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Response of Olfactory Schwann Cells to Intranasal Zinc Sulfate Irrigation

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The response of olfactory Schwann cells was assessed at 2, 4, and 7 days following intranasal zinc sulfate irrigation in 1-month-old mice. Ultrastructural and immunohistochemical observations showed dramatic differences between experimental and control mice which had been washed with saline intranasally. Two days after zinc sulfate treatment, many olfactory nerve bundles contained patchy areas of axonal degeneration, while the cell bodies of the olfactory Schwann cells appeared to have increased in electron density and to have shifted peripherally. Some of the cell bodies protruded from the surface of the axon fascicle, suggesting that the olfactory Schwann cells were in the initial process of migrating away. On the fourth day when most of the olfactory axons had degenerated, some olfactory Schwann cells were aligned immediately beneath the basal lamina of the olfactory epithelium. These cells were immunopositive for the S-100 protein and possessed an expanded perinuclear space. Many olfactory Schwann cells were present in the region beneath the cribriform plate, while some appeared to have passed through the gaps between the bony plates to reach the olfactory bulb. Hence, the results showed that many olfactory Schwann cells migrated towards the olfactory bulb following loss of axonal contact. Furthermore, on the seventh day following zinc sulfate treatment, some olfactory Schwann cells in the vicinity of the olfactory bulb appeared phagocytic, as indicated by their extension of processes around fragments of cell debris and the presence of lysosome-like organelles in the perikaryon. The control mice which had been intranasally irrigated with saline did not demonstrate massive olfactory axonal degeneration, and the morphology of the nasal cavity region was similar to that of normal mice.

Key words: olfactory nerve, degeneration, olfactory bulb, migration, glia

INTRODUCTION

The olfactory nerves are unique in that they are the only neurons of the mammalian nervous system which are continuously renewed throughout an animal's life (Graziadei and Monti Graziadei, 1978, 1979). As mature olfactory neurons (ONs) die, they are replaced by a new population of ONs which are produced from globose basal cells residing in the olfactory epithelium (OE) (Caggiano et al., 1994; Levey et al., 1991). The newly derived ONs project their axons into the olfactory bulb (OB) in the form of fascicles that are ensheathed by processes of olfactory Schwann cells (OSCs) (Cuschieri and Bannister, 1975a,b; Doucette, 1989). These OSCs, also known as ensheathing cells, have generated much interest in recent years. Results from ultrastructural and immunohistochemical studies (Doucette, 1990; Miragall and Dermietzel, 1992), showing the presence of neurite-promoting molecules such as N-CAMs and L1 on OSCs, suggest that these cells could be involved in olfactory axon guidance. Furthermore, recent in vitro results from our laboratory have demonstrated that the OB secretes certain soluble factor(s) which attract OSCs (Liu et al., 1995), leading to the speculation that OSCs could be providing directional cues to the olfactory axons while being influenced by tropic factor(s) from the OB.

Thus far, evidence from in vitro and morphological studies (e.g., Chuah and Au, 1994; Doucette, 1990; Liu et al., 1995) indicates strongly the existence of interaction between OSCs and olfactory axons in regulating the normal development and maintenance of the primary olfactory pathway. More direct evidence from in vivo experimental studies are needed to characterize this complex interaction. In this study we have employed zinc sulfate irrigation of the nasal cavity to destroy the OE, thus specifically eliminating the olfactory axons that the OSCs ensheath. The destruction of the cellular elements of the OE as a result of zinc sulfate irrigation is well documented (e.g., Harding et al., 1978; Nadi et al., 1981), while a few reports have described the consequent degenerative effects in the glomerular and olfactory nerve layer of the OB (Pinching and Powell, 1972; Burd, 1993). However, published reports have neglected to in-

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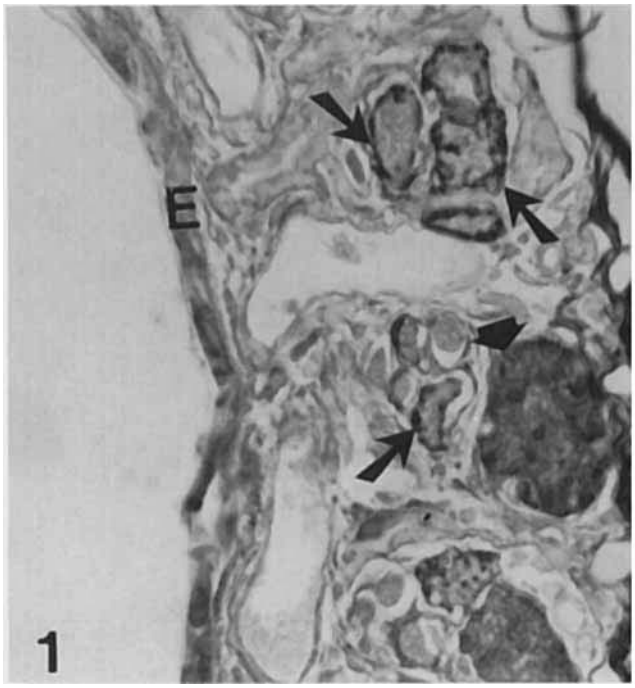


Fig. 1. Olfactory epithelium (E) is reduced to a thin layer 2 days after intranasal zinc sulfate irrigation. Some S-100 immunopositive olfactory Schwann cells appeared to have retracted their processes and to have shifted peripherally in the olfactory nerve bundles (long arrows). In other nerve bundles, the olfactory Schwann cells appeared normal, with extensive processes around groups of axons (short arrow). Consequently, these nerve bundles tend to appear more darkly stained. ×480.

