A growing body of evidence indicates that a significant number of patients with VS experience progressive hearing loss following microsurgical intervention. A controlled prospective study has not been performed, and the existing reports are characterized by substantial interpatient variation with respect to hearing level, definition of hearing preservation, and length of the follow-up period. However, hearing loss ranges from 15–40%, within mean follow-up periods of 5–9 years.5,9,18,32,58,59 In one report as many as 56% of patients (14 of 25) had experienced a decline in hearing quality in the surgically treated ear 20 years after surgery, with only 1 patient experiencing a similar loss in the contralateral ear.47 Although several explanations have been proposed,
none has been demonstrated experimentally, and the primary cause remains unknown.

There are several potential causes of hearing loss following surgery. During surgery the contents of the IAC and the surrounding structures in the CPA are mechanically manipulated, which may cause axon degeneration and/or constriction of the arterial blood supply to the cochlea along with fibrosis and scarring in the CPA.\textsuperscript{20,47} These reported pathological processes are likely to act together with a combinatorial effect.

Reactive gliosis has not been proposed as a cause, but it is often associated with trauma to the CNS, including that caused by ischemia, radiation, genetic disorders, or chemical insult.\textsuperscript{6,13,21,38} A considerable number of quiescent astrocytes can resume proliferation, become hypertrophic, and upregulate GFAP.\textsuperscript{19,28,39,52,56}

The mechanical effects of surgery are complex but can be broken down in terms of various forces, such as stretching, laceration, and compression.\textsuperscript{7} Evaluating the effects of compression is thus clinically relevant. In this report, we demonstrate for the first time that mechanical compression applied to the auditory nerve induces reactive gliosis not only in the auditory nerve but also in the cochlear nucleus. Various aspects of hearing loss that occur after surgical treatment for VS can best be explained in terms of reactive gliosis combined with additional pathophysiological mechanisms described previously. We emphasize the need to investigate pathological changes not only in the axons but also in the astrocytes to thoroughly understand the mechanisms responsible.

**Methods**

*Inducing Auditory Nerve Degeneration by Compression*

Animal experiments were conducted in accordance with the Guidelines for Animal Experiments at Kyoto University. In our experimental model, the axons of the auditory nerve were quantitatively compressed in the CPA without permanent compromise of the blood supply to the cochlea. This was achieved by intraoperative monitoring of CAPs from the auditory nerve as reported elsewhere.\textsuperscript{30,43} Briefly, male Sprague-Dawley rats weighing 400–450 grams each were anesthetized by an intraperitoneal injection of ketamine (100 mg/ml; SANKYO Co.) and xylazine (9 mg/ml; Bayer). After exposing the trunks of the seventh and eighth cranial nerves through right retromastoid craniectomy, simulating the same procedure of the seventh and eighth cranial nerves through right retromastoid craniectomy, simulating the same procedure in both groups, the speed of CR electrode advancement was 200 µm/second during the second advancement (the compression procedure); 60 seconds after the flat point was reached, while the CR electrode was maintained at the flat point, were included in this study to ensure that the IAA was still functionally intact after the flat point had been reached. The flattening of the CAP was caused by impairment of the blood supply to the cochlea through the IAA. Recovery of the IAA caused the CAP to reappear spontaneously, while the CR electrode was maintained at the flat point. The critical time of cochlear ischemia that allows for complete recovery of the CAP has been reported to be 5 minutes or more.\textsuperscript{2,40} In this experimental model, the cessation of blood supply to the cochlea never exceeded 1 minute in either of the advancements of the CR electrode.

In Group A, the CR electrode was advanced 200 µm from the flat point to compress the auditory nerve. Six rats in this group were studied 1 week after compression and another 6 rats were studied 8 weeks after compression.

In Group B, the electrode was advanced 400 µm, thus increasing the compression damage to the nerve. The same numbers of animals were studied at the same time intervals.

In both groups, the speed of CR electrode advancement was 200 µm/second during the second advancement (the compression procedure); 60 seconds after the start of the second advancement, the electrode was withdrawn at 110 µm/second. The temporal bone on the right side was treated and the left side was used as a control.

