The activation of bulbo-spinal controls by peripheral nociceptive inputs: Diffuse noxious inhibitory controls

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Some neurones in the dorsal horn of the spinal cord are strongly inhibited when a nociceptive stimulus is applied to any part of the body, distinct from their excitatory receptive fields. This phenomenon was termed "Diffuse Noxious Inhibitory Controls" (DNIC). DNIC influence only convergent neurones, and these inhibitions can be triggered only by conditioning stimuli which are nociceptive. The inhibitions are extremely potent, affect all the activities of the convergent neurones and persist after the removal of the conditioning stimulus. Only activity of Aδ- or Aδ- and C- peripheral fibres can trigger DNIC.

DNIC are sustained by a complex loop which involves supraspinal structures since, unlike segmental inhibitions, they are not observed in animals in which the cord has previously been transected at the cervical level. The ascending and descending limbs of this loop travel respectively through the ventro-lateral and dorso-lateral funiculi, respectively. We proposed that DNIC result from the physiological activation of some brain structures putatively involved in descending inhibition. However, lesions of the mesencephalon, including the periaqueductal grey (PAG) and the rostral ventromedial medulla (RVM), including nucleus raphé magnus, did not modify DNIC. By contrast, lesions of subnucleus reticularis dorsalis (SRD) in the caudal medulla strongly reduced DNIC. Both electrophysiological and anatomical data support the involvement of SRD neurones in spino-bulbo-spinal loop(s).

In man, very similar results have been obtained by means of combined psychophysical measurements and recordings of nociceptive reflexes (RIII reflex). Painful heterotopic conditioning stimuli depress both the reflex and the associated painful sensation, with stronger effects being observed with more intense conditioning stimuli. By contrast, in tetraplegic patients, heterotopic nociceptive stimulation did not produce any depression of the RIII reflex. Observations were also made on patients with cerebral lesions causing contralateral hemi-analgesia, either a unilateral thalamic lesion or a lesion of the retro-olivary part of the medulla (Wallenberg's syndrome). In the patients with Wallenberg's syndrome, no inhibitions were observed when the nociceptive conditioning stimuli were applied to the affected side whereas if these stimuli were applied to the normal side, they triggered inhibitory effects and post-effects very similar to those seen in normal subjects. These results show that in humans, brainstem - probably reticular- structures seem to play a key role in these phenomena.

The data suggest that nociceptive stimuli, even though there are unquestionably perceived as being painful activate certain inhibitory controls which originate in the brainstem. Since all convergent neurones are subject to DNIC, one can make the assertion that the transmission of nociceptive signals towards higher centres is under the influence of these controls. In other words, the descending inhibitory

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controls may play a physiological role in the detection of nociceptive signals. It is proposed that DNIC constitute both a filter which allows the extraction of the signal for pain and an amplifier in the transmission system which increases the potential alarm function of the nociceptive signals. This hypothesis is supported by the finding that DNIC are blocked by low doses of morphine in both rat and man.

***Key words**: descending inhibition, dorsal horn, medulla oblongata, pain, spinal cord.*

INTRODUCTION

The transmission of nociceptive signals can be modulated by powerful controls at as early a stage as the first spinal relay. These controls include both segmental mechanisms and systems which involve supraspinal structures, and some of them can be triggered by somaesthetic stimuli (see refs in Besson and Chaouch, 1987; Le Bars *et al*, 1986; 1989; Wall, 1989; Willis and Coggeshall 1991; Zieglgänsberger, 1986). This last point is true for segmental mechanisms which can be triggered by stimulation of the corresponding dermatome: the responses of dorsal horn neurones to nociceptive stimuli can be inhibited by innocuous stimulation of large diameter cutaneous fibres. It is generally thought that these phenomena are triggered by the activation of Aαß-fibres alone; however, numerous studies have demonstrated that the activation of Aδ-fibres produces the most powerful segmental inhibitions (see refs in Lee *et al*, 1985). Such effects are essentially restricted to dermatomes and are reflected in the properties of the receptive fields of dorsal horn neurones. They could explain the hypo-algesia which can be elicited by high frequency, low intensity stimulation of peripheral nerves ("Transcutaneous Electrical Nerve Stimulation", TENS) and by some forms of acupuncture or electro-acupuncture. It should be noted however, that the time constant of these clinical effects and of the electrophysiological phenomena are very different: patients can gain pain relief which lasts for hours after such stimulation, whereas the inhibition of neurones in animals or of nociceptive reflexes in man can end as soon as the stimulation stops.

