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Invited Review

Neurotrophins in the developing and regenerating visual system

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Summary. The neurotrophins NGF, BDNF, NT-3 and NT-4 have a wide range of effects in the development and regeneration of neural circuits in the visual system of vertebrates. This review focuses on the localization and functions of neurotrophins in the retina, lateral geniculate nucleus, suprachiasmatic nucleus, superior colliculus/optic tectum, and isthmic nuclei. Research of the past 20 years has shown that neurotrophins and their receptors are localized in numerous visual centers from the retina to the visual cortex, and that neurotrophins influence proliferation, neurite outgrowth and survival of cells in the visual system in vitro and in vivo. A relationship between electrical activity and neurotrophic functions has been established in several visual centers in the CNS, and neurotrophins have been implicated in synaptic plasticity in the visual cortex. Besides functions of neurotrophins as retrograde, target-derived trophic factors, recent data indicate that neurotrophins may have anterograde, afferent as well as local, paracrine actions in the retina, optic nerve and the visual cortex. Some neurotrophins appear to regulate proliferation and survival of glial cells in the optic pathways. Neurotrophins increase the survival of retinal ganglion cells after axotomy or ischemia and they promote the regeneration of retinal ganglion cell axons in some vertebrates. Neurotrophins also rescue photoreceptors from degeneration. These findings implicate the neurotrophins not only as important regulators during development, but also as potential therapeutic agents in degenerative retinal diseases and after optic nerve injury.

Key words: Retina, NGF, BDNF, NT-3, Optic nerve

Abbreviations

BDNF: brain-derived neurotrophic factor
CNS: central nervous system
GCL: ganglion cell layer (retina)
INL: inner nuclear layer (retina)
ION: isthmo-optic nucleus
LGN: lateral geniculate nucleus
NGF: nerve growth factor
NGFR: nerve growth factor receptor (=p75 neurotrophin receptor)
NT-3: neurotrophin-3
NT-4: neurotrophin-4 (neurotrophin-4/5)
ONL: outer nuclear layer (retina)
P75: p75 neurotrophin receptor (75 kD protein)
PE: pigment epithelium (retina)
RGC: retinal ganglion cell
SC: superior colliculus
SCN: suprachiasmatic nucleus
SGC: stratum griseum centrale (optic tectum)
SGFS: stratum griseum et fibrosum superficiale (optic tectum)
TeO: optic tectum
TrkA: tyrosine kinase receptor for NGF
TrkB: tyrosine kinase receptor for BDNF and NT-4
TrkC: tyrosine kinase receptor for NT-3

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Introduction

It was recognized several decades ago that neurons depend on their targets for survival, and that developing neurons are particularly sensitive to axotomy or the removal of their targets (Cowan, 1970; Cunningham, 1982; Provis and Penfold, 1988; Snider et al., 1992). It is now known that the dependence of neurons on their targets is due to trophic molecules which are released by the target neurons and which regulate the survival and other features of developing neurons (e.g., Purves, 1988; Barde, 1989; Snider, 1994; Thoenen, 1995). One important family of neurotrophic factors is that of the nerve-growth-factor-like neuropeptides, collectively called the "neurotrophins." The past 20 years of research have shown that neurotrophins have important functions in visual system development and regeneration in several species of vertebrates.

This review will concentrate on the localization and functions of neurotrophins in the developing vertebrate visual system, with particular emphasis on the retina,

superior colliculus (optic tectum) and isthmic visual centers. This will include studies of neurotrophins in the regeneration of retinal ganglion cell axons. Effects of neurotrophins in the developing visual cortex will be discussed only briefly, since this subject has been covered by several recent reviews (Gu, 1995; Thoenen, 1995; Bonhoeffer, 1996; Cellerino and Maffei, 1996; Pizzorusso and Maffei, 1996). The main goal of this review is to assemble information published in a variety of specialty journals into a coherent framework, and thereby to clarify our current understanding of the roles of neurotrophins in the development, maintenance and regeneration of the visual system in vertebrates.

Neurotrophins and their receptors

Neurotrophins are members of a small family of neuropeptides, which includes NGF, BDNF, NT-3, NT-4 (NT-4/5) and NT-6. They exist as 26-30 kDa homodimers. The neurotrophins are evolutionarily well conserved (Hallböök et al., 1991; Götz and Schartl, 1994). They bind to two types of receptors, trk receptors (trkA, B and C) and the neurotrophin receptor "p75", a 75 kD protein. While the p75 receptor binds all neurotrophins with similar affinity (Rodríguez-Tébar et al., 1990), the three trk receptors bind one or two of the neurotrophins preferentially (trkA-NGF; trkB-BDNF/NT-4; trkC-NT-3, Barbacid, 1994; Fig. 1). The trk receptors are tyrosine kinase receptors with established signal transduction pathways (Greene and Kaplan, 1995). The p75 receptor may also have signalling capacity independent of trk receptors (Dobrowsky et al., 1994; Chao and Hempstead, 1995; Bothwell, 1996; Frade et al., 1996; Carter and Lewin, 1997). Neurotrophins were originally discovered as survival and neurite-growth promoting agents (Purves, 1988). It is now clear that these molecules have many additional effects on neurons and glial cells, including proliferation, transmitter synthesis, cytoskeletal changes, synaptic transmission, reorganization and plasticity (Snider, 1994; Thoenen, 1995; Lewin and Barde, 1996).

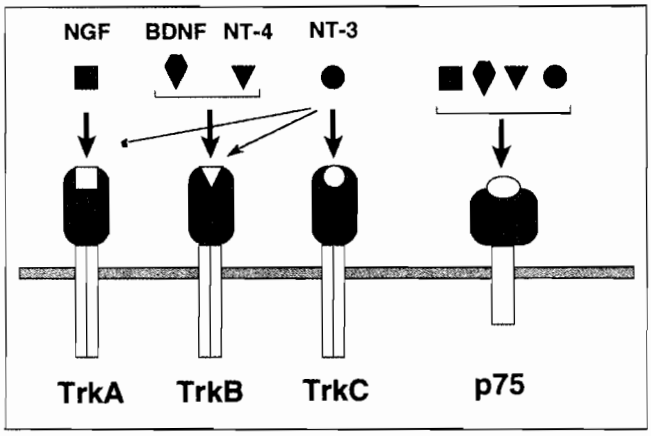

Fig. 1. Cartoon shows specificities of binding of neurotrophins (NGF, BDNF, NT-3 and NT-4) to the tyrosine kinase receptors trkA, trkB and trkC and the common "low-affinity" receptor p75. Modified from Barbacid (1994).

Historical overview

Neurotrophin research has followed circuitous routes. The history of research on neurotrophins in the visual system is easier to follow with knowledge of the chronological sequence of key events. NGF was discovered in the 1950s, BDNF in the 1980s and the other neurotrophins in the 1990s. When the first neurotrophin receptor was cloned it was thought to be an exclusive NGF receptor (because it bound NGF specifically), and hence was named the NGF receptor (NGFR). It was realized only later that BDNF and the other neurotrophins bind to this receptor with similar affinities (Rodríguez-Tébar et al., 1990). Accordingly, this receptor was renamed the p75 or low-affinity neurotrophin receptor to distinguish it from the trk receptors (trkA, trkB and trkC) which can bind the neurotrophins with higher affinities (for reviews, see Kaplan et al., 1991; Barbacid, 1994; Bothwell, 1995). Much of the research on neurotrophins has focused on the sympathetic nervous system, the cholinergic basal forebrain and the hippocampus. A substantial amount of evidence shows that neurotrophins are involved at multiple points in the visual pathways, as will be reviewed here.

Early studies: NGF and optic nerve regeneration

Research into the role of neurotrophins in visual system development and regeneration spans 20 years. The notion that NGF may not only be effective in the peripheral nervous system, but also in the central nervous system (reviewed by Freed, 1976) led to the seminal studies by Turner and Glaze (1977). Using optic nerve regeneration in the newt as a model system (Stone and Zaur, 1940; Sperry, 1943), Turner and Glaze showed a dramatic increase in the number of regenerating retinal ganglion cell (RGC) axons with intraocular application of NGF, and a corresponding decrease in their number with application of NGF antibodies after optic nerve section (Turner and Glaze, 1977; Glaze and Turner, 1978). Similar results were obtained in goldfish (Turner et al., 1980a,b; Yip and Grafstein, 1982), but not in frog (Humphrey, 1988). The mechanism by which NGF was acting remained (and remains) unclear, since NGF did not appear to bind to receptors when it was retrogradely transported from the site of nerve crush to the RGC bodies in goldfish (Yip and Johnson, 1983).

In vitro studies

Neurotrophins were also found to have significant effects in vitro. They induced neurite outgrowth from retinal explants of goldfish (NGF: Turner et al., 1980a,b, 1982), rat (BDNF: Thanos et al., 1989) and chick (NGF, BDNF and NT-3: Hallböök et al., 1996). Neurotrophins

also promoted the survival of dissociated retinal ganglion cells in rat (BDNF: Johnson et al., 1986; NT-4: Cohen et al., 1994; Ary-Pires et al., 1997), chick (NGF: Lehwalder et al., 1989; BDNF: Rodríguez-Tébar et al., 1989) and frog (BDNF: Cohen-Cory and Fraser, 1994). In addition, neurotrophins influenced the survival or neurite elongation of neurons from other visual centers, notably the chick optic tectum (NGF: Michler-Stuke and Wolff, 1987) and the isthmo-optic nucleus (BDNF, NT-3: von Bartheld et al., 1994).

Localization studies

The generation of probes for the localization of the neurotrophins and their receptors in tissue sections by immunocytochemistry (Chandler et al., 1984; Rush, 1984) or in situ hybridization led to a series of studies, mostly in rat (Yan and Johnson, 1988; Koh et al., 1989; Pioro and Cuello, 1990a,b; Carmignoto et al., 1991; Merlio et al., 1992; Pérez and Caminos, 1995) and chick (Heuer et al., 1990; von Bartheld et al., 1991; Hallböök et al., 1995, 1996; Garner et al., 1996), but also monkey (Schatteman et al., 1988), frog (Cohen-Cory and Fraser, 1994) and zebrafish (Sandell et al., 1994; Martin et al., 1995). These studies suggested that numerous visual circuits may be regulated by neurotrophins. The developmental expression of neurotrophins and their receptors was examined in significant detail for the rat retina (Koide et al., 1995; Pérez and Caminos, 1995; Rickman and Brecha, 1995), chick retina and optic tectum (Herzog et al., 1994; Hallböök et al., 1996), chick isthmo-optic nucleus (von Bartheld et al., 1994, 1996b), as well as the frog retina and tectum (Cohen-Cory and Fraser, 1994; Cohen-Cory et al., 1996). These studies provided a framework to determine which cell types in the visual system may signal to each other via neurotrophins.

