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Thalamic Nociceptive Systems

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Thalamic nociceptive systems

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A role for thalamic structures in the processing of signals of nociception and pain has been suggested on the basis of clinical data since the turn of the century. Searches for a 'pain centre' by lesion or stimulation were often disappointing and the electrophysiological data were rare and usually contradictory. However, recent electrophysiological anatomical and neuropharmacological studies, made in various species (mainly rat and monkey) appear now progressively to give some clues in the understanding of pain process at the thalamic level. These studies have been mainly concerned with the areas receiving projections from ascending spinal pathways conveying noxious inputs, either directly by the spinothalamic tract or indirectly by the spinoreticulothalamic pathway. The eventual respective roles of these thalamic structures are considered. Electrophysiological recordings from thalamic structures in a model of experimental pain, arthritic rats, are also presented.

A role for thalamic structures in the processing of nociception and pain has long been suggested from clinical studies; however, numerous difficulties (see Guilbaud *et al.* 1984) have hampered the experimental investigations concerning this problem and data is still rather scanty. In particular, it may be noted that in this type of study the experimenter is obliged to consider the ethical implications related to the fact that experiments have to be performed in 'intact' animals, and therefore with anaesthetized preparations. Since the various anaesthetic agents modify neuronal responses elicited by noxious stimuli at various levels of the central nervous system and since the types of anaesthesia differs greatly from one study to another, discrepancies between the studies on the thalamus and nociception may be related to this problem.

There has also been a marked confusion as regards the delineation and naming of several supraspinal areas (ref. in Guilbaud *et al.* 1984). However, the recent major advances in neuroanatomical studies have added a precision to the terminations of afferent pathways to, and delineation of thalamic areas in various species (Boivie 1971, 1980; Berkley 1980; Peschanski & Besson 1984).

Therefore, electrophysiological data obtained in these species (rat, cat, monkey), taking into account the problem of anaesthesia and anatomical bases, are now providing more consistent clues to the understanding of the integration of nociceptive messages at the thalamic level. Studies have mainly dealt with the structures, which receive projections from spinal neurons through pathways which have been shown to convey noxious inputs, in particular the spinothalamic (s.t.t.) and spinoreticulothalamic (s.r.t.t.) tracts (see Willis, this symposium).

The majority of these studies (reported in the first part of this paper) have been performed in normal animals; however, in an attempt to provide a model for clinical pain, rats rendered arthritic by Freund's adjuvant injection can now be used (Gouret *et al.* 1976; De Castro *et al.* 1981); electrophysiological recordings from thalamic structures in this model of experimental pain will be presented in the second part of this report.

1. Data obtained in normal animals

(a) *Thalamic areas receiving afferents from the reticulothalamic tract*

Postero medial thalamic structures, namely CMPf, receive ascending projections from the gigantocellularis nucleus of the bulbar reticular formation (Bowsher *et al.* 1966; Peschanski & Besson 1984) an area which receives massive projections from the spinoreticular tract (Mehler 1969; Chaouch *et al.* 1983).

As initially described by Casey *et al.* (1966) responses to noxious stimuli obtained for a few medial thalamic neurons in the awake squirrel monkey are greatly depressed by small doses of pentobarbital. In the cat, and the rat, moderately anaesthetized, neuronal responses, although relatively phasic, were repeatedly obtained in the CMPf by applying noxious somatic stimuli (Dong *et al.* 1978; Peschanski *et al.* 1981; references in Guilbaud *et al.* (1984)). Generally the receptive fields of these neurons are diffuse, often involving the whole body. These neurons can also respond to 'tapping' and are intermingled with neurons inhibited by noxious stimuli or uniquely excited by 'tapping'. Neuronal responses to graded noxious heat have been tested in the intralaminar region of the rat (Peschanski *et al.* 1981). The mean threshold for the responses was relatively high, between 48° and 50 °C, and there was no consistent relationship between the temperature of the stimulus and the number of spikes in the discharge (figure 1*a*).