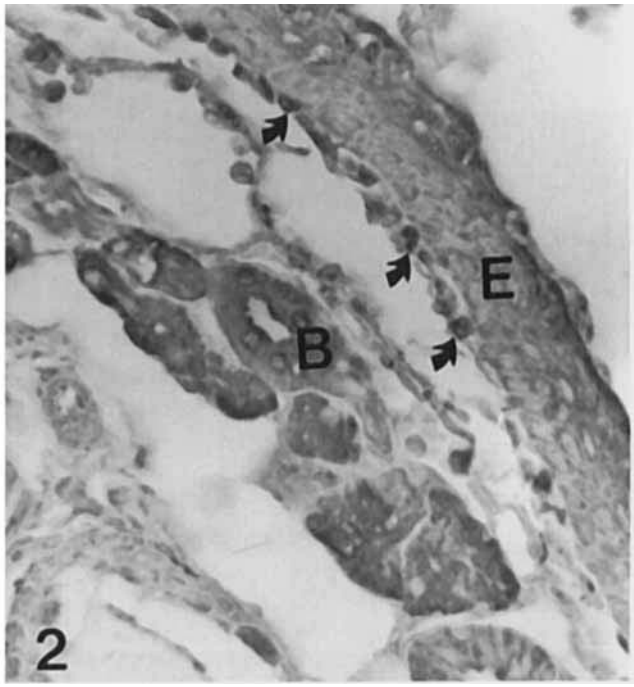


Fig. 2. Four days after zinc sulfate treatment, some S-100-positive olfactory Schwann cells (arrows) are present beneath the olfactory epithelium (E). B, Bowman's glands. ×480.

vestigate the degenerative changes occurring in the olfactory nerves of the lamina propria which are en route to the OB. Consequently, it is not known what happens to the OSCs whose relationship with the olfactory axons has suddenly been severed as a result of neuronal degeneration. The present project involving the application of intranasal zinc sulfate irrigation to induce OE and axon degeneration records the changes and possibly migratory patterns of the OSCs in response to this experimental procedure. The results will provide some insight into the relationship between olfactory axons and OSCs.

MATERIALS AND METHODS

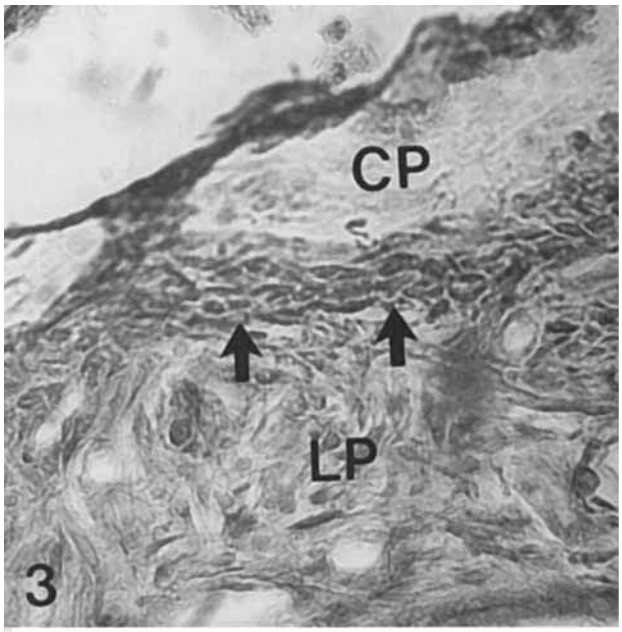
Zinc Sulfate Irrigation

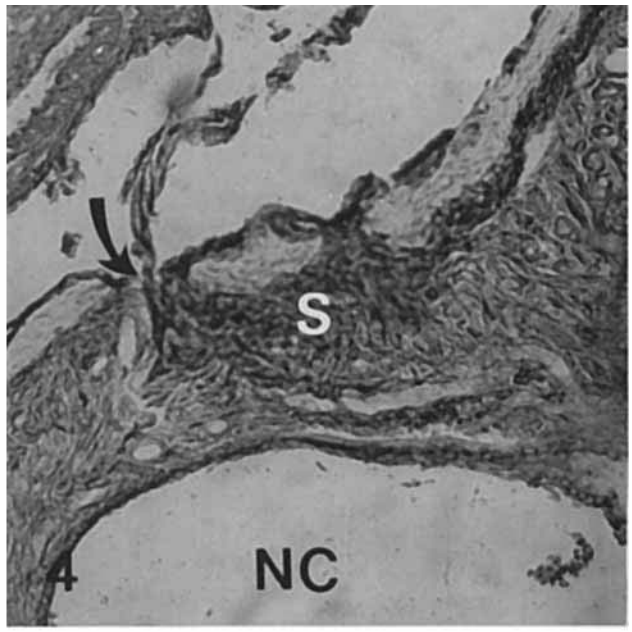
One-month-old male Balb/c mice were obtained from the colony bred at the University of Tasmania and anesthetized with 2.4% Nembutal (30 mg/kg). Experimental mice were administered 100 μl of 0.17 M zinc sulfate, while the control mice received 100 μl physiological saline (0.9%). A 1-ml tuberculin syringe, fitted with a no. 27 needle that had been filed smooth, was used to introduce the solutions to the nasal cavity via the left external nares. Seventeen zinc sulfate-treated mice and 10 saline-treated mice were used in this study. Following intranasal irrigation, mice were allowed to survive 2 days (zinc sulfate, n = 4; saline, n = 3), 4 days (zinc sulfate, n = 7; saline, n = 5), and 7 days (zinc sulfate, n = 6; saline, n = 2).

