Diffuse Noxious Inhibitory Controls (DNIC) in Animals and in Man

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Key words
Acupuncture, DNIC, Electro-acupuncture, Nerve fibres, Neuro-anatomy, Pain pathways, Stimulation induced analgesia, TENS.

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 references in Le Bars et al., 1984; 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 Aβ-fibres alone; however, numerous studies have demonstrated that the activation of Aδ-fibres produces the most powerful segmental inhibitions (Chung et al., 1984; Lee et al., 1985; Sjölund, 1985; Woolf et al., 1980).

Such effects, which are essentially restricted to dermatomes, are derived directly from 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 Stimulation", TENS) and by some forms of acupuncture or electro-acupuncture. It should be noted however, that the time constants 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, another category of somaesthetic stimulus can also induce hypo-algesic effects. Although it seems paradoxical at first, painful stimuli can diminish, or even mask, pain elicited by stimulation of a remote (extra-segmental) part of the body (see references in Le Bars et al., 1984; Le Bars and Villanueva, 1988). 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 use 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 such an hypothesis is correct at as early a stage 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).

1. Diffuse Noxious Inhibitory Controls in animals
In the rat and the cat, the activity of certain dorsal horn neurones can be strongly inhibited by noxious inputs. Such effects do not appear to be somatotopically organised but apply to the whole body and affect all convergent neurones, whether in the dorsal horn of various segments of the spinal cord (Calvino et al., 1984; Le Bars et al., 1979a; Morton et al., 1987) or in the trigeminal nucleus caudalis (Dickenson et al., 1980a). By contrast, DNIC do not affect the other neuronal types which are found in these structures, i.e. noxious-specific, non-noxious-specific, cold-responsive and proprioceptive neurones (Dickenson et al., 1980; Le Bars et al., 1979b).

The principal feature of DNIC is that they can be triggered by conditioning stimuli applied to any part of the body 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 after-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 in convergent neurones, no matter whether it is evoked by noxious or non-noxious, natural or electrical peripheral stimuli or by the direct microelectrophoretic application of excitatory amino-acids (Villanueva et al., 1984a; 1984b). Transcutaneous electrical stimuli applied to the receptive field of convergent neurones activate large (A) and thin (C) fibres, and in studies of DNIC, suprathreshold currents have been employed systematically in this way, to evoke reproducible “C-fibre responses” from convergent neurones. All noxious conditioning stimuli tested to date, have markedly inhibited these responses (Figure 1).

![Figure 1](image)

**Figure 1**
An example of the effect of DNIC upon responses of a convergent unit to A- and C-fibre activation illustrated by a dot display analysis of the neuronal responses with time running upwards. The application of thermal (immersion of the tail in 52°C water), mechanical (pinch of the tail and muzzle) and visceral (i.p. bradykinin) noxious stimuli resulted in strong inhibition of responses to both A- and C-fibres, induced by transcutaneous electrical stimulation of the distal part of the hindlimb. Note the long duration of the after-effects, especially for the C-fibre responses (from Le Bars et al., 1983).

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. In this respect, it is important to note that such a system must be completely different from segmental inhibitory systems which work both in intact and in spinal animals. Furthermore, segmental inhibitions 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).

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

A. Peripheral mechanisms

The relationship between the intensity of a noxious 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 (Le Bars et al., 1981a; Villanueva and Le Bars, 1985). As shown in Figure 2, the threshold for producing DNIC was between 40° and 44°C, and above this temperature (in the 44-52°C range), a highly significant correlation existed between the conditioning temperature and the extent of the inhibition.

![Figure 2](image)

**Figure 2**
Mean percentage inhibitions (ordinate) of C-fibre evoked responses of trigeminal (upper curve) and lumbar (lower curve) convergent neurones, induced by immersion of the tail in water baths at various temperatures (abscissa). Note that no significant effects were observed when 36°C or 40°C was applied to the tail but that there was a highly significant correlation between noxious temperatures (44-52°C) and the extent of the inhibitions (From Le Bars et al., 1986).
(ii) that DNIC act on convergent neurones by a final postsynaptic inhibitory mechanism involving hyperpolarisation of the neuronal membrane (Villanueva et al., 1984a; 1984b).

