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The Deafferented Reticular Thalamic Nucleus Generates Spindle Rhythmicity

M. STERIADE, L. DOMICH, G. OAKSON, AND M. DESCHÊNES

Laboratoire de Neurophysiologie, Département de Physiologie, Faculté de Médecine, Université Laval, Québec G1K 7P4, Canada

SUMMARY AND CONCLUSIONS

1. The hypothesis that nucleus reticularis thalami (RE) is the generator of spindle rhythmicity during electroencephalogram (EEG) synchronization was tested in acutely prepared cats. Unit discharges and focal waves were extracellularly recorded in the rostral pole of RE nucleus, which was completely disconnected by transections from all other thalamic nuclei. In some experiments, additional transections through corona radiata created a triangular island in which the rostral RE pole survived with the caudate nucleus, putamen, basal forebrain nuclei, prepyriform area, and the adjacent cortex. Similar results were obtained in two types of experiments: brain stem-transected preparations that exhibited spontaneous spindle sequences, and animals under ketamine anesthesia in which transient spindling was repeatedly precipitated during recording by very low doses of a short-acting barbiturate.

2. Both spindle-related rhythms (7- to 16-Hz waves grouped in sequences that recur with a rhythm of 0.1–0.3 Hz) are seen in focal recordings of the deafferented RE nucleus. The presence of spindling rhythmicity in the disconnected RE nucleus contrasts with total absence of spindles in cortical EEG leads and in thalamic recordings behind the transection. Oscillations within the same frequency range as that of spontaneous spindles can be evoked in the deafferented RE nucleus by subcortical white matter stimulation.

3. In deafferented RE cells, the burst structure consists of an initially biphasic acceleration-deceleration pattern, eventually leading to a long-lasting tonic tail. Quantitative group data show that the burst parameters of disconnected RE cells are very similar to those of RE neurons with intact connections. In the deafferented RE nucleus, spike bursts of RE neurons recur periodically (0.1–0.3 Hz) in close time-relation with simultaneously recorded focal spindle sequences. The burst occurrence of deafferented RE cells is greatly reduced after systemic administration of bicuculline.

4. The preservation of both spindle-related rhythms in the disconnected RE nucleus, together with our recent experiments showing abolition of spindle oscillations in thalamic nuclei after lesions of RE nucleus (24), demonstrate that RE nucleus is the generator of spindle rhythms.

INTRODUCTION

Spindle waves are high-voltage electroencephalogram (EEG) oscillations at 7–14 Hz that appear during natural states of decreased alertness (drowsiness and EEG-synchronized sleep) and during barbiturate anesthesia. Sequences of EEG spindle waves last for 1.5–2 s and recur periodically with a slow rhythm of 0.1–0.2 Hz (23). The intrathalamic genesis of spindles was first indicated by Morison and Bassett (14) who recorded these oscillations in the intralaminar thalamic region after bilateral decortication and high brainstem transection.

Recent studies in our laboratory provided two lines of experimental evidence favoring the hypothesis that nucleus reticularis thalami (RE) is the generator of thalamic spindle oscillations. *1*) During spindle sequences, RE neurons exhibit images that are reciprocal to those of their targets in the dorsolateral thalamus. Whereas the major spindle-related events in thalamocortical neurons are long-lasting hyperpolarizations interrupted occa-

sionally by short spike bursts, RE neurons discharge continuously throughout the whole spindle sequences during natural sleep (25). The process that underlies the prolonged RE discharges during spindles is a slowly growing and decaying depolarization due to a noninactivating inward current, that is probably Na^+-dependent (15). Since the rhythmic hyperpolarizations of thalamic relay neurons mainly consist of inhibitory postsynaptic potentials (IPSPs) (2, 20) and given the GABAergic nature of RE neurons (5), the hypothesis was advanced that the latter elements generate rhythmic inhibitory events in the

