In Vivo Expression of Neurotrophins and Neurotrophin Receptors Is Conserved in Adult Porcine Retina In Vitro

Mónica García, Valerie Forster, David Hicks, and Elena Vecino

**PURPOSE.** To characterize and compare the expression of neurotrophins (NTs) and their receptors within adult porcine retinal ganglion cells (RGCs) in vivo and in vitro.

**METHODS.** The distribution of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and -4 (NT-4), and their high-affinity receptors TrkA, TrkB, TrkC and low-affinity receptor p75, was analyzed in adult porcine retinal sections by immunohistochemistry. In addition, adult porcine retinas were dissociated and cultured in four different conditions: control, semipurified RGCs, supplemented with BDNF, or seeded on Müller glia feeder layers. Double immunostaining was performed with antibodies to NTs or their receptors combined with neurofilament antibody to identify RGCs in culture.

**RESULTS.** In vivo, immunolabeling of NGF was very faint, BDNF was especially prominent in RGCs and inner nuclear layer cells, NT-3 stained widespread nuclei, and NT-4 was undetectable. TrkA immunoreactivity was visible in the nerve fiber layer, TrkB staining was within RGC bodies, TrkC was undetectable, and p75 was widely expressed across the retina, within the Müller glia. Expression of neurotrophins and their receptors was maintained in all four models of adult RGCs in vitro, showing that expression was not influenced by substrate or culture conditions. We observed prominent staining of TrkA within growth cones, and a clear expression of p75 within a subpopulation of RGCs in vitro.

**CONCLUSIONS.** These findings demonstrate that the expression of NTs and their receptors within adult porcine RGCs is maintained in vitro under conditions of limited interaction with neighboring neurons and deprived of afferent inputs and target tissue. TrkA may be involved in regeneration of nerve terminals. (Invest Ophthalmol Vis Sci. 2003;44:4532–4541) DOI:10.1167/iovs.03-0419

**Neurotrophins (NTs)** are members of a small family of evolutionarily well conserved neuropeptides,1,2 which includes nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and neurotrophin-3 (NT-3) and -4 (NT-4). They act as ligands for tyrosine kinase receptors, which are either high-affinity (Trk family) or low-affinity (p75) receptors. These receptors bind to two types of receptors, the high-affinity Trk receptors (TrkA, TrkB, and TrkC) and the low-affinity receptor p75.

Whereas p75 binds all neurotrophins with similar affinity,3 the three Trk receptors bind one or two NTs in a preferential manner.4 NTs were originally discovered as survival and neurite growth-promoting agents, but it is now known that these molecules exert multiple effects on neurons and glia, including proliferation, transmitter synthesis, cytoskeletal changes, synaptic transmission, reorganization, and plasticity.5–7

NTs are retrograde signaling molecules that are taken up at the target site and transported from axon terminals to the cell body. It has been demonstrated that p75 is retrogradely transported by RGCs,8 and BDNF is transported from the superior colliculus or the optic tectum to RGCs.9 Other studies have shown that BDNF can be transported anterogradely and may act as an afferent factor.10,11 Moreover, it has been shown that a substantial fraction of the BDNF found in retina is derived from local sources, suggesting that BDNF could act as an autocrine trophic factor supporting RGC survival.12–13

Numerous studies have analyzed the effects of NTs on mammalian RGCs after optic nerve section or crush in vivo,14–18 after ischemia,19–22 and in disease states such as diabetes and glaucoma.23 NGF, BDNF, and NT-4 significantly delay cell death of RGCs, but fail to permanently rescue these cells after injury. Recent studies have shown that BDNF administration combined with TrkB transfection further delays axotomy-induced RGC death.24

Retinal localization of NTs and their receptors has been described in different species: fish,25,26 frog,27,28 chick,29 rat,30–33 monkey,34 and humans.35 The pig is an appropriate animal for ophthalmology because the retina presents structural, physiological, and immunologic characteristics similar to humans. The retina of this species possesses a size and cellular composition similar to that of humans, with a macula-like area enriched in cones.36 A transgenic strain exhibiting inherited retinal degeneration similar to human retinitis pigmentosa has been prepared.37 Very recently, successful transplantation of fetal pig retina to recipient adult porcine eyes has been performed.38 Moreover, recently, we have studied the effect of BDNF and different substrates on the survival of cultured adult porcine RGCs.39 The purpose of the present study was to provide additional data validating porcine RGC cultures as a useful model for studying neurotrophic effects in higher mammalian retina, through the analysis of the distribution of neurotrophins and their receptors in vivo and comparison to their expression in vitro.

