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Clinical and electrophysiological expression of deafferentation pain alleviated by dorsal root entry zone lesions in rats

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Object. The aims of this study were to construct an animal model of deafferentation of the spinal cord by brachial plexus avulsion and to analyze the effects of subsequent dorsal root entry zone (DREZ) lesions in this model. To this end, the authors measured the clinical and electrophysiological effects of total deafferentation of the cervical dorsal horn in rats and evaluated the clinical efficacy of cervical DREZ lesioning.

Methods. Forty-three Sprague–Dawley rats were subjected to total deafferentation of the right cervical dorsal horn by performing a posterior rhizotomy from C-5 to T-1. The clinical effects of this deafferentation, namely self-directed mutilations consisting of scraping and/or ulceration of the forelimb skin or even autotomy of some forelimb digits, were then evaluated. As soon as some of these clinical signs of pain appeared, the authors performed a microsurgical DREZ rhizotomy ([MDR], microincision along the deafferented DREZ and dorsal horn). Before and after MDR, single-unit recordings were obtained in the deafferented dorsal horn and in the contralateral (healthy) side. The mean frequency of spontaneous discharge from the deafferented dorsal horn neurons was significantly higher than that from the healthy side (36.4 Hz compared with 17.9 Hz, $p = 0.03$).

After deafferentation, 81.4% of the rats developed clinical signs corresponding to pain following posterior rhizotomy. Among these animals, scraping was observed in 85.7% of cases, ulceration (associated with edema) in 37.1%, and autotomy in 8.5%. These signs appeared a mean 5.7 weeks (range 1–12 weeks) after deafferentation.

Thirteen rats benefited from an MDR; nine (69%) experienced a complete cure, that is, a total resolution of scraping or ulceration (a mean 4.6 weeks after MDR). In contrast, only one of 11 sham-operated animals showed signs of spontaneous recovery ($p = 0.01$).

Conclusions. These results emphasize the role of the spinal dorsal horn in the genesis of deafferentation pain and suggest that dorsal horn deafferentation by cervical posterior rhizotomy in the rat provides a reliable model of chronic pain due to brachial plexus avulsion and its suppression by MDR.

KEY WORDS • dorsal root entry zone • lesioning • deafferentation pain • electrophysiological recording • autotomy • self-directed mutilation syndrome • rat

PAIN following BPA, which is the most typical expression of chronic deafferentation pain in humans,[9,43] is one of the major challenges in terms of medical or surgical management of neuropathic pain. There is experimental and clinical evidence that pain generators in BPA are at least partially located in the deafferented dorsal horn.[3,6,8,15,20,22,31] Lesioning of this target in the DREZ[29,41,42] has turned out to be an efficient surgical treatment for such deafferentation pain. Recently, data from a number of publications have confirmed the clinical efficacy of therapeutic DREZ lesioning.[21,29,35,38,40,45] Despite a significant rate of success in treating BPA (approximately 60–70% according to the literature),[13,34,38,41,44] it is not totally clear where the pain generators are and how DREZ surgery (namely the MDR procedure, which involves the incision of the dorsolateral sulcus and the creation of dotted bipolar coagulations along the DREZ into the dorsal horn apex with the aid of visual guidance)[39] works in humans. Therefore, we conducted animal experiments to study the effects of MDR in a deafferentation pain model of the BPA type. Indeed, experimental DREZ lesioning has not been studied under these conditions as far as we are aware.

The most characteristic symptoms displayed by patients after BPA, including sensory disturbances and spontaneous pain, appear to resemble the symptoms of posterior cervical rhizotomy in the rat, as described by Lombard, et al.[24] The deafferentation syndrome produced in the rat following posterior cervical rhizotomy consists of self-directed mutilation behaviors of the forelimb, which can be considered[4,10,11,37,46,50] to be objective evidence of spontaneous pain. The suggestion that self-mutilation is related to neuropathic pain is supported by many arguments.[50] In an attempt to rid themselves of pain sensations, animals that have undergone rhizotomy self-mutilate in the deafferented area. The appearance of such behavior in rats postrhizotomy and its possible resolution post-MDR allowed for a satisfying evaluation of the analgesic effects of MDR.

Furthermore, electrophysiological changes after deafferentation, mostly characterized by increased spontaneous unitary activity of the dorsal horn neurons,[3,6,8,11,22,23,31]

Abbreviations used in this paper: BPA = brachial plexus avulsion; DREZ = dorsal root entry zone; MDR = microsurgical DREZ rhizotomy; SD = standard deviation.

