Physiol. Res. 46: 475–485, 1997

Abnormal Neuroneal Activities in Intralaminar Thalamic Nuclei Following Chronic Lesions of Nucleus Reticularis Thalami in Rats

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Received February 2, 1997
Accepted August 13, 1997

Summary

Extracellular single unit activity in the intralaminar thalamic nuclei (ncl. centralis lateralis, CL, n=77 and ncl. parafascicularis, Pf, n=163) and in the pretectal area (Pt, n=75) was examined following chronic electrolytic lesions of the nucleus reticularis thalami (nRT) in ketamine-anaesthetized rats after single electrical stimuli to the ventrobasal complex (VB). Extensive alterations of either the ongoing ("spontaneous") activity or the pattern of VB evoked responses were observed. Four major changes were observed in the activity of these intralaminar or pretectal neurones: 1) many neurones were silent, two times more frequently than in a parallel study with control intact rats; 2) the firing pattern of all the other neurones was in the form of tonic (stationary-like) discharge, without burst discharges as previously described in intact animals. They were ranked into classes according to their spontaneous discharge: class I, silent (no resting discharge) 12 %, class II (1–15 Hz), 54 % and class III (>16 Hz), 34 %. Class III neurones were never found in intact rats; 3) electrical stimulation of the VB evoked a short latency orthodromic excitatory response in these neurones but this response was not followed by any slowing or depression of the spontaneous activity in more than 40 % of recorded cells. When it occurred, this pause was shorter than that always observed in intact rats by more than 35 % and longer in 7 % of the responsive cells. All these changes were correlated with the extent of damage to the ipsilateral nRT; 4) VB stimulation evoked prolonged excitatory responses lasting more than 150 ms in 13 % of the responsive cells, and nRT stimulation led to a short latency response followed by a pause of activity. These findings suggest that the nRT is involved in sensory integration and modulation.

Key words

Thalamus – Nucleus reticularis thalami lesions – Ventrobasal complex – Intralaminar nuclei – Pretectal area – Electrical stimulation – Rat

Introduction

In a parallel study (Pollin *et al.* 1997), we describe reciprocal interactions between the intralaminar thalamic nuclei (Pf and CL), the anterior pretectal nucleus (Pt) and the ventrobasal complex (VB) in ketamine-anaesthetized rats. Electrical stimulation of the VB evokes a complex response in the intralaminar neurones with a short latency response followed by a pause in spontaneous activity. The inhibitory process, shown to be of thalamic origin, could not be explained by direct connections since monosynaptic pathways between intralaminar and lateral thalamic nuclei had never received any strong anatomical support (Jones 1985). Since, in the rat, almost all thalamic GABAergic somata (except in lateral geniculate, GL) lie within the nRT, and thalamic nuclei could be interconnected through the nRT, we suggested that intrathalamic loops involving the nRT could account for the major part of the

inhibitory responses, which was further supported after injections of GABA receptor antagonists (Lee *et al.* 1994a).

Preliminary data indicated that partial coagulation of nRT resulted in chronic alteration of neuroneal activity in intralaminar nuclei. Some neurones could become hyperactive or silent, and the inhibitory effect observed after VB or other central stimulation disappeared (Pollin *et al.* 1991). The present study was thus undertaken in order to describe the chronic alteration of spontaneous and evoked neuroneal activity in the intralaminar nuclei. We performed electrical coagulation of nRT in rats in order to:

- better control the size and extent of the lesion since accurate control cannot be attained after chemical lesion
- to obtain a closer analogy to the thalamic lesions observed in humans following a stroke, which involves neurones as well as passing fibres.

Several results have been reported indicating acute functional thalamic changes after nRT lesions (French *et al.* 1985, Steriade *et al.* 1985, Lee and Ebner 1992, Lee *et al.* 1994b). In the present study, we mainly focused our attention on medial thalamic activity and its chronic alterations.

Methods

Experiments were carried out on 39 male Sprague-Dawley rats under ketamine anaesthesia, 2–6 months after partial coagulation of the nRT. Surgery, stimulation, recording and histology are described in a companion paper (Pollin *et al.* 1997).

In order to partially destroy the nRT, small electrolytic lesions (6 mA intensity, 10 s duration) through monopolar stainless steel electrodes were made at different sites in the nRT. The extent of the histologically verified lesions was either restricted to the rostral pole of the nucleus or was more extensive. The animals were included in our database only if the lesions essentially involved the nRT with minimal damage to surrounding structures. In three animals the lesions were performed in the internal capsule, and did not involve the nRT.

All results were expressed as mean ± standard error of the mean (S.E.M.). The mean values of control and coagulated rats were compared using unpaired
t-test. P values less than 0.05 were considered to be significant.

Table 1. Frequency and location of the different classes of neurones

	CL	Pf	Pt	Total	
Class I	7	20	10	37	12 %
Class II	48	94	28	170	54 %
Class III	22	49	37	108	34 %
Total	77	163	75	215	

Results

Out of the 377 neurones encountered in these nuclei during our experiments, 62 units (16.4 %) died before any record could be obtained. In intact rats the percentage was only 6.2 % . Thus, recordings from 240 neurones were taken within the thalamic intralaminar nuclei (CL and Pf), and from 75 neurones in the anterior pretectal nucleus (Pt).