However, there is another category of somaesthetic stimulus which can induce hypoalgesic effects. Although it seems paradoxical at first sight, painful stimuli can diminish, or even mask, pain elicited by stimulation of a remote (extra-segmental) part of the body (see refs in Le Bars *et al*, 1989). This phenomenon has been known of since ancient times and has even been used during surgical procedures on both man and domesticated animals. In the latter category, two examples are the uses of the twitch in horses and of nasal forceps in cattle for performing caudectomies or castrations, both of which are potentially painful operations.

The nature of the controls which underlie these observations is different from that of the inhibitory phenomena described above which are triggered by light stimuli and are essentially segmental. Accordingly, we have developed the working hypothesis that some of the neurones which are involved in the transmission of nociceptive signals can be inhibited by nociceptive stimulation of peripheral territories outside their own excitatory receptive fields. That this applies at as early a stage in sensory pathways as the spinal cord was revealed by the finding that some dorsal horn neurones are strongly inhibited when a nociceptive stimulus is applied to any part of the body distinct from their excitatory receptive fields. For convenience, this phenomenon was termed "Diffuse Noxious Inhibitory Controls" (DNIC).

Diffuse noxious inhibitory controls affect all convergent neurones, that is those neurones activated both by a variety of nociceptive stimuli and by weak mechanical stimulation. The term "convergent neurones" summarizes their main property quite well, *i.e.* that they constitute a strategic site where various types of excitatory and inhibitory influences converge. Various other names are used by different authors for these neurones, *e.g.* "common carriers", "trigger cells", "wide dynamic range cells", "lamina V type neurones", "class 2 neurones", "multireceptive neurones" (see refs in: Besson and Chaouch, 1987;

Le Bars *et al,* 1986; Melzack and Wall 1965; Willis and Coggeshall, 1991; Zieglgänsberger, 1986). These terms can be considered as being synonyms. The cutaneous excitatory receptive fields of these cells exhibit a gradient of sensitivity: in the centre of the receptive field, any mechanical stimulus including small hair movements or light touch, can activate the neurone, whereas at the periphery, only more intense stimuli elicit neuronal responses. In view of the fact that there is overlapping of their receptive fields, the spatial organization of the convergence is likely to play an essential role in elaborating signals from this class of neurones. Since they can also receive nociceptive signals of visceral and/or muscular origin, these neurones are adapted for a global processing of information from both the external environment via the skin and from the internal environment. The idea that convergent neurones may play an important role in the sensory perception of the "body scheme" cannot be excluded.

DIFFUSE NOXIOUS INHIBITORY CONTROLS

In the rat (see refs below), the cat (Morton *et al,* 1987) and probably the monkey (Gerhart *et al,* 1981; Brennan *et al,* 1989), the activity of certain dorsal horn neurones can be strongly inhibited by noxious inputs applied outside their receptive field. Such effects do not appear to be somatotopically organised but apply to the whole body and affect all convergent neurones, including those projecting to the thalamus (Dickenson and Le Bars, 1983), whether in the dorsal horn of various segments of the spinal cord (Cadden *et al,* 1983; Cadden and Morrison, 1991; Calvino *et al,* 1984; Fleischman and Urca, 1989; Le Bars *et al,* 1979a; Morgan *et al,* 1994; Ness and Gebhart, 1991a,b; Schouenborg and Dickenson, 1985; Sher and Mitchell, 1990; Tomlinson *et al,* 1983) or in both caudalis and oralis nuclei of the trigeminal system (Dallel *et al,* 1990; Dickenson *et al,* 1980; Hu, 1990; Morgan *et al,* 1994). By contrast, DNIC do not affect the other neuronal types which are found in these structures, *i.e.* lamina 1 noxious-specific, non-noxious-specific, cold-responsive and proprioceptive neurones (Dickenson *et al,* 1980; Le Bars *et al,* 1979b; Villanueva *et al,* 1984a,b). It should be noted that the inhibitions triggered by heterotopic noxious stimuli are highly sensitive to the type and dose of anaesthetic, an observation which could explain some reports of lesser inhibitory effects (Alarcón and Cervero, 1989; Cervero and Morales, 1988; Gerhart *et al,* 1981; Ness and Gebhart, 1991a,b; Tomlinson *et al,* 1983).

The principal feature of DNIC is that they can be triggered by conditioning stimuli applied to any part of the body, including the viscera, which is distant from the excitatory receptive field of the neurone under study, provided that the stimuli are clearly noxious. Indeed, DNIC can be triggered by any heterotopic nociceptive stimulus whatever its type –mechanical, thermal, chemical, or electrical– whereas non-noxious stimuli are completely ineffective. With strong stimuli, the inhibitory effects are powerful and are followed by long-lasting post-stimulus effects which can persist for several minutes.