Due to these functional characteristics, it is difficult to conceive that these medial thalamic structures could participate in sensory discriminative aspects of nociception. By contrast, on the basis of their main projections areas (striatum, pre-motor cortex) (Jones & Leavitt 1974; Bentivoglio & Molinari 1984; references in Guilbaud *et al.* 1984) they could be involved in motor and arousal defensive reactions in response to noxious stimuli (Albe-Fessard & Besson 1973; Casey & Jones 1978).

(b) *Thalamic areas receiving direct spinothalamic projections*

Studies have concentrated on the lateral thalamus (ventrobasal complex, v.b., and posterior nuclear group, po.), although some have considered the nucleus centralis lateralis (c.l.) of the intralaminar nuclei.

Although it is now well established that c.l. is a major site of projection of the spinothalamic tract (see Willis, this volume) electrophysiological data, concerning this nucleus *per se* are much more scarce, due to the confusion in the delineation of the various intralaminar nuclei. In fact, Peschanski *et al.* (1981) in the rat have drawn attention to the small number of noxious responsive neurons in the ascending branch of the c.l. where the s.t.t. terminates; when present, the characteristics of neuronal responses to somatic stimuli are usually similar in c.l. and CMPf (Dong *et al.* 1978; Peschanski *et al.* 1981). However, Woda *et al.* (1975) have noted that in the cat, thresholds and latencies of the responses elicited by tooth pulp stimulation are lower and shorter in c.l. than in c.m.

After the first systematic study of the po. group of the cat by Poggio & Mountcastle (1960) showing that numerous neurons in these structures are responsive to noxious stimuli, there were several negative studies, this discrepancy being likely to be due to the use of deeply anaesthetized animals (references in Guilbaud *et al.* (1984)). Indeed using cats with moderate anaesthesia, two groups confirmed the results of Poggio & Mountcastle (Dong & Wagman 1976; Guilbaud *et al.* 1977), showing that a great proportion of the neurons recorded in the po. of the cat presented sustained responses to various noxious stimuli (pinches, intra-arterial

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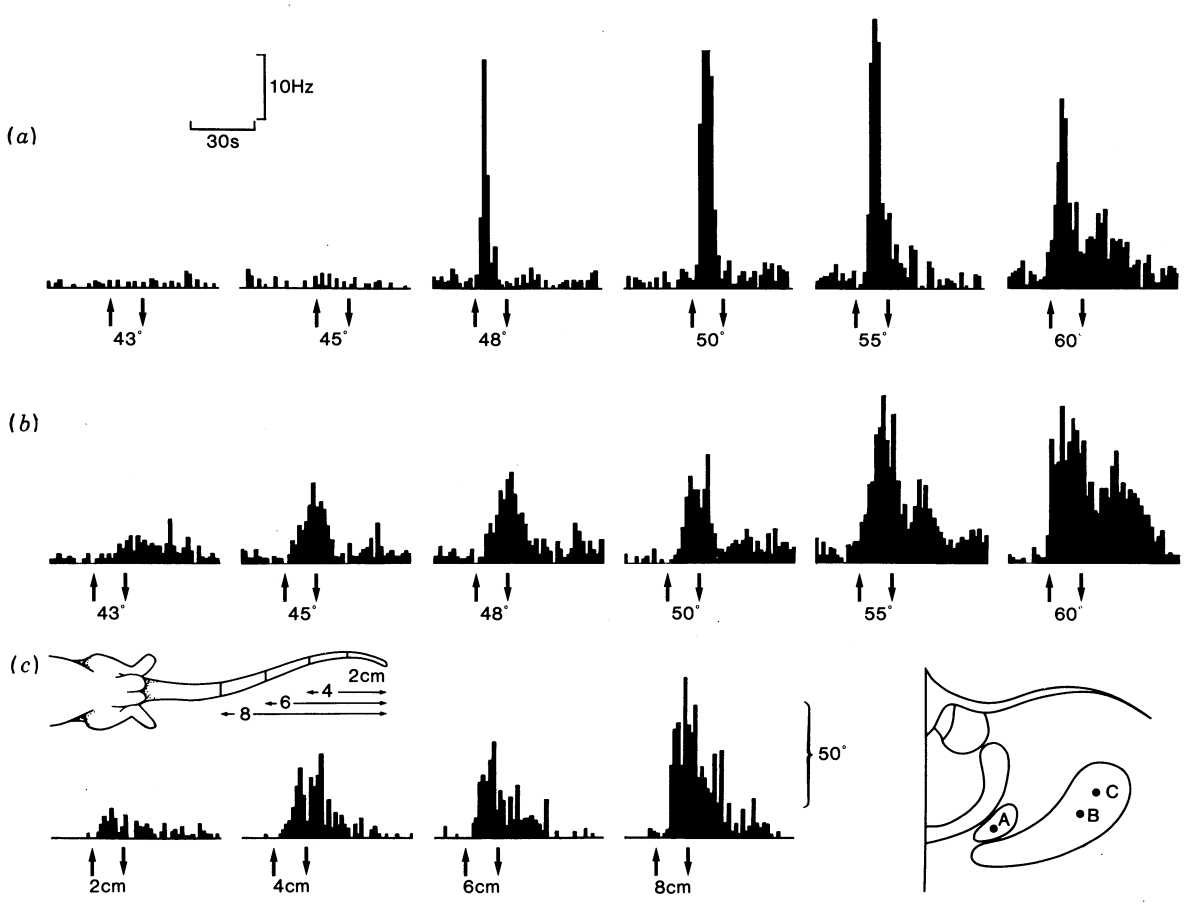

