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Effect of Peripheral Nerve Stimulation on the Dorsal Horn Cell Activity in Cats with Cutaneous Inflammation

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There are some reports showing that an experience of long-enduring pain causes a change in the pain transmission system, suggesting a plastic nature of the nociceptive system. However, most of the studies concerning the analgesic effect of peripheral nerve stimulation dealt with normal animal or human subjects. So, the present study was undertaken to investigate the effect of peripheral nerve stimulation on the dorsal horn cell activity using a tonic pain model, which was made by producing a cutaneous inflammation. The main results are summarized as follows. 1) The evoked activity by electrical or natural stimulation as well as spontaneous activity was enhanced, and the receptive field size was also expanded by the inflammation. 2) Peripheral nerve conditioning stimulation reduced the C-response of the dorsal horn cell in the normal and inflamed group, and the degree of inhibition between the two groups showed no significant difference. 3) Inhibition of the C-response of the dorsal horn cells by peripheral conditioning stimulation was completely reversed by naloxone in the inflamed group whereas there was a partial block in the normal group.

Key Words: Inflammation, carrageenan, acupuncture, peripheral nerve stimulation, analgesia, endogenous opioid system

Transcutaneous electrical nerve stimulation, acupuncture-needling, and electroacupuncture, which appear to work with influence of an increased discharge in peripheral nerve fibers, have widely been used for relief of pain in medical practice.

Many reports have described the analgesic effect of peripheral nerve stimulation (Sweet and Wepsic 1968; Anderson 1979; Willis 1982; Mayerson 1983) and also numerous studies concerning the mechanisms responsible for the analgesia produced by peripheral nerve stimulation were reported (Andersson 1979; Ignelzi and Nyquist 1979; Woolf *et al.* 1980; Mayerson 1983; Sjölund and Schouenborg 1983).

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A plausible explanation of the effects of peripheral nerve stimulation originates from the gate control theory, which focuses on the segmental spinal inhibitory mechanism (Melzack and Wall 1965; Handweker *et al.* 1975; Kerr 1979; Iggo 1980). Although some evidences in support of the spinal mechanism have been reported (Zotterman 1939, Higgings *et al.* 1971, Meyer and Fields 1972, Iggo 1976; Yaksh and Elde 1981; Nam *et al.* 1991), an important role of supraspinal structures associated with the endogenous opioid system, have been emphasized (Du and Chao 1976; Pomeranz and Chiu 1976; Kerr *et al.* 1978; Takeda *et al.* 1979, Kim *et al.* 1991).

Meanwhile, there are some reports showing that an experience of long-enduring pain causes a change in the nociceptive system. For instance, Tasker *et al.* (1983) reported that stimulation in the midbrain and medial thalamus could evoke pain in chronic pain patients whereas comparable stimulation in normal subjects evoked no sensation. In addition, it was found that peripheral nerve section, one of the chronic pain models, changes the con-

tent of the peptide and fluoride resistant acid phosphatase in the substantia gelatinosa (Jessell *et al.* 1979, Barbut *et al.* 1981). Furthermore, peripheral nerve section has been reported to change the receptive fields of neurons in the central nervous system (Devor and Wall 1981a, b), and similar alterations have been observed by producing a cutaneous inflammation (Guilbaud *et al.* 1986). These results suggest strongly that the nociceptive system is plastic; its character can be changed by an experience of long-enduring pain. Presumably such plastic changes could account for the clinical differences between acute and chronic pain.

However, most of the studies concerning the effect of peripheral nerve stimulation dealt with normal animal or human subjects.

So, the present study was undertaken to investigate the analgesic effect of peripheral nerve stimulation in a tonic pain model, which was made by producing a cutaneous inflammation.

MATERIALS AND METHODS

Animal preparations

A total of 50 adult cats (2.0-3.0 kg) of either sex were used in this study. The animals were anesthetized initially with intramuscular injection of ketamine hydrochloride (25 mg/kg). Under the initial anesthesia, the external jugular vein was cannulated for drug injection. A tracheostomy was performed and the animals were ventilated artificially and immobilized with gallamine triethiodide (Flaxedil, an injection of 20 mg i.v. followed by infusion at 4 mg /kg/h). The end-tidal CO_2 concentration was monitored and maintained between 3.5-4.5% throughout the experiment. Rectal temperature was kept near 37°C using a heating blanket.

Decerebration was performed by ligation of the basilar artery and the bilateral common carotid arteries and then further anesthesia was discontinued. Laminectomies were performed at the level of L3-L6.

For test stimulation and peripheral conditioning stimulation, the common peroneal nerve and the tibial nerve were dissected respectively from surrounding connective tissue, and they were placed on a pair of platinum bipolar electrodes.

The animals were fixed at a stereotaxic unit (Narishige Co.), and mineral oil pools were made around exposed spinal cord and peripheral nerves to prevent drying, and the temperature of the pools was maintained by heating coils immersed into them.