*Recordings of ABRs and CAPs of Auditory Nerve*

Auditory brainstem responses were recorded between the base of the earlobe of the operative side (right) and the vertex, with the ground electrode at the base of the forelimb. Click stimuli (100 dB sound pressure level) were presented to the right ear at a rate of 9.5 pulses/second through a tube earphone or a hollow ear bar driven by a 100-µsec rectangular pulse wave fed by a stimulator. Evoked potentials were amplified with a bandpass of 50 Hz to 3 kHz and averaged using a processor (Synax 1100, NEC Medical Systems) with a sampling interval of 20 µsec and 500 data points in each recording. The responses to 100 successive clicks were averaged for ABR recordings and stored in a computer. Alternating clicks were used to stimulate the ABR. During the first and second compression procedures, the CAPs were recorded between the tip of the CR electrode and the vertex, with the ground electrode placed at the base of the forelimb. For CAP recordings, the acoustic nerve potentials evoked by 5 successive clicks were averaged and stored in a computer. This rate led to a continuous CAP recording rate...
of 1 potential every 2.4 seconds before the flat point. The click was picked up at the exit from the earphone with a microphone (ACO 4016, ACO Pacific) connected to the earphone and amplified with a microphone amplifier (MA3, Tucker-Davis Technologies). It was subsequently transferred to an oscilloscope (Iwatsu DS-8812, Iwatsu Electric) for fast Fourier transform analysis, revealing that the frequency of the tones included in the click ranged up to approximately 5 kHz. In contrast to absolute values of amplitudes of ABR, IPLs are relatively independent of the intensity of the stimulus.\textsuperscript{11} We measured IPL between Waves I and II (I–II IPL) and IPL between Waves II and IV (II–IV IPL) to investigate the state of nerve impulse conduction from the cochlea to the brainstem. For statistical analyses, unpaired t-tests were performed using Microsoft Office Excel 2007.

**Immunohistochemical Analysis**

To prepare the temporal bones, each rat was placed in a state of deep anesthesia and was perfused transaortically with 4\% paraformaldehyde in 0.01 M PBS at pH 7.4. The temporal bones were decalcified with 10\% EDTA and HCl solution (pH 7.4) for 2–3 weeks.

After decalcification, the temporal bones were embedded in OCT compound (Sakura Finetechnical) and frozen. Serial 8-µm sections were then cut for immunohistochemical analysis. Midmodiolar sections included 4 good cross-sections of the Rosenthal canal (basal, lower middle, upper middle, and apical) and the widest part of the auditory nerve. These sections were mounted on glass slides, washed in PBS, and dried at room temperature for 30 minutes. They were permeabilized and then blocked with 10\% goat serum in PBS-T (PBS containing 0.2\% Triton X-100) at room temperature for 30 minutes.

To visualize astrocytes in the auditory nerve and cochlear nucleus, anti-GFAP rabbit polyclonal antibody (× 500; DAKO) was applied to the sections and incubated at 4°C for 12 hours followed by washing in PBS-T 3 times for 5 minutes each. A secondary antibody (Alexa Fluor 488 goat anti–rabbit IgG antibody × 500, Molecular Probes, diluted with 10\% goat serum in PBS-T) was applied to the sections at room temperature for 1 hour followed by washing in PBS-T twice for 5 minutes each time.

To visualize neurons, anti–beta III-tubulin mouse monoclonal antibody (× 500; Covance Research Products, Berkeley) was used as the primary antibody and Alexa Fluor 594 goat anti–mouse IgG antibody (× 500, Molecular Probes) as the secondary antibody.

For nuclear staining, the sections were incubated in 4′,6-diamidino-2-phenylindole (DAPI, 2 µg/ml, Molecular Probes) solution at room temperature for 15 minutes. After being rinsed in PBS, the samples were mounted onto glass slides and coverslipped with VECTASHIELD mounting medium (Vector Laboratories). A fluorescence microscope system equipped with appropriate filters (Olympus BX50 and BX-FLA) was used for observation, and samples were photographed with a digital camera (Olympus DP10). Confocal images were obtained with a confocal laser-scanning microscope (TCS-SP2 Leica Microsystems). Images used for the figures were processed with Photoshop (version 6.0, Adobe Systems).

**Results**

** Controls**

In a previous paper we demonstrated that a TZ, the interface between the PNS and the CNS portions of the auditory nerve, can be observed even in routine H & E
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staining. In our present study the TZ was more clearly observed with anti-GFAP immunostaining because astrocytes are found only in the CNS portion of the auditory nerve (Fig. 2).

