Single-Unit Analysis of the Spinal Dorsal Horn in Patients With Neuropathic Pain

*†Marc Guenot, ‡Jean Bullier, §Jean-Pierre Rospars, |Petr Lansky, *Patrick Mertens, and *Marc Sindou

Department of Functional Neurosurgery, P. Wertheimer Hospital, Lyon, France; †INSERM U 371 (National Institute for Health and Medical Research), Bron, France; Institut Federatif de Neurosciences de Lyon, France; ‡Centre de Recherche Cerveau et Cognition, Université Paul Sabatier, Toulouse, France; §Unite de phytopharmacie et mediateurs chimiques, INRA, Versailles, France; and |Academy of Sciences, Prague, Czech Republic

Summary: Despite the key role played by the dorsal horn of the spinal cord in pain modulation, single-unit recordings have only been performed very rarely in this structure in humans. The authors report the results of a statistical analysis of 64 unit recordings from the human dorsal horn. The recordings were done in three groups of patients: patients with deafferentation pain resulting from brachial plexus avulsion, patients with neuropathic pain resulting from peripheral nerve injury, and patients with pain resulting from disabling spasticity. The patterns of neuronal activities were compared among these three groups. Nineteen neurons were recorded in the dorsal horns of five patients undergoing DREZotomy for a persistent pain syndrome resulting from peripheral nerve injury (i.e., nondeafferented dorsal horns), 31 dorsal horn neurons were recorded in nine patients undergoing DREZotomy for a persistent pain syndrome resulting from brachial plexus avulsion (i.e., deafferented dorsal horns), and 14 neurons were recorded in eight patients undergoing DREZotomy for disabling spasticity. These groups were compared in terms of mean frequency, coefficient of variation of the discharge, other properties of the neuronal discharge studied by the nonparametric test of Wald–Wolfowitz, and the possible presence of bursts. The coefficient of variation tended to be higher in the deafferented dorsal horn group than in the other two groups. Two neurons displaying burst activity could be recorded, both of which belonged to the deafferented dorsal horn group. A significant difference was found in term of neuronal behavior between the peripheral nerve trauma group and the other groups: The brachial plexus avulsion and disabling spasticity groups were very similar, including various types of neuronal behavior, whereas the peripheral nerve lesion group included mostly neurons with "nonrandom" patterns of discharge (i.e., with serial dependency of interspike intervals). **Key Words:** Spinal dorsal horn—Unitary recordings—Neurosurgery—Microelectrode—Neuropathic pain.

The role of the spinal dorsal horn in the modulation of pain sensation has been established for a long time (Barron and Matthews, 1935; Eccles et al., 1961; Frank and Fuortes, 1955, 1956; Melzack and Wall, 1965), suggesting that its dysfunction may be the cause of some chronic pathologic pain syndromes. Electrophysiologic recordings of neurons have been performed in the dorsal horn of spinal cords of cats and rats (Albe–Fessard and Lombard, 1983; Anderson et al., 1971; Basbaum and Wall, 1976; Brinkhus and Zimmermann, 1983; Kjerulf and Loeser, 1973; Kjerulf et al., 1973; Lombard et al., 1979), leading to a characterization of different patho-

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logic situations in terms of spiking patterns of single neurons. In the case of deafferented pain (i.e., interruption of the primary afferent pathway between the dorsal root ganglion and the spinal cord), most of these results provide evidence for higher spontaneous firing rates of dorsal horn neurons, often associated with an irregular "burst" activity. For instance, Loeser and Ward (1967) performed dorsal rhizotomies in 17 cats and recorded unitary activities in the corresponding segments of the dorsal horn, comparing these unitary activities with those obtained in 20 normal cats. This pioneering study found major hyperactivity in the deafferented neurons when compared with the nondeafferented ones. For Loeser and Ward (1967), Rexed's layers V, VI, and VII were mostly concerned, and the hyperactivity (first observed 14 days after dorsal rhizotomy) lasted as long as 177 postoperative days at a minimum. These data were later confirmed and specified by several other authors (Albe–Fessard and Lombard, 1983; Albe–Fessard et al., 1985; Bennet, 1994; Lombard and Larabi, 1983; Lombard et al., 1979). It is noteworthy, however, that this hyperactivity was seen mostly during the acute period only, and it tended to decrease with time over several months in the deafferented dorsal horn while increasing during the same period in more central structures of the nociceptive pathways, such as the thalamus and the cortex (Albe–Fessard and Lombard, 1983).

