Memantine Protects Neurons From Shrinkage in the Lateral Geniculate Nucleus in Experimental Glaucoma

Yeni H. Yücel, MD, PhD, FRCPC; Neeru Gupta, MD, PhD, FRCSC; Qiang Zhang, PhD; Andrew P. Mizisin, PhD; Michael W. Kalichman, PhD; Robert N. Weinreb, MD

Objective: To determine whether memantine as a treatment for glaucoma prevents neuron shrinkage in the lateral geniculate nucleus, the major target for retinal ganglion cells.

Methods: Sixteen monkeys with right-eye unilateral experimental glaucoma for 14 months were studied and treated with memantine (n=9) or vehicle only (n=7). Left lateral geniculate nucleus relay neurons (layers 1, 4, and 6) were examined following parvalbumin immunolabeling. Cell body cross-sectional areas and neuron numbers were assessed using unbiased methods. Memantine- and vehicle-treated glaucoma groups were compared using t tests and analysis of covariance.

Results: Compared with vehicle-treated animals, memantine-treated animals showed significantly less mean±SD neuron shrinkage in layers 1 (−4.0%±13.9% vs 28.2%±17.4%; P=.001) and 4 (24.9%±10.0% vs 37.2%±12.3%; P=.04). For layer 6, the difference was not statistically significant (34.2%±10.1% vs 45.3%±14.5%; P=.10). Analysis of covariance results showed significantly less neuron shrinkage in the memantine-treated group for layers 1, 4, and 6 (P<.001; P<.02; and P<.04, respectively). This difference was greatest in layer 1. In each of these layers, neuron numbers did not differ significantly between groups.

Conclusion: Monkeys with glaucoma that were treated with memantine showed significantly less neuron shrinkage in the lateral geniculate nucleus than the vehicle-treated glaucoma group.

Clinical Relevance: The finding that memantine protects adult visual neurons from transsynaptic atrophy in experimental glaucoma could have therapeutic value. Currently, memantine is being tested in an ongoing clinical trial as a treatment for glaucoma.

ARCH OPHTHALMOL. 2006;124:217-225

Author Affiliations:
Departments of Ophthalmology and Vision Sciences (Drs Yücel and Gupta) and Laboratory Medicine and Pathobiology (Drs Yücel and Gupta), the Health Sciences Research Center (Drs Yücel, Gupta, and Zhang), and Glaucoma and Nerve Protection Unit (Dr Gupta), St Michael’s Hospital, University of Toronto, Toronto, Ontario; Departments of Pathology (Drs Mizisin and Kalichman) and Ophthalmology (Dr Weinreb) and the Hamilton Glaucoma Center (Dr Weinreb), University of California, San Diego.

GLAUCOMA, A LEADING cause of blindness, affects at least 67 million people worldwide. Elevated IOP is a major risk factor for this disease characterized by retinal ganglion cell degeneration, optic nerve head changes, and vision loss. In the experimental monkey model of glaucoma, retinal and optic nerve histopathological findings closely mimic histopathological observations in human glaucoma. The persistent elevation of IOP in the monkey induces retinal ganglion cell death, in addition to significant shrinkage and loss of target neurons in the lateral geniculate nucleus (LGN) of the brain. Furthermore, this transsynaptic degeneration in the LGN increases with increasing optic nerve damage. A number of mechanisms implicated in neuronal death in glaucoma include IOP-related mechanical stress to optic nerve fibers leading to blockage of axonal transport, growth factor deprivation, ischemia-hypoxia damage, oxidative stress and formation of free radicals by excessive nitric oxide, inflammatory cytokines (tumor necrosis factor), aberrant immunity, and glutamate excitotoxicity. The latter, excitotoxicity, involving excessive stimulation of the N-methyl-D-aspartate (NMDA) glutamate receptor subtype, has been shown to contribute to the death of retinal ganglion cells in glaucoma relevant to several neurodegenerative diseases, such as Alzheimer disease. Memantine (1-amino-3,5-dimethyladamantane), an NMDA glutamate open-channel blocker, may rescue neurons through its blockade of excessive glutamate receptor activation. All therapies to prevent vision loss in glaucoma have aimed to reduce IOP. Currently, memantine is being tested in an
ongoing clinical trial as a treatment for glaucoma, independent of changes in IOP.