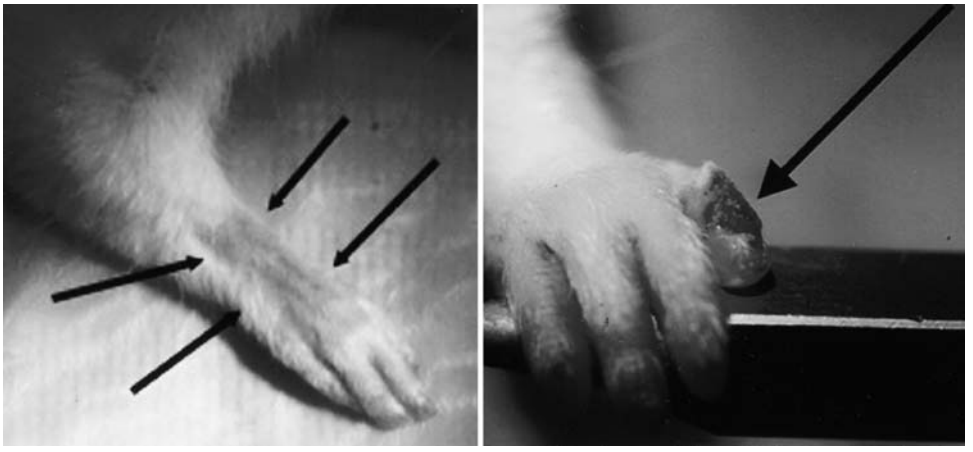

FIG. 1. *Left:* Photograph illustrating an example of a scraping lesion *(arrows)* along the right forearm. *Right:* Photograph depicting an example of an ulcerative lesion *(arrow)* of the digit, associated with edema of the entire forelimb paw.

are supposed to underlie the occurrence of pain and thus self-directed mutilations. A comparison of these functional properties of dorsal horn neurons both before and after MDR would highlight the neurophysiological effect of MDR.

In this paper we focused on the following two points: 1) clinical and electrophysiological study of a reliable animal model of deafferentation pain of the type closest to post-BPA pain that frequently occurs in humans; and 2) the study of the effect of DREZ lesioning in this model.

To achieve these goals, the model of posterior cervical rhizotomy in the rat, as described by Lombard, et al.,[24] was used. The clinical criterion of pain was indicated by the self-directed mutilations, the only available manifestations of pain in the deafferented territory. The electrophysiological effects of deafferentation were studied by obtaining unitary recordings of the dorsal horn neurons with the measurement of spontaneous activity in the deafferented side compared with that in the non-deafferented one. Once self-directed mutilations were observed, the effects of DREZ lesioning on them were studied in a group of rats compared with another group of sham-operated rats. The criterion of a cure was the total disappearance of any sign of self-directed mutilation. The post-MDR electrophysiological modifications were then recorded. Histological examination of the spinal cord was performed at the end of the experiment.

The ability of MDR to reverse completely and definitely, once they occurred, the clinical and electrophysiological manifestations of chronic neuropathic pain displayed in the rats, provided some data in favor of the role of the dorsal horn in the deafferentation pain syndrome.

Materials and Methods

The total sample in this study consisted of 43 male or female Sprague–Dawley rats, each weighing from 300 to 500 g. During this experiment we fulfilled the recommendations of the Committee for Research and Ethical Issues of the International Association for the Study of Pain. The rats exhibited normal sleep–wake cycles, and they were all housed individually. The animals exhibited no evidence of discomfort except for the postrhizotomy self-directed mutilations.

Model of Deafferentation Pain

All animals (43 rats) underwent a right posterior rhizotomy from C-5 to T-1, resulting in total deafferentation of the right cervical spinal cord at these levels.

Surgical Procedure. The animals were anesthetized with the intraperitoneal administration of 4% hydrochloral (1 ml/100 g). Under aseptic conditions, the skin was incised from the occipital bone to T-3. A longitudinal incision was then made along the midline to retract laterally the paravertebral muscles and to expose the posterior aspect of the cervical laminae. A C-3 to T-2 laminectomy was performed and the dura mater was opened longitudinally along the midline with the aid of microscissors. The right posterior rootlets were identified and an intradural section of the C-5 to T-1 right posterior rootlets was completed using microscissors. The dura was then patched using a synthetic graft (Neuropatch) and the wound was closed in layers.

Behavioral Evaluation. In all 43 animals, the clinical effects of the posterior cervical rhizotomy were evaluated biweekly during the months following surgery. Clinical signs were classified as follows: 1) scraping along a forelimb dermatome, caused by a loss of hair due to repetitive chewing along one (or more) right forelimb dermatome (Fig. 1 *left*); 2) ulceration of one or several forelimb digits (Fig. 1 *right*), caused by light biting of the digit(s) or the entire forelimb paw, making them look red and edematous as well as ulcerative; and 3) autotomy of some forelimb digits, caused by severe biting until some of the digits were completely removed.

In all the cases, the interval between the first rhizotomy and the initial manifestation of one of these self-directed mutilations was measured. Animals were observed an additional 12 weeks between the possible appearance of a sign of self-mutilation and DREZ lesion or sham operation (see later). The rats that displayed no sign of self-mutilation were observed for up to 23 months postrhizotomy.

