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Cortical Nociceptive Systems

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Cortical nociceptive systems

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There is evidence that the cerebral cortex is involved in the perception of pain but no specific area appears to be the 'pain centre'. Limited knowledge exists on the cortical processing of the noxious input. The nociceptors are most likely to activate at least two different systems with different characteristics. One has a bilateral cortical projection, no apparent topographical pattern, low synaptic security and excites cells in large areas. This system may give rise to the widespread increase in blood flow and the widely distributed surface potentials recorded in man following a painful stimulus. Noxious stimuli also excite a system with contralateral topographical projection, high synaptic security and termination in lamina IV. This system produces EPSP–IPSP sequences in cells in a restricted cortical area. Pronounced inhibition of cells in lamina IV and more superficial layers is induced by activity in low threshold afferents. Thus, similarly as at the segmental spinal level, the nociceptive input to cortical cells is processed and integrated with the activity in other afferent systems.

1. Introduction

The cerebral cortex is considered to be of major importance in perception of sensory stimuli. Detailed analyses have been made of the connectivity and physiological properties of cells involved in the cortical mechanisms of for example visual, auditory or tactile functions. As a result the pathways and the neuronal properties in these sensory systems have been described in some detail at both thalamic and cortical levels. This knowledge contrasts with the relatively few studies made on the cortical mechanisms that are related to nociception. In comparison with the extensive studies of the functional properties of the peripheral nerve and the spinal cord the nociceptive input at higher levels of the neuraxis have been rather neglected. This is clearly shown in recent reviews of the nociceptive system, e.g. in the review of Yaksh & Hammond (1982) one out of 59 pages deals with the cortical mechanisms in nociception.

It is established that neuronal systems underlying the tactile sensibility are topographically arranged at all levels, including the somatosensory cortex. In contrast, a similar topographical pattern has not been found in the projection to cortex from the nociceptors. Electrical stimulation of the somatosensory cortex in awake man produces sensations of tingling or numbness but not pain (Penfield & Jasper 1954). These findings suggest that the neuronal systems in nociception are differently organized compared to those mediating low threshold sensations. Clinically it is known that even extensive lesions in the cerebral cortex do not eliminate the pain sensation. Following experimental studies of the pain sensitivity in monkeys Minkowski (1917) concluded that the pain sense has an extensive cortical representation. Peele (1944) reached a similar conclusion after large parietal lesions in macaques. After large lesions he found delayed responses to and deficits in localization of painful stimuli. In cats bilateral lesions of area SII increase the behavioural threshold to noxious stimuli, particularly

if also the sulci surrounding SII are damaged (Berkley & Parmer 1974). On the other hand, ablation of SI did not change the threshold of the response although the latency increased. These observations in man and behaving animals suggest that there is no specific, localized pain area in the cortex.

A detailed knowledge of the cortical mechanisms requires recordings of the surface potentials and the activity of individual neuronal elements. Relatively few such studies have been performed. Serious problems are associated with studies of nociceptive activity throughout the neuraxis and these problems are particularly pronounced in studies at the cortical level. Analgetics and anaesthetics decrease or eliminate pain by definition and the cortical mechanisms underlying the perception of pain may be severely affected. At lower levels of the neuraxis, e.g. in thalamus and in the spinal cord, lesions such as decortication or spinalization can be used to prevent sensation due to noxious stimuli. Such lesions cannot be used in the studies of nociceptive reactions in cortex. As a consequence, most studies of the nociceptive influence on cortical activity have been made in anaesthetized preparations and the interpretation of the results should be cautious.

Another problem in the studies of cortical mechanisms of nociception is related to the specificity of the nociceptive stimulation. Intense stimuli eliciting nociceptive activity may induce discharges also in low threshold afferent fibres, which can interfere with the central responses. Consequently, the induced neuronal discharge may differ if the noxious stimulus activates nociceptors only and if low threshold afferents are co-activated, for example at pinching or squeezing soft tissue. It should be noted that most natural stimuli exciting nociceptors also activate other receptors and in the central processing of pain an interaction between the induced activities is an inherent part. One exception may be activity in tooth-pulp afferents. Stimulation of these afferents is considered to be relatively nociceptive specific. The tooth-pulp is innervated mainly by Aδ and C-fibres and the main sensation to any stimulation of these afferents is pain (Sessle 1979). This technique should, however, be used with selection. In some species, e.g. rat, electrical stimulation with intrapulpal electrodes in the mandibular incisors activates periodontal nerve fibres. Several studies have been made of cortical neuronal activity following such stimulation, which unavoidably activates low threshold afferents in the mandibular nerve and thus gives erroneous results (Engstrand *et al.* 1983).