In this context, one would expect to observe high firing rates in the dorsal horns of patients with deafferented pain syndromes. However, such unitary recordings have been performed very rarely. The first case of unitary recording of the dorsal horn in humans was reported by Loeser et al. (1968). It concerned a single patient, operated for a chronic pain syndrome after an L1 level spinal trauma. Hyperactivity was found in three neurons at the T12 level, but no quantification of this hyperactivity was provided. In 1989, Jeanmonod et al. (1989), from our group, performed, on the occasion of therapeutic DREZotomy (i.e., surgical therapeutic lesion of the DREZ [dorsal root entry zone] and dorsal horn), unitary recordings of the dorsal horn in four patients. Two of them were operated for neuropathic pain: The first patient had a brachial plexus avulsion and the second patient had a cauda equina lesion resulting from a gunshot. The recordings obtained in these two patients were compared with the activity of the dorsal horn neurons in the two other patients undergoing DREZotomy for excess of spasticity. A tendency to "deafferentation hyperactivity" was also found in this work, without any burst pattern however.

These studies in humans involved only a few neurons (three neurons in the first study, seven neurons in the second). Such small samples made it impossible to perform any statistically valid comparison between the different groups of patients. For this reason we decided to investigate a greater number of human dorsal horn neurons. The goals were to assess, for the first time, a large sample of single units, regardless of whether abnormal patterns were recordable, and then to distinguish a possible difference, in terms of a spiking pattern, between various pathologic states. Thus, we compared the neuronal activities of the dorsal horns of patients with deafferented pain resulting from brachial plexus avulsion (AVUL group) or from neuropathic pain resulting from peripheral nerve injury (PERIPH group), and a control group (i.e., a group of patients with no pain) corresponding to disabling spasticity (SPAS group).

MATERIAL AND METHODS

Patients

Twenty-two patients were the subjects of intraoperative dorsal horn unitary recordings during microsurgical DREZotomy (MDT) for pain or spasticity. They were 15 men and 7 women, with a mean age of 45 years (range, 28 to 79 years). The study was approved by the local ethics committee because the recording sites in the dorsal horns were bound to be destroyed by the surgical procedure. All the subjects participated on a voluntary basis and provided informed consent.

The patients constituted three groups. A first group of five patients (PERIPH group) underwent MDT for persistent neuropathic pain resulting from peripheral nerve injury. The dorsal horns of these patients were considered nondeafferented dorsal horns, as all lesions were distal to the dorsal root ganglion. The second group of nine patients (AVUL group) underwent MDT for a persistent pain syndrome resulting from brachial plexus avulsion (i.e., a group with deafferented dorsal horns). In the third group of eight patients (SPAS group), MDT was performed for disabling spasticity. These patients had nondeafferented dorsal horns and were considered a control group because they had no pain symptoms. The clinical status of each patient is given in Table 1.