N-methyl-D-aspartate glutamate excitotoxicity is implicated in transsynaptic degeneration in several experimental models and might play a role in LGN degeneration in experimental glaucoma. The purpose of this study was to determine the effect of memantine administration on transsynaptic neuronal atrophy in the LGN following retinal ganglion cell damage in experimental primate glaucoma.

**METHODS**

**ANIMAL SUBJECTS**

All studies of monkeys used in this work (Macaca fascicularis) were performed following the guidelines of the Association for Research in Vision and Ophthalmology Statement on the Use of Animals in Ophthalmic and Visual Research. Experimental glaucoma was induced by argon laser scarification in the right eye of 18 adult cynomolgus monkeys according to the protocol described by Gaasterland and Kupfer. Intraocular pressure measurements were performed with a pneumotonometer (Digilab, Norwell, Mass) under light sedation (intramuscular injection of 5 mg/kg of ketamine hydrochloride) and topical anesthesia (5% proparacaine hydrochloride). The duration of IOP elevation was 14 months. Two groups of monkeys were evaluated and compared: (1) 9 memantine-treated monkeys with glaucoma who received a daily oral dose of 4 mg/kg of memantine and (2) 9 vehicle-treated monkeys with glaucoma (2 brains were excluded because of a lack of perfusion fixation and LGN layer fusion). In both the memantine-treated and vehicle-treated groups, the treatment was continued until death. The data from normal monkeys without glaucoma were also used (n=5). There was no difference in mean IOP (P>.05) or maximum IOP (P>.05) between the vehicle-treated and memantine-treated glaucoma groups.

**TISSUE PROCESSING**

Under deep general anesthesia, animals were perfused through the heart with 4% paraformaldehyde and 0.1% glutaraldehyde in 0.1M phosphate buffer (pH 7.4). The animals with experimental glaucoma were anesthetized with an intramuscular injection of ketamine hydrochloride (10 mg/kg) and acepromazine maleate (0.5 mg/kg) followed by an intravenous injection of ketamine hydrochloride (100 mg). After removal from the skull, brains were fixed by immersion in 4% paraformaldehyde in 0.1M phosphate buffer (pH 7.4) for at least 48 hours. The left LGN was blocked in the coronal plane and cryoprotected by immersion in 10% glycerol and 2% dimethyl sulfoxide in 0.1M phosphate buffer for 2 days and 20% glycerol and 2% dimethyl sulfoxide in 0.1M phosphate buffer for 5 days. The blocks were frozen in isopentane cooled by a mixture of 100% alcohol and dry ice. Coronal sections (50 µm) of the entire LGN were cut serially on a sliding microtome. Every seventh section was mounted onto a glass slide and stained with cresyl violet. Care was taken to use the same tissue processing procedures for all monkey brains.

**IMMUNOCYTOCHEMICAL EVALUATION**

The primary antibody was a monoclonal antibody (clones PA-235; Sigma, St Louis, Mo) against parvalbumin, a calcium-binding protein. The antibody labels relay neurons in the LGN layers that project axons to the visual cortex and have been previously characterized. Immunostaining specificity was verified by omitting the primary antibody.

**MORPHOMETRY**

The tissue sections were viewed using a Reichert bright-field microscope with a color video camera (JVC, Yokohama, Japan) and video and computer monitors. The 6 layers of the
LGN were easily identified on stained sections. The ventral layers 1 and 2 are magnocellular layers, while the remaining dorsal layers 3 through 6 are parvocellular layers. Layers 1, 4, and 6 of the left LGN are connected to the glaucomatous right eye, while layers 2, 3, and 5 are connected to the nonglaucomatous left eye. We specifically analyzed cell bodies of parvalbumin-positive neurons projecting to the primary visual cortex, located in left LGN layers 1, 4, and 6 and connected to the right eye in which optic nerve injury was induced.