**MATERIALS AND METHODS**

**Tissue Collection**

All animal experimentation adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. Eyes of adult pigs were obtained from a local abattoir and transported to the laboratory in cold CO2-independent Dulbecco’s modified Eagle’s medium (DMEM/CO2; Invitrogen-Gibco, Cergy-Pontoise, France). Eyes were dissected within 1 to 2 hours after enucleation.

**Tissue Preparation**

**Retinal Sections.** After sectioning around the cornea was performed, the lens and vitreous were removed and the eye cups fixed by...
immersion in 4% paraformaldehyde for 4 hours. Then the retinas were carefully isolated, cryoprotected in 30% sucrose in PBS for 12 hours at 4°C, embedded in medium (Tissue Tek; Leica, Heidelberg, Germany), and frozen in liquid nitrogen. Retinas were sectioned at 12- to 16-μm thickness in a cryostat, collected onto gelatinized slides, and stored at −20°C. 

**Cell Cultures.** Retinal cell cultures were prepared according to a method previously described.\(^2^\) with the minor modifications reported in García et al.\(^3^\) In the present study, we used only an approximate 1-cm\(^2\) circular area located in the central superior region immediately nasal to the optic nerve head between the principal blood vessels in the retina, chosen because of the relatively constant size and density of RGCs. The sample was chopped into approximate 1- to 2-mm\(^3\) fragments, washed in Ringer’s solution, and incubated in 0.5 mL of 0.2% activated papain (Worthington, Lakewood, NJ) in the same buffer for 20 minutes in a water bath at 37°C. The pieces were gently dissociated by repeated trituration, and isolated cells were seeded in DMEM/Ham’s F-12 (Invitrogen-Gibco) and penicillin-streptomycin (10 IU). For the semipermeable RGC cultures, the RGC layer was isolated by vibratome sectioning; the retinal sample was embedded in 3% agarose and sectioned according to a protocol previously described,\(^4^\) except that the RGC layer was collected instead of the outer nuclear layer. The sample was dissociated as described earlier. After determination of the number of cells and viability by examination of trypsin blue vital dye exclusion using a hemacytometer, cells were seeded at 5 × 10\(^5\) cells/cm\(^2\) onto sterile 12-mm glass coverslips precoated sequentially with poly-lysine (2 μg/cm\(^2\) for 1 hour; Sigma-Aldrich, Cergy-Pontoise, France) and laminin (1 μg/cm\(^2\) overnight; Sigma-Aldrich). Cells were maintained in a humidified incubator at 37°C in an atmosphere of 5%CO\(_2\)/95%O\(_2\) for 24 hours in DMEM-5%FCS, before they were rinsed twice in serum-free DMEM and then maintained in chemically defined medium (CDM) for 5 days. 

**Experimental Treatments.** The different treatments were performed as previously described.\(^5^\) Briefly, cultures were either exposed to 10 ng/mL BDNF (R&D Systems, Abingdon, UK), or seeded on preformed, fully confluent retinal Müller glia (RMG) monolayers. 