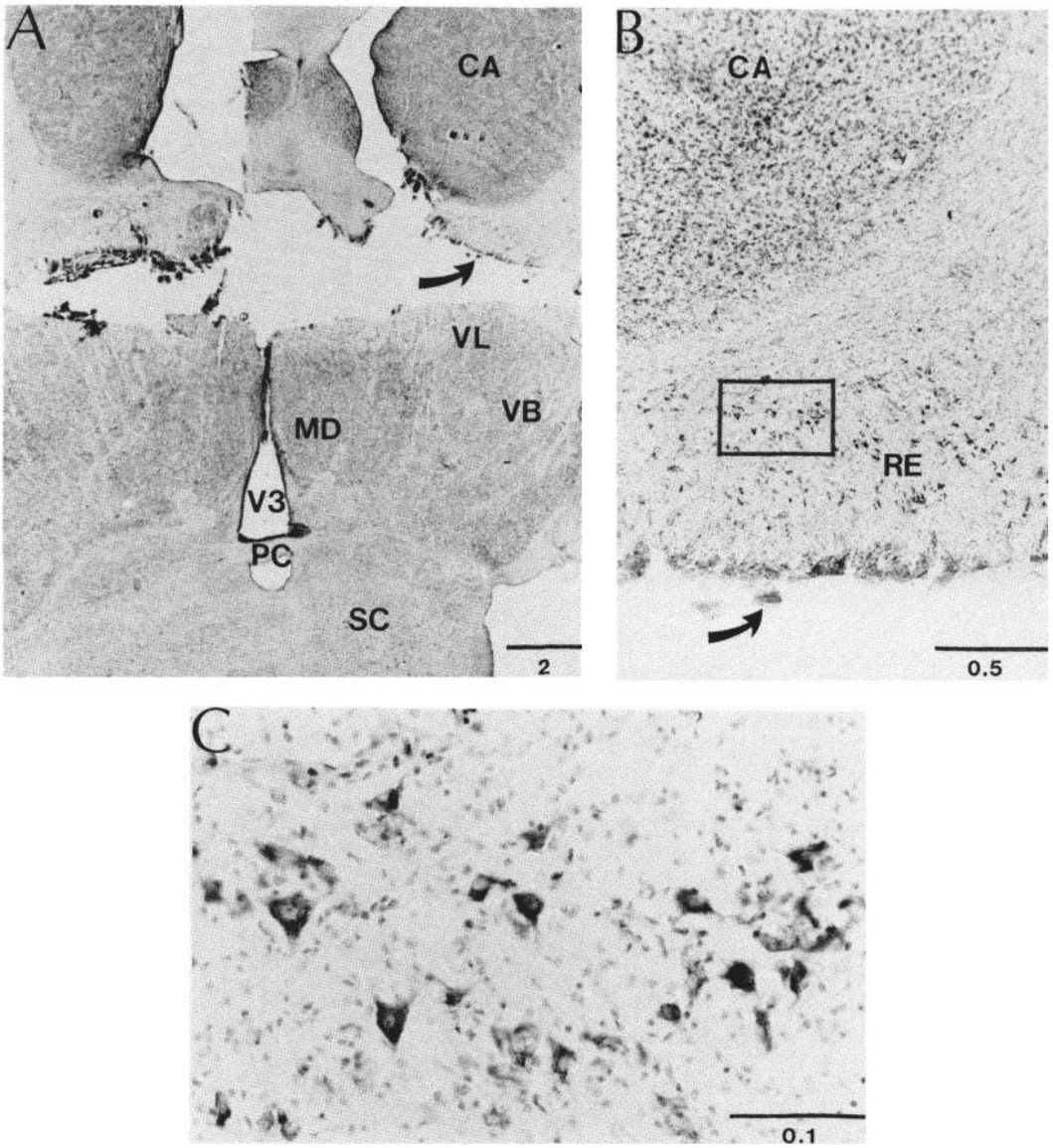

FIG. 1. Disconnection of the rostral pole of reticular (RE) nucleus from other thalamic nuclei. Bilateral thalamic transections. Horizontal sections at plane + 4, stained with cresyl violet. *Oblique arrow* in *right part* of *A* points to the same blood clot shown at higher magnification in *B*; the *rectangular box* within RE nucleus in *B* is shown in more details in *C*. *Horizontal bars* in mm. CA, caudate nucleus; MD, VB, and VL, mediodorsal, ventrobasal, and ventrolateral thalamic nuclei, respectively; PC, posterior commissure; SC, superior colliculus; V3, third ventricle.

former, with the consequence of spreading spindle waves along thalamocortical pathways (23). *2*) The hypothesis outlined above is supported by abolition of both spindle-related rhythms (7–14 Hz and 0.1–0.2 Hz) in thalamic nuclei that are disconnected from their RE inputs by transections in acutely prepared animals or by kainate-induced lesions of RE neurons in chronic experiments (24). Moreover, in anterior thalamic nuclei of cat, which are naturally devoid of RE afferents (27), intracellularly recorded cells do not display spontaneous or evoked spindle oscillations despite the fact that their intrinsic properties are similar to those of other thalamocortical neurons (16).

The lack of spindle oscillations in RE-deprived thalamocortical neurons (24) may be due to the interruption of loop circuits between RE and cortically projecting nuclei. Another possibility, tested and confirmed in the present study, is that RE neurons are generators of

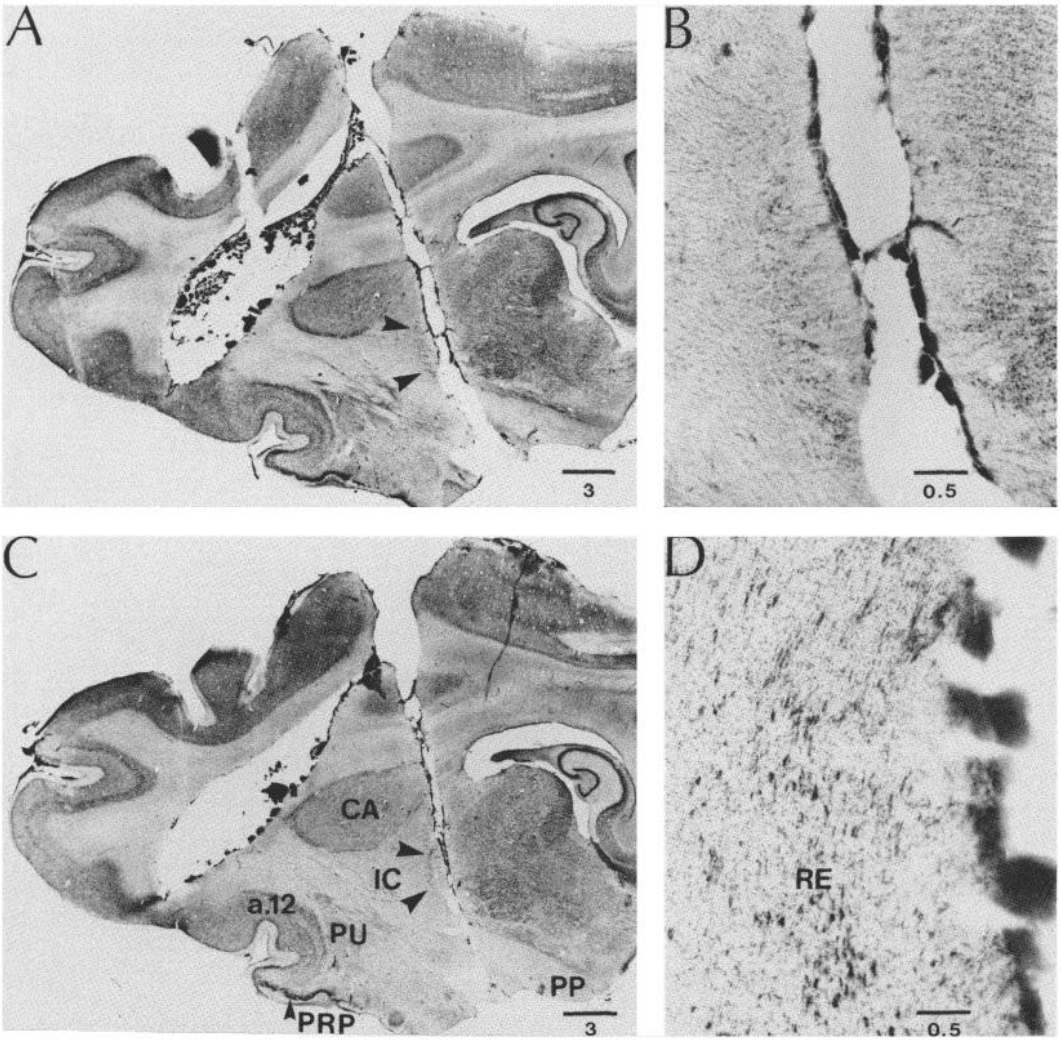

FIG. 2. Disconnection of the rostral pole of reticular (RE) nucleus from its thalamic and cortical inputs. Three different experiments (*A–B, C,* and *D*). Sagittal sections stained with cresyl violet. The rostral pole of RE nucleus is indicated by *arrowheads* in *A* (same part is shown at greater magnification in *B*) and in *C*. The section depicted in *D* has the same orientation as sections *A–C* (the hemorrhagic transection is posterior to RE nucleus). See text for description of structures present in the triangular island shown in *A* and *C*. CA, caudate nucleus; IC, internal capsule; PP, pes pedunculi; PRP, prepyriform cortex; PU, putamen; a.12, orbital area 12.

spindle oscillations, with the implication that both spindle-related rhythms survive in RE nucleus disconnected from its major (thalamic and cortical) input sources.

