THE ROLE OF THE NERVOUS SYSTEM IN THE PROCESSES OF TISSUE REGENERATION

REPORT III. STIMULATION OF THE CEREBRAL CORTEX AND THE HEALING OF WOUNDS OF THE SKIN

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In our previous reports [6-7] it was shown that disturbance of peripheral innervation either by section of the great auricular nerve or by extirpation of the cervical sympathetic ganglia causes retardation of healing of perforating wounds of the ears of rabbits. In the present paper the healing of perforating wounds of the ear was studied in the same animal during stimulation of the central nervous system, namely of the cerebral cortex.

According to V. I. Baiandurov et al., [1], decortication of young animals has no essential effect on their growth, whereas injury to the corpora striata leads to marked delay in growth. O. S. Val'shonok [2] carried out destruction of fields 4 and 6 of one hemisphere and observed no difference in the healing of ulcers on the forelimbs. According to her results, there is no asymmetry in the healing of ulcers either after stimulation of field 4 by the application of a gauze swab soaked in strychinine. On stimulation of field 6 of the same hemisphere by application of gauze soaked in strychnine, a significant asymmetry was observed in all cases, as shown by the fact that an ulcer of the opposite limb reached its maximum development more rapidly and the period for it to heal was longer than in the case of its fellow. This author further points out the effect of stimulation could only be observed while layers 5 and 6 of the cortex remained undamaged. F. G. Popov [5] studied the healing of wounds of the skin in rabbits with injury to the cortex of one hemisphere and found considerable changes on the side opposite to the damaged hemisphere. These changes took the form of edema of the newly formed tissues, earlier maturation of the connective tissue and a tendency towards keratinization of the epithelium. V. A. Zhukhin and his co-workers [4] studied the course of inflammation and the healing of wounds of the skin in dogs after bilateral extirpation of the cerebral cortex with damage to the corpora striata. In this case the process of regeneration of the connective tissue and especially of the integumentary epithelium was retarded by comparison with controls and took place sluggishly. The numerous experiments carried out by V. G. Eliseev and his co-workers [3] showed that after partial extirpation of the cortex the processes of regeneration proceed quite well and injured internal organs recover, whereas if gauze is applied to the surface of the hemispheres healing of wounds takes place but not regeneration of typical organ tissue as such, although the macrophagic and fibroblastic reactions are intensified and the formation of a connective tissue capsule around a foreign body is accelerated.

EXPERIMENTAL METHOD

In the present investigation, carried out on 28 adult rabbits weighing about 2 kg each, we studied the healing of perforating wounds of the ears after the introduction of a foreign body into the subdural space of one cerebral hemisphere. The right ear (corresponding to the operation on the left hemisphere) was the "experimental" one and the left ear the control.

The foreign body used was thick x-ray film cleaned of its emulsion, from which a small plate measuring 1 x 2 cm was cut out; the plate was rounded, folded in two longitudinally and inserted under the dura mater. On the day after the operation standard puncture wounds 6 mm in diameter were inflicted on symmetrically placed areas of both ears. Areas of tissue from the margins of the wound were taken for histological examination on the 1st, 2nd, 4th, 8th, 10th and 16th day after infliction of the wounds. The material was fixed in 20% formalin, cut into sections with a refrigeration microtome, and the preparations stained with hematoxylin – eosin. In 12 rabbits macroscopic observations were carried out and the time of healing of the wounds recorded. Three of these rabbits died before the perforating wounds had healed and the degree of healing was judged by the size of the orifice which remained.

EXPERIMENTAL RESULTS

Histological study of the tissue of the wound margin 24 hours after its infliction showed that at this time a scab is formed along the margin of which there is a well marked leucocytic barrier. The connective tissue of the dermis, especially along the cartilage, is infiltrated by leucocytes throughout the whole extent of a 10 mm long section. The epithelium along the edge of the wound was separated from dead epithelium and formed a thickening. No difference was observed between the wounds of the right and left ears.

Two days after wounding the leucocytic barrier has become more massive, but infiltration of connective tissue in areas remote from the edge of the wound has diminished. The epithelial layer is thickened for a distance of 4 mm from the edge of the wound, and in places it consists of 6-7 layers of cells of the stratum germinativum and 2 rows of cells of the stratum granulosum, reaching 80 μ in thickness (normally the thickness of the epidermal layer here is usually no more than 20 μ and it is formed from 2-3 rows altogether of cells of the stratum germinativum and one incomplete row from the stratum granulosum). Epithelial wedges are formed and these infiltrate under the scab. We did not observe any difference between the conditions of the wounds on the right and left ears.