The peripheral nerve injuries were from various origins (see Table 1). The mean age of the patients in the PERIPH group was 42 years (range, 29 to 69 years). The cause of brachial plexus avulsion was a motorbike accident in six patients, a traffic accident in two patients, and a skiing accident in one patient. The trauma resulted in a total avulsion in four patients (from C5 to T1), concerned C7 to T1 in two patients, C5 to C7 in one patient, C6 to T1 in one patient, and C6 to C8 in the last patient. The

TABLE 1. *Summary of clinical data*

Patient no.	Age, y	Gender	Etiology	Delay, y	Extent of DREZotomy	VAS[†] score, points	
						Preoperative	Postoperative
1	34	M	N. plantaris I.	6	S1–S2 left	9	1
2	38	M	N. occipitalis I.	10	C1–C3 right	4	3
3	29	M	N. plantaris I.	1.5	S1–S2 left	10	10
4	41	M	N. ulnaris I.	9	C8–T1 left	7	7
5	69	F	Upper limb crush	2	C5–T1 left	7	4
6	33	M	Br. pl. avulsion	5	C5–T1 left	4	1
7	30	F	Br. pl. avulsion	2	C7–T1 left	8	2
8	31	M	Br. pl. avulsion	10	C5–C7 left	7	0
9	32	M	Br. pl. avulsion	4	C5–T1 left	7	7
10	49	F	Br. pl. avulsion	2	C6–T1 left	7	4
11	29	M	Br. pl. avulsion	11	C6–C8 left	8	8
12	66	M	Br. pl. avulsion	11	C5–T1 right	10	5
13	79	M	Br. pl. avulsion	5	C5–T1 left	7	0
14	36	M	Br. pl. avulsion	4	C5–C7 right	8	3
15	35	M	Multiple sclerosis	17	L2–S4 bilat	—	—
16	53	M	Multiple sclerosis	13	L2–S3 bilat	—	—
17	56	F	Multiple sclerosis	29	L1–S4 bilat	—	—
18	45	F	Multiple sclerosis	9	L2–S3 bilat	—	—
19	45	M	Multiple sclerosis	27	L2–S4 bilat	—	—
20	34	F	Multiple sclerosis	9	L2–S4 bilat	—	—
21	42	M	Cerebral anoxia	2	L2–S4 bilat	—	—
22	51	F	Multiple sclerosis	17	L1–S4 bilat	—	—

* Delay in years between trauma (or onset of disease) and surgery.

[†] Visual analog scale. A 10-cm line is anchored at one end by a label such as "no pain" and at the other end, "worst possible pain." The patient indicates on the line the spot of his pain intensity.

M, male; N., Nervus; I., Injury; Br. pl., brachial plexus; DREZ, dorsal root entry zone; bilat, bilateral.

mean age of patients in the AVUL group was 43 years (range, 29 to 79 years). Spasticity resulted from multiple sclerosis in seven patients and from cerebral anoxia in one patient. The mean age of the patients in the SPAS group was 45 years (range, 34 to 56 years).

The mean delay between injury (or onset of the disease) and surgery was 5.7 years (range, 1.5 to 10 years) in the PERIPH group, 6 years (2 to 11 years) in the AVUL group, and 15 years (2 to 29 years) in the SPAS group.

The main features of the chronic pain syndrome of the AVUL group were continuous pain with additional paroxysmal crises. The continuous component was of burning type in all patients. There was no allodynia, except in the proximal regions of the upper limb. The dermatomas that depended on avulsed roots had a total sensory loss in all patients. In the PERIPH group, continuous pain with additional paroxysmal crises was also present in all patients. The sensibility changes of the skin territory depending on the injured nerve were constant. It was tactile and thermal hypoesthesia in all patients, associated with mechanoallodynia in three patients. The intensity of pain was measured using a visual analog scale. The preoperative mean score was 7.6 points in the

PERIPH group (5.1 points postoperatively) and 7.3 points in the AVUL group (3.3 points postoperatively).

All patients underwent the same operation—namely, MDT (as described in detail in previous publications [Sindou, 1995; Sindou and Mertens, 1992; Sindou et al., 1974, 1990])—regardless of the etiology: persistent pain (with or without deafferentation of the dorsal horn) or disabling spasticity. The surgical access to the DREZ and the dorsal horn gave the opportunity to have direct access to the spinal dorsal horn to perform unitary recordings.

