Central Visual Pathways in Glaucoma: Evidence for Distal Mechanisms of Neuronal Self-Repair

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Abstract: As in other age-related neurodegenerative diseases, progression of neurodegeneration in glaucoma involves early axonopathy. In glaucoma, this is marked by degradation of active transport along retinal ganglion cell (RGC) axons projecting from the retina to the brain. In experimental systems, transport degradation occurs first in the most distal site in the RGC projection, the superior colliculus (SC) of the midbrain. Even as degradation progresses from one retinotopic sector to the next, important structures in the affected sectors persist, including synapses from RGC axon terminals onto SC neurons. This structural persistence is accompanied by focally increased brain-derived neurotrophic factor in hypertrophic SC astrocyte glia and defines a therapeutic window of opportunity. Thus, central brain structures in glaucoma may respond to disease-relevant stress by induction of mechanisms useful for maintaining retinal signals.

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A NEUROBIOLOGICAL PERSPECTIVE OF GLAUCOMA

A focus in glaucoma research from the neuroscience vantage point includes a shift towards degenerative events in the optic projection to the brain. Many of these events occur early in the pathogenesis and presage actual apoptotic elimination of retinal ganglion cell (RGC) bodies (1). As this shift occurs, the involvement of a larger neuroscience community brings with it the realization that experimental studies of vision loss and its mechanisms in glaucoma are useful tools in a broader context. This utility includes both understanding neurodegenerative progression in other diseases of the central nervous system (CNS) and identifying potential therapeutic targets, especially for age-related diseases (2,3).

Linking progression in glaucoma to other CNS diseases, however useful and accurate, bears with it the danger of a prominent misunderstanding that glaucoma is at its etiological roots a "brain disease"; something that begins in the brain and affects the eye. Glaucoma is not, nor should be construed as, a brain disease, although certain early events in pathogenesis are observed in the brain before the retina or optic nerve (4). In its most general terms and with some noteworthy exceptions (5), glaucoma is a family of diseases in which sensitivity to intraocular pressure (IOP) causes degeneration of the visual pathways. Degeneration arises through stress most likely conveyed at the nerve head involving complex interactions with the RGC axon. Many of these interactions involve biomechanical stressors that affect axon function and occur on a backdrop of other age-related changes (6). This stress can be detected early in the brain, where RGC axon terminals form connections with postsynaptic neurons, but this is not tantamount to the disease originating in the brain.

We are beginning to understand that the visual pathways and visual brain are not passive during progression of glaucoma. Quite the contrary, the retina (7), optic nerve head (8), and higher visual structures (9) all demonstrate

compensatory mechanisms to counter loss of function. Mechanisms of plasticity, remodeling, and adaptability ultimately could be just as relevant for glaucoma and by extension other CNS diseases as they are for complex synaptic functions in the healthy brain. Thus, translational research targeting new therapies must evolve from an exclusive focus on how glaucoma progresses from IOP-related stress at the nerve head to include a new spotlight on intrinsic mechanisms that might counter loss of function.

EARLY PATHOGENESIS INVOLVES THE OPTIC PROJECTION

The visual pathways begin with the projection of RGC axons out of the retina and through the optic nerve to their termination targets in the brain (Fig. 1). RGC axons from each eye cross at the optic chiasm to form the ipsilateral and contralateral projection to the brain. From there, axon terminals provide synapses to neurons in several important nuclei. In primates, the primary target for RGC axons is the lateral geniculate nucleus (LGN) of the thalamus, which relays visual information directly to the primary visual cortex. In rodents, nearly every RGC projects primarily to the superior colliculus (SC) of the midbrain, with axon collaterals extending to other nuclei including the LGN. In all mammals, the SC is the most distal precortical site and therefore the most susceptible to bioenergetic stressors affecting the unmyelinated RGC axon segment in the retina and nerve head (1).

