

Inflammation near the Nerve Cell Body Enhances Axonal Regeneration

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Although crushed axons in a dorsal spinal root normally regenerate more slowly than peripheral axons, their regeneration can be accelerated by a conditioning lesion to the corresponding peripheral nerve. These and other observations indicate that injury to peripheral sensory axons triggers changes in their nerve cell bodies that contribute to axonal regeneration. To investigate mechanisms of activating nerve cell bodies, an inflammatory reaction was provoked in rat dorsal root ganglia (DRG) through injection of *Corynebacterium parvum*. This inflammation enhanced regeneration in the associated dorsal root, increasing 4-fold the number of regenerating fibers 17 d after crushing; peripheral nerve regeneration was not accelerated. A milder stimulation of dorsal root regeneration was detected after direct injection of isogenous macrophages into the ganglion. It is concluded that changes favorable to axonal regeneration can be induced by products of inflammatory cells acting in the vicinity of the nerve cell body.

Satellite glial cells and other unidentified cells in lumbar DRG were shown by thymidine radioautography to proliferate after sciatic nerve transection or injection of *C. parvum* into the ganglia. Intrathecal infusion of mitomycin C suppressed axotomy-induced mitosis of satellite glial cells but did not impede axonal regeneration in the dorsal root or the peripheral nerve. Nevertheless, the similarity in reactions of satellite glial cells during 2 processes that activate neurons adds indirect support to the idea that non-neuronal cells in the DRG might influence regenerative responses of primary sensory neurons.

Peripheral axonal injury induces in motor and sensory nerve cell bodies poorly understood responses that support axonal growth (McQuarrie et al., 1977; Jackson and Diamond, 1984; Richardson and Issa, 1984; Havton and Kellerth 1987; Richardson and Verge, 1987; Jenq et al., 1988). With rare exceptions (Rich and Johnson, 1985; Kanje et al., 1989), perikaryal reactions associated with regeneration have been observed only after axonal lesions that reduce retrograde transport of trophic molecules from Schwann cells and/or target tissues (Richardson and Verge, 1986; Bisby, 1988; Woolf et al., 1990). Whether the

subsequent induction proceeds entirely within individual neurons with injured axons or involves the intermediary action of non-neural cells in the dorsal root ganglion (DRG; Pannese, 1964; Friede and Johnstone, 1967; Leech, 1967; Woodham et al., 1989) or spinal cord (Sjöstrand, 1965; Watson, 1965; Blinzinger and Kreutzberg, 1968; Sumner, 1974; Tetzlaff et al., 1988; Streit et al., 1989) is unknown.

Axons in a crushed dorsal spinal root regenerate more slowly than axons in a crushed peripheral nerve (Wujek and Lasek, 1983) even though both types of axons traverse a similar local milieu determined largely by Schwann cells. The response of sensory neurons to axotomy is relatively mild when the central rather than the peripheral axons are cut (Lieberman, 1974; Perry et al., 1983). Finally, the regeneration of crushed dorsal root axons is accelerated if the corresponding peripheral nerve is cut as a conditioning lesion (Richardson and Verge, 1987). These observations are interpreted to indicate that events in the nerve cell body contributing to axonal regeneration are more strongly induced by peripheral than central axotomy but can benefit the regeneration of either of the 2 axons. Thus, dorsal root regeneration can be used to assay regenerative responses within sensory neurons.

Some inflammatory responses to injury appear to be beneficial to axonal regeneration. In the PNS, macrophages migrate into the distal segment of an interrupted nerve, participate in the removal of axon and myelin debris, stimulate Schwann cell proliferation, and augment the synthesis of NGF by non-neuronal cells (Beuche and Friede, 1984; Lindholm et al., 1987; Perry et al., 1987; Baichwal et al., 1988). In the CNS, resident and hematogenous macrophages at the site of injury stimulate glial proliferation and neovascularization through the release of interleukin-1 (Giulian et al., 1989). Two other immunological cytokines, interleukin-3 and interleukin-6, have been shown to influence neuronal survival and/or process formation (Satoh et al., 1988; Kamegai et al., 1990). On the other hand, the actions of macrophages may sometimes be deleterious to recovery of function after CNS injury (Giulian and Robertson, 1990).