Neuronal Shrinkage

To determine whether memantine attenuated neuron shrinkage in magnocellular and/or parvocellular LGN layers connected to a glaucomatous eye, the cross-sectional area of neurons in the left LGN layers 1, 4, and 6 was measured in memantine-treated animals and compared with that of vehicle-treated monkeys. Left LGN layers 1, 4, and 6 of monkeys with a normal visual system were used as controls, rather than right LGN layers 1, 4, and 6 of the argon laser trabeculoplasty–treated monkeys. To assess the effect of memantine on neuron number, the number of neurons in the left LGN layers 1, 4, and 6 was determined in memantine-treated monkeys with glaucoma and compared with numbers in the left LGN layers 1, 4, and 6 in vehicle-treated monkeys with glaucoma. To assess the neuronal number, stereological procedures that provide unbiased estimates of cell numbers were used. Neurozoom software was used. Neuronal density and layer surface area measurements were performed on immunostained and cresyl violet–stained sections, respectively. The 6 layers of the LGN were easily identified on stained sections. To determine whether memantine has an effect on neuron loss in magnocellular and/or parvocellular LGN layers connected to a glaucomatous eye, neurons in the left LGN layers 1, 4, and 6 were counted in memantine-treated animals and the counts compared with those from the left LGN layers 1, 4, and 6 in vehicle-treated animals.

Neuron Number

To assess the effect of memantine on neuron number, the number of neurons in the left LGN layers 1, 4, and 6 was determined in memantine-treated monkeys with glaucoma and compared with numbers in the left LGN layers 1, 4, and 6 in vehicle-treated monkeys with glaucoma. To assess the neuronal number, stereological procedures that provide unbiased estimates of cell numbers were used.7,8 Neurozoom software was used. Neuronal density and layer surface area measurements were performed on immunostained and cresyl violet–stained sections, respectively. The 6 layers of the LGN were easily identified on stained sections. To determine whether memantine has an effect on neuron loss in magnocellular and/or parvocellular LGN layers connected to a glaucomatous eye, neurons in the left LGN layers 1, 4, and 6 were counted in memantine-treated animals and the counts compared with those from the left LGN layers 1, 4, and 6 in vehicle-treated animals.

Layer Volume

Measurements of the surface area for each layer were made on equally spaced sections (interval, 350 µm) containing all 6 layers of the LGN, starting with a section selected randomly. Areas between the LGN layers were excluded. The LGN layers at low power (×2.5 objective) and a point-counting grid generated by the software were visualized on the computer monitor. Using the mouse, the operator marked the points located on a layer. Each point corresponded to an area of 0.01 mm² for the grid used for layer 1 and 0.0225 mm² for the grid used for layers 4 and 6. Layer surface area was calculated for each section by the software by multiplying the number of points on the layer with the area corresponding to a grid point. Layer surface area for each section was multiplied by the interval (350 µm) between sections and summed by the software to calculate layer volume.

Neuron Density

Neuron density measurements were made on 3 parvalbumin-immunostained sections taken from the anterior, middle, and posterior LGN with 6 layers at high power using an oil immersion objective (×100; numerical aperture = 1.32), bright-field microscope, and color video camera. Immunostained neurons were visualized on the computer and video monitors. Cell body cross-sectional area measurements were made on parvalbumin-immunostained sections at high power using an oil immersion objective (×100; numerical aperture = 1.32), bright-field microscope, and color video camera. Immunostained neurons were visualized on the computer and video monitors. Neuron density measurements were made on 3 parvalbumin-immunostained sections taken from the anterior, middle, and posterior LGN with 6 layers at high power using an oil immersion objective (×100; numerical aperture = 1.32), bright-field microscope, and color video camera. Immunostained neurons were visualized on the computer and video monitors. Neuron density measurements were made on 3 parvalbumin-immunostained sections taken from the anterior, middle, and posterior LGN with 6 layers at high power using an oil immersion objective (×100; numerical aperture = 1.32), bright-field microscope, and color video camera.
rons that came into focus as one focused through the optical box was counted. The excursion along the focusing axis (10 µm) and the thickness of the section were measured with a micrometer (MT12) mounted on the microscope stage. The average neuronal density was adjusted for tissue shrinkage occurring during the tissue processing.

Number of Neurons

The number of neurons in each layer was calculated by multiplying the average density of neurons (neurons/mm²) by layer volume.

Optic Nerve Fiber Counts

Tissue Processing and Staining. After enucleation under deep general anesthesia as described earlier, optic nerves were fixed by immersion in 2.5% glutaraldehyde in 0.1-mol/L phosphate buffer (pH 7.4) for at least 48 hours. After 3 washes with 0.1-mol/L phosphate buffer (pH 7.4), optic nerves were placed in 2% osmium tetroxide in 0.1-mol/L phosphate buffer for 1 hour and then washed again with 0.1-mol/L phosphate buffer. Optic nerve cross-sections (1-mm thick) were taken 2-mm posterior to the sclera and marked with 1 razor-blade slit in the superior quadrant and 2 slits in the nasal quadrant to indicate the orientation. Cross-sections were postfixed in 2% osmium tetroxide for 2 hours, dehydrated in alcohol, and embedded in the embedding mixture. Semithin, 0.5-µm thick cross-sections were cut with a microtome, mounted on glass slides, and stained for myelin with paraphenylenediamine.