Spontaneous activity

The recorded neurones were ranked into three different classes according to the frequency of their spontaneous discharge: class I (no resting discharge) 12 %, class II (1–15 Hz) 54 %, and class III (>15 Hz) 34 % (Table 1). The ongoing activity among the spontaneously discharging neurones did not show any bursting activity. In intact rats, class III neurones were never found in these nuclei.

Evoked activity

The 37 cells of class I (no resting discharge) were activated by at least one of the tested stimuli. Twenty-seven presented only a short latency response, four short latency response followed by a long latency burst of firing with the characteristics of a postinhibitory rebound, and six had only a long latency burst of firing.

The 278 cells of class II or III could be described according to their responses to the different peripheral and central stimulations: 1) non-responsive cells (43 cells, 15.5 % vs 11 % in intact rats). These cells seemed to be unaffected by any of the tested stimuli; 2) only silenced cells (15 cells, 5.4 %). The pause in spontaneous activity immediately followed the stimulation without any spikes or practically no spikes after the stimulation. These pauses were most often terminated by a burst of firing with the characteristics

of a postinhibitory rebound; 3) short latency excitatory responsive cells (220 cells, 79.1 %). Time-locked discharges followed the stimulation. These responses showed a similar pattern whatever the stimulus applied (VB, cortex, striatum, face or limb). But, these short latency excitatory responses were not always followed by a depression of spontaneous activity, whereas a long duration pause was always observed in non-lesioned animals. The characteristics of the response remained stable even up to four hours. When a pause followed the excitatory response, most neurones presented, at the end of the silent phase, a long latency burst of discharges which appeared to be a rebound phenomenon.

Stimulation-induced pauses of activity

VB stimulations

The most striking observation in these rats was the large number of units (43 % of the 230 VB responsive cells) which did not demonstrate any slowing or depression of spontaneous activity following VB stimulation (Table 2). Among these 98 neurones, 29 were class II and 69 class III. In intact rats, all the excitatory responses were followed by a silent phase.

Table 2. Summary of response properties of CL, Pf and Pt neurones after VBa and/or VBp stimulations.

	Class I	Class II	Class III	II + III	I + II + III	% of total
Short latency response	30	130	86	216	246	78 %
Only silenced or rebound	3	9	5	14	17	5 %
Response	33	139	91	230	263	83 %
No response	4	31	17	48	52	17 %
Total	37	170	108	278	315	
	Class II	Class III	II + III	% of total II + III responses		
Pause of activity	110	22	132	57 %		
No pause	129	39	98	43 %		

As previously seen in non-lesioned animals, some class I cells presented a long latency rebound (6 of the 33 responsive cells). The 132 spontaneously active neurones (class II and III) were inhibited following VB stimulation. The mean duration of the "silent phase" of all these 138 cells was shorter than in intact rats (183 ± 9.5 ms and 232 ± 4 ms, respectively, $p < 0.0001$). The overall duration ranges were from 30 to 550 ms (Fig. 1). Forty-eight neurones (36 % vs 3 % in intact rats) presented a pause of spontaneous activity (shorter than 150 ms) and nine had a longer pause (more than 400 ms), a duration which was never recorded in intact rats under the same anaesthetic conditions (Fig. 2).

Other stimulations

Striatal stimulation was followed by a pause of activity or a long latency rebound in 38 (26 class II, 7 class III and 5 class I) of the 51 responsive units (217 ± 18 ms vs 240 ± 18.6 ms in intact rats). Among these 38 units, eight did not respond to VB stimulation and three (2 class III and 1 class II) did not present a pause of activity after VB stimulation. Besides, among the 12 spontaneously active neurones (3 class II and 9 class III) which were not inhibited by striatal stimulation, two class II neurones were only silenced and one class III did not respond at all after VB stimulation. The nine remaining neurones were also not inhibited by VB. As after VB stimulation, the duration of the silent period was short (less than 150 ms) in more than 65 % of the responsive cells (vs 20 % in intact rats).

Cortical stimulation was followed by a pause of activity in 13 of the 15 tested neurones (218.9 ± 18.9 ms vs 260 ± 25 ms in control rats); all these class II neurones were also inhibited by VB stimulation.

Electrical stimulation applied to the vibrissal area or the forepaw were tested in five neurones. When it occurred, the response was not always followed by a silent period and the duration of the remaining pauses of spontaneous activity was also shorter than that observed in intact rats.