2. Cortical surface responses

Field potentials have been recorded following tooth-pulp stimulation in cats, monkeys and man. In early studies the potentials appeared as negativities in the somatosensory area where initially positive potentials could be elicited by activation of low threshold afferents in similar receptive fields (Van Hassel 1969; Vyklický *et al.* 1972; Andersson *et al.* 1973). These observations were at variance with the findings made in experiments with cortical lesions and it could be suspected that the restricted response area after noxious stimulation was a result of the general anaesthesia. Such a suspicion was strengthened by the wide distribution of cortical potentials observed after tooth-pulp stimulation in awake human subjects (Chatrian *et al.* 1975). An involvement of extensive cerebral cortical areas in the perception of pain was also suggested by the findings of large zones of increased blood flow following a painful

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stimulus to the skin as compared to a localized increase of blood flow in the post-central gyrus after a tactile stimulus (Lassen *et al.* 1978).

The appearance and distribution of cortical field potentials following tooth-pulp stimulation was recently reinvestigated in our laboratory (Andersson *et al.* 1977; Roos *et al.* 1982). Cats were kept under chloralose anaesthesia and the upper and lower canine teeth were stimulated electrically via implanted electrodes. From behavioural experiments in the cat it is known that nocifensive responses can be elicited by such stimulation at an intensity close to that giving the sensation of pain when applied to human teeth. The electrical responses were recorded from the coronal and adjacent gyri. In contrast to previous experiments not only an initially negative but also a positive–negative response could be recorded following electrical stimulation of contralateral tooth pulps (figure 1*a*). The amplitude of the response was only about 10% of that following cutaneous stimulation and the latency longer: 10 ms compared to 4 ms at cutaneous stimulation: but the appearance of the potentials was similar.

The initially positive surface responses evoked by tooth pulp stimulation were confined to the contralateral cytoarchitectonic area 3b of the coronal gyrus acccording to the atlas of Hassler & Muhs-Clement (1964), thus in a region where low threshold cutaneous afferents from the perioral region and whiskers project. The distribution of the initially positive evoked potentials can be correlated to potentials evoked from contralateral low threshold afferents (Landgren & Olsson 1980). There appeared to be an overlap between the projection from the whiskers and the canine teeth suggesting convergence to this zone from tooth-pulp and cutaneous afferents (figure 1*a*). Both the upper and lower contralateral canine teeth evoked initially positive surface responses in this region. The projection areas showed some overlap, but the mandibular tooth evoked maximum response more laterally (figure 1*b*). This finding suggests that the tooth-pulp afferents have a topographical projection overlapping that from the skin and in agreement with the finding that low threshold cutaneous afferents in the inferior alveolar and the mental nerves evoke maximum response more laterally than the maxillary nerve (Landgren & Olsson 1980).

In cortical areas surrounding the initially positive response, tooth-pulp stimulation evoked initially negative potentials (figure 1*a*). The distribution of this response was wide and extended apparently outside the area of investigation. Stimulation of ipsilateral tooth-pulp afferents elicited an initially negative response in a similar large area but the latency was slightly longer. Ipsilateral stimulation elicited positive–negative responses only exceptionally.

The study of the surface potentials evoked by tooth-pulp stimulation suggests that a noxious stimulus activates at least two projection systems. One system is topographically organized and overlaps that from low threshold afferents, another system has a bilateral extensive cortical projection without an apparent topographical pattern.

The possibility exists that the surface negative potentials could be mediated via the same system as that giving the initially positive response. This is unlikely, however, since it had a bilateral distribution and there was no systematic increase in the latency of the negativity with increasing distance from the area with initial positivity. Furthermore, the initially positive response could be significantly increased in amplitude by local application of a strychnine solution or depressed by cooling the cortical surface. These manipulations did not change the amplitude of negativities recorded at some distance from the manipulated initially positive response (Roos *et al.* 1982).