When the general characteristics of DNIC are analysed, one striking feature is their capacity to affect all kinds of activity of convergent neurones, no matter whether it is evoked by noxious or non-noxious, natural or electrical peripheral stimuli or by the direct micro-electrophoretic application of excitatory amino-acids (Villanueva *et al,* 1984a,b). All noxious conditioning stimuli tested to date, have markedly inhibited these responses.

DNIC are not observed in anaesthetised or decerebrate animals in which the spinal cord has been sectioned (Cadden *et al,* 1983; Le Bars *et al,* 1979b; Morton *et al,* 1987). It is, therefore, obvious that the mechanisms underlying DNIC 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. DNIC are also very different from the propriospinal inhibitory processes which can be triggered by noxious inputs (Cadden *et al,* 1983; Fitzgerald, 1982; Gerhart *et al,* 1981).

Interestingly, a C-fibre reflex recorded from biceps femoris muscle, elicited by electrical stimulation of the sural nerve, was reported to be strongly inhibited in intact anaesthetized rats by both mechanical and thermal noxious heterotopic stimuli applied to the muzzle, a paw or the tail, and by colorectal distension (Falinower *et al,* 1993; 1994). These inhibitory effects disappeared when the C-fibre reflex was recorded in spinal animals, or ipsilaterally to a rostral unilateral lesion of the dorso-lateral funiculus (DLF). These observations are in keeping with several earlier reports: the reflex discharge in the common peroneal nerve following electrical stimulation of the sural nerve in the rat was found to be inhibited by pinching the muzzle or tail (Schouenborg and Dickenson, 1985); the gastrocnemius medialis reflex evoked by sural nerve stimulation in the decerebrate rabbit was reported to be inhibited by electrical stimulation of the contralateral common peroneal or either ipsi- or contralateral median nerves (Taylor *et al,* 1991); the digastric reflex evoked by tooth pulp stimulation in the cat was found to be inhibited by toe pinch, percutaneous electrical stimulation of a limb or electrical stimulation of the saphenous nerve (Banks *et al,* 1992; Cadden, 1985; Clarke and Matthews, 1985).

In man, very similar results have been obtained by means of electrical stimulation of the sural nerve at the ankle which elicits a nociceptive reflex in the biceps femoris muscle (the RIII reflex): Painful heterotopic conditioning stimuli, no matter whether thermal, mechanical or chemical in nature, depress such a reflex, with stronger effects being observed with more intense conditioning stimuli (Willer *et al,* 1984). By contrast, in tetraplegic patients, heterotopic nociceptive stimulation did not produce any depression of the RIII reflex (Roby-Brami *et al,* 1987).

The peripheral and central mechanisms involved in DNIC are considered below.

Peripheral mechanisms

The relationship between the intensity of a stimulus and the strength of the resultant DNIC was investigated by studying the effects of various temperatures applied to the tail, on the C-fibre responses of lumbar and trigeminal convergent neurones to transcutaneous electrical stimulation of their receptive fields on the hindpaw or face. A highly significant correlation existed between the conditioning temperature in the 44-52° C range and the extent of the inhibition (Le Bars *et al,* 1981a; Villanueva and Le Bars, 1985). In man, the extent of the inhibition of the RIII reflex is also related directly to the intensity of the noxious conditioning stimuli (Willer *et al,* 1989).

These data suggest that DNIC are triggered specifically by the activation of peripheral nociceptors whose signals are carried by Aδ- and C-fibres (see refs in Handwerker and Kobal, 1993; Raja *et al,* 1988). Indeed, we found that when trigeminal convergent neurones were directly excited by the continuous electrophoretic application of DL-homocysteic acid (DLH), the percutaneous application of single square-wave, electrical stimuli to the tail always induced a biphasic depression of the resultant activity (Bouhassira *et al,* 1987). 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 fibres triggering the inhibitions: these were found to be 7.3 and 0.7 m/s, which fall into the Aδ- and C-fibre ranges, respectively. Such inhibitions could be evoked from any part of the body and recorded from any convergent neurones.

Central mechanisms

As already mentioned, DNIC are known to be sustained by a complex loop involving supraspinal structures since, unlike segmental inhibitions, they are not observed in animals in which the spinal cord has previously been transected at the cervical level (Cadden *et al,* 1983; Le Bars *et al,* 1979b; Morton *et al,* 1987). The ascending and descending limbs of this loop travel through the ventro-lateral and dorso-lateral funiculi respectively (Villanueva *et al,* 1986a, b). Since thalamic lesions do not affect DNIC (Villanueva *et al,* 1986b), it has been proposed that they result

from a physiological activation of some of the brainstem structures which produce descending inhibition. In this context, the more efficient structures exert their actions through bulbo-spinal inhibitory pathways which are confined to the dorso-lateral funiculi (see references in: Fields and Basbaum, 1989; Fields and Besson, 1988; Willis and Coggeshall, 1991).