It was found that when trigeminal convergent neurones were directly excited by the electrophoretic application of di-homocysteate (DLH), the percutaneous application of single square-wave, electrical stimuli (10mA; 2ms) 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 (Figure 3). When the two stimulation sites were 100 mm apart, it was possible to use these differences in latency, to estimate the conduction velocities of the peripheral fibres triggering the inhibitions. For the onset of the earlier and later components of the inhibition, the mean differences between the latencies from the two sites of stimulation were 13.6 and 147.7 ms respectively, which corresponds to peripheral conduction velocities of 7.3 and 0.7 m/s. Such conduction velocities fall into the Aδ and C-fibre ranges, respectively.

Although peripheral unmyelinated and thin myelinated fibres can respond to stimuli below the pain threshold (Adriansen et al., 1983; Cybels et al., 1979; Torebjörk et al., 1984; Van Hees and Cybels, 1972), the relationship between activity in such fibres and nociceptive reactions or pain, is a classical one (Adriansen et al., 1983; Dubner and Beitel, 1976; Cybels et al., 1979; Lamotte and Campbell, 1978; Torebjörk et al., 1984; Van Hees and Cybels, 1972). However, the thresholds for triggering the Aδ and C-fibre components of DNIC were found to be in the 0.25-0.5mA and 1.2mA ranges respectively, which might suggest a contribution by non-nociceptive afferents.

The importance of Aδ-fibre activation in the production of analgesia or antinociceptive effects by somatic electrical stimulation has been suggested by several authors (Chung et al., 1984; Kawakita and Funakoshi, 1982; Lee et al., 1985; Sjölund, 1985; Woolf et al., 1980). In this respect, our results showed that, by comparison with the C-fibre component, the Aδ-fibre component of inhibition was easier to elicit and had a more constant magnitude and duration: it was found with lower intensities of percutaneous electrical stimulation and rapidly reached its maximal effect when the current was increased. Applying stronger intensities of

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**Figure 3**

Example of heterotopic activation of Aδ- and C-fibres triggering inhibitions in a trigeminal convergent neurone (from Bouhassira et al., 1987).

A. Schematic representation of the experimental design. Neurones with receptive fields located ipsilaterally on the muzzle were recorded in the trigeminal nucleus caudalis. The continuous electrophoretic application of an excitatory amino acid, di-homocysteic acid (DH), induced a steady discharge from the neurone under study. The repetitive application of individual percutaneous, electrical stimuli of adequate intensities to the base (a) or the tip (b) of the tail induced biphasic depressions of activity which affected convergent neurones exclusively.

B. Individual example of the biphasic inhibitory processes triggered by repetitive, single, percutaneous, electrical stimuli (2ms duration, 10mA, 0.66Hz, 200ms delay) applied to the base (a) or the tip (b) of the tail on the discharge evoked in a trigeminal convergent neurone by the continuous electrophoretic application of DH (17nA). Peristimulus histograms (bin width: 1ms left; 5ms right) were constructed from 100 trials. The earlier component of the inhibition is shown in detail in the left part of the figure, while the whole biphasic inhibition is shown on the right. Note that both components appeared earlier when the base (a) as opposed to the tip (b) of the tail was stimulated.
peripheral stimuli gave rise to inhibitory effects of similar magnitude. This difference between the Aδ- and C-fibre components is probably due to the fact that, in addition to having lower thresholds, the Aδ-fibres responsible for the earlier inhibitions produce a more synchronised input to the spinal cord than do the slower C-fibres. The "safety" of the Aδ-fibre component of inhibition is illustrated in Figure 4, in which currents of 1mA were applied percutaneously to the base of the tail at different frequencies. This intensity of stimulation was chosen because it had been found to induce clear Aδ- but not C-fibre, components of DNIC. Note that the inhibitory processes followed increasing frequencies of stimulation, although they were slightly less effective with the highest frequency employed (8 Hz). This observation reinforces the proposal that Aδ-fibres play an important role in the induction of analgesia or hypoalgesia by procedures using transcutaneous stimulation, since such procedures often involve these frequencies.

