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Sensitization of Spinal Neurons by Non-noxious Stimuli in the Awake but Not Anesthetized State

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Background: The observation that peripheral trauma causes enhanced spinal neuronal excitability has provided the scientific rationale for the concept of "preemptive analgesia." The premise has been that only noxious stimuli cause sensitization in sensory pathways, but this premise has not been tested in the conscious state.

Methods: Responses of single spinal neurons were recorded in instrumented sheep that were untrained and free from drugs or recent surgery, in either fully conscious or halothane-anesthetized states. Receptive field (RF) size was measured before and after non-noxious mechanical conditioning stimulation.

Results: Noxious conditioning stimuli in anesthetized sheep caused enlargement of RF areas, as expected. Conditioning with nonpainful scratching or other stimuli was without effect in anesthetized animals; in marked contrast, it caused enlargement of RF size in conscious animals, in which 29 of 33 wide dynamic range units but only 1 of 12 low-threshold mechanoreceptive neurons were affected.

Conclusions: Sensitization of spinal sensory neurons evidently is a process that is not restricted to pathologic pain states but rather that occurs under normal physiologic conditions independent of painful stimuli. The significance of such sensitization processes therefore needs reevaluation. The sensitization triggered by non-nociceptive afferents is likely to be opioid-resistant and therefore may contribute to the rather disappointing results seen in several clinical trials of "preemptive analgesia." (Key words: Hyperalgesia. Nociception. Preemptive analgesia. Sensitization. Spinal cord.)

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‡ Niv D, Devor M: Does the blockade of surgical pain preempt postoperative pain and prevent its transition to chronicity? Newsletter of the International Association for the Study of Pain (IASP) Nov/Dec 1993.

THE changes that underlie altered pain sensation in ongoing pain states have received much attention in recent years. There is good evidence that intense nociceptive inputs to the spinal cord or trigeminal nucleus, whether from normal skin,¹⁻⁸ muscle⁹ or viscera,¹⁰ or inflamed tissue,¹¹ can trigger enhanced excitability that is reflected as an enlargement of neuronal receptive fields (RFs) and a decreased threshold for nociceptive responses. Attempts to prevent such sensitizing effects underlie the concept of "preemptive analgesia."¹²⁻¹⁴‡

The assumption in all of these deliberations is that increased sensitivity of spinal neurons is triggered specifically by nociceptive input. Although this appears to be true under the experimental conditions tested, it has not been examined specifically in the conscious, drug-free state. Anecdotal comments from previous studies on conscious animals imply that spinal neuronal sensitivity may be altered secondarily to an animal's state of attention.^{15,16} It seemed important to establish what types of stimuli can alter spinal neuronal sensitivity under normal awake conditions. We now report that in awake but not in anesthetized animals, the RFs of spinal dorsal horn neurons are modified dynamically even with non-noxious peripheral stimulation. This finding demands a reappraisal of the significance of altered spinal neuronal sensitivity.

Methods and Materials

Experiments were performed on eight female sheep chronically prepared to permit extracellular recording of single spinal neurons either when the animals were awake or when they were reversibly anesthetized with halothane. In either case, they had recovered from the preparative surgery and had not undergone any training program. Full details of the preparation have been published previously.^{17,18} All surgical, care, and recording procedures were approved by the U.K. Home Office.

Insertion of Implant

For the initial operation to install an indwelling implant, sheep were anesthetized with halothane in nitrous oxide/oxygen (2:1). The last lumbar intervertebral junction was exposed. Steel screws were inserted into the lateral processes and bodies of the two vertebrae, and dental acrylic were built up around them to form a solid base that immobilized this junction. A 20-mm diameter hole was drilled in the vertebrae, centered on the junction, and a hollow titanium implant was mounted over it. The dura mater was left intact. A map of the vessels of the dorsal surface of the cord was made for future reference for electrode penetration sites. The wound was closed, leaving the implant protruding permanently through the skin; a double mechanical barrier maintained sterility of the exposed spinal canal.

Clinical Care and Therapy

Perioperative analgesia was provided for as long as was deemed advisable on standard veterinary grounds (generally 2–3 days) with buprenorphine (2.5 µg/kg twice daily; Temgesic, Reckitt and Colman) and the nonsteroidal antiinflammatory drug flunixin (0.5 mg/kg twice daily; Finadyne, Schering-Plough). Antibiotic (ampicillin 2 mg/kg twice daily; Penbritin, SKB) was administered for 1 month. During the first 3–6 postoperative days, dexamethasone (60 reducing to 15 µg/kg twice daily; Dexadreson, Intervet) was administered to reduce any tendency for swelling around spinal nerves.