Electrophysiological Recordings. Unitary activities were recorded using a microelectrode in the right (deafferented) dorsal horn and were compared with those of the left (healthy dorsal horn) side. The extracellular microelectrode analysis of spontaneous neuronal activity was performed to determine whether deafferentation hyperactivity could be found in the right dorsal horn of the rats. For each rat, the mean frequency of spontaneous neuronal discharges of the dorsal horn subjected to rhizotomy was compared with that of spontaneous discharges recorded at the same time in the left (healthy) dorsal horn. These recordings were obtained during the second surgery, which was undertaken to complete the MDR (see later), with the use of a floating 20-μm tipped tungsten-in-glass dual microelectrode, which is described elsewhere.[18] The penetration depth of the microelectrode was 1 mm, which is the minimal depth required to reach Rexed layers IV to V of the dorsal horn in the rat. The elec-

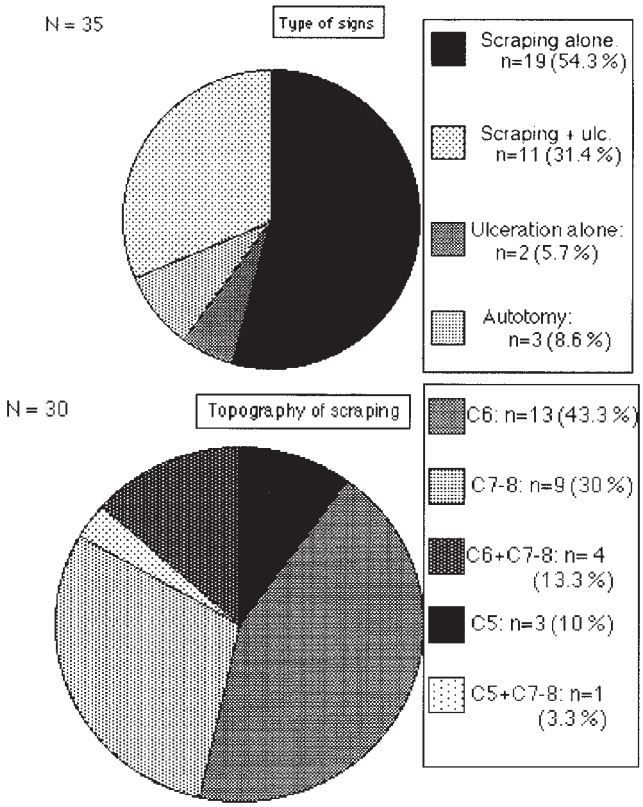

FIG. 2. *Upper:* Pie chart indicating the types of clinical signs of self-inflicted mutilations (before MDR). *Lower:* Pie chart demonstrating the topographic distribution of the scraping phenomena (before MDR). N = number of rats; ulc. = ulceration.

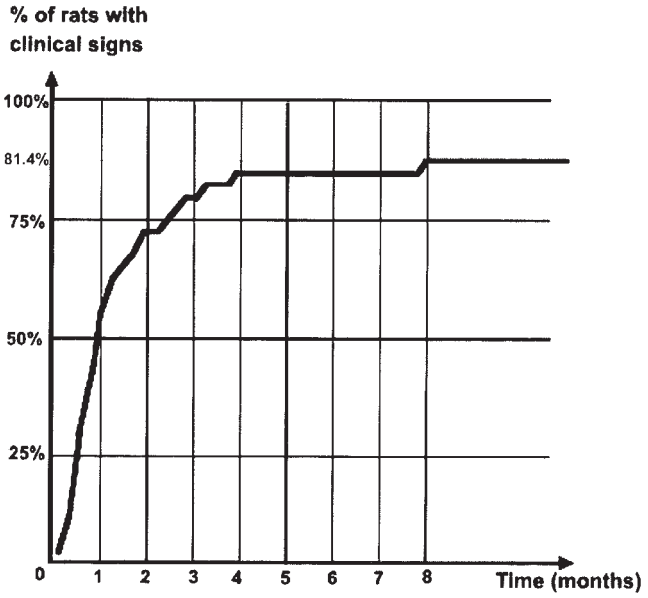

FIG. 3. Graph demonstrating the time course of the appearance of the first clinical sign of self-directed mutilation.

trode was always implanted at the C-7 level. Indeed, this level corresponds to the most deafferented cervical level on the right side, because it is exactly in the middle of the posterior cervical rhizotomy. The microelectrode was connected to a headstage (Digitimer Neurolog, Ltd, Hertfordshire, UK), an amplifier (× 10,000), and a signal filter (900–15,000 Hz; Digitimer Neurolog, Ltd). The data analysis was performed using a spike sorter (Alpha Omega MSD; Alpha Omega Engineering, Nazareth, Israel) to isolate single units from the recording. The spike sorter proved to be the only way to identify with certitude small- or medium-sized spikes along the recording file and to be certain of the stability of the recordings. It also proved to be the only way to ensure that the results represented single-unit activity. Commercially available software (CED Spike 2 software; Cambridge Electronic Design, Ltd, Cambridge, England) was used to calculate the discharge frequencies. Recordings of the right and left cervical dorsal horn neurons in the 43 rats were obtained for a total of 115 single units collected. Sixty neurons were associated with the dorsal horn subjected to rhizotomy and 55 neurons with the healthy dorsal horn.