METHODS

Preparation and recordings

Acute experiments were conducted on 24 adult cats. Eighteen animals were anesthetized with ketamine administered intramuscularly with an initial dose of 40 mg/kg. Supplementary doses of ketamine (15–20 mg/kg) were given during the experiments. Because spindling rhythmicity is not manifest in the EEG of animals under ketamine, we precipitated spindle sequences with Brevital at doses of 1–2 mg/kg iv. It is known that such doses of short-acting barbiturates induce rhythmic spindle sequences after 15–30 s, and several minutes later previous EEG patterns resume spontaneously (22, 24). The re-

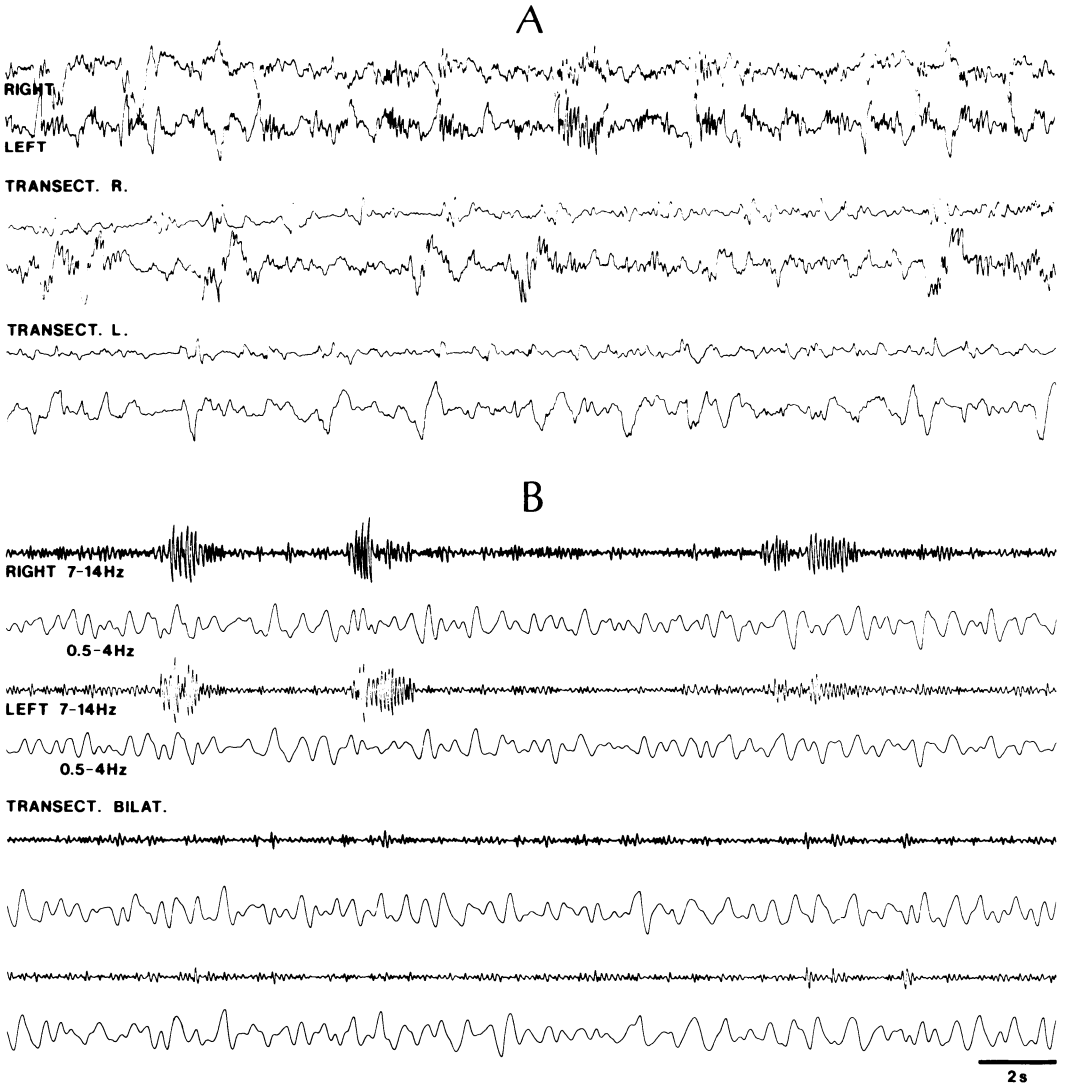

FIG. 3. Abolition of spindle rhythms in cortical electroencephalogram (EEG) after rostral thalamic transections. Two experiments on brain stem-transected preparations. In *A*, original EEG recordings from right and left precruciate gyri before thalamic transections (*top*); *below*, activity of the same leads after right transection; *bottom*, left transection added. In *B*, cortical EEG activity filtered for spindles (7–14 Hz) and slow waves (0.5–4 Hz); right and left precruciate EEG rhythms are shown before and after bilateral thalamic transections. Note in both *A* and *B*, abolition of spindles and preservation of slow waves in cortical EEG after rostral thalamic transections.

maining six animals underwent low collicular transections (Bremer's cerveau isolé preparations) under ether anesthesia and exhibited spontaneous spindle activity during recording. In addition to ketamine anesthesia or brain stem transections, the wound edges and pressure points were carefully and repeatedly infiltrated in all animals with xylocaine 2%. The animals were placed in a stereotaxic apparatus, paralyzed with gallamine triethiodide, and artificially ventilated with CO_2 level of the expired air maintained at 3.8 ± 0.2%. The internal temperature was kept between 37 and 39°.