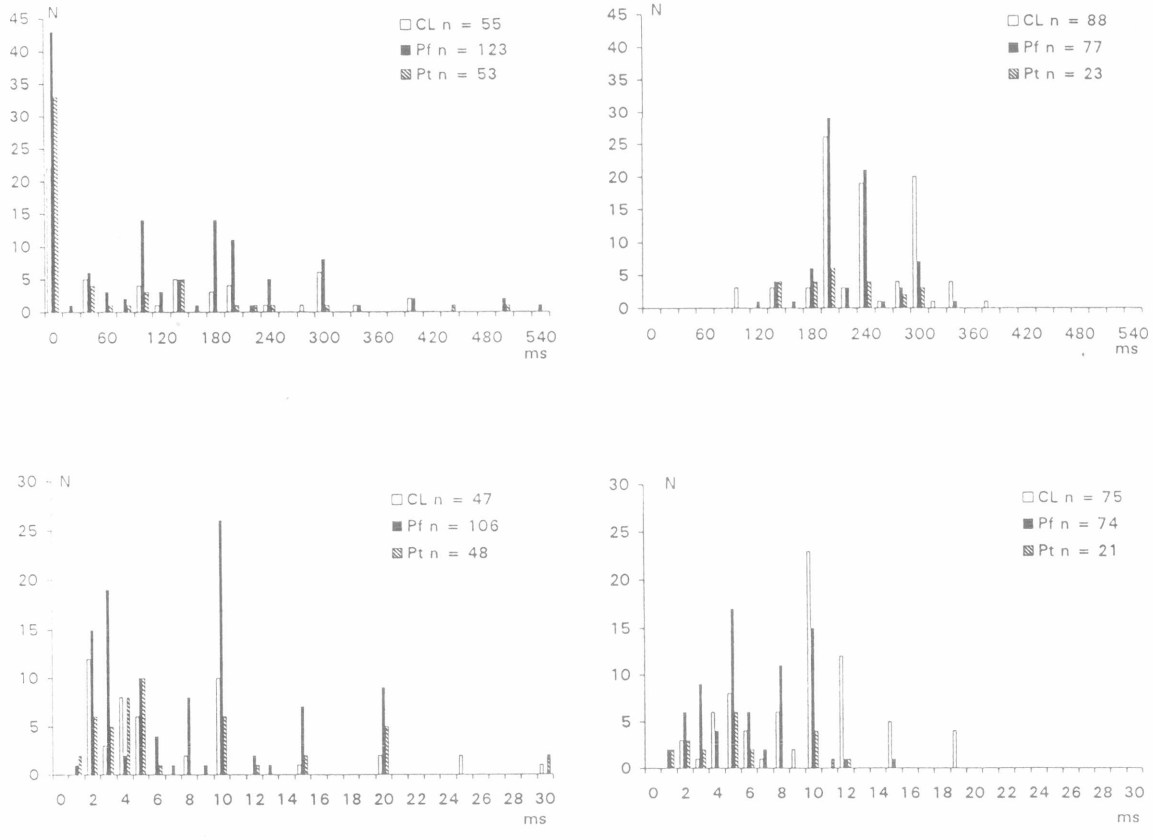

Fig. 1. *Histogram of silent phase duration in intralaminar nuclei (Pf and CL) and anterior pretectal nucleus (Pt) after VBa or VBp stimulation in lesioned animals (upper left) and in intact animals (upper right). Note the large number of units which did not exhibit any depression of spontaneous activity in lesioned animals. In control rats all the responsive neurones presented a silent phase. Lower part: histogram of response latencies in intralaminar nuclei (CL and Pf) and in anterior pretectal nucleus (Pt) after VBa or VBp stimulation in lesioned animals (left) and in intact rats (right).*

Short latency excitatory responses

VB stimulations

Out of the 263 neurones responsive to VBa and/or VBp stimulation (Table 3), 246 (94 %) presented a short latency excitatory response (7.75 ± 0.44 ms). As in intact animals, the cells could be classified according to the latency of their excitatory responses (Fig. 1). In the Pf, the average latencies were higher than in the control rats (7.85 ± 0.5 ms, n = 106 and 6.2 ± 0.3 ms, n = 74, respectively, p = 0.016); cells with latency from 1 to 5 ms (very short latency response) were less frequent than in the intact rats (39 % vs 52 %). In the CL, the average latencies did not differ significantly from those of the non-lesioned rats but the proportion of cells with short latency response (> 5 ms) decreased (57 % vs 76 %) (Fig. 1).

The excitatory discharge could consist of any number of spikes from 1 to 10 (1 or 2 in 60 % of the cases), and could last up to 40 ms, a duration never observed in control rats. Moreover, we recorded 33 units (13.4 %) with prolonged excitatory responses (ranged from 100 to 300 ms). They could be described as a phasic high frequency discharge of activity, and were called "long duration responses" (LDR). Among these, 23 were not inhibited by VB electrical stimulation; 20 belonged to class III, three to class II. Eight LDR were observed in neurones which were still inhibited after VB stimulation; the silent period could take place before or after the LDR, five were class III and three class II. Moreover, two LDR were obtained in silent cells. All but eight LDR were observed after both VBa and VBp stimulations. The characteristics of the LDR were somewhat different after VBa or VBp stimulation. Two neurones responded with a LDR after one of the VB stimulations and a short latency response to the other.