Activity, competition and axon terminal arbors

The expression of neurotrophin mRNA in several visual centers was found to be up-regulated by physiological stimuli (cortex: Castrén et al., 1992; Schoups et al., 1995; optic tectum: Herzog et al., 1994; Herzog and Barde, 1994; Hallböök and Carri, 1995; Hallböök et al., 1995; retina: Hallböök et al., 1996), indicating that neurotrophins may play a crucial role in the activity-dependent formation of neural connections (Fawcett and O'Leary, 1985; Shatz, 1990). Activity may be necessary for the release of neurotrophins or trophic activation of responsive cells (Lipton, 1986; Blöchl and Thoenen, 1995; Meyer-Franke et al., 1995; McAllister et al., 1996). The neurotrophins NGF (reviewed by Gu, 1995; Thoenen, 1995; Cellerino and Maffei, 1996) and BDNF (Cabelli et al., 1995) were shown to influence the formation of ocular dominance columns. Since expression of trkA is thought to be very low or non-existent in the cerebral cortex, the effects of NGF may be mediated via cholinergic basal forebrain projections (Thoenen, 1995; Bonhoeffer, 1996), while BDNF or NT-4 may be the trophic signal for which the LGN axons compete in the visual cortex (Cabelli et al., 1995; Riddle et al., 1995). BDNF was also shown to modulate terminal branching of retinal ganglion cell axons in vivo in the developing frog optic tectum (Cohen-Cory and Fraser, 1995).

Axonal transport

Conventionally, the neurotrophins have been thought of as retrograde signalling molecules, which are taken up at the target and are transported from the axon terminus to the cell body (neurotrophic hypothesis, Purves, 1988). Consistent with this, the p75 receptor is retrogradely transported by RGC (Carmignoto et al., 1991), BDNF is transported from the superior colliculus/optic tectum to RGC (Fournier et al., 1997; Herzog and von Bartheld, 1997) and from the retina to the isthmo-optic nucleus (ION, von Bartheld et al., 1994, 1996b). NT-4, after transport from the visual cortex to the lateral geniculate nucleus (LGN), prevents the hypotrophy of LGN neurons that normally occurs after monocular deprivation (Riddle et al., 1995). Recent studies have shown that trafficking of neurotrophins is more complex than simple retrograde transport. Neurotrophins may act in an autocrine fashion (Acheson et al., 1995) or they can be transported anterogradely and then may act as a paracrine, afferent factor (von Bartheld et al., 1996a; Zhou and Rush, 1996; Conner et al., 1997). Neurons in the visual system are known to be regulated by afferent trophic influences (Cowan, 1973; Ostrach and Mathers, 1979; Cunningham, 1982; Adler, 1986; Clarke, 1991, 1992; Catsicas et al., 1992; Galli-Resta et al., 1993; Linden, 1994). Trk receptors are expressed on dendrites of cortical neurons (Fryer et al., 1996) and neurotrophins differentially affect dendritic arbors of pyramidal neurons in the ferret visual cortex (McAllister et al., 1995, 1997), implicating axo-dendritic transfer as a likely mode of action. Similarly, BDNF produced in the retina may support RGC in a paracrine fashion (Cohen-Cory et al., 1996; Garner et al., 1996; Herzog and von Bartheld, 1997). Such data suggest that trophic regulation of neural circuits is more complex than previously assumed.

Effects during early development

The neurotrophins were initially envisioned as signals which are required for the survival of neurons *after* they have made contact with their targets, at a time when they undergo developmental cell death and compete for synaptic space or trophic support (Cowan et al., 1984; Purves, 1988). Increasing evidence now shows that neurotrophins also have important functions during early development and that these functions may differ from those during later stages (Lewin and Barde, 1996). Notably, NGF is a mitogen for Müller cells (Ikeda and Puro, 1994), NT-3 stimulates oligodendrocyte

proliferation in the optic nerve (Barres et al., 1993, 1994; Barres and Raff, 1994), and BDNF appears to be essential for the normal myelination of optic nerve fibers (Carrol et al., 1996). Blocking antibodies to NT-3 impair the normal development of the retina in chick embryos (Bovolenta et al., 1996), and NGF appears to induce cell death in the early retina by binding to the p75 receptor (Frade et al., 1996). Thus, neurotrophins may have significant effects on proliferation, cell lineages, survival and differentiation in the early developing visual system, as has been indicated in other CNS centers (Cattaneo and McKay, 1990; Weiss et al., 1996). Gene deletion experiments (knock outs for the neurotrophins or their receptors) and antisense oligonucleotide experiments have yielded surprisingly few obvious deficits in CNS neurons (Snider, 1994), including RGC (Jones et al., 1994; Carrol et al., 1996; Rickman and Rickman, 1996). CNS neurons may have access to multiple trophic factors and thereby may compensate for the loss of one or two of them (Snider, 1994). Moreover, deficiencies in synaptic plasticity may be difficult to detect (Thoenen, 1995).

Regeneration of retinal ganglion cell axons

The initial findings by Turner and Glaze (1977) that NGF promoted regeneration of the optic nerve in the newt, and the subsequent studies showing effects of NGF in enhancing RGC survival after optic nerve sectioning in the adult rat (Carmignoto et al., 1989), indicated that neurotrophins may be of therapeutic value after optic nerve injury. Renewed interest in the potential clinical application of neurotrophins prompted numerous studies evaluating the effects of all four neurotrophins on mammalian RGC after optic nerve section or crush (Maffei et al., 1990; Mey and Thanos, 1993; Mansour-Robaey et al., 1994; Rabacchi et al., 1994; Cui and Harvey, 1995; Aguayo et al., 1996; Peinado-Ramon et al., 1996; Sawai et al., 1996), ischemia (Siliprandi et al., 1993; Unoki and LaVail, 1995) and in disease states such as diabetes (Hammes et al., 1995) and glaucoma (Nickells, 1996). The neurotrophins NGF, BDNF and NT-4 significantly delayed cell death of RGC, but failed to permanently rescue these neurons from axotomy-induced cell death.

The following sections of this review will systematically proceed from the retina to downstream visual CNS centers, and summarize where the neurotrophins and their receptors are expressed, which functions have been shown or are assumed, and discuss pathophysiological and clinical implications.

Retina

The retina requires retrograde signals from the superior colliculus/optic tectum (SC/TeO, Hughes and McLoon, 1979) and the lateral geniculate nucleus (LGN) and provides anterograde trophic signals for these targets (Cowan, 1973; Catsicas et al., 1992). In addition, the retina is a site of intrinsic trophic signalling (de Araujo and Linden, 1993; Linden, 1994). Consistent with these functions, neurotrophins and their receptors are expressed in the retina of all vertebrates so far examined. Neurotrophins expressed by retinal cells may signal within the retina, or they may be transported along the optic nerve to affect downstream visual centers.

Since different cell types intermingle in most retinal layers (Fig. 2) it can be difficult to identify labeled cell types within a certain layer unless double-labeling or an ultrastructural analysis is performed. The following sections will concentrate on in situ hybridization data rather than immunocytochemical data for the neurotrophins, because it is not clear with immunocytochemical localization whether the labeled cells produce the neurotrophin or whether it accumulates after uptake from other sources. For earlier antibody studies it has to be kept in mind that cross-reactivity with other neurotrophins was not tested, and these antibodies may not be as specific as initially thought (Acheson et al., 1991; Murphy et al., 1993). Moreover, immunocytochemistry as well as in situ hybridization are relatively insensitive techniques for the detection of low-abundance trophic molecules such as the neurotrophins (Anderson et al., 1995; Ibáñez, 1996). The lack of label in tissue sections thus does not necessarily mean that the neurotrophin is expressed at levels which are functionally negligible.

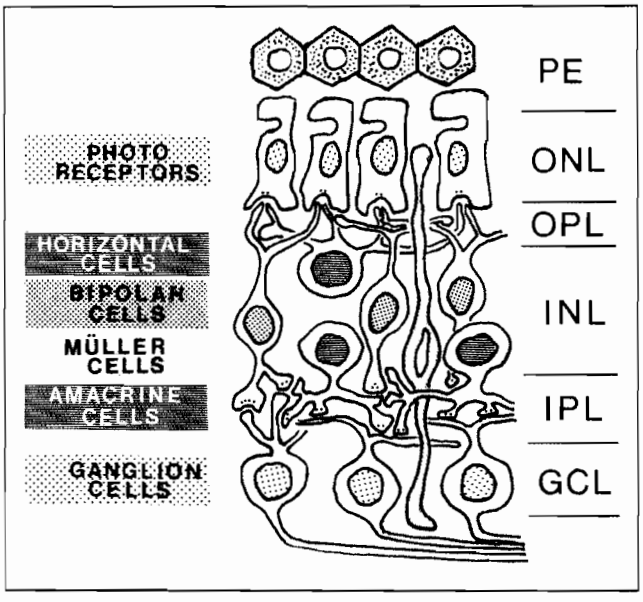

Fig. 2 Schematic representation of the location and the connections between the cell types within the layers of the retina. For abbreviations, see list at beginning of this review. For reasons of simplicity, displaced ganglion cells and displaced amacrine cells are not included.

NGF

Very little NGF protein and NGF mRNA were

described in the adult rat retina (Korsching et al., 1985; Maisonpierre et al., 1990), but NGF protein (Finn et al., 1987) and pro-NGF protein was detected in the retina by immunocytochemistry (Chakrabarti et al., 1990). NGF mRNA has been detected in the chick retina (Ebendal et al., 1982, 1986; Ebendal and Persson, 1988; Large et al., 1989; Frade et al., 1996; Hallböök et al., 1996). NGF mRNA increases with a peak at about 15 days of incubation and remains at intermediate levels after hatching (Large et al., 1989; Hallböök et al., 1996).

BDNF

Relatively small amounts of BDNF mRNA were found in the adult (Maisonpierre et al., 1990), but were not detected in the embryonic rat retina (Ernfors et al., 1992). Expression of BDNF mRNA was localized by in situ hybridization in the neonatal and adult rat retina (Pérez and Caminos, 1995). BDNF is also expressed in the retina of chick (Herzog et al., 1994; Hallböök et al., 1996; Johnson et al., 1996) and frog (Cohen-Cory and Fraser, 1994). The developmental time course was examined in both of these species. A developmental peak with decreasing levels in the adult were described by Cohen-Cory and Fraser (1994) and Herzog et al. (1994), whereas Hallböök et al. (1996) found relatively high levels maintained in the adult. The reason for these differences is not clear, but may be due to differences in the techniques used for quantification or possibly activity levels which influence BDNF expression (see below).