At the fundus of the IAC, multiple tiny osseous canals, called the TSF, allow the axons to pass from the Rosenthal canal along the auditory nerve (modiolus) toward the CNS (Figs. 2 and 3).

Throughout the control specimens, the length of the astrocytic processes toward the basal cochlear turn tended to be longer than those toward the middle and apical cochlear turns (Fig. 2 right). It was noted, however, that these astrocytic processes never entered into the TSF in any cochlear turn, even in the basal cochlear turn in controls. With the exception of those in the basal turn, the length of the astrocytic processes never exceeded approximately 75 µm.

Electrophysiological and Morphological Changes After Compression

In rats the CNS portion of the auditory nerve is relatively long, and hence, the TZ is situated within the IAC as in humans (Figs. 2 and 3). Because of this anatomical relationship, the compression in the CPA cistern always injured the CNS portion where astrocytes are abundant.

Group A. One week after compression, the general shape of the ABR was preserved but the peak amplitudes were attenuated and the latencies of Waves II, III, and IV were prolonged (Fig. 4). The I–II IPL increased from 0.34 ± 0.03 msec before compression to 0.40 ± 0.03 msec (mean ± SD). The II–IV IPL increased from 0.64 ± 0.03 msec to 0.66 ± 0.04 msec (Fig. 5). The I–II IPL was significantly prolonged after compression (p < 0.05) but the II–IV IPL was not. After compression, an unlabeled region was observed just beneath the compression site (Fig. 6). Within this region, GFAP immunoreactivity was lost, indicating the mechanical disruption of the astrocytes. The shape of the TZ was essentially unchanged and the astrocytic outgrowth at the TZ was limited. In the cochlear nucleus we did not observe any change in GFAP staining (data not shown).

Eight weeks after compression the general configuration of the ABR was preserved but the peak amplitudes were attenuated and the latencies of Waves II, III, and IV were prolonged (Fig. 7). The latency of the I–II IPL increased from 0.34 ± 0.02 msec to 0.41 ± 0.03 msec (p < 0.05) and the II–IV IPL decreased from 0.64 ± 0.01 msec to 0.63 ± 0.03 msec (not significant) (Fig. 5). There was no significant difference in the I–II IPLs between 1 week and 8 weeks after compression. Labeling for GFAP showed that the astrocytic processes elongated enormously from the TZ toward the PNS portion of the auditory nerve (Fig. 8A and B). The length of a substantial number of astrocytic processes was more than 200 µm. The elongated processes ran in parallel with the residual auditory neurons. They entered much further into the TSF in the basal portion of the cochlea compared with the middle cochlear turns (Fig. 8B and C). At the compression site, small, unlabeled areas were observed. Confocal images disclosed a dense meshwork of gliotic tissue at and in the vicinity of the lesion epicenter and fragments of neurons were scattered in this gliotic tissue (Fig. 8D). In the cochlear nucleus, hypertrophic astrocytic processes were abundant around the soma of the neurons (Fig. 8E single asterisks) in comparison with the control (Fig. 8F), and in a limited area they formed a meshlike structure of gliotic tissue (Fig. 8E double asterisks).

Group B. One week after compression, the ABR was hardly discernible (Fig. 9). Immunohistochemically, a large area unlabeled for GFAP was observed at the compression site (Fig. 10), and it was much larger than that observed in Group A (Fig. 6). The IAC was filled with swollen auditory nerve tissue, a finding not observed in any of the rats in Group A at either time point or in the Group B rats 8 weeks after compression (see below). Astrocytic outgrowth from the TZ was, however, limited (Fig. 10 large arrowheads) and in the cochlear nucleus there was no obvious change in GFAP staining (data not shown).

Eight weeks after compression, the peaks of the ABR could not be identified (Fig. 11). The growth of astrocytic processes was much more extensive than in Group A at 8 weeks postcompression (Fig. 12). The length of many processes was more than 300 µm. The astrocytic outgrowth was most evident at the basal portion of the cochlear turn, where the processes elongated and occupied all the orifices of the TSF. Confocal images showed that they ran parallel with the residual auditory neurons within the TSF. In the lesion epicenter, dense gliotic tissue surrounded neural tissue fragments. Similar dense gliotic tissue occupied the cochlear nucleus, where the neurons were tightly surrounded by ramified gliotic tissue. This pathology was only rarely observed in the Group A animals (Fig. 8E). The transverse diameter of the auditory nerve at and proximal to the compression site was reduced considerably, and this finding was more pronounced in this subgroup than in the Group A rats killed at 8 weeks (Figs. 12A and 8A, respectively).

