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Report

Chronically CNS-Injured Adult Sensory Neurons Gain Regenerative Competence upon a Lesion of Their Peripheral Axon

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Summary

Several experimental manipulations result in axonal regeneration in the central nervous system (CNS) when applied before or at the time of injury [1–6] but not when initiated after a delay [5–10], which would be clinically more relevant. As centrally injured neurons show signs of atrophy and degeneration [11–13], it raises the question whether chronically injured neurons are able to regenerate. To address this question, we used adult rodent primary sensory neurons that regenerate their central axon when their peripheral axon is cut (called conditioning) beforehand but not afterwards. We found that primary sensory neurons express regeneration-associated genes and efficiently regrow their axon in cell culture two months after a central lesion upon conditioning. Moreover, conditioning enables central axons to regenerate through a fresh lesion independent of a previous central lesion. Using in vivo imaging we demonstrated that conditioned neurons rapidly regrow their axons through a fresh central lesion. Finally, when single sensory axons were cut with a two-photon laser, they robustly regenerate within days after attaining growth competence through conditioning. We conclude that sensory neurons can acquire the intrinsic potential to regenerate their axons months after a CNS lesion, which they implement in the absence of traumatic tissue.

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Results

Regeneration-Associated Genes Are Upregulated in Centrally Injured Sensory Neurons after a Peripheral Lesion

We tested whether dorsal root ganglia (DRG) primary sensory neurons can gain axonal growth competence after central nervous system (CNS) injury. Characteristic of CNS axons, DRG neurons do not regenerate their central axons after a spinal cord injury [6]. However, regeneration can still be achieved by lesioning their peripheral axon before performing the central lesion [5, 6]. This phenomenon is mediated by transcriptional changes [14] and is known as preconditioning. However, when the peripheral lesion is made after the central lesion, the central axons fail to regenerate [5, 6].

We first examined whether centrally injured adult rat primary sensory neurons would upregulate regeneration-associated genes (RAGs) upon a subsequent peripheral lesion (i.e., conditioning) [14–20]. To this end, we first transected the dorsal columns and then we unilaterally cut and ligated the sciatic nerve, which includes the peripheral axons of the lumbar 4 (L4) and L5 DRG neurons, 2, 4, or 8 weeks later (see Figure S1 available online). Levels of RAG transcripts were quantified by semiquantitative real-time PCR from RNA extracts of the L4 and L5 DRGs.

We found that all tested RAGs were upregulated in DRG neurons conditioned 2, 4, or 8 weeks after the CNS lesion (Figure 1A). *Neuropeptide Y* was upregulated over 80-fold, *galanin* over 20-fold, *small proline-rich protein 1A* (*Sprr1a*) over 150-fold, *vasoactive intestinal peptide* (*Vip*) over 150-fold, *arginase* over 15-fold, *growth-associated protein 43* (*Gap 43*) about 3-fold, and *activating transcription factor 3* (*Atf-3*) over 8-fold. Importantly, a similar upregulation was induced in animals that were either conditioned before CNS injury or underwent peripheral lesion only (Figure S1 and Figure 1A). A dorsal column lesion alone did not significantly affect the expression of RAGs compared to unlesioned controls, except for *Vip* and *Sprr1a*, which were slightly, and transiently, upregulated (Figure 1A). Upregulation of RAGs in animals that were conditioned before or after CNS injury was reflected at the protein level. Western blot analysis showed an increase of GAP 43 protein in the chronically injured sensory neurons upon conditioning 8 weeks after the CNS injury (Figures S1 and S2). Furthermore, immunohistochemistry revealed that ATF-3 was specifically expressed in large- and medium-size myelinated N52-positive DRG neurons upon conditioning 8 weeks after the CNS injury (Figures S1 and S2).

Together, our results indicate that the temporal order of the central and peripheral lesions does not affect the degree of upregulation of RAGs in the DRG neurons. They also show that even after chronic injury, RAG expression can be induced in adult sensory neurons.