**Immunohistochemistry.** 

**Sections.** Sections were thawed and rinsed twice in PBST buffer (0.1 M phosphate-buffered saline containing 0.25% Triton X-100, Sigma-Aldrich) for 10 minutes. Sections were then incubated overnight at 4°C in a humidified chamber with the following antibodies diluted in PBST buffer and containing 1% bovine serum albumin (BSA; fraction V; Sigma-Aldrich): NGF (dilution 1:500, no. 549), BDNF (dilution 1:200, no. 546), NT-3 (dilution 1:500, no. 547), NT-4/5 (dilution 1:500, no. 545), TrkA intracellular domain (dilution 1:500; no. 118; all from Santa Cruz Biotechnology, Santa Cruz, CA); TrkB intracellular domains (rabbit anti-TrkB diluted 1:100; no. 119; Transduction Laboratories, Louisville, KY); TrkC intracellular domains (dilution 1:250; no. 117; Santa Cruz Biotechnology); and anti-human p75 antibody (dilution 1:1500; kindly provided by Moses Chao, New York University School of Medicine, NY). Sections were then rinsed in PBST and incubated for 1 hour in goat anti-rabbit IgG-Texas red (10 μg/mL; Molecular Probes, Eugene, OR) and 1:1000 4,6-diamidino-2-phenylindole (DAPI; Molecular Probes) to visualize the nuclei. Sections were incubated for 1 hour with an anti-neurofilament (NF) 200-kDa subunit monoclonal antibody diluted 1:200 (Molecular Probes) and anti-neurotrophin or anti-neurotrophin receptor polyclonal antibody, at the concentrations indicated earlier, washed with PBS, and incubated for 1 hour with goat anti-mouse IgG conjugated to a fluorophore (Bodipy FL; 10 μg/mL, for the monoclonal primary antibody; Vector Laboratories, Burlingame, CA) or goat anti-rabbit IgG-Texas red (10 μg/mL, for the polyclonal primary antibody; Molecular Probes). Nuclei were stained with DAPI (1:1000; Molecular Probes). Incubated with the fluorescent secondary antibody. Preparations were washed with PBS, mounted, and observed as just described.

Immunocytochemical control experiments consisted of omission of the primary antibody, omission of the secondary antibody, and use of the corresponding nonimmune serum.

**RESULTS.**

**Adult Porcine Retina In Vivo.** In retinal sections (Fig. 1), NGF immunostaining was very faint, with only a few immunopositive cells in the ganglion cell layer (GCL). In addition, NGF-immunoreactive fibers were visible as a dotted pattern at the vitreal surface of the inner plexiform layer (IPL; Fig. 1B). BDNF immunolabeling was distinct in the cell cytoplasm of all RGCs (large, medium, and small) as well as in many cells in the inner nuclear layer (INL), including amacrines cells along the vitreal border (Fig. 1C). Cells in the INL and GCL were also immunolabeled with anti-N1-5. The pattern of N3-immunoreactivity differed among cells, with most displaying only nuclear localization, whereas others exhibited cytoplasmic staining in addition. Intense NT3-immunoreactivity was also observed in the nerve fiber layer (NFL; Fig. 1D). NT-4 immunoreactivity was detected in retinal sections as scant, weakly labeled vertical fibers crossing the IPL, probably corresponding to RMG (Fig. 1E). No NT-4 immunopositive RGCs were observed.

With respect to NT receptors, TrkA immunolabeling was detected in astrocytes localized within the NFL and GCL. In the latter, the resolution is insufficient to conclude whether TrkA is present at the cell surface or only in astrocytes surrounding ganglion cells (Fig. 1G). Faint Trk-B immunoreactivity was observed in the three different types of RGCs (large, medium, and small). Axons were not labeled, as shown by the absence of immunoreactivity within the NFL (Fig. 1H). TrkC was absent from both the GCL and NFL, being exclusively localized within photoreceptor outer segments (not shown; Fig. 1I). p75 was present in RMG, showing intense labeling present throughout the retina from the outer to inner limiting membranes (OLM and ILM, respectively). It was difficult to confirm the presence of p75 within the plasma membrane of RGCs because of the surrounding RMG (Fig. 1J). 

**Adult Porcine Retina In Vitro.** In most cases the immunolabeling patterns of neurotrophins and their receptors did not differ between the four experimental conditions examined. As a consequence, results are not given for each condition, unless specific differences were observed. NGF was mainly localized to RGC somata, its distribution in neurites being restricted to the region most proximal to the cell body. The pattern of NGF immunoreactivity was diffuse but showed a number of intense dots located in the cytoplasm. This pattern of immunoreactive dots was present in all examined cells, regardless of cell size or culture conditions (Figs. 2A–F). BDNF expression was observed in all RGCs, mainly in the somata and very seldom in neurites in both control and RMG feeder layer cultures. In addition to RGCs, many other neurons unstained by NF antibodies showed intense BDNF immunoreactivity. These cells were probably amacrine cells and possibly other types from the INL (Figs. 2G–J). There was distinct RGC subpopulation-dependent staining for
NT-3 in culture: large RGCs expressed NT-3 in the cell body and neurites (Figs. 3A, 3B), whereas small RGCs showed immunoreactivity only in the nucleus (Figs. 3C, 3D). Cultured cells other than RGCs also showed this heterogeneity in labeling: most of the RMG nuclei were immunostained for NT-3, and many small neurons showed NT-3 immunoreactivity either in the nuclei or in the cytoplasm (Figs. 3A–D, 4A). NT-4 antibody did not reveal any visible staining of RGCs or other cells (Figs. 3E, 3F).