The major goal of these experiments was to ascertain whether intervention near nerve cell bodies could enhance axonal regeneration. An inflammatory reaction within the DRG was chosen as one possible method of stimulation because of the interplay between macrophages and neural repair mentioned above. In addition, some attention was paid to the reactions of satellite glial cells and their possible influence on regenerative responses within neurons.

Materials and Methods

Experiments were performed on 219 adult female Sprague-Dawley rats weighing approximately 200 gm and 54 isogenous Lewis rats used for

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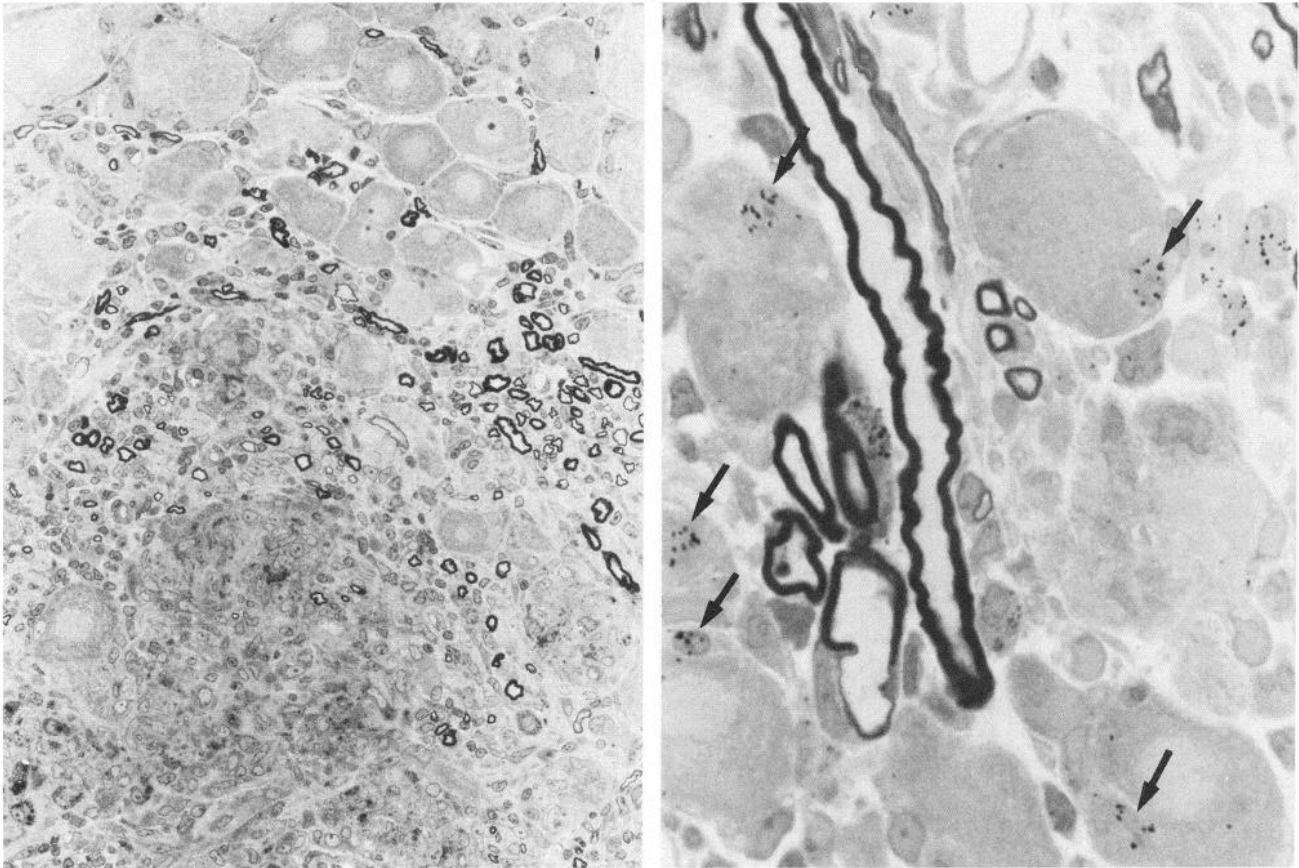