A

Gene	conditioned after CNS injury			conditioned before CNS injury			peripheral lesion			CNS injury		
	2 weeks	4 weeks	8 weeks	2 weeks	4 weeks	8 weeks	2 weeks	4 weeks	8 weeks	2 weeks	4 weeks	8 weeks
neuropeptide Y	85.7 ± 4.8	139.5 ± 24.3	131.7 ± 7.3	102.0 ± 6.7	107.4 ± 2.3	46.7 ± 8.0	157.2 ± 1.7	152.9 ± 12.5	100.1 ± 9.7	2.0 ± 0.1	0.8 ± 0.1	1.9 ± 0.3
galanin	24.4 ± 3.7	29.8 ± 4.1	26.4 ± 5.6	12.6 ± 0.3	9.1 ± 0.6	6.2 ± 0.9	17.2 ± 0.3	11.7 ± 6.3	8.5 ± 0.6	1.1 ± 0.1	0.9 ± 0.1	0.9 ± 0.1
Sprr1a	264.9 ± 58.2	442.1 ± 115.7	340.8 ± 70.3	105.7 ± 21.8	105.7 ± 9.3	48.9 ± 15.8	231.1 ± 31.9	173.5 ± 23.6	88.1 ± 24.4	3.7 ± 0.6	1.9 ± 1.7	3.2 ± 1.5
Vip	299.2 ± 54.4	181.9 ± 15.6	170.7 ± 37.7	273.2 ± 33.0	362.0 ± 60.4	228.2 ± 21.4	442.1 ± 70.1	345.9 ± 129.6	349.1 ± 52.4	8.1 ± 0.8	1.3 ± 0.0	2.6 ± 0.9
arginase	18.2 ± 2.3	20.0 ± 5.5	16.2 ± 2.9	12.0 ± 1.0	10.4 ± 0.7	6.1 ± 0.7	15.3 ± 1.5	13.2 ± 6.8	7.3 ± 0.8	1.0 ± 0.2	1.0 ± 0.4	1.6 ± 0.3
Gap 43	2.6 ± 0.2	4.2 ± 0.1	4.3 ± 1.6	2.7 ± 0.3	2.9 ± 0.1	2.0 ± 0.3	3.1 ± 0.2	2.4 ± 1.2	2.6 ± 0.2	0.7 ± 0.1	1.0 ± 0.1	1.1 ± 0.1
Atf-3	8.0 ± 0.9	17.9 ± 7.8	16.2 ± 0.7	7.9 ± 0.1	16.5 ± 3.9	13.5 ± 0.8	9.3 ± 3.0	10.8 ± 2.4	22.6 ± 5.3	0.6 ± 0.0	1.0 ± 0.4	2.4 ± 0.2

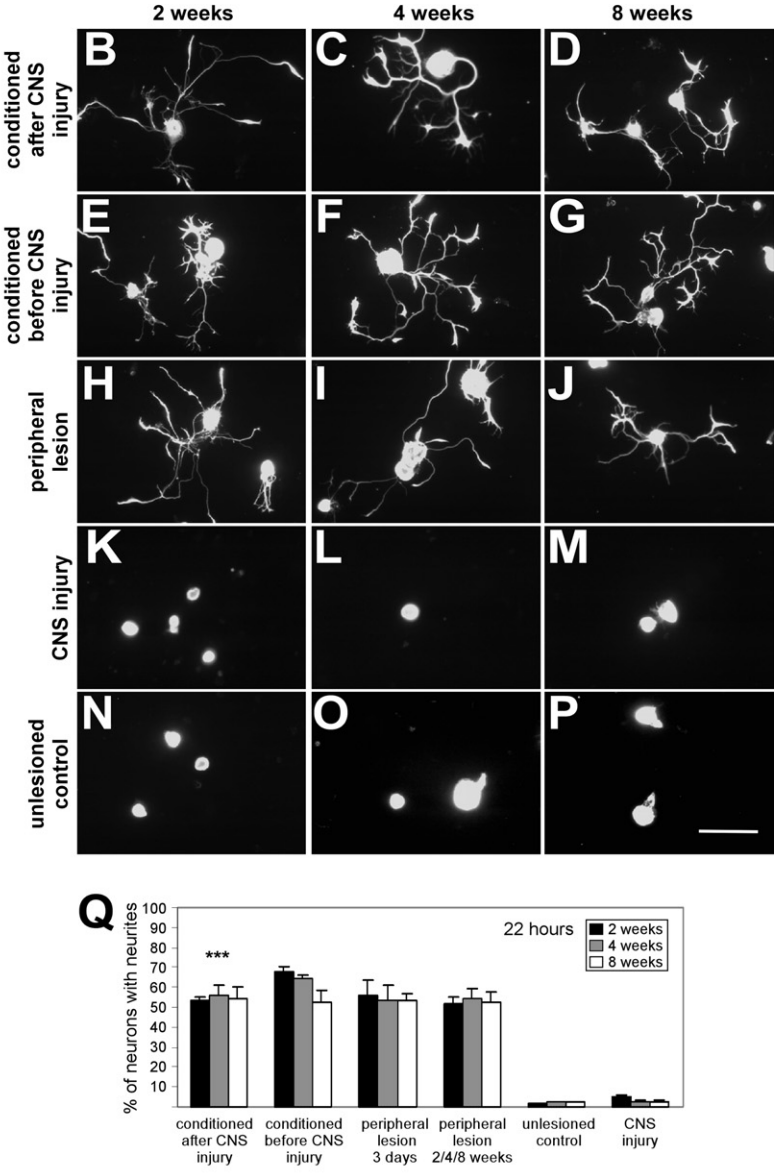

Figure 1. DRG Neurons Conditioned before or after CNS Injury Upregulate RAGs and Show Enhanced Growth on a Permissive Substrate