Test stimulation and recording of dorsal horn cell activity

To investigate the analgesic effect of the peripheral nerve stimulation, we considered the dorsal horn cell activity elicited by C-fiber activation or noxious mechanical stimulation as the index of pain. For the recording of the activity of dorsal horn cells, a carbon-filament-filled glass microelectrode was inserted using a pulse motor microdrive manipulator (Narishige Co.) into the lumbosacral spinal cord where the largest cord dorsum potential could be recorded upon stimulation of the common peroneal nerve.

As soon as a single unit activity was obtained, we started to record the dorsal horn cell activity elicited by applying the electrical stimuli to the common peroneal nerve and natural stimuli to the skin within the receptive field.

Electrical stimuli were applied with a train of 3 pulses (50 Hz) at a strength suprathreshold for C fibers (10 mA, 500 μsec duration) to maximize the dorsal horn cell response.

In natural stimuli, as a form of innocuous stimulus, the skin was brushed repeatedly with a hair brush, and as a noxious one the skin was squeezed using a pair of serrated forceps. All the cells used in this study were wide dynamic range cells which are known to be associated with pain transmission.

Induction of inflammation

After recording of the dorsal horn cell activities elicited by electrical and natural stimulation, 2% carrageenan (0.15 ml) was injected subcutaneously in the receptive field to induce inflammation. And then, during 3 hours after carrageenan administration, we examined the changes of cell responses evoked by electrical and natural stimulation as well as background activity.

Peripheral nerve stimulation (conditioning stiumlation) and naloxone administration

As conditioning stimulus, square-wave electrical pulses were applied to the ipsilateral tibial nerve at 2Hz for 15 min. The strength of the conditioning stimulus was adjusted to activate all fiber groups, including C-fibers (10 mA intensity, and 500 μsec duration). The dorsal horn cell activities elicited by electrical and natural stimulation were recorded before and 0, 5, 10, 15, 30, 60 min after the conditioning stimulation.

To explore a possible involvement of endogenous opioid substances in the inhibition produced by conditioning stimulation, the opioid antagonist naloxone was administrated intravenously at 5 min before the end of the conditioning stimulation, and the effect of the conditioning stimulation was compared with that without naloxone administration.

In the inflamed cats, we also employed the same procedures as in the normal group and analyzed the analgesic effect of conditioning stimulation and naloxone reversibility.

Data analysis

The activity of the single dorsal horn cell was amplified and fed into a window discriminator; the output of which was used by a computer to compile post or peristimulus time histograms. The responses elicited by electrical stimulation were accumulated by 3 successive stimuli (1 every 10 sec).

Because the evoked dorsal horn cell activities were varied from one unit to another, data are expressed as percentage of discharges in the control state. For each observation time, statisitical analyses were performed by paired t-test and independent t-test for comparing the data from the same cells and the different cells, respectively. Two-tailed p values less than 0.05 were considered significant.

RESUSTS

The effect of inflammation on the activities of dorsal horn cells and the receptive field sizes

Recordings were made from a total of 15 wide dynamic range cells. During 3 hours following carrageenan injection, we monitored the changes of spontaneous activity as well as electrically or naturally evoked activities of the cells. After carrageenan administration spontaneous activity increased gradually with time, and after 3 hours, reached 328.2±79.4% (mean±S.E.) of the control value. We could find the expansion of the receptive field sizes as well (Fig. 3).

Activities evoked by electrical and natural stimuli also increased after inflammation. In particular, the increase of the response of the cell elicited by brushing was most prominent, reaching maximally to 305.1±60.2% of the control value prior to carrageenan injection. By contrast, a relatively slight increase of A or C-response was found after inflammation (Fig. 3).

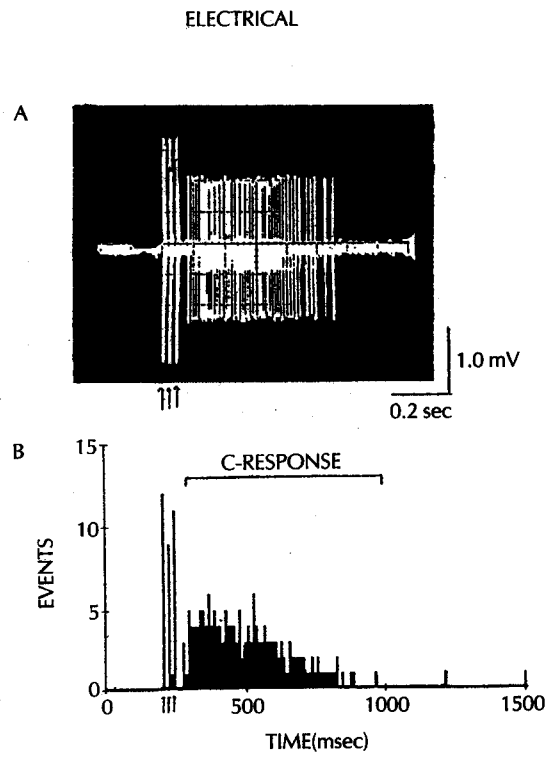

Fig. 1. *Single-unit activity of dorsal horn cell elicited by electrical stimulation. A: three consecutive electrical pulses (10 mA, 500 μsec duration; an intensity suprathreshold for C fibers) were applied to the common peroneal nerve at the times indicated by arrows. Spikes were photographed on the oscilloscope face. B: the poststimulus time histogram shows A and C-fiber evoked response by the same test stimuli as in A. The histogram was compiled from responses to 3 successive stimuli. Bin widths are 10 msec.*