Figure 1. Responses of thalamic neurons to noxious heat. In (*a*) Responses of neuron A located in the CMPf to graded noxious heat stimuli of the tail (15 s duration every 3 min in a hot water bath of 8 cm). Note the high threshold of the response and its non-systematic increase with the intensity of the stimulus. (*b*, *c*) Responses of neurons B and C located in the v.b. to noxious heat stimuli of the tail. In (*a*) and (*b*) temperatures from 43 to 60 °C were used. Note the threshold at 43 °C, and the linear relation between the number of spikes in the response and the intensity of the stimulus. In (*c*) a temperature of 50 °C (15 s every 3 min) was applied in a hot water bath from 2 to 8 cm. Note the clear relation between the response and the stimulated area.

injection of algogenic substances in the limbs, intense electrical stimulations of cutaneous nerves); a proportion of these cells were also activated by light tactile stimuli. Although usually large, the receptive field of these neurons were definable. When the fields were bilateral they were curiously strictly symmetrical; moreover, for 40% of the neurons the receptive fields were contralateral. Therefore in the cat, po. neurons can play a role in the processing of noxious inputs providing some information as to the location at the body surface.

By contrast, in this species, it seems clear that neurons of the v.b. complex (especially by Rinvick's criteria (1968)) are unresponsive to cutaneous noxious stimuli (Guilbaud *et al.* 1977; see reference in Guilbaud *et al.* 1984). This negative result corresponds well with the anatomical data, which emphasize the fact that the spinothalamic tract does not project to the core of the v.b. complex in the cat (Boivie 1971; Berkley 1980). Some neurons responsive to algesic stimulation of muscle and tendon have been found in the v.b. complex of cat (Kniffki & Mizumura 1983; Honda *et al.* 1983); these cells, however, were interestingly essentially located in the shell receiving spinothalamic and spinocervicothalamic terminals surrounding the central core described as receiving the main tactile projection (Boivie 1971; Berkley 1980).

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On the other hand, in rat and monkey, spinal afferents to the v.b. have been observed, scattered among projections originating in the dorsal column nuclei (Lund & Webster 1967; Mehler 1969; Boivie 1979; Berkley 1980) and in these species there is a significant number of v.b. 'noxious responsive' neurons (Hellon & Mitchell 1975; Guilbaud *et al.* 1980; Kenshalo *et al.* 1980; Casey 1983), which are intermingled with 'non-noxious responsive' units. The majority of these neurons are exclusively activated by noxious stimuli in rat (Guilbaud *et al.* 1980), whereas in monkey (Kenshalo *et al.* 1980; Casey 1983) they are mainly non-specific nociceptive neurons, i.e. activated by both noxious and non-noxious stimuli. This could reflect interspecies differences and/or a variability of responsiveness due to differences in the experimental conditions: animals were anaesthetized with Halothane (Guilbaud *et al.* 1980), or with chloralose and pentobarbital (Kenshalo *et al.* 1980), or were awake (Casey 1983).

