


D Le Bars and J C Willer, Diffuse Noxious Inhibitory Controls (DNIC). In: Allan I. Basbaum, Akimichi Kaneko, Gordon M. Shepherd and Gerald Westheimer, editors The Senses: A Comprehensive Reference, Vol 5, Pain, M. Catherine Bushnell and Allan I. Basbaum. San Diego: Academic Press; 2008. p. 763-774.

# 5.50 Diffuse Noxious Inhibitory Controls (DNIC)

**D Le Bars**, INSERM U-713, Paris, France

**J C Willer**, INSERM U-731, Paris, France





## Glossary

***allodynia*** Pain caused by stimuli that would not normally cause pain (i.e., non-noxious stimuli).

***basic somesthetic activity*** Description of the ongoing activity in somatosensory pathways in the absence of any deliberate stimuli but including stimuli provided by the environment.

***blink reflex*** Exteroceptive reflex of the orbicularis oculi muscles usually evoked by stimuli such as a mechanical tap on the glabella or by electrical currents delivered to the skin in the periorbital region.

***Brown-Séquard syndrome*** Patient with a hemisection of the spinal cord of traumatic origin.

***bulbospinal control*** A neural control mechanism originating in the brainstem and projecting to the spinal cord.

***dermatome*** Area of skin innervated by nerves from a given segment of the spinal cord.

***descending inhibition*** Inhibition of spinal cord function produced by pathways originating in the brain.

***diffuse noxious inhibitory controls (DNICs)*** Neural controls triggered by noxious stimulation of widespread areas of the body which exert an inhibitory influence on wide-dynamic-range (WDR) neurons.

***electromyography (EMG)*** All electrophysiological methods for exploring the physiology and pathophysiology of peripheral nerves and muscles.

***excitatory receptive field*** Area of the body (surface or interior) which when stimulated will produce excitation of a given neuron.

***hemianalgesia*** Loss of pain sensation from one half of the body.

***heterotopic*** Part of the body remote from the area of interest (e.g., the excitatory receptive field of a neuron).

***Hoffmann reflex (H reflex)*** Monosynaptic reflex from the calf muscles elicited by electrical stimulation of the sciatic nerve.

***inhibitory receptive field*** Area of the body (surface or interior) which when stimulated will produce inhibitory effects on the activity of a given neuron.

***jaw-opening reflex*** Exteroceptive reflex produced by stimulation of facial or intraoral afferents and involving activation of jaw opening muscles (e.g., the digastric) and/or inhibition of activity in jaw closing muscles (e.g., the masseter).

***jerk reflex*** Myotatic monosynaptic reflex usually elicited by a percussion of a muscle's tendon using a reflex testing hammer.

***Lasègue's maneuver*** Elevation of a lower limb in an extended position on a patient lying on a bed. This technique explores the Lasègue's sign which is the painful limitation of the angle of elevation in cases of radicular compression of the sciatic nerve.

***microelectrophoretic application*** Application of a substance in its ionic form from a microelectrode by the application of electrical current.

***monoarthritis*** Inflammation of a single joint.

***mononeuropathy*** A disturbance of function or pathological changes in a single nerve.

***nociceptive stimulus*** Stimulus that activates nociceptive afferents (which could be a noxious stimulus or an electrical stimulus).

***noxious stimulus*** Stimulus that causes or threatens to cause tissue damage.

***polyarthritis*** Inflammation of several joints.

***propriospinal mechanism*** Neural mechanism mediated entirely within the spinal cord.



*The Senses: A Comprehensive Reference,* vol. 5, pp. 763-773

***$R_{III}$ reflex*** Electromyographic response elicited by electrical painful stimulation of the (purely cutaneous) sural or ulnar nerve by recording from the biceps femoris (lower limb) or biceps brachialis (upper limb), respectively. So-named because it involves activation of group III (A$\delta$) afferents.
***subnucleus reticularis dorsalis (SRD)*** Brainstem nucleus located ventral to the cuneate nucleus, between trigeminal nucleus caudalis and the nucleus of the solitary tract.
***supraspinal mechanism*** Neural mechanism that involves structures above the spinal cord.
***tetraplegic*** Patient with a complete transection of traumatic origin at a high level of the spinal cord thus affecting all four limbs.
***transcutaneous electrical nerve stimulation (TENS)*** Technique for inducing analgesia/hypoalgesia by electrically stimulating peripheral nerves through the skin (i.e., with electrodes placed on the skin).
***trigeminal nucleus caudalis*** Most caudal part of the trigeminal sensory nuclear complex (or of the trigeminal spinal nucleus); also sometimes called the medullary dorsal horn.
***ventrolateral quadrant*** Part of the spinal cord where spinoreticular and spinothalamic fibers travel.
***Wallenberg's syndrome*** Patient with a unilateral lesion of the retro-olivary part of the brainstem resulting from the ischemia of a posterior cerebellar artery.
***wide-dynamic-range (WDR) neurons*** Neurons of the dorsal horn activated by both noxious and non-noxious stimuli.

## 5.50.1 Introduction

Painful stimuli can diminish or even mask pain elicited by stimulation of a remote (extrasegmental) part of the body (see references in Melzack, R., 1989; Le Bars, D. and Willer, J. C., 2002). This phenomenon has been known since ancient times as illustrated by the Hippocrates' aphorism: "If a patient be subject to two pains arising in different parts of the body simultaneously, the stronger blunts the other." Numerous popular therapeutic methods for the alleviation of pain – some used spontaneously by patients – take advantage of this common clinical observation. It is often referred to as counter-irritation or counter-stimulation. In Kabylia, for example, healers treat rheumatic pain by placing a red-hot scythe close to the abdomen of the patient and then vibrating it at a frequency of about 3 Hz, in order to create a series of acute burning-type painful sensations.

A working hypothesis was developed that some of the neurons involved in the transmission of nociceptive signals might be inhibited by nociceptive stimulation of peripheral territories outside their own excitatory receptive fields. Such a hypothesis was found to be correct at as early a stage in the processing of nociceptive signals as the spinal cord. This phenomenon was termed diffuse noxious inhibitory control (DNIC). Since these spinal neurons are involved in mediating both pain and nociceptive reflexes, DNIC can be studied at three related endpoints: spinal neuronal activities, reflexes, and sensations. The first two are accessible in animals while the last two can be studied in human beings (Figure 1).