Early in pathogenesis, age-related neurodegenerative disorders like glaucoma involve axonal dysfunction, including diminished active transport to and from major projection targets in the brain (11,12). One of the earliest pathogenic events in both chronic and inducible experimental models of glaucoma is degradation of active anterograde axon transport from the retina to the brain (4,7,13). Anterograde transport in rodent models fails first at the most distal site in the projection, the SC, and degrades over time in a distal-to-proximal progression before failing completely in the retina (4) (Fig. 2). There are intriguing metabolic possibilities to explain why failure occurs first at the most distal site. These are reviewed elsewhere (1,14,15). Anterograde transport is more metabolically demanding than retrograde axonal transport, due to differences in the molecular machinery utilized (16). In models of glaucoma, transport from RGC axon terminals in the brain to the cell body in the retina persists long after anterograde transport is depleted, probably as long as the axon itself survives structurally (1,17). The relative sustainability of retrograde transport suggests that trophic factors derived from brain targets may still be useful for RGCs through interactions with the axon terminal. This may explain why, in models of acute nerve injury, brain-derived neurotrophic factor (BDNF) is most efficacious at protecting RGCs when delivered both through the eye and the visual brain (18).

Several important points arise from rodent studies using active anterograde transport to the SC as a functional outcome measure. Age is the critical determinant of transport failure, with elevated IOP serving as an additional factor that increases the likelihood of failure (1,4,19,20). In multiple experimental models, both chronic and inducible,

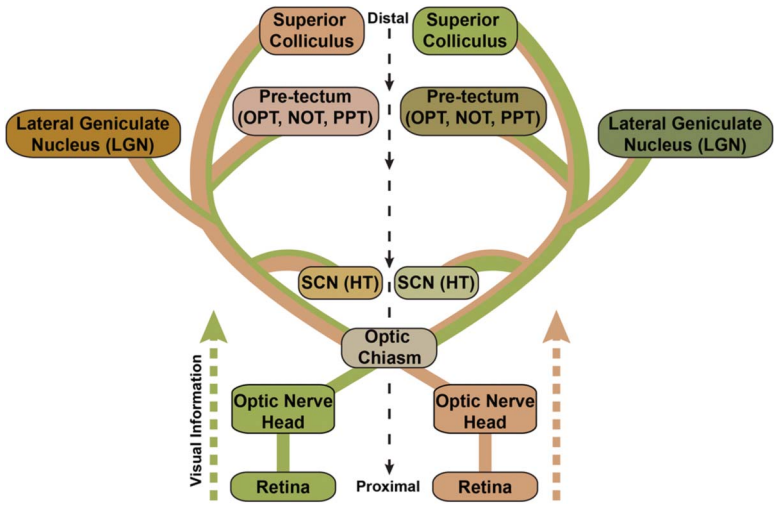

FIG. 1. Retinal projection in the rodent brain. Schematic diagram illustrates the dominant contralateral projection of the retina in the rodent visual system. Retinal ganglion cell (RGC) axons exiting the retina through the optic nerve head cross at the optic chiasm to join either the ipsilateral or contralateral optic tract in the brain. Central targets for RGC axons are highly conserved across mammals and include the suprachiasmatic nucleus (SCN) of the hypothalamus (HT) and the olivary pretectal nucleus (OPT), nucleus of the optic tract (NOT), and posterior pretectal (PPT) nucleus of the pretectum in the subcortical midbrain. In primates, the lateral geniculate nucleus (LGN) of the thalamus is the primary RGC recipient. Across mammals, the superior colliculus of the midbrain is the most distal direct target for ascending RGC axons. In rodents, all or nearly all RGCs project to the colliculus, while extending axon collaterals to nuclei lying more proximal to the retina, that is, anterior to the colliculus (10). There are numerous interspecies differences in the strength of RGC projections to specific targets.

