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DIFFUSE NOXIOUS INHIBITORY CONTROLS (DNIC). II. LACK OF EFFECT ON NON-CONVERGENT NEURONES, SUPRASPINAL INVOLVEMENT AND THEORETICAL IMPLICATIONS

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SUMMARY

(1) Diffuse noxious inhibitory controls (DNIC) were tested for their effect on noxious only, non-noxious and proprioceptive cells in the dorsal horn of the intact anaesthetized rat. Unlike convergent neurones, as described in the previous paper, there was no effect of DNIC on these neurones. It is concluded that convergent neurones are specifically inhibited by DNIC.

(2) The effect of DNIC could not be demonstrated for convergent neurones in the spinal animal. Thus the neuronal substrate for DNIC must involve supraspinal structures.

(3) Because of the level of firing in convergent neurones induced by hair and touch receptors, presumably constantly and randomly activated in the freely moving animal, a noxious message arriving at higher centres may be partly masked by this background noise. On the basis of the known role of convergent neurones in nociception, we propose the following mechanism which may interpret this paradoxical convergence: two pools of convergent neurones are influenced by a painful peripheral stimulation, one segmental pool being activated whilst the remaining population of cells is inhibited; the "contrast" between the messages from these two pools may well produce a significant pain signalling output from the convergent dorsal horn cells.

(4) These results and their theoretical implications are discussed with regard to the concept of the "analgesic system", certain clinical observations and the paradoxical pain relieving effects of counterirritation and some forms of acupuncture.

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INTRODUCTION

On the basis of the diffuse noxious inhibitory controls (DNIC) on convergent neurones we have described in the previous paper [41], we have extended the study to include the possible effects of DNIC on other dorsal horn neurones such as the noxious only, non-noxious and proprioceptive cells. The involvement of supraspinal structures in the effect of DNIC has also been investigated by an equivalent study of the convergent neurones in the spinal animal.

Owing to the differential effects of DNIC on dorsal horn neurones, we will propose a mechanism which may provide the means whereby convergent neurones might transmit noxious messages to higher central structures. The results are also discussed with regard to the concept of the "analgesic system" and certain paradoxical pain-relieving effects of noxious stimuli including counterirritation, certain forms of acupuncture and some clinical observations.

METHODS

The methods of preparation of the animals were identical to those previously described [41], except for the spinal animals where a transection of the spinal cord at the cervical level was made. Anaesthesia was continued throughout the experimental period in these animals so as to replicate the conditions used for the intact animals.

RESULTS

(I) Non-convergent neurones in the intact animal

(1) General findings

In addition to the 68 convergent units described in the previous article [41], a further 86 non-convergent neurones were studied in the same animals. These neurones were classified according to Menétrey et al. [55] in the rat as noxious only units (n = 13), cells activated by only non-noxious stimuli (n = 55) and proprioceptive cells (n = 18). Fig. 1 shows the histological localization of these neurones. In these 86 neurones only three were found to be under diffuse noxious inhibitory controls (DNIC), in direct contrast to the 67/68 convergent neurones under the influence of DNIC. The effect of DNIC was tested against the responses of these non-convergent neurones to both transcutaneous electrical stimulation and to natural peripheral stimuli. The results obtained will be discussed below for each class of neurone.

(2) Noxious only units

Thirteen of these neurones were fully tested and only one was found to be under the influence of DNIC. These cells were located in the marginal layer

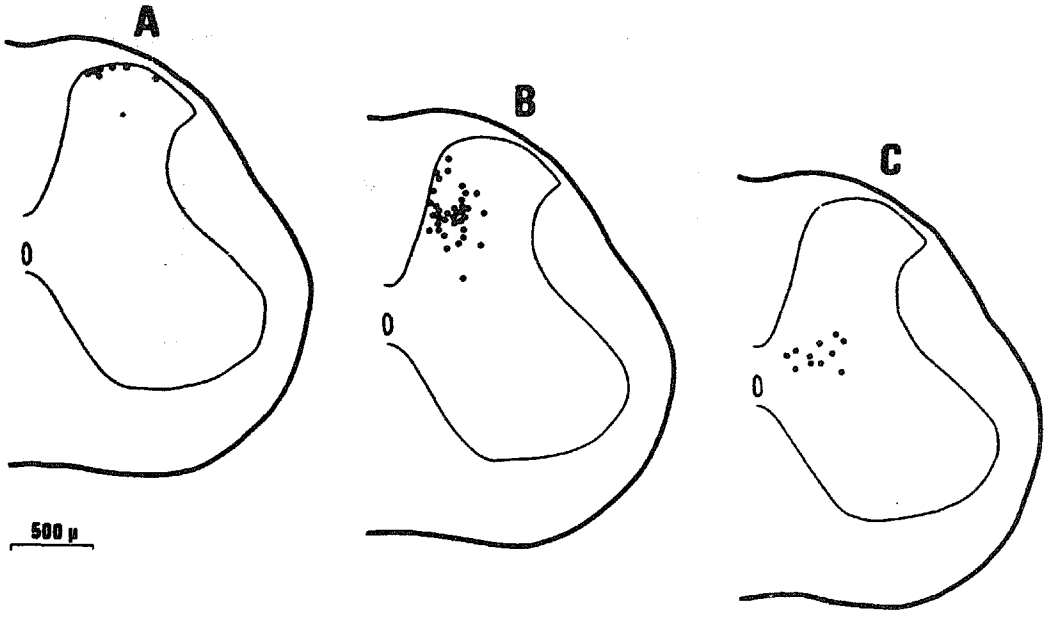

Fig. 1. Histological localization of the non-convergent neurones successfully marked by pontamine blue. A: noxious only units (n = 8), the star marks the neurone under DNIC. B: non-noxious units (n = 36). C: proprioceptive units (n = 11).

of the dorsal horn (lamina 1). The peripheral receptive fields were smaller (0.06 ± 0.01 cm^2) than those of the convergent neurones (0.57 ± 0.12 cm^2). The neurones could only be activated by strong pinch and noxious heat and received a clear C fibre input with a weak (11/13) or no A fibre input. However with respect to this latter property, the cells could never be activated by innocuous stimuli such as touch, air jet, stroking, pressure or hair movements.

The one neurone under inhibitory control had the C fibre response inhibited by pinch applied to the tail and ear in a fashion similar to that seen for the convergent neurones. However, histological controls (Fig. 1) revealed that this neurone was located deeper than the other neurones of this class. The other 12 noxious only cells were not inhibited even with extremely powerful peripheral stimulation sufficient to produce a 100% inhibition of the convergent neurones.

(a) DNIC versus C fibre responses (Fig. 2). C fibre responses of these noxious only units were easily obtained by transcutaneous electrical stimulation of the peripheral excitatory receptive field (threshold 1.63 ± 0.23 mA with a 2 msec duration pulse). The response was generally manifested by 1—5 bands, each containing a few spikes at a latency of between 150 and 300 msec.