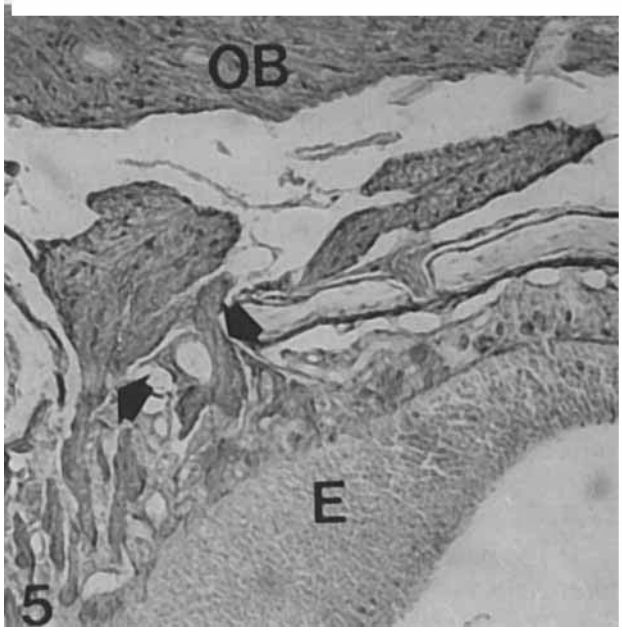
Light Microscopy and Immunohistochemistry

The mice were deeply anesthetized by an intraperitoneal injection of 10% Nembutal (40 mg/kg) and perfused with Bouin's fixative. Immediately following perfusion, the head was removed, skinned, and trimmed of extraneous tissues. Specimens were immersed in Bouin's fixative 24 hr prior to processing for embedding in paraffin. Serial sections of 7-μm thickness were made in either the coronal or sagittal plane, covering the entire extent of the nasal cavity. Some sections were stained with hematoxylin and eosin to demonstrate the histology of the olfactory mucosa, and others were selected for immunohistochemistry. These were placed on slides coated with 0.5% gelatin.

The immunohistochemical procedure used was the avidin-biotin-peroxidase (ABC) technique developed by Hsu et al. (1981), using the protocol provided by the Vectastain kit (Vector Laboratories, Burlingame, CA).







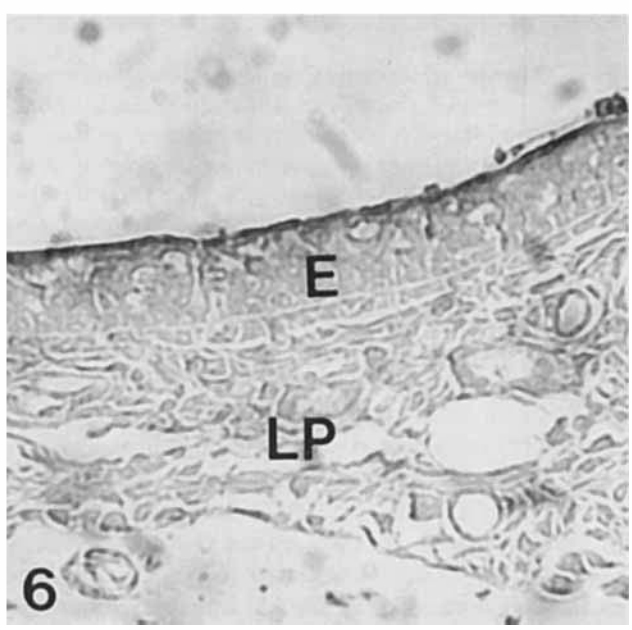


Fig. 3. Four days after zinc sulfate treatment, much of the lamina propria (LP) is devoid of olfactory nerve bundles. Groups of S-100-positive olfactory Schwann cells (arrows) are present beneath the cribriform plate (CP). ×500.

Fig. 4. Four days after zinc sulfate treatment. Where there are gaps (arrow) in the cribriform plate, some olfactory Schwann cells (S) can be observed apparently streaming through to the olfactory bulb. NC, nasal cavity. ×240.

Fig. 5. Control specimen, 4 days after saline treatment. Normal morphology is observed. The olfactory epithelium (E) is intact, and olfactory nerve bundles course through the gaps of the cribriform plate (arrows) en route to the olfactory bulb (OB). S-100-positive olfactory Schwann cells appear as dark specks randomly distributed among the axons. ×240.