Figure 1. *Left*, In this L₅ DRG removed 4 d after injection of *C. parvum*, numerous inflammatory cells are seen in the lower part of the photograph, with relative sparing of the upper area. Semithin plastic section stained with toluidine blue. Magnification, 220 \times . *Right*, Light microscopy radioautography of L₅ DRG 4 d after *C. parvum* injection and 90 min after intrathecal injection of tritiated thymidine. Five labeled satellite glial cells are seen (arrows), as well as several labeled inflammatory cells. Magnification, 1100 \times .

transplantation of macrophages. Surgical procedures were performed under general anesthesia (pentobarbital, 50 mg/kg, i.p.) with sterile microsurgical techniques.

To prepare macrophages, Lewis rats were injected intraperitoneally with *Corynebacterium parvum* (3.5 mg in saline) and reanesthetized 3 d later for harvesting of macrophages by peritoneal lavage. Total and differential cell counts were obtained by hemocytometer and smears stained with Turk's solution. Macrophages were concentrated by centrifugation and resuspended in Eagle's basal medium with 5% fetal calf serum before injection.

For injections into the fifth lumbar dorsal root ganglion (L₅ DRG), the ganglion was exposed by laminectomy. Either macrophages (20,000–200,000 cells), *C. parvum* (35 μ g), saline, Eagle's basal medium, or fetal calf serum was injected in a final volume of 1 μ l. Injections were made through a micropipette with a tip diameter of 50–100 μ m attached by polyethylene tubing to a 1- μ l syringe. The injection system was filled with mineral oil, and the required sample was drawn into and delivered from the micropipette tip.

For chronic intrathecal injection of mitomycin C, an osmotic pump was installed subcutaneously and connected to silicon tubing (0.6-mm outer diameter) that entered the subarachnoid space at the lumbosacral junction and passed 2 cm rostrally. The infusion was at the rate of 400 ng/hr (Pellegrino and Spencer, 1985; Hall, 1986) in either 0.5 or 1.0 μ l volume.

To study regeneration in the central axons of primary sensory neurons, L₅ dorsal spinal roots were crushed near their ganglia with #5 jeweler's forceps for 10 sec, and the crush site was marked with a #10 suture. Rats were killed 17 d later, and segments of the dorsal roots 10 mm and 15 mm from the crush site were embedded in plastic. In cross sections 1 μ m thick and stained with toluidine blue, fibers with thin myelin sheaths were counted blindly under oil-immersion light mi-

croscopy (Richardson and Verge, 1987). Sections with large numbers of spared fibers with normal myelin sheaths were rejected.

To study regeneration in the peripheral axons of primary sensory neurons, the right sciatic nerve was crushed at the obturator tendon. Rats were killed 13 d later, and thinly myelinated fibers were counted in the sural nerve 15 and 20 mm from the crush site.

Mitosis of satellite glial cells was studied in 57 rats with previous sciatic nerve transection or ganglionic injection of *C. parvum*. The site of transection of the sciatic nerve was at its origin from the fourth lumbar (L₄) and L₅ spinal nerves. Tritiated thymidine (50 μ Ci in 200 μ l saline) was injected by fine catheter into the subarachnoid space 90 min before death. Animals were perfused with formaldehyde, and the L₄ and L₅ DRG were removed and embedded in plastic. For light microscopy, sections were cut 1 μ m thick, dipped in emulsion (Kodak NTB2), exposed in the dark for 6 weeks, and developed. Sections were examined under oil-immersion light microscopy, and labeled cells were defined as those containing more than 5 silver grains. For electron microscope radioautography (Kopriwa, 1973), celloidin-coated sections 70 nm thick were dipped in emulsion (Ilford L4), exposed in the dark for 16 weeks, developed, and stained with lead citrate.