NT-3

Significant amounts of NT-3 mRNA are expressed in the adult rat retina (Maisonpierre et al., 1990), but were not seen at embryonic stages in this species (Ernfors et al., 1992). Despite the high levels of NT-3 mRNA detected by Northern blot (Maisonpierre et al., 1990), nothing is known about the localization of NT-3 transcripts within the mammalian retina. NT-3 mRNA is expressed in the chick retina (Hallböök et al., 1996; von Bartheld et al., 1996a). The time course of NT-3 mRNA expression shows a substantial increase at 12-15 days of incubation in the chick retina (Hallböök et al., 1996) which correlates with the time when exogenous and endogenous NT-3 are effectively transported from the retina to the optic tectum (von Bartheld et al., 1996a; von Bartheld, 1997).

NT-4

Due to low levels of expression, NT-4 mRNA has been difficult to detect by in situ hybridization (Ibáñez, 1996), and there are currently no published data for the retina. The avian NT-4 gene has not been cloned (Lewin and Barde, 1996; Strohmaier et al., 1996).

p75 receptor

p75 receptors (="NGF receptors") are expressed in the retina of rat, ferret, monkey and chicken (Schatteman et al., 1988; Yan and Johnson, 1988; Large et al., 1989; Escandón and Chao, 1990; Heuer et al., 1990; Maffei et al., 1990; Carmignoto et al., 1991; Henderson, 1991; von Bartheld et al., 1991; Takahashi et al., 1993a; Allendoerfer et al., 1994; Ugolini et al., 1995; Hu et al., 1996). In general, levels of expression are significantly higher in younger animals than in older ones.

TrkA

TrkA is expressed in the developing retina of rat, mouse and chick (Escandón and Chao, 1990; Ernfors et al., 1992; Zanellato et al., 1993; Karten et al., 1995; Rickman and Brecha, 1995; Ugolini et al., 1995; Frade et al., 1996; Llamosas et al., 1997).

TrkB

TrkB is expressed in the retina of rat, ferret, chick, frog and zebrafish (Ernfors et al., 1992; Jelsma et al., 1993; Takahashi et al., 1993a; Valenzuela et al., 1993; Allendoerfer et al., 1994; Escandón et al., 1994; Cohen-Cory and Fraser, 1994; Martin et al., 1995; Okazawa et al., 1995; Koide et al., 1995; Pérez and Caminos, 1995; Rickman and Brecha, 1995; Ugolini et al., 1995; Cohen-Cory et al., 1996; Garner et al., 1996; Hallböök et al., 1996; von Bartheld et al., 1996a). TrkB mRNA was initially not detected in the retina of 6-12 day-old chick embryos by using in situ hybridization (Dechant et al., 1993), but a later study showed the expression of trkB (and of isoforms containing various kinase deletions) in the chick retina throughout development, including E6-12 (Garner et al., 1996). Several isoforms of chick trkB have been described with deletions and insertions in the cytoplasmic tyrosine kinase or extracellular ligand binding domains (Garner et al., 1996; Strohmaier et al., 1996). Two forms of full-length trkB exist in zebrafish, trkB1 and trkB2, which are differentially expressed in the retina (Martin et al., 1995).

TrkC

TrkC is expressed in the retina of rat, ferret, chick, frog, and zebrafish (Ernfors et al., 1992; Rodríguez-Tébar et al., 1993; Valenzuela et al., 1993; Allendoerfer et al., 1994; Cohen-Cory and Fraser, 1994; Escandón et al., 1994; Kittlerová et al., 1995; Martin et al., 1995; Okazawa et al., 1995; Bovolenta et al., 1996; Hallböök et al., 1996; von Bartheld et al., 1996a). Rat retina expressed full-length trkC as well as truncated isoforms lacking a kinase domain (Valenzuela et al., 1993). Two full-length trkC forms were found in zebrafish, trkC1 and trkC2, which are differentially expressed in the retina (Martin et al., 1995).

Localization of neurotrophins and their receptors in the retina

Pigment epithelium

NGF, BDNF and NT-3 mRNAs are expressed in human pigment epithelium in vitro (Ishida et al., 1997) and these cells secrete NGF (Dicou et al., 1994; Ishida et al., 1997). NGF-like immunoreactivity and p75 label was found in the adult BB rat (Chakrabarti et al., 1990). NT-3 mRNA is expressed early in the pigment epithelium of chick embryos, decreasing from 5 to 9 days of incubation (E5 to E9, Bovolenta et al., 1996). BDNF increases the expression of bFGF in the pigmented epithelial cells (Hackett et al., 1997). Whether neurotrophins expressed by the pigment epithelium have physiological effects on photoreceptors or other retinal cells remains to be determined.

Photoreceptors

Low levels of BDNF mRNA are expressed in the photoreceptor layer of the developing chick retina (Hallböök et al., 1996), and BDNF-like immunoreactivity can be detected in photoreceptors of chick embryos (Fig. 3A,B). Pan-trk antibodies label photoreceptors in fish (Sandell et al., 1994) and a light non-specific label is produced with trkA and trkB antibodies in rat photoreceptors (Rickman and Brecha, 1995). Immunolabel for all three trk receptors (trkA, B and C) has been described for mouse photoreceptors (Llamosas et al., 1997). Intraocular NGF delays cell death of photoreceptors in C3H mice, a strain with a single gene mutation leading to photoreceptor degeneration (Lambiase and Aloe, 1996), and NGF combined with bFGF retards cell death of mouse photoreceptors in vitro (Caffé et al., 1993). TrkB mRNA or protein has not been detected in photoreceptors of rats (Pérez and Caminos, 1995), but trkB mRNA expression has been reported in photoreceptors of chick (Garner et al., 1996). TrkB and/or trkC protein has been detected by immunolabeling after exposure to light in chicks (Okazawa et al., 1994). BDNF and, less so, NT-3, promote the survival of light-damaged rat photoreceptors (LaVail et al., 1992).

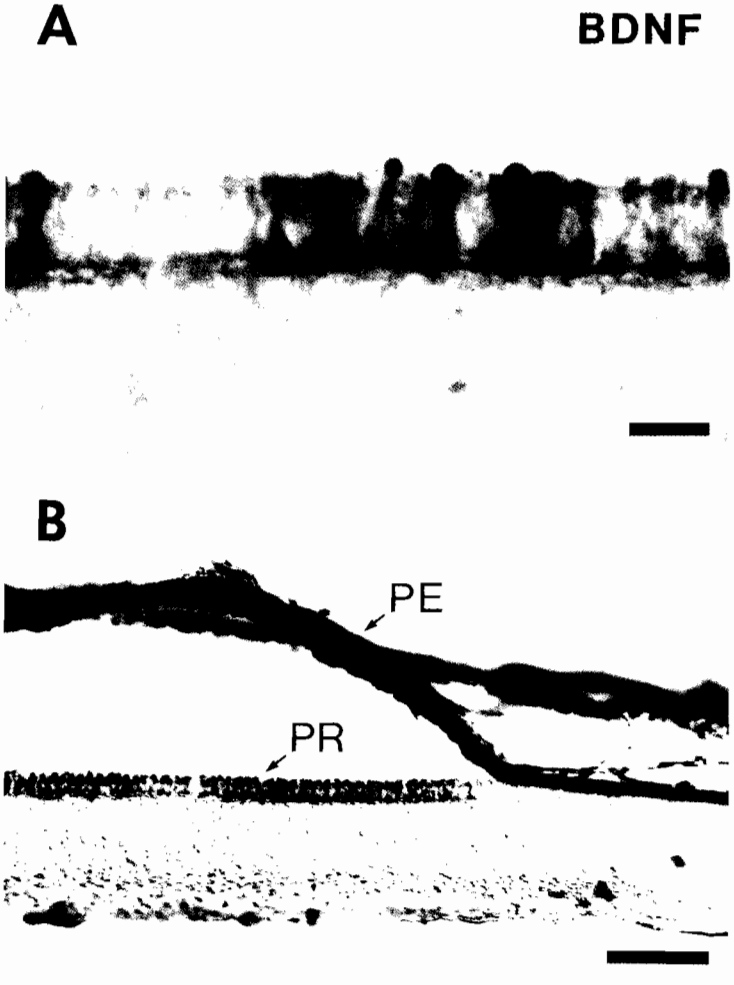

Fig. 3. Sections through the retina of chick embryos at 15 days of incubation immunolabeled with an antibody for BDNF (for information on this antibody, see Jungbluth et al., 1994; Herzog and von Bartheld, 1997). **A.** Some, but not all photoreceptors are labeled. **B.** BDNF-like immunoreactivity was detected in photoreceptors only when the pigment epithelium was detached from the retina, presumably enhancing penetration of the antibody by lifting of the tissue section from the slide during immunoprocessing. PE: pigment epithelium; PR: photoreceptor layer. Scale bars: 10 μm (A) and 50 μm (B).

Thus, BDNF produced by photoreceptors themselves, or obtained from other retinal sources, may promote the survival of this cell type. Evidence for paracrine trophic interactions between photoreceptors has been obtained from transgenic mice expressing a mutant rhodopsin gene (Huang et al., 1993).

Inner nuclear layer (INL)

All neurotrophins and their receptors are expressed in some cells in the INL of at least some species (Fig. 4), but often it was not possible to identify what cell types they are. For example, BDNF is expressed in the INL of rat and chick (Pérez and Caminos, 1995; Hallböök et al., 1996), trkC is expressed in the INL in frog (Cohen-Cory and Fraser, 1994), and trkB1, trkB2 and trkC1 are expressed in the zebrafish INL (Martin et al., 1995).