## 5.50.2 A Spinally Mediated Process

Combined psychophysical measurements and recordings of nociceptive reflexes in man have shown that the spinal cord is involved in the phenomenon of pain inhibiting pain (Willer, J. C. *et al.*, 1984). Electrical stimulation of the sural nerve at the ankle simultaneously induces a nociceptive reflex in a knee flexor muscle (the $R_{III}$ reflex) and a pinprick type of painful sensation in the territory of the nerve (Willer, J. C., 1977). Both the reflex and the sensation have strong relationships with the stimulus intensities – with the thresholds for both parameters being practically identical.

One line of study involved recording these parameters (i.e., the reflex and pain) before, during, and after the application of heterotopic conditioning stimuli such as the immersion of a hand in a thermoregulated water bath at various temperatures (Figure 2, upper panels). When the temperature of the bath was lower than 45 °C, the immersion of the

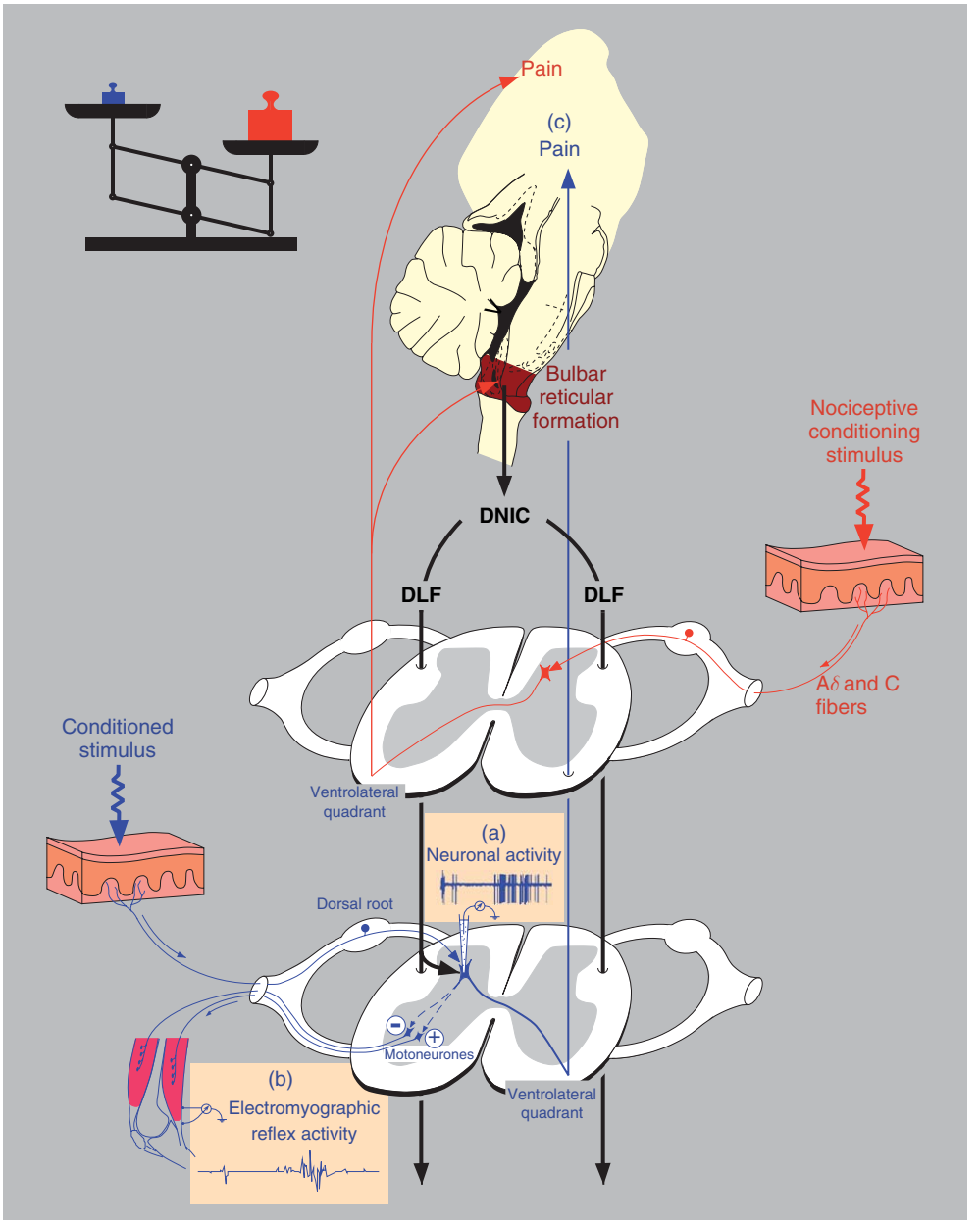
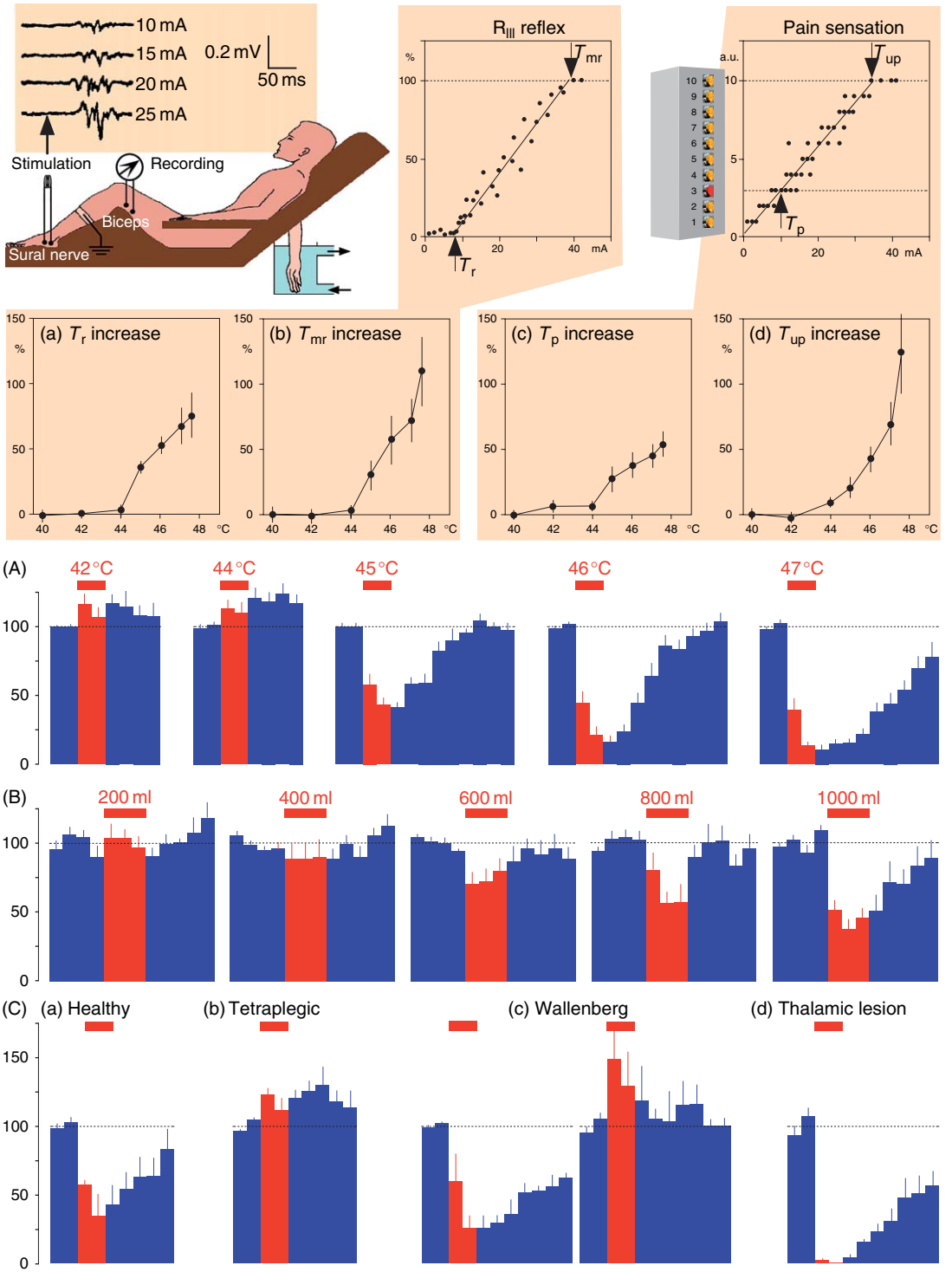



