Involvement of the Caudal Medulla in Negative Feedback Mechanisms Triggered by Spatial Summation of Nociceptive Inputs

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Gall, Olivier, Didier Bouhassira, Djamel Chitour, and Daniel Le Bars. Involvement of the caudal medulla in negative feedback mechanisms triggered by spatial summation of nociceptive inputs. J. Neurophysiol. 79: 304–311, 1998. In the rat, applying noxious heat stimuli to the excitatory receptive fields and simultaneously to adjacent, much larger, areas of the body results in a surface-related reduction in the responses of lumbar dorsal horn convergent neurons. These inhibitory effects induced by spatial summation of nociceptive inputs have been shown to involve a supraspinally mediated negative feedback loop. The aim of the present study was to determine the anatomic level of integration of these controls and hence to ascertain what relationships they might share with other descending controls modulating the transmission of nociceptive signals. The responses of lumbar convergent neurons to noxious stimulation (15-s immersion in a 48°C water bath) applied to increasing areas of the ipsilateral hindlimb were examined in several anesthetized preparations: sham-operated rats, rats with acute transections performed at various levels of the brain stem, and spinal rats. The effects of heterotopic noxious heat stimulation (tail immersion in a 52°C water bath) on the C-fiber responses of these neurons also were analyzed. The electrophysiological properties of dorsal horn convergent neurons, including their responses to increasing stimulus surface areas, were not different in sham-operated animals and in animals the brain stems of which had been transected completely rostral to a plane 2.8 mm remote from interaural line (200 μm caudal to the caudal end of the rostral ventromedial medulla). In these animals, increasing the stimulated area size from 4.8 to 18 cm² resulted in a 35–45% reduction in the responses. In contrast, relative to responses elicited by 4.8 cm² stimuli, responses to 18 cm² were unchanged or even increased in animals with transections at more caudal level and in spinal animals. Inhibitions of the C-fiber responses elicited by heterotopic noxious heat stimulation were in the 70–80% range during conditioning in sham-operated animals and in animals with rostral brain stem transections. Such effects were reduced significantly (residual inhibitions in the 10–20% range) in animals with transections >500 μm caudal to the caudal end of the rostral ventromedial medulla and in spinal animals. It is concluded that the caudal medulla constitutes a key region for the expression of negative feed-back mechanisms triggered by both spatial summation of nociceptive inputs and heterotopic noxious inputs.

METHODS

Surgical preparation

Experiments were performed on male Sprague-Dawley rats weighing 200–250 g. The animals were housed with ad libitum access to food and water in a room illuminated from 06:00 to 18:00 h. Anesthesia was induced by 2.5% halothane in a N₂O/O₂ mixture (2:1). Tracheal and jugular canulae were inserted. The animal then was paralyzed by intravenous injection of gallamine triethiodide (Flaxedil) and ventilated artificially. The rate (50–55 strokes/min) and volume of ventilation were adjusted to maintain a normal
acid-base equilibrium (end-tidal CO₂: 3.5–4.5%) as assessed with a capnometer (Capnomac II, Datex Instruments, Helsinki, Finland), which also measured O₂, N₂O and halothane levels throughout the experiment. Heart rate was monitored continuously and core temperature maintained at 37 ± 0.5°C by means of a homeothermic blanket system.

The animals were mounted in a stereotaxic frame. In 33 animals, the brain stem was transected acutely, at different levels between −1 and −5 mm from interaural coronal plane, as described previously (Bouhassira et al. 1995a). Briefly, after fenestration of the occipital bone and aspiration of the cerebellum, a surgical knife was inserted medially through the brain stem until contact with the skull was felt at which point the knife was moved gently from side to side. To ensure complete transection, 2–3 mm of brain stem substance rostral to the cut were removed by aspiration. Hemostasis was achieved by thermocoagulation and the application of gelfoam. Twelve sham-operated control animals underwent the same procedure (including aspiration of the cerebellum) except for brain stem transection. In another 12 animals, the brain stem was not transected and the spinal cord was sectioned at the level of the rostral border of the second cervical vertebrae. After these procedures, a laminectomy was made to enable electrophysiological recordings to be made from the lumbar dorsal horn (segments L₁–L₄).