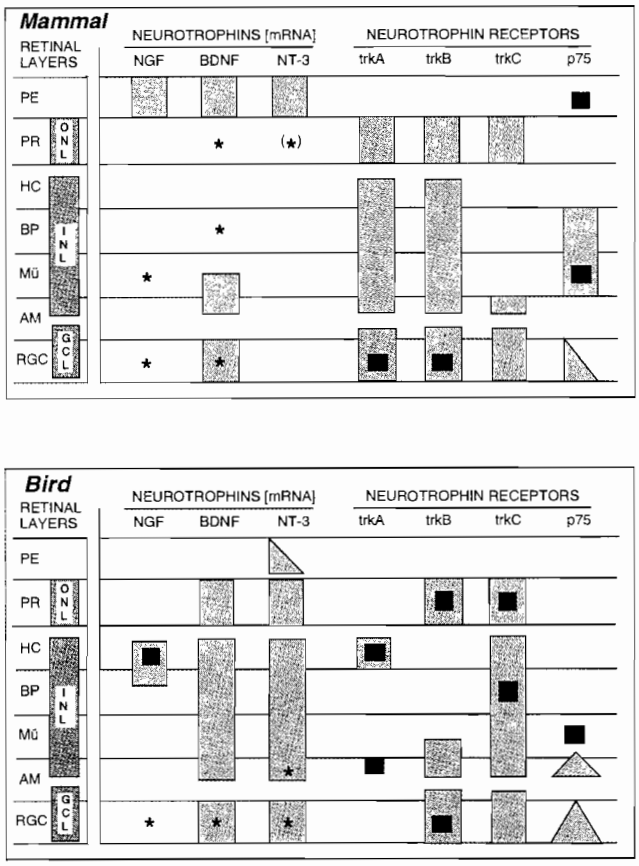

Fig. 4. Summarizing scheme of the expression of the neurotrophins and their receptors in the layers of the retina in mammals (upper panel) and birds (lower panel). The retinal layers are indicated on the left. The gray bars indicate label in layers containing several different cell types. Black squares indicate label in identified cell types within these layers. The developmental time course of expression in cell layers, if known, is indicated by increasing or decreasing thickness of the gray bar. Evidence for functional effects of neurotrophins on identified cell types is indicated by asterisks. NT-4 is not included because it has not been localized in the retina. Lack of symbols (e.g. for NT-3 in mammals) does not mean that it is not expressed; it may simply have not yet been localized. For details and references, see the text in the section RETINA. Abbreviations (used only in the Figures): AM, amacrine cell; BP, bipolar cell; HC, horizontal cell; Mü, Müller cell; PE, pigment epithelium; PR, photoreceptor; for other abbreviations, see list in the beginning of this review.

Horizontal cells

In the developing chick retina some horizontal cells show trkA immunoreactivity (Karten et al., 1995) and some appear to express trkA mRNA as well as NGF mRNA (Hallböök et al., 1996). Thus, horizontal cells may support themselves with NGF in an autocrine or paracrine fashion. Consistent with this notion, previous studies have indicated that horizontal cells secrete a diffusible factor which supports the same cell type (Hammang et al., 1993). Horizontal cells may also express BDNF mRNA (Herzog and von Bartheld, 1997).

Bipolar cells

TrkC mRNA expression has been reported in bipolar cells in the chick embryo (Hallböök et al., 1996). Bipolar cells may also express BDNF (Pérez and Caminos, 1995). Bipolar cells from rat pups are supported by BDNF in vitro (Berkovich et al., 1996).

Müller cells

Müller glia have been reported to secrete NGF in rat (Dicou et al., 1994). p75 neurotrophin receptors are expressed by Müller cells in monkey (Schatteman et al., 1988) and rat (Chakrabarti et al., 1990; Carmignoto et al., 1991), and this has been confirmed at the ultrastructural level in adult rat (Hu et al., 1996). p75 receptor is upregulated in Müller cells of rats with experimental diabetes (Hammes et al., 1995). Müller cells from embryonic chick retina express p75 receptor in vitro (T.H. Large and G. Weskamp, cited in Large et al., 1989). Müller glia probably express trkA and trkB in rat (Rickman and Brecha, 1995). NGF has mitogenic effects on Müller cells from the adult human retina in vitro and this mitogenic effect is thought to be due to the activation of high-affinity (trkA) receptors (Ikeda and Puro, 1994). NGF prevents the cell death of Müller cells in rats with experimental diabetes (Hammes et al., 1995). Since Müller cells appear to produce NGF and respond to NGF, this factor may act in an autocrine fashion.

Amacrine cells and displaced ganglion cells

Rat amacrine cells appear to express BDNF mRNA (Pérez and Caminos, 1995). Relatively low levels of BDNF mRNA were found in the chick INL (Herzog and von Bartheld, 1997). This layer contains a subpopulation of amacrine cells which are the target cells of the isthmo-optic nucleus (Uchiyama and Ito, 1993). These neurons respond to BDNF with increased survival (von

Bartheld et al., 1994; Primi and Clarke, 1996), and their target cells are thought to express BDNF and to provide isthmo-optic axons with BDNF. Due to the low levels of BDNF mRNA expressed by amacrine cells, this remains to be shown. Amacrine cells (or displaced ganglion cells) express p75 receptor mRNA in chick embryos (von Bartheld et al., 1991) and some amacrine cells express trkA (Karten et al., 1995). NGF does not induce choline acetyltransferase activity in embryonic chick amacrine cells in vitro (Hofmann, 1988), possibly indicating that trkA is not expressed in cholinergic amacrine cells. TrkA is expressed though in a population of GABAergic amacrine cells in chicken (Karten et al., 1995). Amacrine cells likely express trkB (Garner et al., 1996) and trkC (Hallböök et al., 1996). Consistent with the expression of trkC, NT-3 supports the survival of a subpopulation of chick amacrine cells in vitro (de la Rosa et al., 1994). Thus, amacrine cells may respond to neurotrophins, but they may also produce neurotrophins for other cell types.

Retinal ganglion cells

NGF mRNA has been detected in RGC of rat (Zanellato et al., 1993) and BDNF mRNA in the GCL of neonatal and adult rat (Pérez and Caminos, 1995) and chick (Hallböök et al., 1996). Presumptive RGC in the ganglion cell layer (GCL) express p75 in the developing rat (Eckenstein, 1988; Yan and Johnson, 1988; Carmignoto et al., 1991; Rickman et al., 1992), monkey (Schatteman et al., 1988), ferret (Henderson, 1991) and chick (Heuer et al., 1990; von Bartheld et al., 1991). In older animals, p75 expression is much reduced in the GCL and its absence has been noted in adult rat RGC (Hu et al., 1996), but p75 is upregulated after injury (Maffei et al., 1990). The p75 receptor is anterogradely and retrogradely transported by RGC axons in rat (Carmignoto et al., 1991). RGC do not appear to provide major trophic support to cells in the INL, since very little cell death was observed in the INL after elimination of the RGC (Beazly et al., 1987).

TrkA is expressed in identified RGC of the neonatal rat (Zanellato et al., 1993; Rickman and Brecha, 1995), consistent with the survival effects of NGF on injured mammalian RGC (Carmignoto et al., 1989; Hammes et al., 1995). Exogenous NGF is not transported anterogradely by RGC of the adult rat (Ferguson and Johnson, 1990), possibly because of the lack of p75 receptor in adult rat RGC (Hu et al., 1996). Attempts to show retrograde transport of radio-iodinated NGF from the optic tectum/superior colliculus to RGC by gamma-counting failed in goldfish (Yip and Johnson, 1983) and rat (Carmignoto et al., 1989). TrkA$^{-/-}$ mice develop corneal opacities, probably due to a sensory defect in the blink response (Smeyne et al., 1994); other defects in the retina or eye have not been detected. TrkA expression has not been localized in the early chick retina (Frade et al., 1996), it is not expressed in RGC at later stages (Hallböök et al., 1996). Although chick RGC do not appear to express trkA in vivo, they may do so in vitro or after axotomy. Effects of NGF on avian RGC have been controversial. Some studies failed to see an effect in vitro (Carri and Ebendal, 1983; Johnson, 1989) while others noted that NGF increased the survival of purified RGC in vitro (Lehwalder et al., 1989) and axotomized RGC in vivo (Ehrlich et al., 1990). Likewise, NGF promoted neurite outgrowth from chick retinal explants in some studies (E6: Hallböök et al., 1996), but not in others (E9: Acheson et al., 1991).

Full-length trkB mRNA has been detected in rat RGC (Jelsma et al., 1993) or GCL (Pérez and Caminos, 1995; Ugolini et al., 1995), and in the GCL of chick (Hallböök et al., 1996; von Bartheld et al., 1996a) and frog (Cohen-Cory and Fraser, 1994). TrkB protein may be present on RGC terminals in the ferret LGN (Cabelli et al., 1996). Transport of iodinated BDNF to RGC was demonstrated by autoradiography in adult rats (Fournier et al., 1997) and chick embryos (Herzog and von Bartheld, 1997). The effects of BDNF on RGC in vitro are well documented: BDNF supports the survival of RGC from several species including rat (Johnson et al., 1986; Thanos et al., 1989), chick (Rodríguez-Tébar et al., 1989), and frog (Cohen-Cory and Fraser, 1994; Cohen-Cory et al., 1996). The role of BDNF for the survival of RGC in vivo is less clear. Normal numbers of RGC develop in BDNF$^{-/-}$ mice (Jones et al., 1994; Carrol et al., 1996) and injection of antisense trkB oligonucleotides does not reduce the numbers of rat RGC (Rickman and Rickman, 1996). The myelination of fibers in the optic nerve of BDNF$^{-/-}$ mice, however, is significantly reduced (Carrol et al., 1996), as well as the firing of the RGC (Rothe et al., 1996). Injection of BDNF in the SC of young hamsters reduces normal developmental cell death of RGC (Frost et al., 1997), while exogenous BDNF does not prevent the normal developmental cell death in chick RGC (Cellerino et al., 1995; Drum et al., 1996). BDNF increases the axon length of frog RGC in vitro (Cohen-Cory and Fraser, 1994) and regulates the complexity of terminal arbors in vivo (Cohen-Cory and Fraser, 1995). BDNF can promote outgrowth of RGC axons into regions to which they would normally not extend (Panni et al., 1994), but a physiological role of neurotrophins as *tropic* factors for visual neurons is doubtful (Tessier-Lavigne and Placzek, 1991; Mey and Thanos, 1992). NT-4 promotes the survival of developing and adult rat RGC in vitro (Cohen et al., 1994; Ary-Pires et al., 1997), rescues rat RGC from developmental cell death (Cui and Harvey, 1994) and both BDNF and NT-4 increase RGC survival after lesioning of the optic tectum (Cui and Harvey, 1995).

TrkC mRNA is expressed in the GCL of rat (Ernfors et al., 1992; Kittlerová et al., 1995), frog (Cohen-Cory and Fraser, 1994) and chick (de la Rosa et al., 1994; Hallböök et al., 1996; von Bartheld et al., 1996a). TrkB and/or trkC have been detected by immunocytochemistry after exposure to light in the chicken GCL (Okazawa et al., 1994). NT-3 enhances the survival of

embryonic chick RGC in vitro during a distinct developmental period (E9-11, de la Rosa et al., 1994) and treatment of chick embryos with NT-3 antibodies delays or prevents the differentiation and axon outgrowth from RGC (Bovolenta et al., 1996). NT-3 does not promote the survival, neurite branching or axon growth of RGC in frog or mammal (Cohen-Cory and Fraser, 1994, 1995; Sawai et al., 1996). RGC neurons transport exogenous and endogenous NT-3 from the retina to the optic tectum in chick embryos (von Bartheld et al., 1996a; von Bartheld, 1997). In conclusion, several neurotrophins have effects on RGC. NT-3 is important during early stages, while BDNF and NT-4 (and NGF, at least in mammals) have survival and neurite-promoting effects during later stages of development and after axotomy and other injuries.