Histological inspection of DRG and spinal nerves was performed in some rats. For this purpose, appropriate tissue was embedded in plastic, sectioned, and stained with toluidine blue.

Results

Appearance of DRG following injection

Injection of *C. parvum* provoked a brisk inflammatory response in the DRG (Fig. 1). Many mononuclear inflammatory cells and some polymorphonuclear leukocytes were seen in the DRG 3

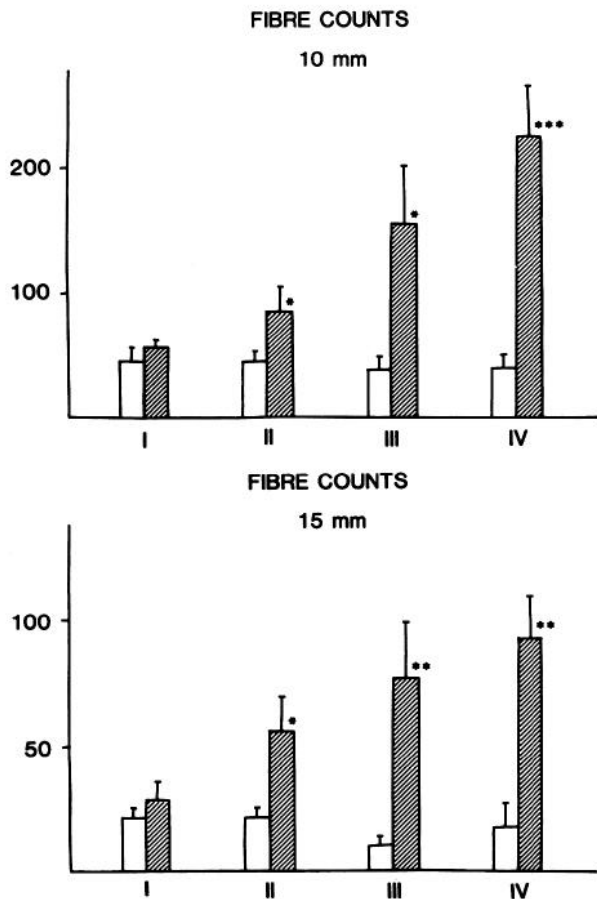
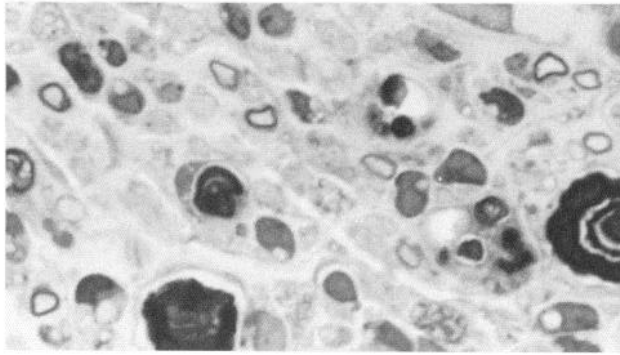


Figure 2. *Top*, Cross-section of an L₅ dorsal root crushed 17 d before death showing 9 fibers that have regenerated and acquired a thin myelin sheath. Magnification, 1100 \times . *Bottom*, Counts of regenerating fibers in L₅ dorsal roots associated with 4 types of conditioning stimuli. In all rats, the left dorsal root served as a control with no injury to the left L₅ DRG or sciatic nerve. Groups I, III, and IV consisted of Sprague-Dawley rats, and group II consisted of Lewis rats. I, Control injections of 1 μ l saline, fetal calf serum, or culture medium were made into the right L₅ DRG when the roots were crushed (27–32 roots from 34 rats). II, Isogenous peritoneal macrophages were injected into the right L₅ DRG the time of root crush (27–32 roots from 35 rats). III, *C. parvum* was injected into the right L₅ DRG either at the time of crushing or 1 week earlier (15–19 roots from 19 rats). IV, The right sciatic nerve was cut at the hip when the roots were crushed (9–13 roots from 14 rats). Rats were killed 17 d after root crushing, and thinly myelinated fibers were counted in sections 10 and 15 mm from the crush site of the left (open bars) or right (hatched bars) dorsal roots. Bars represent mean \pm SEM. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$ left versus right by the Student's *t* test.