Fig. 6. Seven days after zinc sulfate treatment, most areas of the olfactory epithelium (E) and lamina propria (LP) remain devoid of S-100-positive olfactory Schwann cells. ×300.

Tissue sections were deparaffinized and the following solutions were sequentially applied at 37°C: normal goat serum (diluted 1:50, incubated 20 min); rabbit anti-S-100 protein (Sigma Chemical Co., St. Louis, MO; diluted 1:200, incubated 30 min); biotinylated antibody solution (diluted 1:200, incubated 30 min), and avidin bound to

biotinylated peroxidase complex (diluted 1:50, incubated 45 min). Between each serum treatment, sections were washed for 10 min in phosphate-buffered saline (PBS) at room temperature. After incubation with peroxidase complex and washing with PBS, the sections were incubated for 4 min in a solution made up of 0.015% hydrogen peroxide and 0.05% diaminobenzidine tetrahydrochloride in 0.05 M Tris buffer, pH 7.2. Control sections were incubated with normal rabbit serum in place of the primary antiserum.

Transmission Electron Microscopy

Following anesthesia with 10% Nembutal (40 mg/kg), mice were perfused with a solution containing 2% glutaraldehyde, and 2% paraformaldehyde in 0.08 M sodium cacodylate buffer (CB), pH 7.2. After approximately 15 min of perfusion, the animals were decapitated and the heads were stored in fixative at 4°C for 12–24 hr. Olfactory mucosa was removed from the turbinate and nasal septum, washed in CB, postfixed for 60 min in 1% osmium in CB, washed in distilled water, en bloc-stained in 4% uranyl acetate, and dehydrated in an alcohol series of increasing concentration (50–100%). The tissue was embedded in Epon (Procure 812) and cut with a diamond knife on an LKB ultramicrotome. Sections were contrasted with 4% uranyl acetate (30 min) followed by lead citrate (5 min) and viewed in a Phillips CM100 transmission electron microscope (Phillips Scientific & Industrial Pty. Ltd., Australia).

RESULTS

Light Microscopy and Immunohistochemistry

The normal structure of the mouse olfactory mucosa has been described extensively in previous studies (Adams, 1972; Cuschieri and Bannister, 1975a,b; Harding et al., 1977). There was no observable difference in histology between the olfactory mucosa in saline-treated mice and that in normal untreated mice, indicating that the force of fluid moving through the nasal cavity was not excessive, and thus no mechanical damage was done.

In the experimental mice it was found that unilateral zinc sulfate irrigation affected both right and left sides of the nasal cavity. Two days after zinc sulfate treatment, massive areas of OE were found to have detached from the underlying lamina propria. Consequently, the nasal cavities were often filled with cellular debris. Routine hemotoxylin and eosin staining revealed that many of the nerve bundles appeared intact, but immunohistochemical staining showed some variability in the distribution of S-100 protein-positive OSCs. Some of the nerve bundles were more intensely stained than others (Fig. 1). This variability in the staining pattern of the nerve bundles suggested that some of the S-100 protein-positive OSCs may have withdrawn some of their processes, and had shifted their cell bodies to a more peripheral location in the nerve bundle.