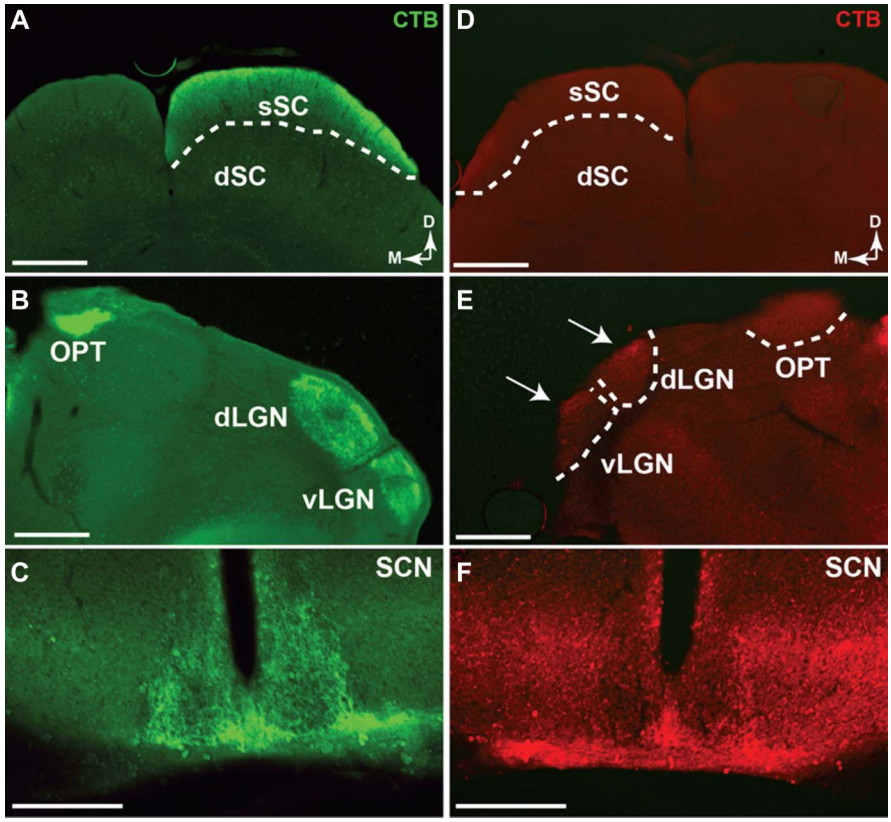

FIG. 2. Deficits in axon transport progress distal to proximal. **A**, Cross section (*coronal plane*) through the superior colliculus (SC) from an 8-month DBA2J mouse following intravitreal injection of cholera toxin β (CTB). *Dashed line* demarcates fully intact anterograde transport of CTB in retinal recipient region in superficial SC (sSC), just dorsal to deep (dSC). **B**, In same brain, anterograde transport of CTB is also intact in structures more proximal to the retina, including the olivary pretectal nucleus (OPT) and dorsal and ventral lateral geniculate nucleus (dLGN and vLGN), as well as the suprachiasmatic nucleus (SCN), as shown in (**C**). The contralateral SC from the same brain (**D**) demonstrates a complete depletion of CTB transport from the retina. In distal to proximal progression, transport has also failed in the OPT but persists at a residual level in the LGN, as indicated by the arrows (**E**). More proximally, in the SCN (**F**), axonal transport remains intact. Scale = 500 μm (**A**, **B**, **D**, and **E**) or 100 μm (**C** and **F**).

deficits in anterograde transport are detected earlier than a variety of other pathogenic outcomes, including axon degeneration in the optic nerve and RGC body loss in the retina. This chronology renders transport readout in the SC a convenient outcome measure for experimental interventions (7,13,21,22). Finally, degradation of axon transport in the SC is spatially progressive, filling in from one retinotopic sector to the next. In early progression, a given SC is very likely to contain both affected and unaffected regions. This provides a convenient internal control for investigations directed at how postsynaptic structures in the optic projection respond to glaucomatous challenges, a topic we take up below.

A THERAPEUTIC WINDOW IN PROGRESSION

Across different experiment models, both chronic (e.g., DBA2J mouse) and inducible, degradation of anterograde axonal transport to the brain marks the beginning of an important window of opportunity for intervention. This window is defined by the interval during progression between the onset of deficits in axon function and actual degeneration of RGC axons in the optic projection, which occurs later. These functional deficits can be detected quite early, either through axonal or retinal physiology (14,23,24). A similar interval likely exists in human glaucoma, where reversal of physiological deficits can occur with timely IOP-lowering interventions (25). Experimental interventions that target this period of functional quiescence in the projection and are successful in restoring axon transport also abate subsequent steps in pathogenesis. For example, daily topical application of a potent and highly selective inhibitor of retinal p38 MAPK activity was effective at stopping progression entirely in the microbead occlusion-inducible rat model (13), as was systemic delivery of the alpha-2 adrenergic receptor agonist brimonidine in another inducible model (21). In these cases, for control/vehicle cohorts, deficits in anterograde transport exceeded axon degeneration in the optic nerve which, in turn, exceeded