(A) The level of upregulation of RAGs in DRG neurons in the ipsilateral versus contralateral/unlesioned sides of the rats at 2, 4, and 8 weeks in the groups conditioned after or before CNS injury and in the peripheral-lesioned-only group, and in lesioned versus unlesioned rats at 2, 4, and 8 weeks after CNS injury (only dorsal column lesion group). All genes in the group conditioned after CNS lesion were significantly upregulated compared to the control CNS-injury-only group ($p < 0.05$ for *Vip* and *Atf-3* and $p < 0.001$ for the rest, by ANOVA). White indicates an increase of less than 2-fold, gray between 2- and 5-fold, pink between 5- and 45-fold, and orange more than 45-fold. Data are shown as the mean ± standard error of the mean (SEM). The DRG neurons from rats conditioned after (B–D) or before CNS injury (E–G), peripheral lesion only (H–J), central lesion only (K–M), and unlesioned (N–P) rats, after 2 weeks (B, E, H, K, and N), 4 weeks (C, F, I, L, and O), or 8 weeks (D, G, J, M, and P), were cultured for 22 hr on poly-lysine substrate and stained with Tuj-1 antibody. Scale bar represents 100 μm.

(Q) Percentage of neurons bearing long neurites (mean ± SEM). DRG neurons in the group conditioned after CNS injury show significantly higher values compared to unlesioned and CNS-injury-only groups (***$p < 0.001$ by ANOVA), but not compared to the group conditioned before CNS injury or the peripheral-lesion-only group ($p > 0.05$ by ANOVA).

Centrally Injured Sensory Neurons Exhibit Enhanced Neurite Outgrowth on Permissive and Inhibitory Substrates upon Conditioning

Although upregulation of RAGs has been correlated to an increased regenerative ability, the key regulatory genes that set DRG neurons in a growth-competent state still remain elusive [15, 21]. We therefore tested whether CNS-injured DRG neurons that were subsequently conditioned extended neurites in cell culture. The neurons were plated on poly-lysine and neurite outgrowth was assessed by measuring their number and average length. We only assessed neurons with a cell body diameter larger than 30 μm, which are known to be proprioceptive neurons [22].

We found that 53% ± 2% of the DRG neurons that were conditioned 2 weeks after CNS injury (Figure S1) exhibited neurites (Figures 1B and 1Q). This result was comparable to DRG neurons that were either conditioned before CNS injury or conditioned only (Figures 1E, 1H, and 1Q). In contrast, only few DRG neurons exhibited neurite outgrowth when they received a central lesion only (Figures 1K and 1Q) or no lesion (Figures 1N and 1Q) as observed previously [14, 23]. Unconditioned neurons remained healthy in culture as they formed neurites when cultured for longer periods (data not shown) [14]. Enhanced neurite outgrowth of DRG neurons from rats conditioned before, after, or without CNS injury was also observed at 4 (Figures 1C, 1F, 1I, and 1Q) and 8 (Figures 1D, 1G, 1J, and 1Q) weeks. DRG neurons conditioned either before or after CNS injury also showed enhanced neurite lengths. Independent of when the conditioning occurred, about 50% of the cells had neurites longer than 100 μm (Figure S3), a more than 20-fold increase compared to DRG neurons that were centrally lesioned only or unlesioned (Figure S3).

Importantly, DRG neurons conditioned after CNS injury also showed enhanced axonal growth when confronted with growth-inhibitory CNS myelin substrates in cell culture. More than half of these as well as neurons that were conditioned before a CNS injury or conditioned only grew neurites within 40 hr after plating on myelin substrate (Figure S4). The average length of neurites was similar irrespective of whether the peripheral lesion was made prior to or subsequent to the CNS lesion (Figure S5). Together, our data show that neurons conditioned after CNS injury grow axons as efficiently as those conditioned before CNS injury both on a permissive substrate as well as on inhibitory myelin.

CNS-Injured Sensory Neurons Regenerate Their Axons through a Second, Fresh Lesion in the Spinal Cord upon Conditioning

Although CNS-injured DRG neurons attain axonal growth competence upon subsequent conditioning when cultured, they do not regenerate in vivo [5, 6]. It is possible that the peripheral lesion may set the centrally injured DRG neurons into a growth-competent state, but the traumatic scar tissue forming at the injury site may hinder the implementation of their intrinsic potential. We therefore assessed whether centrally injured DRG neurons that were subsequently conditioned regenerated their axon beyond a fresh central lesion. To this end, central axons of adult rats were transected and a peripheral lesion was made 2 weeks later. Then, 1 week later, the central axons were transected again caudally to the first lesion (Figure S6). Axonal regeneration through the fresh lesion was assessed 6 weeks later with anterograde axonal tracing.