In a recent study (Bing et al., 1990), we recorded C-fibre-evoked activities of trigeminal convergent neurones and observed the effects of manual acupuncture applied by a traditional Chinese acupuncturist, to a hindpaw, at the ST.36 "Zusanli" point or at a non-acupoint. In keeping with some previous results from the Department of Physiology, at Kirin Medical College in Changchun (1977), we were able to demonstrate that manual acupuncture applied to the hindpaw can induce strong inhibitory effects on the C-fibre responses of trigeminal convergent neurones; these inhibitory effects occurred both during and after the application of acupuncture. Identical inhibitory effects were observed regardless of whether acupuncture was applied at "Zusanli" or at a non-acupoint or if noxious heat was applied to the hindlimb (Figure 5).

These observations raise the question as to what is the nature of the effective stimuli which can trigger such processes. As previously mentioned, DNIC are triggered exclusively by Aδ- or Aδ-and-C-fibre activation. Interestingly, acupuncture has also been shown to be more efficacious in animals with stimulation intensities that recruit thin afferent fibres, more particularly Aδ- and C-fibres (Chen et al., 1981). From a clinical standpoint, the art of the practitioner is to elicit the "needling sensation" or "De-chi" which is a combination of the ache that one might experience in muscular fatigue, together with numbness and feelings of distension - as if the needled region had become oedematous - and of a heaviness sometimes associated with soreness, tingling or warmth (Macdonald, 1989; see also Mann, 1974).

B. Central mechanisms

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; 1986b). Since thalamic lesions do not affect DNIC, it has been proposed that they result from a physiological activation of some of the brainstem structures which produce descending inhibitions (Figure 6). In this context, the more efficient structures exert their actions through serotonergic bulbospinal inhibitory pathways which are confined to the dorso-lateral funiculi (see references in Fields and Besson, 1988).
Comparison of DNIC- and acupuncture-induced inhibitions of convergent neurones (from Bing et al., 1990).

A. Schematic representation of the experimental design. Convergent neurones with receptive fields located ipsilaterally on the muzzle were recorded in the left trigeminal nucleus caudalis (a). Their responses following percutaneous electrical stimulation of their receptive fields were conditioned by manual acupuncture applied at the "Zusanli" point, or at a close, non-acupoint on the right hindpaw (b). Acupuncture effects were compared with the effects elicited by immersion of the extremity of the left hindpaw in 45°C water.

B. Examples of the effects of different conditioning stimuli on C-fibre-evoked responses of a trigeminal convergent neurone. The histograms represent the temporal evolution (abscissa: time) of the C-fibre responses (ordinate: number of spikes computed within the 60-100ms following each stimulus) of the neurone to percutaneous electrical stimulation (2ms; 0.67Hz). Between the 65th and 90th stimulus presentations (arrowed in the upper parts of the figures) the left hindpaw was immersed in a 45°C waterbath, or manual acupuncture was applied either at "Zusanli" or at a non-acupoint on the right hindpaw. Note that both noxious heat and acupuncture induced a depression of neuronal activity followed by after-effects of variable duration.

C. Summary of the inhibitory effects elicited by different conditioning stimuli applied to the hind paws on the C-fibre responses of trigeminal convergent neurones. Histograms represent the percentage inhibitions observed during and within the 44 seconds ("after 0-22s; 22-44s.") following the immersion of the left hindpaw in a 45°C waterbath (filled columns), or acupuncture applied at "Zusanli" (open columns), or at a non-acupoint (hatched columns) on the right hindpaw. Note that the inhibitory processes induced by noxious heat and by acupuncture were essentially the same.

Figure 6
Triggering of descending inhibitory controls by nociceptive stimulation (from Le Bars and Willer, 1991).
It may be noted that electrical stimulation of the Nucleus Raphé Magnus produces inhibitions of spinal convergent neurones which are as potent as DNIC.