**Electrophysiological recordings**

Recordings were commenced 30–45 min after the end of the preparatory surgery. Single neurons were recorded extracellularly in the right or left lumbar dorsal horns with the animals now anesthetized with 0.5% halothane in 33% O₂ and 67% N₂O.

Recordings were made with glass micropipettes (10–15 MΩ) filled with 5% NaCl and pontamine sky blue. Neurons were classified as convergent on the basis of their responses to both innocuous and noxious mechanical stimulation of their receptive fields. Light mechanical stimuli produced with a blunt probe and noxious pinch were used to characterize each recorded unit and to delineate its excitatory receptive field, which was taken as the area of skin from which the cell could be activated by such stimuli. The receptive field area of the cell was reexamined before each thermal stimulus was applied (see further text). Recording sites in the lumbar dorsal horn were marked using dye electrophoresis from the micropipettes at the end of the experiments.

**Thermal stimulation procedure**

To investigate the effects of spatial summation from nociceptive afferents, we tested for each neuron the responses elicited by noxious stimuli applied to two different areas of the ipsilateral hindpaw, namely, area 1, all five digits (4.8 cm²), and area 2, the paw ±20 mm below the knee (18 cm²). The noxious stimuli involved immersing the area for 15 s in a 48°C water bath. These thermal stimuli were applied in random order with a 10-min interval. In a previous study (Bouhassira et al. 1995b), we showed that such a procedure allowed the recording of reproducible responses without significant sensitization or desensitization phenomena. To reduce further the possibility of sensitization or desensitization resulting from repetitive noxious stimulation (Cervero et al. 1988; Cook et al. 1987; Ferrington et al. 1987; Kenshalo et al. 1979, 1982), no more than two neurons, one in each side of the cord, were recorded in each animal. Only cells that presented no serious changes in spike amplitude or wave form during the complete experimental procedure were considered.

None of the stimuli significantly modified heart rate (any changes were <5 beats/min). Blood pressure was not monitored in all the animals. Results concerning cardiovascular changes observed in a similar series of brain stem transected animals are reported elsewhere (Bouhassira et al. 1995a).

**Electrical stimulation procedure**

After the thermal stimulation sequence, the effects of applying electrical stimuli to the center of the receptive field of the recorded unit were investigated. All the neurons studied gave responses with latencies corresponding to A- and C-fiber inputs.

To investigate the effects of the transections on DNIC, we tested, on the same neurons, the effects of heterotopic noxious stimuli on the C-fiber responses evoked by electrical stimulation of their receptive fields. A sequence of 105 electrical stimuli (percutaneous single square-wave pulses, 2-ms duration, at an intensity of twice the threshold for C-fiber evoked responses) was applied once every 1.5 s. A multichannel analyzer (Tracor TN 1710) was used online to build poststimulus histograms (PSH). The first 50 responses were not taken into consideration because they showed either habituation or, more usually, ‘wind-up’ phenomena. The PSH built from the 50th to the 65th responses was used as a control for the posteffects to be observed during the first 22 s after the removal of the conditioning stimulus. The PSHs were analyzed with respect to the control PSH. Only the C-fiber component is considered in the present report.

**Histological determination of the levels of transection**

At the end of the experiments, animals were anesthetized deeply (3.5% halothane) and perfused through the heart with saline followed by a 10% formalin solution to enable histological sections to be prepared. The level of transection was considered as the most rostral areas of the brain stem spared by the transection. All the sections were examined by the same observer, who was unaware of the electrophysiological results, with reference to the stereotaxic atlas of the rat brain by Paxinos and Watson (1986).

For analysis purposes, the levels of transections were pooled into four groups (I–IV) as represented in Fig. 1. Animals were assigned to group I when the most rostral brain stem plane spared by the transection was located between −1 mm to the interaural line (the caudal end of locus coeruleus dorsally to the trapezoid body ventrally) and −1.8 mm (the rostral third of the medial vestibular nucleus dorsally to the rostral third of the lateral paragangiocellular nucleus ventrally). In group II, the levels of transections were located between −2 mm to the interaural line (the medial third of the medial vestibular nucleus dorsally to the lateral paragangiocellular nucleus ventrally) and −2.8 mm (the caudal third of the medial vestibular nucleus dorsally to the inferior olive ventrally). In group III, transections were located between −3.3 mm to the interaural line (the caudal end of the medial vestibular nucleus dorsally to the medial inferior olive ventrally) and −4 mm (the solitary nucleus dorsally to the caudal third of the inferior olive ventrally). In group IV, the transections extended between −4.2 mm to the interaural line (the hypoglossal nucleus dorsally to the lateral reticular nucleus ventrally) and −5 mm (the caudal end of the hypoglossal nucleus dorsally to the lateral reticular nucleus ventrally).