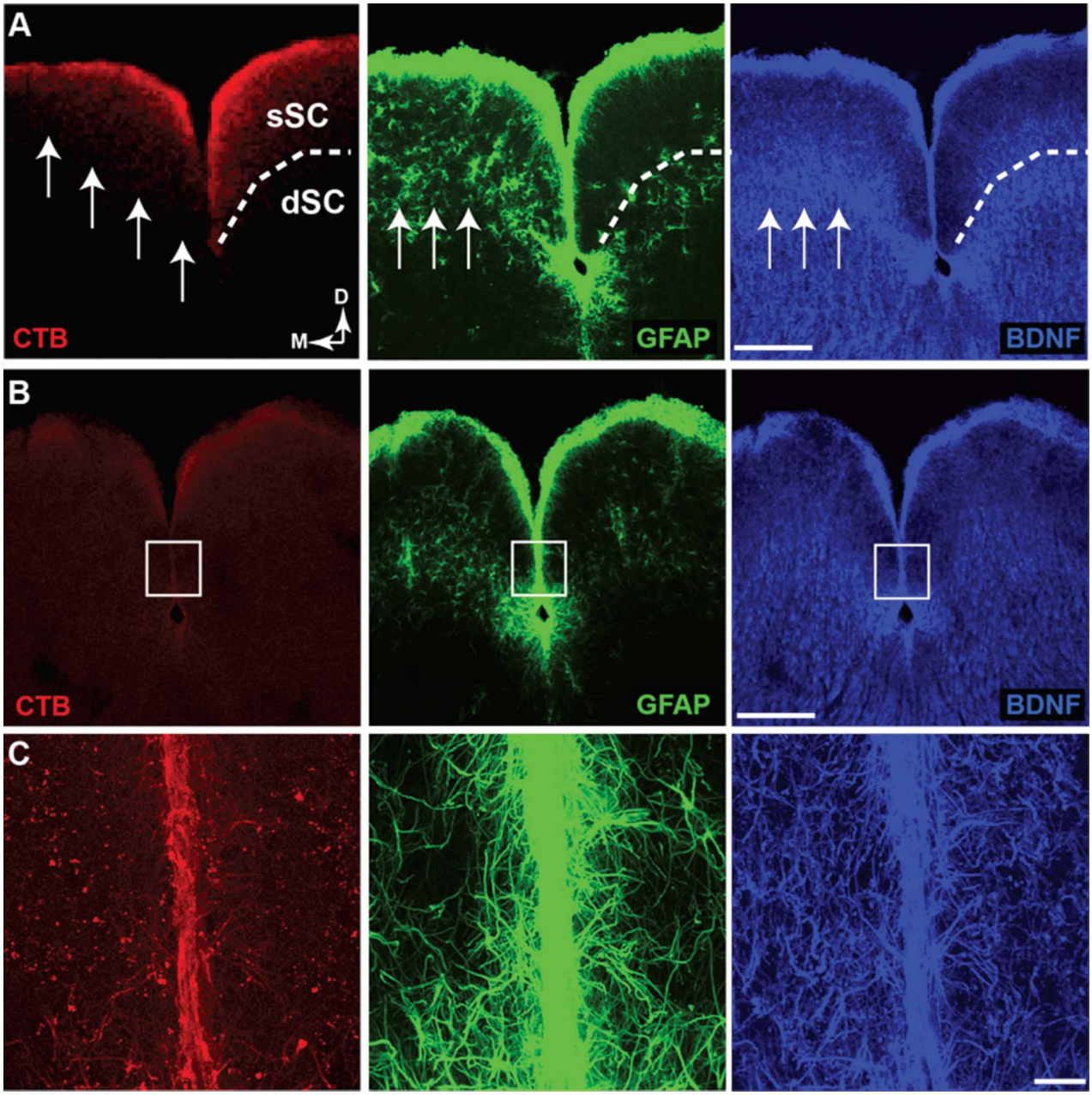

FIG. 3. Deficits in axon transport coincide with focal increases in brain-derived neurotrophic factor (BDNF). **A**, Coronal section through the superior colliculus (SC) of a 10-month DBA2J mouse following bilateral intravitreal injection of cholera toxin B (CTB) shows fully intact anterograde transport in sSC from one eye (*dashed line*) with degradation of signal in the opposing SC (*arrows*). Staining for glial acidic fibrillary protein (GFAP) shows increased astrocyte hypertrophy in same SC, while BDNF also increases. **B**, SC from a 10-month DBA2J mouse shows bilateral deficit in anterograde transport of CTB, corresponding to a more uniform distribution of hypertrophic GFAP-labeled astrocytes and BDNF. Higher magnification images of the midline (*boxed region*) between the 2 SC (**C**) shows depleted CTB signal corresponding to increased BDNF in hypertrophic astrocytes. Scale = 200 μm (**A** and **B**) or 20 μm (**C**).