In 15 of 24 animals frontal thalamic transections were made in both hemispheres. The cuts were made with a single-edged razor blade at plane 11.5–12 by lowering the instrument for 20–22 mm from the cortical surface and swinging it from the midline to lateral planes 9–10. After such transections, the rostral pole of RE nucleus was completely disconnected from the posteriorly located thalamic nuclei (Figs. 1 and 2). Even though it has been demonstrated that the cerebral cortex does not exhibit spindle oscillations in athalamic animals (28), we further attempted to deafferent the rostral pole of RE nucleus not only from its thalamic inputs but also from neocortical projections. In nine animals, in addition to bilateral thalamic transections, we made oblique transections of corona radiata from the posterior or middle suprasylvian gyri to the orbital gyri. In such preparations (Fig. 2), we created a triangular island in which the rostral pole of RE nucleus coexisted with the caudate nucleus, putamen, entopeduncular nucleus, nucleus basalis of Meynert and adjacent basal forebrain areas, prepyriform cortex, and orbital area 12 around the presylvian sulcus. The presence of these structures in the island where RE recordings were made is dealt with in DISCUSSION. We introduced an array of stimulating wires made from used microelectrodes (tips bared 0.1–0.2 mm, ~0.5–1 mm apart) into the white matter above the caudate nucleus and tested the effect of bipolar stimulation (0.05–0.2 ms pulses, 0.1–0.2 mA) on the deafferented RE nucleus.

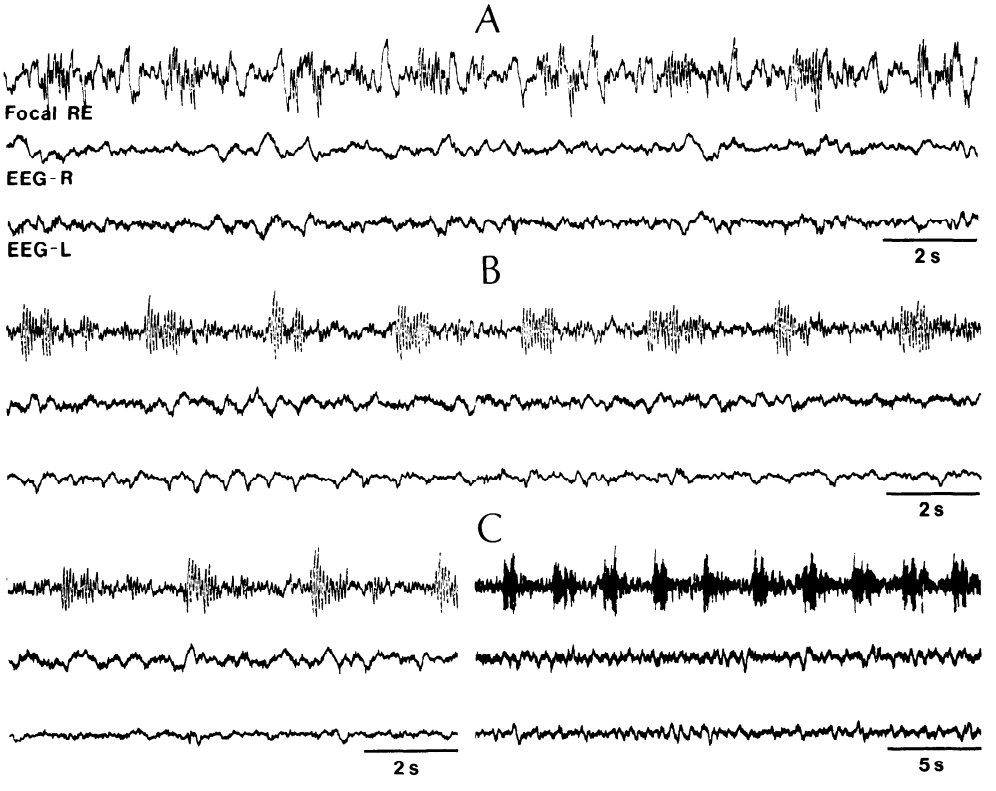

FIG. 4. Spindle rhythms in thalamically disconnected reticular (RE) nucleus. Recordings of focal waves by means of a microelectrode inserted in the rostral pole of RE nucleus after bilateral thalamic transections. *A–C*: 3 different dorsal to ventral foci; *A* separated from *C* by ~1.4 mm. These spindle sequences were not seen dorsally to point *A* and ventrally to point *C*. In *A*, *B*, and *C*, the 3 *traces* depict focal waves in RE nucleus, right and left EEG from the surface of postcruciate gyri.

Recordings of cortical EEG waves were made from the surface of pericruciate and suprasylvian gyri of both hemispheres. Discharges of single neurons and focal waves were extracellularly recorded in the rostral pole of RE nucleus by tungsten microelectrodes (1–3 μm tip diam, 2–6 MΩ at 1 kHz) lowered just in front of thalamic transections, at frontal planes 12–13. Unit discharges and focal waves were simultaneously recorded on direct (50–10,000 Hz) and FM (1–700 Hz) channels of a tape recorder, along with surface cortical EEG waves and trigger stimulation pulses. In four experiments, subconvulsive doses of bicuculline were administered intravenously (0.15–0.20 mg/kg) to study their effects on burst discharges of GABAergic RE neurons.

At the end of experiments, the animals were deeply anesthetized with pentobarbital and perfused intracardially with formaldehyde and saline. Histology was done with horizontal and sagittal frozen