Data are presented as means ± SE. Background activity was analyzed during the 10 s preceding each stimulation period. Noxious-heat evoked responses were calculated as the total number of
RESULTS

Recordings were made from 70 convergent neurons: 12 in sham-operated control animals, 8 in group I, 12 in group II, 14 in group III, and 12 in group IV brain stem-transected animals, and 12 in the spinal (C2) animals (see Fig. 1 and methods for the group assignment rules). In all the preparations, convergent neurons were located similarly in the deep layers of the dorsal horn as evidenced by the dye electrophoresed from the micropipettes at the end of the experiments.

General characteristics of the cells

The excitatory receptive fields of the recorded units were located distally on the ipsilateral hindpaw and covered one to five digits. The mean area of the excitatory receptive fields were not significantly different between sham-operated, spinal, and any group of transected animals [F(5,64) = 1.01, n.s.]. These data are reported in Table 1. Subsequent receptive field mapping before the second noxious heat stimulation revealed only inconsistent and nonsignificant changes [F(1,138) = 0.86, n.s.].

As summarized in Table 1, spontaneous activity was similar for neurons recorded in sham-operated and in group I and II transected animals but was significantly higher for neurons recorded in the most caudally transected animals (groups III and IV) and the spinal animals [F(5,64) = 4.14, P = 0.025]. In addition, in all the preparations, spontaneous levels of firing before the first and the second test were not significantly different [F(1,138) = 1.37, n.s.].

Spatial summation of noxious heat

Individual examples of the responses elicited by the small and large thermal stimuli in the different preparations, are presented in Fig. 2. In sham-operated and in groups I and II transected animals, the responses elicited by the 18 cm² stimulus were clearly smaller than those elicited by 4.8 cm². By contrast, in groups III and IV and in spinal animals, the responses elicited by the two stimulus areas did not appear to be different.

Cumulative results concerning noxious-heat evoked-responses (expressed as mean firing rate during the 15 s) in the different experimental groups are reported in Table 1. The mean discharge rate elicited by immersion of the digits (4.8 cm²) was similar in all preparations, except for neurons recorded in group IV, which displayed a surprisingly low discharge rate.

In sham-operated and in group I and II transected animals, increasing stimulus size from 4.8 to 18 cm² resulted in a 35–40% reduction in the responses. In contrast, in groups III and IV and in the spinal animals, the responses elicited by the 18 cm² stimuli were not significantly different from those evoked by the 4.8 cm² stimuli. Such differences were not dependent on the order of application of the stimuli.

Global comparison of thermal stimulation sequences e.g., 4.8–18 cm² or 18–4.8 cm² revealed no significant differences in the recorded responses [F(1,136) = 1.15, n.s.]. Furthermore, as stressed earlier, indicators of sensitization such as the background discharge rate of the recorded units or the sizes of their excitatory receptive fields were not modified significantly during the course of the experiments.

The influence of the level of brain stem transection on the pattern of responses to graded thermal stimuli is summarized in Fig. 3, where the results are expressed as percentages (100 × response to 18 cm²/response to 4.8 cm²). In sham-operated animals, the mean discharge rate elicited by immersion of the entire paw (18 cm²) was 65 ± 9% of the mean discharge rate elicited by immersion of the digits (4.8 cm²). Similar effects were observed in group I and group II transected animals (responses elicited by the 18 cm² stimuli were 58 ± 12% and 54 ± 8% of the responses evoked by the 4.8 cm² stimuli, respectively). In contrast, no decrease, or even an increase in the responses elicited by the larger stimulus, was observed for neurons recorded in group III and IV transected animals and in the spinal animals (the mean values being 114 ± 23% in group III transections, 127 ± 13% in group IV transections, and 120 ± 14% in the spinal animals). Analysis of variance revealed significant intergroup differences between sham-operated, group I, group II, group III, group IV, and spinal animals [F(5,64) = 4.82, P = 0.008].