Methods

The unitary recordings were obtained by means of a specially designed floating, double microelectrode, which has been described in detail previously (Guenot et al., 1999).

During each surgical procedure, the double microelectrode was implanted "free hand," using the surgical microscope, in the dorsal horn (Fig. 1), by means of a simple microsurgical bipolar forceps. The penetration depth of the microelectrode was 4 mm, which is the minimal required depth to obtain stability of the microelectrode. The electrode is floating so it is assumed that
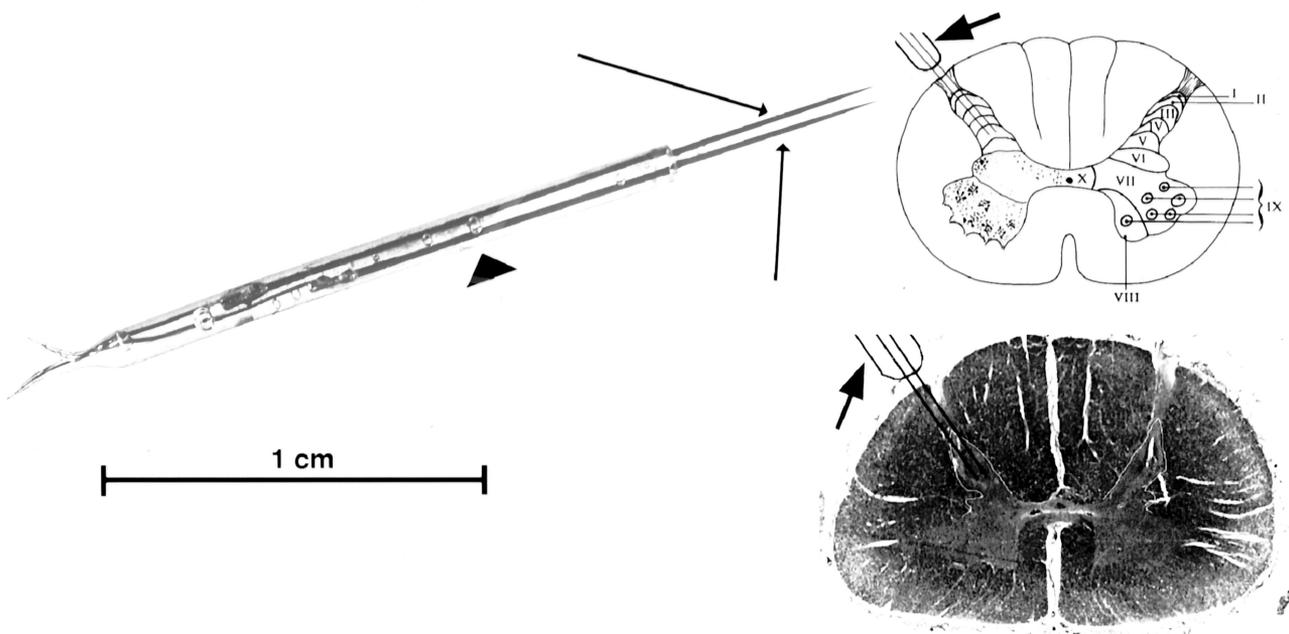
FIG. 1. (**Left**) Photograph of the floating double microelectrode designed for unitary recordings of the human spinal dorsal horn neurons. The arrows indicate tungsten in glass microelectrodes, glued together in a rigid nylon sleeve (**arrowhead**) filled with silicon rubber. The two independent tips are separated by 300 μm. (Photograph by J. P. Borach.) (**Upper right**) Schematic drawing of the dual microelectrode (**arrow**) after implantation in the dorsal horn (roman numerals, Rexed's layers). (**Lower right**) Schematic drawing of the dual microelectrode (**arrow**) after implantation, superimposed on a histologic slice of the spinal cord.