In vitro expression of TrkA was observed in RGCs, with receptor distribution appearing concentrated within nerve terminals. TrkA-immunoreactivity within the neurites was visible but faint, whereas there was prominent immunolabeling of TrkA within the growth cone where NFs were no longer present (Figs. 4B, 5A–D). The robust expression of this receptor in growth cones was evident in all conditions independent of the substrate or culture conditions (Fig. 4B). TrkB-immunolabeling was more intense and occurred in both RGC soma and neurites. The presence of BDNF in the culture medium or the use of RMG feeder layers did not affect expression of this receptor (Figs. 5E–H). RGCs in vitro were not detectably immunopositive to anti-TrkC. Intense p75-immunolabeling was observed in a subpopulation of RGCs. In both semipure RGC cultures and those growing on RMG feeder layers, some cells were clearly p75 immunopositive, whereas adjacent ones of similar size and morphology were nonimmunoreactive (Figs. 6A–D). In addition, RMG also expressed p75 (Fig. 6D). Comparison of the detailed staining patterns of p75 and NF immunoreactivity in RGCs revealed the former to have a slightly broader profile, outlining the plasma membrane (Figs. 6E–G). In addition, a few NF-immunonegative processes were labeled by anti-p75 (Figs. 6F, 6G).

**DISCUSSION**

The expression and distribution of NTs and their receptors within adult porcine RGCs, except for TrkA and p75, were similar in vivo and in vitro. Moreover, BDNF addition or use of RMG as a feeder layer did not influence expression. These results indicate that adult porcine RGCs, after dissociation and separation from their targets and presynaptic inputs, and with only limited interaction among neighboring neurons, are able to maintain their normal in vivo expression of these molecules. The intrinsic capacity for in vitro re-expression of in vivo characteristics has also been demonstrated in postnatal feline RGCs.

**NGF and TrkA**

Our results demonstrate that porcine retina expresses NGF at low levels as has been described in other species. It has been reported that NGF promotes functional recovery of RGCs after ischemia and enhances the survival of axotomized RGCs in adult rats. Moreover, retro-ocular administration of NGF reduces RGC loss in an experimental model of ocular hypertension in rabbits, suggesting a neuroprotective role for NGF.

Effects of NGF on neurite outgrowth are not clear, although it has been found that NGF promotes neurite outgrowth in chick and fish retinal explants.

NGF acts mainly through TrkA receptors. Expression of TrkA in pig RGCs was at the limit of detection, consistent with data obtained for RGCs of adult rat retinas. Recently, it has been reported that the number of RGCs that express Trk receptors increases during the initial period of axonal regeneration. This situation has also been described in fish, in which TrkA expression in RGCs increases during axonal regeneration. In human retinas it has been observed that TrkA immunoreactivity on RGC axons decreases as development advances, suggesting that, as neurons mature, they become less dependent on NT for survival and downregulate expression of their receptors. However, one study has described the presence of TrkA in adult human optic nerve, suggesting that NTs may be essential for normal maintenance of glial cells. TrkA expression is not detected in chick RGCs in vivo, but is...
detected in vitro,\textsuperscript{45} where receptor expression could be a response to the low amounts of NTs in culture conditions. An explanation for the robust TrkA immunostaining observed in growth cones could concern exploration for favorable target sources of NGF, the enrichment of terminal TrkA receptor facilitating the capture of trophic factor. Additional experiments specifically blocking TrkA receptors are needed, to demonstrate the physiological role of this receptor within RGCs. In addition to RGCs, we observed intense TrkA immunolabeling in the NFL of porcine retina. Double immunostaining with anti-TrkA and anti-GFAP shows that these immunopositive fibers correspond mainly to astrocytes,\textsuperscript{46} and TrkA-immunopositive astrocytes were also found in cultures.