The dura mater was cleaned daily with physiologic saline. Gentamicin (5 mg in 1 ml, Cidomycin intrathecal, Roussel) was applied daily over the first month. Topical steroid therapy (dexamethasone, 2 mg in 1 ml; Dexadreson, Intervet) was maintained for as long as the animals lived to reduce the tendency for fibrous thickening of the dura mater.

Recording Sessions

Recording sessions were started a week or more after the initial surgery, once the sheep had recovered fully from any postoperative stiffness/lameness (which subsided over 48 h) and analgesic therapy had been stopped.

During recording sessions, animals were held in a sling, with their hooves just touching or just off the floor. At all times, they had access to food and water and remained within sight of another sheep. They appeared comfortable, eating and displaying no nervous-

ness; importantly, they chewed the cud, an activity readily disrupted by stress. Sessions lasted 3–6 h and were terminated as soon as the animal showed signs of restlessness.

The implant was fitted with both a micromanipulator and an electrode microdrive; a glass-coated tungsten electrode (0.4–3.6 MΩ) was then inserted through the dura mater under visual control provided by an arthroscope. Single-cell extracellular recordings were made using conventional procedures, and all records were stored on tape for subsequent detailed analysis.

Recording sessions were held over an average of 3.5 months per animal; at this stage the dura mater became too thickened to be penetrable by microelectrodes. In a final recording session with halothane anesthesia (as above), the dura mater was removed and several electrolytic lesions were made at defined depths and locations with respect to the surface vessels. After the animal had been killed with an overdose of pentobarbital, the spinal cord was removed for histology. Locations of recording sites were reconstructed. The prolonged delay between recording sessions and subsequent histology inevitably reduces the accuracy of histologic reconstructions; estimates of cell depth are considered accurate only to within 0.2 mm.

Testing of Receptive Field Size and Plasticity

Noxious stimuli could not be used to map the RF of units before test stimulation, whether in awake or unconscious animals. First, such repeated noxious stimulation is ethically unjustified in awake animals. Second, it would elicit vigorous withdrawal reflexes, which would result in loss of the recorded unit. Third, it would have affected the validity of subsequent conditioning procedures, whether noxious or non-noxious, and whether in awake or anesthetized animals. The RF areas described below are therefore non-nociceptive. Any increase in the cells' RF area indicates that more neurons will be activated by a constant stimulus. If these neurons also have nociceptive inputs (see below), such a recruitment of neurons is likely to result in enhanced nociceptive responsiveness.^{19,20}

RFs were characterized using the following techniques on clipped but unshaved skin. (Repeated shaving of the skin of the whole hindquarter was not practical, especially as it probably would have resulted in some degree of skin irritation.) A series of 17 custom-made von Frey filaments spanned the range from 1 to 125 mN. Stimulation with von Frey bristles was performed in two steps: positioning of the bristle onto the

skin, and, after checking for lack of activation, bending of the bristle. The remaining wool hair was short enough for the lateral bending of the bristles not to be a serious problem. A soft 1.25-cm paintbrush was used to stroke the skin. Squeeze/pinch stimuli were applied using a series of modified forceps, each of which was spring-loaded to produce a constant force over a smooth circular tip of either 16 or 24 mm². The forceps were applied to a fold of skin and were only closed to the preset force once any low-threshold response had subsided.

The low-threshold RF area of single spinal neurons was mapped with the von Frey bristle having a force about 5 mN greater than the lowest threshold observed (which varied over the range 1–30 mN). The RF was defined by working outward from the center of the RF until no response was found. The limits were marked on the skin with a felt-tip pen. These limits were rechecked using the same bristle to ensure accuracy to within 3–5 mm, an error that was not significant given the RF sizes involved in this species.

Non-noxious conditioning stimuli were applied to the RFs of all neurons to examine whether the RF area could be altered, and the RFs were mapped again immediately. The conditioning non-noxious stimuli were applied 3 times for 10 s with 10-s intervals, using one or more of the following methods: calibrated von Frey bristles (5 mN above threshold), stroking with a paintbrush, squeezing a fold of skin (0.75–10 N over 24 mm² and 10 N over 16 mm²), or manual tapping, rubbing, or gently scratching the skin. In initial experiments, scratching appeared subjectively to be the most effective of these low-intensity forms of stimulus at eliciting RF changes and so was used in most tests of non-noxious conditioning. If there was no change in RF area after one such conditioning trial, the conditioning protocol was repeated once. Where there was any expansion, further testing was restricted (in the interests of not triggering further changes) to mapping the limits of the RF at 5-min intervals. Where no expansion occurred, the cell was classified as nonexpanding.