The effect of peripheral nerve conditioning stimulation on the dorsal horn cell activity in normal cats

Dorsal horn cell activities elicited by electrical and natural stimulation were recorded before and 0, 5, 10, 15, 30, 60 min after conditioning stimulation. Immediately after the conditioning stimulation, the C-response of the cells was decreased to 53.8 ±3.7% whereas the A-response was 81.0±6.3% of the pre-stimulus control value, and gradually recovered with time (Fig. 4).

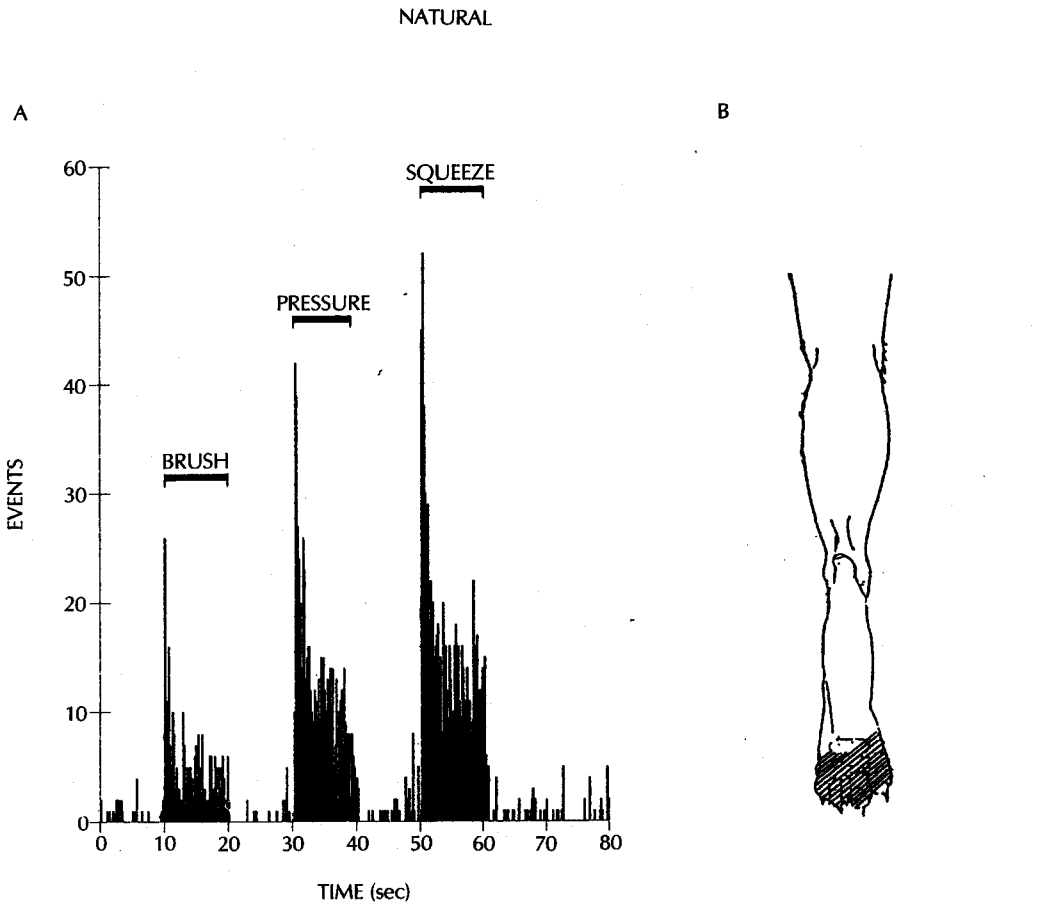

Fig. 2. *Peristimulus time histogram from response to natural stimulation. A: the cell responded to both innocuous and noxious mechanical stimuli within the receptive field, representing a wide dynamic range cell. Bin widths are 200 msec. B: the receptive field of the cell is indicated by the hatched area.*

Comparable results were obtained from response elicited by natural stimulation; dorsal horn cell response to noxious mechanical stimulation (squeeze) was reduced to 36.7±4.5% whereas innocuous stimulation (brush) was to 58.3±6.6% of the control value (Fig. 4).

These results indicate that the conditioning stimulation employed in this study, produced a differential inhibition of the dorsal horn cell activity; inhibition was greater in response to the noxious stimulus than to the innocuous one.

The effect of peripheral nerve conditioning stimulation on the dorsal horn cell activity in cats with cutaneous inflammation

Parameters of the conditioning stimuli were the same as those in normal cats. Dorsal horn cell activities elicited by electrical and natural stimulation were recorded before and 0, 5, 10, 15, 30, 60 min after the conditioning stimulation.