All 12 neurones were completely unaffected by noxious pinch applied to the tail (n = 12), the contralateral hind paw (n = 9), the muzzle (n = 3) or the ears (n = 4). During these periods of noxious mechanical stimulation, the C fibre response was unchanged both in terms of the number of spikes

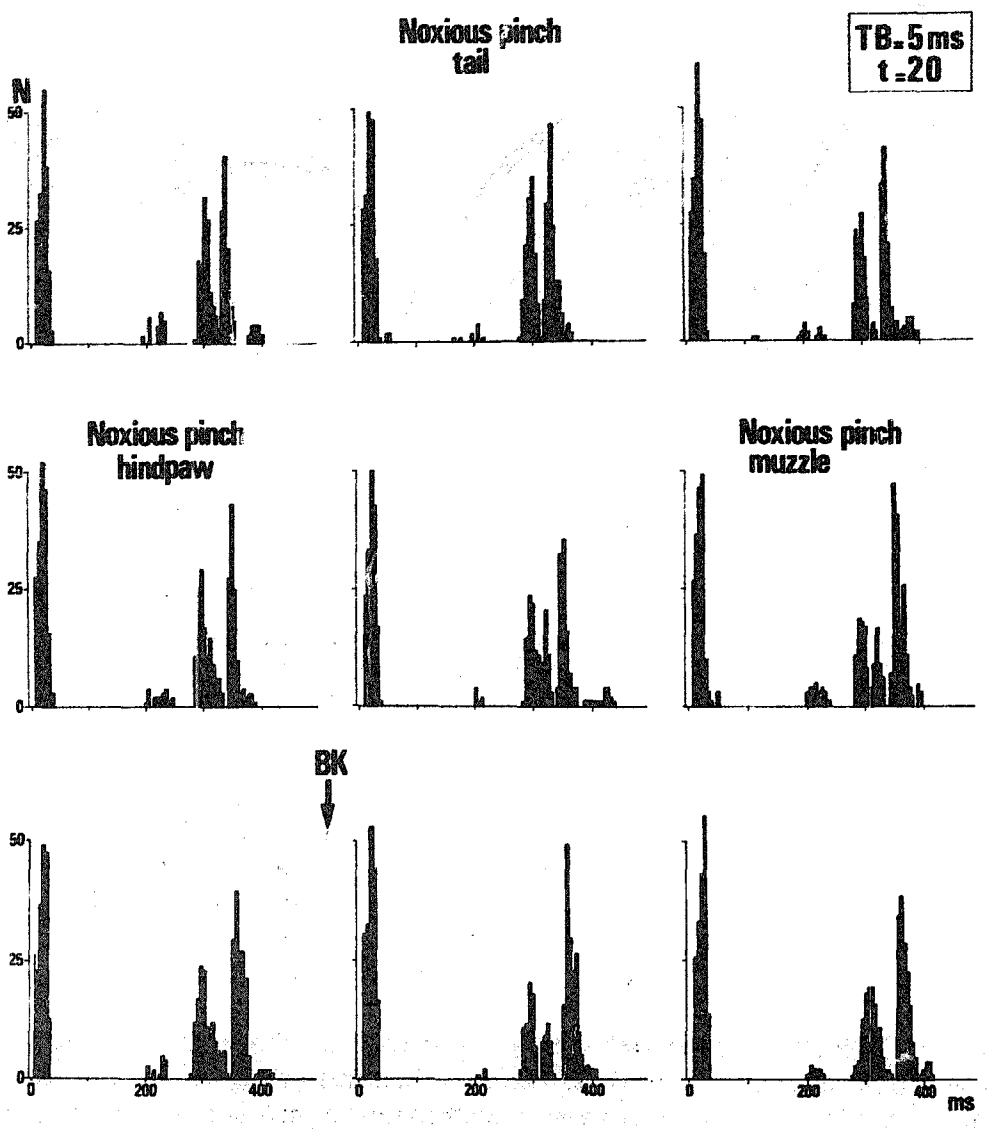

Fig. 2. A series of poststimulus histograms showing the lack of DNIC on a noxious only marginal layer unit. The A and C fibre responses are unaltered by noxious pinch or intraperitoneal bradykinin. TB = time base; t = number of trials; N = number of spikes.

evoked and the latency of the response. In the case of the convergent neurones, these stimuli would produce inhibitions of between 60—100% of the supramaximal C fibre response. The 12 noxious only units were unaffected by DNIC even at threshold C fibre stimulation currents.

Intraperitoneal bradykinin and noxious heating of the tail were also without effect on the C fibre responses of the 6 cells tested. Electrical stimulation of the tail which inhibits convergent neurones at a mean threshold voltage of 2.9 mA was completely without effect on the C fibre response of these noxious units even at currents of up to 14 mA.

(b) DNIC versus natural cutaneous stimulation (Fig. 3). None of the 12 lamina 1 noxious only units exhibited any spontaneous activity. Due to the tendency of these neurones to depolarize following prolonged cutaneous activation, the effect of DNIC on the activity produced by tonic pinch was difficult to test. All neurones showed responses to noxious radiant heat although only three produced a stable level of activity to a temperature step without the problems of depolarization. DNIC was tested against the activity induced by noxious heat steps for these 3 cells. Again, as for the C fibre response, the activity produced by noxious heat in these cells was unchanged following pinch or noxious heat applied to the tail or pinch of the contralateral hind paw. Thus these noxious only neurones are not under the influence of DNIC.

(c) Ipsilateral inhibitory fields. 3/13 units were found to possess strictly ipsilateral inhibitory fields located on the paw or thigh and which could be activated by tactile stimulation.

(3) Innocuous units

Fifty-five single units were recorded which responded only to innocuous peripheral stimuli such as hair movement, stroking, light pressure and touch. Generally these neurones were located (Fig. 1) intermediate in the dorsal horn between the noxious only and the convergent units. For these innocuous units, the peripheral receptive fields ranged from small point-like to large, in some cases including the whole paw. Transcutaneous electrical stimulation produced an Aα fibre response of short latency and no C fibre response was seen. Two units were found to be possibly under DNIC, whilst the remaining 53 were not influenced at all by peripheral noxious stimulation. The results will be discussed below in terms of the peripheral activating stimulus.

(a) DNIC versus Aα fibre responses. Aα fibre responses with a latency of 5—7 msec were seen in all 55 cells. The Aα fibre responses were tested at threshold current (0.56 ± 0.14 mA for a 0.2 msec duration pulse), knowing that the Aα fibre response of the convergent neurones was influenced to a greater extent at this level than at supramaximal stimulation [11].