The ventrobasal neuronal responses to various noxious stimuli (thermal, mechanical) are sustained and usually an after-discharge outlasting the stimulation duration is present. Their functional role would seem to be supported, in the rat, by the fact that they are strongly depressed by very low doses of morphine (Benoist *et al.* 1983). The receptive fields of the noxious responsive neurons are often large and bilateral (mainly in the rat), and in this species are often symmetrical; they can also be limited or contralateral, but mainly in the monkey. Moreover, although a strict somatotopy similar to that described for the classical 'lemniscal' non-noxious responsive units (reference in Mountcastle 1980) cannot be found for noxious responsive units, they do exhibit a preferential location, rostrocaudal in the rat, latero-medial in the monkey: neurons responding to stimuli applied to the posterior part of the body being located in the rostral (for the rat) or the lateral (for the monkey) region of the v.b. When tested with graded temperatures, response thresholds of these neurons are clearly in the noxious range ($\geqslant 43\ ^{\circ}C$) and their discharge frequency can be related to the intensity of the stimulus, to its duration, and sometimes to the area of application (figure 1*b*).

These various functional characteristics suggest the hypothesis that the v.b., by contrast to the CMPf could participate, to some extent, in sensory discriminative aspect of nociception. This seems to be also supported by the fact that neurons presenting comparable functional properties have been recorded in the somatosensory cortex of rat (Lamour *et al.* 1982, 1983) and monkey (Kenshalo & Insensee 1983) where it is well known that v.b. neurons massively project to.

It therefore appears that thalamic structures receiving noxious messages, either directly by the s.t.t. or indirectly by the s.r.t.t., participate in different aspects of nociception.

2. Data obtained in arthritic rats

In rats suffering from arthritis there are profound changes in the responses of thalamic neurons (v.b., CMPf, c.l.) to somatic stimuli as compared with those observed in normal animals (Gautron & Guilbaud 1982; Kayser & Guilbaud 1984). There are few neurons activated by intense mechanical stimulation compared with normal rats, whereas many cells are driven by mild stimulation of the joints or adjacent inflamed areas (light pressure, movement, sometimes brushing) (figure 2).

For instance in the v.b. of arthritic rats more than 50% of the somatosensory neurons are driven by such stimuli. The responses so produced exhibit unusual patterns with after discharge of long duration (figure 2*c*). The threshold of these neurons to heating is paradoxically

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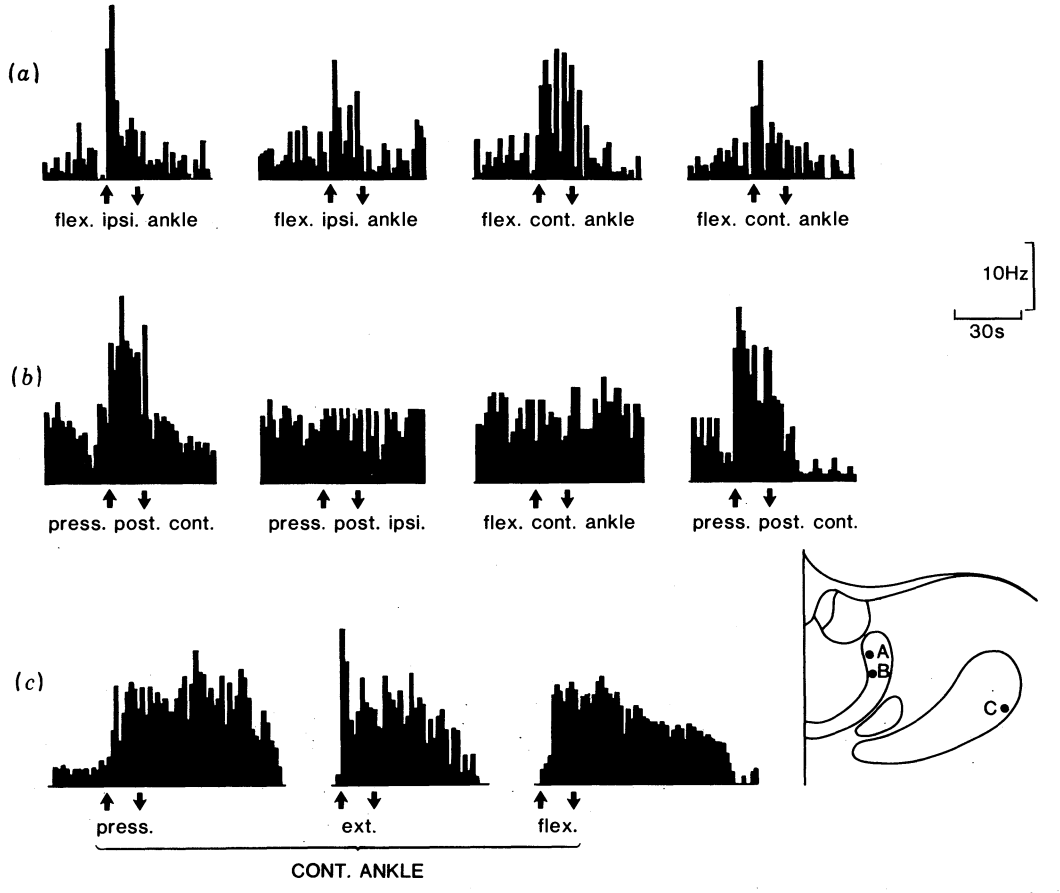