**Figure 1** Nociceptive signals activate dorsal horn neurons, which in turn transfer the information to the brain to elicit pain and to spinal interneurons (broken blue line) to elicit somatic and vegetative reflexes. The effects on motoneurons through polysynaptic pathways trigger a movement that moves the stimulated area away from the stimulus. This movement results from both excitatory (e.g., contraction of flexor muscles) and inhibitory mechanisms – the latter affecting antagonist muscles. In animals, one can record from neurons (a) and from muscles (b) but the sensation (c) cannot be assessed. In man, on the other hand, one cannot record from neurons but it is possible to monitor both the sensation and the reflex activities. In an experimental paradigm designed for the study of pain inhibiting pain phenomena, one requires a conditioned stimulus (here in blue) with the corresponding endpoints (a, b, or c) and a conditioning stimulus (here in red). A painful focus activates dorsal horn neurons that send an excitatory signal through the ventrolateral quadrant toward higher centers, including the lower brainstem. This signal activates DNICs, which will inhibit WDR neurons through the dorsolateral funiculi (DLF). With two painful foci, the resulting sensation will depend on the balance of the nociceptive information elicited from the two sources. The power of such nociceptive information depends on the three dimensions of any nociceptive stimulus, namely strength, duration, and area. In an experimental situation designed to observe inhibitions of the response to the conditioned stimulus, the beam of the balance should tilt in favor of the conditioning stimulus. This is illustrated in Figure 2 where the response to a 20 ms duration series of electrical pulses is inhibited by the stimulation of the hand for 2 min.



hand did not elicit any change in the stimulus–response relationships. By contrast, temperatures between 45 and 47.5 °C caused the stimulus–response curves to shift to the right as a direct function of the temperature. Similar effects were observed when other painful procedures were applied as conditioning stimuli (e.g., cold, pressure, exercise under ischemia, high-intensity transcutaneous electrical nerve stimulation) (Willer, J. C. *et al.*, 1984; 1989; Danziger, N. *et al.*, 1998; France, C. R. and Suchowiecki, S., 1999; Sandrini, G. *et al.*, 2000).

The temporal evolution of these phenomena can be studied by applying a heterotopic conditioning stimulus while the sural nerve is stimulated at a constant intensity (Figure 2, lower panels). This procedure revealed aftereffects of long duration. For example, a 2 min immersion of the hand in a 47 °C water bath completely abolished the $R_{III}$ reflex and it took more than 9 min to achieve a full recovery (Figure 2(A)). Very similar effects were produced by visceral stimulation (gastric or rectal distension) in healthy volunteers (Bouhassira, D. *et al.*, 1994; 1998). During gastric distension for example (Figure 2(B)), the inhibitory effects increased with the volume of distension and the resultant sensation. As with the inhibitions elicited by stimulation of somatic structures, these visceral-evoked inhibitions were correlated to the intensity of the conditioning stimuli. However, they could be triggered by stimuli which were unpleasant but not quite painful (Figure 2(C)). When they become clearly painful, the duration of the inhibitory effects outlasted the duration of the distension by several minutes.