The effects of noxious conditioning stimuli were examined only in anesthetized animals, for reasons implied above. The same animals were used in interleaved recording sessions while anesthetized with halothane (1–2% in oxygen/nitrous oxide > 2:1). Tracheal and esophageal tubes and an intravenous infusion were in place. Depth of anesthesia was maintained constant as judged by weak palpebral reflexes, very weak pedal

reflex, and moderately constricted pupils. The noxious conditioning stimuli were applied centrally in the RF for 10 s, repeated 3 times with 10 s intervals, using calibrated forceps that were clearly painful when applied to a fold of the experimenters' skin. Because animals were to recover from anesthesia within a few hours, conditioning noxious pinch stimuli were applied only at strengths that were not tissue-damaging (15–35 N applied over 16 mm²).

At the end of the protocol for each cell, a brief mechanical stimulus at a noxious intensity (as above) was applied to the center of the RF. In awake sheep, such noxious stimuli elicited withdrawal reflexes that often caused the unit to be lost. Retrospective monitoring of taped records permitted a distinction between an injury discharge by the neuron (resulting from damage to it by movement of the electrode, in which case there was a paroxysmal discharge with altered spike configuration) and a nociceptive response that was cut short by sudden loss of the unit. If the unit responded more vigorously to noxious than to the non-noxious stimuli tested previously, it was classified as a wide dynamic range (WDR; convergent) neuron. Remaining cells were characterized as low-threshold mechanoreceptive (LTMR). Cell position was estimated from depth readings in combination with histology performed after the last recording session in each animal.

RF areas were copied onto tracing paper from the marks made on the skin and subsequently were measured using a drawing tablet. Mean values, standard errors of the mean, and ranges of RF areas are indicated (cm²).

Nonparametric statistical analysis was performed using the Mann-Whitney U test or Wilcoxon's matched pairs test. A probability level of <0.05 was considered significant.

Results

Tests of RF plasticity were performed on 91 neurons; 48 cells were recorded in animals that were awake, drug-free, and free from recent surgery, and the remaining 43 in the same sheep during sessions under anesthesia with halothane. The locations of all cells examined are illustrated in figure 1. The majority of those neurons that have cutaneous RFs and that are recorded under such conditions have WDR properties^{18,21}; most of the cells in this study were of this sort (33 of 48 in awake, and 27 of 43 in anesthetized sheep). An example of the properties of such a

WDR neuron in an awake sheep is illustrated in figure 2, which shows the characteristic graded responses to increasing intensity stimulation. The RFs of the neurons studied were localized to areas of the hind limb, tail, and perineum ipsilateral to the spinal recording site; they never crossed the midline. For any given limb area, the size of RFs varied over a wide range. Under halothane anesthesia, the mean size was larger ($P < 0.01$; for values, see below).

Receptive Field Plasticity with Halothane Anesthesia

The 43 neurons examined under conditions of halothane anesthesia were used to verify whether the expansion of RF area that is elicited by noxious stimulation in various acute preparations (*i.e.*, in the presence of recent surgical trauma and often of anesthetic) also occurs in such a chronic preparation.

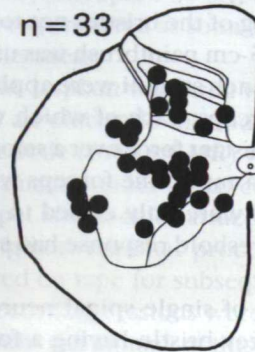
With WDR neurons recorded under anesthesia in the dorsal horn, a detectable increase in the size of the low-threshold RFs was obtained with 8 of the 17 units tested with noxious (but not tissue-damaging) conditioning stimuli; a decrease in RF area was never seen (table 1). Figure 3 shows an example of this effect on a dorsal horn unit; after conditioning with noxious stimulation, the unit became responsive outside the previous RF. Data for all neurons tested are shown in figure 4. The average size of all WDR RFs before stimulation was $87 \pm 20 \text{ cm}^2$ (mean \pm SEM; range 13–370 cm^2). The control RF area of the eight neurons affected was similar to this ($75 \pm 17 \text{ cm}^2$, range 28–190 cm^2). The RF area of these units increased by a mean of $33 \pm 7 \text{ cm}^2$ (range 5–67 cm^2). This increase was significant ($P < 0.01$). All neurons were tested every 5 min for 20 min after the conditioning stimulus to assess the duration of the sensitization. With three of the eight neurons, the size of the RFs had recovered to their initial sizes within 20 min; with the other five, no recovery was seen at this time.