Inhibition of the C-fiber response elicited by heterotopic noxious heat stimulation

The thresholds for the C-fiber evoked responses elicited by transcutaneous electrical stimulation (2-ms duration) were not influenced by the level of transection; mean values of 2.1 ± 0.49, 2.8 ± 0.75, 2.5 ± 0.38, 3.0 ± 0.34, 2.7 ± 0.45, and 2.7 ± 0.23 mA were obtained for sham-operated, group I, group II, group III, group IV, and spinal animals,
TABLE 1. Summary of the main electrophysiological data obtained in the experimental groups

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Receptive Field Area, cm²</th>
<th>Background Activity, ap/s</th>
<th>4.8 cm² stimulus, ap/s</th>
<th>18 cm² stimulus, ap/s</th>
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<tbody>
<tr>
<td>Sham</td>
<td>12</td>
<td>1.7 ± 0.2</td>
<td>2.9 ± 0.8</td>
<td>83.9 ± 11.8</td>
<td>58.3 ± 12.0</td>
</tr>
<tr>
<td>Group I</td>
<td>8</td>
<td>1.7 ± 0.3</td>
<td>2.2 ± 0.9</td>
<td>95.7 ± 12.0</td>
<td>58.7 ± 13.3</td>
</tr>
<tr>
<td>Group II</td>
<td>12</td>
<td>1.6 ± 0.2</td>
<td>2.7 ± 0.8</td>
<td>97.5 ± 20.6</td>
<td>58.1 ± 18.4</td>
</tr>
<tr>
<td>Group III</td>
<td>14</td>
<td>1.9 ± 0.2</td>
<td>15.9 ± 2.2*</td>
<td>85.8 ± 16.2</td>
<td>79.7 ± 14.5</td>
</tr>
<tr>
<td>Group IV</td>
<td>12</td>
<td>2.0 ± 0.4</td>
<td>18.9 ± 2.6*</td>
<td>49.3 ± 10.5†</td>
<td>59.9 ± 12.1</td>
</tr>
<tr>
<td>Spinal</td>
<td>12</td>
<td>2.0 ± 0.3</td>
<td>11.5 ± 2.0*</td>
<td>86.2 ± 14.0</td>
<td>94.4 ± 13.8</td>
</tr>
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</table>

All data are means ± SE. Spontaneous and evoked activity are expressed as action potentials/second (ap/s). * Comparison versus sham-operated, group I or group II: P < 0.05. † Comparison versus group II: P < 0.05.

FIG. 2. Individual examples of the responses of convergent neurons recorded in the different preparations (from bottom: sham, groups I, II, III, and IV, transected, and spinal animals). Each histogram (binwidth = 0.5 s) represents the responses evoked by the immersion of 4.8 cm² (left) or 18 cm² (right) of the ipsilateral hindpaw. Timing of the stimulus (15-s duration) is indicated by the horizontal bar below each histogram. In the sham-operated and the group I and II transected animals, the responses elicited by the 18 cm² stimulus were smaller than that evoked by the 4.8 cm² stimulus. In contrast, in group III and IV transected and spinal animals, the responses elicited by the 2 stimulation areas were not different; note also that spontaneous activity and poststimulus discharges were higher in these preparations.

FIG. 3. Bar charts representing the noxious heat (48°C, 15 s) evoked responses to stimulation of the whole paw (18 cm²) as percentages of the responses to stimulation of the digits alone (4.8 cm²) in the different groups of animals. In sham-operated animals, the mean discharge rate elicited by immersion of the whole paw was 65% of the mean discharge rate elicited by the immersion of the digits. A similar effect was observed in group I and group II transected animals. In contrast, convergent neurons responded to increasing the stimulus area with no reduction or even an increase in the response. Significant intergroup differences in these percentage values existed between neurons recorded in sham-operated, group I and group II animals and those recorded in group III, group IV, and spinal animals (**P < 0.01, ***P < 0.001 vs. sham operated).