In agreement with previous reports, sensory axons of rats that were conditioned before CNS injury regenerated into and beyond the injury site (Figures 2C, 2D, and 2I, white arrowheads) [6, 23]. When animals were conditioned after CNS injury, the sensory axons failed to grow [5, 6]. Many axons had retracted from the caudal edge of the lesion (Figures 2A, 2B, and 2I, red arrowheads). This was also the case in rats that received a central lesion only [6] (data not shown). In contrast, in all rats conditioned after an initial CNS injury, axons regenerated into and beyond the second, more caudally placed fresh central lesion (Figures 2E–2I, white arrowheads). The longest regenerating axons per animal grew on average 1.3 mm, which was similar to animals that were conditioned before CNS injury.

Hence, regardless of a previous CNS injury, conditioning sets neurons in a growth-competent state in vivo; this growth potential is manifested by their regeneration through a fresh CNS lesion.

Conditioned DRG Neurons Rapidly Initiate Axon Growth

As preconditioned axons regenerate, it suggests that they grow across the lesion before the damaged spinal cord tissue becomes inhospitable. In contrast, DRG neurons conditioned after CNS injury would acquire the growth competence too late to grow across the injury site. To test this possibility, we studied the growth response of DRG neurons that were conditioned before CNS injury via in vivo imaging. We also assessed the growth response in neurons conditioned after CNS injury when confronted with a fresh CNS lesion. GFP-M transgenic mice that express green fluorescent protein (GFP) in a few neurons were used [24]. For in vivo imaging, a small unilateral lesion was performed at the L1 level of the spinal cord. Specifically, we carefully transected central axons of the L4 and L5 DRG neurons in the dorsal columns close to the dorsal vein (Figures 3A, 3E, and 3I; Movie S1; and Figure S7). Degeneration and regeneration of the cut axons were monitored for up to 48 hr (Figures 3A–3L). After completing the in vivo imaging, the DRGs and spinal cords were dissected to validate that the targeted axons originated from DRG neurons with their peripheral extension in the sciatic nerve.

During the first 5 to 7 hr postinjury, small sprouts emerged from the tip of many axons from neurons conditioned before a central lesion. Similarly, neurons conditioned after an initial central lesion also showed small sprouts at the fresh lesion (Figures 3F and 3J, green arrowheads). In contrast, unconditioned neurons did not form sprouts but their axons retracted from the lesion (Figure 3B, red arrowheads). At 24 hr postinjury, the extensions that sprouted from axons conditioned either before or after CNS injury elongated further and penetrated the fresh injury site (Figures 3G and 3K, white arrowheads). Some of these sprouts grew perpendicularly or inversely to the caudal-to-rostral axis of the spinal cord. Remarkably, many of the regenerating sprouts grew several hundred micrometers beyond the lesion within 48 hr postinjury and had a thin growth tip (Figures 3H, 3L, and 3M, white arrowheads; 422 ± 121 μm and 345 ± 84 μm, respectively). In contrast, unconditioned axons retracted from the lesion and formed retraction bulbs (Figures 3D and 3M). These results show that conditioning enables primary sensory neurons to rapidly grow through a fresh CNS lesion.

Laser-Lesioned Central Axons Regenerate upon Subsequent Conditioning

It is possible that with time the damaged spinal cord tissue might have become too inhospitable not only for unconditioned but also for growth-competent neurons (Figure S8).

