the denervated vaso-tissue barrier after exposure to ionizing radiation as exemplified by disturbances of the blood-eye barrier arising after total denervation of the iris (removal of the afferent and sympathetic nerve supplies and division of the oculomotor nerve) followed by irradiation of the eye.

EXPERIMENTAL METHOD

Destruction of an afferent neuron is accompanied, as a rule, by the development of neuroparalytic keratitis, a typical dystrophic process [2-5, and others]. Only when the trigeminal nerve was divided proximally to the gasserian ganglion, as in Gaule's experiments, was keratitis not produced [6]. We have attempted to obtain denervated eyes with no sign of the development of keratitis. Careful protection of the cornea, after removal of its afferent nerve supply, from accidental injury enabled us to attain our object.

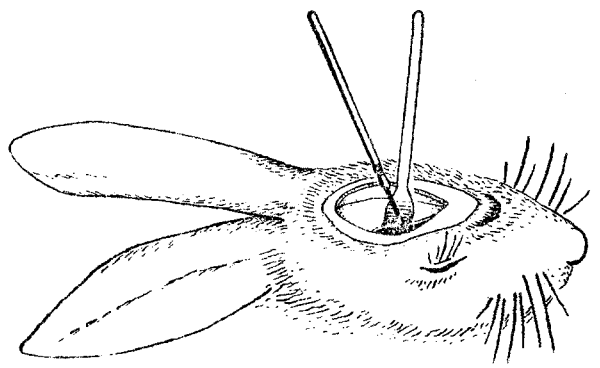

Fig. 1. Scheme of the operation of simultaneous division of the first branch of the trigeminal nerve with the sympathetic fibers and the oculomotor nerve under the experimenter's direct vision.

The operation of simultaneous division of the trigeminal, sympathetic, and oculomotor nerves was carried out under visual control and with minimal trauma to the afferent neuron. The scheme of the operation is shown in Fig. 1. The skin was incised along the sagittal line, the subcutaneous tissues and periosteum were retracted to the sides, as much of the parietal bones as possible was removed, and the cerebral hemispheres were exposed. The dura was incised and retracted. Next, by means of a special spatula, the brain was elevated and, with one movement of a narrow scalpel, the first branch of the trigeminal nerve and the oculomotor nerve situated immediately above the trigeminal were divided on the right side. The dura, the periosteum, and the subcutaneous areolar tissue were then sutured in layers with catgut, after which the skin was sutured. In some rabbits the superior cervical sympathetic ganglion was removed 24 h before this operation. In most cases, however, we did not do this, because we considered that the sympathetic nerve supply to the eye could be removed by dividing the sympathetic fibers passing together with the trigeminal nerve. Removal of the superior cervical sympathetic ganglion was not performed for the further reason that this operation often led to the development of a reactive pneumonia in the animals. Moreover, no difference was observed between the permeability disturbances in the rabbits subjected to operation by these two methods.

Success in the operation depended, on the one hand, on exercising all possible care and avoiding trauma during displacement of the brain, and on the other hand on preservation of the uninjured dura and periosteum. The operation was performed on 40 rabbits. Most of the animals died during the first week after operation or during the operation itself, as a result of cerebral edema. Fifteen rabbits took part in the experiment, of which five were controls.

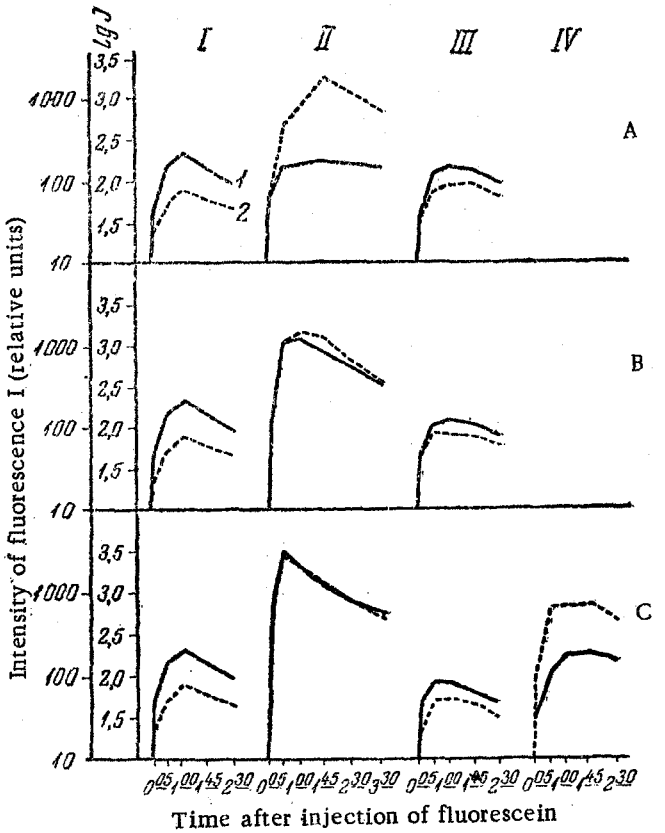

Fig. 2. Fluorescence of the anterior divisions of the control left (1) and denervated right (2) eye. I) Mean values of the intensity of fluorescence of the aqueous humor before irradiation; II) the same, 1 h after irradiation; III) the same, in the period of normalization; IV) the same, on the day before or the day of death of the animals. A) Local irradiation of the denervated eye; B) local irradiation of both eyes; C) whole-body irradiation.