Thus the effect of DNIC was searched for under the most favourable conditions. Notwithstanding this threshold response, at currents producing one or two Aα spikes per stimulation, only two cells were inhibited by noxious pinch applied in these cases to the muzzle and tail. In these two cases, the effect we observed was weak and not easily reproducible. The remaining 53 neurones were unaffected, the response being unchanged both in terms of number of spikes and latency. Noxious pinches applied to the tail (n = 48), forepaws (n = 8), contralateral hind paw (n = 48), ears (n = 28) and muzzle (n = 15) were all completely ineffective in altering the Aα fibre response. Innocuous peripheral stimulation was equally ineffective except when applied to the inhibitory ipsilateral fields of the 3 neurones found

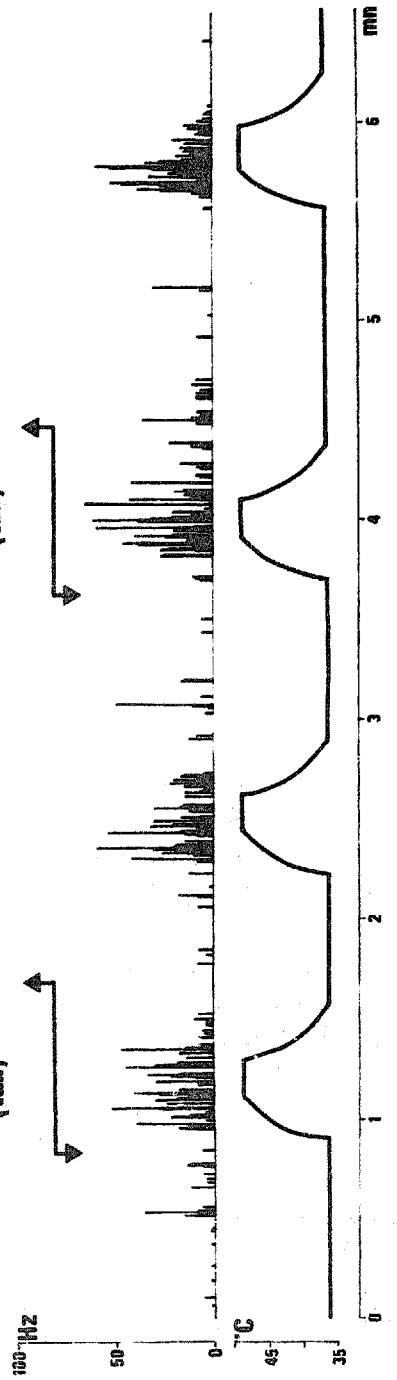

Fig. 3. The lack of effect of DNIC on the response of a noxious only unit to noxious radiant heat applied to the peripheral receptive field. The heating steps are shown below the ratemeter record.

possessing these fields. In all cases tested bradykinin i.p. had no effect on the A fibre response of these non-noxious units (n = 8).

(b) DNIC versus natural stimulation. A high level of activity was induced in the 10 neurones tested by stroking the receptive field or by gentle pressure. Using this activating stimulus, again no DNIC was found (Fig. 4B). Pinching the tail and hind paw (n = 10), ears (n = 6) and intraperitoneal bradykinin (n = 3) did not alter the level of activity induced by natural

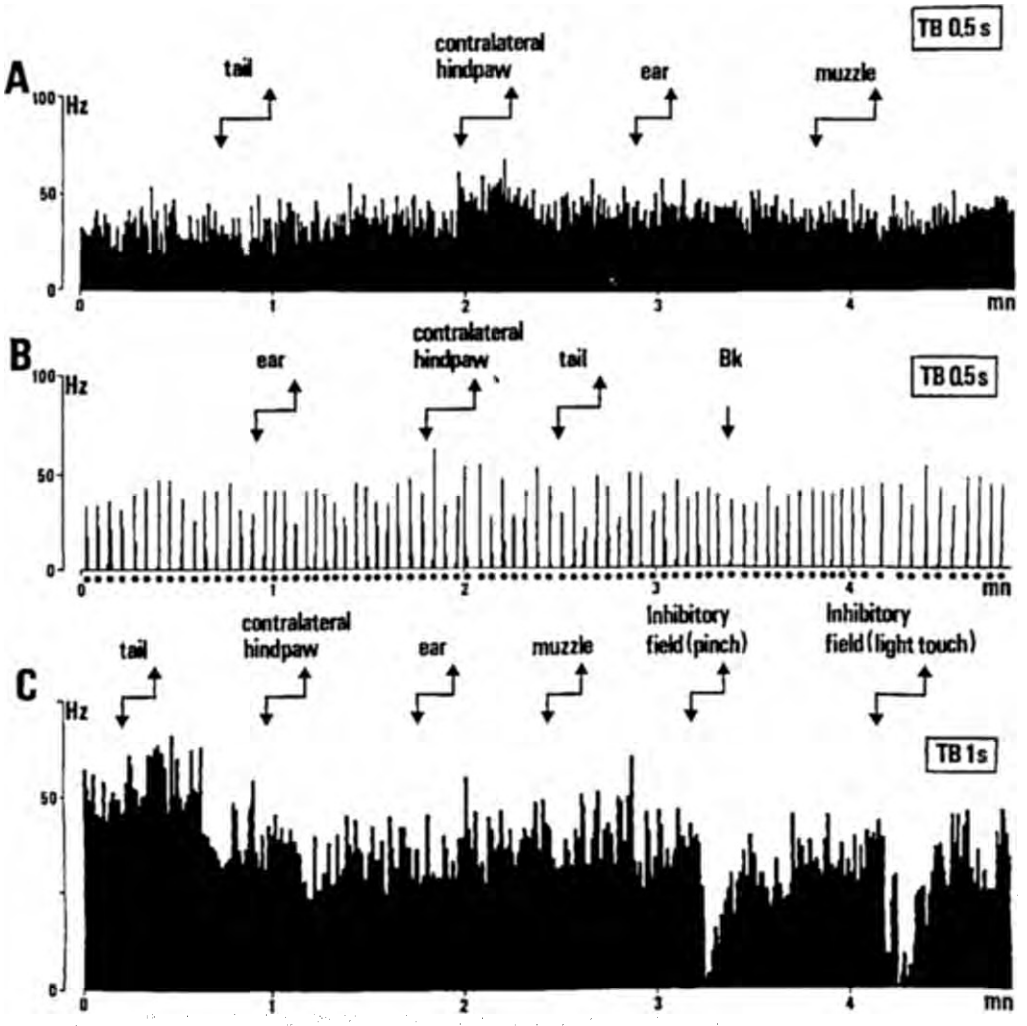

Fig. 4. The lack of effect of DNIC on 3 types of activity of 3 different non-noxious neurones. A: spontaneous activity. Pinch applied to various parts of the body has no effect on the spontaneous activity. B: response to tactile stimulation. Light touch (represented by the black circles) applied to the receptive field of an innocuous neurone produced a phasic response which is unaffected by pinch applied to various areas of the body or by intraperitoneal bradykinin (Bk). C: response to sustained pinch. The activity produced by sustained pinch applied to the receptive field is unaltered during plurisegmental noxious pinch whereas pinch or touch applied to the ipsilateral inhibitory receptive field produces a reduction of activity.

tactile stimulation. A 60—100% inhibition was found under the same conditions for the convergent neurones.