In cats with inflammation, immediately after the conditioning stimulation, A and C-responses of the dorsal horn cells were inhibited to 81.3±6.7 and 60.8±5.4% of the control value respectively, also

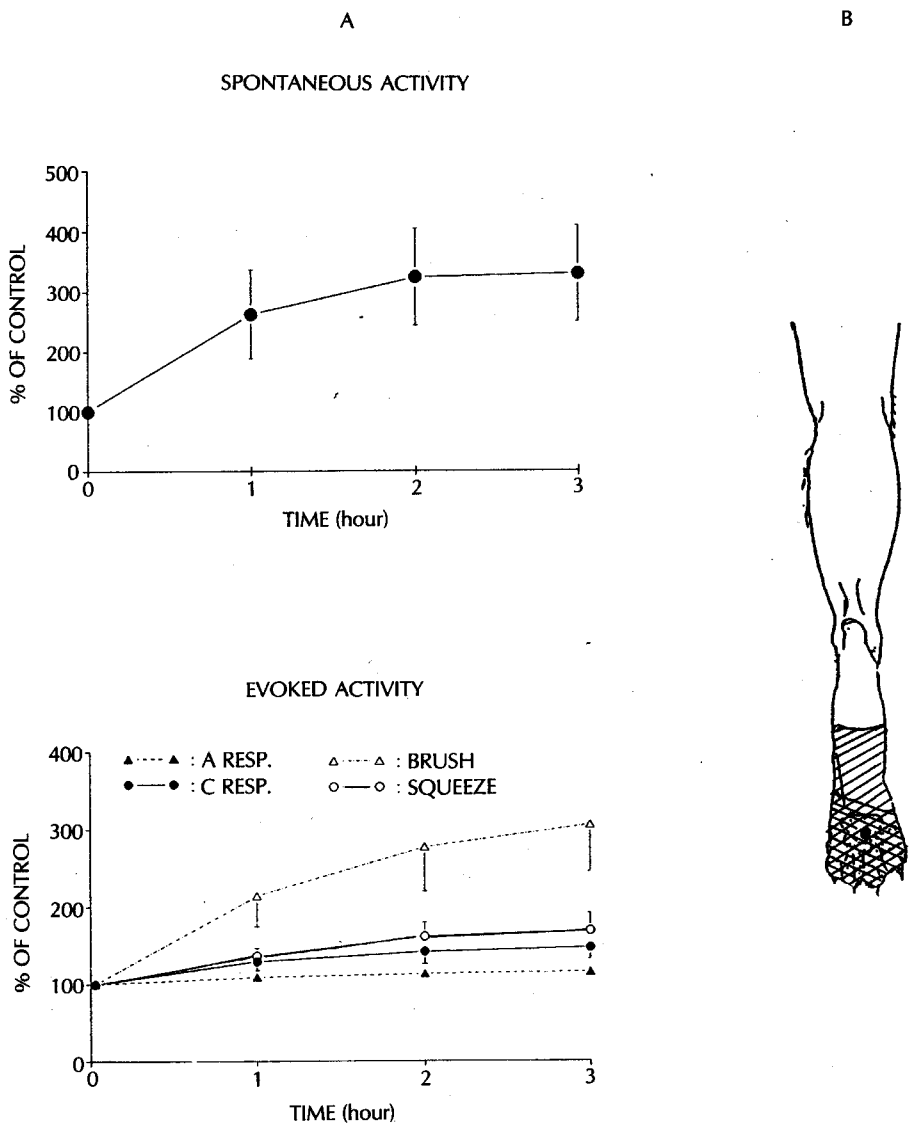

Fig. 3. *Time course of changes of dorsal horn cell activity and receptive field size after inflammation. A: spontaneous and evoked activity of the cells increased gradually with time. B: receptive field of the cell was also expanded. Crossed hatched area: original receptive field before induction of the inflammation. Hatched area: expanded receptive field after the inflammation. Black dot: a region where carrageenan was administered subcutaneously. Each data point represents mean ± S.E. of 15 units*

indicating a differential inhibition shown as in normal cats. In addition, the magnitude of the inhibition showed no significant difference compared with that obtained from normal cats (Fig. 5). These results suggest that long-enduring pain, as in these experimental conditions, may not have any influence on the analgesic effect caused by peripheral conditioning stimulation. On the other hand, the responses elicited by brushing and squeezing were inhibited, immediately after the conditioning stimulation, to 34.2±8.9% and 29.8±6.2% respectively. This indicates that the difference of inhibition be-

