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The expression of erythropoietin and its receptor in the developing rat retina

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Evidence from a number of studies indicates that the erythropoietin (EPO) does not only affect the haematopoietic system, but it exhibits neuroprotective and neurotrophic properties in the central nervous system and in the retina. Both the erythropoietin and its receptor (EPOR) are expressed in the retina, however, their cellular distribution and physiological role are not known. In the present study, we examined developing postnatal and adult rat retinas by EPO- and EPOR-specific antibodies with single and double labeling techniques in order to identify the temporal and spatial onset of their expression in the mammalian retina.

Retinas from Sprague-Dawley rats of different developmental ages were collected and analysed by immunohistochemistry. Following fixation and cryoprotection 10 µm thick frozen sections were cut from each specimen and stained with EPO and EPOR-specific antibodies. In double labelling experiments the horizontal cell-specific anti-calbindin antibody and the cone-specific marker PNA were also used. The labelling was visualised by the ABC method or by fluorescent antibodies and analysed by light or confocal microscopy.

At the time of birth the EPO-specific staining resulted a strong cytoplasmatic labelling in the ganglion cell layer and a weak, diffuse staining in the neuroblast layer. On the following days strong membrane immunoreactivity appeared in the developing horizontal and amacrine cells, and by the end of the first postnatal week the entire inner nuclear layer became positively stained. From the beginning of the second postnatal week on immunopositivity in the inner and outer plexiform layers and in the developing photoreceptor processes was also observed. The same result was found in the adult, where the cells of the ganglion cell layer and the inner nuclear layer, both plexiform layers and the photoreceptor inner segments bound the EPO-specific antibody. The staining pattern of the EPOR-specific antibody and the time of onset of the immunopositive elements showed big similarity to that of the EPO-specific antibody.

Since the spatial and temporal onset of the expression of the erythropoietin and its receptor correlates with the postnatal developmental events of rat retina, our findings suggest the involvement of the erythropoietin in the regulation of cell maturation, developmental apoptosis and synaptogenesis.

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Centrifugal visual fibers arising from the limbic system and the hypothalamus

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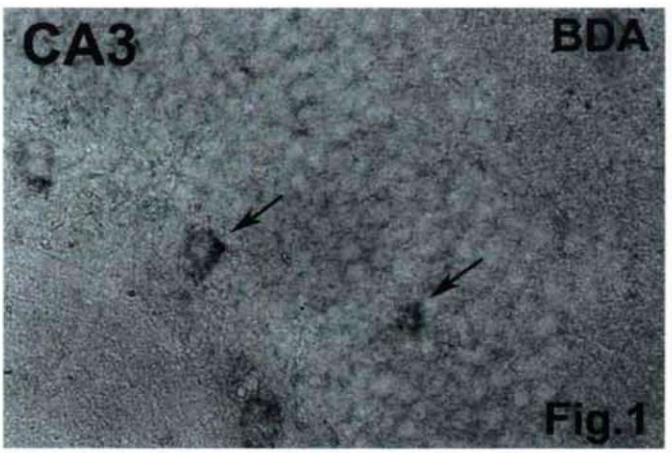
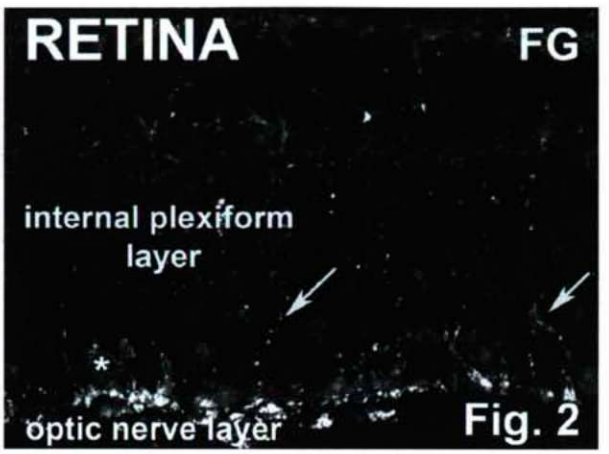
It is already known that the optic nerve contains centrifugal fibers which are positive to VIP, LHRH or PACAP, but their origin had not yet been fully elucidated.

In our experiments utilizing the retrograde and anterograde transport of tracers (biotinylated dextran amine[BDA] and Fluorogold [FG], respectively) we have provided direct evidence for the cells of origin of a limboretinal and hypothalamoretinal pathways in rats and the termination of the centrifugal visual fibers in the retina using light microscopic approach. With the use of adult male rats following intravitreous injection of 10 000 kD BDA into the right eye, we have found retrogradely labeled





BDA neurons in subregions of the hippocampus (in CA1, CA3) and dentate gyrus at both sides. We have also observed BDA containing neurons in the induseum griseum, lateral habenulae and in the olfactory tubercle. In the hypothalamus 1-2 BDA positive cells were seen in the lateral acessory magnocellular and in the supraotic (SO) nuclei. The major part of labeled cells were observed in the hippocampal formation (Fig. 1, arrows indicate labeled cells). It was estimated that the total number of retrogradely labeled cells in this formation is 1495±516. We have seen fiber labeling in the retinorecipient suprachiasmatic nucleus and in the primary visual center, the lateral geniculate body, but labeled nerve cell bodies in these structures were never seen indicating that the tracer was transported anterogradely in these structures. Iontophoretic administration of FG into the hippocampal formation, where the major part of BDA labeled cell bodies were observed, has resulted in labeled fibers in the optic nerve and in the retina at both ipsi- and contralateral sides indicating that the retrogradely labeled cells in the hippocampus and the dentate gyrus among others are the cells of origin of centrifugal visual fibers (Fig. 2, arrows indicate FG labeled fibers in the internal plexiform layer, * shows an unlabeled ganglion cell). Double labeling revealed that the retrogradely labeled neurons in the hippocampus were also positive to LHRH or to VIP or to PACAP. Some of the BDA positive cells in the induseum griseum and in the olfactory tubercle were LHRH immunopositive, and some of them in the SO and in the dentate gyrus were PACAP immunopositive, and some of them in the dentate gyrus were VIP immunopositive. On the basis of our results it was concluded that the abovementioned structures of the limbic system and the hypothalamus send LHRH, VIP and PACAP containing fibers to the retina where they terminate. The potential importance of these centrifugal fibers remain unknown, but like in other sensory organs, they provide central feedback to this sensory system and they might influence the visual input of the retina to the central nervous system.

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