Discussion

In this study we demonstrate for the first time that compression of the auditory nerve induces reactive gliosis not only in the auditory nerve but also in the cochlear nucleus. This can occur even with minimal degradation of the ABR. Thus, reactive gliosis should potentially be regarded as a “third causative factor,” in addition to neural and vascular factors, for hearing loss following surgical treatment for VS.

Glial Scar Formation and Degree of Injury

Glial scars are formed in the adult CNS following various insults and constitute a physical and molecular barrier unfavorable to axon survival and regeneration. In our present study, the gliotic tissue was observed at the lesion epicenter and in the vicinity of the compression site 8 weeks postcompression. Normal tissue architecture was lost, and fragments of auditory neurons were surrounded by reactive astrocytes (Figs. 8D and 12D). Reported ultrastructural findings of degenerating and degenerated...
axon terminals surrounded and phagocytosed by reactive astrocytes after deafferentation may correspond to our results.4,10,17,23

Our results also show that the higher level of compression applied to animals in Group B caused greater degradation of the ABR, increased astrocytic outgrowth from the TZ, higher levels of gliosis in the cochlear nucleus, and larger areas lacking GFAP labeling close to the compression site. In spinal cord injury, the hemorrhagic zone at the lesion epicenter cavitates as a result of necrosis several days after trauma.22,55 Hemorrhagic foci have been observed previously within the auditory nerve trunk following mechanical trauma.45 This study shows that they decrease between 1 and 8 weeks after surgery, suggesting invasion by reactive astrocytes. The observed swelling of the auditory nerve within the IAC was much less for low levels of compression and after the longer survival period. Hence, it is likely that swelling occurs only in acute stages of severely compressed auditory nerves, and that it is caused by edema as observed in the optic nerve.25

Astrocytic Proliferation and ABR Deterioration

In small experimental animals, Wave I of the ABR is generated from the extracranial (intratemporal bone) portion of the auditory nerve, Wave II reflects synaptic activity in the cochlear nucleus, and the subsequent waves reflect electrical activity in the pons/upper brainstem.33,46 Because the compression site in our experiments was situated at the IAM, the IPL between Waves I and II was prolonged, but from Wave II through Wave IV the latencies were unaffected.

In our present study, the astrocytic processes elongated conspicuously from the TZ toward the PNS portion of the auditory nerve, ran parallel with the residual auditory neurons, and entered into the TSF, particularly

![Fig. 2. Photomicrographs showing the TZ of the normal auditory nerve. The interface between the central and peripheral portions of the auditory nerve is clearly observed with anti-GFAP immunostaining (green) because of the presence of astrocytes only in the CNS portion of the auditory nerve. Note that the astrocytic processes toward the basal cochlear turn are longer than those toward the other cochlear turns (arrowheads in the right panel). The astrocytic processes never entered into the TSF in any cochlear turn even in the basal cochlear turn in controls. In this rat, the length of the astrocytic processes from the TZ was less than 75 µm, the longest distance of astrocytic extension in controls in all the cochlear turns except the basal turn (dotted line in the right panel). The dotted line in the left panel indicates the border between the intra- and extracranial compartments. Anti-GFAP and anti–beta III-tubulin (clone Tuj1) immunostaining. Bar = 500 µm (left) and 250 µm (right). AuN = auditory nerve; BS = brainstem; SGC = spiral ganglion cell.](image)