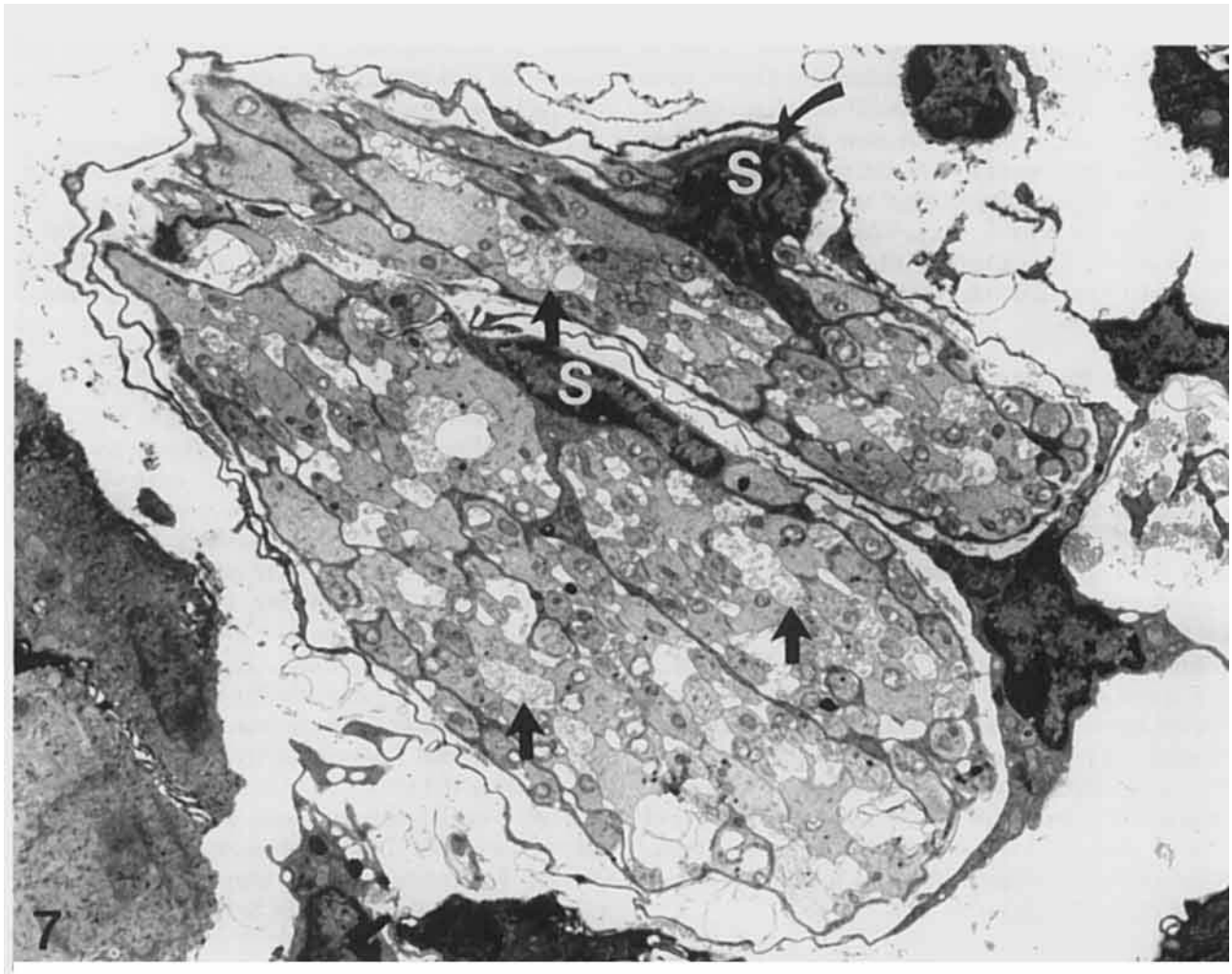
Four days after zinc sulfate treatment, a thin epithelium usually 2 cells thick was present on most of the lamina propria lining the turbinates and septum. It is uncertain whether this is a remnant of the original OE, or if it had arisen from new dividing cells. Some olfactory nerve bundles were still present, but they appeared reduced in size. Other regions, particularly the lamina propria of the nasal septum, and the region immediately beneath the cribriform plate, were devoid of nerve bundles. In these areas, S-100 protein-positive OSCs were often located in a linear pattern immediately beneath the basal lamina of the OE (Fig. 2). While some OSCs were found scattered in the lamina propria, many were present immediately beneath the bone forming the cribriform plate (Fig. 3). Where there were gaps, the spaces were often filled with S-100-positive OSCs seemingly attempting to get through to the OB (Fig. 4). The high concentration of OSCs in these focal regions stands in marked contrast to the fibrillar-appearing olfactory nerves that normally fill these gaps (Fig. 5).

In mice with 7 days of survival time, the morphology of the OE did not seem to have changed appreciably. However, immunostaining with anti-S-100 antiserum showed the absence of immunoreactive cells beneath the OE (Fig. 6). Sections obtained from various parts of the nasal cavity also contained few S-100-positive cells.

Electron Microscopy

Changes in olfactory nerve bundles in experimental mice were observed as early as 2 days after zinc sulfate irrigation. Although some of the nerve bundles appeared ultrastructurally similar to those in the saline-treated mice, many contained patchy areas of axonal degeneration. Areas of degeneration were marked by the presence of spaces often containing vesicles of various sizes (Fig. 7). Interestingly, there was also widespread presence of membranous vesicles scattered in the lamina propria of the zinc sulfate-treated mice. The degenerating olfactory nerve bundles had an irregular outline, while the cell body of the OSC was peripherally located. Sometimes it protruded from the surface of the nerve, giving the impression that it was initially in the process of migrating away (Fig. 7). The cytoplasm of the OSC also increased in electron density.