In the ventral horn, the control RF area of the ten WDR neurons tested averaged $99 \pm 41 \text{ cm}^2$ (range 6–360 cm^2). Expansion of the RF area after this protocol of noxious stimulation occurred with only two of the ten WDR neurons (fig. 4, table 1).

The same protocol, again under anesthesia, was followed with 16 LTMR neurons. The size of prestimulation cutaneous RFs varied from 4 to 330 cm^2 (mean $75 \pm 21 \text{ cm}^2$). Enlargement of RFs was seen with only 3 of these 16 neurons (by 6–170 cm^2 from 19–330 cm^2); 1 was in dorsal and 2 in ventral horn.

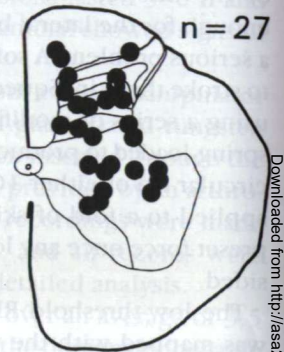
A. WDR

n = 33



CONSCIOUS

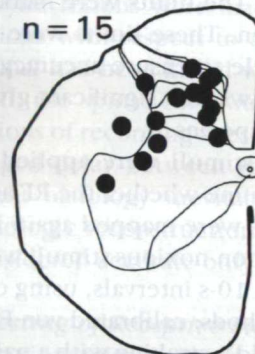
n = 27



HALOTHANE

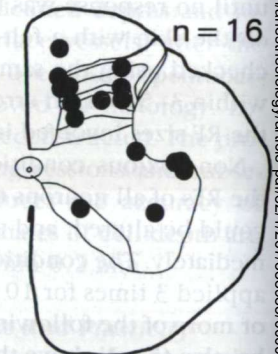
B. LTMR

n = 15



CONSCIOUS

n = 16



HALOTHANE

Fig. 1. Locations of neurons tested for changes in receptive field (RF) size following conditioning with non-noxious stimulation within the RF. The units were recorded in the lumbar spinal cord of chronically prepared sheep that were either fully conscious (*left*) or reversibly anesthetized with halothane (*right*). Locations of wide dynamic range (WDR, or convergent) neurons are shown in the upper figures and of low-threshold mechanoreceptive (LTMR) neurons in the lower figures.

All of these 27 WDR and 16 LTMR neurons examined in anesthetized sheep also were tested (before the noxious conditioning stimulation) with mechanical conditioning stimuli below the threshold for eliciting discomfort in humans or reflex withdrawal in conscious sheep. In no case was a unit's RF affected. An example of this lack of effect is shown in figure 3 for the same unit that was subsequently affected by noxious conditioning stimulation.

Receptive Field Plasticity with Awake Conditions

The results were notably different when identical non-noxious conditioning protocols were performed in

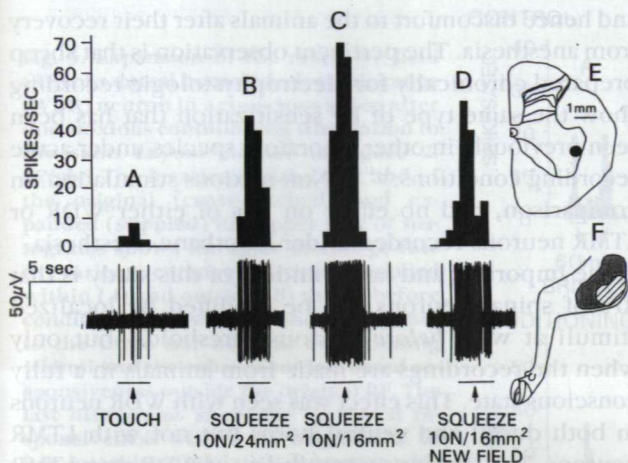


Fig. 2. Responses of a single neuron in the lumbar spinal cord of an awake sheep. (A-D) Histograms of spike activity and, below, the original spike records on the same time scale. The location of the neuron in the cord is shown in E and the receptive field (RF) in F. This neuron displayed wide dynamic range (WDR) properties, responding in a graded manner to light manual touch (A) of the receptive field, non-noxious squeeze at different intensities (B, 10 N over an area of 24 mm²; C, same force over 16 mm²) and (as tested at the end of the recording session) to noxious pinch stimuli (not shown). After conditioning with low-threshold stimuli (manual scratching, 10 s 3 times with 10-s intervals, that activated the neuron; not shown), the RF expanded from the control size (hatched area) to an area 380% this size (stippled in F). (D) A response to stimulation within this expanded RF, from which no spikes were elicited before conditioning.