the depth remains constant during the recording period. All the operations were performed with the patient under general anesthesia (continuous intravenous perfusion of propofol 3 to 6 mg/kg per hour, in association with ketamine 0.5 mg/kg per hour). The electrode was implanted just before the MDT was performed. The signal was recorded on a digital cassette recorder (Cygnus Technology Inc., Delaware Water Gap, USA) for further off-line analysis. The data analysis was performed by means of a spike sorter (Alpha Omega MSD; Alpha Omega Engineering, Nazareth, Israel) used to isolate single units from the recording. The spike sorter proved to be the only way to identify with certainty small or medium-size spikes in the recording file, and to be certain of the stability of the recordings, thus ensuring that the results do represent single-unit activity (Fig. 2). CED Spike 2 software (Cambridge Electronic Design Ltd., Cambridge, UK) was used to calculate the discharge frequencies and the interspike intervals (ISIs).

Statistical Analysis

The three groups were compared statistically with reference to three characteristics: mean frequency, coefficient of variation, and neuronal behavior.

The mean frequency of the discharge, in Hertz, was obtained by calculating the inverse of the value of the mean ISI of each recording file.

The coefficient of variation of the discharge was defined as the ratio of the standard deviation to the mean of the ISIs of a recording file. The coefficient of variation is a meaningful measure of the specific variability of a neuronal discharge. It can be interpreted as a normalized standard deviation. This quantity can be applied to the "random" category only, because in this case mean and standard deviation do not vary in time.

Other qualitative properties of the neuronal discharge were characterized by the results of the nonparametric test of Wald–Wolfowitz (Wald and Wolfowitz, 1943). This test detects some type of "memory" or "order" in the discharge in contrast with complete randomness. It is able to reveal a trend in the length of ISIs, and consequently in the firing frequency. When the result of the test is not significant, the neuronal discharge can be considered devoid of any significant trend, which means that ISIs are distributed independently and identically. The principle of this test is the following: The ISI values found in a unitary discharge are divided in two groups: + if they are above the value of the median of all ISIs and − otherwise. The sequences of + and − signs is then