Table 3. Comparison of mean latencies and proportion of "very short latency" (VSL) and "short latency" (SL) responses in lesioned and intact rats.

	n	Mean latencies	VSL 1–5 ms	SL >5 ms	n	Mean latencies	VSL 1–5 ms	SL >5 ms
CL	47	7.4±1.0 ms	43 %	57 %	75	9.3±0.5 ms	24 %	76 %
Pf	106	7.8±0.5 ms	39 %	61 %	74	6.2±0.3 ms	52 %	48 %
Pt	48	7.9±1.1 ms	74 %	26 %	21	5.7±0.8 ms	71 %	29 %

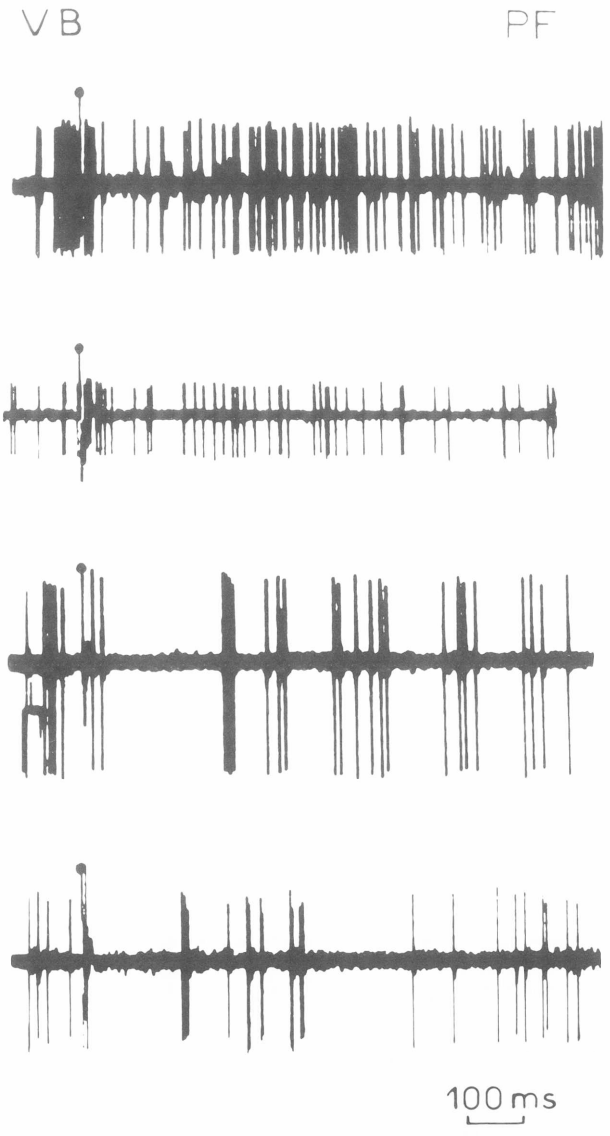

Fig. 2. *Responses of four Pf neurones (one of class III and three of class II) to VB stimulation recorded in the same track, (3 superimposed traces in each row). Short latency excitatory responses are present in these 4 neurones, but the silent phases are strongly reduced in the first two neurones (one of class III and one of class II) while the inhibition is increased in the third one and similar to those observed in intact rats in the fourth (deepest) one (calibration: 100 ms).*

Other stimulations

Out of the 51 cells responsive to striatal stimulation, 30 (59 %) presented a short latency excitatory response; one third was antidromic. The average latencies were higher than in control animals (10.4±2.1 ms and 7.8±1.4 ms, n=31 respectively). Four of them responded with LDR, as well as after VB stimulation.

Following cortical stimulation, eight of the 15 responsive neurones presented a short latency excitatory response. Among these, two were LDR cells, they also responded to VB stimulation with LDR.

An LDR could be evoked following stimulation applied to the forepaw as well as after VB stimulation in three neurones.

Location and pattern of abnormal activity

Normal as well as modified neurones were recorded either in the intralaminar thalamic area (CL and Pf) or in the Pt area.

Neurones demonstrating class II spontaneous activity with responses to VB stimulation were not intermingled with modified neurones. Some microelectrode tracks were homogeneous whatever the class of neurones recorded. For example, only class I and/or class III were recorded in a rat with large nRT coagulation (Fig. 3). When both normal and modified neurones were recorded in the same track, the normal neurones were sometimes found dorsally and more frequently laid in the deepest portion of the track (Figs 2 and 4). When the lesion was limited to the dorsal nRT, modified neurones were only found in the dorsal part of the track (Fig. 5). Thus, clusters of

modified neurones laid within clusters of normal neurones. Modified neurones were more frequently recorded in the posterior nuclei (Pf and Pt) than in CL, and as a general rule, were more frequent in the dorsal and medial part of these nuclei.

The absence of a pause in activity and/or the presence of LDR were frequently recorded in the same unit. However, some units presented only one of these patterns suggesting that different mechanisms are involved in these three abnormal patterns.