RGC body loss in the retina. Correspondingly, with treatment, rescue of transport was a surrogate marker for survival of RGC axons and bodies (13, 21).

A key avenue of investigation addresses how RGC postsynaptic targets in the brain respond to glaucomatous stressors and whether this response includes mechanisms that promote RGC axon survival. At one end of the spectrum, postmortem samples of LGN from human patients with significant visual field loss also show a correspondingly high loss of tissue (26). With prolonged exposure to elevated IOP, non-human primate LGN demonstrates significant depletion of neurons postsynaptic

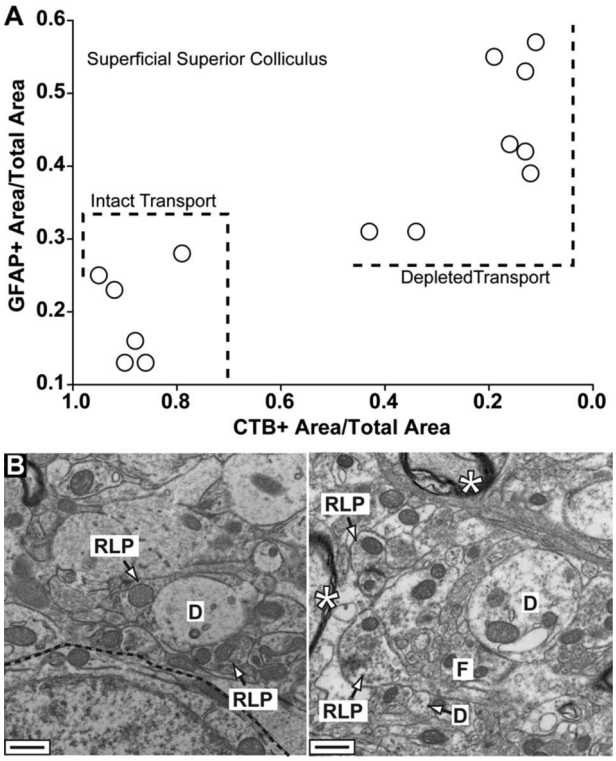

FIG. 4. Glial acidic fibrillary protein (GFAP) increases with diminished axon transport in superior colliculus. **A**, Fraction of GFAP-labeled area in superficial superior colliculus (SC) increases as fraction of area containing transported cholera toxin B (CTB) decreases. Quantified from individual coronal section through 8- and 10-month DBA2J SC, as described elsewhere (33). **B**, Electron micrographs through superficial SC from 12-month (*left*) and 14-month (*right*) DBA2J shows intact axon terminals with synapses from RGCs (round vesicles, large profile, pale mitochondria) and intracollicular inhibitory neurons (F) in proximity to a collicular relay neuron (*dashed line*) and dendrites (D). For definitions of axon terminal morphologies, see (34). At these ages in the DBA2J, anterograde transport from the retina is typically completely depleted (4). Scale = 0.5 μm.

to RGC axon terminals (27–29). Even so, loss of LGN neurons generally lags by 20%–30% RGC axon degeneration in the optic nerve (29). Our studies show similar persistence of postsynaptic neurons and of RGC synaptic terminals in the SC well after axonal transport from the retina is depleted completely (4). This is so for both the DBA2J mouse model of hereditary pigmentary glaucoma and the microbead occlusion model. Thus, just as RGC axons in the optic nerve persist for a period of time after loss of anterograde transport so, too, do their axon terminals and synapses with relay neurons in the brain.