The hypothesis that these structures participate in triggering DNIC seems to be confirmed by the findings that DNIC are profoundly reduced following: electrolytic lesions of Nucleus Raphé Magnus, the administration of blockers of serotoninergic receptors and section of the dorso-lateral funiculus; conversely, DNIC are potentiated by the administration of 5-hydroxytryptophane, a precursor of serotonin (see references in Le Bars, 1986; Villanueva and Le Bars, 1988). The parallel between the two types of inhibition - i.e. DNIC and that induced by stimulation of Nucleus Raphé Magnus - is supported by the facts that both are sensitive to naloxone (Le Bars et al., 1981b), which suggests that endogenous opioids participate in these phenomena, and both act finally by hyperpolarisation of the neuronal membrane. However, these analogies do not prove the identity of the mechanisms which are brought into play; the precise determination of the supraspinal structures involved in DNIC has still to be carried out.

We have already emphasised some analogies between DNIC and acupuncture-induced inhibitions. A further one is the observation that in both cases, the inhibitory effects and after-effects are reduced by the same order of magnitude by systemic naloxone (Le Bars et al., 1981b), which suggests that endogenous opioids participate in these phenomena, and both act finally by hyperpolarisation of the neuronal membrane. However, these analogies do not prove the identity of the mechanisms which are brought into play; the precise determination of the supraspinal structures involved in DNIC has still to be carried out.

The reversal of acupuncture analgesia by naloxone has been described previously (Liang, 1978; Mayer et al., 1977; and see references in Han and Terenius, 1982; He, 1987). Such an effect is particularly obvious when low frequency, high intensity stimuli are used (Huang et al., 1986; Sjölund and Eriksson, 1979; Willer et al., 1982). Interestingly, the hypoalgesia elicited by TENS which involves segmental mechanisms - is not affected by naloxone (Hansson et al., 1986; Lundeborg, 1985; Sjölund and Eriksson, 1979; Willer et al., 1982).

II. Diffuse Noxious Inhibitory Controls in man

In man, exactly analogous results have been obtained in studies which have combined psychophysical measurements with the recording of nociceptive reflexes (Willer et al., 1984, 1989). Electrical stimulation of the sural nerve at the ankle simultaneously induces a nociceptive reflex in a flexor muscle of the thigh (the Rrr reflex) and a painful sensation in the territory of the nerve. Painful heterotopic conditioning stimuli, no matter whether thermal, mechanical or chemical in nature, increase the thresholds of both the reflex and the associated painful sensation, with stronger effects being observed with more intense conditioning stimuli (Figure 7). These inhibitory phenomena are exerted selectively on nociceptive responses and do not affect monosynaptic reflexes of proprioceptive origin. These results demonstrate that in man, a painful conditioning stimulus can depress both a pre-existing pain and its associated nociceptive reflex at as early a stage as the first spinal relays for

![Figure 7](http://aim.bmj.com/)

**Evidence for DNIC in man (from Willer et al., 1989)**

A: Experimental set-up used for eliciting a nociceptive reflex (Rrr) by stimulation (stim.) of the sural nerve (s.n.) and recording (rec.) from the left Biceps femoris muscle (bf). An example of the Rrr reflex is shown at the top of the diagram (calibrations: horizontal 25ms; vertical 100V). The reflex evoked by just threshold (1.2 times threshold) stimulation, is studied before, during, and after a 2 minute period of immersion of the right hand in a thermostatically controlled waterbath.

B: Examples of the effects of heterotopic thermal conditioning stimulation on the Rrr reflex. Each trace represents the average of 10 successive full-wave rectified responses recorded during a one minute period. For each experimental sequence, the temporal evolution is shown from back to front, the 2 minute conditioning period indicated by arrows being in the third and fourth minutes.

The non-painful temperature (44°C, left) did not modify the reflex. By contrast, the painful temperatures (45, 46, 47°C) depressed the reflex during and after the application of the conditioning stimuli. The extent of these depressions was temperature dependent.