Table 1. Lack of influence of *C. parvum* injection into DRG on regeneration of peripheral sensory axons

	Sural nerve fiber counts	
	15 mm	20 mm
L ₄ and L ₅ DRG intact or saline injected	46 \pm 22 (13)	20 \pm 7 (13)
L ₄ and L ₅ DRG injected with <i>C. parvum</i>	32 \pm 8 (11)	4 \pm 1 (10)

Distances in mm are from crush site to site of counting. Data are means \pm SEM of thinly myelinated fibers 13 d after crushing, with numbers of nerve sections counted in parentheses.

d and 17 d after injection. The infiltrates were patchy such that some neurons were surrounded by inflammatory cells and other neurons were remote from such cells. Four days after injection of *C. parvum* into the DRG, no wallerian degeneration was seen in the spinal nerve, but at 17 d, mild to moderate wallerian degeneration was evident.

Seventeen days after injection of macrophages, few abnormalities were seen upon light microscopy inspection of DRG; in particular, few or no macrophages were seen at this time.

Effects of DRG injection on axonal regeneration

Ganglionic injection of *C. parvum* stimulated axonal regeneration in the dorsal root as measured by counts of thinly myelinated fibers 17 d after crushing (Fig. 2). At both 10 and 15 mm from the DRG, fiber counts were significantly higher in roots associated with *C. parvum* injection than in contralateral roots with uninjected DRG. Results were similar whether *C. parvum* was injected at the time of dorsal root crush or 1 week previously. The stimulatory effect of *C. parvum* injection on dorsal root regeneration was slightly less than that of sciatic nerve transection. Direct injection of isogenous macrophages into the DRG also increased counts of regenerating fibers in the dorsal root, albeit to a lesser extent than *C. parvum* injection. Fiber counts were increased to a similar extent with 3 different numbers of macrophages. In control rats, injection of saline, Eagle's basal medium, or fetal calf serum did not significantly influence regeneration in the corresponding roots.

In contrast to dorsal root axons, peripheral axons were not stimulated in regeneration by *C. parvum* injection into the L₄ and L₅ DRG. Thirteen days after sciatic nerve crush, counts of newly myelinated fibers 15 or 20 mm distal in the sural nerve were, if anything, decreased by injection of *C. parvum* into the ganglia (Table 1).

Proliferation of satellite glial cells

In thymidine radioautography studies of L₄ and L₅ DRG after nerve transection, labeled cells could be divided into 5 general categories. Satellite glial cells were defined as those in direct contact with neurons. Other labeled cells in the vicinity of nerve cell bodies were polymorphic, slightly larger than satellite glial cells, and sometimes close to capillaries. Labeled Schwann cells were found in portions of spinal roots coursing through or near the DRG. Other labeled cells in the spinal roots were not Schwann cells. Finally, some labeled cells were found in connective tissue surrounding the ganglia. Labeling indices for satellite glial cells and other cells near neurons were arbitrarily defined as the number of labeled cells with more than 5 silver grains divided