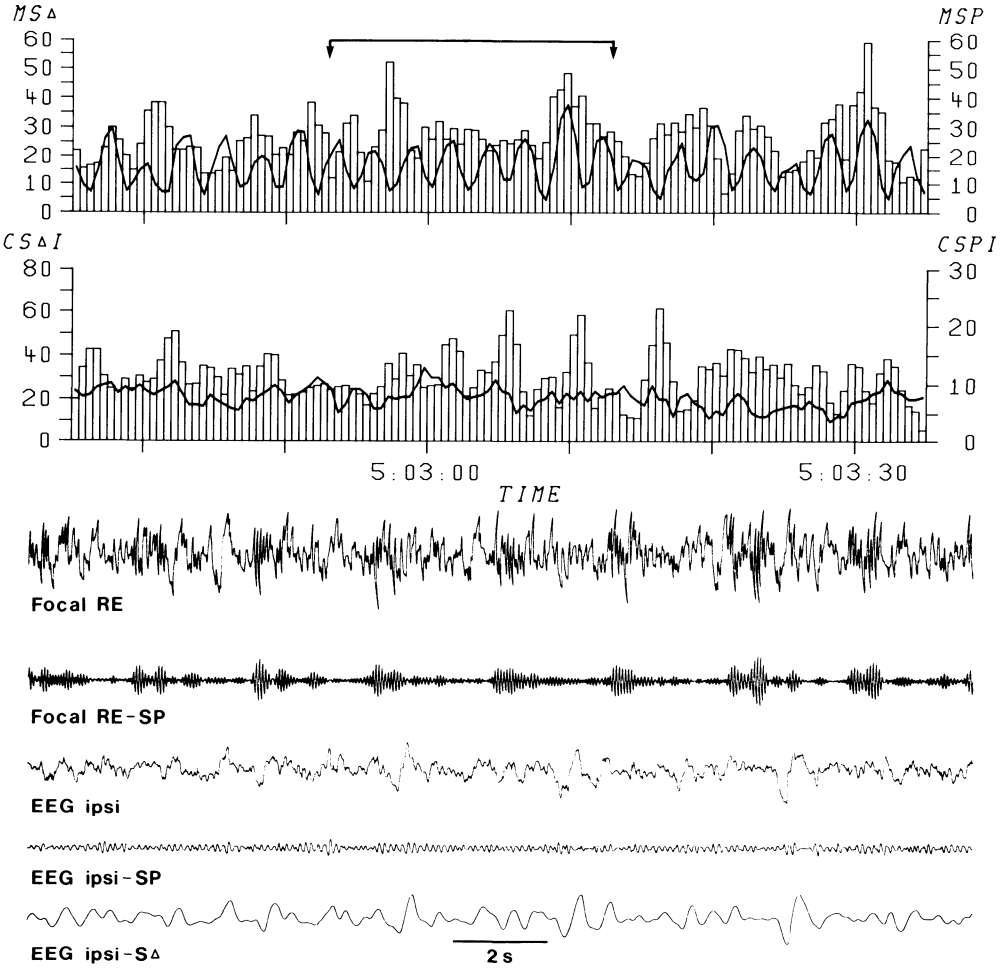

FIG. 5. Rhythmic spindling in rostral pole of reticular (RE) nucleus disconnected from thalamic and neocortical projections. At *top*, 2 computer-generated graphs. *First graph*: filtered spindle waves (7–14 Hz, MSP, *continuous line*) and slow waves (0.5–4 Hz MSΔ, bar graph) recorded by the microelectrode in RE nucleus. *Second graph*: filtered spindle waves (CSPI) and slow waves (CSΔI) of ipsilateral neocortical electroencephalogram (EEG). *Ordinates* represent averaged amplitudes that were normalized between the highest (100%) and the lowest (0%) wave amplitudes during a given epoch. To preserve relative amplitudes between spindles and slow waves, the 2 channels were normalized to the highest value of both channels (see further details in Ref. 25). *Abscissas* represent real time; moving average of three 0.5-s bins. Below, the five ink-written traces depict the part indicated between *arrows* in the top computer-generated graph: focal RE waves, filtered spindle waves from focal RE recording, ipsilateral EEG at the precruciate cortical surface, and filtered spindles and slow waves from ipsilateral EEG. Note abolition of spindles in ipsilateral neocortex (but persistence of slow waves) after rostral thalamic and corona radiata transections, contrasting with persistence of rhythmic spindle sequences in deafferented RE. See further comments on RE spindles in text.

sections (80 μm) stained with thionine and cresyl violet.

Analyses

We plotted average amplitudes of cortical EEG and RE focal waves as a function of time and analyzed filtered spindle waves between 7 and 16 Hz and slow waves between 0.5 and 4 Hz (see Fig. 5). The effects of short-term noise were avoided by plotting data with a three-bin equally weighted moving average (see further details on amplitude normalization of EEG and RE focal waves in Ref. 25). Discharges of single RE neurons were analyzed sequentially together with simultaneously recorded focal waves reflecting spindle oscillation in a pool of neighboring RE cells (see Fig. 9).

To determine whether or not the disconnection of RE neurons from their thalamic and cortical inputs may change the intrinsic structure of RE cells' spike bursts, we made quantitative evaluations of burst parameters in groups of deafferented RE neurons and compared these parameters with those found in intact RE neurons (3). The criteria for automatic computer selection of RE cells' bursts from the stored interval data bank were: the preburst and postburst intervals were >100 ms, and the sum of the first 5 intervals in the burst did not exceed 100 ms.

RESULTS

Spontaneous and evoked spindle oscillations in the deafferented RE nucleus

Cortical EEG activity was recorded before as well as after the right and left thalamic transections to ascertain that complete cuts of thalamocortical projections were made, with the consequence of abolishing cortical spindles. Following each successful thalamic transection, spindles were abolished in ipsilateral cortical leads, whereas slow waves were left intact (Fig. 3). The preservation of cortical slow waves is in keeping with previous data on athalamic preparations (28).

In clear contrast with absence of spindles at the cortical level and in ventroanterior (VA) thalamic recordings just behind the transection, focal recordings in RE nucleus showed waxing-and-waning spindles, grouped in sequences that recurred periodically (Figs. 4 and 5). In the deafferented RE nucleus, spindle rhythmicity occurred without barbiturates in brain stem-transected preparation and was induced by low doses of Brevital in animals under ketamine anesthesia. At first sight, the