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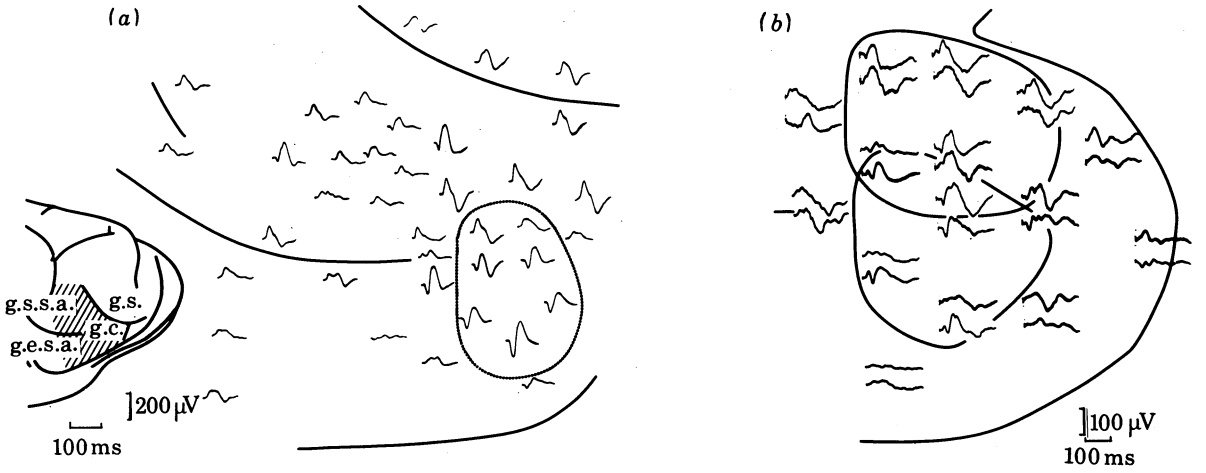

FIGURE 1. Cortical surface potentials elicited by electrical stimulation of contralateral canine teeth in cat. (*a*) Distribution of initially positive and initially negative potentials to stimulation of the contralateral maxillar canine tooth. Encircled area represents the zone of projection from contralateral whiskers (Landgren & Olsson 1980). (*b*) Distribution of responses to stimulation of contralateral (upper encircled area) and mandibular (lower encircled area) canine teeth. Abbreviations: g.s. =gyrus sigmoideus; g.s.s.a. =gyrus suprasylvius anterior; g.e.s.a. =gyrus ectosylvius anterior; g.c. =gyrus coronalis.

3. SINGLE UNIT ACTIVITY

In electrophysiological studies single cortical neurons have been reported to respond to noxious stimuli. Mountcastle & Powell (1959) found some units in S1 'driven by stimuli which are clearly injurious to the skin'. These cells had large receptive fields and could be inhibited by light mechanical stimuli. Andersson *et al.* (1973) found neurons in S1 of monkeys, excited by squeezing and pinching. Similar observations were made by Kenshalo & Isensee (1980). The neurons responding to noxious stimuli had large, often bilateral receptive fields. After transection of the dorsal half of the spinal cord at a low thoracic level in cats many cells in S1, which were rapidly adapting to tactile stimuli in restricted contralateral receptive fields of the forelimb gave a response with a sustained, long-lasting discharge during noxious mechanical stimulation of the hind limbs (Andersson 1962).

Some neurons in area SII of the cat, particularly in its caudal region responded exclusively or primarily to noxious stimuli (Carreras & Andersson 1963; Whitsel *et al.* 1969). Many of these neurons had large bilateral receptive fields, sometimes including the entire body. Other neurons in SII could be excited by both noxious and tactile stimuli.

The first attempt to make a systematic study of the activity in cortical neurons following noxious stimulation was made by Biedenbach *et al.* (1979). In baboons they recorded tooth-pulp-evoked cellular activity in the depth of the posterior bank of the central sulcus. Two classes of neurons were influenced by tooth-pulp stimulation. Type A neurons responded with constant, short latency (mean 13.6 ms) at single electrical stimuli, whereas type B neurons were discharged only by a series of stimuli. Type B neurons showed longer latency (mean 24.9 ms) and the probability of discharge was low. One third of the neurons were excited only from a single pulp, 40% from multiple pulps and the remaining from both tooth-pulp and soft tissue. The same cell could show both type A and type B characteristics depending on the tooth-pulp that was stimulated, suggesting that the synaptic connections were different.