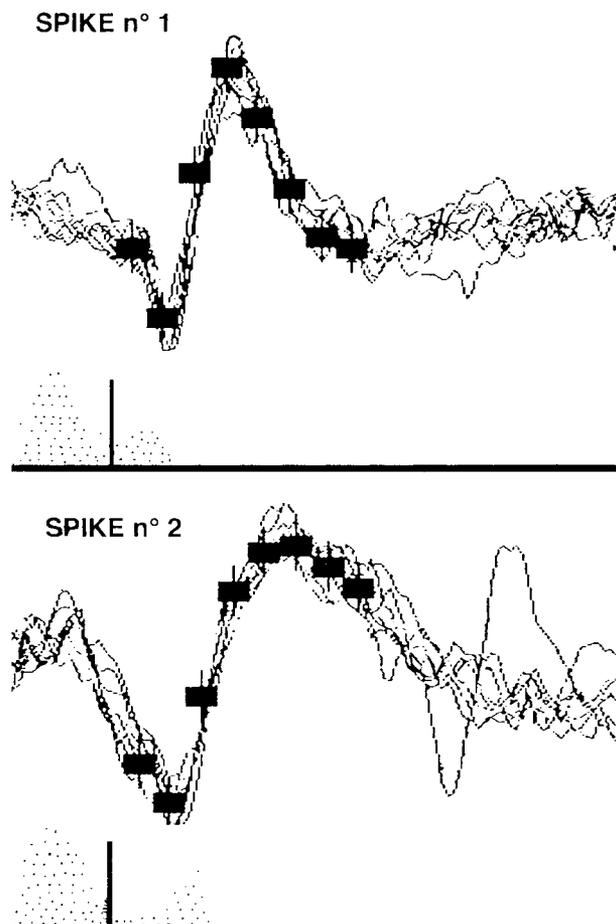## SPIKE n° 1

SPIKE n° 2

FIG. 2. Spike sorting. Example of discrimination between two different spikes recorded on the same tip, as displayed by the Spikes Sorter (MSD Alpha Omega Ltd.). As a first step, a spike template is defined for events corresponding to the signal crossing above a threshold level. Then, every waveform compatible with this template is recognized as a spike. For each spike, the Spike Sorter gives a time stamp and calculates the sum of squares of the differences between the template and the waveform. Below the spikes are presented the histograms of the sums of squares of differences between the templates and the waveforms for many repetitions of the same spike. When the spike cannot be isolated, the histogram has a continuous unimodal shape. When the isolation is good, an isolated mode separated from the rest of the histogram is observed (humps at the left of the vertical bar). This allows one to isolate with certainty single-unit activity from multiunitary recordings.

analyzed. Two possibilities can occur. In the first, +'s are mostly in the first half of the recording file and −'s are in the second half, or vice versa, indicating the presence of an organized pattern of ISIs. This neuronal behavior is termed "nonrandom." In the second eventuality, the + and the − are distributed randomly, without any tendency or regularity, in which case the neuronal behavior is termed "random."

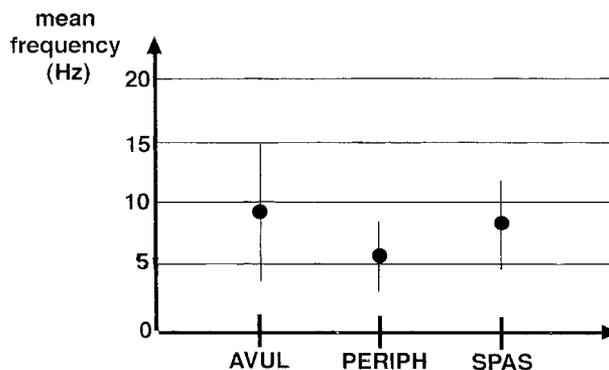With respect to these characteristics (mean frequency,

FIG. 3. Histogram of mean frequencies (in Hertz) of discharge according to pathology. Bars represent standard deviation.

coefficient of variation, and neuronal behavior), the three groups of patients were compared by means of appropriate statistical tests with a two-tailed design, and $P < 0.05$ was considered significant. Analyses were performed with SyStat version 7.

Additionally, a last parameter was taken into account—namely, the presence of "bursts" in the recording file. A burst was defined by the occurrence of more than three spikes in 10 msec.

RESULTS

A total of 64 stable and well-isolated neurons were recorded in the 22 patients: Nineteen neurons were recorded in the PERIPH group, 31 dorsal horn neurons were recorded in the AVUL group (deafferented dorsal horns), and 14 neurons were recorded in the SPAS group.

The mean frequency of the discharges (inverse of the mean value of the ISIs of each group) was (Fig. 3) 9.1 Hz in the AVUL group (range, 2.7 to 66.6 Hz; standard deviation [SD], 11.1 Hz), 5.8 Hz in the PERIPH group (range, 2.6 to 76.9 Hz; SD, 5.1 Hz), and 8.3 Hz in the SPAS group (range, 1.6 to 38.5 Hz; SD, 6.7 Hz). There was no significant difference between the different groups in term of mean frequency of the discharge ($P = 0.7$, Kruskal–Wallis test).

The mean coefficient of variation of the discharge of the "random" neurons was 1.06 in the AVUL group (SD, 0.65), 0.87 in the PERIPH group (SD, 0.84), and 0.73 in the SPAS group (SD, 0.59). This is shown in Fig. 4. The coefficient of variation tended to be higher in the deafferented dorsal horn group than in the two other groups, but this was not significant ($P = 0.4$, analysis of variance).