A reduced number of olfactory nerve bundles showing various degrees of axonal degeneration were still observable in the lamina propria 4 days after zinc sulfate treatment. In many of them, the spaces resulting from the degeneration of axonal fascicles were often ringed by a multilamellated structure (Fig. 8), while the perinuclear space between the two membranes which constitute the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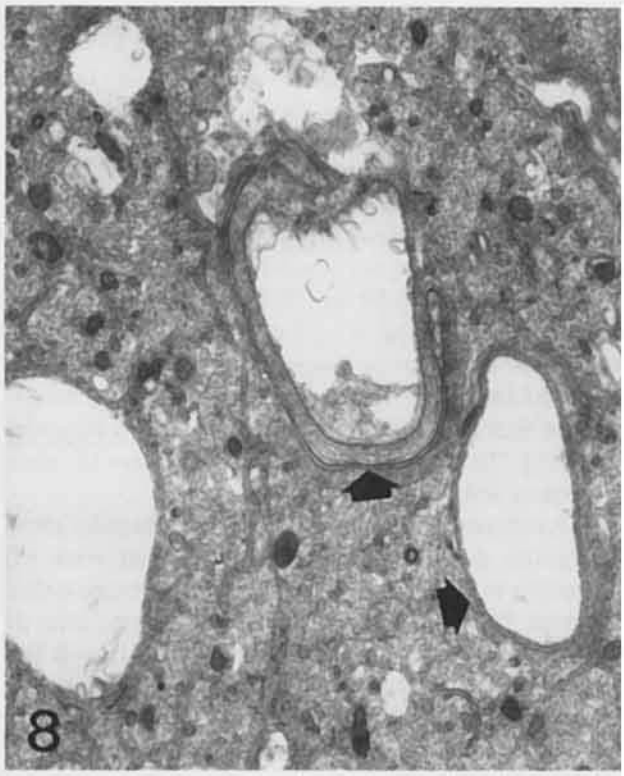
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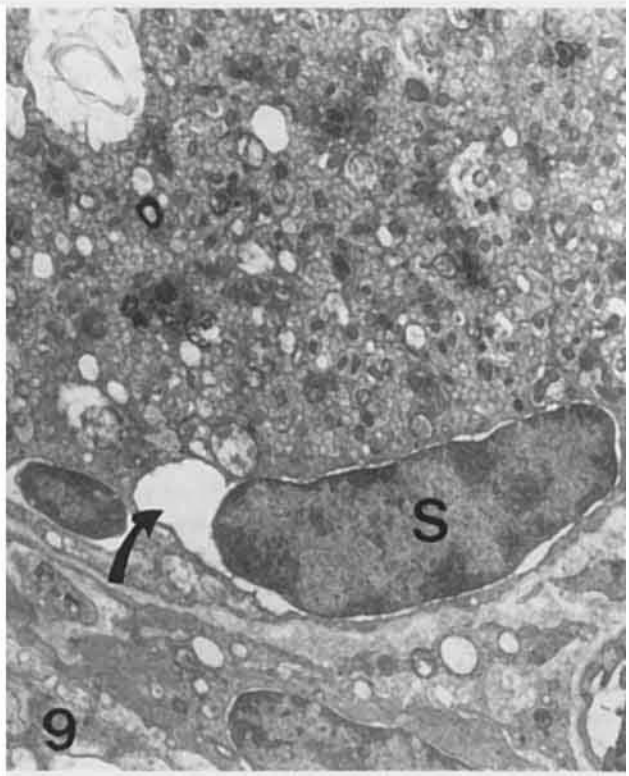
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nuclear envelope of the OSC was grossly dilated (Fig. 9). Nevertheless, the nuclear pore remained intact. It is unlikely that the exaggerated perinuclear space was an artifact, because this finding was specifically found only in OSCs; surrounding cells, such as fibroblasts, did not demonstrate this unusual morphology.

In agreement with the immunohistochemical observations, some OSCs were found to be closely apposed to the basal lamina of the OE. As described above, they could be distinguished from other cells by the expanded perinuclear space and the irregular cytoplasmic processes (Fig. 10). Hence, the evidence suggests that many of the olfactory axons which were originally ensheathed by OSCs had degenerated, and that some of the OSCs had subsequently migrated to the vicinity of the OE. Specimens from the control group did not show OSCs located immediately beneath the OE basal lamina.

Interestingly, 7 days following zinc sulfate treatment, there were no longer aggregations of OSCs beneath the OE basal lamina. Instead, OSCs, as well as phagocytic cells, could easily be found in the periphery of the OB. Although some phagocytic cells were likely to be astrocytes resident in the OB, there were some that resembled OSCs. These cells extended processes around fascicles of axons, while at the same time there appeared to be phagocytosing cellular debris (Fig. 11). In addition, these cells expressed extracellular matrix material which contributed to the glia limitans around the OB (Fig. 11), a structure that is normally attributed to the OSCs (Doucette, 1991). Intermediate filaments and membrane-bound organelles resembling secondary lysosomes and residual bodies were present in the cytoplasm. Olfactory Schwann cells bearing phagocytic features were not observed in the saline-treated mice.

DISCUSSION

This is the first report to document the response of OSCs to the degeneration of olfactory axons following intranasal zinc sulfate irrigation. The results show that as the olfactory axons degenerate, the OSCs undergo morphological changes and at the same time migrate to other sites. Some of them are drawn to the vicinity of the OE remnant, while a greater number of them are apparently attracted to the OB. Ultrastructural observations also indicate that OSCs are capable of phagocytic functions, assisting in the removal of cell debris.

Previous in vitro experiments from our laboratory have shown that the OB secretes soluble factor(s) that attract OSCs (Liu et al., 1995). The aggregation of OSCs beneath and within the gaps of the cribriform plate, subsequent to axon degeneration, lends further support to the tropic effect of the OB. It also suggests that in the normal primary olfactory pathway, many OSCs could be arrested in their migration to the OB by their interaction with the olfactory axon bundles that they ensheath. Interaction of this nature has been demonstrated in the developing ventral root of the chick embryo (Bhattacharyya et al., 1994). It was found that ablation of lumbar motor neurons resulted in the failure of retention of Schwann cell precursors in the region of the ventral root. Instead, the Schwann cell percursors continued to migrate distally away from their original destination.