In addition, four of these neurones could be tonically activated by prolonged pinch by means of the application of an artery clip to the excitatory receptive field. All 4 cells tested in this manner were unaffected by noxious pinch applied to various parts of the body (Fig. 4C).

(c) DNIC versus spontaneous activity. The majority of non-noxious units presented no or a low level of spontaneous activity. However, 4 cells were found to have a high order of such activity. Noxious pinch applied to the tail, contralateral paw, ears and muzzle produced no alteration in the spontaneous rate (Fig. 4A).

(d) Ipsilateral inhibitory fields. Three cells were found to possess ipsilateral inhibitory fields from which inhibitions of evoked activity could be induced by light mechanical stimulation (see Fig. 4C).

(4) Proprioceptive neurones

Eighteen neurones, situated (Fig. 1) more ventrally in the dorsal horn than the convergent neurones, were found to present a regular tonic discharge related to the position of the articulation and to respond phasically to joint movement and/or deep tissue pressure. These cells gave A fibre only responses to electrical stimulation of the periphery and the effect of noxious stimulation was tested either against this response or the activity produced by joint movement. In none of these neurones was any influence of DNIC found.

With A fibre responses, noxious pinch applied to the tail (n = 7), contralateral paw (n = 6) or the muzzle (n = 2) had no inhibitory effect. Using natural stimulation (Fig. 5), again pinching the tail (n = 15), contralateral hind paw (n = 11), ears (n = 4) or intraperitoneal bradykinin (n = 3) were without effect on these neurones. Thus as for the noxious only and innocuous neurones, the proprioceptive units are not influenced by DNIC.

(II) Convergent neurones in the spinal animal

(1) General findings

Eighteen convergent neurones were recorded in the dorsal horn of the spinal animal. In all respects these neurones were equivalent to those found in the intact animal: the cells responded to noxious heat, strong pinch, pressure and light touch and received A and C fibre inputs. The responses of these neurones to peripheral stimulation were qualitatively identical to those seen in the intact rat. In addition these neurones had a similar distribution in the dorsal horn to the convergent neurones recorded in the intact rat (Fig. 6). However, whereas 98% of the convergent neurones in the intact rat were under the influence of DNIC, not one of these 18 units was inhibited by noxious peripheral stimulation applied to those areas of the body tested in the intact animal. The only inhibitory effects seen were those induced by stimulation of the ipsilateral inhibitory receptive field, a phenomenon the

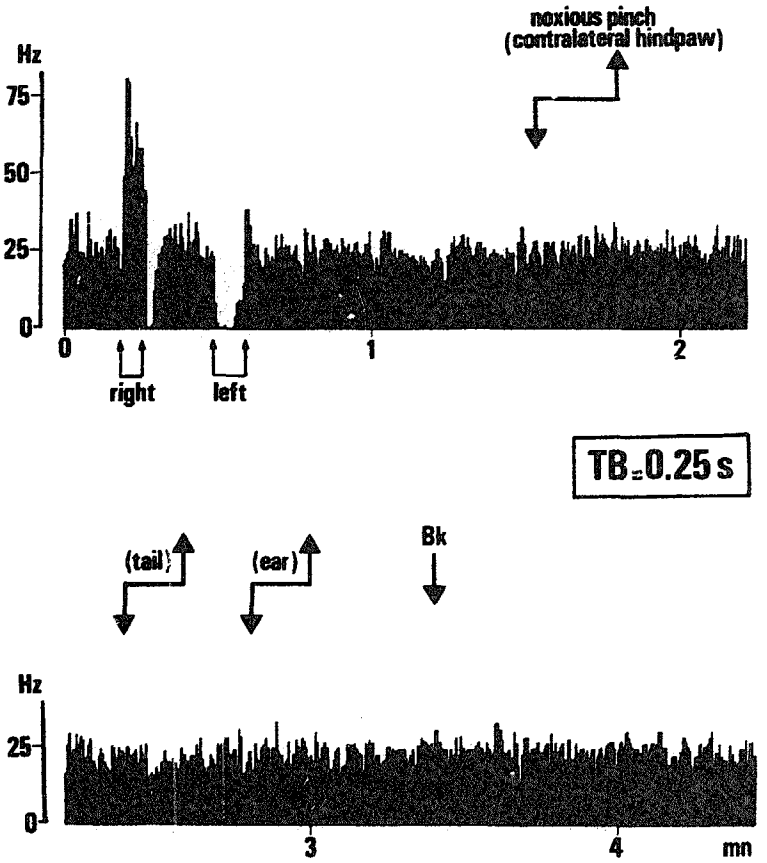

Fig. 5. A continual record of the activity of a proprioceptive neurone related to the angle of the paw joint (activation when moved to the right, inhibited to the left). Noxious pinch and intraperitoneal bradykinin have no effect on this activity.

existence of which is more frequently observed in the spinal rat. Convergent neurones (61%, 11/18) in the spinal animal had this ipsilateral field compared with 11% in the intact animal [41].

Thus DNIC is removed by a spinal section.

(2) Response to transcutaneous electrical stimulation

All neurones showed A and C fibre responses qualitatively identical to those seen in the intact animal. The noxious stimuli effective in the intact rat in inhibiting the A and C fibre responses had no effect in the spinal animal.

(a) Noxious pinch versus C fibre response. Noxious pinch applied to the tail had no effect on the 18 cells tested even at threshold C fibre stimulation. Noxious mechanical stimulation of the contralateral hind paw (n = 16) similarly was without effect.

In two cases mechanical stimulation of the base of the tail was found to produce a reduction of the C fibre response. Further investigation revealed

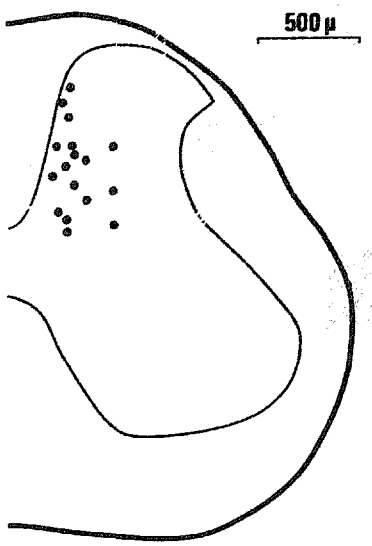

Fig. 6. Histological localization of 17 of the convergent neurones recorded in the spinal rat. The recording sites were marked with pontamine blue and are illustrated on a transverse section of the lumbar cord.

that this effect could not be elicited from the medial areas or tip of the tail usually efficient in the intact animal; in fact the effect was due to an ipsilateral inhibitory field extending to include the base of the tail. Bearing this out, the inhibition from this area could be activated by both light touch and pinch unlike the specifically noxious DNIC.