The mean frequency (in Hz) of the discharge of the two groups of neurons (healthy side compared with the side subjected to rhizotomy) were compared by means of an appropriate statistical test, with a two-tailed probability level lower than 0.05 considered to be significant. Analyses were made using appropriate software (Statworks; Cricket Software, Inc., Philadelphia, PA).

Experimental MDR

When autotomy occurred (three cases), which is an irreversible phenomenon, the rat was excluded from the study and killed immediately by means of a barbiturate overdose; no DREZ lesioning was performed in these animals. The rats that exhibited no self-mutilation (five cases) were obviously not subjected to DREZ lesioning. Moreover, eight rats that displayed signs of self-mutilation were not subjected to DREZ lesioning to ensure that these mutilations were not spontaneously reversible. Among the 27 remaining rats, 16 were subjected to MDR and 11 constituted a control group.

Surgical Procedures. Sixteen rats displaying at least one of the signs of self-mutilation were subjected to MDR. Three of these 16 rats died during surgery due to anesthesia problems and thus were excluded from the study. General anesthesia used during this procedure was the same as that used during the dorsal rhizotomy. After reopening the skin, muscles, and dural layers, the surgical procedure in the right DREZ consisted of a microincision extending from the C-5 to T-1 levels along the deafferented dorsolateral sulcus into the DREZ and the dorsal horn, oriented 35° ventrally and medially at a depth of 1 mm inside the right posterolateral sulcus. This microincision was made with the aid of a surgical microscope by using a razor blade and microscissors that mechanically destroyed the dorsal horn. Because of the small size of the rat's spinal cord, coagulation by either radiofrequency thermocoagulation or bipolar forceps was not performed to avoid widespread lesions outside the DREZ or the dorsal horn. The dura mater was then closed using the same synthetic graft as that used in the first rhizotomy operation, and the wound was again closed in layers.

A control group of 11 rats that also displayed similar signs of self-mutilation was selected to undergo a sham operation. The sham operation involved a similar induction of anesthesia; followed by a simple reopening of the skin, muscles, and dura, with no DREZ lesioning; and a wound closure similar to that described earlier. The interval between the first observed sign of self-mutilation and MDR or sham operation was 12 weeks.

Behavioral Evaluation. Through biweekly observations, the clinical course of the 13 rats post-MDR was compared with that of the 11 that underwent sham operation. Postoperative conditions consisted of a status quo of the clinical signs (scraping and/or ulcerative lesions), a worsening of them, or a total resolution of them. The cure was considered to be a total resolution of all self-mutilations. With respect to the postoperative clinical course (cured or uncured), the group of rats that underwent MDR was compared with the group of sham-operated rats by calculating appropriate statistical tests with a two-tailed probability level of less than 0.05 considered to be significant. Analyses were performed using commercially available software (Statworks).

Electrophysiological Recordings. The electrophysiological conse-

quences of MDR were evaluated in the 13 rats by obtaining unitary recordings of the right dorsal horn and comparing them with the unitary activity of the left (healthy) dorsal horn. This recording session was performed at the end of the post-MDR follow up, just before killing the rat. These electrophysiological recordings were made using the same microelectrode and procedure as those for the postrhizotomy recording.

Histological Study. The cured rats were kept under observation for 8 additional weeks to ensure no recurrence of self-mutilations. The rats were then killed with an overdose of barbiturate agents, and the cervical medulla from each was removed for histological examination. After fixation with aldehydes, 50-μm-thick sections of the DREZ lesion were sliced with the aid of a freezing microtome. Sections were mounted on gelatin-coated slides and stained with cresyl violet. The slides were then examined using light microscopy to assess the accurate location and exact size of the lesion. Reconstructions of damaged areas were made using an overhead projector and a camera lucida. The criteria used in determining the boundary between intact and damaged tissue were based on the borders of parenchymal loss resulting from the mechanical effect of the DREZ lesioning surgery. In the 13 rats that underwent MDR the cervical medullae were removed and examined. The size of the DREZ lesion was compared between cured and uncured animals.

Results

Before MDR

Behavioral Evaluation. All rats exhibited total sensory loss in the right forelimb postrhizotomy, as assessed by the absence of any reaction to applied painful stimuli (strong pinches). The deafferented limb was not paralyzed in any of the animals, because all of them could use the limb for locomotion with apparent normal strength.

A total of 35 (81.4%) of the 43 rats inflicted self-directed mutilations. Among these 35 rats, the self-directed mutilations (Fig. 2) occurred as follows. There was scraping along a forearm dermatome contralateral to the site of MDR in 30 (85.7%) of 35 animals; it was isolated in 54.3% of the cases and associated with ulcerations in 31.4%. The scraping affected the shoulder (C-5 dermatome) in 13.3%, the forearm and thumb (C-6) in 56.6%, and the forelimb paw (C7–8) in 46.6%. Except for its appearance at the C-5 dermatome (shoulder), the scraping never reached a more proximal part of the upper limb than the forearm; that is, the elbow or arm was never affected. Scraping appeared a mean of 7 weeks after deafferentation (range 1–36 weeks, SD ± 7.2 weeks).