Clinical pains can also activate this type of inhibition. Thus, in patients suffering from sciatic pain due to a herniated disk, a Lasègue's maneuver of the affected leg, which elicits a typical radicular pain, also blocks the $R_{III}$ reflex, both in the affected and

**Figure 2** (Upper panels) Experimental setup for recording the nociceptive $R_{III}$ flexion reflex from the biceps femoris muscle in the lower limb using surface electrodes. The reflex is evoked by electrical stimulation of the ipsilateral sural nerve. The insert shows typical examples of electromyographic (EMG) responses elicited by increasing stimulus intensities (from top to bottom). The subjective sensation was estimated by the subject on a 10-level scale (box with switches shown in insert), with the pain threshold being defined as level 3. Examples of stimulus–response curves for the nociceptive reflex and subjective reports of sensations produced by a wide range of stimulation intensities applied randomly are shown on the left and right graphs, respectively. Note the close correlations between (1) the reflex threshold ($T_r$) and the pain threshold ($T_p$) around 10 mA; and (2) the stimulus intensities producing maximal responses, that is, the threshold of the maximal reflex recruitment ($T_{mr}$) versus the threshold of unbearable pain ($T_{up}$). Such recruitment curves were built before and during a 2 min period of immersion of the right hand in a thermoregulated water bath. No effects were seen at lower temperatures but a shift of the curves to the right was elicited when the temperature reached painful levels (45 °C and above). The shift applied to the reflex (a, b) and sensation (c, d) thresholds. (Lower panels) The temporal evolution of the reflex can be monitored by employing repeated, constant, stimulation of the sural nerve (1.2 times threshold every 6 s). The individual $R_{III}$ reflex is expressed in terms of the percentages of the mean value recorded during a control period. Each vertical bar represents the mean of ten responses recorded during 1 min. Graphs show pooled data from several subjects. (A) Effects of immersion of the hand. The nonpainful temperature (42 and 44 °C, left) did not modify the reflex. By contrast, the painful temperatures (45, 46, and 47 °C) depressed the reflex during and after the period of conditioning. The extent of these depressions was temperature dependent. Note the long duration (around 10 min) of the inhibitory posteffects following the application of the highest temperature (47 °C, right). (B) Effects of visceral stimulation. Gastric distension by means of a balloon introduced into the proximal part of the stomach was applied for a 3 min period. The inflation of the balloon in volumes of 200 or 400 ml did not modify the $R_{III}$ reflex, whereas volumes of 600, 800, and 1000 ml produced inhibitions correlated to the volume of distension. The 600 and 800 ml distensions were unpleasant while the 1000 ml volume was clearly painful. (C) Effects of nociceptive electrical stimuli (20–25 mA) applied to the upper limb of healthy volunteers or patients with lesions of the spinal cord or the brain. (a) In healthy volunteers; (b) in tetraplegic patients, the conditioning stimulus did not inhibit the $R_{III}$ reflex; (c) in patients with a Wallenberg syndrome (unilateral lesion of the retro-olivary part of the brainstem) the conditioning stimuli did or did not inhibit the $R_{III}$ reflex depending on whether it was applied to the normal hand (ipsilateral to the brain lesion) or the analgesic hand (contralateral to the brain lesion); and (d) in patients with thalamic lesions, the conditioning stimulation applied to the analgesic hand (contralateral to the brain lesion) did produce inhibition of the $R_{III}$ reflex. (Upper panels) Adapted from Willer, J. C., Roby, A., and Le Bars, D. 1984. Psychophysical and electrophysiological approaches to the pain relieving effect of heterotopic nociceptive stimuli. Brain 107, 1095–1112. (A) Adapted from Willer, J. C., De Broucker, T., and Le Bars, D. 1989. Encoding of nociceptive thermal stimuli by diffuse noxious inhibitory controls in humans. J. Neurophysiol. 62, 1028–1038. (B) Adapted from Bouhassira, D., Chollet, R., Coffin, B., *et al.* 1994. Inhibition of a somatic nociceptive reflex by gastric distention in humans. Gastroenterology 107, 985–992. (C) Adapted from Roby-Brami, A., Bussel, B., Willer, J. C., and Le Bars, D. 1987. An electrophysiological investigation into the pain-relieving effects of heterotopic nociceptive stimuli: probable involvement of a supraspinal loop. Brain 110, 1497–1508; and De Broucker, T., Cesaro, P., Willer, J. C., Le Bars, D. 1990. Diffuse noxious inhibitory controls (DNIC) in man: involvement of the spino-reticular tract. Brain 113, 1223–1234.

in the nonaffected leg (Willer, J. C. *et al.*, 1987). When the Lasègue's maneuver is performed on the healthy limb, it is painless and has no effect on the reflex. In patients suffering from neuropathic pain, the $R_{III}$ reflex is inhibited when pain is triggered by pressure ('static allodynia'), but not when it is triggered by light brushing ('dynamic allodynia') (Bouhassira, D. *et al.*, 2003). Interestingly, it is generally agreed that the former is due to the activation of nociceptive processes via A$\delta$- and C-fibers, while the latter is due to the activation of A$\beta$-fibers.

In summary, a painful conditioning stimulus can depress both a preexisting pain and its associated nociceptive reflex at the first spinal relays for the transmission of nociceptive information. Interestingly, nociceptive brainstem reflexes such as the blink or jaw-opening reflexes are also inhibited by remote painful stimulation (Pantaleo, T. *et al.*, 1988; Maillou, P. and Cadden, S. W., 1997; Ellrich, J. and Treede, R. D., 1998). By contrast, nonnociceptive reflexes such as jerk or Hoffmann reflexes remain unaffected during such procedures. One must stress here that there has to be an obvious imbalance between the conditioned and the conditioning stimuli for a clear depressive effect to be seen. For instance, in the examples shown in Figure 2, the conditioned stimuli were short (20 ms) trains of electrical shocks, whereas the conditioning stimuli were applied over time periods of several seconds to large areas of the body. Clearly, spatiotemporal summation is required to elicit visible inhibitory effects because of the reciprocal nature of the phenomenon triggered by two remote painful foci. A balance, the beam of which tips (or does not tip) in favor of one or other pain, could symbolize the net result of such a reciprocal process (Figure 1, upper left). Of course, clinical situations are always much more complicated than these experimental situations which are deliberately designed to simplify the problem under analysis. More particularly, it seems likely that the existence of multiple painful foci would produce very complicated interactions between excitatory and inhibitory processes.