![Fig. 3. Schematic illustration showing the anatomical relationships between the auditory nerve and the surrounding structures. The auditory nerve is a bundle of bipolar neurons that form synaptic contacts with the hair cells peripherally and cochlear nucleus cells centrally. The cell bodies of the auditory neurons (spiral ganglion cells) are housed in the Rosenthal canal. The TSF is an osseous canal through which the axons of the auditory nerve pass from the Rosenthal canal to the axis of the auditory nerve (modiolus). CN = cochlear nucleus; CPAC = CPA cistern; HC = hair cell; RC = Rosenthal canal; TB = temporal bone.](image)
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in the basal region of the cochlea. Massive proliferation of astrocytic processes within the modiolus may physically compress the adjacent nerve fibers, especially within the narrow canals of the TSF. If so, then this could be a cause of hearing loss. Moreover, enhanced glial activity in the region of the cochlear nucleus might have caused both structural and functional changes among synaptic complexes and postsynaptic neurons. Progressive degeneration of axons has been reported to occur over 8 months and more than 1 year after peripheral insult to the auditory nerve/cochlear nucleus (noise-induced hair cell damage) and spinal cord injury, respectively. Thus, the attenuation of Wave II of the ABR may have been caused both by reactive gliosis related to cochlear nucleopathy and by reduction of auditory nerve activity in the cochlear nucleus.

Within Group A, statistically significant differences in the I–II IPLs were not observed between 1 and 8 weeks after compression. However, some auditory nerve degeneration must have developed without being detected in the ABR recordings. Our fast Fourier transform analysis revealed that the click that we used included frequencies up to approximately 5 kHz. The stimulator used was designed for use in humans, and its power spectrum normally stimulates the apical, middle, and upper basal turns of the cochlea; in rats, however, it stimulates only approximately one-quarter of the length of the cochlea. Thus, the ABRs in our experiments did not cover the potential electrophysiological changes associated with the auditory nerve dysfunction due to the massive outgrowth of astrocytic processes in the lower apical, middle, and basal turns. In one study on rats in which the cochlea was surgically removed, GFAP immunoreactivity increased in the cochlear nuclei 2 days after the surgery, remained intense for 3–8 days, and then declined by Day 21. In another study, the GFAP reaction occurred on Day 1, increased in intensity at Days 4–21, and then remained elevated until Day 45 in the cochlear nucleus (the longest observation time in the study). Our results suggest that

**Fig. 4.** Auditory brainstem responses in a Group A rat, before and 1 week after compression. The general configuration of the ABR was maintained after compression, but the amplitude of each peak was attenuated and the latencies of Waves II, III, and IV were prolonged. The IPL between Waves I and II (I–II IPL) and that between Waves II and IV (II–IV IPL) before compression are indicated by doubleheaded horizontal arrows. Comp = compression.

**Fig. 5.** Bar graphs showing the mean IPLs (±1 SD) between Waves I and II (I–II IPL) and between Waves II and IV (II–IV IPL), 1 week and 8 weeks after compression in Group A. The I–II IPL was significantly prolonged after compression but the II–IV IPL was not. There was no significant difference between the I–II IPL at 1 week and that at 8 weeks postcompression. ms = msec; n.s. = not significant. *p < 0.05.
reactive gliosis continues at least to the 8th week post-compression, and longer-term studies are needed to describe the full consequences of the response.

Clinical Extrapolations

Various clinical observations can be explained by reactive gliosis combined with the previously reported pathophysiological mechanisms. Several reports have demonstrated that the presence of adhesion in the interface between the auditory nerve and the tumor is the most significant negative prognostic factor in hearing preservation surgery, regardless of tumor size.24,36,51,61 The less adhesion, the less mechanical force needed to separate the auditory nerve from the tumor surface, leading not only to less trauma-induced auditory nerve degeneration but also to less reactive gliosis.

“Cochlear nucleopathy” may “naturally” occur as a VS increases in volume. As the cochlear nuclei are located at the entrance of the fourth ventricle and the shape of the fourth ventricle is inevitably distorted in accordance with tumor growth, the cochlear nuclei cannot escape from the effects of mechanical stress and reactive gliosis. In patients with neurofibromatosis Type 2, the outcome of auditory brainstem implant placement was less favorable in those cases in which the VS compressed and distorted the brainstem than in those in which it did not.31 In the former, reactive astrocytic proliferation in the cochlear nuclei may have modified synaptic organization leading to less effectiveness of the implant, although larger tumors can be expected to cause more advanced degeneration than smaller ones.