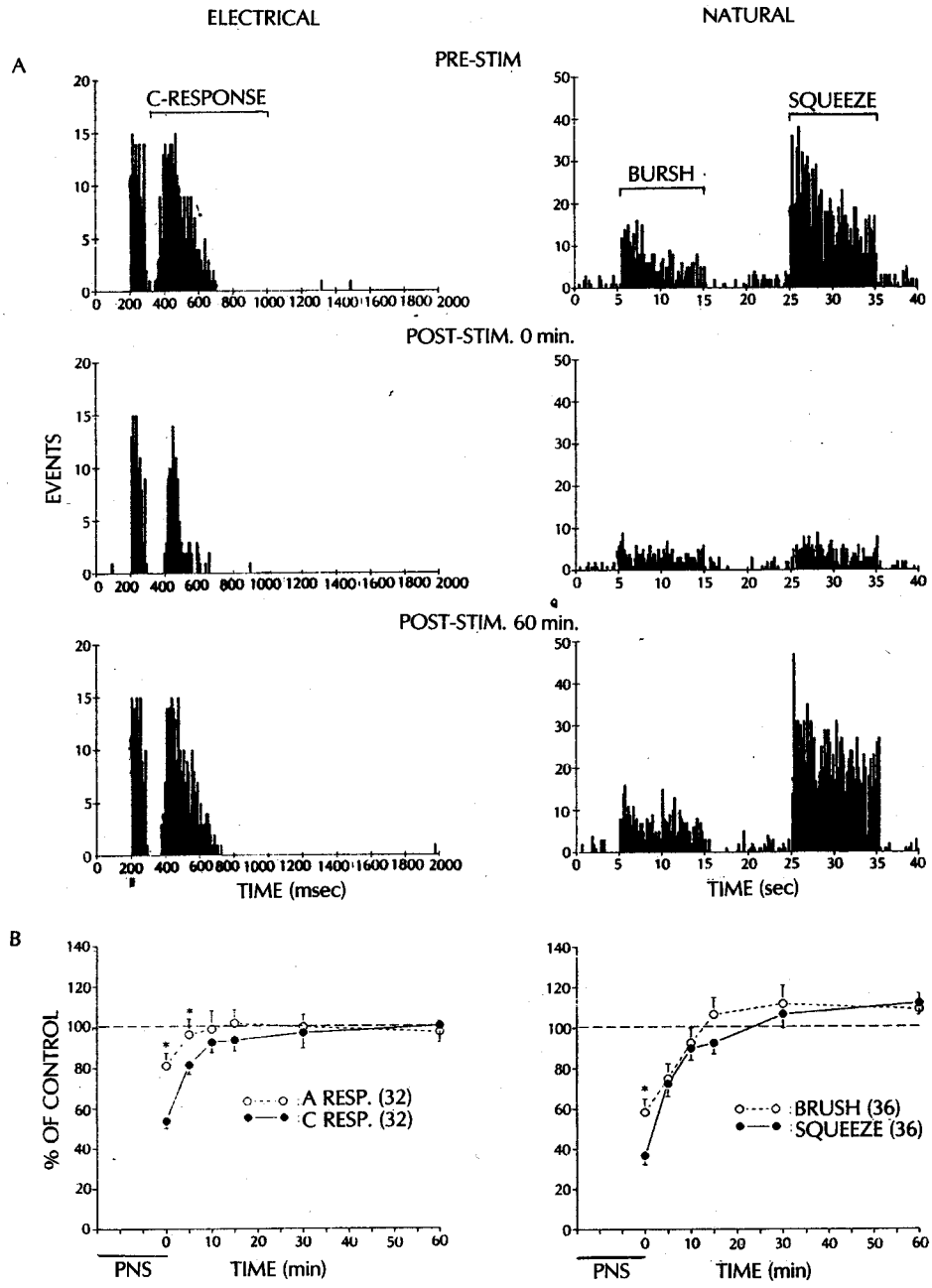

Fig. 4. *Inhibition of dorsal horn cell activity by the conditioning stimulation in normal cats. A: peristimulus time histogram showed an inhibition of dorsal horn cell activity elicited by the electrical or natural stimulation following the conditioning stimulation. Bin widths are 200 msec. B: Activities were expressed as a percentage of the pre-stimulus control values. Asterisks indicate significant differences between A and C-response or brush and squeeze response.*
A dashed line indicates control level.
PNS: peripheral nerve stimulation
Each data point is the mean ± S.E.
( ) represents the number of recorded units