It would be logical to propose that there exists between olfactory axons and OSCs some form of mutual affinity which could be mediated by the expression of certain adhesion molecules. One possible candidate is N-CAM, which is present on both OSCs and olfactory axons (Miragall et al., 1989; Chuah and Au, 1993). The affinity of olfactory axons for OSCs would counteract the attraction of the OB, thereby preventing all OSCs from taking eventual residence in the olfactory nerve layer of the OB. This would account for the distribution of OSCs in the normal olfactory pathway, along the entire course of the olfactory nerves and in the olfactory nerve layer of the OB (Doucette, 1989).

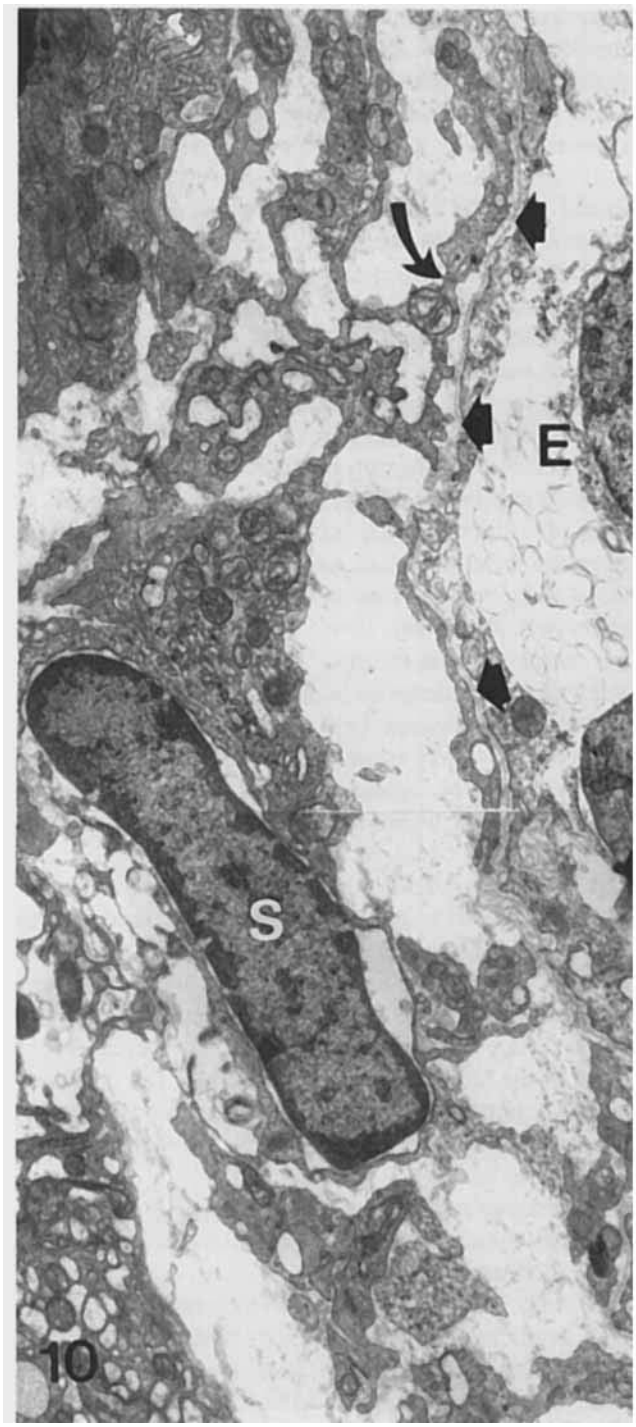
Another intriguing observation in our study was the linear placement of the OSCs beneath the OE basal lamina 4 days after zinc sulfate irrigation. It is conceivable that these were OSCs which were originally associated with segments of olfactory axons distant from the OB. Consequently, the concentration of chemoattractant(s) from the OB might be too low at these sites to elicit a tropic response from the OSCs. The reasons for their apparent attraction to the OE are uncertain; nor are we clear about the fate of these cells. Further investigations into the turnover rate of OSCs and their relationship to ONs could provide some insight into this phenomenon.

In the course of our observations, we noted striking ultrastructural changes in the cell bodies of the OSCs in the first 4 days following zinc sulfate treatment. It appeared that OSCs reacted dramatically to the massive degeneration of olfactory axons that was taking place

Fig. 7. Two days after zinc sulfate treatment, areas of axonal degeneration are marked by spaces containing vesicles (arrows). In this olfactory nerve bundle, one of the cell bodies (curved arrow) of the olfactory Schwann cells (S) is shown protruding out of the surface, possibly in the initial stages of migration. ×7,000.

Fig. 8. Four days after zinc sulfate treatment, some of the spaces resulting from the degeneration of axons are ringed by multilamellated structures (arrows). ×15,600.

Fig. 9. In the olfactory nerve bundles that still remain in the lamina propria 4 days after zinc sulfate irrigation, the olfactory Schwann cell (S) contains a dilated perinuclear space (arrow). ×8,500.