Morphometric Analysis. Morphometric analysis was performed using bright-field microscopy with the camera lucida. At low power, optic nerve cross-sections were divided into 4 quadrants (superior, inferior, temporal, and nasal) of approximately equal area. Each quadrant was further divided into peripheral and central sectors according to the paler staining observed in the peripheral zone, which contains less myelin. For each sector on the optic nerve cross-sections, the total neuroglial area was estimated by point counting at low power. A point-counting grid was projected on the section as seen under the microscope through the camera lucida. Each point corresponded to an area of 0.0196 mm². Points were counted through the binocular using a manual counter. A point was considered to be within the neuroglial area if it was on myelinated nerve fibers or the extra-axonal matrix. Sampling of a field for each sector was determined in an unbiased and systematic fashion. For each field, neuron shrinkage was compared between the 2 treatment groups, with percentage of optic nerve fiber loss as a covariate.

STATISTICAL ANALYSIS

A t test was used to compare neuron number and mean neuron shrinkage in the LGN of the memantine-treated and vehicle-treated groups, in addition to mean IOP, maximum IOP, and percentage of optic nerve fiber loss comparisons. Using the general linear models procedure of SAS statistical software (SAS Institute Inc., Cary, NC), neuron shrinkage was compared between the 2 treatment groups, with percentage of optic nerve fiber loss as a covariate.

RESULTS

There was no statistically significant difference in mean IOP (P > .05) or maximum IOP (P > .05) between the memantine- and vehicle-treated ocular hypertensive groups (Table). For the animals included in this study, percentage of optic nerve fiber loss ranged from ~26% to 93% in the memantine-treated group and from 0% to 100% in the vehicle-treated group (Table). There was no statistically significant difference in mean ± SD percentage of optic nerve fiber loss between the memantine-treated and vehicle-treated groups (30.9% ± 47.2% vs 44% ± 43.4%; P > .05).

A qualitative assessment of LGN neuron histologic features in vehicle- and memantine-treated animals (monkeys 97 and 106) is shown in Figure 1. Parvalbumin-immunoreactive relay neuron cell bodies in vehicle-treated layers 1, 4, and 6 show shrunken and ovoid cell bodies (Figure 1A, C, and E). In memantine-treated layers 1, 4, and 6 (Figure 1B, D, and F), neuronal cytoplasm was larger in comparison. Based on similar neuropathological observations in other monkeys, systematic and stereological measurement of relay neuron size was performed to compare the memantine- and vehicle-treated glaucoma groups.

NEURON SIZE

Magnocellular Layer 1

The mean ± SD cross-sectional area of parvalbumin-positive neurons in the left LGN magnocellular layer 1 ranged from 197 ± 79 to 304 ± 99 µm² in the memantine-treated glaucoma group and from 135 ± 63 to 256 ± 71 µm² in the vehicle-treated glaucoma group (Table). The mean ± SD cross-sectional areas of relay neurons in magnocellular layer 1 were greater in the memantine-treated
glaucoma group than in the vehicle-treated glaucoma group (248±33 µm² vs 171±41 µm²; P = .001). In the normal non-glaucoma group, the mean±SD neuron area for layer 1 was 238.5±12.4 µm².³ The percentage of frequency distribution of neuron radius in the memantine-treated group was dramatically shifted to the right compared with the vehicle-treated group (Figure 2). An increase in the frequency of larger neurons was seen along with a corresponding decrease in the frequency of smaller neurons. In the memantine-treated glaucoma group, the parvalbumin-positive relay neurons in the left LGN magnocellular layer 1 showed a statistically significant decrease in the level of shrinkage compared with the vehicle-treated glaucoma group (mean±SD, −4.0%±13.9% vs 28.2%±17.4%; P = .001) (Figure 3).