Increasing the level of stimulation to twice threshold resulted in mean responses of 17.4 ± 2.5, 11.7 ± 1.7, 13.8 ± 2.7, 15.0 ± 2.2, 17.9 ± 4.2, and 14.6 ± 3.3 C-fiber latency action potentials per stimulus for the respective groups [F(5,64) = 1.35; n.s.]. Increasing the level of stimulation to twice threshold resulted in mean responses of 17.4 ± 2.5, 11.7 ± 1.7, 13.8 ± 2.7, 15.0 ± 2.2, 17.9 ± 4.2, and 14.6 ± 3.3 C-fiber latency action potentials per stimulus for the respective groups [F(5,64) = 1.35; n.s.]. The percentage inhibition of the C-fiber—evoked responses induced by the noxious heterotopic stimulus, i.e., immersion of tail in a 52°C water bath, are presented in Fig. 4. In sham-operated animals and in group I and II transected animals, inhibition of the C-fiber—evoked responses elicited by application of heterotopic noxious heat stimuli were in the 70–80% range during conditioning. Poststimulus effects—in the 30–35% range—were observed during the subsequent 22 s in these animals. In contrast, significantly smaller inhibitions—in the 10–20% range—were observed in group III, group IV, and spinal animals [F(5,64) = 8.15, P < 0.001]. The postconditioning effects also were reduced significantly (5–10% range) in these animals.

DISCUSSION

The spatial summation of nociceptive inputs can trigger a supraspinally mediated feed-back inhibition of activity in
dorsal horn convergent neurons (Bouhassira et al. 1995b). We now have confirmed these results and provided additional information regarding the anatomic localization of the neuronal circuits involved in these processes. The relationships between these controls and previously described tonic and phasic descending inhibitory controls will be discussed.

The general electrophysiological properties of convergent neurons and the relationship between their responses and the stimulus area were very similar in the sham-operated animals and those with rostral brain stem transections. In contrast, the spontaneous activity of the neurons increased and the inhibitions triggered by spatial summation of nociceptive afferent decreased, in animals transected more caudally than a plane 500 μm caudal to RVM (i.e., in groups III and IV) and in the spinal animals.

It seems very unlikely that cardiovascular changes induced by the transection could explain the present results. In a previous study using a similar methodology for brain stem transections (Bouhassira et al. 1995a), we showed that decreases in resting arterial blood pressure and heart rate appeared only in animals with brain stem transections at the most caudal level, corresponding to group IV and spinal animals. These results were in keeping with classical data, which indicate that only destruction of the whole rostrocaudal extent of the rostral ventrolateral medulla induces significant reductions in resting blood pressure and heart rate (see references in Chalmers and Pilowsky 1991; Dampney 1994; Spyer 1994).

The inhibitory phenomena triggered by spatial summation of nociceptive inputs are very different from segmental inhibitory controls. Indeed, the latter have been observed in both intact and spinal animals (see references in Besson and Chaouch 1987; Willis and Coggeshall 1991) and are activated preferentially by nonnoxious stimuli applied to the inhibitory receptive field that often surrounds the excitatory receptive field of convergent neurons (Besson and Chaouch 1975; Handwerker et al. 1975; Hillman and Wall 1969; Price et al. 1978; Wagman and Price 1969). For all the neurons in the present study, the smaller stimulus area (4.8 cm²) completely covered their excitatory receptive fields. In fact, for the majority of the recorded units, this area was 1.5–2 times larger than that of their excitatory receptive fields. In a previous study (Bouhassira et al. 1995b), we showed that such an area was not large enough to trigger significant inhibition due to spatial summation. These results do not exclude the possibility that segmental influences, whether excitatory or inhibitory, are the main source of modulation of the activity of convergent neurons when nociceptive inputs are restricted to small areas.