Surprisingly, lesions of the following structures did not modify DNIC: periaqueductal grey (PAG), cuneiform nucleus, parabrachial area, locus coeruleus/subcoeruleus, rostral ventromedial medulla (RVM) including nucleus raphé magnus, gigantocellular and paragigantocellular nuclei (Bouhassira *et al,* 1990; 1992a; 1993a, b). By contrast, lesions of subnucleus reticularis dorsalis (SRD) in the caudal medulla strongly reduced DNIC (Bouhassira *et al,* 1992b). The SRD is located ventral to the cuneate nucleus, between trigeminal nucleus caudalis and the nucleus of the solitary tract and contain neurones with characteristics which suggest that they have a key role in processing specifically nociceptive information (Bing *et al,* 1989; 1990a; Roy *et al,* 1992; Villanueva *et al,* 1988; 1989; 1990; 1991). Indeed, they are unresponsive to visual, auditory or proprioceptive stimulation but are preferentially or exclusively activated by nociceptive stimuli and have "whole-body" receptive fields; they encode precisely the intensity of cutaneous and visceral stimulation within noxious ranges and are activated exclusively by cutaneous Aδ- or Aδ- and C-fibre peripheral volleys; they send descending projections through the dorsolateral funiculus that terminate in the dorsal horn at all levels of the spinal cord (Bernard *et al,* 1990; Villanueva *et al,* 1994a).

On the basis of these results, one can conclude that the most caudal part of the medulla, including at least the SRD, is involved in the loop sustaining DNIC in the rat. This conclusion is in agreement with data obtained in patients with cerebral lesions causing contralateral hemi-analgesia, either a unilateral thalamic lesion or a lesion of the retro-olivary part of the medulla (Wallenberg's syndrome). In the former group, the RIII reflex was strongly depressed, as in normal subjects, by nociceptive conditioning stimuli applied to the affected side which were not felt as painful. By contrast in the patients with Wallenberg's syndrome, no inhibitions were observed when the nociceptive conditioning stimuli were applied to the affected side whereas if these stimuli were applied to the normal side, they triggered inhibitory effects and post-effects very similar to those seen in normal subjects. These results show that in humans, thalamic structures and consequently spino-thalamic pathways are not involved in DNIC whereas brainstem –probably reticular– structures seem to play a key role in these phenomena (De Broucker *et al,* 1990). In addition, it is suggested that DNIC are likely to constitute a system modulating the spinal transmission of nociceptive signals independently of the descending inhibitory controls originating from those midbrain and medullary structures which have been implicated in the postulated "endogenous pain inhibitory system(s)" (Basbaum and Fields, 1984; Fields and Basbaum, 1989; Liebeskind *et al,* 1976).

HYPOTHESES

Is pain triggered by a gradient of activity between two populations of spinal neurones? (Le Bars *et al,* 1979b; 1986; Le Bars and Villanueva, 1988)

The data presented in brief above, indicate that nociceptive stimuli activate certain inhibitory controls which originate in the brainstem (see Fig 1). Since all convergent neurones, including those projecting to the thalamus (Dickenson and Le Bars, 1983), are subject to DNIC one can make the assertion that the transmission of nociceptive signals towards higher centres is under the influence of these controls. This has actually been confirmed for nociceptive reticular neurones recorded in the caudal brainstem (Villanueva *et al,* 1994b).

These descending inhibitory controls, which seemed to have a function directly related to analgesic phenomena, may in fact have a physiological role in the detection of nociceptive signals. Such an interpretation seems to go against good sense, but perhaps this would not be so if one takes into account