**BDNF and TrkB**

Most if not all RGCs express BDNF and TrkB, both in vivo and in vitro. The source(s) of retinal BDNF are somewhat controversial. It has been demonstrated that BDNF is produced in target tissues and is retrogradely transported through the optic nerve to the retina.\textsuperscript{47} Neurons in the superior colliculus express BDNF mRNA,\textsuperscript{11} suggesting the existence of retrograde transport of this NT. Moreover, the presence of TrkB within RGC axons in the optic nerve has been detected,\textsuperscript{48} and accumulation of TrkB and BDNF has been described in optic nerve head during chronic glaucoma in monkeys.\textsuperscript{47} Other investigators have demonstrated the presence of BDNF mRNA\textsuperscript{49} and

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**Figure 2.** Photomicrographs of cultured RGCs double immunostained with NF and NT antibodies. (A, D, G, I) NF; (B, C, E, F) NGF; (H, J) BDNF. (A–C) Cells growing in control conditions (A, B, arrows). (C) Higher magnification of (B), to visualize in detail the immunofluorescent dots corresponding to high local concentrations of NGF (open arrowheads). (D–F) Cells growing on RMG feeder layers (D, E, arrows). (F) Higher magnification of (E) showing immunofluorescent dots within the cell body (open arrowhead). Note that the neurites of the cell in (E) were not immunolabeled. (G, H) Cells growing in control conditions. (H) BDNF-immunolabeled RGCs labeled by NF (arrows), as well as other small cells not corresponding to RGCs. (I, J) Cells growing on RMG. Note that RGCs (I) were positive for BDNF (arrows), with an additional population of small BDNF-immunoreactive cells, probably amacrine cells (open arrowheads). Scale bar, 25 μm.
protein\textsuperscript{13,22,29} in mammalian RGCs. Furthermore, BDNF has being demonstrated to be anterogradely transported in the central nervous system of rat\textsuperscript{11,50} and chicken,\textsuperscript{10} acting as a survival factor for postsynaptic neurons in the superior colliculus and lateral geniculate nucleus.\textsuperscript{51}

It has been demonstrated that RGCs can upregulate gene expression of BDNF in response to RGC axonal injury\textsuperscript{52} or after ischemic insults.\textsuperscript{22,28} BDNF-immunopositive RGCs and the percentage of RGCs expressing TrkB are increased after axotomy, suggesting that intrinsic rescue mechanisms may contribute to short-term survival.\textsuperscript{53} Axonal transport of TrkB has been implicated because intensive and persistent TrkB labeling in the NFL has been seen in adult rat retina after experimental optic nerve lesion,\textsuperscript{18} suggesting that TrkB may be axonally transported and stored in axons. Axonal transport of TrkB receptors may thus occur in both directions, either produced in RGC somata and anterogradely transported\textsuperscript{59} or alternatively sequestered at nerve terminals and retrogradely transported to RGC somata.\textsuperscript{54}

Injections of BDNF within the retina enhance RGC survival, indicating the presence of functional NT receptors within in vivo RGCs. Exogenous application of BDNF promotes survival of RGCs in vivo after axotomy,\textsuperscript{14-17} in moderately chronic hypertensive eyes in rats,\textsuperscript{55} and after optic nerve damage in cats.\textsuperscript{30} In addition, BDNF supports the survival of cultured RGCs from several species including rat,\textsuperscript{57} chick,\textsuperscript{58} and frog.\textsuperscript{26} It has also been shown that BDNF promotes regeneration of RGC neurites in culture\textsuperscript{26,59} and increases axonal length of frog\textsuperscript{26} and porcine RGCs in culture.\textsuperscript{36} In addition, BDNF regulates the complexity of terminal arbors of RGCs in vivo.\textsuperscript{26} All these effects of BDNF on cultured RGCs are in agreement with our results in vitro and in vivo, where both BDNF and TrkB were present in RGCs and thus possibly act in an autocrine manner\textsuperscript{9,13} rather than only as a retrogradely transported survival factor, as has been believed.