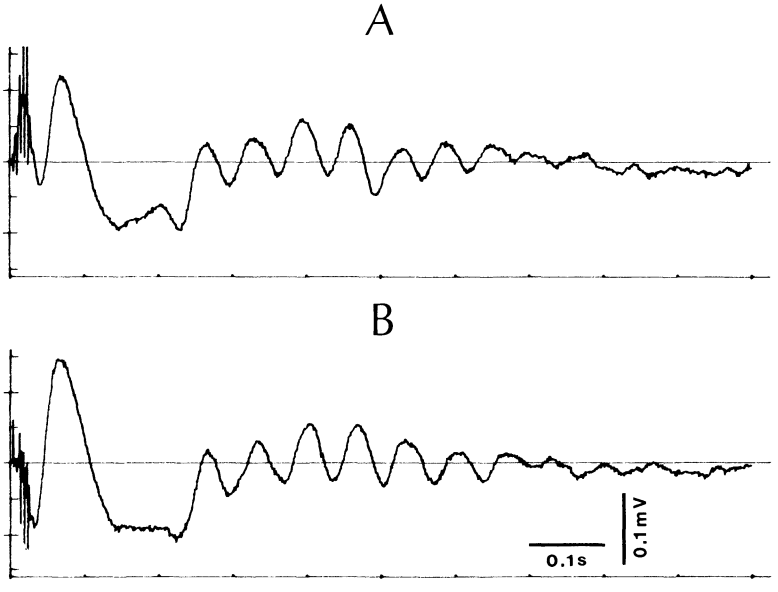

FIG. 6. Evoked oscillations in the deafferented RE nucleus (thalamic and cortical transections) by stimulating the white matter overlying the caudate nucleus. Fifty averaged traces. *A* and *B*: recordings in two foci of the rostral RE pole separated by 0.4 mm. Five shock-trains applied in each case. The series of 15–16 Hz oscillatory waves begin with a latency of ~250 ms, after a triphasic field potentiel and last for ~500 ms. Note similarity between events in *A* and *B*, the only difference being that in *A* the shock-train triggers an initial upward (negative) deflection.

spindle-related rhythms of the deafferented RE nucleus were indistinguishable from those (7–14 Hz and 0.1–0.2 Hz) seen in the intact thalamus. Subtle differences were seen, however, and they concerned the frequencies of both rhythms. The frequency of spindle waves was often in the upper range (14 Hz) and sometimes even higher (15–16 Hz). The relatively high frequency of spontaneous spindles in the disconnected RE nucleus fits in with the frequency (15–16 Hz) of oscillations evoked in the same experiments by a pulse-train to the white matter (Fig. 6). As to the slow rhythm of spontaneously occurring spindle sequences, instead of their periodic recurrence at 0.1–0.2 Hz seen in the intact RE nucleus (25), spontaneous spindle sequences recurred in many instances at 0.3 Hz in the deafferented RE nucleus (see Figs. 4 and 5).

In some foci of the deafferented RE nucleus,

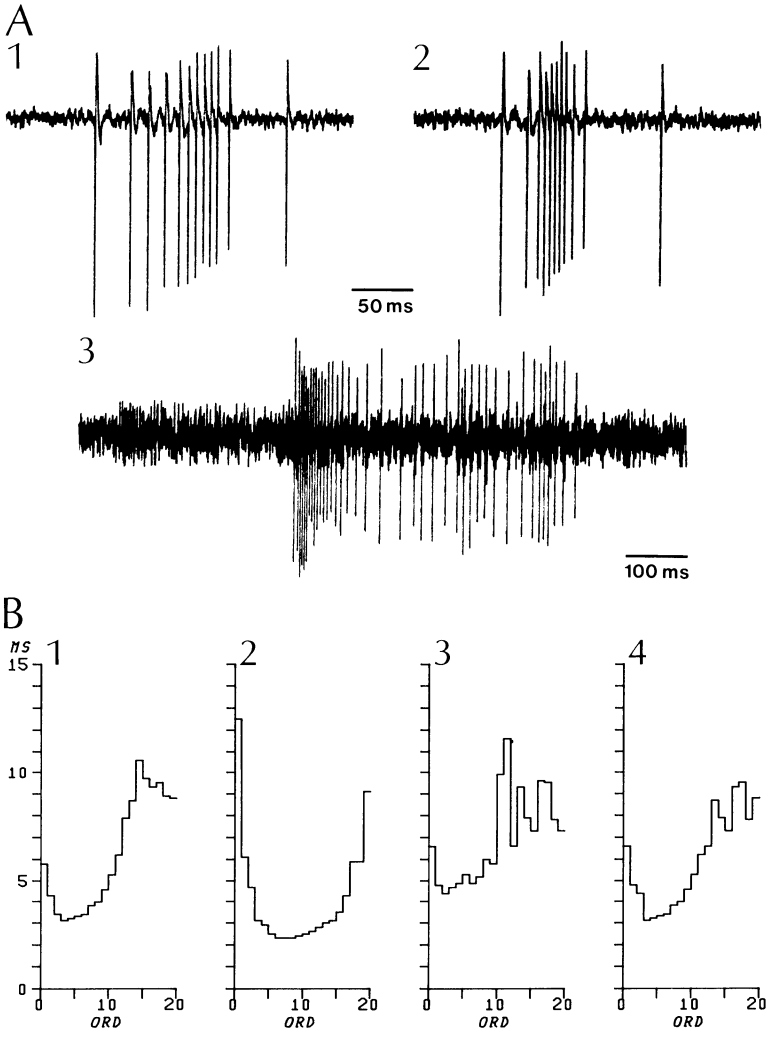

FIG. 7. Burst features of deafferented reticular (RE) neurons. Oscillographic recordings in *A* depict bursts of 2 different cells (*A, 1* and *2*, and *A3*) recorded in animals with brain stem transections; negativity upward. In *B*, plots of median interval length (*ordinate*, in ms) versus serial or ordinal (ORD) position of intervals in the bursts (*abscissa*). *B1–B3* are 3 different RE neurons; *B1* recorded in brain stem-transected preparation and *B*, 2 and 3 in 2 preparations with Brevital-induced spindling; 21 bursts, 24 bursts, and 31 bursts were analyzed in *B1, B2*, and *B3*, respectively. *B4* represents the 76 bursts of the 3 neurons.

spindle rhythms were the only distinct activity, the waves during interspindle lulls descending to the level of background noise (Fig. 4, *B* and *C*). In other adjacent foci, the whole spectrum of waves with frequencies lower than 7 Hz was seen between spontaneous spindle sequences (Figs. 4*A* and 5).

We finally note that foci exhibiting spindle oscillations were distributed throughout the disconnected rostral pole of RE nucleus but, along a microelectrode track, such foci could be revealed in a restricted zone, whereas more dorsally or ventrally explored districts did not show rhythmic activities. This was the case of the experiment illustrated in Fig. 4 where above focus *A* and below focus *C*, separated by ~1.5 mm, spontaneous spindle sequences did not appear; and the experiment shown in Fig. 6, where spindlelike oscillations could be evoked from the white matter only within 1 mm of the microelectrode trajectory through the RE nucleus.