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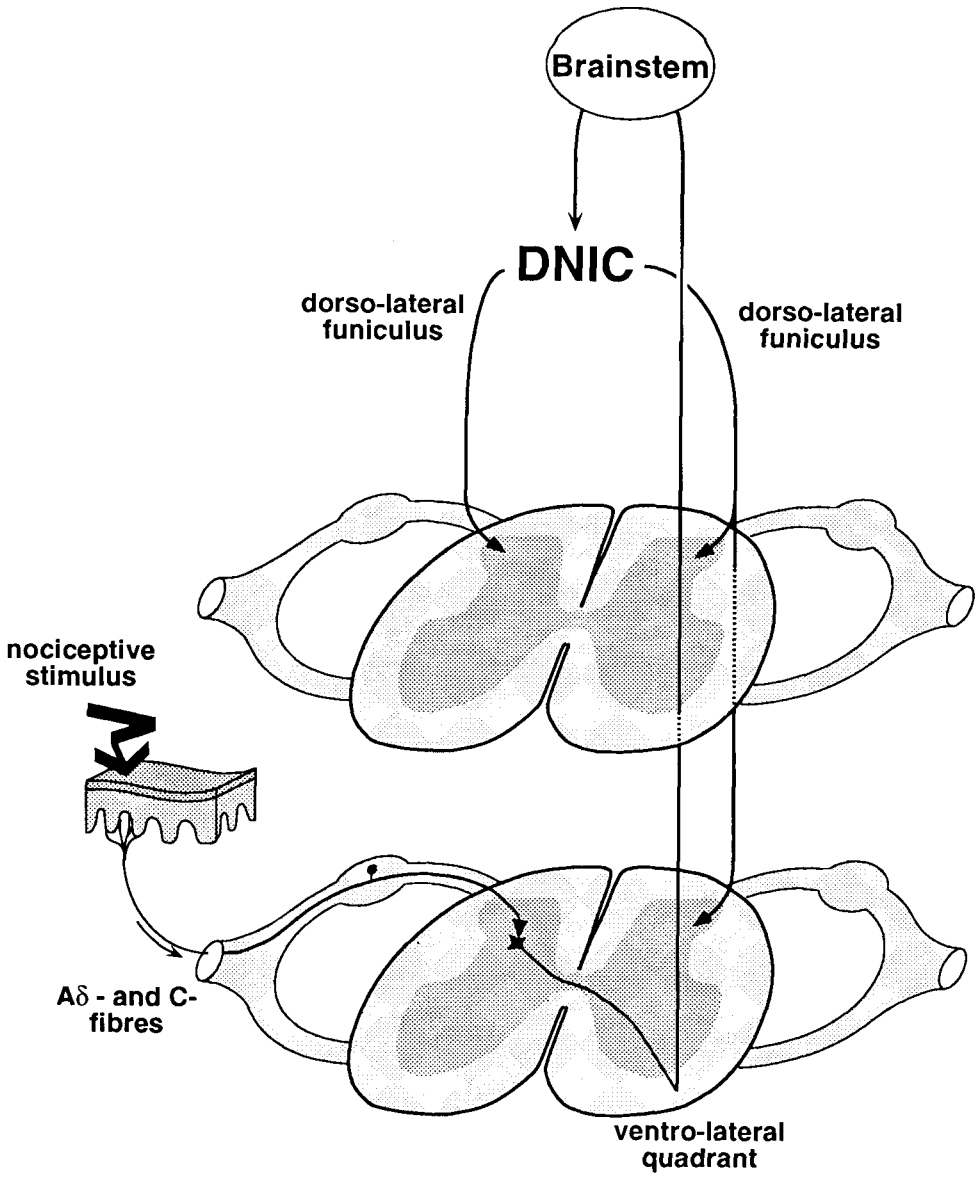

Fig 1. Triggering of descending inhibitory controls by nociceptive stimulation. When a noxious focus appears in a region of the body, dorsal horn neurones are activated and send an excitatory signal through the ventrolateral quadrant towards higher centres, including the lower brainstem. This signal activates diffuse noxious inhibitory controls (DNIC) which, after travelling through the dorso-lateral funiculus, will inhibit spinal and trigeminal convergent neurones.

a paradoxical property of convergent neurones. These units do indeed respond, and sometimes very well, to non-nociceptive stimuli (*e.g.* rubbing, hair movements) and thus are randomly and perpetually being activated by all the somaesthetic stimuli arising from the environment (Le Bars and Chitour, 1983). Such activity, once transmitted towards higher centres, could constitute a basic somaesthetic activity or "background noise" from which the brain's centres could extract a significant nociceptive signal only with difficulty (Fig 2A). DNIC could constitute the filter by which a specific nociceptive signal would be extracted from this basic somaesthetic activity. This basic somaesthetic activity might have an essential role in the sensory perception of the "body scheme", which is profoundly disorganized during clinical pain.