(b) Noxious heating of the tail versus C fibre response. Eleven convergent neurones were tested in the spinal animal for the effect of noxious heat applied to the tail as in the intact animal. In all these cells, the C fibre response was completely unaltered during the application of hot water at temperatures between 46 and 54°C, a stimulus that produced a mean 74% inhibition in the intact animal.

(c) Bradykinin i.p. versus the C fibre response. In the 15 cells tested, bradykinin i.p. was without effect on the C fibre response in the spinal animal.

(d) Transcutaneous electrical stimulation of the tail versus C fibre response. Ten cells were studied for the effect of transcutaneous electrical stimulation of the tail (TEST) on the C fibre response, this stimulation having a threshold for inhibition in the intact rat of 2.94 mA [41]. In the spinal animal, TEST even with currents of up to 10.5 mA were completely inefficient in inhibiting the C fibre response.

(e) Aα fibre response. There was no change in the Aα fibre response induced by threshold stimulation during intraperitoneal bradykinin, noxious pinch or electrical stimulation of the tail.

(3) Responses to natural stimulation

(a) DNIC versus response to radiant heat (Fig. 7). Six neurones were

found to give a stable response to radiant heat applied to the excitatory receptive field and this stimulus was used to test the effect of DNIC in these cases. Again no effect was seen — noxious pinch applied to the tail (n = 6), hind paw (n = 4), bradykinin (n = 3) and noxious heat (n = 3) were all without effect on the response to radiant heat.

(b) DNIC versus responses to tonic pinch. In the 5 neurones tested with the activity produced by tonic pinch applied to the excitatory receptive

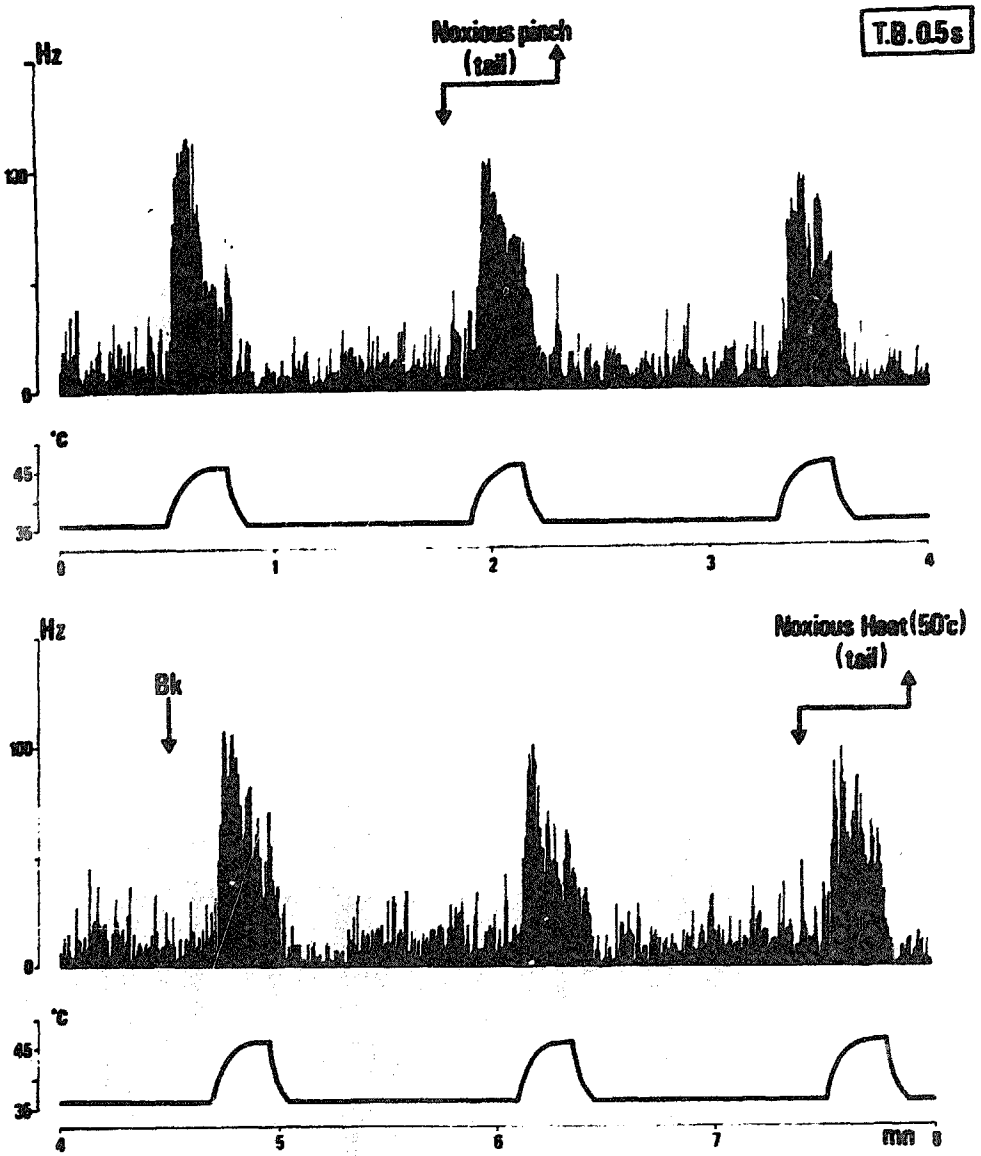

Fig. 7. The lack of effect of pinch, noxious heat and bradykinin i.p. on the response to radiant heat applied to the peripheral receptive field of a convergent neurone in the spinal animal. The temperature steps are given below the ordinate. The trace is a continual record.