## 5.50.3 A Spinally Mediated Process Involving Supraspinal Structures

Are the inhibitory mechanisms described above due to propriospinal mechanisms or do they involve supraspinal structures? To answer this question, the effects on the $R_{III}$ reflex in the right leg, of nociceptive conditioning stimuli applied to the fourth and fifth fingers of the left hand were compared in normal subjects and tetraplegic patients with lesions of traumatic origin at the cervical-5–7 level (Roby-Brami, A. *et al.*, 1987). In the normal subjects (Figure 2(Ca)), the painful conditioning stimuli strongly depressed both the $R_{III}$ reflex and the associated pain. By contrast, in the tetraplegic patients, nociceptive stimulation of the same territories, which, being in the cervical-8 and thoracic-1 dermatomes, were clinically unaffected by the spinal lesion, and did not produce any depression of the $R_{III}$ reflex (Figure 2(Cb)). One can therefore conclude that the inhibitory effects triggered by heterotopic nociceptive stimuli are sustained by a loop that includes supraspinal structures.

In order to identify, or at least localize, these supraspinal structures, observations were made on patients with cerebral lesions causing contralateral hemianalgesia (De Broucker, T. *et al.*, 1990). These were patients with either a lesion of the retro-olivary part of the medulla (Wallenberg's syndrome, Figure 2(Cc)) or a unilateral thalamic lesion (Figure 2(Cd)). In the former group, no inhibitions were observed when the (not felt) nociceptive conditioning stimulus was applied to the affected side of the body, contralateral to the brain lesion. If this stimulus was applied to the normal side, ipsilateral to the brain lesion, it was felt as painful and triggered inhibitory effects very similar to those seen in normal subjects. By contrast, in the patients with a thalamic lesion, the $R_{III}$ reflex was strongly depressed, as in normal subjects, by the nociceptive conditioning stimulus applied to the affected side (which was not felt as painful). Thalamic structures and consequently spinothalamic pathways, are therefore not involved in DNIC, whereas brainstem – probably reticular – structures seem to play a key role in these phenomena. These observations also demonstrate unambiguously that such phenomena can be elicited in the absence of a painful sensation, provided the nociceptive nature of the information reaches some brain structures. This suggests that the observed phenomenon does not result from a competition between the two attentional foci that the conditioned and the conditioning pain represent in the healthy volunteers. This is an important observation as it is known that the perception of pain is sensitive to attentional processes (Bushnell, M. C. *et al.*, 1985; Willer, J. C. *et al.*, 1979).

An exceptional case was also reported in a patient with a Brown-Séquard syndrome due to a hemisection

of the spinal cord (left side, T6 level) produced by a knife-stab in the back (Bouhassira, D. *et al.*, 1993). The $R_{III}$ reflexes elicited by stimulation of cutaneous afferents in the ulnar and sural nerves were studied in the upper and lower limbs by recording from the biceps brachialis and biceps femoris muscles, respectively. For each limb, the $R_{III}$ reflex was elicited regularly before, during, and after periods of nociceptive electrical conditioning stimulation applied successively to the other three limbs. Inhibitions of around 90% followed by strong poststimulus effects were observed in all situations except that (1) no inhibition could be obtained when the conditioning stimuli were applied to the lower right limb (contralateral to the spinal lesion), and (2) the $R_{III}$ reflex in the lower left limb was completely insensitive to any of the conditioning stimuli. These results strongly suggest that in human beings (1) the ascending part of the loop subserving DNIC is completely crossed at the spinal level, and (2) the descending part is confined to the white matter ipsilateral to the limb being tested.

## 5.50.4 A Model in the Rat

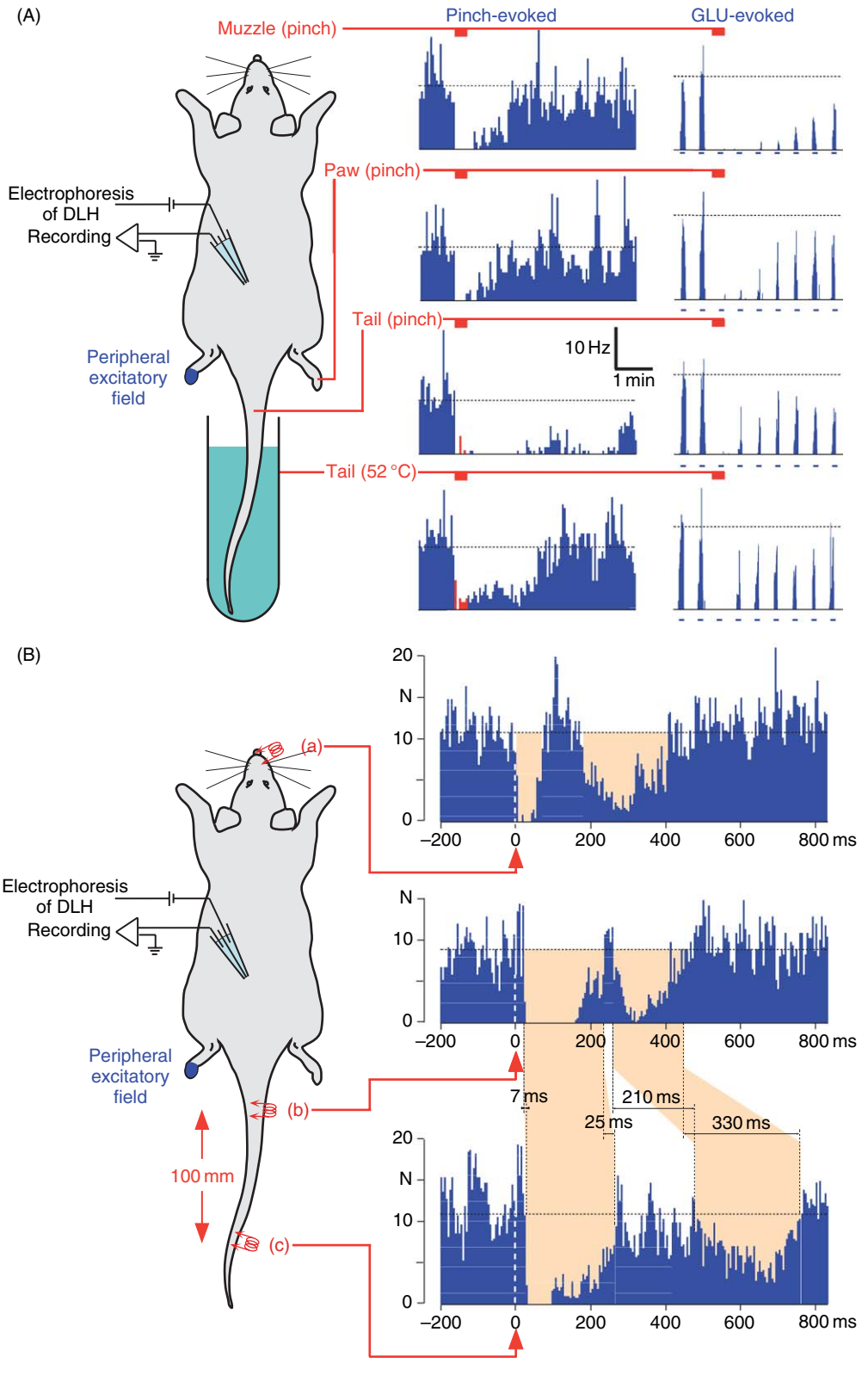
Another nociceptive reflex – this time recorded in the anaesthetized rat – is the C-fiber reflex which can be elicited by electrical stimulation of the sural nerve and recorded from the biceps femoris muscle. This reflex can be strongly inhibited by both mechanical and thermal noxious heterotopic stimuli applied to the muzzle, a paw or the tail, and by colorectal distension. These inhibitory effects on the C-fiber reflex did not occur in spinal animals, or ipsilateral to a rostral unilateral lesion of the dorsolateral funiculus (DLF). Such observations are consistent with several reports showing the inhibition of reflexes or the increase of nociceptive thresholds elicited by heterotopic noxious conditioning. For example, the reflex discharge in the common peroneal nerve following electrical stimulation of the sural nerve in the rat was inhibited by pinching the muzzle or tail; the gastrocnemius medialis reflex evoked by sural nerve stimulation in the decerebrate rabbit was inhibited by electrical stimulation of the contralateral common peroneal or of the ipsi- or contralateral median nerves; the digastric reflex evoked by tooth pulp stimulation in the cat was inhibited by toe pinch, percutaneous electrical stimulation of a limb or electrical stimulation of the saphenous nerve. In behavioral experiments, intraperitoneal or cutaneous injections of an irritant agent or noxious heat all produce an increase in nociceptive thresholds in distant somatic structures, notably the tail (e.g., tail flick test) and paws (e.g., paw withdrawal test). (See references in Le Bars, D. *et al.*, 2001.)