awake animals. Light mechanical stimulation was tested for effects on the RF size of 33 WDR and 15 LTMR neurons. In the dorsal horn, the RFs of nearly all WDR neurons expanded (10 of 11 cells). An example is shown in figure 5; in this case, brushing and gentle scratching had no effect, but the RF area was increased markedly after repeated squeezing of a fold of skin at well below threshold for eliciting a withdrawal reflex. With this neuron, there was a parallel increase in the

sensitivity within the original RF, but this effect was not constant between units. The population data on RF expansion are shown in figure 6 and the incidence of expansion in table 1. In these awake animals, the size of the control RFs for all WDR averaged 51 ± 17 cm² (range 5–210 cm²). The control RF area for those cells that showed RF expansion was similar (53 ± 18 cm²), and their RF area expanded by an average of 43 ± 10 cm² (range 10–120 cm²). This was highly significant ($P < 0.001$). No appreciable recovery of RF size was seen 20 min after the enlargement in all but two of the cases studied; these two had recovered by 80% and 100%, respectively, at 20 min.

When the same protocol was followed with ten LTMR neurons in the dorsal horn, none showed any change in the size of their RF from a mean control area of 28 ± 8 cm² (range 3–91 cm²).

Similar results were obtained with neurons located in the ventral horn. Expansion of RFs was seen with 19 of 22 WDR neurons recorded in conscious sheep; the degree of this expansion is illustrated for one neuron in figure 2. Under awake conditions, the size of all RFs was 33 ± 8 cm² (range 1–160 cm²); for those cells showing expansion the control area was 35 ± 9 cm² (range 1–160 cm²) and the area of enlargement averaged 81 ± 23 cm² (range 2–410 cm²), being a very significant expansion ($P < 0.001$). This degree of expansion was not significantly different than that seen with dorsal horn neurons. Of two ventral horn LTMR neurons tested with light mechanical stimulation under awake conditions, one showed enlargement of its RF area (by 44 cm², from 27 cm²).

Discussion

These results indicate that expansion of the RFs of WDR neurons occurs in anesthetized sheep after

Table 1. Expansion of Cutaneous RFs in Sheep

	WDR Dorsal Horn		WDR Ventral Horn		LTMR Dorsal and Ventral Horn		Total Cells Tested
	Awake	Halothane	Awake	Halothane	Awake	Halothane	
Light stimulation	10 of 11	0 of 17	19 of 22	0 of 10	1 of 15	0 of 16	48
Noxious stimulation	Not tested	8 of 17	Not tested	2 of 10	Not tested	3 of 16	43
Total cells	11	17	22	10	15	16	91

RF = receptive field; WDR = wide dynamic range; LTMR = low-threshold mechoreceptive.

Tests were performed on WDR and LTMR neurons, in dorsal and ventral horn, and in both awake and halothane anesthetized sheep. Values are the number of neurons tested in each group of experiments and the incidence of RF expansion found.