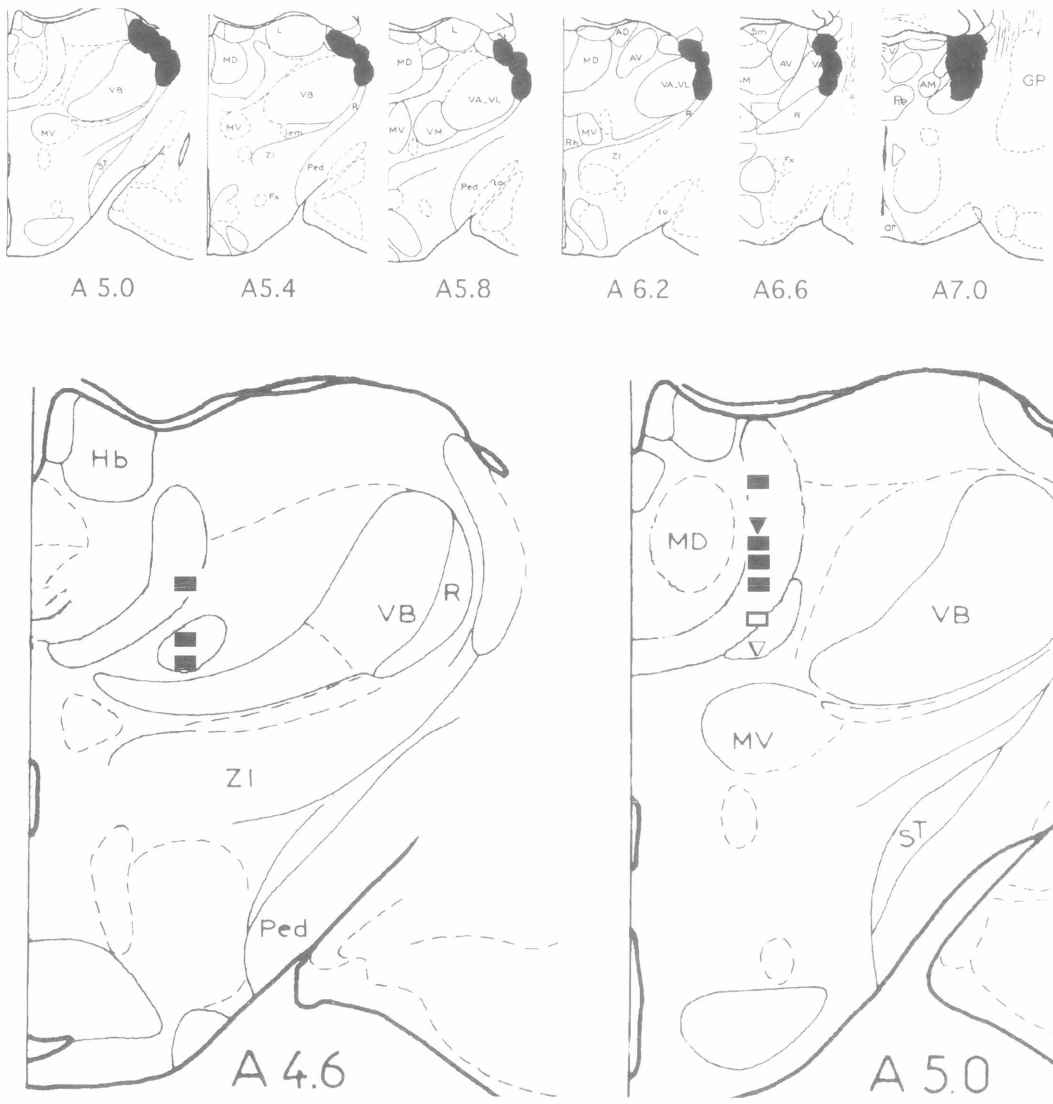

Fig. 3. *Representation of the extent of the nRT coagulation (upper part) and of the location of different recorded units with their characteristics (spontaneous activity, and the duration of the pause of activity). Squares represent neurones which did not demonstrate any pause of activity after central or peripheral stimulations; triangles represent neurones with a pause of activity < 150 ms. Black symbols correspond to class III neurones, whereas white symbols to class II. Note that after a large nRT coagulation involving the dorsolateral aspect of the nucleus, 8 out of 10 neurones were not inhibited, the two remaining were inhibited for less than 150 ms. The majority of neurones belongs to class III.*

Capsular coagulation

In three rats, the electrical coagulation affected capsular fibres and did not involve any portion of the nRT. The only significant change recorded among 15 neurones concerned a shortening of the duration of the VB-evoked pause of activity (135±9 ms), which was similar to that observed in control decorticated rats with intact nRT (Pollin *et al.* 1997).