Note the long duration (around 10 minutes) of the inhibitory post-effects following the application of the highest temperature (47°C, right).
the transmission of nociceptive information.

The following question arises: are the inhibitory mechanisms purely spinal or, alternatively, do they involve supraspinal structures? To answer this, we compared the effects on the RII reflex in the right leg, of nociceptive conditioning stimuli applied to the 4th and 5th fingers of the left hand in normal subjects and tetraplegic patients with lesions of traumatic origin at the C5, C6 or C7 level (Roby-Brami et al., 1987).

In the normal subjects, as previously, the painful conditioning stimuli caused a strong depression of both the RII reflex and the associated pain. By contrast, in the tetraplegic patients nociceptive stimulation of the same cutaneous territories, which, being in the C8 and T1 dermatomes, were clinically unaffected by the spinal lesion, did not produce any depression of the RII reflex recorded in the contralateral leg. These results demonstrate that in man, as in animals, the inhibitory effects triggered by heterotopic nociceptive stimuli are most likely sustained by a loop which includes supraspinal structures.

These results also lead to a subsidiary question: is it possible to identify, or at least localise, these supraspinal structures? A tentative answer has been obtained by observations made on patients with cerebral lesions causing contralateral hemi-analgesia (De Broucker et al., 1990). These were patients with either a unilateral thalamic lesion (identified and delineated by a CT scan), or a lesion of the retro-olivary part of the medulla (Wallenberg's syndrome).

In the former group, the RII reflex on the normal side 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 after-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.

Finally, it has been shown that naloxone can block these inhibitory phenomena which are triggered by nociceptive stimulation (Willer et al., 1990). There must therefore be at least one opioidergic link in the spino-bulbo-spinal loop which is implicated in these inhibitory processes.

Thus, the following features are shared by the RII reflex and associated painful sensations in humans and by dorsal horn convergent neurones in the rat spinal cord:

1) The RII reflex and the responses of convergent neurones to electrical stimulation of their cutaneous receptive fields are similarly inhibited by various heterotopic nociceptive stimuli.
2) The extent of the inhibitions is directly related to the intensity of the conditioning stimulus.
3) The inhibitions are followed by after-effects which can last for several minutes.
4) The inhibitions are mediated by a spino-bulbo-spinal loop, the ascending part of which is composed of the spino-reticular tract and synaptic relays in the brainstem. In addition, there is at least one opioidergic link in this loop both in the rat and in man.

Such similarities allow one to conclude that the inhibitory processes observed in man and DNIC in the rat share common mechanisms; the existence of DNIC in humans is therefore more than likely.

III. Hypotheses

The data described above suggest that nociceptive stimuli, even though unquestionably perceived as being painful, activate certain inhibitory controls which originate in the brainstem. In order to interpret the physiological meaning of these findings one has to take into account a paradoxical property of convergent neurones. These units do indeed respond to non-nociceptive stimuli.

![Figure 8](http://aim.bmj.com/)

**Figure 8**

**Hypothetical interpretation of the global activity of all convergent neurones involved in nociception at spinal and trigeminal levels.**

- **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 somesthetic activity will be reduced or abolished (E).
- **Morphine, either systemically at low doses, intracerebrally, or intra-ventricuilarly blocks DNIC and thus restores the background noise (F).** At high systemic doses or intratraecally, 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 efficats strong analgesia (H).** (From Le Bars and Villanueva, 1988).
(e.g. rubbing or hair movements) and thus are randomly but permanently being activated by all the somesthetic stimuli arising from the environment. The resulting basic somesthetic activity will be transmitted towards higher centres and could constitute a "background noise", from which the brain's centres could extract a significantly nociceptive message only with difficulty (Figure 8A). DNIC could constitute a filter by which a specific nociceptive signal would be extracted from this basic somesthetic activity (Le Bars et al., 1979b; 1986; 1988).