POSSIBLE MECHANISMS OF SELF-REPAIR IN GLAUCOMA

Structural persistence in the optic projection is testimony to the resilience of the CNS and offers clues to possible intrinsic prosurvival mechanisms in glaucoma. Postsynaptic structures in the brain respond to disease-relevant stressors, including degraded axon transport, in ways believed to promote recovery of axon activity. This response may include a certain degree of synaptic remodeling to compensate for loss (30–32). As we have shown (33), in retinotopic sectors of depleted transport in the SC, astrocyte glia become hypertrophic compared with SC regions with intact transport (Figs. 3, 4A). These same astrocytes demonstrate increased levels of BDNF that is likely sequestered after release from SC neurons (33). These changes occur before elimination of important structures in the SC, including synapses from RGC axons and dendrites of SC postsynaptic neurons (Fig. 4B). These dendrites also can be visualized with antibodies against MAP2, which show similar persistence of label (Fig. 5). Increases in BDNF occur with other injury models, including N-Methyl-D-aspartate (NMDA)-induced excitotoxicity and acute elevations in IOP (35–37). Interestingly, increased glial acidic fibrillary protein and BDNF coincident with loss of anterograde transport is not restricted to the colliculus, but also is apparent in more proximal structures of the optic projection (Fig. 6).

Why would retinorecipient targets in the brain respond this way to disease-relevant stressors? One possibility lies in the fact mentioned earlier that retrograde axonal transport in the optic projection persists in glaucoma as long as RGC axons themselves (1,17). BDNF is implicated in axonal guidance and RGC dendritic arborization during development (38). Whereas retinal-derived BDNF inhibits dendritic arborization, BDNF shuttled in retrograde fashion along RGC axons promotes outgrowth (39). In the adult visual system, when IOP is elevated acutely, retrograde transport of exogenously applied BDNF from the SC to the retina is greatly diminished (40). Thus, SC-derived BDNF might be uploaded to RGC neurons in retinotopic sectors challenged by degradation of anterograde axon transport for the purpose of protecting RGC dendritic arbors in the retina. Supporting this hypothesis, combined application of exogenous BDNF to the eye and brain is far more effective in protecting RGCs than application to the eye alone (18,41).

In our studies, the greatest fraction of BDNF was found to be in stored membrane vesicles and not observed directly in RGC axon terminals (33). We argued that perhaps vesicle-stored BDNF in SC neurons is released and sequestered by astrocytes in response to diminished RGC axonal transport to promote synaptic activity and survival. In the CNS, BDNF contributes to maintenance of synaptic function and plasticity of neural circuits (42,43). Astrocytes are likely to play an important role. In the hippocampus, astrocytes expressing the TrkB.t1 receptor isoform bind extracellular BDNF for storage before release into the extracellular space (44). This pathway could explain the high levels of BDNF in both SC neurons and astrocytes as a mechanism to