Ulceration was associated with edema of the forelimb digit in 13 (37.1%) of 35 rats. Note that ulceration itself always involved a single digit. The accompanying edema was limited to the digits or extended to the entire paw, but never reached the forearm. Distal ulceration and edema were associated with more proximal scraping in most cases (84.6%). Ulceration appeared a mean 3.5 weeks (range 1–11 weeks, SD ± 2.9 weeks) after deafferentation. When both scraping and ulceration were present, ulceration preceded scraping in all cases but one (91.6%) and appeared an average of 1.9 weeks before scraping.

Autotomy of the forelimb digits was observed in three (8.6%) of 35 rats. It was preceded by light edema of the forelimb paw in one case and was a sudden phenomenon in the other two cases. It involved one digit in one rat, two digits in another, and the entire forelimb paw in the third. Note that the forearm itself was never involved. Autotomy

TABLE 1

Postrhizotomy electrophysiological findings: mean frequency of spontaneous unitary activity of the deafferented dorsal horn neurons compared with that of the healthy dorsal horn neurons in 43 rats

Animal No.	Mean Frequency (Hz)	
	Nondeafferented Side	Deafferented Side
1	0.5	1.6
2	3.5	16.5
3	6.2	7
	0.8	18.9
4	16.1	48.6
5	53	59.4
6	18.7	53.2
7	24.8	48.6
	34.2	52.9
8	5.8	19.3
9	6.4	28.1
10	20.4	57.7
11	10.2	38.8
	20.1	31.4
12	3.9	6.1
13	12.1	48
14	2.1	45.8
15	28.9	5.9
	37.5	44.4
	25.3	36.7
16	34.6	15.8
	37.5	42.4
17	47.9	143.6
18	7.6	16.6
	not done	16.9
19	5.6	71.3
20	42.9	141.5
21	14.9	19.4
22	1.2	7.4
23	2.1	75.9
24	3	33.4
25	9.3	45.2
26	14.7	17.7
	17	27.3
27	18.9	50.6
28	4.2	62.9
29	65.1	81.9
30	6.9	22.1
31	3.1	20.4
32	1.2	7.1
33	11.7	8.3
	44.3	63.8
	not done	11.2
34	35	81.7
	2.1	64.3
35	10.3	23
	82.5	6.3
	not done	3.9
	not done	5.8
	not done	4.4
36	2	25.6
	0.4	8.1
37	0.5	31.4
38	8.1	15.3
39	29	38.8
	3.5	44.2
40	31.1	64.9
41	11.3	13.6
42	7.2	19
43	40	60.9
total no. of recordings	55	60
mean value	17.9 ± 18.1	36.4 ± 29.8