Propriospinal inhibitory mechanisms acting on lumbar dorsal horn convergent neurons also have been described in various species including rats (Cadden et al. 1983; Zhang et al. 1996), cats (Sandkühler et al. 1993), and monkeys (Gerhart et al. 1981; Hobbs et al. 1992). Foreman and his colleagues demonstrated that somatic or visceral noxious inputs can trigger potent inhibitions of convergent neurons activities via a relay in the upper cervical cord (Hobbs et al. 1992; Zhang et al. 1996). Even though low spinal transections were not performed in the present study, the level of residual inhibitions seen in groups III, group IV, and spinal animals are very low. Hence our results do not support an important participation of the upper cervical cord in the negative feedback mechanisms triggered by spatial summation. One cannot exclude, however, that both mechanisms may act additively or synergistically to modulate the processing of nociceptive information by convergent neurons in intact animals.

The major finding of the present study is that phasic descending inhibitory controls triggered by spatial summation of nociceptive inputs are integrated in the most caudal part of the medulla. Thus these controls are topographically independent of the multiple modulatory controls originating from more rostral brain stem structures (see references in Besson and Chaouch 1987; Fields and Basbaum 1989; Willis 1988; Willis and Coggeshall 1991). Notably, the PAG-RVM system is not directly involved in this negative feedback loop. The participation of the RVM in an inhibitory feedback loop initially had been proposed (Bassbaum and Fields 1984; Fields and Basbaum 1989). However, on the basis of the electrophysiological properties of RVM neurons, it subsequently was suggested that both facilitatory and inhibitory controls acting on the spinal transmission of nociceptive signals originate in this region (Fields 1992; Fields et al. 1991). The RVM also might be involved in the integration of adaptive cardiovascular responses induced by noxious stimuli (see references in Lovick 1991; Thurston and Randich 1992) and/or in the modulation of the motor facet of nociceptive reflexes (Lundberg 1964, 1982; Morgan et al. 1994, 1995).

DNIC also were reduced significantly in animals transected more caudally than a plane 500 μm caudal to RVM (i.e., in groups III and IV) and in the spinal animals. This result confirms a previous study (Bouhassira et al. 1995a). Thus the level of integration of descending inhibitory controls triggered by spatial summation and DNIC appeared to be identical. Indeed, in all six types of preparation, a strong correlation existed between inhibitions triggered by spatial summation and inhibitions triggered by heterotopic noxious stimuli. This result supports the view that spatial summation, whether obtained by increasing the surface of a single stimulated area or by applying an additional stimulus to a remote part of the body, can trigger negative feedback loops acting...
on dorsal horn convergent neurons. In both cases, the inhibitory controls are subserved by neuronal pathways organized in the most caudal part of the medulla.

Such a role of the caudal medulla in descending modulatory systems acting on dorsal horn noci-responsive neurons has been suggested previously (Aicher and Randich 1990; Almeida et al. 1996; Gebhart and Ossipov 1986; Gebhart and Randich 1990; Janss and Gebhart 1988a,b; Morgan et al. 1989; Ren et al. 1990). Thus in addition to segmental, propriospinal, and supraspinal descending systems originating from other brain stem structures, the caudal medulla represents another specific level for the modulation of nociceptive signals. Such a role is further supported by recent electrophysiological and anatomic data that indicate that the subnucleus reticularis dorsalis (SRD) is involved in both the transmission and the modulation of nociceptive information (Villanueva et al. 1996). Other caudal medullary structures such as the nucleus of the solitary tracts and the lateral reticular nucleus, also might be involved in the modulation of the spinal transmission of nociceptive signals (Aicher and Randich 1990; Gebhart and Ossipov 1986; Gebhart and Randich 1990; Janss and Gebhart 1988a; Janss et al. 1987; Morgan et al. 1989; Ren et al. 1990).