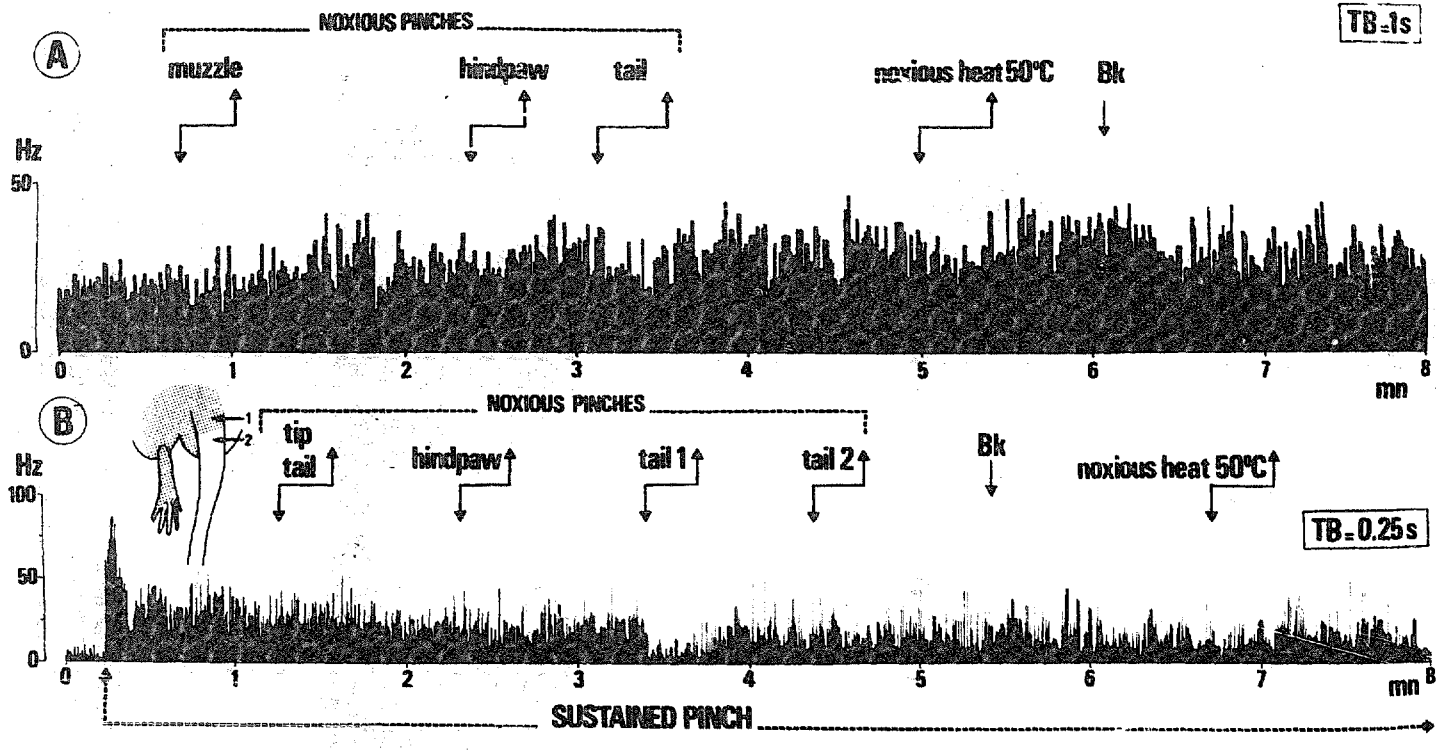

Fig. 8. The absence of DNIC in the spinal animal. A: the upper trace illustrates the lack of inhibition of the spontaneous activity of a convergent neurone by noxious peripheral stimulation. B: the lower trace again shows the lack of the effect of DNIC in the spinal animal against the response induced by sustained pinch applied to the peripheral receptive field (shown in black). The only inhibitory effect seen was when pinch was applied within the large ipsilateral inhibitory field of the neurone (stippled area).

field, noxious pinch of the tail and hind paw, intraperitoneal bradykinin and noxious heat were all without effect on this high level of activity. One of the cells described in Section II.2.a was tested for the effect of tail pinch against the response induced by sustained pinch. Again for the C fibre response the same effects due to the ipsilateral inhibitory receptive field were found (Fig. 8B).

(IV) Spontaneous activity

This activity without any stimulation of the receptive field was more commonly encountered in the spinal animal than in the intact rat. Noxious pinch applied to the tail (n = 5), contralateral hind paw (n = 3), bradykinin (n = 3) and noxious heat (n = 2) were again completely ineffective (Fig. 8A).

DISCUSSION

In the preceding paper [41], we have described inhibitory controls emanating from the periphery which exert a powerful effect on convergent neurones in the dorsal horn. Such an effect seems to need a certain level of nociceptor recruitment to be efficacious, but when this level is reached by temporal or spatial summation the effect is extremely powerful. This kind of inhibition can be induced from widespread areas of the body and therefore has been designated as diffuse noxious inhibitory controls (DNIC). DNIC is only induced by noxious peripheral stimulation, innocuous stimulation being without effect. Mechanical noxious, noxious heat and visceral noxious stimuli produce the same degree of inhibition. The inhibitions act on all activities of these convergent neurones and influence both the responses due to high and low threshold afferents, the latter, to some extent, being less influenced.

By contrast, we have shown in the present paper that non-convergent units such as noxious only units, innocuous units and proprioceptive neurones are not under the influence of DNIC, suggesting that this property is a specific feature of dorsal horn convergent cells. The lack of effect of DNIC on the various responses of marginal layer noxious only units was clear. Pinch, noxious heating of the tail and intraperitoneal bradykinin were without effect as was electrical stimulation of the tail even at currents many times higher than those producing complete inhibition of the convergent neurones. Similarly the innocuous units and proprioceptive neurones were also not under the control of the system. This specificity of DNIC strongly supports the involvement of neural mechanisms, thus ruling out a participation of non-specific phenomena such as vasomotor reactions.

The effect of DNIC on the convergent neurones could not be demonstrated in the spinal animal even with extremely powerful noxious peripheral stimulation. Therefore the mechanisms underlying DNIC are not confined to the spinal cord and must ascend to and redescend from supraspinal levels,

suggesting that a complex system is recruited when a painful stimulus is applied. In this respect, it is important to note that such a system is completely different from segmental inhibitory systems which are operative in both spinal and intact animals. For instance in our experiments, ipsilateral segmental inhibitory fields were found as expected in both intact and spinal animals. Furthermore these kinds of inhibition can be induced by large myelinated fibres [see refs. in 6,12,53,57,67,70]. In addition, our results are also different from heterosegmental and heterosensory inhibitory effects described in the chloralose anaesthetized cat which affected all dorsal horn units tested [9].

In our experiments, excitatory dorsal horn responses recorded during the stimulation of their receptive field were used as a non-conditioned or a conditioned response for conditioning heavy painful stimuli applied to other parts of the body. Since both noxious and non-noxious stimuli were used as conditioned tests, our results give rise to two situations that one can envisage in the dorsal horn of the intact animal. Firstly, in a situation where two noxious stimuli are applied with the one applied to the excitatory field of the neurone being weaker, an almost total blockade of this neuronal response will result. In other words, when two simultaneous noxious stimuli are applied on two distant parts of the body, the pool of convergent dorsal horn units related to the slighter stimuli is inhibited. In the second situation, in the absence of a noxious input to a pool of convergent neurones, the spontaneous activity and the responses to tactile stimulation in this pool are inhibited by a noxious stimulus applied to another area of the body. Hence, a noxious stimulus can excite the corresponding segmental pool of neurones whilst inhibiting the activity related to non-noxious stimulation of the other dorsal horn convergent neurones.