## 5.50.5 The Role of Wide-Dynamic-Range Neurons

In several species (rat, mouse, cat, and probably monkey), most WDR and some nociceptive-specific neurons are strongly inhibited by a noxious stimulus applied outside their excitatory receptive fields. Such effects do not appear to be somatotopically organized but apply to the whole body. Figure 3 shows examples of recordings from lumbar WDR neurons in the rat. The activities of these neurons – whether elicited by pinching their receptive field or by applying an excitatory amino acid to their membranes – were strongly inhibited by noxious mechanical (pinch of the muzzle, the contralateral hindpaw or the tail) or thermal stimuli (immersion of the tail in a 52 °C water bath) (Figure 3(A)). These examples illustrate the whole body inhibitory receptive fields of WDR neurons as recorded in intact rats. Interestingly, such inhibitory controls are exacerbated during clinical pains, for example, when an animal suffers from monoarthritis, polyarthritis or a peripheral mononeuropathy (Danziger, N. *et al.*, 2000; 2001).

These properties of dorsal horn neurons were observed at the level of various segments of the spinal cord and in both nucleus caudalis and nucleus oralis of the trigeminal system – thus suggesting a general organization. In keeping with the human studies shown in Figure 2, there is a clear relationship between the intensity of the conditioning stimulus and the strength of the resultant DNIC. With strong stimuli, the inhibitory effects are powerful and followed by long-lasting poststimulus effects, which can persist for several minutes. In some cases, the inhibitory effects can involve a complete abolition of activity for a long period of time following removal of the conditioning stimuli ('switch off') and the activity can be restored to preconditioning levels by further manipulations of the excitatory receptive field ('switch on') (Cadden, S. W., 1993). (See references in Le Bars, D., 2002.)

With regard to the viscera, some differences should be noted: visceral stimuli, for example, distension of the colon or urinary bladder, generally produce inhibitions with slower rates of onset and recovery but



starting at intensities below a painful level (Cadden, S. W. and Morrison, J. F. B., 1991). It was proposed that these differences might have reflected different amounts and patterns of activity in the relevant primary afferent fibers rather than being due to different central neural mechanisms. Again, this is consistent with human studies (e.g., Figure 2(B)).

In any case, these data suggest that DNICs are triggered specifically by the activation of peripheral nociceptors whose signals are carried by A$\delta$- and C-fibers. In order to investigate further the types of peripheral fiber involved in DNIC, use was made of the facts that (1) trigeminal and spinal dorsal horn neurons respond with relatively steady discharges to the microelectrophoretic application of excitatory amino acids; and (2) DNICs act by a final postsynaptic inhibitory mechanism involving hyperpolarization of the neuronal membrane. It was found that when trigeminal WDR neurons were directly excited by the microelectrophoretic application of glutamate, the percutaneous application of single square-wave, electrical stimuli to the tail always induced a biphasic depression of the resultant activity. Both the early and late components of this inhibition occurred with shorter latencies when the base rather than the tip of the tail was stimulated. Such differences in latency were used to estimate the mean conduction velocities of the peripheral fibers triggering the inhibitions: the means were found to be 7.3 and 0.7 m s$^{-1}$, which fall into the A$\delta$- and C-fiber ranges, respectively. Such biphasic inhibitions could be elicited from any part of the body and recorded from any WDR neurons. Figure 3(B) shows a recording from a lumbar WDR neuron with an excitatory receptive field located on the extremity of the ipsilateral hind paw: two components of inhibition were induced by the activation of A$\delta$ and C-fibers, respectively, when a single 2 ms duration shock of 10 mA was applied to the muzzle, the base or the tip of the tail.