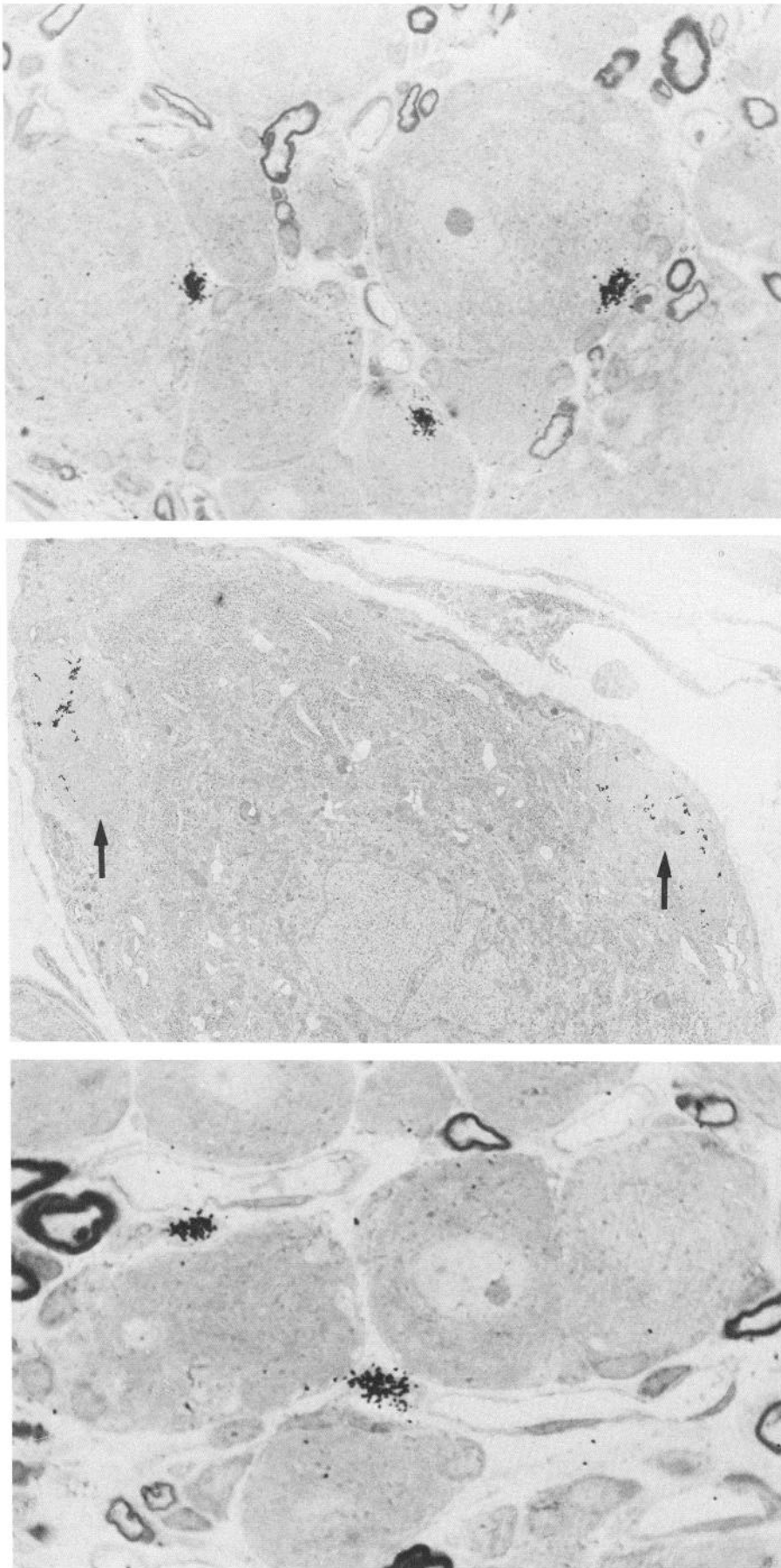


Figure 3. *Top,* Mitosis of several satellite glial cells is demonstrated by radioautography of a semithin section of an L₅ DRG removed 4 d after sciatic nerve transection and 90 min after intrathecal injection of tritiated thymidine. Magnification, 1100 \times . *Center,* Two proliferating satellite glial cells (arrows) surrounding a single neuron are seen in this electron microscope radioautograph. Sciatic nerve transection and injection of thymidine were the same as in the preparation above. Magnification, 3700 \times . *Bottom,* The 2 thymidine-labeled cells are close to capillaries and not in direct contact with neurons. They could be hematogenous. Magnification, 1100 \times .