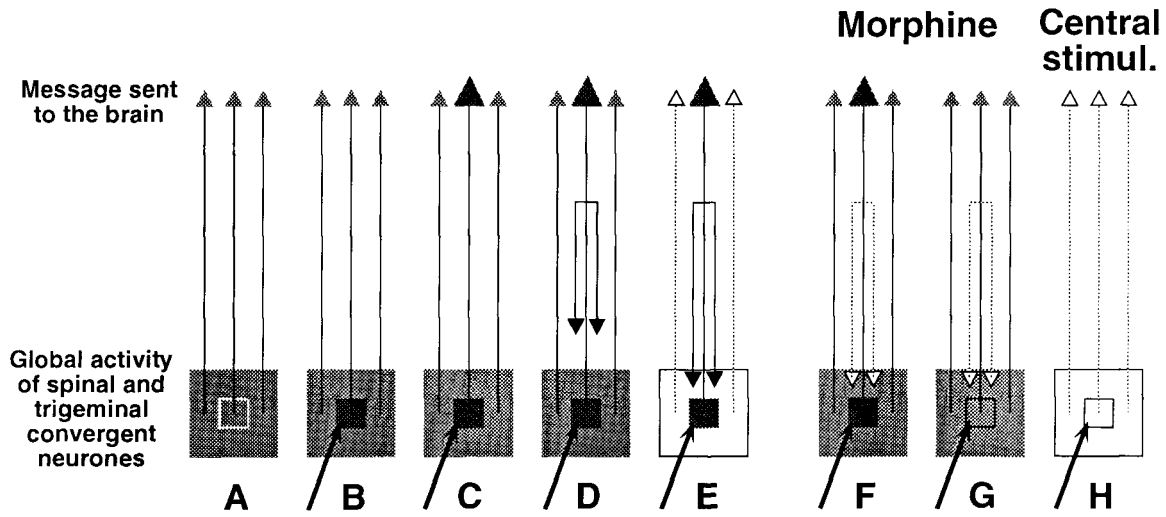

Fig 2. Hypothetical interpretation of the global activity of all convergent neurones involved in nociception at spinal and trigeminal levels. At "rest", because of the properties of these neurones, such activity would not be negligible and thus a basic somaesthetic signal would be sent towards the brain (A). A nociceptive focus will activate some convergent and nociceptive specific neurones (B), which in turn will transmit an excitatory signal towards supraspinal centres (C). This will trigger DNIC (D), which will inhibit those convergent neurones which were not directly affected by the initial stimulus, and thus the background noise which constitutes the basic somaesthetic activity will be reduced or abolished (E).

Morphine -either systemically at low doses, intracerebrally or intraventricularly- blocks DNIC and thus restores the background noise (F). At high systemic doses or intrathecally, morphine blocks the spinal transmission of nociceptive information and, therefore, further reduces the contrast (G). Electrical stimulation of some zones in the brainstem blocks the activities of the whole neuronal population and therefore elicits strong analgesia (H).

Indeed, when a noxious focus occurs in a region of the body (Fig 2B), both convergent and specific nociceptive neurones are activated and send an excitatory signal towards higher centres (Fig 2C). This signal will secondarily activate DNIC (Fig 2D) which will inhibit all those spinal and trigeminal convergent neurones which were not directly activated by the initial stimulus (Fig 2E). Such a mechanism will improve the "signal-to-noise ratio" by increasing the contrast between the activity of the segmental focus of excited neurones and the silence of the remaining population, by a mechanism reminiscent of, albeit more generalized than, the lateral inhibitions which are observed at various levels of most sensory systems (Kandel and Jessell, 1991). The destination of such a "picture", its recognition, and its processing by cerebral centres remain unsolved problems. As an hypothesis, one can propose that the brain is able to recognise this picture and this would infer that DNIC constitute not only a filter which allows the extraction of the signal for pain but also –and this is perhaps more important– an amplifier in the transmission system which increases the potential alarm function of the nociceptive signals. During clinical pain therefore, it is conceivable that the global message sent by convergent neurones is polymorphic, or even complex, and that a large variety of syndromes could result from this state of affairs.

It will probably be difficult to demonstrate the validity of the proposed model in a formal fashion. However, one can argue about the theoretical implications and try to submit them to experimental testing. In this way, the hypothesis is reinforced by two types of observation: the first, related to the effects of opioids and the second, to some behavioural and clinical observations.

Effects of morphine on DNIC

According to the model, it should be possible to produce hypo- or hyper-algesic effects by manipulations which affect excitatory and/or inhibitory phenomena. An intensification of the contrast effect should facilitate the recognition of nociceptive signals by higher centres; in this respect, we have already noted that in a model of chronic pain, the arthritic

rat, hyper-algesic phenomena occur together with an exacerbation of DNIC (Calvino *et al,* 1987). Conversely, a reduction of the contrast should hinder the recognition of the signals and thus produce a hypo- or analgesic effect. In order to verify this hypothesis, one can ask whether or not an analgesic drug such as morphine can produce a recovery in the somaesthetic background activity which would normally be depressed by DNIC. In fact, DNIC have been found to be extremely sensitive to the systemic or intra-cerebroventricular administration of low doses of morphine (Bouhassira *et al,* 1988a; 1988b; Le Bars *et al,* 1981b). These effects are dose-dependent, stereospecific and naloxone-reversible. Descending inhibitory controls from the brainstem, at least those triggered by peripheral nociceptive stimuli, are therefore depressed by morphine. Interestingly, such effects of low doses of systemic morphine were confirmed upon the inhibitions triggered by heterotopic noxious stimuli both on the C-fibre reflex in the rat (Falinower *et al,* 1993) and the RIII reflex in man (Le Bars *et al,* 1992).