Figure 4 summarizes the available data on layer- and cell type-specific expression of neurotrophins and their receptors in the mammalian and avian retina. While the overall pattern between the two species is similar, there are some differences, notably the absence of trkA expression in RGC of birds (and frogs and fish, not shown).

Optic nerve

Glial cells in the optic nerve may express neurotrophins for other glial cells, or they may be targeted to RGC axons. Neurotrophins may also be delivered to glial cells after anterograde transport from the retina or retrograde transport from RGC targets in the brain. Cells in the optic nerve express NGF, NT-3 and NT-4 mRNAs (Ceccatelli et al., 1991; Condorelli et al., 1995; Elkabes et al., 1995), and possibly BDNF mRNA (Elkabes et al., 1995). NGF immunoreactivity has been reported in the mouse optic nerve (Finn et al., 1987). Increased levels of NT-3 mRNA have been observed in the optic tract after colchicine treatment (Ceccatelli et al., 1991). Astrocytes express NT-3 mRNA in vitro and may secrete NT-3 which acts on oligodendrocytes (Barres et al., 1994). Glial cells in the optic nerve express trkA (Elkabes et al., 1995) and truncated trkB and trkC receptors lacking the tyrosine kinase domain as well as full-length trkB and trkC (Jelsma et al., 1993; Barres et al., 1994; Condorelli et al., 1995; Elkabes et al., 1995; Robinson and Miller, 1996). Truncated trkB mRNA is significantly more abundant than full-length trkB mRNA in the optic nerve (Jelsma et al., 1993). Expression of trkB and trkC decreases during development (Elkabes et al., 1995). Expression of p75 mRNA has not been detected in the optic nerve of chick embryos (Heuer et al., 1990). Consistent with the expression of trkB and trkC, NT-3 alone, and BDNF in combination with other factors, promote the survival of oligodendrocytes (Barres et al., 1993). The ability of RGC axons to promote oligodendrocyte survival does not depend on electrical activity (Barres and Raff, 1994). NT-3 also increases proliferation of oligodendrocyte precursors in the optic nerve (Barres et al., 1994; Robinson and Miller, 1996; but see Ibarrola et al., 1996). In vivo, this effect may depend on electrical activity of RGC axons, possibly by stimulating NT-3 production and/or NT-3 release (Barres and Raff, 1994). In BDNF$^{-/-}$ mice, the RGC axons are normal in number, but the number of myelinated fibers is significantly reduced (Carrol et al., 1996). Thus, BDNF and NT-3 have major effects on glial cells. They may be involved in matching the numbers of oligodendrocytes with those of RGCs axons and thereby regulate the normal development of the optic nerve (Barres and Raff, 1994; Lewin and Barde, 1996).

Lateral geniculate nucleus (LGN)

The LGN may obtain trophic support from its target, the visual cortex as well as its afferents, the RGC. In addition, the LGN neurons may provide trophic support to their afferents from the retina (Williams and Rakic, 1988). It has been reported that the developing and adult rat LGN expresses NGF mRNA (Lauterborn et al., 1994), BDNF mRNA and, transiently, NT-3 mRNA (Schoups et al., 1995), but BDNF mRNA was not detected in the LGN by in situ hybridization (Castrén et al., 1995; Conner et al., 1997). LGN neurons may provide RGC axons with neurotrophins which then are retrogradely transported to the RGC cell bodies in the retina.

The LGN of developing rats contains p75 receptors (Yan and Johnson, 1988); the major fraction of the p75 protein in the LGN may be located on the RGC nerve fibers (Eckenstein, 1988). Allendoerfer et al. (1994) failed to immunoprecipitate p75 from the ferret LGN. Expression of trkA has not been detected in the LGN. Consistent with the lack of trkA and possibly p75, NGF is not retrogradely transported from the cortex to the LGN (Domenici et al., 1994), yet systemic NGF prevents the shrinkage of cells in the monocularly deprived LGN (Carmignoto et al., 1993). TrkB mRNA is expressed in the LGN of rat (Ringstedt et al., 1993; Bozzi et al., 1995; Schoups et al., 1995) and chick (Garner et al., 1996). TrkB protein has been detected in ferret and rat LGN cells by immunolabeling (Cabelli et al., 1996; Yan et al., 1997). Confocal analysis revealed trkB immunolabel on LGN fibers in the layer IV of visual cortex identified by double-labeling (M.A. Silver, personal communication) and fibers, but not cell bodies, in the LGN are BDNF-immunoreactive (Conner et al., 1997). When fluorescent beads coated with NT-4 are injected into the visual cortex of ferret, they are transported retrogradely to LGN neurons and prevent the hypotrophy of LGN neurons that normally occurs after monocular deprivation (Riddle et al., 1995), while NGF, BDNF and NT-3 have no effect. Thus, LGN neurons may utilize or require NT-4 as a retrograde trophic signal from visual cortex. The rat LGN also expresses trkC mRNA (Schoups et al., 1995) and NT-3 can be cross-linked to trkC receptors in ferret LGN (Allendoerfer et al., 1994).

Suprachiasmatic nucleus (SCN)

The SCN in the hypothalamus is involved in the generation of circadian rhythms. It receives input from several sources, including the retina and the LGN (Morrin, 1994). Cells in the ventromedial SCN express NGF (Ojeda et al., 1991) and NT-3 mRNAs (Lehman et al., 1996) and possibly BDNF mRNA (Liang et al., 1995, 1996). BDNF mRNA was not detected in SCN neurons by other investigators (Castrén et al., 1995). The adult rat SCN contains abundant p75 receptor protein, mostly in nerve fibers and terminals in its ventral part (Sofroniew et al., 1989), while neuronal cell bodies are labeled in its dorsal part (Kiss et al., 1993), but the SCN does not appear to express p75 mRNA (Koh et al., 1989). Most of the p75 in the SCN is derived from the RGC and the cholinergic basal forebrain projections (Bina et al., 1997). Recent reports on the expression of neurotrophins and trk receptors in the SCN differ between investigators and between species. Mammalian SCN may contain trkA and trkB mRNAs (Lehman et al., 1996; Liang et al., 1996), and chicken SCN expresses trkB (Garner et al., 1996). Injections of NGF into the SCN or the ventricle cause phase shifts of the circadian rhythm in hamsters and rats (Bina and Rusak, 1996; Golombek et al., 1996a) and increase the expression of c-fos in the SCN (Golombek et al., 1996a). The unperturbed circadian rhythm is normal in $p75^{-/-}$ mice, but phase shift responses to brief pulses of light are significantly decreased (Golombek et al., 1996b). These data show that neurotrophins, acting at least in part through the p75 receptor, are involved in the regulation of circadian rhythms.

Superior colliculus (SC)/optic tectum

The tectum may be a source of neurotrophins for its afferents, the RGC (Nurcombe and Bennett, 1981) and

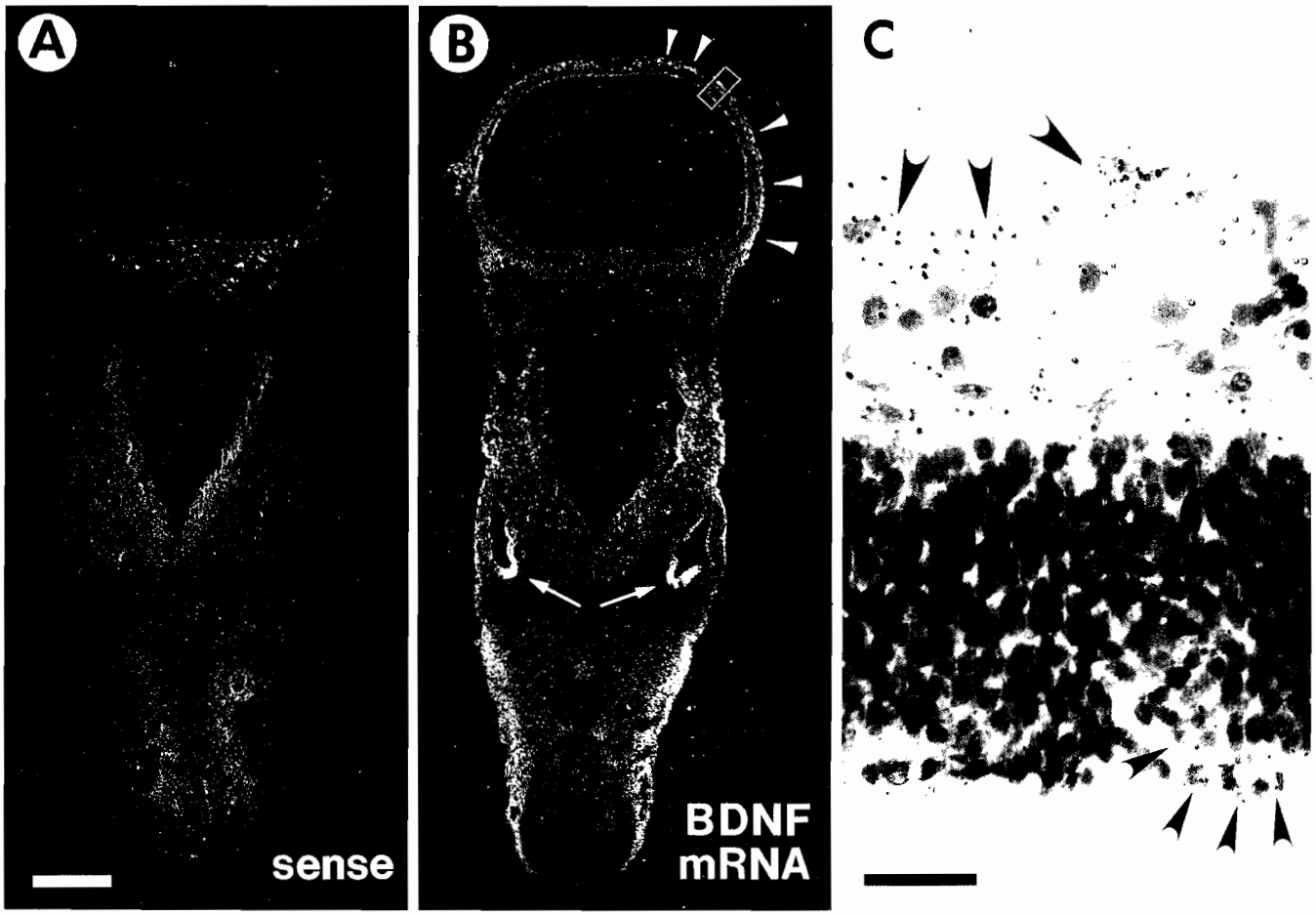

Fig. 5. Sections through a chick embryo of 4.5 days of incubation hybridized with a sense probe **(A)** and a probe for chicken BDNF **(B, C)**. The adjacent sections (A,B) show the developing optic tectum (top), the otocysts (center) and the spinal cord (bottom). Note heavy expression of BDNF mRNA in parts of the otocyst (B, arrows) and moderate expression in the mesenchyme adjacent to the optic tectum (B, arrowheads). The boxed area in B is shown at higher magnification in a brightfield view (C). BDNF mRNA is expressed predominantly in the perineural mesenchyme (primitive meninges, large arrowheads) rather than the neural tissue (small arrowheads). Thus, the early peak of BDNF expression in the E4-5 chick optic tectum (Herzog et al., 1994) may be due to expression in the meninges rather than the neural tissue. Scale bars: 500 μm (A,B), 20 μm (C).