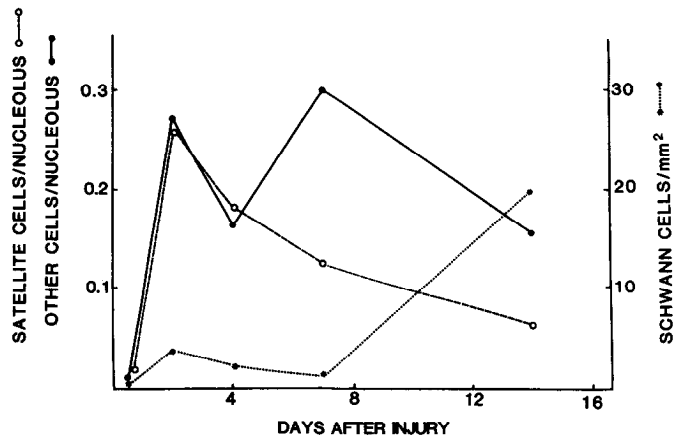


Figure 4. Labeling of non-neuronal cells in L₄ DRG removed at several intervals after sciatic nerve transection. Satellite cells are those directly contiguous to nerve cell bodies, and other cells are noncontiguous but in neuronal portions of the ganglion. The index for these 2 types is defined as the number of cells containing more than 5 silver grains divided by the number of neuronal nucleoli in the same section. Numbers of labeled Schwann cells are divided by the areas of spinal root tissue in the sections (2–5 DRG per point and 107–327 nuclei counted per DRG).

by the number of neuronal nucleoli in the same section. The density of labeled Schwann cells was expressed per mm² of cross-sectional area of spinal root in the section. The last 2 groups of labeled cells in spinal roots and connective tissue were not studied in detail.

In confirmation of earlier studies (Friede and Johnstone, 1967), satellite glial cells were seen to proliferate with maximum activity during the first week after nerve transection (Figs. 3, 4). However, as many or more labeled cells in neuronal portions of the DRG were of some other type (Fig. 3); at least some were suspected to be monocytes/macrophages (Smith and Adrian, 1971). The proliferation of Schwann cells in nearby roots became conspicuous only during the second week after injury. Although animal-to-animal variation made it difficult to compare numbers of labeled cells at different times, the ratios among the 3 labeling indices at a given time were relatively stable.

Four days after *C. parvum* injection, the mitotic index of satellite glial cells was comparable to that after peripheral nerve transection. In comparison to nerve transection, *C. parvum* injection elicited relatively more mitotic activity of Schwann cells, endothelial cells, and inflammatory cells in the ganglion (Fig. 1).

Effects of mitomycin C on axonal regeneration

In studies of axonal regeneration in L₅ dorsal roots, chronic intrathecal infusion of mitomycin C did not significantly change

Table 3. Lack of influence of intrathecal mitomycin C on regeneration of peripheral sensory axons

	Sural nerve fiber counts	
	15 mm	20 mm
Intrathecal saline	57 ± 21 (9)	17 ± 6 (10)
Intrathecal mitomycin C	80 ± 17 (9)	16 ± 4 (9)

Distances (in mm) are from crush site to site of counting. Data are means ± SEM of thinly myelinated fibers at 17 d, with numbers of sections counted in parentheses.

counts of regenerating fibers (Tables 2, 3). In both left and right L₅ roots associated with normal and cut sciatic nerves, the fiber counts in mitomycin-infused rats were similar to those in other rats with no infusion of mitomycin C. Also, mitomycin C delivered in this way did not retard regeneration in the sural nerve. The dosage and method of administering mitomycin C were adequate to reduce from 0.18 (108/614) to 0.08 (20/266) the labeling index of satellite glial cells in L₄ DRG 4 d after nerve transection.

Discussion

Effects of inflammation on the nerve cell body

Previous studies indicated that unknown responses of nerve cell bodies to peripheral axonal injury can promote regeneration of sensory axons (McQuarrie et al., 1977; Richardson and Verge, 1987). The present observations suggest that similar reactions can be elicited by more direct stimulation of the nerve cell body. Injection into the DRG of either macrophages or the inflammatory agent *C. parvum* significantly enhances axonal regeneration in the dorsal root. Because some wallerian degeneration was observed in spinal nerves after ganglionic injection of *C. parvum*, the possibility must be considered that *C. parvum* stimulates dorsal root regeneration merely by proximal interruption of peripheral axons. However, the trauma of injection alone does not suffice to stimulate dorsal root regeneration, and the hypothesis that *C. parvum* and/or macrophages are selectively toxic to peripheral rather than central sensory axons seems implausible. We conclude that axonal regeneration can be augmented by extracellular stimuli that act in the vicinity of the nerve cell body.