Another finding in this study concerns tonic descending inhibition. The existence of tonic descending inhibitory controls has been suggested on the basis of both behavioral and electrophysiological experiments (see references in Besson and Chauouch 1987; Willis 1988). It was observed that the excitability of lumbar convergent neurons was higher (as evidenced by increased spontaneous activity and responses to noxious stimuli and/or by increased receptive field sizes) after reversible cooling (“cold block”) of the cervical spinal cord (Besson and Chauouch 1975; Brown 1971; Cervero and Plenderleith 1985; Handwerker et al. 1975; Laird and Cervero 1990; Wall 1967). The descending pathways involved in tonic descending inhibition probably are located in the dorsolateral funiculus (Jones and Gebhart 1987; Pubols et al. 1991; Sandkühler et al. 1987; Villanueva et al. 1986). Duggan and his colleagues concluded on the basis of a series of studies in the cat that the main supraspinal source of tonic descending inhibition was in an area ventral to the facial nucleus (Foong and Duggan 1986; Hall et al. 1982; Morton et al. 1983, 1984). The supraspinal origin of tonic descending inhibition in the rat is not known. The present results suggest that some tonic descending inhibition was removed in the most caudally transected animals (group III, group IV, and spinal animals) because the spontaneous activity of convergent neurons was significantly higher in these animals. However, under our experimental conditions, the mean size of excitatory receptive fields, the threshold and magnitude of C-fiber evoked responses, the responses evoked by the stimulation of the 4.8 cm² area (the mean number of spikes and the pattern of the responses) were not significantly different between sham-operated animals and those with brain stem or spinal transections. Such a differential effect on evoked and nonevoked activities has been observed previously (Janss and Gebhart 1988b; Jones and Gebhart 1987; Villanueva et al. 1986).

The present data also raise some questions concerning the role of spatial summation in the processing of nociceptive information. Painful stimuli encountered in clinical practice are not punctuate and always involve a large number of excitatory receptive fields of peripheral fibers and central neurons. However the study of noci-responsive spinal neurons has centered almost exclusively on their receptive fields. The investigation of the behavior of such neurons in situations closer to those for clinical pain has allowed us to characterize a nonmonotonic transmission function. Increasing the injured area results in two functionally opposite effects: an increase in the number of neurons activated and a decrease in the responses of the individual neurons. The consequences of such opposite effects on the resulting output of the spinal cord and finally on the elaboration of pain sensation may be questioned. This point already has been the subject of study of several investigators. When tested with radiant heat, over areas extending ≥200 cm², it has been reported that little or no spatial summation exist for heat pain threshold (Greene and Hardy 1958; Hardy et al. 1940; Marks and Stevens 1973; Stevens and Marks 1971; Stevens et al. 1974). In contrast, studies conducted with contact stimulators invariably established a significant decrease in pain threshold when stimulus area was increased (Defrin and Urca 1996; Kojo and Pertovaara 1987; Machet-Pietropaoli and Chery-Crozé 1979). The perceived pain intensity to suprathreshold contact heat stimulation also was found positively correlated with the stimulus area in the 0–3 cm² range (Douglass et al. 1992; Price et al. 1989).

One can speculate that one source of such discrepancies lies in variable involvement of the descending inhibitory controls triggered by spatial summation. Indeed, as stressed above, the stimulation of small areas might not be sufficient to trigger significant inhibition due to spatial summation, hence leading to an increase of the net input received by supraspinal target neurons when the stimulated area increases over a narrow range. A further increase of the area could slow down such encoding function by triggering descending inhibitions, as shown here. In this respect, it would be interesting to investigate psychophysically the effects of very large noxious stimulations able to recruit a population of noci-responsive neurons extending from L₄ to S₁ dermomes for example, thus comparable in size with our present data.

Alternatively, it is possible that, as the number of activated spinal neurons increases, a decrease in individual responses of these neurons will have little influence on the global input received by supraspinal target neurons involved in the elaboration of pain sensation. This proposal might be investigated during recordings of target supraspinal neurons. Villanueva et al. (1989) examined the effects of spatial summation on SRD neurons and observed that such neurons encode the stimulus area with an accelerating function within a restricted range (≥6 cm²), whereas further increase in stimulus area resulted in a decrease of the responses. Interestingly, in animals with lesion of the dorsolateral funiculus, the responses of SRD neurons to stimulation of increasing areas became positively accelerating over the range studied (0.9–25 cm²) (Villanueva et al. 1996). Obviously, further studies are needed to examine the encoding of the tridimensional characteristics of noxious events, namely intensity duration and area, in other supraspinal structures involved in pain processing.

In conclusion, the present data emphasize the role of the
caudal medulla in descending modulatory systems acting on dorsal horn noxious-responsive neurons. The phasic controls originating from this area seems to be dependant on the spatial characteristics of noceptive stimuli. Such an interpretation does not exclude the possibility of interactions with other spinally or supraspinally organized modulatory systems in the processing of noceptive information.

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