isthmic projections. Tectal neurons may also provide neurotrophins for intrinsic connections within the tectum. Removal of the eye causes extensive neuronal death in the optic tectum (Filogamo, 1950; Kelly and Cowan, 1972) and in other visual centers (reviewed by Cowan, 1973). Thus, the tectum appears to require trophic signals, possibly neurotrophins, transported from the retina (Clarke, 1991; Catsicas et al., 1992; Garner et al., 1996; von Bartheld et al., 1996a).

NGF mRNA is expressed in the chick optic tectum (Ebendal et al., 1986; Large et al., 1989) and NGF protein appears to be present in the goldfish optic tectum (Benowitz and Greene, 1979; Benowitz and Shashoua, 1979). NGF has effects on neurite outgrowth from E6 chick tectum (Michler-Stuke and Wolff, 1987). However, very little NGF protein was detected in the rat superior colliculus (Korsching et al., 1985), and exogenous NGF does not seem to be transported from the tectum/SC to the retina in goldfish or rat (Yip and Johnson, 1983; Carmignoto et al., 1989).

BDNF mRNA was localized to the SC of adult mouse (Leibrock et al., 1989; Hofer et al., 1990), and scattered cells strongly expressing BDNF mRNA were noted in the superficial layers of the SC of adult rat and pig (Wetmore et al., 1990; Gall et al., 1992). The gray layers of the SC (but not the nerve fiber layer) contain BDNF-immunoreactive fibers (Conner et al., 1997). Levels of BDNF mRNA are low in the postnatal rat SC, but they increase during later stages of development (Friedman et al., 1991; Rickman et al., 1992). BDNF is also expressed in the developing optic tectum of the chick (Herzog et al., 1994; Hallböök et al., 1996; Johnson et al., 1996) and frog (Cohen-Cory and Fraser, 1994; Cohen-Cory et al., 1996). The expression of BDNF mRNA has been quantified in chick and frog. It is biphasic in the chick, with a first peak at E4 and a second peak at E11, and then decreases to low levels in the adult tectum (Herzog et al., 1994). A similar time course was shown in the frog tectum (Cohen-Cory and Fraser, 1994). Subsequent in situ hybridization experiments with oligonucleotide probes (Hallböök et al., 1995) and riboprobes (Herzog and von Bartheld, 1997) showed that two retinorecipient layers of the chick tectum express BDNF: the SGFS and the SGC. Specifically, layers SGFSg and i, and scattered cells in SGC are labeled. BDNF mRNA expression is particularly strong in the perineural mesenchyme (primitive meninges) adjacent to the developing optic tectum of E4-5 chick embryos (Fig. 5A-C), indicating that the early peak at E4-5 (Herzog et al., 1994) may be due to expression in the mesenchyme rather than the neuronal tectal tissue. A similar reciprocal shift in the expression of another neurotrophin (NT-3) was noted in the early retina (Bovolenta et al., 1996). The amount of BDNF mRNA in the chick tectum is decreased when electrical activity in the optic nerve is abolished with tetrodotoxin (Herzog et al., 1994) or when chicks are dark-reared (Hallböök and Carri, 1995). Injection of BDNF or NT-4 increases the activity of glutamic acid decarboxylase in the SC of rat (Altar et al., 1994). Exogenous BDNF injected into the adult rat SC or the chick tectum is transported retrogradely to RGC in the retina (Fournier et al., 1997; Herzog and von Bartheld, 1997), consistent with the notion that BDNF is a target-derived trophic factor for RGC.

NT-3 mRNA has been described in the SC of rat with decreasing levels from the newborn to the adult (Rickman et al., 1992), but has not been detected in the chick tectum (Hallböök and Carri, 1995; von Bartheld et al., 1996a). Exogenous NT-3 is anterogradely transported by RGC axons to the tectum where it is released and transferred to dendrites of tectal neurons (von Bartheld et al., 1996a). Likewise, endogenous NT-3 is transported to the optic tectum from the retina (von Bartheld, 1997), a relatively rich source of NT-3 (Hallböök et al., 1996).

p75 receptor is expressed in the ferret SC (Henderson, 1991; Allendoerfer et al., 1994) and in the adult rat SC, possibly in neuroglia or nerve fibers (Yan and Johnson, 1988, 1989; Koh et al., 1989; Pioro and Cuello, 1990b). Some p75 appears to be intrinsic to the SC as immunolabel persists after eye removal (Harvey, 1994). Very little p75 mRNA was detected in the adult rat SC (Ernfors et al., 1988; Koh et al., 1989). p75 is expressed in the chick tectum (Large et al., 1989; Escandón and Chao, 1990; Heuer et al., 1990). The developmental time course of expression in the chick tectum was analysed by in situ hybridization (von Bartheld et al., 1991). p75 is expressed in layer SGFS sublayers b, c and i in chick embryos (nomenclature of LaVail and Cowan, 1971), especially between E13 and E18 (von Bartheld et al., 1991).

TrkA is transiently present in the chick tectum, as shown by NGF crosslinking and binding studies (Raivich et al., 1987; Escandón and Chao, 1990), but trkA mRNA was not detected in the tectum by in situ hybridization (R. Williams, personal communication). Since the locus coeruleus is a particularly strong source of trkA in the developing chick (von Bartheld et al., 1995) and the coeruleus axons innervate the avian tectum (Rodman and Karten, 1995), the trkA protein in the tectum may be localized to the noradrenergic coeruleus nerve fibers.

TrkB mRNA is expressed in the mammalian SC (Merlio et al., 1992). In the SC of ferrets, full length and truncated trkB are expressed, and the truncated trkB increases during development relative to the full-length trkB (Allendoerfer et al., 1994). TrkB protein was detected by immunocytochemistry in the ferret and rat SC (Cabelli et al., 1996; Yan et al., 1997). TrkB protein and mRNA is expressed in the chick tectum (Escandón et al., 1994; Garner et al., 1996). Truncated trkB is also expressed (Escandón et al., 1994; Garner et al., 1996). Since truncated trkB mRNA is expressed in the retina, but truncated trkB protein is not immunoprecipitated (Escandón et al., 1994), it has been suggested that this receptor isoform may be specifically targeted to RGC axons (Garner et al., 1996). Two forms of the catalytic

receptor have been shown to be expressed in the chick tectum: a shorter one with increased specificity for BDNF, and a longer one which also binds NT-3 and NT-4 (Strohmaier et al., 1996).

TrkC mRNA is expressed in the SC of mammals (Merlio et al., 1992; Allendoerfer et al., 1994) and in the chick tectum (Escandón et al., 1994; Hallböök and Carri, 1995; von Bartheld et al., 1996a). The chick tectum also expresses truncated trkC (Okazawa et al., 1993a,b). Binding studies indicate that trkC protein is located predominantly in superficial layers of the chick tectum (von Bartheld et al., 1996a) which contain the apical dendrites of SGFS and SGC neurons and receive RGC afferent input (Hunt and Brecha, 1984).

These data are consistent with the notion that BDNF is a target-derived trophic factor for RGC axons. In addition, BDNF may be a trophic factor for additional afferents to the tectum such as the isthmic nuclei in birds (see below), and NT-3 may carry an afferent trophic signal from the retina to the tectum.

Isthmo-optic nucleus (ION)

The ION of birds provides centrifugal innervation to the retina where it projects onto a subpopulation of amacrine cells (Uchiyama and Ito, 1993). The ION presents a unique model system for the study of developmental cell death and its trophic regulation. It critically depends on the retina during a distinct period of development which is likely due to dependence on trophic factors provided by the target (Catsicas and Clarke, 1987; Clarke, 1992; von Bartheld et al., 1994, 1996b). The retina appears to contain a reserve of these trophic factors (Blaser and Clarke, 1992). The ION of chick embryos expresses the p75 neurotrophin receptor (von Bartheld et al., 1991), and expression is developmentally regulated with a peak at E13 (the onset of developmental cell death) and a gradual decline of p75 receptor mRNA expression thereafter (von Bartheld et al., 1996b). The ION expresses full-length trkB mRNA (Garner et al., 1996), but little, if any, trkC, and no trkA (von Bartheld et al., 1996b; von Bartheld, 1996). The ION also expresses a shorter form of the catalytic trkB which binds BDNF with much higher specificity than NT-4, NT-3 or NGF (Strohmaier et al., 1996). Expression of BDNF and NT-3 mRNAs has not been detected in the ION (von Bartheld, unpublished).

Both BDNF and NT-3 promote neurite outgrowth from explants of the ION of E13 chick embryos, while NGF has no effect (von Bartheld et al., 1994). BDNF increases the survival of dissociated ION neurons in vitro (von Bartheld et al., 1994). Intraocular BDNF also enhances the survival of ION neurons in vivo (von Bartheld et al., 1994; Gunther et al., 1996; Primi and Clarke, 1996), while NT-3 increases survival only after systemic application (von Bartheld et al., 1994). NGF significantly enhances developmental cell death in the ION after intraocular or systemic application (von Bartheld et al., 1994), possibly by competing the binding and transport of BDNF at the level of the p75 receptor (von Bartheld et al., 1996b) or by death signalling via p75 (Frade et al., 1996).