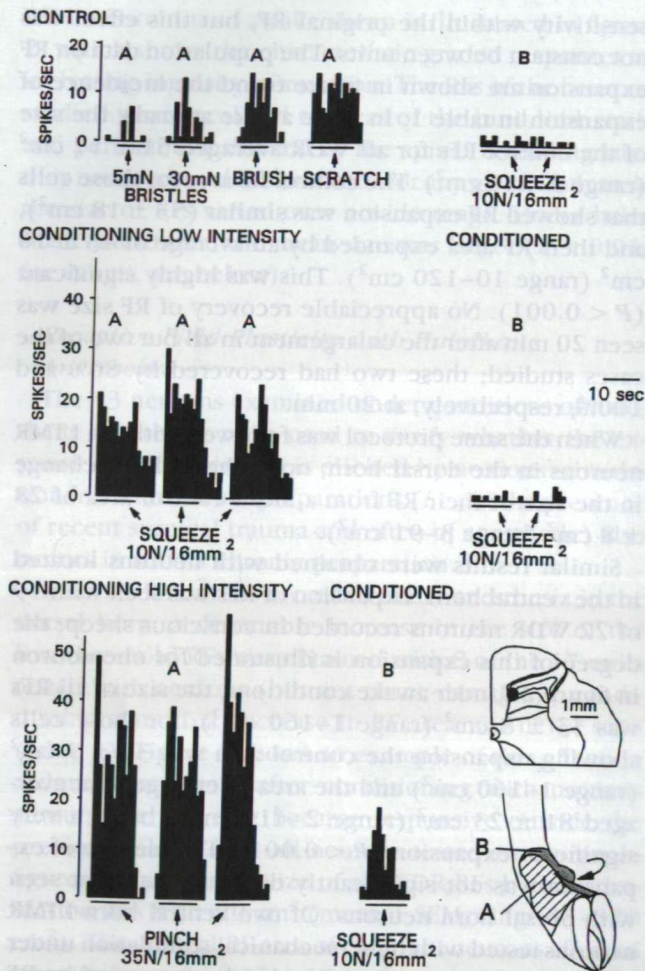


Fig. 3. Expansion of the receptive field (RF) of a dorsal horn wide dynamic range (WDR) neuron in a halothane-anesthetized sheep after noxious but not non-noxious conditioning stimulation to the skin. (Insets) The estimated location of the unit and the areas of the original (cross-hatched) and expanded (stippled) RF; the latter extended to the lateral aspect of the foot (arrow). The histograms are of spike discharges in response to stimulation of the skin within (A) or outside (B) the original RF. Upper row shows responses during the control period. Middle row shows responses to three non-noxious conditioning stimuli (10-s squeezes of a fold of skin) followed by tests at site B. Bottom row shows responses to the three noxious conditioning stimuli, which resulted in responsiveness outside the original RF. The greater discharge rate with noxious stimulation (35 N over 16 mm²) indicates that this was a WDR unit.

noxious stimulation within the RF of the recorded neuron. The degree of the RF expansion seen in these sheep was somewhat less than has been reported in other studies with noxious conditioning stimulation.^{5-7,9-11} This may be readily explained by the low grade of noxious stimulus that was used here to avoid tissue damage

and hence discomfort to the animals after their recovery from anesthesia. The pertinent observation is that sheep prepared chronically for electrophysiologic recording show the same type of RF sensitization that has been seen previously in other laboratory species under acute recording conditions.^{1,4-13} Non-noxious stimulation, in comparison, had no effect on RFs of either WDR or LTMR neurons recorded under halothane anesthesia.

The important and novel finding of this study is that RFs of spinal neurons can be modified by localized stimuli at well below noxious threshold—but only when the recordings are made from animals in a fully conscious state. This effect was seen with WDR neurons in both dorsal and ventral horns but not with LTMR neurons. The greater susceptibility of WDR than LTMR neurons to modulation of RF characteristics has been observed over many years.^{22,23} High-threshold mechanoreceptive (nocispecific) neurons cannot be assessed in this sort of test; the only way to identify and assess the RFs of such units is with noxious stimulation, which would preclude measuring the effects of solely non-noxious conditioning.

The fact that sensitization occurs with such low levels of stimulation introduces a difficulty in investigating the process itself: any further stimulation applied during characterization of the new RF would be expected to cause further alteration. To minimize this problem, testing was limited (with few exceptions) to mapping the RF limits at 5-min intervals; it is therefore not possible from these experiments to comment on the degree

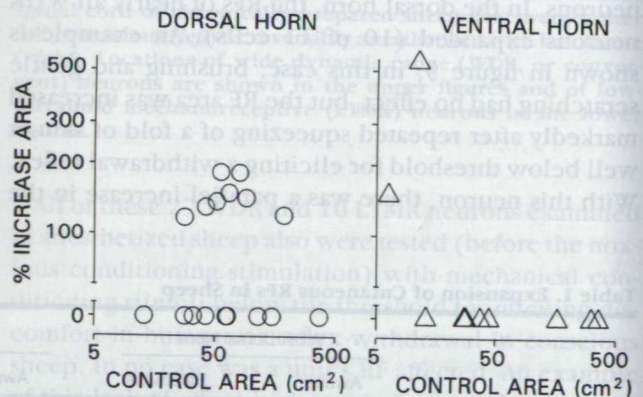
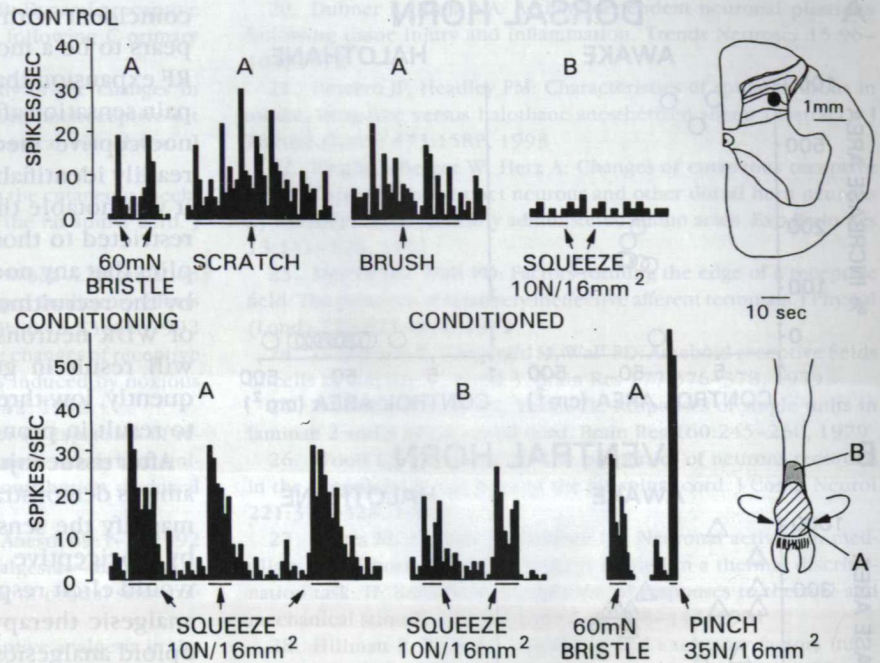