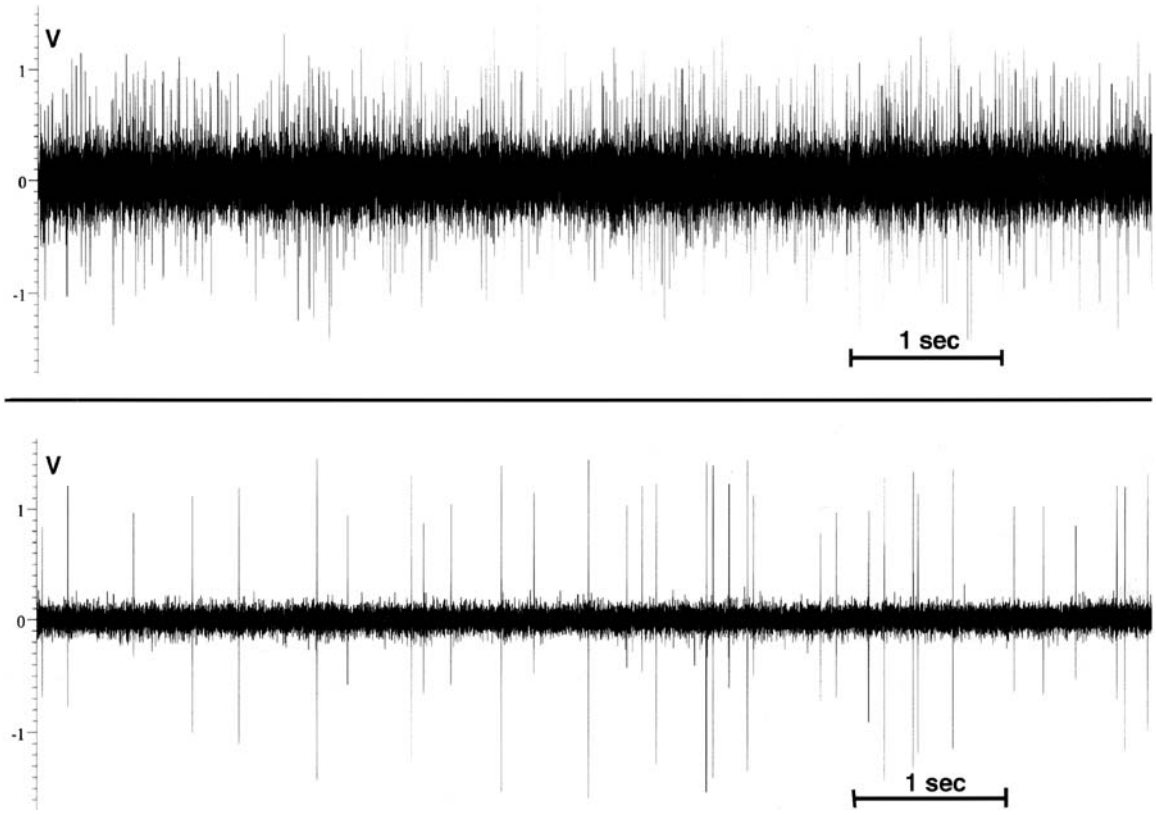

FIG. 4. Electrophysiological recordings of spontaneous single-unit activity of deafferented dorsal horn neurons (right C-7, *upper*), compared with nondeafferented ones (left C-7, *lower*). The deafferented dorsal horn neurons tend to display a significantly higher spontaneous firing rate than the nondeafferented ones.

appeared a mean 6.5 weeks (range 2–13 weeks, SD ± 5.7 weeks) after deafferentation.

On average, all clinical signs appeared a mean 5.7 weeks (range 1–36 weeks, SD ± 6.6 weeks; Fig. 3) after deafferentation. No spontaneous resolution of the signs of self-mutilation appeared before DREZ lesioning. No spontaneous resolution of the signs of self-mutilation appeared in the group of eight rats that did not undergo DREZ lesioning.

Electrophysiological Data. One hundred fifteen single units were recorded: 60 neurons were associated with the dorsal horns subjected to rhizotomy and 55 neurons with the healthy dorsal horns. All cells in the healthy dorsal horn responded to somatic stimulation during recording, whereas none in the deafferented C-7 level of the dorsal horn did. The spontaneous firing rate was the only parameter considered to be relevant in this study, so that the response modalities and receptive fields of the neurons in the healthy dorsal horn were not investigated further. Spontaneous activities (mean frequency of the discharge) of these 115 neurons are summarized in Table 1. Some samples of deafferented and nondeafferented neuron recordings are demonstrated in Fig. 4. The mean frequency of spontaneous discharge in the deafferented dorsal horn neurons was 36.4 ± 29.8 Hz (± SD), compared with 17.9 ± 18.1 Hz (± SD) in the nondeafferented dorsal horn neurons ($p = 0.03$, t-test).

After MDR

Behavioral Evaluation. Among the 13 rats that successfully underwent MDR, nine (69.2%) displayed complete resolution of scraping and/or ulceration of the forelimb paw (Fig. 5). The mean time for total reversal of clinical signs was 4.6 weeks (range 3–9 weeks, SD ± 1.8; Fig. 6) after MDR, with no recurrence in the following 2 months (postcure follow up 8 weeks). The time required for the disappearance of signs was the same for scraping and ulceration. The resolution of the signs was always so fast that a complete cure could be achieved in less than 2 weeks. Among the four uncured animals, one was followed for 29 weeks without observed improvement. This animal was killed as soon as we noted a worsening of the ulceration. The other three rats had to be killed rapidly (1, 3, and 4 weeks after MDR) because they showed autotomous behavior.

Among the 11 rats that underwent sham operations, only one displayed a spontaneous resolution of the clinical signs. In that animal, the clinical signs (ulceration of the forelimb paw) appeared 2 weeks postrhizotomy and completely disappeared 11 weeks after sham operation. The animal was killed 12 weeks after complete disappearance of the ulceration. The mean duration of follow up after sham operation was 15 weeks (range 3–43 weeks).

Data from this study shows that MDR led to the reversal of signs of self-mutilation (considered to be, at least partially, a clinical expression of deafferentation pain) in 69.2% of the rats. The group treated using MDR had statistically significant positive effects compared with those that underwent sham operation ($p = 0.01$, Fisher test).

Electrophysiological Findings. For each animal, five to 10

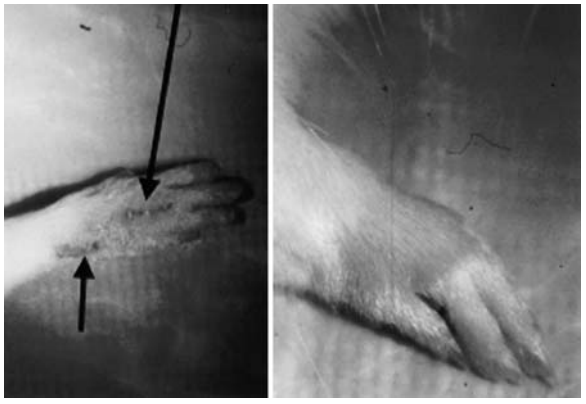

FIG. 5. Photographs illustrating evidence of complete cure. *Left:* Before MDR, there was scraping of the forearm *(arrows). Right:* Five weeks after MDR, the forearm skin recovered and regained a normal aspect, indicating a complete cure.