The ION is uniquely suited for quantitative studies of neurotrophin transport. All neurotrophins tested, NGF, BDNF, NT-3 (von Bartheld et al., 1994, 1996b) and NT-4 (von Bartheld, unpublished) are transported retrogradely to the ION after intraocular injection, although with distinct efficiencies (NT-3>BDNF=NT-4>NGF). The transport of all neurotrophins is receptor-mediated (von Bartheld et al., 1996b). While NGF binds exclusively to p75 during retrograde transport, both p75 and trkB contribute to BDNF transport. Significant fractions of NT-3 bind to p75, trkB and trkC during transport (von Bartheld, 1996). The activation of trkB at the axon terminals by BDNF appears to be functionally important, since the tyrosine-kinase inhibitor K252a induces cell death despite undiminished transport of BDNF (von Bartheld et al., 1996b). The ION receives afferent innervation from tectal neurons in layer SGFSh (Uchiyama, 1989) on which it depends for survival during development (Clarke, 1985). Since neurons in this layer contain BDNF (Herzog and von Bartheld, 1997), it is possible that ION neurons also receive BDNF trophic support by anterograde transport from the tectum, in addition to the BDNF which they likely receive from the target cells in the retina. It should be noted that trophic responses of the ION have been investigated with exogenous neurotrophins, and it needs to be confirmed that endogenous neurotrophins have the roles which are strongly suggested by the current data (Fig. 6).

Other brainstem visual nuclei

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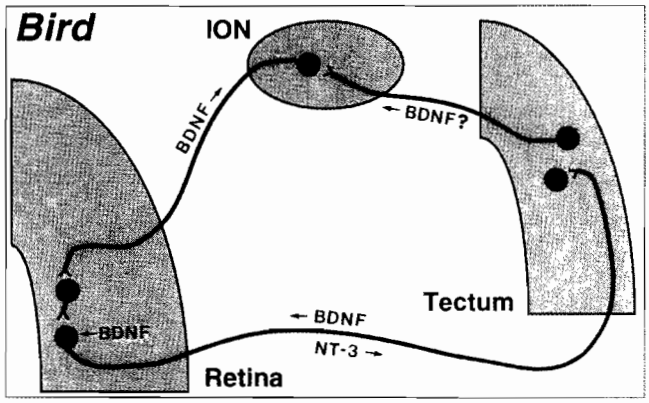

Fig. 6. Summarizing scheme of the potential trafficking of the neurotrophins BDNF and NT-3 in the centrifugal and centripetal innervation of the avian retina. BDNF may support ganglion cells in the retina as an afferent trophic factor as well as a retrograde trophic factor transported from the optic tectum (Herzog and von Bartheld, 1997). The ganglion cells may transport NT-3 as an anterograde trophic factor to neurons in the optic tectum (von Bartheld et al., 1996a). The isthmo-optic nucleus (ION) may receive BDNF as a retrograde trophic factor from amacrine neurons in the retina (von Bartheld et al., 1996b) as well as an anterograde factor from tectal neurons. Thus, neurotrophins may support neurons in multiple pathways of the avian visual system.

neurotrophins or their receptors in pretectal, accessory optic pathways or the Edinger-Westphal nucleus. In the chick, the ION is not the only brainstem nucleus which is affected by retinal target ablation (Ostrach and Mathers, 1979; Page et al., 1993). It is thought that as a consequence of anterograde transneuronal degeneration of tectal neurons, central afferents of tectal neurons are also deprived of their trophic support. These afferents include the parvocellular and magnocellular isthmic nuclei and the lateral spiriform nucleus which project onto the SGFS and the SGC (Hunt and Brecha, 1984). All three nuclei express high levels of full-length trkB receptors (Garner et al., 1996). The parvocellular and magnocellular isthmic nuclei also express p75 receptors (von Bartheld et al., 1991). These neurons, therefore, may transport and utilize BDNF produced by tectal neurons for trophic support (Garner et al., 1996). Since the parvocellular and magnocellular isthmic nuclei are reciprocally connected with the tectum, these nuclei may also receive anterograde trophic support from BDNF-expressing tectal neurons, a possibility which will be technically difficult to distinguish from the retrograde route of delivery. Neurotrophins may also play important roles in synaptic plasticity. Administration of BDNF increases transmitter release (Thoenen, 1995). BDNF expression in the tectum is positively regulated by activity (Herzog et al., 1994; Hallböök and Carri, 1995; Hallböök et al., 1995). Therefore, BDNF may play a key role in the shaping of visual connections as well as the processing of visual information.

Visual cortex

As mentioned in the INTRODUCTION, the effects of neurotrophins on visual cortex and ocular dominance column formation are currently controversial and under

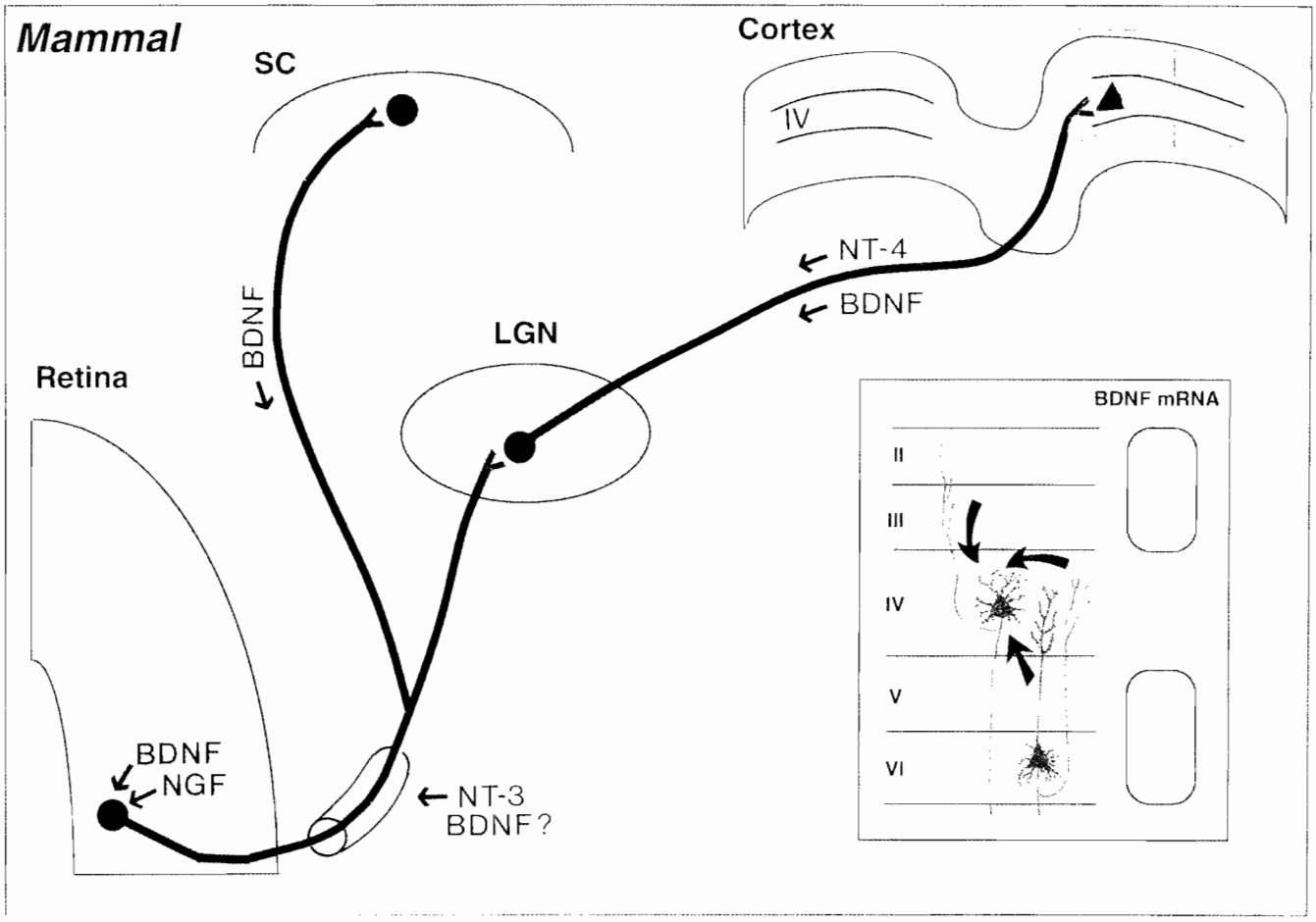

Fig. 7. Summarizing scheme of the potential trafficking of neurotrophins in the visual centers in mammals. BDNF and NGF may support ganglion cells in the retina after transport from the superior colliculus (SC) or after paracrine action in the retina. NT-3 and BDNF act on glial cells in the optic nerve. Neurons in the lateral geniculate nucleus (LGN) may require NT-4 or BDNF after retrograde transport from layer IV in the visual cortex. BDNF protein may be provided to LGN axons by pyramidal neurons in layer IV. These neurons do not seem to produce BDNF themselves, but they may take it up from neurons in layers II/III or VI with which the layer IV neurons entertain intimate connections (Gilbert and Wiesel, 1979). For abbreviations, see list in beginning of this review.

investigation (for recent reviews, see Gu, 1995; Thoenen, 1995; Bonhoeffer, 1996; Cellerino and Maffei, 1996). Only one commonly overlooked aspect will be dealt with here. BDNF and NT-4 appear to be the most likely candidates for a direct action on LGN fibers in layer IV of visual cortex (Cabelli et al., 1995). Layer IV contains fibers with dense p75 immunolabel (Mrzljak and Goldman-Rakic, 1993), and LGN fibers contain trkB receptors in layer IV (M.A. Silver, personal communication). The problem with BDNF or NT-4 as retrograde trophic signals from pyramidal neurons in layer IV to LGN fibers is that BDNF or NT-4 mRNAs have not been detected by in situ hybridization in this layer, while pyramidal neurons in layers II/III and V/VI do express BDNF (Castrén et al., 1992; Cellerino et al., 1996). Nevertheless, LGN target neurons (pyramidal neurons) in layer IV may contain BDNF protein obtained from layer VI neurons with axon collaterals in layer IV or from their own processes which contact neurons in layers II/III (Gilbert and Wiesel, 1979). This possibility should not be neglected, because layer VI neurons are intimately connected to layer IV neurons by dendritic and axonal arbors (Gilbert and Wiesel, 1979). Thus, even if BDNF is not expressed by postsynaptic neurons, this does not necessarily preclude the possibility that they may contain BDNF and that BDNF may be transferred to LGN fibers (Fig. 7). It has been shown that some neurons can accumulate and possibly re-use neurotrophins taken up from other sources (Castrén et al., 1995; von Bartheld et al., 1996a). Another possibility is that pyramidal neurons in layer IV may express functionally significant levels of BDNF or NT-4 which are merely too low to be detected by in situ hybridization (Ibáñez, 1996).