Fig. 4. Areas of receptive fields (RFs) of lumbar spinal wide dynamic range (WDR) neurons in dorsal (left) and ventral horns (right) in halothane-anesthetized sheep. In each panel, the relationship is shown of RF area before conditioning stimuli were applied to the receptive field at noxious intensities (X axis), and the percentage increase in this area caused by the conditioning stimuli (Y axis). No cells showed a decrease of RF area. Note the logarithmic scales.

Fig. 5. Expansion of the receptive field (RF) of a dorsal horn wide dynamic range (WDR) neuron in a conscious sheep after non-noxious conditioning stimulation to the skin. Layout similar to figure 2. (Right) The locations of the unit and of the original (cross-hatched) and expanded (stippled) RF. Upper row of histograms shows the spike discharge rate to various cutaneous stimuli applied within (A) and outside (B) the RF before conditioning. Lower row shows response to the three non-noxious conditioning stimuli and the subsequent increased responsiveness outside the original RF. The last histograms show the increased responsiveness within the original RF to low-intensity stimulation (compare with first response in upper row); and finally, a test with a noxious pinch stimulus that both activated the cell vigorously (identifying it as a WDR unit) and elicited a brisk withdrawal response that caused the cell to be lost.



of sensitization occurring within the original RF nor on the details of the time course of the process. However, it was clear, for a minority of units tested, that the sensitivity of the original RF was enhanced (fig. 5), but this effect was not quantified. It was also clear that enlargement of the RF had occurred within 1 min of conditioning and that it could last for at least 5 min (the first time at which further mapping stimuli were applied). With many neurons, no recovery was seen after 20 min; however, this may be an overestimate of the duration, given that the testing of RFs may have prolonged the effect.

Alterations of spinal neuronal RF size and sensitivity in the absence of noxious stimulation have been reported before, but in most of these cases, the cause of the variations was not established.²⁴⁻²⁶ In one report, low-threshold stimulation in acute preparations was observed to reduce RF area,²⁵ whereas in the current study, non-noxious stimulation only triggered enhancement of WDR RF size. There also is clear evidence from the trigeminal system of trained monkeys that the responses of WDR units to non-noxious as well as noxious stimuli can be altered by attention states.²⁷

The increases in RF were not trivial. The RF areas of 10/11 WDR neurons in the dorsal horn were increased by an average of 330% (fig. 6) and those of 19/22 WDR neurons in the ventral horn by 410%. Moreover, this

increase in RF area was greater and occurred with a higher proportion of neurons than was the case after stimulation *above* the noxious threshold in a similar population of WDR neurons recorded in the same animals under halothane anesthesia (145%).

It is evident from these results that marked expansion of the RFs of spinal WDR neurons is not restricted to being a pathologic response to tissue-damaging stimuli. Rather, under normal conscious conditions, neuronal RF area is controlled dynamically by a range of sensory inputs including those to stimuli that are well below the threshold for pain (or reflex withdrawal). The same process does not occur under halothane anesthesia. It may be relevant that the RFs of WDR neurons under halothane anesthesia were significantly larger than under awake conditions. The larger size under halothane could reflect a removal of descending inhibitory controls that are known to restrict RF area²⁸; if such control mechanisms are partially inactivated by the anesthetic, it may follow that dynamic changes of RF properties also are suppressed. Enlargement of RF area also has been seen, but only with a minority of neurons, after pentobarbital administration to chronically prepared cats²⁹; such enlargement is at variance with the smaller RFs seen in acutely prepared cats under halothane anesthesia *versus* after decerebration (*e.g.*, reference 30).