Indeed, when a noxious focus appears in a region of the body, both convergent and nociceptive specific neurones are activated (Figure 8B) and send an excitatory signal towards higher centres (Figure 8C). The signal secondarily activates DNIC (Figure 8D) which will inhibit all those spinal and trigeminal convergent neurones which were not directly concerned with the initial stimulus (Figure 8E). Such a mechanism improves 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. 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 becomes polymorphic, or even complex, and that a large variety of pain syndromes could come about in this way.

According to the above model, hypo- or hyper-algesic effects could result from manipulations which affect excitatory and/or inhibitory phenomena. An intensification of the contrast effect should facilitate the recognition of nociceptive signals by higher centres; consistent with this, in a model of chronic pain, the arthritic rat, hyper-algesic phenomena occur together with an exacerbation of DNIC. Conversely, a reduction of the contrast should hinder the recognition of the signals and thus produce an analgesic effect. In order to verify this hypothesis, one can test whether or not the reference analgesic drug, morphine, can produce a recovery in the somesthetic background activity which would normally be depressed by DNIC. In fact, DNIC have been found to be extremely sensitive to the administration of low doses of morphine (Le Bars et al., 1981c).

In view of the potentially important role of convergent neurones in nociception, a second direct implication of the model is that there are interactive phenomena between nociceptive signals from remote 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 have been based on this principle. These empirical observations have been confirmed under conditions of scientific objectivity and such phenomena are often designated as "counter-irritation" or "counter-stimulation" (see references in Le Bars et al., 1984; Le Bars and Villanueva, 1988). DNIC probably represent, at least in part, the functional substrate for these observations; the experiments in human described above confirm this hypothesis.

The question arises as to what mechanisms underlie the hypoalgesic effects of transcutaneous electrical nerve stimulation (TENS) and electro-acupuncture, and whether they might share common neuronal substrates.

As stated in the introduction, it seems possible to distinguish between two means of producing hypoalgesia by somatic stimulation. TENS can be effective when applied at high frequencies and intensities below the pain threshold with the resulting pain relief being localised and often limited to the stimulated segment (Andersson, 1979). The efficiency of this procedure can be explained by segmental inhibitory processes triggered by low threshold afferents, and the "gate control" theory has been proposed as its neuronal basis (Melzack and Wall, 1965; Wall, 1978). In some cases, acupuncture probably activates such processes, especially when the needles are applied in the vicinity of the pain.

However, the mechanisms underlying TENS and acupuncture at sites with or without a segmental relationship to the source of pain are still controversial and, in any case, cannot be explained with a single theory (Satran and Goldstein, 1973; Nathan and Rudge, 1974; Andersson and Holmgren, 1975; Jeans, 1979). In this respect, it has been shown that stronger analgesic effects can be elicited with TENS, by using a critical level of stimulation which produces an unpleasant, but not quite painful sensation (Andersson, 1979; Melzack, 1984). This reinforces the idea that Aδ-fibre activation is important in the production of analgesia by somatic stimulation, especially if one takes account of the fact that TENS is more effective and induces extrasegmental antinociceptive effects when Aδ-fibres are activated (Chung et al., 1984). We have already mentioned that the pain relief produced by acupuncture can have a widespread distribution when the stimulation is strong enough to induce the feeling of “De-Chi”, which is an unpleasant sensation that is probably related to activity in thin peripheral fibres. Furthermore, it has been shown that antinociceptive effects elicited by acupuncture are stronger when the stimulation intensities are sufficient to recruit Aδ- and C-fibres (Chen et al., 1981; Kawakita and Funakoshi, 1982).
We have proposed that DNIC may well form the neural basis for the pain-relieving effects of these procedures in which afferent Aδ- or Aδ- and C-fibres play an important role. This suggestion is strongly supported by the finding that regardless of whether inhibitions of trigeminal convergent neurones are triggered by immersion of a hindpaw in 50°C water, or by manual stimulation of the ST.36 "Zusanli" point on the tibialis anterior muscle, they are reduced to a similar extent (Figure 9) by systemic naloxone.

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