Ten rabbits were exposed to the action of ionizing radiation approximately $1\frac{1}{2}$ weeks after operation: 3 rabbits received whole-body irradiation in a dose of 1000 r, 3 rabbits received local irradiation of the right (denervated) eye, also in a dose of 1000 r, and 4 rabbits received local irradiation of both eyes in the same dose. The animals died from 2 weeks to 2 months later; only two rabbits survived.

To prevent mechanical injury to the insensitive cornea, the eyelids on the side of the operation were fixed together by Michel's clips. As a result of these precautionary measures, keratitis did not develop in the rabbits dying in the course of the first 3 weeks after operation. Five of the 8 rabbits surviving 4 weeks or more, and also the animals surviving the whole experiment, developed clouding of the cornea of the right eye from 1-2 months after operation (1 unirradiated rabbit and 4 rabbits whose eyes were irradiated in a dose of 1000 r).

Whole-body irradiation of the rabbits in a dose of 1000 r was given by means of a three-tube roentgen-ray apparatus (dose rate 29.7 r/min, voltage 180 kV, current 20 mA, skin-focus distance 60 cm). Local irradiation of the eyes in a dose of 1000 r was given by means of the RUM-3 apparatus (dose rate 64 r/min, voltage 180 kV, current 20 mA, skin-focus distance 30 cm). One eye and the brain of the rabbits were screened from the direct course of the roentgen rays by means of a lead sheet, 10 mm thick, placed above the animals' head.

The permeability of the vessels of the anterior portion of the eye was expressed in terms of the intensity of luminescence of fluorescein penetrating into the aqueous humor of the eye after intravenous injection into the animal [1]. Parallel determinations were made of the penetration of intravenously injected dye into the aqueous of the right eye, on the side of the operation, and of the intact left eye. The results were treated by statistical methods.

EXPERIMENTAL RESULTS

From 1 to 1½ weeks after denervation of the iris of the right eye, the permeability of its blood-eye barrier to fluorescein injected into the animal's blood stream was slightly lowered by comparison with the intact left eye.

Whole-body irradiation of the animals in a dose of 1000 r was accompanied by a marked increase in the intensity of luminescence of the fluorescein in the aqueous of both eyes, demonstrating a disturbance of the permeability of the blood-eye barrier to the dye both in the eye on the side of the operation and in the intact eye. The initial reaction to irradiation was then replaced by a period of normalization of the passage of the dye into the anterior chamber fluid of both eyes. Shortly before, or on the day of the animal's death, an increase in the permeability of the blood-eye barrier was observed both on the side of the operation and on the intact side, due to general disturbances of the vital activity of the animal organism on the eve of death. The permeability of the blood-eye barrier on the operated side was greater under these circumstances than that on the intact side (Fig. 2C). No visible disturbances of the nutrition of the denervated eye, such as corneal opacity, or the appearance of a cataract, which are usually accompanied by an increase in the permeability of the blood-eye barrier, were observed at this period. These differences in the changes in permeability of the blood-eye barrier on the side of the operation were evidently a reflection of the profound disturbance of the trophic state of the denervated blood-eye barrier.

In the case of local irradiation of the denervated eye alone or of both eyes, the initial disturbances of the permeability of their blood-eye barriers appeared with the same regularity as in the case of whole-body irradiation of the animals: an increase in the permeability of the blood-eye barrier of the irradiated eye was observed, and was followed by a period of normalization of the passage of dye into the anterior chamber fluid. Preliminary denervation of the iris had no effect on the character of the disturbance of the permeability of its blood-eye barrier (Fig. 2A, B). In the animals dying at various intervals after operation and local irradiation of the eyes, no changes in permeability took place before death. A marked increase in the intensity of luminescence of the fluorescein penetrating into the anterior chamber fluid of the eye on the side of the operation was observed after local irradiation of the eyes only when opacity of the cornea of the denervated eye was present. This change in permeability was due to the development of a local dystrophic process (neuroparalytic keratitis).

The change in the permeability of the blood-eye barrier to the dye resulting from total exposure to ionizing radiation was thus demonstrated equally on the side of the operation and on the intact side. Total denervation of the iris did not prevent the initial disturbances of the permeability of the blood-eye barrier after local irradiation of the eyes.

The results of these experiments show that the initial reaction of disturbance of the blood-eye barrier as a result of exposure to ionizing radiation is evidently local in character. It does not depend on the integrity of the peripheral innervation apparatus. Denervation of the iris is, however, followed by trophic changes, which are shown, first, by a decrease in the permeability of the blood-eye barrier of the denervated eye from 1 to 1½ months after the operation; secondly, by a more marked increase than on the intact side in the permeability before death of the animals as a result of total exposure to lethal doses of ionizing radiation, and, finally, by the most probable appearance of keratitis after irradiation of the eye on the side of the operation.

The peripheral innervation apparatus thus determines the trophic state of the eye, but has no effect on the magnitude and character of the initial reaction of a change in the permeability of the blood-eye barrier as a result of radiation injury to the eye.

SUMMARY

A complete denervation of the iris of the right eye was attained in rabbits by division of the first branch of the trigeminal nerve with sympathetic fibers and of oculomotor nerve located in the immediate vicinity of the first branch of trigeminal nerve. The operation was carried out under visual control.

Total irradiation of animals in a dose of 1000 r or local irradiation of the eye in the same dose disturbed the hematoophthalmic barrier permeability for the eye both on the operated and the intact side. Evidently, these disturbances had nothing to do with the intactness of the peripheral innervation apparatus.

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