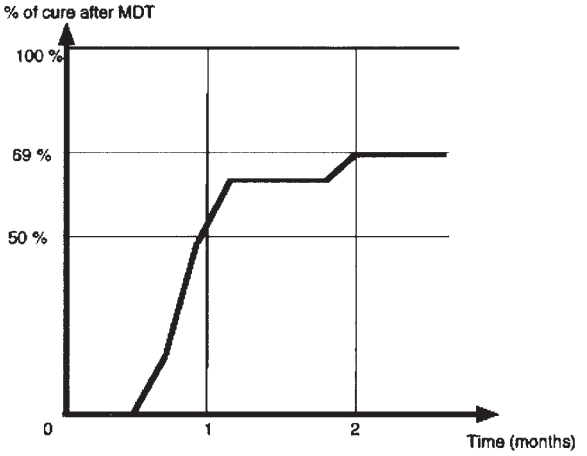

FIG. 6. Graph depicting the time course of complete cure after MDR.

trials were completed at the right C-7 level to record post-MDR unitary activity of the deafferented dorsal horn neurons. The microelectrode was left in place during several minutes for each trial. No single-unit activity could be recorded in the right dorsal horn of any of the rats that underwent MDR and, in fact, all attempts resulted in a flat signal, signifying the lack of any spontaneous unitary activity.

Histological Findings. In all cases morphological changes consisted of a sharply delineated lesion extending from the Lissauer tract to the neck (Rexed lamina V–VI) of the dorsal horn. The lesion was always triangular, with an upper base and a deep, medially oriented apex. The base of this triangular lesion could be variable in size, so that a narrow band of the lateral portion of the dorsal horn was left in place in many cases. The apex was always located at a constant depth from the surface of the spinal cord (1 mm). Lesions consisted of mainly neuron cell body loss, which was due to the mechanical action of the MDR, surrounded by a light gliosis. Surrounding white matter was intact in all cases. The base of the dorsal horn, the ventral horn, and the contralateral side were also intact in all cases. There was no obvious difference in the topography and size of the DREZ lesion, comparing those in cured and uncured rats. There was no particular sparing of some dorsal horn areas in uncured animals compared with those in cured ones (Fig. 7).

Discussion

Our work in the rat demonstrates the efficacy of lesioning the spinal dorsal horn for reversing the manifestations of self-mutilation induced by cervical posterior rhizotomies ($p < 0.01$). This is the first experimental study of the effects of MDR in an animal pain model specifically intended to be approximate to what occurs in humans after BPA, with a special focus on long-term clinical follow up before and after MDR. This latter element constitutes the main difference in the study by Rossitch, et al.,[37] who performed DREZ lesioning in the rat along with the simultaneous removal of the C-5 to T-2 dorsal root ganglia. Their results indicated an attenuation and a delayed onset of self-mutilations when ganglionectomies were performed with DREZ lesioning.

Choice of the Animal Model

To focus on the chronic deafferentation pain syndrome, we chose to use the rat model of cervical posterior rhizotomy as initially described by Basbaum[5] and further developed by Lombard, et al.,[24] in an attempt to mimic the pathological situation resulting from a posttraumatic BPA in humans. The validity of this animal model with regard to this purpose is supported by much evidence.

With respect to morphological criteria, BPA results in an interruption of the primary afferent pathway between the dorsal root ganglion and the dorsal horn. It thereby constitutes a deafferentation, as does posterior rhizotomy. The only morphological difference between the rat model and posttraumatic BPA in humans is the absence, in the model, of intraspinal gliosis and/or microcystic cavities that sometimes occurs in BPA in humans.[27]

With respect to clinical data, it appears that the incidence of early pain in humans is reported to be as high as 90% following BPA.[33] Fortunately, the condition of some patients who develop early pain syndromes improves with time.[30]

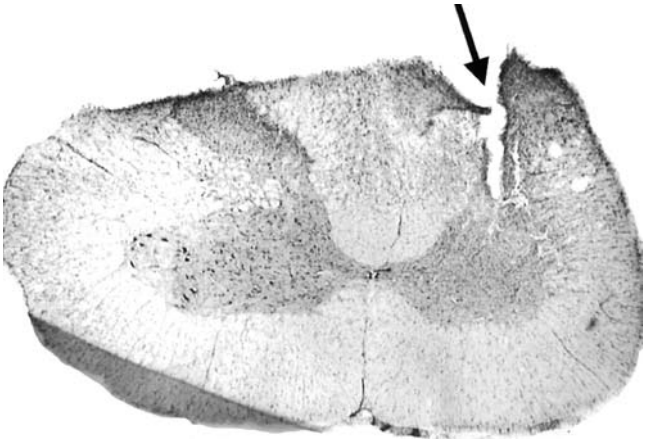

FIG. 7. Photomicrograph exhibiting a histological section of the spinal cord (50-μm horizontal slice) post-MDR displaying a selective lesion involving the right dorsal horn and DREZ *(arrow).*