The cortical activity induced by tooth-pulp stimulation has been further studied in cat by

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Roos *et al.* (1983*a*, *b*). Under chloralose anaesthesia extra- and intracellular recordings were made from neurons in the coronal and adjacent gyri. Relatively few cells (7%) received input exclusively from tooth-pulp afferents. A large majority (70%) of cells with input from tooth-pulps were excitated from large, often bilateral cutaneous fields. The extensive convergence in many cells would be revealed only in intracellular recordings. A comparison between the intracellularly recorded synaptic input and the extracellularly recorded discharge pattern showed that the latter only reveals a fraction of the synaptic input to the cell (table 1).

TABLE 1. NUMBERS AND PERCENTAGES OF CELLS GIVING ACTION POTENTIALS RECORDED EXTRACELLULARLY COMPARED WITH THE INTRACELLULARLY RECORDED SYNAPTIC INPUT IN THE SAME CELLS AT STIMULATION OF TOOTH-PULP AND CUTANEOUS AFFERENTS

(Abbreviations as in figure 2.)

	extracellular response	EPSP	EPSP+IPSP
co. max. can.	27 (22%)	74 (61%)	8 (7%)
ip. max. can.	20 (16%)	57 (47%)	5 (4%)
co. max. lip	91 (75%)	93 (76%)	47 (38%)
ip. max. lip	47 (38%)	83 (68%)	29 (24%)
			total $n=122$

The analysis of the cellular activity revealed regional and laminar differences with regard to the input from the tooth-pulp. In superficial cells (laminae I and II) extensive convergence was commonly observed. In many cells EPSPs were obtained from all tested tooth-pulps and also from large cutaneous fields. The EPSPs from the tooth-pulp had varying latencies and amplitudes at successive stimuli (figure 2). The excitatory input from the tooth-pulps was found in cells in a large cortical area extending outside the zone with initially positive surface response to stimulation of contralateral tooth-pulps. IPSPs were not observed in superficial cells

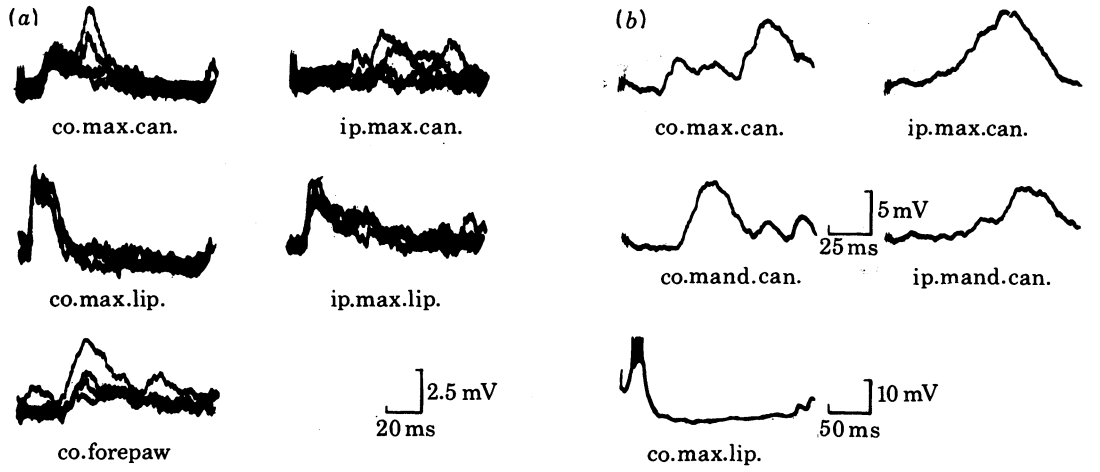

FIGURE 2. Synaptic potentials in cells in lamina II evoked by electrical stimulation of tooth-pulp and cutaneous afferents. (*a*) Cell with EPSPs of variable latency and amplitude from all tested inputs. (*b*) EPSPs of long latency from tooth-pulp afferents and EPSP–IPSP from cutaneous afferents. Abbreviations: co. = contralateral; ip. = ipsilateral; max. = maxillar; mand. = mandibular; can. = canine tooth.

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following tooth-pulp stimulation. In many of these cells stimulation of low threshold cutaneous afferents elicited an EPSP, often with superimposed spikes, followed by a long-lasting IPSP (figure 2*b*).