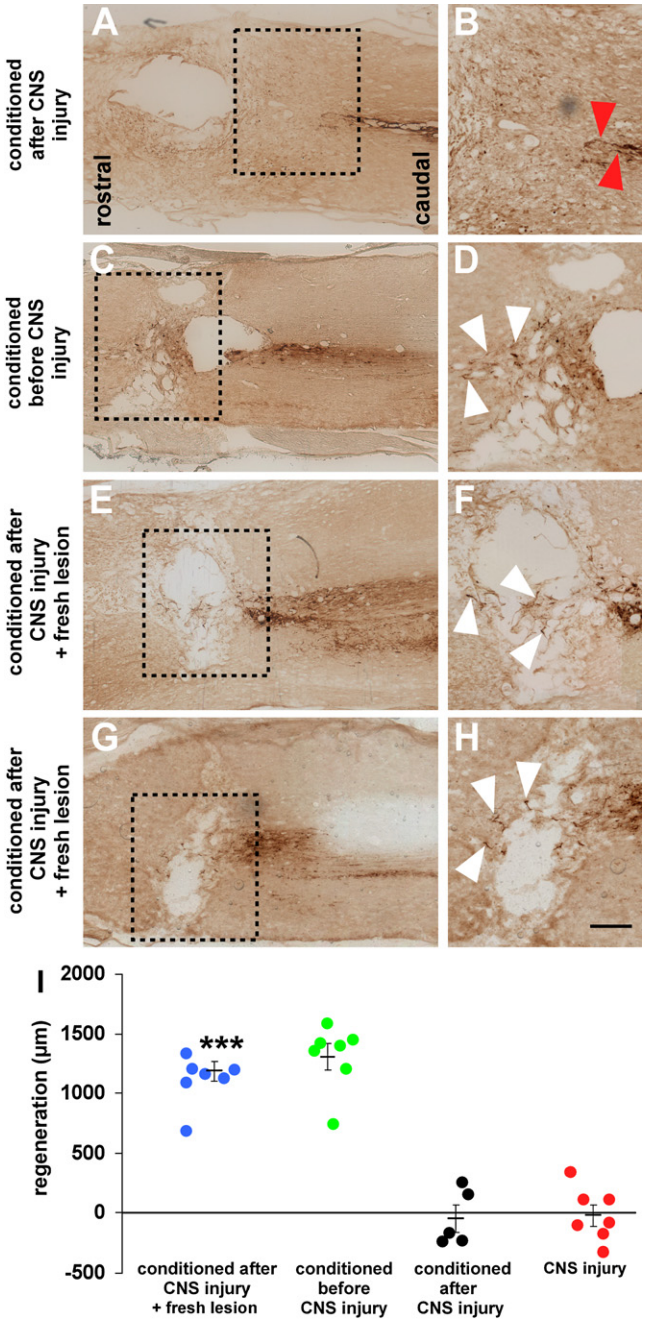

Figure 2. A Conditioning Lesion Implemented after a CNS Injury Results in Regeneration of Central Sensory Axons into and beyond a Second, Fresh, Central Lesion Caudal to the First Central Lesion

Horizontal sections of the spinal cords (rostral to the left).

(A and B) A conditioning after CNS injury does not result in sensory axon regeneration. Stalled axons are indicated by red arrowheads. (B) is a higher magnification of (A).

(C and D) A conditioning lesion implemented before the central lesion (i.e., the classic preconditioning paradigm) results in sensory axon regeneration into and beyond the lesion (white arrowheads). (D) is a higher magnification of (C).

(E–H) Conditioning after a central lesion causes axon regeneration into and beyond a second, fresh, central lesion performed caudally to the first central lesion. The second central lesion was made 1 week after conditioning (Figure S6). Axons regenerate into the lesion and at the rostral edge of the lesion site (white arrowheads). (F) and (H) are higher magnifications of (E) and (G), respectively.

To test this possibility, we aimed to lesion central sensory axons without creating traumatic tissue. Specifically, we used a two-photon laser [25] to transect single GFP-labeled sensory axons in the spinal cord (Movie S2 and Figures 4B, 4G, and 4L, yellow arrowheads). This resulted in small damage and minimal scarring of the surrounding nervous tissue.

Using the two-photon lesion paradigm, we found that DRG neurons conditioned before central axotomy rapidly grew their axon within 2 days (Figure 4H; average length: 495 ± 107 μm). In contrast, unconditioned axons degenerated and retracted after laser axotomy (Movie S2) and showed only little sprouting during the first 2 days (Figure 4S; average length: 27 ± 10 μm). The conditioned axons continued growing in different directions at later time points (Figures 4I, 4J, 4Q1, and 4S; average length: 681 ± 141 μm). The effect of conditioning is mediated by changes in transcription [14] that sets the DRG neurons into a growth-competent mode within approximately 2 days [23, 26]. Thus, as expected, conditioning after central axotomy (performed in the example imaged in Figure 4M) resulted in modest sprouts at 2 days after sciatic nerve lesion (Figures 4N and 4T; 107 μm ± 25 μm). However, at 6 days after conditioning, axons showed an 8-fold increase in length (Figures 4O and 4T; 240 μm ± 43 μm) compared to unconditioned axons (9 days after two-photon axotomy for both; Figures 4E and 4T; 33 μm ± 14 μm). After the experiment, we examined the degree of gliosis at the lesion by GFAP immunostaining. Only a few GFAP-positive astrocytes were found at the two-photon lesion (Figures 4P_2, 4Q_2, and 4R_2, purple arrows). We also observed that the regenerative axonal sprouts grew in different directions. Some of the sprouts traversed the lesion epicenter in the conditioning paradigms (Figures 4Q_3 and 4R_3, white arrowheads). Two-photon laser-cut axons remained responsive to conditioning for longer times. When the neurons were conditioned 1 week after the laser axotomy, the axons showed extensive regeneration. Fourteen days after the two-photon cut (7 days after conditioning), the axons were 1 mm long (Figure S9; average length: 965 ± 164 μm), whereas unconditioned neurons showed only continuous modest growth (Figure S9; average length: 283 ± 74 μm). Together, our results show that primary sensory neurons can be set in a regenerative state after a central injury that they carry out in the absence of scarring.