DNICs are not observed in anesthetized or decerebrate animals in which the spinal cord has been sectioned. It is therefore obvious that the mechanisms underlying DNICs are not confined to the spinal cord and that supraspinal structures must be involved. Such a system is therefore completely different from segmental inhibitory systems, which work both in intact and in spinal animals, and can be triggered by the activation of low-threshold afferents. DNICs are also very different from the propriospinal inhibitory processes that can be triggered by noxious inputs. It should also be noted that DNIC are blocked by increasing the anesthetic regimen (Jinks, S. L. *et al.*, 2003).

The ascending and descending limbs of this loop travel through the ventrolateral and dorsolateral funiculi, respectively. Since thalamic lesions do not affect DNICs, it has been proposed that they result from a physiological activation of some of the brainstem structures that produce descending inhibition

**Figure 3** (A) Example of inhibitions of a spinal WDR neuron elicited by noxious heterotopic stimuli. Recordings were made in the lumbar dorsal horn from a WDR neuron with a receptive field located on the ipsilateral hind paw. The neuron was activated either by a sustained pinch of its receptive field or by regular (once a minute) microelectrophoretic applications of the excitatory amino acid, glutamate (GLU, 20 nA, horizontal bars). Conditioning stimuli were pinch of the muzzle, the contralateral hind paw or the tail, and immersion of the tail in a 52 °C water bath (from top to bottom, respectively). Note that all these conditioning stimuli virtually blocked both the pinch-evoked and the DLH-induced firing. In the latter case, the inhibitions remained for several minutes in most cases, suggesting that WDR neurons were hyperpolarized for a long time following the conditioning stimulation. (B) Example of heterotopic activation of A$\delta$- and C-fibers triggering inhibitions in a spinal WDR neuron. Left: Schematic representation of the experimental design. Recordings were made in the lumbar dorsal horn from a WDR neuron with a receptive field located on the ipsilateral hind paw. The continuous microelectrophoretic application of the excitatory amino acid, DL-homocysteic acid (DLH) induced a steady discharge from the neuron under study. The repetitive application of individual percutaneous electrical stimuli of adequate intensities to the contralateral muzzle (a), the base (b), or the tip (c) of the tail induced biphasic depressions of the neuronal activity. Right: Peristimulus histograms (bin width 5 ms) prepared during the continuous microelectrophoretic application (15 nA) of DLH onto the membrane of the neuron. The broken white lines show the timing of percutaneous electrical stimulation (10 mA; 2 ms duration; 0.66 Hz; 200 ms delay; 100 sweeps). The broken black line represents the mean firing calculated during the prestimulation control period (−200 to 0 ms). Two waves of inhibition can be seen. They occurred earlier when the base of the tail (b) was stimulated instead of the tip (c). The time gaps are shown as yellow areas between the histograms, for both inhibitory components. The gap was 7 and 25 ms for the beginning and the end of the first component; it was 150 and 290 ms for the beginning and the end of the second component. Knowing that the distance between b and c was 100 mm, one can easily calculate the conduction velocities of fibers that elicited the first and second components: 4–14 m s$^{-1}$ and 0.3–0.7 m s$^{-1}$ respectively. These fibers therefore belong to the A$\delta$- and C- groups, respectively. (A) Adapted from Villanueva, L., Cadden, S. W., and Le Bars, D. 1984. Evidence that diffuse noxious inhibitory controls (DNIC) are mediated by a final post-synaptic inhibitory mechanism. Brain Res. 298, 67–74.

(see Chapter 5.49). Surprisingly, DNICs were not modified by lesions of the following structures: the periaqueductal gray (PAG), cuneiform nucleus, parabrachial area, locus coeruleus/subcoeruleus, rostral ventromedial medulla (RVM). By contrast, lesions of subnucleus reticularis dorsalis (SRD) in the caudal medulla strongly reduced DNICs. The SRD is located ventral to the cuneate nucleus, between trigeminal nucleus caudalis and the nucleus of the solitary tract and contains neurons with characteristics that suggest they have a key role in processing specifically nociceptive information (Villanueva, L. *et al*., 1996). Indeed, they are preferentially or exclusively activated by nociceptive stimuli from a whole-body receptive field; they encode the intensity of cutaneous and visceral stimulation within noxious ranges; and they are activated exclusively by activity in A$\delta$- or A$\delta$- and C-peripheral fibers. In addition, they send descending projections through the dorsolateral funiculus that terminate in the dorsal horn at all levels of the spinal cord. The fact that the supraspinal loop sustaining DNICs is confined to the most caudal part of the medulla was confirmed in a series of experiments where the potency of DNIC was tested in animals with complete transections at different levels of the brainstem.

## 5.50.6 Summary and Conclusions

There is a body of evidence, based on both human and animal experiments, which strongly suggests that the phenomenon of 'pain inhibiting pain' is sustained by a well-defined neurological substratum based on a spino-reticulo-spinal loop. DNICs are in fact a very special and generalized case of lateral inhibition and it is very likely that they subserve a related function. Although lateral inhibition is sometimes thought of in terms of creating illusions, such phenomena play an important role in other senses (see Chapters 1.01 and 3.30). It is very probable that DNICs, as revealed by the empiric observation that pain inhibits pain, also play an important role in pain processing, probably by focusing the pain network onto a particular part of the body. The DNIC system could be understood as a filter allowing the extraction by the brain of a clear signal of pain from a basic somesthetic activity provided by dorsal horn WDR neurons (see Chapter 5.25). If these statements are correct, then defocusing should alleviate the unpleasantness of pain. Interestingly, the reference analgesic drug, morphine, blocks DNICs in both man and animals (Le Bars, D. *et al*., 1992).

Many sources of descending inhibition from the brain that modulate the spinal transmission of nociceptive information have been described in animals (see Chapters 5.41 and 5.49). To date, the only descending inhibitory mechanisms that have been described in man are DNICs.

## References


Bouhassira, D., Chollet, R., Coffin, B., Lemann, M., Le Bars, D., Willer, J. C., and Jian, R. 1994. Inhibition of a somatic nociceptive reflex by gastric distention in humans. Gastroenterology 107, 985–992.

Bouhassira, D., Danziger, N., Guirimand, F., and Attal, N. 2003. Comparison of the pain suppressive effects of clinical and experimental painful conditioning stimuli. Brain. 126, 1068–1078.