Cells in laminae III and IV showed commonly a different input pattern. Many of the cells received an EPSP from tooth-pulp and discharged action potentials followed by an IPSP or a period of decreased excitability. Stimulation of contralateral tooth-pulp afferents induced short latency steeply rising EPSPs succeeded by a hyperpolarization (figure 3*a*). Synaptic input from cutaneous afferents in large bilateral fields was common. Stimulation of contralateral low threshold afferents elicited frequently large IPSPs. Ipsilateral stimulation elicited responses with more long-lasting EPSPs and smaller or no IPSPs. The excitatory pattern was often complex. Figure 3*b* illustrates a cell in lamina IV excited from ipsilateral and contralateral teeth. It received a prolonged excitation and the later EPSP appears to be superimposed upon an IPSP elicited mainly from contralateral afferents. Rapidly rising EPSPs with cell discharge and IPSP were found mainly in lamina IV cells in the projection area of the contralateral tooth-pulp characterized in surface recordings by an initial positivity. In cells outside this area, tooth-pulp stimulation elicited EPSPs without a succeeding IPSP.

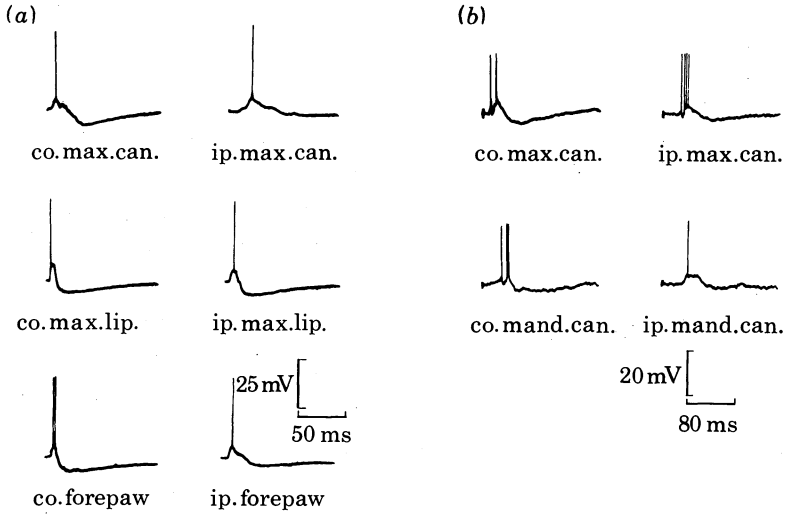

FIGURE 3. Intracellular potentials in cells in cortical lamina IV. (*a*) Cell with EPSP–IPSP sequences (except Ip. max. can.) following stimulation of tooth-pulp and cutaneous afferents. (*b*) Cell with complex EPSP–IPSP sequences evoked by electrical stimulation of tooth-pulp afferents. Abbreviations as in figure 2.

Cells excited by tooth-pulp stimulation were also found in deep cortical layers (laminae V and VI). These cells received convergent input including low threshold afferents. In intracellular recordings long-lasting EPSPs from large, often bilateral receptive fields, were common. IPSPs were not usually found but stimulation of contralateral afferents often gave a short excitation suggesting an inhibitory process in the pathway to these cells.

The latency distribution of intracellularly and extracellularly recorded action potentials showed marked laminar differences. The average latency in lamina IV was significantly shorter (18.9 ms) than in laminae I and II (35.3 ms). The latencies of cells in laminae V and VI were also significantly longer (28.7 ms) than that in lamina IV.

Lamour *et al.* (1983*b*) recently reported studies of the nociceptive input from the skin and deep tissue to the cortex of rats under Halothane–nitrous oxide anaesthesia. The nociceptive

neurons were either specific and activated only by noxious stimuli or convergent with input also from low intensity stimuli. On average, the receptive fields of the cells with noxious input were larger than those activated only by low threshold afferents. The nociceptive neurons responded with sustained or phasic discharges in a way suggesting that they could encode stimulus parameters such as the intensity of a noxious temperature and the size of a cutaneous area receiving noxious stimulation. A laminar organization of cells influenced by noxious stimuli was observed by Lamour *et al.* (1983*a*). Neurons driven by noxious stimuli to the skin or deep tissue were found almost exclusively in deep layers and in particular in lamina VI. In contrast, neurons driven by tactile stimuli were located mainly in lamina IV.