Burst discharges in deafferented RE neurons and their relations with focal spindle oscillations

Forty-five RE neurons were isolated and their burst discharges were recorded during

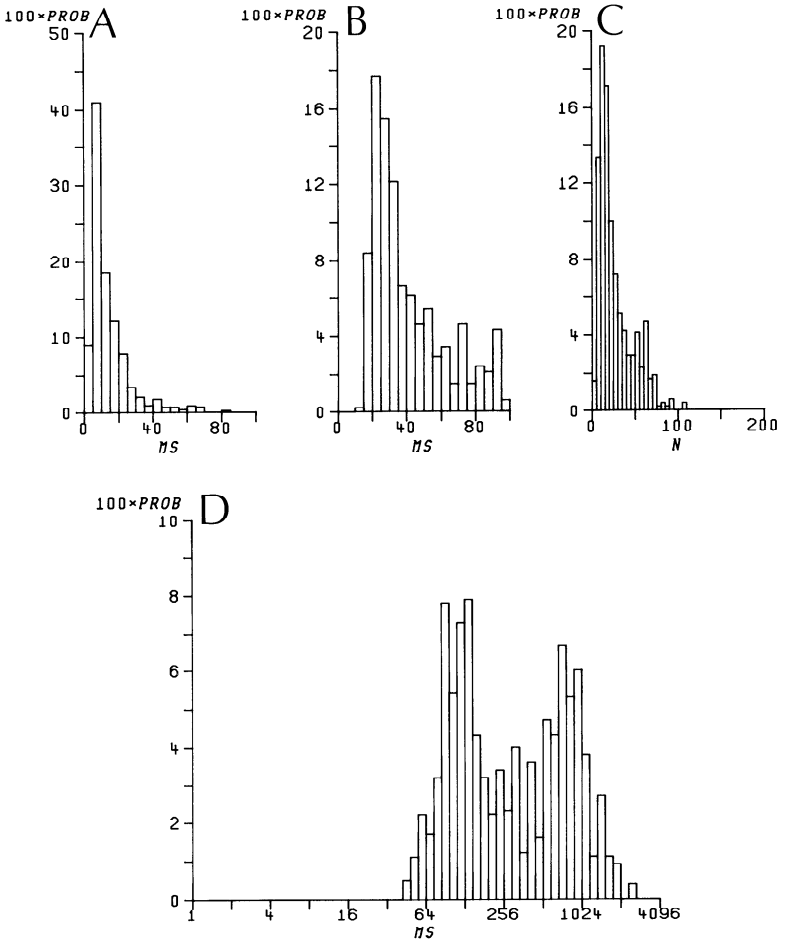

FIG. 8. Distribution of burst parameters in 350 bursts of 7 reticular (RE) cells recorded in different experimental conditions: spontaneous spindling in brain stem-transected preparations and spindling precipitated by 1–2 mg/kg Brevital. Percent probability on *ordinate;* time (in milliseconds) on *abscissa* in *A, B,* and *D*; in *C*, number of burst intervals on *abscissa. A*: duration of the 1st interval; *B*: duration of 1st 5 burst intervals; *C*: number of burst intervals; *D*: burst duration.

spontaneously occurring spindles in brain stem-transected preparations or during spindle sequences precipitated by 1–2 mg/kg of Brevital in other animals.

As known (3, 25), the bursts of cat's RE cells during natural EEG synchronization are essentially different from those of thalamocortical neurons. In the latter, the spike bursts are short (generally 10–20 ms), the intraburst frequency is high (>250 Hz), and there is a progressive lengthening in the duration of successive intraburst intervals. In RE neurons, the bursts have initially biphasic accelerando-ritardando patterns, eventually leading to a long-lasting tonic tail; altogether, the duration of RE bursts is extremely variable and extends between 50 ms and 1.5 s, with values most often between 100 and 500 ms. These differences between bursts of RE and thalamocortical neurons are so striking that they indeed assess, even before histology, that the microelectrode is within RE limits.

Figure 7 shows the initial acceleration followed by deceleration of discharges in bursts of deafferented RE cells, the variability of successive bursts that may reach the peak frequency after five intervals (Fig. 7, *A1*) or after two intervals (Fig. 7, *A2*), and the prolonged tonic tail that appears after the core of the burst (Fig. 7, *A3*). The intrinsic structure of the initial biphasic pattern is shown for three RE neurons (Fig. 7, *B1–B3*) by plotting the median interval length versus the serial or ordinal position of successive intervals in the bursts (Fig. 7, *B4* depicts the averaged values of all three cells depicted in Fig. 7, *B1–B3*). The parameters of 350 bursts recorded in different experiments from seven deafferented RE neurons (Fig. 8) are as follows: the duration of the first interval is between 5 and 15 ms in ~60%