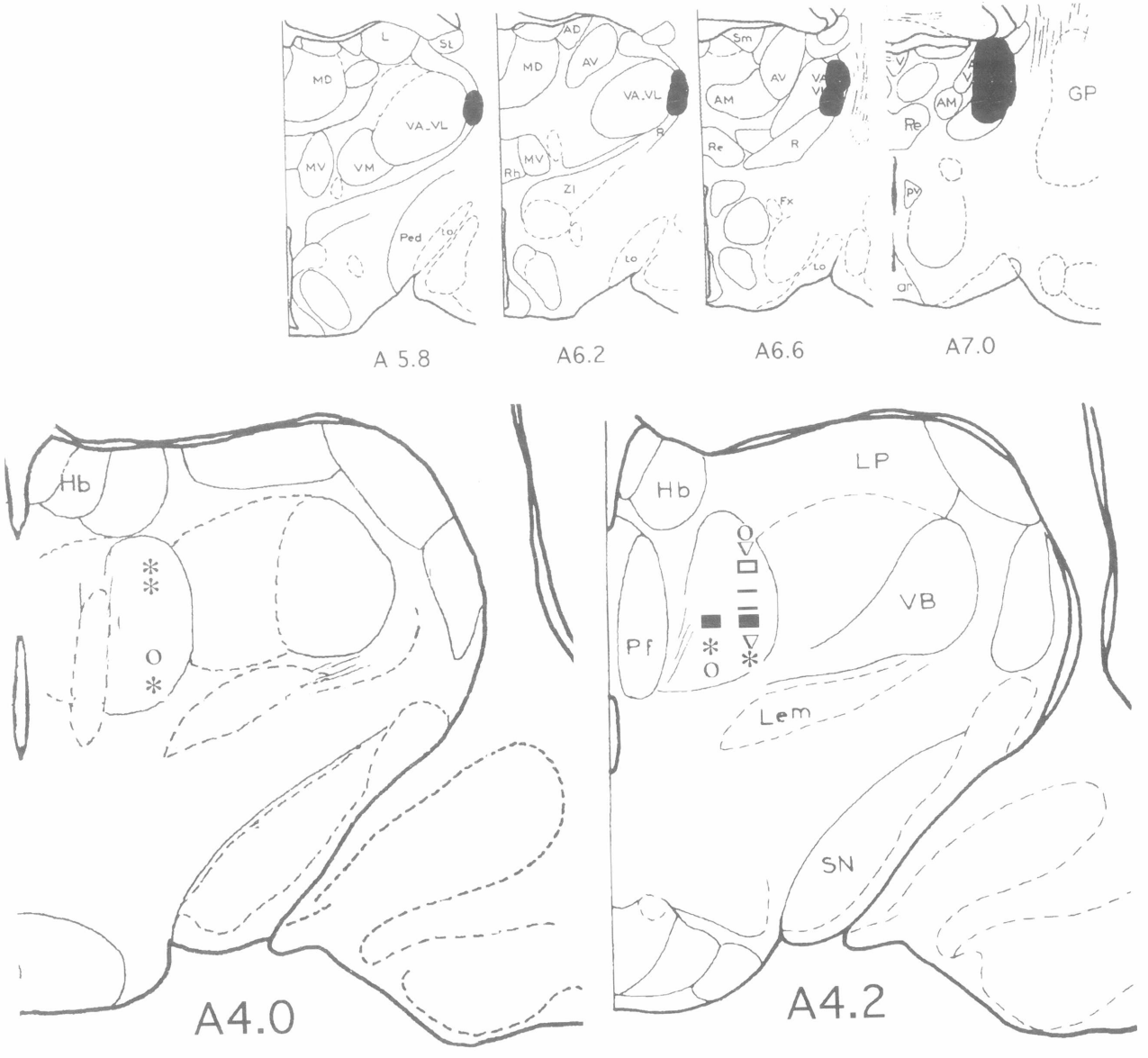

Fig. 4. *Representation of the position and of the characteristics of recorded units in a rat with a restricted nRT coagulation. The symbols are the same as in Fig. 3. Circles represents neurones with a pause of activity <250 ms and >150 ms. Asterisks represents neurones with a pause of activity >250 ms, all these belong to class II. Class I neurones are represented by hyphen. Note that in this rat few neurones are class III and that "normal" neurones were found dorsally and ventrally.*

Discussion

The aim of the present study was to analyze the effects of the chronic lesion of the nRT upon intralaminar thalamic neurones, and to compare them with ischaemic or haemorrhagic thalamic strokes in man. Thus, we performed electrical coagulations of rostral and lateral thalamic areas and destroyed intrinsic nRT neurones as well as thalamocortical and corticothalamic pathways. The rostral part of the nRT is larger and has been demonstrated to be the major source of efferents to the intralaminar nuclei (Pollin *et*

al. 1991). The coagulations often led to simultaneous lesions of the external portions of ventral nuclei and/or capsular lesions. Our results should hence differ from experiments performed after acute surgical thalamic lesions (Steriade *et al.* 1985) or kainic acid lesions (Peschanski *et al.* 1983).

These chronic laterothalamic lesions induce extensive alterations of either the spontaneous activity or the pattern of intralaminar thalamic VB-evoked responses. responses.