These results and their possible implications provide a basis to discuss several important questions regarding certain concepts in pain and analgesia. These include the role of convergent neurones in pain, and a mechanism which possibly explains certain types of analgesia induced by peripheral stimuli such as counterirritation, electroacupuncture or some clinical observations. Furthermore, these results and their theoretical implications give rise to some questions about the concept of "intrinsic analgesia systems" [45, 48] modulating pain transmission; an alternative hypothesis being that such systems may in reality be part of the pain sensory system. This idea will be discussed below.

DNIC and the signalling of pain by convergent neurones

On the basis of current knowledge, convergent neurones [37,66], those responding both to high and low threshold afferents play a major role in the transmission of painful messages: they are activated by a variety of painful stimuli from cutaneous [30,54,65], muscular [25,38] and visceral [31,59, 62] origins; they are strongly excited by pain-producing substances [5,31] and project in some ascending pathways such as the spinothalamic, spino-

reticular and spinocervico-thalamic tracts [1,11,13,29,43,64,69]. Knowing that pain of muscular and visceral origin can be particularly intense and is probably the pain most frequently observed in clinical practice, the importance of convergent neurones in signalling pain is further emphasized since such projections onto noxious only neurones located in the marginal layer of the dorsal horn [17] have not yet been described. Furthermore, it has been demonstrated that on the basis of studies on convergent cells in the monkey compared with psychophysical measurements in man, that activation of convergent units is sufficient to produce pain [49,60].

However, despite the above evidence, the response characteristics of convergent neurones present some paradoxical points. One is that these neurones can present similar or greater levels of activity to innocuous peripheral stimulation than for their response to noxious stimulation. For instance, whereas convergent units respond in a graded fashion to radiant heat or pressure-pinch application up to and above noxious levels, they are also often strongly activated by light mechanical stimuli such as stroking or hair movements. In these cases, rapid repetition of the light mechanical stimuli can result in an equal or even a greater level of firing than, for example, that produced by sustained noxious pinch. These observations are particularly obvious in decerebrate or intact animals since, under these conditions, the response of convergent neurones to A fibre low threshold inputs is favoured as the high threshold responses are under a more pronounced tonic descending inhibition emanating from the brain stem [7,10,33]. Consequently, in the intact animal, a high level of impulses could reach supraspinal structures via convergent units when repetitive innocuous peripheral stimulations are applied. On the basis of these conflicting observations, it has always been difficult to imagine how the excitatory responses of dorsal horn convergent neurones can be involved in a specific pain signalling message which reaches the brain. We propose an interpretation of the results presented in this and the previous report which could explain the involvement of convergent units in the transmission of nociceptive messages.

When an intense nociceptive stimulus is applied to the periphery, there will be a segmental pool of convergent neurones excited by their thin afferent inputs surrounded by a larger pool composed of the other convergent neurones which have their activity inhibited simultaneously by the stimulus. In the absence of a painful stimulation these two pools of convergent neurones would transmit information received from a variety of non-noxious receptors, thus providing information comprised of a basic noise transmitted to higher levels of the central nervous system. We envisage that in the freely moving animal, the activity of the whole population of convergent units would be of relatively high order due to the continual at random activation of non-noxious receptors, such as the hair and touch receptors. This basic "somatosensory noise", transmitted to higher centres, would not allow the extraction of a meaningful signal. During an intense nociceptive stimulus, both the noxious only and convergent units send a positive signal towards the higher centres. Concurrently this signal will activate the DNIC

which descends to inhibit all those spinal convergent neurones not activated by the initial noxious stimulus. This results in a considerable reduction of the "noise", thus providing a high level of contrast between the positive signal and the signals emanating from the rest of the spinal convergent neurones. In other words, the noise invading the higher centres of the brain is reduced simultaneously with the arrival of the positive painful signal which clearly stands out. This widespread inhibitory system could perhaps be the mechanism behind the clear signal produced from convergent neurones. If so, the question of the specificity of pain sensation would be approached in a new light since the system of contrast may provide a specific signal in a non-specific system.

If the preceding hypothesis is assumed, one can imagine that such a system is involved in situations where the sensation of pain is strong but poorly localized. On the other hand well localized pain, for instance, that evoked by pin-prick may well be mediated by noxious only cells the activity of which is not affected by DNIC as we have demonstrated. In a similar way the signal transmitted by the non-noxious only neurones does not require such a system and correspondingly we have found that these cells are not influenced by DNIC.

DNIC and the inhibiting of pain by the "intrinsic analgesic system"

The idea of an independent endogenous pain inhibitory system situated in the mesencephalon and brain stem and descending to inhibit the activity of dorsal horn nociceptive neurones has been extensively reviewed recently [23,45,48]. The final part of this system is believed to be a descending partly serotonergic projection from the caudal raphe [8,23,48].

On the basis of our results presented here one could imagine that due to the ascending/descending nature of the inhibitory loop originating from the peripheral nociceptors, DNIC could in fact involve the endogenous pain inhibitory system. DNIC inhibits the C fibre response of convergent neurones and also to a lesser extent the A fibre response — similar effects to those induced by stimulation of the nucleus raphe magnus [24,32,42,61]. At present, there has been no systematic study of the effect of nucleus raphe magnus stimulation on the responses to noxious only cells. However, in the case of innocuous cutaneous and proprioceptive cells, neither raphe stimulation [4,24,32] nor DNIC have an influence on these neurones.

The idea that the inhibitory loop involved in DNIC may be part of the analgesic system, or at least the serotonergic part of this system, is strongly supported by the fact that in recent experiments performed in animals depleted of 5-HT, we found a strong reduction of this kind of inhibition. Therefore DNIC seems to be to a great extent dependent on the integrity of the descending serotonergic system. These considerations do not question the analgesic effects produced by central electrical stimulation but suggest that surprisingly the "intrinsic analgesic system" may not be an independent

entity but comprise part of the pain signalling system — "the contrast" we have put forward in these papers.

If it is verified that DNIC and certain analgesic systems share some common characteristics, the existence of the two pools of neurones we have postulated may resolve certain problems implicit in the present ideas concerning the physiological significance of the analgesic systems. For example, the idea of a negative feedback loop [22] presents a logistic problem as in this schema the spinal neurones excited by a noxious stimulation activate the analgesic system which then, in turn, inhibits the same spinal neurones. Whereas this hypothesis would seem to be compatible with the sensation of acute sharp pain, the existence of chronic severe pain would be difficult to explain due to a permanent inhibition of the neurones subserving the sensation. The schema we propose involving DNIC may resolve this problem on the basis of a separation of the activating pool of neurones from the inhibited pool. The mechanism which protects the excited pool of convergent neurones from DNIC induced by their own activity still remains to be elucidated. In any case, during the central electrical stimulation of the "intrinsic analgesic system", both pools of neurones will be inhibited, leading to a widespread and powerful analgesia.