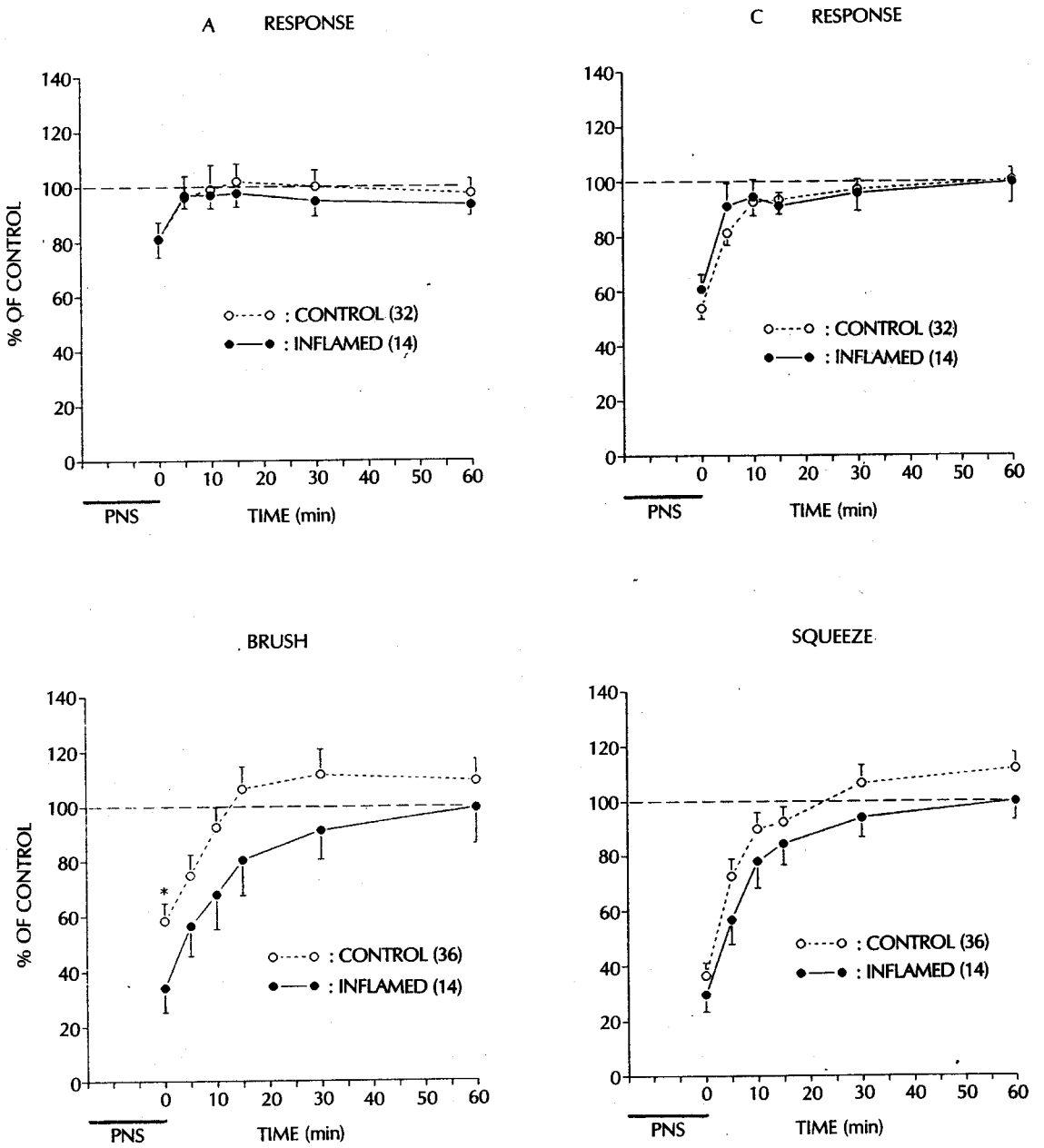

Fig. 5. *Comparison of average effects of the conditioning stimulation on the dorsal horn cell activity between normal and inflamed cats. In cats with inflammation, the same conditioning stimulus as in fig. 4 was applied at 3 hours following the injection, of carrageenan. No significant differences were found between normal and inflamed cats except in the response evoked by brushing immediately after the conditioning stimulation. Asterisk indicates a significant difference between control and the inflamed group.*
A dashed line indicates control level.
PNS: peripheral nerve stimulation
Each data point is the mean ± S.E.
( ) represents the number of recorded units

tween brushing and squeezing was not remarkable when compared with that between A and C-response. The inhibition of response of the cell to brushing was greater compared to normal cats (Fig. 5). These results may suggest a possibility that in cats with inflammation, activated afferent fiber groups by brushing contain not only A-fibers but also some afferent fibers linked by sensitized nociceptors.