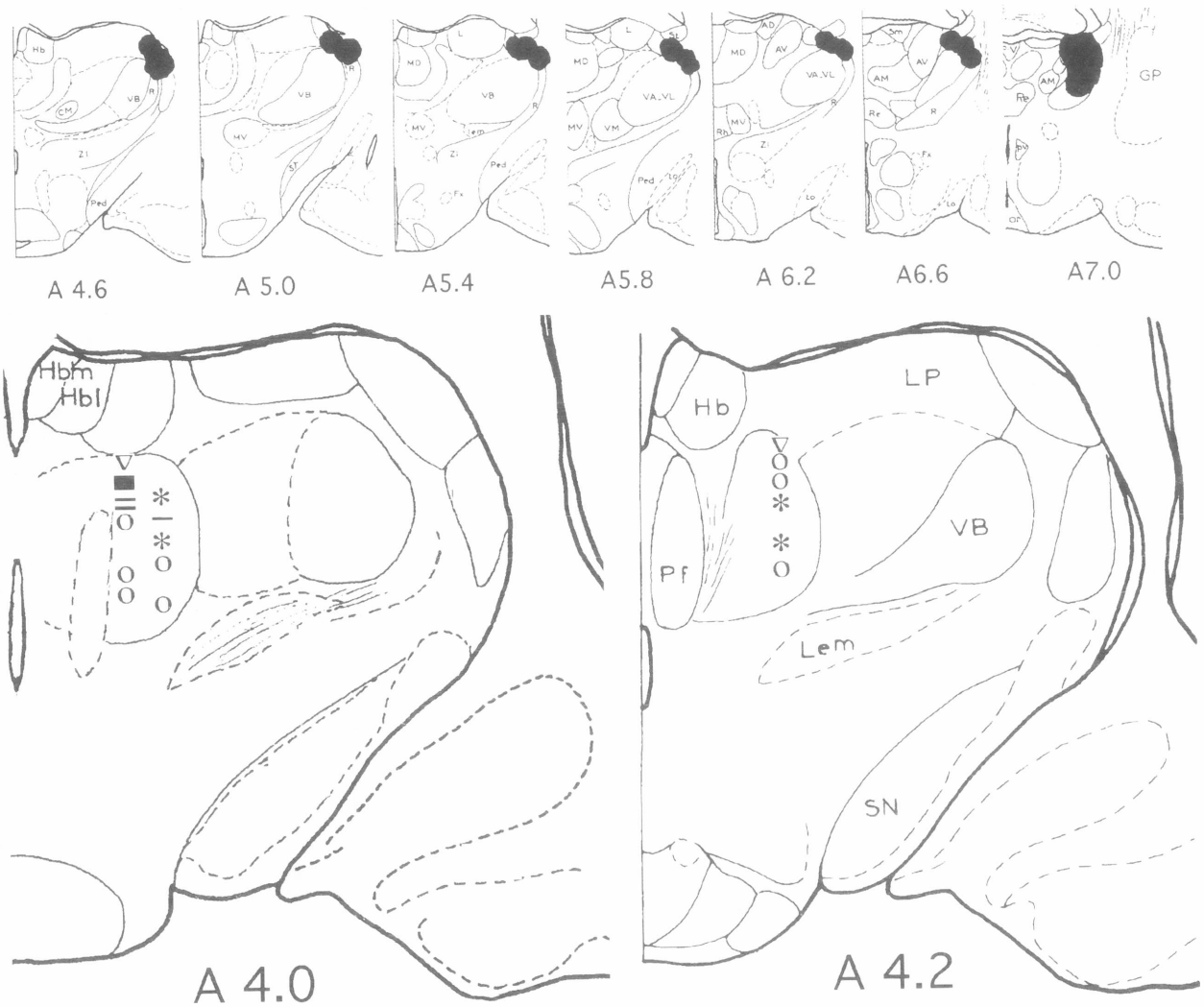

Fig. 5. *Representation of the location and characteristics of neurones recorded in a rat with a dorsal coagulation of the nRT. Note that changes are only recorded in the dorsal part of the tracks.*

Spontaneous and evoked activities

One third of neurones was silent if we include neurones which exhibited an injury discharge. These neurones two times more frequent than in intact rats (Pollin *et al.* 1997). On the contrary, more than 34 % of neurones had an abnormal increase of spontaneous discharge frequency, suggesting an extensive alteration of their connections. These results cannot be due to technical differences between the two experimental series.

The effects of electrical stimulations (VB, cortex, striatum and peripheral) were also dramatically modified in many neurones:

– the normal pause of activity frequently disappeared or was shortened, and in some rare instances, even prolonged;

– the excitatory responses disappeared in some neurones. However, in most cases, they were increased to more than 2 spikes (in 30 % of the cases vs less than 10 % in control rats) or replaced by a very peculiar LDR.

It must be stressed that these three abnormal patterns (modified spontaneous activity, lack of inhibition and LDR) were frequently (75 %) observed in the same neurones: most of the LDR (76 %) were recorded class III neurones, but two were obtained in silent cells. Interestingly, few units presented a LDR after VBa stimulation, while VBp stimulation elicited a complex response similar to that observed in intact rats. It can be hypothesized that, in these cases, the inhibitory network of the caudal part of the nRT remained intact. Nevertheless, it was possible to record units in which only one of these abnormal patterns could be encountered separately. This suggests that different mechanisms could be involved in these responses.