Obviously further experimental proof is required to verify these concepts but several seemingly paradoxical analgesic effects found in man and animals using stimuli sufficient to produce DNIC can be explained by our results. These are discussed below.

DNIC and the pain-relieving effect of counterirritation and acupuncture

One must again stress that our results are obviously independent of the large fibre mediated analgesic effects, the analgesia produced only by segmental stimulation, as the effects we have found are produced by noxious stimuli applied to plurisegmental areas and involved supraspinal structures. Therefore the pain-relieving effects of transcutaneous nerve stimulation (TNS) or certain forms of acupuncture involving segmental mechanisms are certainly not subserved by DNIC.

However, DNIC may well form the neural basis of the pain-relieving effects of counterirritation where a peripheral nociceptive stimulus is used against pain originating elsewhere. This phenomenon has been known and used since antiquity as illustrated by the use of the electric discharges of torpedo as a pain-relieving method [39]. The existence of such pain-relieving stimuli has been confirmed in man more recently using various counterirritants such as heat, cold and electrical stimuli [28,34,58,68] which are painful or at least unpleasant. Furthermore painful cutaneous electrical stimulation lowers the sensation of chronic somatic pain [51]. In a same way, it has been demonstrated [2] in animal experiments that stimulation of the tooth pulp which is obviously painful is able to increase the threshold of escape behaviour induced by foot shock (up to 700%). In the rat, hypertonic saline injected intraperitoneally [35,40], sustained pinch applied to the paws and

tail [18] and electrical stimulation of the tail at currents sufficient to produce vocalization [14] also induce strong analgesic effects when the test for analgesia is applied to other areas of the body. Thus in the chronic animal analgesia can be produced by peripheral stimuli similar to those we have found effective in inhibiting the convergent neurones of the dorsal horn. Analgesic effects with other peripheral stimuli have been described recently [35].

Whether these effects of counterirritation are equivalent to those produced by certain techniques of acupuncture is not clear but it seems likely that at least in some cases the two methods share common mechanisms. A characteristic of classical Chinese pain-relieving acupuncture is a sensation (Teh Ch'i) of paraesthesia associated with muscular contraction emanating from the point of stimulation; this sensation is described as being at least unpleasant. A certain time, in which the stimulus intensity is progressively increased, is required to reach this state. In this respect, Mann [47] has concluded for effective analgesia in Western man, the painful sensation resulting from the stimulation point should be the maximum that the patient can support. These clinical observations are supported by the fact that there seems to be an increased efficacy of electroacupuncture with parameters producing a feeling of pain at the stimulation site than with less intense stimulation [21]. These authors suggested that deep high threshold receptors or nerve fibres were involved in the effects they observed. Their report only used homosegmental stimulation but Andersson et al. [3] have concluded that the therapeutic pain-relieving effects of electroacupuncture stimulation cannot be explained by homosegmental mechanisms alone. In addition, the question arises as to the specificity of acupunctural points. Lynn and Perl [46] have presented evidence for a non-specificity of acupuncture on the basis that acupuncture induces hypoalgesia in widespread areas of the body, not only the classical target areas. Reciprocally, painful electrical stimuli whether applied to near or far acupuncture or trigger points produce analgesic effects [51]. Further supporting evidence is provided by Andersson et al. [3] who have found that the analgesic effects of electroacupuncture using large surface electrodes were greater than to those produced by needles. Finally Levine et al. [14] and Melzack et al. [26,27,52] have also suggested that acupunctural stimuli which produce painful effects at the site of stimulation act in a similar way to the counterirritation principle. "Acupuncture and transcutaneous electrical stimulation both fall in the category of "hyperstimulation analgesia" and are simply methods of producing brief pain to relieve chronic intense pain" [26].

Many of the effects described in this section are produced by peripheral electrical stimulation applied at parameters similar to those we have found effective in inhibiting convergent neurones, i.e. causing a sensation of pain at the stimulation site. All produce analgesic effects on pain situated within other segments of the body. We therefore propose that DNIC might be the neuronal basis of these pain-relieving effects.

The assertion that, in some cases, the acupuncture technique may involve

DNIC is strongly supported by provoking results obtained by Chinese workers, although the question of the specificity of acupunctural points is rarely investigated on the basis of the position of the points inducing the effect. However, it has been reported that the analgesia produced is widespread and bilateral but with a greater segmental effect [15]. This latter point may relate to the involvement of the large fibre mediated segmental effects in addition to a DNIC mediated widespread effect. A description of the sensation of the acupunctural stimulation is also rarely given but it can be interpreted that, in some cases, thin fibres are at the origin of the analgesic effects they observe. For instance, in man, a vascular occlusion (lasting 20 min) applied to the upper arm does not affect the analgesic effect induced by the needling of points located below the level of occlusion [15]. Under these conditions, it is well known that conduction is primarily reduced in large myelinated fibres, slow conducting fibres being affected to a lesser extent. Furthermore, with an almost identical occlusion in man, pain is the only sensation remaining following peripheral stimulation of the occluded area [34].

A series of experiments [16,20,63] using electroacupuncture versus viscero-somatic reflex discharges strongly supports the idea of the ascending-descending nature of mechanisms subserving this kind of analgesia: inhibitions disappeared in spinal preparations, but remained after decerebration, suggesting that the brain stem is a main link in these phenomena. More precisely a lesion of the median region of the medulla including mainly the nucleus raphe magnus produces a strong reduction of the inhibitory effects which in addition, according to sectioning experiments, require the ventrolateral and the dorsolateral funiculus as respectively ascending and descending pathways. These results strongly suggest that both ascending pain pathways and descending inhibitory pathways are involved. Finally the analogy between some forms of electroacupuncture and DNIC is supported by the fact that in the spinal trigeminal nucleus, convergent units are inhibited by electroacupuncture whereas noxious only units are unaffected [19].

In conclusion, a number of pain-relieving stimuli share some common characteristics: the painful or unpleasant nature of the stimulus; widespread analgesic effects; associated long lasting post-effects; a requirement of ascending-descending pathways with presumably the "analgesic system" as a link and final inhibitory effects upon convergent units. DNIC as we have described seems to offer the neuronal basis of such phenomenon.

Further clinical evidence for the existence of a pain inhibiting system of peripheral origin is the observation that organic pain raises pain thresholds in other areas of the body [36,56] and that an anterolateral cordotomy which relieved root pain in paraplegics produced a lowering of the pain threshold in other body areas [36]. To explain these clinical effects, Melzack [50,51] has suggested the existence of a "central biasing mechanism" including a spinal-supraspinal loop which would be activated by small fibre inputs from the periphery and would inhibit the sensation of pain from other areas. DNIC may well fit at least some of the requirements of this system.

Thus, to conclude, we propose that DNIC may, on the one hand, explain certain paradoxical pain-relieving effects and on the other, allow, by means of a contrast system, a significant pain signalling message to emanate from the convergent neurones of the dorsal horn.

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