We also examined the influence of peripheral

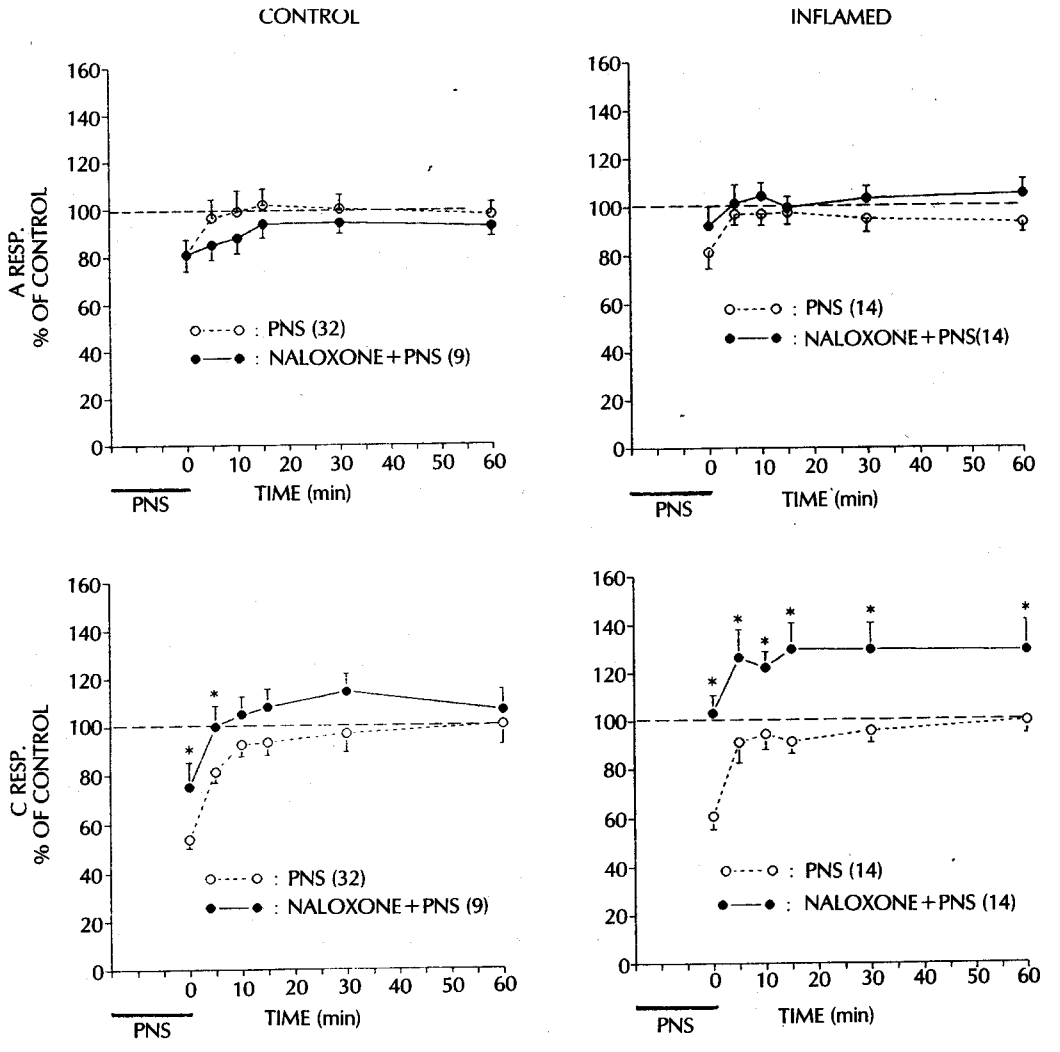

Fig. 6. *Influence of naloxone on the effect of conditioning stimulation on the electrically evoked dorsal horn cell activities in normal and inflamed cats. In normal cats, inhibition of C-response by conditioning stimulation was partially reversed by naloxone, by contrast, completely reversed in the inflamed group. Asterisks represent significantly different values from the one obtained without naloxone.*
A dashed line indicates the control level.
PNS: peripheral nerve stimulation
Each data point is the mean ± S.E.
( ) represents the number of recorded units

nerve conditioning stimulation on the receptive field size, but could not find any appreciable changes of the size.

The influence of naloxone on the effect of peripheral nerve conditioning stimulation in normal and inflamed cats

It is well known that naloxone is a opioid receptor blocker. So, by means of this substance, we explored a possible involvement of endogenous opioid substances in the inhibition produced by the conditioning stimulation in normal and inflamed cats.

In normal cats, we found that the inhibitions of C-responses of the dorsal horn cells by the conditioning stimulation were partially reversed by application of naloxone, whereas those of A-responses were not (Fig. 6). These results suggest that the endogenous opioid system is, in part, involved in the mechanism responsible for analgesia produced by conditioning stimulation.

By contrast, in cats with inflammation, inhibition of C-response of the cells by the conditioning stimulation was completely reversed and even exceeded the control level by naloxone (Fig. 6), indicating that the analgesic mechanism in inflamed cats have greater dependency upon the endogenous opioid system compared to that in normal cats.

DISCUSSION

Carrageenan, a polysaccharide, has commonly been used to induce inflammation and hyperalgesia in pharmacologic tests of antiinflammatory and analgesic drugs (Winter *et al.* 1962; Vinegar *et al.* 1969; Di Rosa *et al.* 1971; Ferreira *et al.* 1978).

Meanwhile, it has been reported that the inflammation causes a sensitization of Aδ mechanoreceptor or C polymodal nociceptor, which may enhance the background activity of afferent fibers (Anton *et al.* 1985; Russell *et al.* 1987), and these alterations were known to be mediated by chemical substances i.e. histamine, serotonin, kinin, and prostaglandin (Nakano and Taira 1976; Kumazawa and Mizumura 1980; Guilbaud *et al.* 1985; Besson and Chaouch 1987; Mense and Meyer 1988). On the other hand, Woolf (1983) reported that post-injury hypersensitivity is mediated in part by a central mechanism. In the present study, although we did not confirm the activities of the afferent fibers, it is assumed that a sensitization of nociceptors should contribute, at least in part, to the enhanced activities of the dorsal horn cells, and the fact that the electrically evoked response of the dorsal horn cell was increased by the inflammation also suggests a possible involvement of the central nervous system in sensitization of the dorsal horn cells.