The periaqueductal grey (PAG) represents one of the major supraspinal sites for the action of morphine in producing analgesia (see refs in Yaksh and Rudy, 1978). This region contains both terminals which are immunoreactive to endogenous opioids, including ß-endorphin, enkephalins and dynorphin, and opioid binding sites notably of the μ subtype (see refs in Bouhassira *et al,* 1992c). Further electrophysiological data support the hypothesis that the lifting of DNIC following systemic morphine is due at least in part to binding of the drug within the PAG since: (i) microinjections of morphine (5 μg) directly within the PAG produced a significant depression of DNIC (Dickenson and Le Bars, 1987); (ii) as already mentioned, DNIC were depressed in a dose-dependent fashion after microinjections of morphine within the third ventricle and in these experiments autoradiographic controls with tritiated morphine indicated that the morphine reached the PAG throughout its rostro-caudal extension (Bouhassira *et al,* 1988a); (iii) the effect of systemic morphine disappeared in PAG-lesioned animals (Bouhassira *et al,* 1992c). Incidently, these results also demonstrated that the lifting of DNIC in normal animals following a low systemic dose of morphine was not due to an action on the afferent pathways, notably those within the spinal cord activated by the conditioning stimulus. Thus, although the PAG is not directly involved in the loop subserving DNIC, it can modulate these controls indirectly. The relationship between DNIC and the other pain modulatory systems is, therefore, more complex than expected. However, the neural network between the periaqueductal grey and the DNIC circuit has yet to be determined.

The effects of systemic morphine on DNIC in animals with lesions of the rostral ventromedial medulla (RVM) were also tested. This region which includes the nucleus raphé magnus and adjacent reticular nuclei, contains a large number of terminals and cell somata which are immunoreactive to endogenous opioids and opioid binding sites of the μ subtype (see references in Bouhassira *et al,* 1993a,b). The RVM has been implicated in the antinociceptive effects of morphine by behavioural studies using local microinjections of opioids (see references in Yaksh and Rudy, 1978) and by electrophysiological recordings from RVM neurones (see references in Fields *et al,* 1991). It was therefore possible that the depression of DNIC following systemic morphine both involved the periaqueductal grey and was mediated through the RVM. The effects of morphine on DNIC were compared in sham-operated rats and animals in which electrolytic lesions of the RVM had been performed either one or three weeks earlier. DNIC were similarly reduced, again in a naloxone-reversible fashion, following morphine injections in sham-operated animals and animals tested one week after lesioning of the RVM. By contrast, DNIC were not significantly altered by morphine in animals tested three weeks after lesioning. This time-dependent attenuation of the effects of morphine indicates that the RVM is not directly involved in the reduction of DNIC induced by systemic morphine, but suggests that electrolytic lesions of the RVM induce long-term modifications of the opioidergic and/or other system(s) which mediate(s) the action of morphine. Interestingly, behavioural studies of the antinociceptive effects of morphine in RVM-lesioned

animals have produced similar time-dependent effects (see refs in Bouhassira *et al,* 1993).

On the basis of the striking similarities between the effects of electrolytic lesions of either the PAG or the RVM on the pharmacological responses in both the behavioural and DNIC studies, it was suggested that the blockade of DNIC has a functional role in the behavioural effects of low doses of systemic morphine (see refs in Bouhassira *et al,* 1993).

Taken together, these data are difficult to interpret within the framework of the hypotheses generally proposed to explain morphine analgesia. In fact, some authors claim that morphine, in addition to its indisputable spinal effect, acts by increasing the descending inhibitory controls from the brainstem (Fields and Basbaum, 1989) thus giving a second - indirect - mechanism for blocking nociceptive inflow at the spinal level. The arguments which support this hypothesis are very controversial (see refs in: Advokat, 1988; Bouhassira *et al,* 1988a; Duggan and North, 1984).