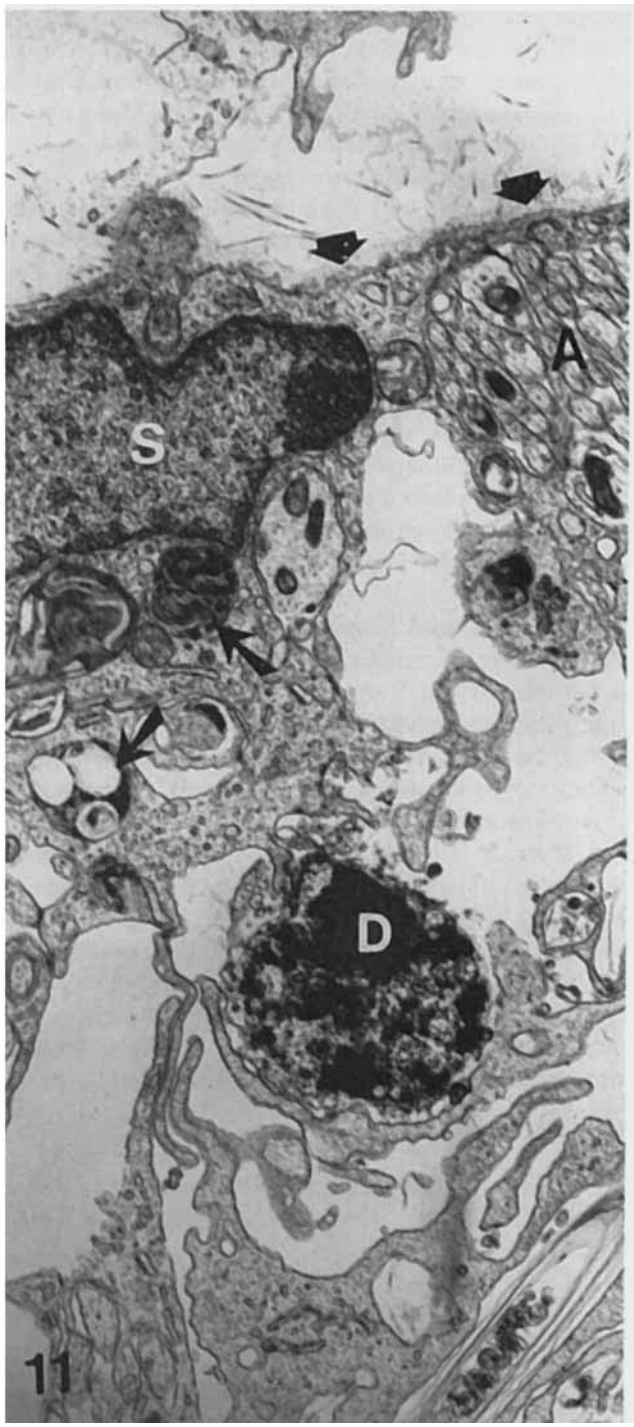


Fig. 10. Olfactory Schwann cell (S) found beneath the basal lamina (short arrows) of the olfactory epithelium (E). The olfactory Schwann cell extends elaborate processes (curved arrow), which appear to contact the basal lamina. × 12,500.

Fig. 11. Olfactory Schwann cell (S) located in the periphery of the olfactory bulb. This Schwann cell contributes to the formation of the glia limitans (short arrows), while at the same time it ensheathes bundles of axons (A). The cell also contains lysosome-like organelles (long arrows), and extends processes which are closely associated with degenerating cell debris (D). × 14,300.

during this period. These changes in the OSCs were not surprising, insofar as it is well documented in the peripheral nervous system, both in vivo and in vitro, that gene expression in Schwann cells is regulated by their contact with axons (e.g., Brunden et al., 1990; DiStefano and Diane, 1990; Walter, 1993; Wu et al., 1994). Some of these alterations in Schwann cells resulting from interruption of normal axon:Schwann cell interactions include downregulation of myelin genes (LeBlanc and Poduslo, 1990), and upregulation of BDNF (Meyer et al., 1992) and p75 NGF receptor expression (Taniuchi et al., 1988). The increased electron density of the cytoplasm, as well as the expanded perinuclear space in the OSCs of experimental mice, probably reflect a drastic change in the physiology of the cells.

Another ultrastructural alteration suggested an adaptation to a function that has hitherto not been associated with OSCs. Based on morphological evidence, previous researchers have reported that the phagocytic cells present in the OB following lesions to the olfactory nerves are probably astroglial, microglial, or hematogenic in origin (Graziadei and Monti Graziadei, 1980; Doucette et al., 1983; Burd, 1993). Interestingly, Caggiano and Brunjes (1993) showed that microglial cell density in the OB is not affected by increased ON degeneration resulting from external naris closure. Although it was difficult to identify all the phagocytic cells that were observed in our study, it is likely that some of them were OSCs. The most convincing evidence is the fact that some of these phagocytic cells contained intermediate filaments scattered loosely throughout the cytoplasm, and these filaments ensheathed fascicles of axons and contributed to the formation of the glia limitans. Astrocytes and microglia in the OB normally do not express extracellular matrix material for the formation of the glia limitans (Doucette, 1990). Also, astrocytes possess conspicuous bundles of intermediate filaments (Doucette, 1984) which are absent in microglia (Peters et al., 1976).

The results of this study demonstrate and confirm findings from our previous in vitro experiments (Chuah and Au, 1994; Liu et al., 1995) that cellular interaction among olfactory axons, OSCs, and the OB is involved in the development and maintenance of the primary olfactory pathway. Elimination of olfactory axons leads to both morphological and physiological changes in the OSCs.

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