FIGURE 2. Responses of thalamic neurons to joint stimuli in two arthritic rats. (*a*) Responses of a neuron located in the c.l. and presenting the usual characteristics of the intralaminar type. (*b*) Responses of a neuron recorded in the same track as (*a*), exclusively activated by a contralateral receptive field and by only a type of stimulus (i.e. pressure). Note also the good reproducibility of the responses by contrast with responses of (*a*). (*c*) Responses of a neuron located in the v.b. to various mild stimuli of the contralateral ankle (ipsilateral stimuli were inefficient). Note the particularly long after-discharges.

increased (48 °C or more) compared to that of nociceptive neurons in normal animals. By contrast, the phenomena of sensitization following a first series of graded thermal stimuli, are more pronounced and more frequent than in normal rats. These v.b. neurons responding to joint stimuli are also able to encode the thermal stimulus intensity. Finally, the functional indication of these v.b. neuronal responses seems supported by the fact that their responses are strongly depressed by aspirin (Guilbaud *et al.* 1982) which is well known to be particularly efficient against arthritic pain.

As in normal rats the response characteristics of numerous intralaminar neurons, mainly those located in the CMPf, differentiate them from those recorded in the v.b. (figure 2*a–c*): their receptive fields are diffuse, their responses are not so sustained and they rarely present an after-discharge.

Again these data suggest a differential role in pain processes of both these structures according to their afferents being in either the s.t.t. or s.r.t.t. However, the most common and striking observation in these arthritic rats is the great ease of producing neuronal responses in both medial and lateral thalamic areas by mild joint stimulation.

Interestingly in these pathological conditions, by contrast with normal animals, numerous neurons recorded in the ascending branch of the c.l. can be driven by joint stimulation and a great number of them exhibit, as do the v.b. neurons, a contralateral receptive field (figure 2*b*). This electrophysiological observation is in good agreement with anatomical data showing that this thalamic area receives dense s.t.t. projections (see Willis, this volume).

Finally, some differences observed in the responsiveness of thalamic neurons in normal and arthritic animals suggests, as does a study of the Sm1 cortex (Lamour *et al.* 1983), that the mechanical information elicited at the periphery by mild stimulation of the inflamed joints could arrive at neuronal population(s) different, at least in part, from those influenced by noxious cutaneous messages in normal rats. Whether the involvement of new categories of neurons in pathological conditions is determined by a peripheral process only (Guilbaud *et al.* 1984), or also by the occurrence of additional central mechanism(s), is still a complex issue. Whatever these various mechanisms, the occurrence of reproducible neuronal responses by stimulation, which induce nociceptive reactions when they are applied to the inflamed joints of freely moving animals, underlines the particular interest of this model.

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