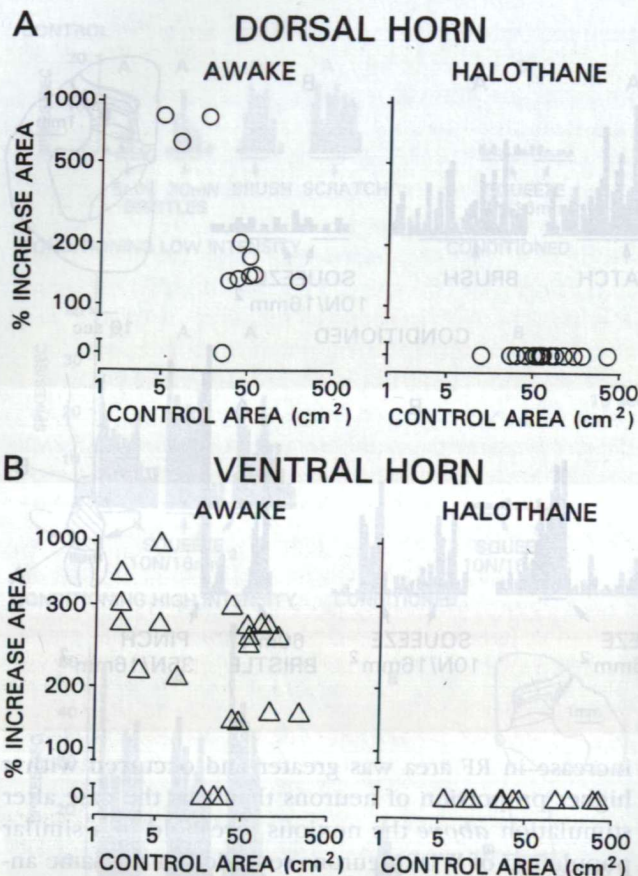


Fig. 6. Areas of receptive fields (RFs) of wide dynamic range (WDR) neurons in dorsal horn (top) and ventral horn (bottom) in conscious (left) and halothane-anesthetized sheep (right). Panels as in figure 4. In this case, the conditioning stimuli were of low intensity, well below threshold for evoking a withdrawal reflex in conscious animals. Note logarithmic scales.

The finding of dynamic control over RF size by non-noxious mechanical stimuli, most of which will be mediated *via* A β afferents, requires a reconsideration of the function of such changes of RF size. Expansion of the RFs of single cells will result, *via* well demonstrated mechanisms of spatial summation,^{19,20} in the recruitment of more spinal neurons after any given peripheral stimulus. This mechanism would be well suited to a form of (presumably subconscious) "attention," so that any stimulus that is maintained for an unusual duration, even if it is harmless, will result in a greater input from that RF; this will permit the organism to respond in the most appropriate manner to continuously varying levels of sensory input from low-threshold receptors. Indeed, changes in RF characteristics have already been seen

coincident with altered attentiveness.^{15,16,27} This appears to be a more plausible physiologic function for RF expansion than one that is limited to an increase in pain sensation after stimuli that already activate central nociceptive mechanisms; the latter would serve no readily identifiable physiologic purpose. Nonetheless, it was notable that the units showing expansion were restricted to those that had WDR properties. This implies that any nociceptive input also would be affected by the recruitment process, so increasing the number of WDR neurons activated. It is established that this will result in greater pain responsiveness.³¹ Consequently, low-threshold sensitization would be expected to result in pronociception too.

After tissue injury, such as clinical surgery, the mechanisms demonstrated here therefore would presumably magnify the sensitizing effects known to be triggered by nociceptive inputs. These low-threshold inputs would elicit responses that are likely to be resistant to analgesic therapy, because it is well established that opioid analgesics preferentially reduce responses mediated by A δ - and C-fiber afferents rather than those mediated by A β afferents.³² This mechanism therefore might reduce the postulated advantages of clinical "preemptive" analgesia and could be a contributing factor to the disappointing results in many of the clinical trials of preemptive opioid analgesia for postoperative pain.¹⁴ Further tests with other types of stimulus and monitoring other parameters of the RF will be needed to clarify this hypothesis.

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