4. Conclusions

Available data suggest that the cerebral cortex receives input from noxious stimuli and most likely it is important in the perception of a painful stimulus. Our present knowledge allows only speculations about the processing of the noxious information. There is no evidence suggesting that any particular cortical area or region is specific in this respect. Rather, the input from the nociceptors seems to be superimposed upon a topographical projection from low threshold receptors. Intracellular recordings from the area of topographical projection from tooth-pulp afferents showed EPSP–IPSP sequences similar to those elicited in this region from the appropriate low threshold trigeminal afferents. Both inputs appear to be mediated via thalamocortical systems from cells in the ventrobasal complex and with termination in the cortical lamina IV. Hypothetically such a projection system should be appropriate to signal certain stimulation parameters such as localization of a painful stimulus. In addition to this projection, there appears to be another system with widespread and bilateral projection, which elicits exclusively excitation in a large number of cortical cells. The origin of this system is not known but it may arise in the intralaminar thalamic nuclei. Hypothetically this projection system may underlie the adversive effect of noxious stimuli. Commonly, cells excited by nociceptors are inhibited by the input from low threshold cutaneous receptors, particularly in contralateral but also in ipsilateral fields. The long-lasting IPSPs elicited in these cells may effectively counteract the depolarization from nociceptors.

There appear to be laminar differences in the input and in the characteristics of the induced activity. The results from cat and rat are different with regard to the localization of cells driven by noxious stimuli, but the experimental situations were quite different with regard to both anaesthesia and the employed noxious stimuli. It is possible that the different results are the expected outcome due to the cortical organization. Electrical stimulation revealed excitation from tooth-pulp afferents but excitation *and* inhibition from low threshold cutaneous afferents as characteristic features in cells in lamina IV and in more superficially situated cells. In laminae V and VI the inhibition from cutaneous afferents was weak. Mechanical noxious stimulation of the skin such as pinching excites both nociceptors and low threshold afferents. The latter may induce a sustained inhibition of many cells receiving input from the nociceptors, thus preventing their discharge. Cells in the deeper layers (laminae V and VI) received long-lasting excitation but less inhibition and may discharge also during the presence of the inhibitory action from low threshold afferents. The differential balance between excitation from nociceptors and inhibition from other afferents may be of major importance in the perceptive mechanism of pain.

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Present evidence suggests that any type of anaesthesia severely depresses neuronal activity in the cortex. In the awake animal neurons in the somatosensory cortex may be activated by different stimulus modalities in large and changing receptive fields. In barbiturate anaesthesia the receptive field of such neurons may be small and modality specific, suggesting that an important part of the input to the cells is eliminated. In the experiments of Lamour *et al.* (1983*a*, *b*) a mixture of Halothane and nitrous oxide was used to maintain a light anaesthesia, which should allow a study of the nociceptive input in a less depressed state. Each of these drugs has, however, a clearly depressive effect on the cortical neuronal activity. Even a moderate level of Halothane (0.75 %) in the breathing air profoundly diminishes long latency excitatory components in the cortical response to peripheral stimuli whereas the short latency 'specific response' is unchanged. Halothane also decreases the size of the receptive fields characteristic of the non-specific components in the sensory response (Chapin *et al.* 1981). Nitrous oxide (67 %) in oxygen administered to an awake animal eliminates within a few minutes the responsivity to tactile stimuli in superficial cortical cells (McKenna *et al.* 1984). An even more pronounced depression may occur of responses elicited by noxious stimuli. In contrast, quite non-specific properties of cortical neurons have been reported under chloralose anaesthesia, i.e. the receptive field of the neurons were large and they responded to several modalities of sensory stimulation (Harding *et al.* 1979).

In the experiments of Lamour *et al.* (1983*a*,*b*) the Halothane–nitrous oxide anaesthesia may have decreased the excitatory action of the unspecific system in the superficial cells, giving a tendency to decreased discharge to noxious stimuli. In addition, these cells will be inhibited by the co-activation of low threshold receptors during mechanical noxious stimulation. The dual effect of anaesthesia and inhibition should be most pronounced in the superficial laminae, thus giving a bias to activation of cells in deeper layers where the inhibition is weak.

The interaction between the different ascending projection systems has similarities with the gate control system in the spinal cord (Melzack & Wall 1965). Modulation of the nociceptive system may occur via control systems also at the cortical level. In particular it should be expected that the excitability of cortical cells is influenced by hitherto undefined systems related to higher mental functions such as emotions. Already the available data on cortical function in nociception suggest that the pain sensation to a noxious stimulus is not directly related to the activity in nociceptors, but is a complex phenomenon due to multiple factors.

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