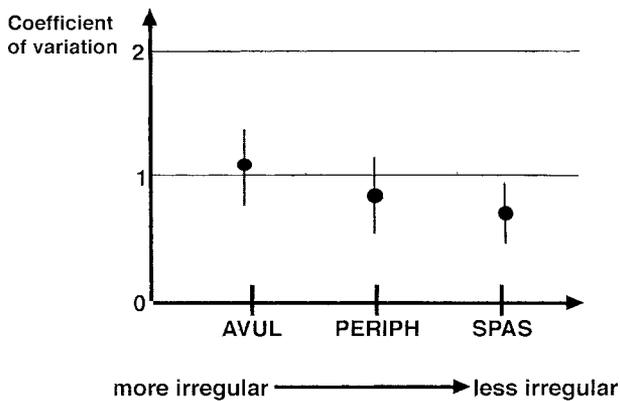The results of the Wald–Wolfowitz test are shown in

FIG. 4. Coefficient of variation of the discharge of the "renewal" neurons according to pathology. Bars represent standard deviation.

Table 2. This table displays a significant difference in terms of the proportion of the different types of neuronal behavior between the PERIPH group and the other two groups. Indeed, the AVUL and SPAS groups are very similar, including a similar number of random and nonrandom neurons. They contrast with the PERIPH group, which includes mostly neurons with a nonrandom behavior ($r = 10.7$, $P = 0.03$; χ^2 test).

Two neurons, recorded in two different patients, and displaying a typical burst activity according to our definition were found. Both of them belonged to patients in the AVUL group.

DISCUSSION

Using the special microelectrode we developed previously, we were able to collect in quite good intraoperative condition 64 unitary recordings in three different groups of human dorsal horn neurons.

Although not significant, some signs in favor of deafferentation hyperactivity were found in the deafferented dorsal horn neurons (AVUL group)—namely, a trend toward more irregular and burst discharges. Furthermore, the discharge pattern of the dorsal horn neurons of

TABLE 2. *Results of the Wald–Wolfowitz test according to the groups of pathologies*

Randomness	AVUL	SPAS	PERIPH
Random, %	55	57	16
Nonrandom, %	45	43	84
Total, %	100	100	100

$P = 0.03$, χ^2 test.
AVUL, brachial plexus avulsion group; SPAS, spasticity group; PERIPH, peripheral nerve injury group.

patients operated for peripheral nerve injury showed a more nonrandom activity when compared with the other groups, and the latter result is the only one that is significant.

The failure to find a significantly higher firing rate in the deafferented dorsal horns is in contrast to what has been reported in many animal experiments (Anderson et al., 1971; Basbaum and Wall, 1976; Bennet, 1994; Brinkhus and Zimmermann, 1983; Dalal et al., 1999; Kjerulf and Loeser, 1973; Loeser and Ward, 1967; Lombard and Larabi, 1983; Lombard et al., 1979; Pubols and Goldberger, 1980). These authors performed various types of posterior rhizotomies, resulting in an interruption of the primary afferent pathway between the dorsal root ganglion and the dorsal horn. It thereby constituted, by definition, a deafferentation, similar to what brachial plexus avulsion does in humans. They demonstrated a higher firing rate of the deafferented dorsal horn neurons compared with the nondeafferented ones. Similarities between deafferentation hyperactivity and a kind of epileptogenic activity were emphasized by Ward (1972), who suggested a causal relationship between the rate decrease in synaptic inputs and the autonomic hyperactivity of the second-order neuron. The exact mechanisms of this hyperactivity is supposed to be the result of interactions between postsynaptic membranes and the glia, resulting in a decrease of the potassium gradient and leading to a strong enough depolarization to create repeated discharges. Fujioka et al. (1992), using spinal cord potential recordings during DREZotomies, demonstrated decreased descending inhibition after deafferentation. Nakata et al. (1979) support the hypothesis of changes in the neurochemical processes of the dorsal horn as the cause of deafferented pain.