On the other hand, the data reported herein come within the scope of the model according to which a contrast between two neuronal populations is fundamental to the triggering of pain (Fig 2E). Indeed, morphine at a systemic dose low enough not to depress the excitatory signals from the spinal relay, or if given by the intra-cerebro-ventricular route, can restore the background noise by decreasing DNIC and thus reducing the contrast (Fig 2F); with larger doses, an additional mechanism for reducing the contrast is achieved by the direct spinal depressive effect of the drug (Fig 2G); this effect can be mimicked by administering the drug intrathecally (Villanueva and Le Bars, 1985).

This interpretation does not question the fact that analgesia can be obtained by direct electrical stimulation of some supraspinal structures such as nucleus raphé magnus: in this case, all convergent and nociceptive specific neurones are inhibited, the contrast is completely abolished, and the analgesia is indeed powerful (Fig 2H).

In any case, our view is in accord with clinical and behavioural studies of the characteristics of morphine analgesia. In man, morphine is analgesic at low doses (0.15 mg/kg) similar to those that lift DNIC (ED50 = 0.6 mg/kg) and almost identical to the doses that block the inhibitory post-stimulus effects (ED50 = 0.13 mg/kg). It is interesting to note that these low doses are without effect on the behavioural tests in animals in which threshold measurements are made using acute cutaneous nociceptive stimuli, but are clearly effective against nociceptive reactions elicited either by prolonged stimuli from deep structures such as experimental arthritis (Kayser and Guilbaud, 1983; Pircio *et al,* 1975), intraperitoneal injections of algogenic agents (Niemegeers *et al,* 1975) or vocalisation elicited by the activation of C-fibres (Ardid *et al,* 1993; Kraus and Le Bars, 1986). Additionally, the direct spinal action of morphine, far from counteracting the supraspinal action, tends to amplify it for two major reasons. It is generally agreed that morphine acts on the nociceptive-related activities of convergent cells without altering their responses to innocuous stimuli (Le Bars *et al,* 1976; Duggan and North, 1984). This property would not have functional significance if the convergent neurons were able to discriminate the two types of information. In contrast, this observation is particularly significant in the light of our hypothesis, as the spinal action will not hinder or counteract the supraspinal effect of morphine in restoring the "background somaesthetic activity" from the sensory milieu. Furthermore, it is clear that the direct depression of activity in the spinal cord by morphine will lead to a reduced activation of the loop subserving DNIC, and so result in a recovery of the level of somaesthetic activity. Our results, showing that intrathecal morphine is able to block DNIC (Villanueva and Le Bars, 1986), provide evidence to support this premise. Effects such as this will facilitate the supraspinal effect of lifting DNIC and signify that the spinal and supraspinal actions will not simply be additive but will be synergistic. Consistent with this hypothesis, behavioural studies have demonstrated clearly that the analgesia produced by intracerebroventricular administration of morphine is potentiated by intrathecal injection of morphine (Yeung and Rudy, 1980).

Clinical implications

If one accepts that convergent neurones have an important role in nociception, then a second direct implication of the model is that there are interactive phenomena between nociceptive signals from different areas of the body and, hence, between pains with distinct topographical origins. Evidence for such interactions in animals have been reported, but more convincing observations have been made in humans with the common observation that "one pain can mask another". For centuries, a large number of popular medical practices for relieving pain, including some forms of acupuncture, have been based on this principle (see: Bing *et al,* 1990b; Macdonald, 1989; Mann, 1974). These empirical observations have been confirmed under conditions of scientific objectivity and such phenomena are often designated as "counter-irritation" or "counter-stimulation" (see refs in Le Bars *et al,* 1989). Interestingly, as early as 1940, Wolff *et al* reported that, in man, a heterotopic pain could block the morphine induced rise in the pain threshold to radiant heat and concluded that "the threshold-raising action of opium derivatives....was reduced or obliterated by pain". In any case, DNIC probably represent, at least in part, the functional substrate for these observations; the experiments in humans further support this hypothesis.

CONCLUSIONS

The results reported above indicate that the three routes of administration of morphine which are used for alleviating pain in man - systemic, intrathecal, ICV - can be correlated with a reduction in DNIC. It could be rather disconcerting to think of two opposing manipulations - the activation of DNIC by counterirritation procedures and its blocking by morphine - leading, in therapeutic terms, to the same end point, *i.e.* hypoalgesia. We feel, however, that this apparent paradox reflects the complexity of the spinal transmission of nociceptive signals and provides an insight into the likely role of convergent neurones in the encoding of nociceptive and non-nociceptive sensory information. In this context, we believe that the existence of gradients of activity within a neuronal population should be taken into consideration in pharmacological and biochemical studies of nociceptive transmission towards higher centres.

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