Bouhassira, D, Le Bars, D., Bolgert, F., Laplane, D., and Willer, J. C. 1993. Diffuse noxious inhibitory controls (DNIC) in man. A neurophysiological investigation of a patient with a form of Brown-Séquard syndrome. Ann. Neurol. 34, 536–543.

Bouhassira, D., Sabate, J. M., Coffin, B., Le Bars, D., Willer, J. C., and Jian, R. 1998. Effects of rectal distensions on nociceptive flexion reflexes in humans. Am. J. Physiol. 275, G410–G417.

Bushnell, M. C., Duncan, G. H., Dubner, R., Jones, R. L., and Maixner, W. 1985. Attentional influences on noxious and innocuous cutaneous heat detection in humans and monkeys. J. Neurosci. 5, 1103–1110.

Cadden, S. W. 1993. The ability of inhibitory controls to 'switch-off' activity in dorsal horn convergent neurones in the rat. Brain Res. 628, 65–71.

Cadden, S. W. and Morrison, J. F. B. 1991. Effects of visceral distension on the activities of neurones receiving cutaneous inputs in the rat lumbar dorsal horn; comparison with effects of remote noxious somatic stimuli. Brain Res. 558, 63–74.

Danziger, N., Gautron, M., Le Bars, D., and Bouhassira, D. 2001. Activation of diffuse noxious inhibitory controls (DNIC) in rats with an experimental peripheral mononeuropathy. Pain 91, 287–296.

Danziger, N., Rozenberg, S., Bourgeois, P., Charpentier, G., and Willer, J. C. 1998. Depressive effects of segmental and heterotopic application of transcutaneous electrical nerve stimulation and piezo-electric current on lower limb nociceptive flexion reflex in human subjects. Arch. Phys. Med. Rehabil. 79, 191–200.

Danziger, N., Le Bars, D., and Bouhassira, D. 2000. Diffuse Noxious Inhibitory Controls and Arthritis in the Rat. In: Pain and Neuroimmune Interactions (*eds*. N. E. Saadé, A. V. Apkarian, and S. J. Jabbur), pp. 69–78. Kluwer Academic Press.

De Broucker, T., Cesaro, P., Willer, J. C., and Le Bars, D. 1990. Diffuse noxious inhibitory controls (DNIC) in man: involvement of the spino-reticular tract. Brain 113, 1223–1234.

Ellrich, J. and Treede, R. D. 1998. Characterization of blink reflex interneurons by activation of diffuse noxious inhibitory controls in man. Brain Res. 803, 161–168.

France, C. R. and Suchowiecki, S. 1999. A comparison of diffuse noxious inhibitory controls in men and women. Pain 81, 77–84.

Jinks, S. L., Antognini, J. F., and Carstens, E. 2003. Isoflurane depresses diffuse noxious inhibitory controls in rats between

0.8 and 1.2 minimum alveolar anesthetic concentration. Anesth. Analg. 97, 111–116.

Le Bars, D. 2002. The whole body receptive field of dorsal horn multireceptive neurones. Brain Res. Rev. 40, 29–44.

Le Bars, D. and Willer, J. C. 2002. Pain Modulation Triggered by High-Intensity Stimulation: Implication for Acupuncture Analgesia. In: Acupuncture: Is there a Physiological Basis? (*eds*. P. Li, A. Sato, and J. Campbell), International Congress Serie 1238, pp. 11–29. Elsevier.

Le Bars, D., De Broucker, T., and Willer, J. C. 1992. Morphine blocks pain inhibitory controls in humans. Pain 48, 13–20.

Le Bars, D., Gozariu, M., and Cadden, S. W. 2001. Animal models of nociception. Pharmacol. Rev. 53, 597–652.

Maillou, P. and Cadden, S. W. 1997. Effects of remote deep somatic noxious stimuli on a jaw reflex in man. Arch. Oral. Biol. 42, 323–327.

Melzack, R. 1989. Folk Medicine and the Sensory Modulation of Pain. In: Textbook of Pain (*eds*. P. D. Wall and R. Melzack), pp. 897–905. Churchill Livingstone.

Pantaleo, T., Duranti, R., and Bellini, F. 1988. Effects of heterotopic ischemic pain on muscular pain threshold and blink reflex in humans. Neurosci. Lett. 85, 56–60.

Roby-Brami, A, Bussel, B., Willer, J. C., and Le Bars, D. 1987. An electrophysiological investigation into the pain-relieving effects of heterotopic nociceptive stimuli: probable involvement of a supraspinal loop. Brain 110, 1497–1508.

Sandrini, G., Milanov, I., Malaguti, S., Nigrelli, M. P., Moglia, A., and Nappi, G. 2000. Effects of hypnosis on diffuse noxious inhibitory controls. Physiol. Behav. 69, 295–300.

Villanueva, L., Bouhassira, D., and Le Bars, D. 1996. The medullary subnucleus reticularis dorsalis (SRD) as a key link in both the transmission and modulation of pain signals. Pain 67, 231–240.

Villanueva, L., Cadden, S. W., and Le Bars, D. 1984. Evidence that diffuse noxious inhibitory controls (DNIC) are mediated by a final post-synaptic inhibitory mechanism. Brain Res. 298, 67–74.

Willer, J. C. 1977. Comparative study of perceived pain and nociceptive flexion reflex in man. Pain 3, 69–80.

Willer, J. C., Boureau, F., and Albe-Fessard, D. 1979. Supraspinal influences on nociceptive flexion reflex and pain sensation in man. Brain Res. 179, 61–68.

Willer, J. C., De Broucker, T., and Le Bars, D. 1989. Encoding of nociceptive thermal stimuli by diffuse noxious inhibitory controls in humans. J. Neurophysiol. 62, 1028–1038.

Willer, J. C., Roby, A., and Le Bars, D. 1984. Psychophysical and electrophysiological approaches to the pain relieving effect of heterotopic nociceptive stimuli. Brain 107, 1095–1112.

Willer, J. C., Barranquero, A., Kahn, M. F., and Salliere, D. 1987. Pain in sciatica depresses lower limb cutaneous reflexes to sural nerve stimulation. J. Neurol. Neurosurg. Psych. 50, 1–5.