**NT-3 and TrkC**

Many cells within the GCL expressed NT-3 both in vivo and in vitro, including RGCs, displaced amacrine cells, and glial cells. Localization of immunoreactivity was mainly within the nucleus and perinuclear cytoplasm, similar to that described in other species, including fish\textsuperscript{21} and rat.\textsuperscript{29} The function of NT-3 has been closely correlated with correct development, because it has been observed that antibodies that block NT-3 impair normal retinal development in chick embryos.\textsuperscript{60} NT-3 promotes conversion of neuroepithelial cells into neurons during chicken retinal development\textsuperscript{60} and facilitates the differentiation of retinal neurons in culture.\textsuperscript{64} In addition, NT-3 promotes
the survival of differentiated RGCs.\textsuperscript{61} Responsiveness of differentiated RGCs to NT-3 occurs preferentially within a narrow period of retinal development, coincidental with the time that RGC axons reach their field of innervation. This developmental period also coincides with the time of maximal arborization and synapse formation within the retina.\textsuperscript{61} Therefore, NT-3 has a role in central nervous system development that is distinct from and earlier than its role in promoting survival of differentiated neurons. It has been suggested that the two actions are probably exerted through two distinct types of NT-3 receptors,

\textbf{Figure 4.} Color photomicrographs of cultured RGCs in control conditions. (A) Triple staining with NT3 (red), NF (green), and DAPI (blue). Arrow: RGCs showing NT3-immunoreactivity in the nucleus; other retinal cells did not reveal visible nuclear staining for this NT (open arrowheads). (B) Double immunostaining of TrkA (red) and NF (green). TrkA expression was present in the soma in addition to the growth cones (open arrowheads), where NFs were no longer present. Scale bar, 25 μm.
the first type appearing coincidentally with the main onset of retinal differentiation, the second type being expressed later when most retinal cells have already differentiated. We also observed NT-3 immunoreactive fibers in the NFL. It has been demonstrated that astrocytes express and may secrete NT-3, which could stimulate oligodendrocyte proliferation in the optic nerve. Recently, it has been demonstrated that NT-3 is produced by RGCs in chicken embryos and that some of this NT-3 is transported anterogradely to the optic tectum, possibly to regulate survival, synapse formation, or dendritic growth of tectal neurons. The p75 receptor is exported along RGC axons to the retinotectal terminals and may act as a carrier for NT-3.

We did not find TrkC-immunopositive RGCs either in vivo or in vitro. Similar results have been found in other species. During chicken retinal development, TrkC mRNA is present in all cell layers, whereas its protein product has been only localized within the inner retinal layers. TrkC is not expressed in rat retina during development, and the proportion of TrkC-immunopositive RGCs in adult rat is low.

p75

p75 is clearly expressed only by RMG in vivo, but it is present with high intensity in soma and most neurites of a subpopula-
tion of RGCs in vitro. It is difficult to confirm whether RGCs express p75 in vivo, because RMG processes tightly surround them. Other investigators have reported that p75 is not detected in adult rat RGCs,63 and it has been shown that in vivo p75 labeling is restricted to RMG.64 However, another study demonstrated the presence of p75 mRNA in a subpopulation of RGCs,65 in agreement with the findings of the present study in vitro. Because Müller cells are immunopositive for p75 in retinal sections, we chose two opposite conditions: RGCs growing in semipure cultures, in which Müller cells are absent, and RGCs on Müller cell monolayers. In this way, we were sure that p75-immunolabeled Müller cells did not mask p75-immunoreactivity in RGCs in vitro.

It has been described that presumptive RGCs express p75 during development in rat,8 monkey,31 and chick.60 Thus, it is possible that cultured RGCs re-express molecules normally found during development. In older animals, expression of p75 is much reduced in the GCL, and its absence has been noted in adult rat RGC.64 The p75 receptor has been implicated in the retrograde axonal transport of BDNF, NT-3, and NT-467 and is the major carrier of exogenous NT-3 during anterograde axonal transport.68 Differential retrograde and anterograde axonal transport of NTs and/or differential signaling of cell death or survival may be regulated by p75 targeting.68 It is possible that p75 delivers NT-3 from the cell body to the axon terminal by anterograde action, and takes BDNF back from the terminals to the cell body by a retrograde mechanism.69

In summary, our study demonstrates that the distribution of NTs and their receptors in the retina of the adult pig resembles that described in other mammals. Expression is conserved in RGCs in vitro, suggesting that, although culture conditions differ greatly from the in vivo environment, RGCs maintain the capacity to express these molecules in the absence of normal cellular interactions. It is plausible that re-expression of Trk receptors at the growing neurite tip may be involved in regeneration and/or guidance.

References

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