It is well known that receptive fields of the dorsal horn cells were dynamic in nature, not dependent only on anatomical connections, but also on various conditions i.e. inflammation, tissue injury, and activation of C-primary afferents (Cook *et al.* 1987). Possible mechanisms of expansion of the receptive field may be either a sensitization of the peripheral receptor or an enhanced excitability of the dorsal horn cell. However, Hylden *et al.* (1989) executed experiments to rule out possible peripheral factors contributing to expansion of the receptive field, and concluded that a role of dorsal horn mechanisms was of importance. They proposed a long-term depolarizations in the dorsal horn neurons produced by neuropeptides such as substance P and calcitonin gene-related peptide (Ryu *et al.* 1988) as a reasonable mechanism for enhanced excitability during inflammation since these neuropeptides are found in nociceptive afferents and are released during inflammation (Oku *et al.* 1987).

Recently, neuroscientists involved in pain research are becoming increasingly interested in the possible molecular and chemical changes that follow a prolonged painful stimuli. In particular, the role of proto-oncogenes such as c-*fos*, has been a popular topic in chronic pain research. Interest in c-*fos* related to pain was first provoked by the important findings that in the rat spinal cord, the proto-oncogene c-*fos* is rapidly expressed in the post-synaptic dorsal horn neurones following noxious heating or chemical stimulation of the periphery (Hunt *et al.* 1987). Similar results have since been found in response to heating, injection of carrageenan into skin, joint and viscera and electrical stimulation of peripheral C-fibers (Bullitt 1989; Menetrey *et al.* 1989; Presley *et al.* 1990). A recent important development has been the identification of the proenkephalin gene as a possible target gene for c-*fos*, suggesting the possibility that c-*fos* might participate in the regulation of opioid gene expression at the spinal level (Sonnenberg *et al.* 1989). This suggestion is supported by the results of Draisci and Iadarola (1989) that after peripheral inflammation, there is an immediate large rise in c-*fos* mRNA coinciding with a modest increase in enkephalin precursor mRNA. But the vast majority of neurons expressing c-*fos* did not contain opioid peptides suggesting that the increase in c-*fos*

activity following peripheral inflammation may also have effects other than the regulation of opioid peptide levels. In the present experiment, after peripheral conditioning stimulation, C-response in cats with inflammation was reversed completely by naloxone, whereas in normal cats, partially reversed, indicating the analgesic effect by peripheral conditioning stimulation in cats with inflammation was more dependent upon the endogenous opioid system than in normal cats. Having considered the cited investigations, it seems to be possible that these differences may be resulted, at least in part, from the increased synthesis of opioid peptides in cats with inflammation.

In both normal and inflamed cats, C-responses showed greater inhibition than A-responses by the peripheral conditoning stimulation, suggesting a differential inhibition on innocuous and noxious response. These results were comparable with previous investigations (Paik *et al.* 1988). And concerning the response associated with pain, it was found that a degree of inhibition of C-response by peripheral conditioning stimulation was not statistically different between the two groups. These results suggest that long-enduring pain in these experimental conditions has no influences on the analgesic effects by peripheral conditioning stimulation although there are some reports that chronic pain or stressful conditions such as long-term labor may finally deplete endorphin levels, so transcutaneous electrical nerve stimulation may in fact lose its effectiveness (Gintazler 1980; Houck *et al.* 1980).

In this study, we found greater inhibition of response elicited by brushing, immediately after the conditioning stimulation, in the cats with inflammation than in the normal cats. These results may be possible if we assume that receptors activated by brushing in cats with inflammation contain a portion of the sensitized nociceptors. This assumption may be reasonable because there are a number of reports supporting a sensitization of cutaneous nociceptor by inflammation (Anton *et al.* 1985, Russell *et al.* 1987), and Coggeshall *et al.* (1983) also reported that joint inflammation sensitizes articular nociceptors to be active not only at rest, but also during innocuous normal joint movements.

In the present experiment, it was found that a degree of inhibition of response by squeezing was greater than that of C-response following peripheral conditioning stimulation. This discrepancy might be explained by considering the previous reports that some low threshold mechanoreceptors with unmyelinated afferent fibers are present, particularly in the cat (Iggo 1960; Bessou *et al.* 1971).

In conclusion, we confirmed the sensitization of the dorsal horn cells by inflammation, but we could not find any influence of long-enduring pain, in these experimental conditions, on the degree of analgesic effects by the conditioning stimulation. We found that the analgesic mechanism in cats with inflammation showed greater dependency upon the endogenous opioid system than in normal cats. However, further study may be required to clarify what neuronal mechanisms are responsible for greater dependency upon the endogenous opioid system in cats with inflammation.

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