There are some caveats with respect to extrapolation from our results to the situation in human patients. First, the length of the auditory nerve differs markedly between rats and humans. In rats the cisternal portion is approximately 0.5 mm at most (Fig. 2), whereas in humans it is approximately 10–15 mm.26,34,54 Reactive gliosis may be more severe where the compression site is so much closer to the brainstem.29,42 Second, in our study the changes to the ABR were created on purpose by traumatizing the “normal” auditory nerve. Under clinical conditions, trauma to the normal auditory nerve may be very rare. In the clinical setting, the ABR configuration in patients with VS is often already distorted before surgical intervention, with the tumor mass causing auditory nerve dysfunction through mechanical compression. This is especially the case with respect to the intracanalicular portion of the auditory nerve. In a study in which the intracanalicular pressure was directly measured in the patients with VS, the pressure within the IAC was significantly elevated, and the authors concluded that pressure from tumor growth in the IAC might be responsible for hearing loss.3 The morbid auditory nerve in the patients with VS could be significantly more sensitive to the same insult than the normal auditory nerve.27 Third, we observed ABR decline and remarkable astrocytic proliferation 8 weeks after compression. In contrast, delayed hearing loss has been reported years after surgery in patients who have undergone VS surgery with preserved hearing.5,9,18,32,58,59 Therefore, our results may be better applied to “subacute” hearing loss in VS surgery. Typically, these patients wake up with hearing after surgery but suffer hearing loss 1–2 months later. However, the time course in gliosis may be different in humans and rats, and it is important to carry...
Fig. 8. Morphological changes in the auditory nervous system 8 weeks after compression in Group A (the same rat as in Fig. 7). The astrocytic processes elongated enormously from the TZ toward the periphery (A and B). The length of many astrocytic processes was more than 200 µm from the TZ (dotted lines in B) and they ran parallel with the residual auditory neurons (the arrowhead in B indicates an astrocytic process and the arrows, auditory neurons). The astrocytic processes penetrated the TSF more deeply in the basal portion of the cochlea (C) than in the middle portion (B). (Panels B and C are enlargements of areas indicated by “(B)” and “(C)” in panel A.) At the compression site (large arrow in A), small, unlabeled areas were observed (asterisks in A). At and in the vicinity of the lesion epicenter, a dense meshwork of gliotic tissue containing the fragments of neurons (arrows in D) was observed (the area indicated by “(D)” in panel A is enlarged in panel D). Hypertrophic astrocytic processes were observed in the cochlear nucleus (single asterisks in E). Meshlike structure of gliotic tissue was occasionally seen (double asterisks in E). F: Cochlear nucleus region in control. Anti-GFAP and anti-beta III-tubulin (clone Tuj1) immunostaining. Bar = 500 µm (A), 100 µm (B), 100 µm (C), 10 µm (D), 50 µm (E), and 50 µm (F).
Conclusions

We applied compression, a constituent mechanical factor in complex operative procedures, to the auditory nerve of rats while recording ABRs to measure the related hearing loss quantitatively. We found for the first time that a substantial reactive gliosis occurs in both the peripheral and central auditory pathways within 1–8 weeks and is associated with significant degradation of the ABR. This finding warrants further research to test the possibility that in the longer term the gliosis may correlate with and may even cause continued hearing loss. Reactive gliosis may be a primary cause of progressive hearing loss following microsurgical treatment for VS.

Disclosure

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References


Fig. 12. Morphological changes in the auditory nervous system 8 weeks after compression in a Group B rat (the same animal as in Fig. 11). Extensive astrocytic outgrowth from the TZ was evident (A–C). The length of many astrocytic processes was more than 300 µm from the TZ (dotted lines in B). In the basal turn of the cochlea where the astrocytic outgrowth was greatest, the elongated processes occupied all the orifices of the TSF (arrowheads in C). The rectangle in C is enlarged in the inset; the astrocytic processes (indicated by arrowheads) ran parallel with the residual auditory neurons (indicated by arrow). In the lesion epicenter, dense plexiform gliotic tissue surrounded neural tissue fragments (arrows in D). Multiple, small areas unlabeled for GFAP were observed at the compressed site (asterisk in A). In the cochlear nucleus, neurons were surrounded by dense gliotic tissue (asterisk in E; cochlear nucleus region in control, F). The transverse diameter of the auditory nerve at and proximal to the compression site was reduced in comparison with that in the Group A rats at 8 weeks postcompression (Fig. 8). The small arrows in the Rosenthal canals in B and C indicate the residual spiral ganglion cells after compression. Anti-GFAP and anti-beta III-tubulin (clone Tuj1) immunostaining. Bar = 500 µm (A), 100 µm (B), 200 µm (C), 25 µm (D), 25 µm (E), and 25 µm (F).
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