We provide several possible explanations for the lack of manifestation of deafferentation hyperactivity in our study:

First, because of the relatively large tip of our microelectrode, it is likely that our recordings favored large-size wide dynamic range neurons. Thus, our recordings may have been biased toward neurons showing less activity than smaller neurons that may have been recorded in some other animal studies.

Second, it is possible that the anesthetic constraints of the recordings may cause a decrease in the basic spontaneous neuronal activity (Kishikawa et al., 1995). Indeed, one could argue that the use in our study of ketamine as an anesthetic agent may have suppressed possible hyperactivity because it is a noncompetitive NMDA-receptor antagonist (Nikolajsen et al., 1996). Whatever the role of anesthetic conditions, they cannot,

for obvious ethical reasons, be modified deeply in humans, contrary to what can be done in animals.

Third, the duration of the intraoperative recordings never exceeded a few minutes because we had to avoid, for ethical reasons, lengthening the surgical operation.

Lastly, and probably more importantly, the delay between the brachial plexus avulsion and the time of surgery, ranging from 2 to 11 years (average: 6 years), may constitute another explanation for the lack of hyperactivity, because supraspinal structures may have become involved in the genesis of a chronic pain syndrome (see Albe–Fessard et al. [1985] and Rinaldi et al. [1991] for review). In the rat, this supraspinal involvement consists mostly of an epilepticlike activity composed of a train of rhythmic, 10-Hz slow waves accompanied by numerous bursts, appearing in the ventralis posterior thalamic nuclei in the months after deafferentation. This supraspinal involvement may have contributed to some extent to the poor clinical result of some DREZotomies, and could explain the satisfactory results that can be obtained with thalamic procedures (Gybels and Tasker, 1999; Gybels et al., 1993) or cortical precentral stimulation (Mertens et al., 1999).

The only significant result of our study is that the dorsal horn neurons of patients operated for a chronic pain syndrome resulting from a peripheral nerve trauma (section or crush) tend to have a nonrandom activity, in contrast with patients in the other two groups, whose neuronal activities are more random. It is probable that this nonrandom feature of the activity of the dorsal horn neurons in case of peripheral nerve injury is the result of the remaining connections between the dorsal horn and the dorsal root ganglion. It has been reported (Gold, 2000; Han et al., 2000; Kajander et al., 1992; McLachlan et al., 1993; Ramar et al., 1997; Study and Kral, 1996; Tabo et al., 1999; Tal and Eliav, 1996; Zhang et al., 1997) that ectopic spontaneous discharges can originate in dorsal root ganglion neurons after peripheral nerve lesions in the rat. These discharges are likely to have a driving role in the spontaneous activity of the dorsal horn, thus modifying its neuronal behavior. Moreover, it has also been stated (see Gold [2000] for review) that changes in uninjured afferents neighboring the injured afferents may maintain a pain state induced by a peripheral nerve lesion. The result of our test may reflect the influence of the remaining intact fibers on the dorsal horn neurons. Whatever the answers to these questions may be, the possible roles of the dorsal root ganglion and of the remaining afferent inputs in such a trend in dorsal horn firing rate remain to be investigated further.

The SPAS group was referred to here as a control group because these patients did not present any pain symptoms and because only the central nervous system was thought to be involved in the etiology in all spastic patients. Because of the multiple central nervous system lesions of these patients, we are aware that some modification of descending modulation to the dorsal horn neurons could explain our results. However, this group constituted the only nonpainful "control" group we could constitute.

In conclusion, our statistical analysis shows that the dorsal horn neurons of patients operated for pain resulting from peripheral nerve injury display a nonrandom activity, in contrast to those in the other groups. Second, the deafferented dorsal horn neurons tend to have a more irregular and more burst activity than the neurons belonging to the other groups.

Although difficult to perform in humans, such studies can help to bring insight into the understanding of mechanisms of chronic neuropathic pain, which are still difficult to treat in clinical practice.

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