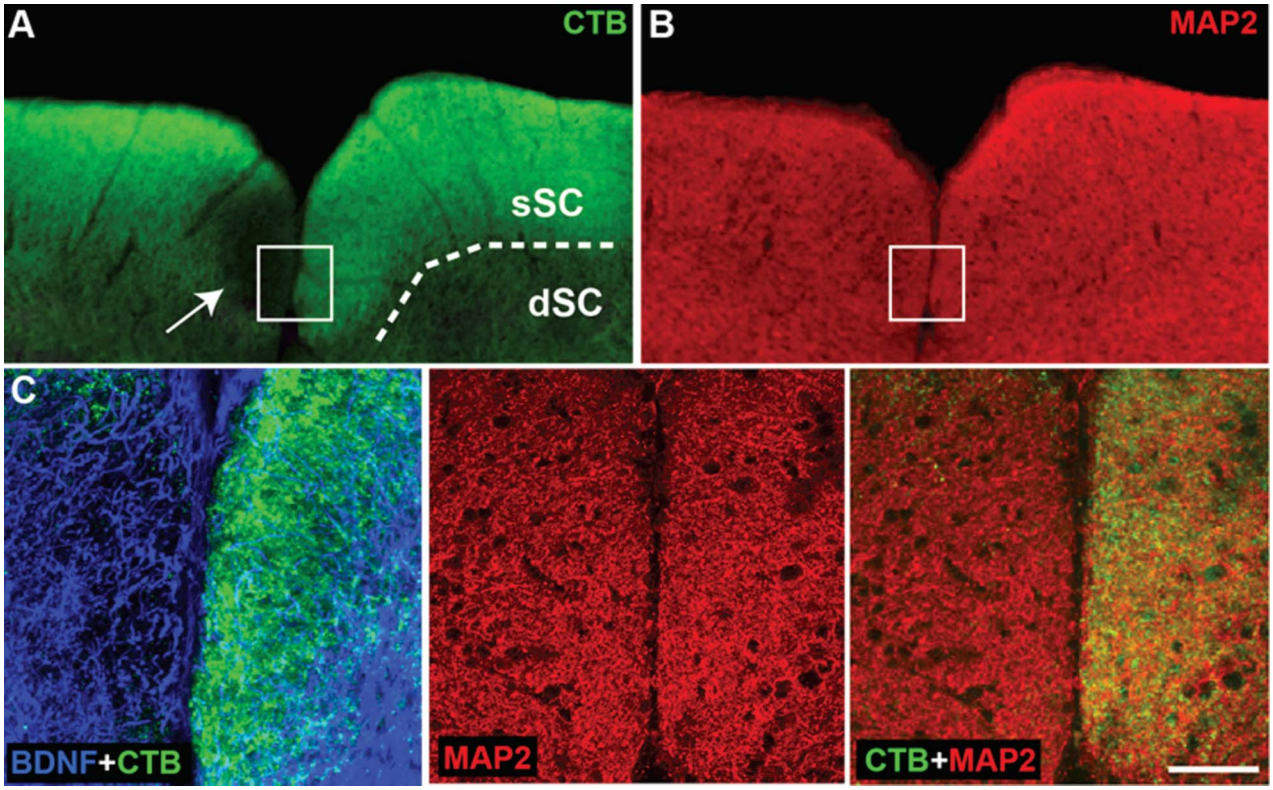

FIG. 5. Persistence of neuronal structure. **A**, superior colliculus (SC) from a 3-month DBA2J mouse shows a focal deficit in cholera toxin B (CTB) transport from the retina (*arrow*) near the midline to the fellow SC, which has intact transport (*dashed line*). **B**, Label for microtubule-associated protein 2 (MAP2) in the dendritic arbors of SC neurons remains unchanged despite the transport deficit. **C**, Higher magnification images of the midline between the 2 SC (*boxed region* in **A** and **B**) shows increased brain-derived neurotrophic factor (BDNF) where CTB transport is depleted and consistent MAP2 staining. Scale = 20 μm for **C**.

conserve local excitatory interactions from RGC axon terminals (33). In support of this, in experimental Huntington disease, overexpression of BDNF in astrocytes conserves striatal synapses (45). Such a mechanism could also contribute to the highly plastic coordination of residual retinal input to the brain to optimize binocular visual field coverage observed recently in human patients (9).

CONCLUSIONS: A PLACE FOR SELF-REPAIR IN NEW THERAPIES?

Our research demonstrates that depletion of anterograde axonal transport from the retina to central brain targets marks a period of functional degradation with persistence of structures important to the transmission of visual signals, including RGC axon terminals and their synapses. It seems reasonable that the focal increase in BDNF coincident with spatial sectors of transport degradation ought to support this persistence. We have argued elsewhere that anterograde transport is roughly twice as metabolically demanding as retrograde, suggesting that early pathogenesis involves a critical challenge to available bioenergetics that reduces axon signaling capacity through metabolic vulnerability (1). There may be additional mechanisms embedded within structural persistence that serve to support synaptic transmission from RGC axon terminals in a way that compensates for diminishing resources. Neurodegeneration in glaucoma involves numerous complex signaling pathways, both those intrinsic to the RGC itself and those involving interplay with extrinsic glial and vascular elements. These pathways contribute to biomechanical insults, glial inflammation, oxidative stress, excitotoxicity, trophic deprivation, and proapoptotic cytokines (1,46). The traditional viewpoint is that these pathways converge in a unidirectional push towards apoptotic RGC death. Experimental neuroprotective therapies generally address a single disease-relevant pathway and have met with outcomes that tend to be equivocal for clinical use. A more effective strategy might be to devise therapies that "piggyback" or exploit the intrinsic capacity for the visual system to fight back against progression, by the sort of mechanisms hinted at by our results with structural persistence. To reach that point will require a better understanding of the mechanisms through which RGC axons and their target neurons interact early in glaucomatous progression.