Healing of Perforating Wounds in Rabbits During Stimulation of the Cerebral Cortex

Serial No.	Rabbit No.	Time for healing of wounds (in days)		Ratio of healing time of right ear to healing time of left (in %)	Note
		right ear (experimental)	left ear (control)		
1	17	76	89	85	
2	18	26	29	89	
3	19	20	25	80	
4	20	0.5×0.5	1×3	—	Died after 30 days
5	21	22	24	91	
6	22	32	49	65	
7	23	2×2	4×4	—	Died after 30 days
8	24	29	35	83	
9	25	44	2×3	—	Observation ended after 86 days
10	26	44	44	100	
11	27	55	69	80	
12	28	5×6	7×7	—	Died after 30 days

Four days after wounding there is already considerable epithelial regeneration as far as the cartilage and, in some places, actually penetrating it. The leucocytic infiltration of the connective tissue is no longer evident; the formation of new, young connective tissue is seen, especially beneath the regenerating epithelium. Some delay is now observed in the growth of the regenerating epithelium in the left ear by comparison with the right.

Eight-ten days after wounding, in all cases the infiltration of epithelium under the scab is now finished

and the regenerating epithelium of the internal and external surfaces of the helix of the ear merge together. There is regeneration of the dermis over a variable length, projecting beyond the cut edge of the cartilage. There is a difference between this regeneration in the right and left ears: in the right ear the regeneration is seen to extend over a longer distance and is thicker.

Sixteen days after wounding areas of regeneration are seen to project far beyond the cut edge of the cartilage, and in all cases the length of the regenerating area is greater in the right ear.

Macroscopic observations showed that in 11 out of 12 cases the wounds on the right (experimental) ear healed more quickly, although the differences were variable, as can be seen from the Table. Of 8 rabbits in which the perforating defects closed in both ears, in 7 cases closure of the orifice took place more rapidly on the right, on the side opposite to the operation, but in one case the wound defects closed simultaneously after 44 days. In three cases the wounds did not succeed in closing on either ear, but the residual orifice was smaller on the right ear. Finally in one rabbit the defect on the right ear closed after 44 days, and on the left ear at this time an orifice remained open, measuring 2-3 mm, which persisted until the 86th day when the observations were discontinued.

Thus the experimental results showed that the insertion of a foreign body in the subdural space does not lead to asymmetry in the course of the wound in the first few days. Starting on the 4th day, and becoming more marked subsequently, a speeding up appears in the regenerative process on the side opposite to the cerebral hemisphere on which the operation was performed. The microscopic findings are in agreement with the results of the healing times of the wounds.

The results of this investigation are similar to those of our previous work [8] on the study of healing of wounds in rabbits after partial decortication.

The resemblance between the results obtained suggests that both extirpation of a small area of cortex and the insertion of a foreign body into the brain tissue in our experiments led to the same physiological effect, i.e. to stimulation of the residual, larger area of cortex, and causing activation of the processes of regeneration. The possibility of such activation is also shown by the results of our investigations (Prizhivoit and Aubakirov [9]), in which it was shown that stimulation of the cerebral cortex by injection of caffeine accelerates the course of regeneration in the skin.

Our findings are in agreement with the observations of Popov (1954), who established the presence of asymmetry of the processes of regeneration after unilateral trauma to the forebrain in rabbits. At the same time they differ from the findings of O. S. Val'shonok [2]. This may possibly be due to the fact that O. S. Val'shonok's work was done on dogs, and more important, she used stronger forms of stimulation which could affect not only the cortex of one hemisphere but also the opposite cortex and the subcortical ganglia.

In our experiments the rate of closure of the perforating defect of the ear was determined by the processes taking place in the connective tissue. The marked acceleration of these processes during stimulation of the cortex is in agreement with the findings of V. G. Eliseev [3] of acceleration of the fibroblastic reaction and the more rapid formation of a connective tissue capsule around a foreign body under similar conditions.

The same type of effect on the process of regeneration in rabbits after removal of a part of the cortex and the application of a gauze swab was observed by A. A. Savinovskaia [10], who studied the mitotic activity in the mesothelium after the injection of air into the peritoneal cavity, and found that chronic irritation had a more pronounced effect than partial decortication. These results are in agreement with our own observations.

Our experiments have thus shown that by stimulation of the cerebral cortex of adult rabbits it is possible to influence the course of the process of regeneration (the healing of wounds of the skin) and that disturbance of cortical activity does not cause any retardation in the process of regeneration, as we have seen after disturbance of the peripheral innervation [16, 17], but may even lead to acceleration of regeneration.

SUMMARY

The author studied the healing of penetrating wounds in the rabbit's ears. He inserted a foreign body, a piece of x-ray film, under the dura mater on the surface of the left cerebral hemisphere of these experimental animals. A quicker healing of the wounds was noted on the right side, as compared with the left (i.e. on the side innervated by the mechanically stimulated cerebral hemisphere).

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