Discussion

In primary sensory axons, a peripheral lesion preceding a central lesion results in growth of the central axons through and beyond the lesion without the need for additional interventions to decrease the growth-inhibitory nature of the CNS [6, 23, 26]. This phenomenon is known as preconditioning of the DRG neurons and can be mimicked by increasing cyclic adenosine monophosphate (cAMP) cellular levels [23, 26]. For an axonal growth effect to be conferred, the peripheral lesion (i.e., conditioning) has to be implemented prior to, or at least

(I) Each dot represents the longest regenerating axon of each animal in the following groups: conditioned after CNS injury with a second caudal fresh lesion (blue dots; n = 7), conditioned before CNS injury (green dots; n = 7), conditioned after CNS injury (black dots; n = 5), and central lesion only (red dots; n = 7). *** indicates $p < 0.001$, by ANOVA, compared to the group conditioned after CNS injury and the CNS-injury-alone group. Average length of regenerating axons and standard errors are indicated with black lines. In all spinal cord images, the rostral direction is to the left as indicated in (A). Scale bars represent 250 μm (A, C, E, and G) and 125 μm (B, D, F, and H).

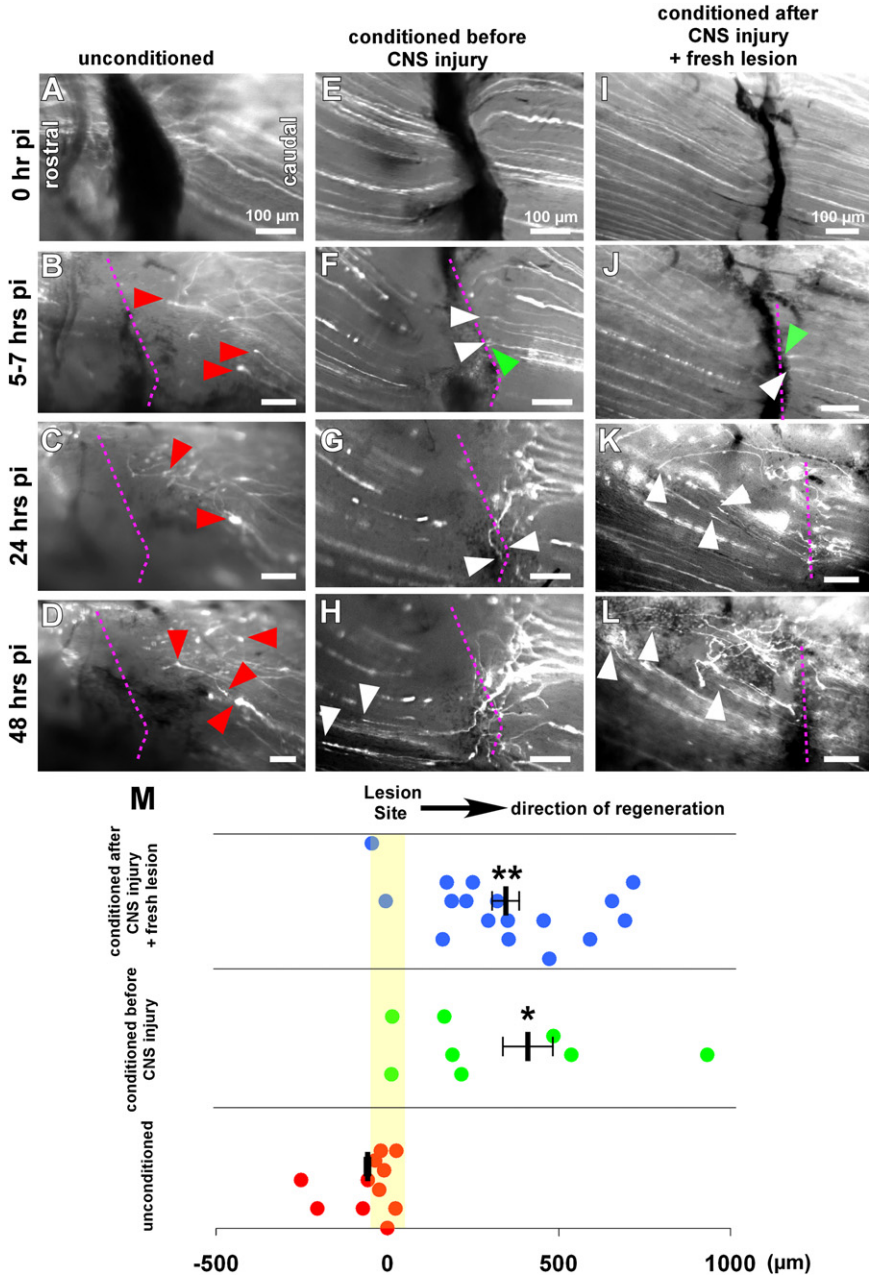

Figure 3. Conditioned Axons Rapidly Initiate Regrowth

Live in vivo images of GFP axons in GFP M mice that received a central lesion only (unconditioned) (n = 11 animals) (A–D), conditioning lesion before CNS injury (n = 8 animals) (E–H), or conditioning lesion after CNS injury plus a second, fresh, central lesion (n = 17 animals) (I–L). The mice were imaged at 0 hr (A, E, and I), 5–7 hr (B, F, and J), 24 hr (C, G, and K), and 48 hr (D, H, and L) postinjury (pi). Lesion sites are depicted by purple dotted lines. Red arrowheads indicate retraction bulbs, green arrowheads indicate initial sprouts, and white arrowheads indicate regenerating sprouts that cross the lesion site in mice that received conditioning lesion before or after CNS injury. In all spinal cord images, the rostral direction is to the left as indicated in (A). Scale bars represent 100 μm.