**Parvocellular Layer 4**

The mean±SD cross-sectional area of parvalbumin-positive neurons in the left LGN parvocellular layer 4 ranged from 103±38 to 170±42 µm² in the memantine-treated glaucoma group and from 95±32 to 157±39 µm² in the

---

*(Figure 1. Parvalbumin-immunostained lateral geniculate nucleus relay neurons. Neurons from vehicle-treated monkey 106 with ocular hypertension (17% nerve fiber loss) in layers 1, 4, and 6 are shown in A, C, and E, respectively. Neurons in the same layers from memantine-treated monkey 97 (16% nerve fiber loss) are seen in B, D, and F. Neuron cell body size appears larger in layers 1 and 4 in the memantine-treated monkey (B and D) compared with the vehicle-treated monkey (A and C). Less difference was noted between memantine-treated (F) and vehicle-treated (E) neurons in layer 6. Scale bar indicates 10 µm.)*
vehicle-treated glaucoma group (Table). The mean ± SD cross-sectional areas of relay neurons in parvocellular layer 4 were greater in the memantine-treated glaucoma group compared with the vehicle-treated glaucoma group (152 ± 20 µm² vs 127 ± 25 µm²; \(P = .04\)). In the normal nonglaucoma group, the mean ± SD neuron area for layer 4 was 202.6 ± 20.8 µm². The percentage of frequency distribution of neuron radius in the memantine-treated group was shifted to the right compared with the vehicle-treated group (Figure 2). An increase in the frequency of larger neurons was seen along with a corresponding decrease in the frequency of smaller neurons. In the memantine-treated glaucoma group, the parvalbumin-positive relay neurons in the left LGN parvocellular layer 4 showed a statistically significant decrease in the level of shrinkage compared with vehicle-treated glaucomatous controls (mean ± SD, 24.9% ± 10.0% vs 37.2% ± 12.3%; \(P = .04\)) (Figure 3).

**Parvocellular Layer 6**

The mean ± SD cross-sectional area of parvalbumin-positive neurons in the left LGN parvocellular layer 6

---

**Figure 2.** Percentage of frequency distribution histograms to compare cross-sectional area measurements (radius scale, in micrometers) in the memantine-treated glaucoma group \(n=9\) with the vehicle-treated glaucoma group \(n=7\) for left lateral geniculate nucleus magnocellular layer 1 (A), parvocellular layer 4 (B), and parvocellular layer 6 (C), connected to the right glaucomatous eye.
ranged from 98±38 to 172±35 µm² in the memantine-treated glaucoma group and from 80±23 to 151±44 µm² in the vehicle-treated glaucoma group (Table). The mean±SD cross-sectional area of relay neurons in parvocellular layer 6 showed the trend to be greater in the memantine-treated glaucoma group than the vehicle-treated glaucoma group; however, this trend was not statistically significant (145±22 µm² vs 120±32 µm²; \( P = .10 \)).

In the normal nonglaucoma group, the mean±SD neuron area for layer 6 was 219.7±35.8 µm². The percentage of frequency distribution of neuron radius in the memantine-treated group was slightly shifted to the right compared with the vehicle-treated group (Figure 2). Although there was also less shrinkage in the neurons of layer 6 in the memantine-treated glaucoma group compared with the vehicle-treated group, the difference was not statistically significant (mean±SD, 34.2%±10.1% vs 45.3%±14.5%; \( P = .10 \)) (Figure 3).

### RELATIONSHIP BETWEEN OPTIC NERVE FIBER LOSS AND LGN NEURON SHRINKAGE

For all 3 layers, there was a statistically significant linear relationship between neuron shrinkage and optic nerve fiber loss (magnocellular layer 1, \( P < .003 \); parvocellular layer 4, \( P < .001 \); parvocellular layer 6, \( P < .001 \)). Separate analysis of covariance results for each layer show that the differences between shrinkage in memantine-treated LGN neurons and vehicle-treated neurons are statistically significant when optic nerve fiber loss is included as a covariate (magnocellular layer 1, \( P < .001 \); parvocellular layer 4, \( P < .02 \); parvocellular layer 6, \( P < .04 \)) (Figure 4).

Furthermore, an analysis of covariance set up to test hypotheses among the layers finds that when compared at their mean value of optic nerve fiber loss (36.6%), the difference in shrinkage in layer 1 between the memantine-treated and vehicle-treated groups is highly statistically significant (\( P < .001 \)), the difference in shrinkage in layer 4 between groups is statistically significant (\( P = .03 \)), and the difference in shrinkage in layer 6 between groups is not statistically significant (\( P = .09 \)).