Degeneration and regeneration of retinal neurons after injury: effects of neurotrophins

Retinal ganglion cells (RGC)

Sectioning of the optic nerve in mammals causes the degeneration of many RGC (Allcutt et al., 1984; Provis and Penfold, 1988), a failure to regenerate axons and to connect with their normal targets, and thereby leads to permanent loss or impairment of vision (Aguayo et al., 1991). This presents an obvious clinical problem. The responses of RGC to injury of their axons differ with age and between species. The loss of RGC is more severe in developing mammals than in adults (Allcutt et al., 1984; Snider et al., 1992). In cold-blooded vertebrates RGC are generated in the eye throughout the lifetime of the animal. In many of these species RGC regenerate their axons, regrow to their former targets, and vision is largely restored after optic nerve section (Stone and Zaur, 1940; Sperry, 1943; Grafstein, 1986).

The differences between species in their capacity to regenerate retinal projections have stimulated research into the molecular events responsible for regeneration (Adler, 1986; Bray et al., 1991; Aguayo et al., 1996; Frisén, 1997). This process can be divided into three major components: First, it is important to maintain RGC in a viable state after injury. Second, the RGC need to be induced to regrow an axon in the former pathway, and finally, the axons have to connect with the appropriate target and make functional contacts. In this context, neurotrophins have received considerable attention because they support the survival of RGCs in vitro (Johnson et al., 1986; Lehwalder et al., 1989; Rodríguez-Tébar et al., 1989; Thanos et al., 1989; Cohen et al., 1994; Cohen-Cory and Fraser, 1994; Castillo et al., 1994), and promote the outgrowth of RGC neurites (Turner et al., 1980a,b, 1982, 1983; Johnson and Turner, 1982; Thanos et al., 1989; Takahashi et al., 1993b; Cohen et al., 1994; Cohen-Cory and Fraser, 1994, 1995; Hallböök et al., 1996; Sawai et al., 1996).

Historically, the effects of neurotrophins were first examined in the regenerating visual system of amphibians and fish (Turner and Glaze, 1977; Glaze and Turner, 1978; Turner et al., 1980a,b). NGF was found to accelerate and enhance regeneration (Turner and Glaze, 1977), while antibodies to NGF showed the opposite effect (Glaze and Turner, 1978). A series of morphological studies confirmed these results in newt and goldfish (Turner and Glaze, 1978; Turner and Delaney, 1979a,b), but, unexpectedly, not in frog (Humphrey, 1988). Later studies in goldfish extended the results from newt (Turner et al., 1980a,b; Yip and Grafstein, 1983) and showed neurite outgrowth in response to NGF (Turner et al., 1982). When exogenous NGF was applied to the site of nerve crush it was retrogradely transported to the retina, but, surprisingly, this transport was not receptor-mediated (Yip and Johnson, 1983). The mechanism by which NGF was acting on RGC thus remained unclear.

In vivo studies in mammals and birds showed that NGF, as well as BDNF and NT-4, delay cell death of RGC after injury (NGF: Carmignoto et al., 1989; Maffei et al., 1990; Ehrlich et al., 1990; Rabacchi et al., 1994; BDNF/NT-4: Mey and Thanos, 1993; Voci et al., 1993; Mansour-Robaey et al., 1994; Cui and Harvey, 1995; Aguayo et al., 1996). In addition, NGF and BDNF promote RGC survival after ischemic damage (Siliprandi et al., 1993; Unoki and LaVail, 1995) and experimental diabetes (NGF: Hammes et al., 1995). BDNF and NT-4 promote neurite outgrowth from regenerating RGCs (Villegas-Pérez et al., 1988; Sawai et al., 1996). BDNF reduces axonal die-back from lesioned RGC (Weibel et al., 1995) and increases mRNA levels for GAP 43 (Fournier et al., 1997). Consistent with the effects of NGF and BDNF/NT-4, the receptors trkA and trkB are expressed in RGC (Jelsma et al., 1993; Zanellato et al., 1993). The p75 receptor is transiently upregulated after optic nerve injury (Maffei et al., 1990) which may promote the retrograde transport of neurotrophins. NGF has been proposed to be produced and presented by Schwann cells to regenerating peripheral nerve fibers (Johnson et al., 1992). Could NGF or other trophic factors play a similar role for optic nerve fibers? While

the rescue studies after optic nerve injury are promising, they also show limitations of the neurotrophins in that the death of the large majority of RGC could not be prevented (Aguayo et al., 1996). It is now thought that additional trophic factors, other than NGF or BDNF/NT-4, are essential for RGC survival and regeneration after optic nerve injury (Schwartz et al., 1982; Schulz et al., 1990; Schwalb et al., 1995; Mey and Thanos, 1996; Fournier and McKerracher, 1997). Nevertheless, neurotrophins remain as one of the most promising therapeutic agents for the increase in the number of surviving RGC and promotion of neurite outgrowth from these cells.

Photoreceptors

Besides the RGC, neurotrophins have been shown to promote the survival of other cell types in the retina, notably photoreceptors (Steinberg, 1994; Adler, 1996). Degeneration of photoreceptors can be induced by noxious stimuli such as exposure to intense light (Faktorovich et al., 1990, 1992). Several growth factors and cytokines, including the neurotrophins (BDNF and, less so, NT-3), can rescue photoreceptors from damaging effects of light in vivo (LaVail et al., 1992). NGF also retards cell loss in mouse photoreceptors in vitro when it is combined with bFGF (Caffé et al., 1993).

An eye towards the future

Proliferation and differentiation

As in other parts of the nervous system (Cattaneo and McKay, 1990; Weiss et al., 1996), neurotrophins are important during early stages of visual development. Findings that neurotrophins can act as mitogens in vitro (Barres et al., 1994; Ikeda and Puro, 1994) suggest similar functions in vivo. Recent in vivo studies demonstrated that endogenous neurotrophins have major effects in the early development of the retina and optic nerve (Bovolenta et al., 1996; Carrol et al., 1996). Neurotrophins may be part of the "switch" from proliferation to differentiation. In vitro studies and detailed examination of knock-out mice revealed functions of BDNF and NT-3 on myelination and possibly neural-glial interactions (Barres et al., 1994; Carrol et al., 1996). It will be of interest to determine the sources of these neurotrophins and how they may interact with other factors to regulate the numbers of neurons and glial cells.

Developmental cell death

Neurotrophins and their receptors appear to be involved not only in the "classic" late developmental cell death which occurs after the establishment of connections with the target (Cowan et al., 1984), but also in early developmental cell death prior to target contact. During early stages NGF bound to p75 appears to be a death signal (Frade et al., 1996), while at later stages neurotrophins promote the survival of retinal neurons. BDNF is not absolutely essential for RGC survival in vivo (Jones et al., 1994; Carrol et al., 1996), but it is in vitro (Johnson et al., 1986) and possibly after injury (Voci et al., 1993, cited in Garner et al., 1996). It will be a challenge to dissect the functions of the endogenous neurotrophins and how they regulate cell survival during development.

Trafficking of neurotrophins

Trafficking of neurotrophins is important because the sites of release and transport determine the function of neurotrophins (Curtis and DiStefano, 1994; Lo, 1995; Thoenen, 1995; Oppenheim, 1996). The visual system has contributed substantially to the knowledge of trafficking, due to the experimental advantages of quantification of the injected factors in the eye and their transport to laminated visual centers. p75 is retrogradely and anterogradely transported by RGC (Carmignoto et al., 1991). Exogenous neurotrophins are differentially transported from the retina to the optic tectum/superior colliculus (Ferguson and Johnson, 1990; von Bartheld et al., 1996a) and NT-3 has been localized in retinotectal synapses after anterograde transport (von Bartheld et al., 1996a). Molecular aspects of neurotrophin transport, the role of truncated receptors, and mechanisms of neurotrophin release are currently under investigation (Garner et al., 1996; von Bartheld et al., 1996a,b; von Bartheld, 1996; Bacten et al., 1997). These studies will be important for an understanding of the functions of neurotrophins in synaptic plasticity (Thoenen, 1995; Fryer et al., 1996).

Ocular dominance columns and branching of axons and dendrites

Another focus of intense study is the effects of neurotrophins on axonal arbors (Cohen-Cory and Fraser, 1995), in particular in the model system of ocular dominance columns (Cabelli et al., 1995; Riddle et al., 1995). These studies suggested that BDNF and/or NT-4 may regulate developing LGN axonal arbors based on electrical activity. Neurotrophins also have effects on the branching of dendritic processes (McAllister et al., 1995, 1996, 1997). This work has shown that exogenous and endogenous neurotrophins differentially regulate dendritic arbors. These studies are consistent with the concept that neurotrophins are released pre- or postsynaptically, act on receptors expressed on the pre- or postsynaptic membranes, strengthen synapses, and stimulate or maintain functional branches. Lack of positive feedback, on the other hand, may reduce the release of neurotrophins and thereby induce withdrawal and loss of synaptic connections. It is a challenging task for the future to provide clear evidence for such roles of the endogenous neurotrophins in vivo.

Maintenance of RGC and regeneration after optic nerve injury

Based on its clinical importance, several groups are examining which trophic factors increase the survival and regeneration of RGC after injury. These studies have shown small, but significant, effects of neurotrophins which delay the death of RGC after injury (Mansour-Robaey et al., 1994; Aguayo et al., 1996), with less convincing effects on long-term survival. Given the striking actions of BDNF in vitro, it needs to be examined if the intraocular or optic nerve application of neurotrophins is effective (Castillo et al., 1994), and whether the neurotrophins actually arrive in the appropriate subcellular organelles to exert their beneficial effects. It is becoming evident that no one single trophic factor will be the solution (Barres et al., 1993; Lindsay et al., 1994; Mey and Thanos, 1996), but that an optimal cocktail of different factors, acting synergistically or sequentially, may provide for optimal support and stimulation of injured RGC.

In the past decade, neurotrophins have proven to be involved in many more functions in development and physiology than previously anticipated. This multitude of functions is reflected by the expression of neurotrophins and their receptors in many different cell types. While generating a higher level of complexity and therefore initially more confusion, this allows us to gain a more accurate picture of the extent to which neurotrophins are intertwined in nervous system development and function. As we learn more about new roles of neurotrophins, it will become possible to evaluate the potential of neurotrophins as therapeutic agents and utilize them successfully to halt degenerative diseases and to restore functional circuits after injury.

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