(M) Length quantification of regenerating sprouts in mice that received a central lesion only (red dots), a conditioning lesion before CNS injury (green dots), and a conditioning lesion after CNS injury plus a second, fresh, central lesion (blue dots) as measured from the epicenter of the lesion site (indicated as 0 on the x axis). Arrow indicates rostral direction of growth. Average length of regenerating axons and standard errors are indicated with black lines. * indicates $p < 0.01$ and ** indicates $p < 0.001$ by ANOVA compared to the unconditioned group.

at the same time as, the central lesion. When the peripheral lesion is performed after the central lesion, the central sensory axons fail to regenerate.

Here, we investigated the underlying mechanisms for the distinct regenerative responses (Figure S10). We found that DRG neurons conditioned after CNS injury acquire an intrinsic growth competence that is qualitatively and quantitatively similar to that of neurons conditioned before CNS injury. This was observed up to 2 months after the initial central lesion, the longest time period tested. In support of our findings, adult rat rubrospinal neurons are able to regenerate their axotomized axon several months after a spinal cord injury in response to administration of neurotrophic factors near the cell bodies [27].

DRG neurons conditioned after CNS injury also acquire the ability to grow their central axons in vivo but they only implement their potential in the absence of traumatic tissue. Two-photon lesioned axons initiate regenerative sprouting 3 days after a peripheral lesion. The sprouts appear to grow in random directions, which is probably to be due to the lack of proper guidance cues [28].

Clearly, the discrepancy in the timing of changes occurring at the site of a central lesion and acquisition of axonal growth competence via a preceding or subsequent conditioning is crucial for the different regenerative responses. Conditioning of DRG neurons induces retrograde signaling mechanisms [29, 30] that activate the expression of RAGs (Figure S10) setting neurons in a growth-competent state within 2 days [23, 26]. Hence, with a preconditioning the DRG neurons already express molecules necessary for axonal growth prior to the central lesion. Indeed, using in vivo imaging we found that conditioned axons immediately initiate growth to traverse the lesion within 48 hr, when tissue scarring is not yet evident (Figure S10). DRG neurons conditioned after the CNS lesion do acquire growth competence but this occurs after the scar has developed [31]. Hence, traumatic tissue is not only inhibitory for unconditioned but also for growth-competent neurons. In conclusion, successful regeneration of axons by preconditioned DRG neurons appears to result from rapid crossing of the lesion site prior to accumulation of cells and molecules inhibitory to axon growth, including reactive astrocytes. Consistent with our results, lesioned sensory axons respond favorably to cAMP application initiated 2 weeks postinjury and regain neuronal function in zebrafish, which does not form a glial scar after spinal cord injury [32].