Location of abnormal activity

Clusters of modified and normal neurones can lay close together, but need not be intermingled in the same area. Normal and modified neurones can be recorded either in separate tracks or in separate portions of the same track. In our results, clusters of modified neurones often lay dorsally and medially to groups of normal neurones. This latter observation can be accounted for by the topographical organization of the nRT and its connections (Pollin *et al.* 1991). It has been shown that an electrolytic lesion of the visual part of nRT abolished the inhibition of GL neurones (Sumitomo *et al.* 1976, French *et al.* 1985). Since most of our lesions involved the rostral and dorsal part of the nRT, we suggest that this partial chronic coagulation of the nRT induces focal alterations of activity pattern (spontaneous activity and evoked responses) in the dorsal and medial part of these thalamic nuclei (CL, Pf, Pt).

The proportion of very short latency responses (<5 ms) decreased in the Pf (39 % vs 52 % in intact rats) mainly after more anterior VBa stimulation (38 % vs 66 %). This result may be due to a lesion of passing fibres in the rostral part of the thalamic nuclei. The decrease in the proportion of short latency responses (> 5 ms) observed in the CL (57 % vs 76 %) may also be explained by the interruption of some thalamocortical pathways.

The loss of the normal inhibitory function of the nRT neurones could explain the modifications of spontaneous ongoing activity and the increase in the spike number of evoked responses. In the same type of experiments, we have shown that neither chronic decortication nor mesencephalic lesions could induce such modifications (Pollin *et al.* 1997). Furthermore, the alterations recorded in 3 rats, with isolated capsular lesions, closely mimicked the modifications encountered in decorticated rats (shorted duration of the pause of activity).

From such experiments, we suggest that these lesions altered one major control network of the medial thalamus; i.e. the nRT. These neurones are mainly GABAergic and serve inhibitory functions since electrical stimulation of the nRT induces inhibition in thalamic nuclei, which can be mimicked by local infusion of either GABA agonists in thalamic nuclei or GABA antagonists in the nRT itself (Pollin *et al.* 1991). The elimination of this inhibitory pathway can explain the loss of inhibitions and of the LDR as well as the acceleration of spontaneous activity. Local injections of GABA receptor antagonists have been reported to induce VPM high frequency activity (Lee and Ebner 1992).

At least two mechanisms could explain the presence of silent neurones or neurones with slow activity as well with the prolonged inhibition: 1) deafferentation from the cerebral cortex. It has been shown that cortical spreading depression is followed by a depression of spontaneous activity in the relay nuclei (Albe-Fessard *et al.* 1983); 2) extensive alterations of intrinsic nRT networks. Intrinsic nRT connections, described by different authors (Cajal 1911, Spreafico *et al.* 1987), can explain the fact that the lesion may induce more complex alterations than only the loss of inhibitory effect. Further experimental data are required to clarify this point, including focal neuroneal lesions with kainic or ibotenic acid and pharmacological experiments.

Relevance to central pain

The implication of intralaminar and medial thalamus in the genesis of pain has long been emphasized (Albe-Fessard and Besson 1973, Albe-Fessard *et al.* 1985, Tasker 1986). Whereas nociceptive pathways are relayed in the VB (Guilbaud *et al.* 1981), the role of the reticulothalamic projections onto medial thalamic nuclei has been emphasized in pathological pain (Bowsher 1976, Jeanmonod *et al.* 1993). Shosaku *et al.* (observed in one rat an acute state of hyperalgesia following nRT lesion by kainic acid. A somatotopic organization as well as topical connection with thalamic relay nuclei was demonstrated in nRT (Jones 1975, Pollin and Albe-Fessard 1979, Pollin and Rokyta 1982, Shosaku *et al.* 1984). A GABAergic reciprocal inhibition has been shown in the rat between VPL and VPM and has been correlated to pathological pain (Roberts *et al.* 1992). Medial thalamic neurones display abnormal bursting activity in pain patients (Rinaldi *et al.* 1991, Jeanmonod *et al.* 1993). These data and our results support the hypothesis that the role of the medial thalamus in central pain is critical. A thalamic hyperactivity is suggested by cerebral imaging in central pain patients (Cesaro *et al.* 1991). Our data indicate that chronic lesions of the lateral thalamus, destroying the nRT, break down an inhibitory central system. It

should, however, be noted that the lesioned rats did not demonstrate any behavioural evidence of chronic pain.

In conclusion, our results support the contention that the nRT is involved in the reciprocal control mechanism between relay nuclei of the thalamus. This control network is topically organized. The loss of inhibition from the nRT is a putative mechanism for mediating central pain.

Acknowledgements

We gratefully acknowledge the critical comments given by Prof. P. Buser on an earlier draft of this manuscript. We are also grateful to Prof. C.C. Hunt and Dr. M. Sobel for revising the English. This study was supported in part by the Grant Agency of the Czech Republic (Grant IGA-MZ-CR-1325-3), Université Paris 7 and CNRS (to R.R.)

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