The beneficial effect of *C. parvum* on dorsal root regeneration is deduced to result from stimulation of the nerve cell body by some component of the inflammatory reaction. The stimulus to nerve cell bodies seems less likely to arise from *C. parvum* itself than from inflammatory cells, which are shown to stimulate neurons by themselves (Fig. 2). One or more of the cytokines from inflammatory cells (Rappolee et al., 1988) could act on neurons either directly or through the release of neurotrophic molecules from satellite glial cells. The latter suggestion

Table 2. Lack of influence of intrathecal mitomycin C on regeneration of central sensory axons

	Dorsal root fiber counts			
	Right		Left	
	10 mm	15 mm	10 mm	15 mm
Right sciatic nerve cut alone	220 ± 40 (12)	94 ± 17 (13)	38 ± 9 (11)	18 ± 10 (9)
Plus intrathecal mitomycin C	314 ± 85 (5)	164 ± 50 (5)	143 ± 64 (5)	40 ± 23 (5)

Distances (in mm) are from crush site to site of counting. Data are means and SEM of thinly myelinated fibers at 17 d, with numbers of sections counted in parentheses.

gains some credibility from previous observations that interleukin-1 can stimulate the proliferation of astrocytes (Giulian et al., 1989) and the release of NGF from non-neuronal cells in peripheral nerves (Lindholm et al., 1987). The molecular mechanisms by which an inflammatory response stimulates DRG neurons and their relationship to the axotomy signal are unknown.

Possible functions of non-neuronal cells in DRG

The fact that satellite glial cells react in a similar way to axotomy and *C. parvum* injection raises again the possibility that these cells participate in inducing a propensity for regeneration within sensory neurons. For motoneurons (Tetzlaff et al., 1988) and presumably also for sensory neurons, some of the reactions of perineuronal cells are rapid enough to precede the major changes of neuronal protein synthesis that favor axonal growth. The failure of mitomycin C to inhibit regeneration does not exclude the possibility that satellite glial cells participate in the axotomy-initiated signal to the nerve cell body. This toxin prevents DNA replication but should not interfere with transcriptional changes leading to putative neurotrophic proteins that might be released from satellite glial cells. Proof that satellite glial cells help to induce retrograde neuronal responses to axotomy will require further knowledge of neurotrophic molecules from perineuronal cells and gliotrophic signals from neurons (Aldskogius and Svensson, 1988; Kanje et al., 1989; Olsson et al., 1989).

After nerve transection, peak mitosis of satellite cells precedes peak mitosis of nearby Schwann cells by at least 1 week. The Schwann cells are probably proliferating in response to retrograde death of some sensory neurons and their axons (Aldskogius et al., 1985); the signal for proliferation of satellite glial cells is unknown.

Relevance of the observations to other axons

The presence of an inflammatory reaction in the DRG is beneficial to dorsal root regeneration but not to peripheral nerve regeneration. Probably, the latter regeneration is normally assisted by reactions of the nerve cell bodies that are much stronger after peripheral nerve crush than after dorsal root crush. Inflammation near the nerve cell body appears capable of mimicking the response caused by peripheral nerve injury but not of supplementing this response if it has already been invoked.

Lack of contribution from the nerve cell body is thought to be one factor that impedes the regrowth of injured axons in the CNS (Barron, 1983). Even in the favorable environment provided by peripheral nerve grafts, only a small proportion of most populations of CNS axons elongate substantially; their nerve cell bodies appear not to be activated adequately except by axotomy close to the nerve cell body (Richardson et al., 1984; Aguayo, 1985; Tetzlaff et al., 1990). The results described here suggest that it might be possible to enhance the characteristically sluggish responses of CNS neurons to injury by some intervention near the nerve cell body.

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