### NEURON NUMBER

The mean±SD LGN neuron numbers in the memantine-treated glaucoma group were not significantly different from those observed in the vehicle-treated glaucoma group for layer 1 (17 636±5 987 vs 19 266±7 983; \( P = .64 \)), layer 4 (43 810±14 424 vs 35 299±12 198; \( P = .23 \)), and layer 6 (77 368±22 488 vs 73 762±32 988; \( P = .64 \)).
In experimental glaucoma, memantine reduces transsynaptic atrophy in LGN neurons. Greater LGN neuron size that corresponds to a reduction of neuron shrinkage was observed in the memantine-treated glaucoma group compared with the vehicle-treated glaucoma group. The level of IOP elevation was similar in both groups, indicated by no statistically significant differences in mean and maximum IOP (Table). Retinal injury related to IOP was also similar between groups because the difference in normalized right eye–left eye retinal ganglion cell density between both groups was not significant, although retinal ganglion cell density in the inferior retina was greater in a subgroup of memantine-treated animals with glaucoma and moderately elevated IOP ($n=4$). Optic nerve injury related to IOP was also similar in both groups (Table). Data regarding percentage of frequency distribution in the memantine-treated group compared with the vehicle-treated group demonstrated an increase in the frequency of larger neurons, with a corresponding decrease in the frequency of smaller neurons. Taken together, these findings support a memantine-mediated protective effect on cell size and not a preferential loss of small neurons. The effect of memantine on neuron size was greater for magnocellular compared with parvocellular neurons in experimental glaucoma. While further studies are needed, this raises the possibility that certain neuron populations may be more responsive to the effects of memantine.

The actual number of surviving neurons was not significantly different between the memantine- and vehicle-treated glaucoma groups. This suggests that in response to injury, other neuron parameters, such as cell size as examined in this study, might be more sensitive in the assessment of potentially useful drugs against the transsynaptic degenerative process. Cell size changes in the LGN have in fact been shown to correspond to changes in the level of spontaneous and evoked single-cell activity. Additionally, functional studies in memantine-treated animals show larger visual evoked potential amplitudes than untreated animals. These observations support the notion that memantine-induced maintenance of the size of LGN relay neurons projecting to the primary visual cortex may correspond to improved visual function in the geniculocortical pathway. A recent study showed that cell body shrinkage of relay neurons occurs along with dendritic shrinkage. Because parvalbumin is expressed mainly within the cell body rather than within the dendrites, further studies are necessary to explore dendritic and synaptic pathologic features of LGN neurons in experimental glaucoma.

Memantine, an NMDA open-channel blocker, attenuated neuron atrophy in degenerating LGN neurons, suggesting that excessive activation of these sites contributes to the pathobiology of glaucomatous neural degeneration. Memantine may be acting on the NMDA receptor subtype in the LGN expressed by the relay neurons. In addition, the systemic administration of memantine may act on NMDA receptors located in the retina and the visual cortex, each major sources of excitatory input to the LGN. In addition to its direct effect on the NMDA receptor, memantine has been shown to increase the expression of brain-derived neurotrophic factor and its specific receptor trk B implicated in cell growth. Thus, the protective effect on cell size seen in the memantine-treated group may relate to enhanced endogenous growth factor expression in the LGN. The possible effects of memantine on the expression of growth factors in the LGN in glaucoma have yet to be determined.

Memantine has been shown to reduce the retinal injury in several experimental models, including rat ocular hypertension, glutamate toxicity, ischemia/reperfusion, and partial optic nerve crush injury. Using the monkey model of glaucoma, this study demonstrates that memantine prevents transsynaptic LGN neuron shrinkage. Other models of transsynaptic degeneration have also suggested involvement of glutamate excitotoxicity. This type of degeneration is implicated in the progression of the disease process in several neurologic diseases and is particularly relevant to Alzheimer disease. Although memantine has been approved for clinical use in moderate to severe Alzheimer disease, to our knowledge, there is no evidence to date that it modifies the underlying pathologic features of the disease. Our findings implicate glutamate excitotoxicity in the pathobiology of transsynaptic injury in glaucoma and suggest that treatment with NMDA antagonists such as memantine might slow the spread of neural degeneration. Further studies are needed to determine whether these effects prevent blindness in glaucoma.

Submitted for Publication: September 14, 2004; final revision received March 3, 2005; accepted April 4, 2005.

Acknowledgment: We acknowledge Barbara Thomson, MSc, and Tamara Arenovich, MSc, Department of Statistics, University of Toronto.

REFERENCES