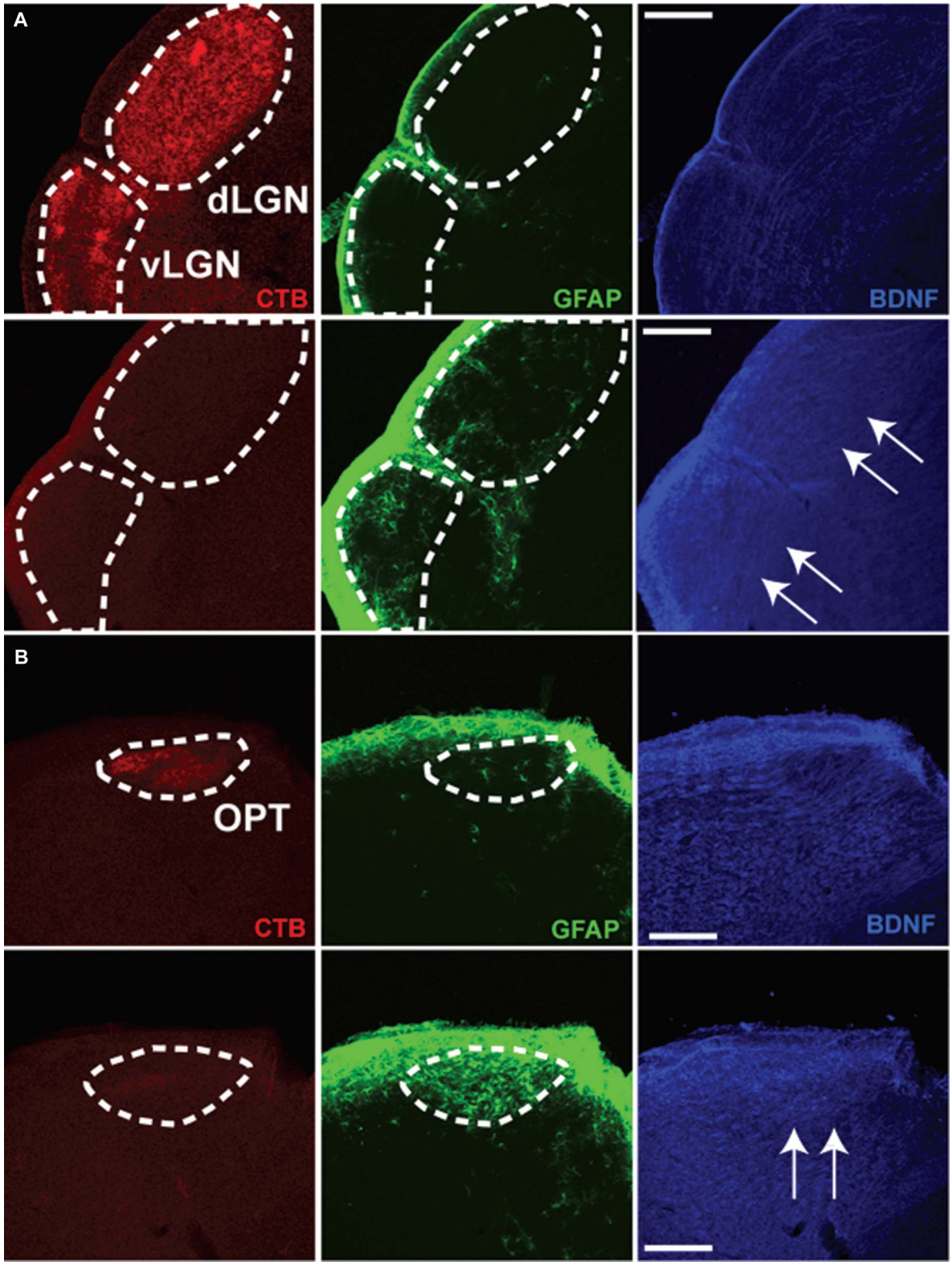

FIG. 6. Focal increases in glial acidic fibrillary protein (GFAP) and brain-derived neurotrophic factor (BDNF) coincide with transport deficits in other visual structures. **A**, Coronal sections through the dorsal and ventral lateral geniculate nucleus (LGN) from a 5-month (*top panel*) and 10-month (*bottom*) DBA2J following intravitreal injection of cholera toxin B (CTB) immune-labeled for GFAP and BDNF. With depletion of anterograde transport in the 10-month LGN, GFAP and BDNF (*arrows*) increase as in the superior colliculus (SC) (Fig. 3). **B**, Similarly, in the olivary pretectal nucleus (OPT) from the same 5-month (*top panel*) and 10-month (*bottom*) animals, loss of transport is associated with increased GFAP and BDNF (*arrows*). Scale = 200 μm.

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