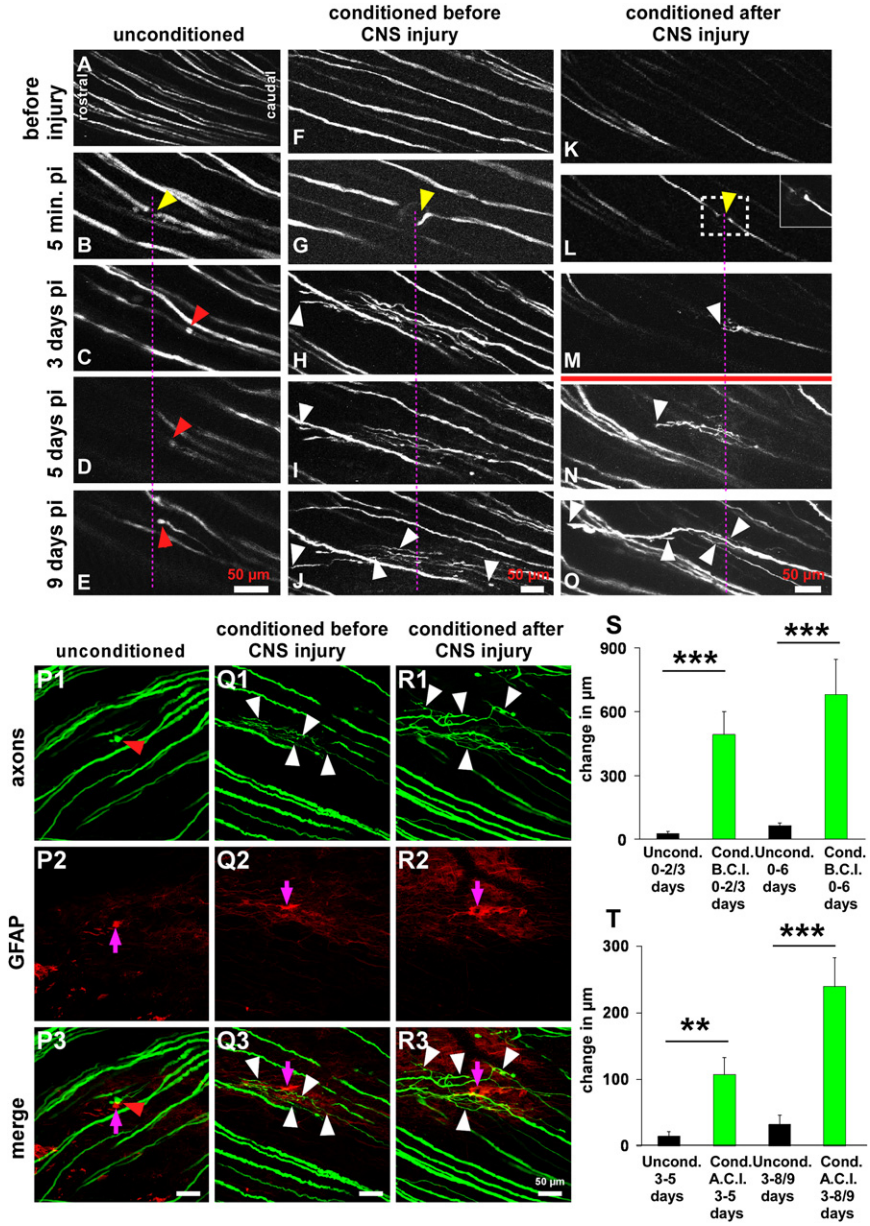

Figure 4. Two-Photon Lesioned Axons Show Enhanced Regeneration when Followed by a Conditioning Peripheral Lesion

Two-photon imaging and lesioning of GFP mice that received a central lesion only (unconditioned) (A–E), a conditioning before CNS injury (F–J), and a conditioning after CNS injury (K–O). The mice were imaged before injury (A, F, and K), at 5 min (B, G, and L), 3 days (C, H, and M), 5 days (D, I, and N), and 9 days (E, J, and O) postinjury. Lesion made with a two-photon laser is indicated with yellow arrowheads. White and red arrowheads indicate regenerating and stalled axons, respectively. Red line between (M) and (N) indicates the application of the peripheral lesion (conditioning) at 3 days after two-photon laser lesion. The purple dotted lines in the lesion sites align the images at the two-photon lesion. After two-photon imaging, the mice were perfused and spinal cords were stained with GFAP to reveal reactive astrocytes in central lesion only (P_1–P_3), conditioned before (Q_1–Q_3) or after CNS injury mice (R_1–R_3). Regenerating axonal sprouts in mice conditioned before (Q_1) and after (R_1) CNS injury. Extent of scar formation after two-photon laser is minimal as revealed by GFAP staining of reactive astrocytes indicated by purple arrows at the lesion site (P2, Q2, and R2). Overlay showing the regenerating sprouts marked with white arrowheads and GFAP-stained reactive astrocytes indicated with purple arrows (P_3, Q_3, and R_3). In all spinal cord images, the rostral direction is to the left as indicated in (A). Scale bars represent 50 µm (E, J, O, and P_3–R_3). Length quantification of sprouts in mice conditioned before (n = 8 animals) (S) or after CNS injury (n = 7 animals) (T) compared to unlesioned controls (n = 8 animals) at the indicated time points. Data are shown as the mean ± SEM. B.C.I. denotes before central injury; A.C.I. denotes after central injury. **p < 0.05 and ***p < 0.01 by unpaired t test.

Our data have interesting implications for current efforts to identify and characterize regeneration-inducing genes and signaling pathways that stimulate axon regeneration by mimicking the conditioning effect as induced in DRG neurons via a peripheral lesion [17–21, 23, 26]. The present results predict that manipulating key effectors involved in conditioning after spinal cord injury would enable axon regeneration only upon concomitant reduction of traumatic scar tissue. Indeed, administration of the phosphodiesterase inhibitor rolipram 2 weeks after spinal cord injury, which increases the cAMP level in neurons and attenuates the gliosis, improves regeneration [33].

In summary, our data provide evidence that chronically injured DRG neurons can acquire robust regenerative potential. The implementation of the growth competence, however, is hampered by traumatic changes at the lesion site. Our data indicate that inducing a conditioning effect combined with interventions that reduce the growth-inhibitory nature of the scar may provide promising therapies for chronic spinal cord injury.

Supplemental Data

Supplemental Data contain Supplemental Experimental Procedures, ten figures, and two movies and can be found with this article online at http://www.cell.com/current-biology/supplemental/S0960-9822(09)00974-9.

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