Pain persists in approximately one third of patients for longer than 3 years.[32,33] In our experiment, 81.4% of the rats displayed at least one manifestation of self-directed mutilation after dorsal rhizotomy, which is comparable with the incidence of early pain in humans suffering from BPA. This incidence is also similar to that reported in most papers dealing with autotomous behavior induced by primary afferent pathway lesions.[2,4–8,10,11,22–24] The question has been raised for a long time whether these self-mutilations are due to the neuropathic pain itself or to sensory and/or trophic disturbances created by peripheral nervous system dysfunction. It is now well accepted,[4,11,48,50] despite previous controversy, that these signs—namely, scraping, ulceration (due to light biting), and autotomy—can be considered to be clinical signs of pain, rather than trophic manifestations or even a random behavior of the rat against its useless limb. Furthermore, note that compulsive self-injurious behaviors can sometimes be observed in humans with neuropathic pain.[25] Consequently, the self-directed mutilations described in this report are regarded with certitude as an indication of chronic neuropathic pain, and their post-MDR disappearance are considered to be indicative of a cure.

With respect to neurophysiological data, unitary recordings of the spontaneous activity of the dorsal horn neurons subjected to rhizotomy were obtained in our experiment, with the aim of ascertaining the nature of the electrophysiological modifications in the dorsal horn caused by deafferentation. Indeed, data from previous electrophysiological studies[3,6,8,11,17,22,23,28,31] showed the presence of a higher firing rate of the deafferented dorsal horn neurons, compared with that of the nondeafferented side. In most publications this has been called "deafferentation hyperactivity".[47] Our results, before MDR, coincide with such a deafferentation hyperactivity. Similarities between this deafferentation hyperactivity and a kind of epileptogenic activity was emphasized by Ward, who suggested a causal relationship between the rate decrease in synaptic inputs and the autonomic hyperactivity of the second-order neuron. Whatever the mechanism resulting in a higher firing rate of the deafferented dorsal horn neurons, the subsequent neuropathic pain is supposed to originate mainly from such hyperactivity.[4,10]

Consequences of DREZ Lesioning

This study demonstrates the clinical efficacy of DREZ lesioning in an animal model of deafferentation pain due to cervical posterior rhizotomy. We showed that MDR can provide a complete cure of the manifestations of self-mutilation in 69% of the rats in this study, which is very different from the rate of cure achieved in the sham-operated ones ($p < 0.01$).

Similar results are reported in most of the series dealing with DREZ lesioning after BPA in humans.[14,16,49] Nashold and Ostdahl[29] reported long-term pain relief of more than 75% in 56% of the cases studied. The rate of good results was 87% in the series conducted by Dreval,[12] 68% in the series of Thomas and colleagues,[44,45] 63% in the series of Samii and colleagues,[38] and 67% in our group.[13,40] The similarities between our results and those from other clinical series support the role of the DREZ and the dorsal horn as surgical targets in cases of deafferentation pain.

To our knowledge, post-MDR unitary recordings of the deafferented dorsal horn have never been reported in the literature. Because of the destruction of the major part of the dorsal horn, we found no sign of unitary activity in the dorsal horn of the 13 rats post-MDR. This lack of activity can partially be explained by the severe anatomical conditions of the spinal cord during the third and last reoperation. Regardless, it provides a supplementary argument in favor of a relationship between neurophysiological hyperactivity and pain.

Our post-MDR histological findings were very similar among the 13 studied cases, with no noticeable sparing of some dorsal horn areas in the uncured animals and with no spinal cord damage from the dorsal horn. In every case, a major portion of the dorsal horn was found to be destroyed, including, as reported in previous clinical papers,[19,26,36] the tract of Lissauer, the substantia gelatinosa, and the dorsal horn neurons of the Rexed layers I to V-VI. Considering the lack of correlation between the anatomical extent of the lesion and the results, the possible explanation for the failures of MDR procedures, in animals as well as in humans, seems to be the possible involvement of the thalamus, as mentioned in some previous works.[1]

Conclusions

This study validates the use of the animal model, previously developed by Lombard, et al.,[24] of chronic neuropathic pain resulting from cervical posterior rhizotomy as a paradigm of deafferentation pain from BPA.

The ability of the DREZ lesioning of the deafferented dorsal horns of the rats to alleviate the signs of deafferentation pain completely in 69% of the cases supports the role of the dorsal horn in deafferentation pain.

Such a model of DREZ lesioning may also prove useful in further studies to understand better the deafferentation pain syndrome mechanisms and to identify the causes and solutions of MDR failures.

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