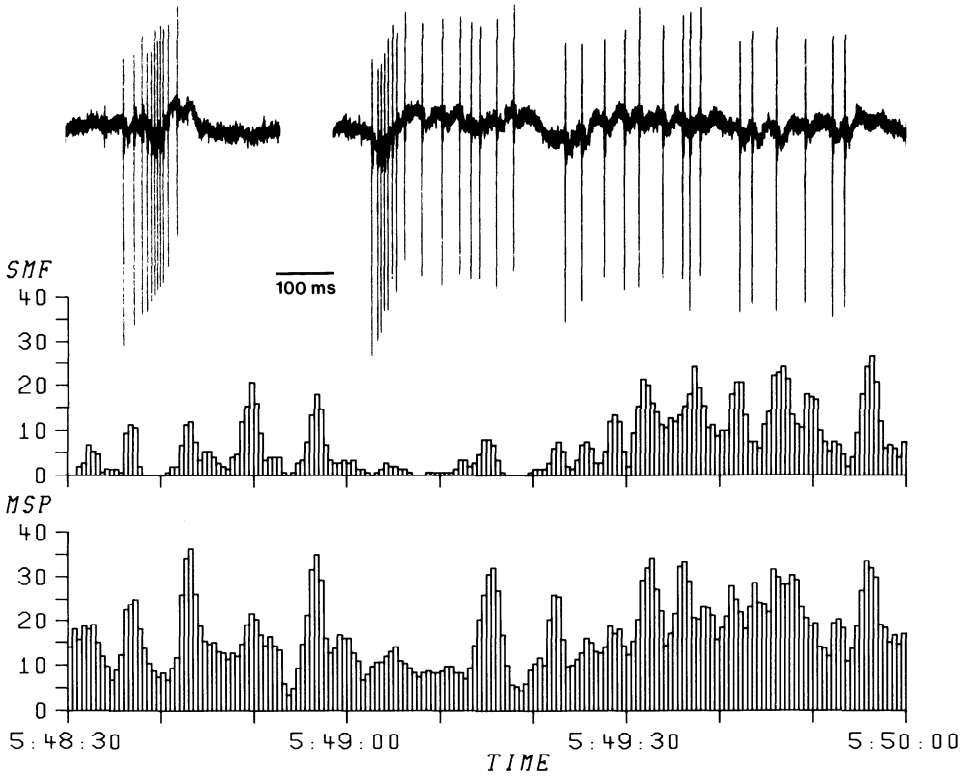

FIG. 9. Slow rhythm of spindle sequences and burst oscillations in deafferented reticular (RE) nucleus by thalamic and cortical transections. Discharges of a single RE cell were simultaneously recorded with focal spindle oscillations. Sequential mean frequency (SMF) of the neuron is depicted with the normalized amplitudes of focal waves filtered for spindle waves (MSP). *Abscissa* indicates real time. At *top*, 2 bursts from this period, one consisting of the biphasic acceleration-deceleration pattern, the other consisting of this core leading to the long-lasting (0.7 s) tonic tail.

of bursts (Fig. 8*A*); the total duration of the progressively shorter first five intervals peaks between 20 and 35 ms (Fig. 8*B*); the number of intervals peaks between 10 and 15, with more than half of all bursts having 10–30 intervals (Fig. 8*C*); and the duration of the whole burst extends between 50 ms and 2 s, with two peaks at 100–125 ms and at 0.5–1 s (Fig. 8*D*).

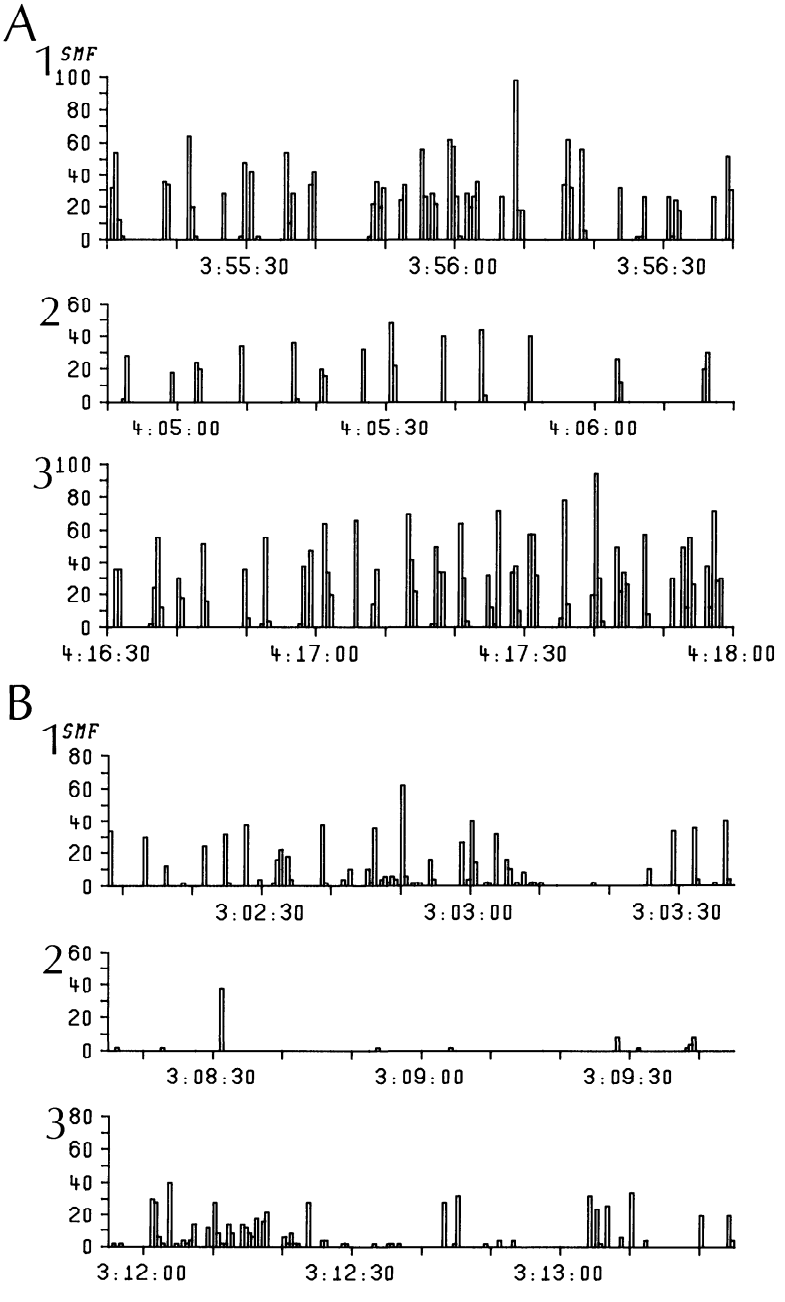

FIG. 10. Reduction of spike bursts in deafferented RE neurons by bicuculline. *A* and *B*, 2 different neurons. Bicuculline administered iv, 0.2 mg/kg. In both cases: 1, sequential mean frequency (SMF) in a control period, just before administration of bicuculline; 2, 8 min (*A*) and 5 min (*B*) after bicuculline administration; 3, recovery of the control pattern (*abscissas* indicate real time).

All these parameters are almost identical to those analyzed quantitatively in bursts of RE neurons with intact connections (3), and they are very dissimilar to burst parameters of intact (3, 11) or RE-deprived (24) thalamocortical neurons.

Burst discharges of deafferented RE neurons occurred in close time-relation with focal spindle oscillations, simultaneously recorded through the same microelectrode. Both unit and field events recurred periodically, with a slow rhythm of 0.1–0.3 Hz (Fig. 9).

Since the burst discharges in a disconnected RE nucleus are likely generated by the dendrodendritic apparatus of GABAergic RE neurons (see DISCUSSION), we attempted to block the suspected inhibitory events underlying the bursts by using subconvulsive doses of bicuculline. As in previous experiments dealing with the effects of intravenous bicuculline on spontaneous (24) or evoked (4) bursts of thalamic neurons, the maximum effect was reached in six investigated neurons after quite long latencies, 5–9 min. Three neurons could be recorded for sufficient periods of time to compare the effect of bicuculline with control and recovery periods. The burst occurrence per minute was determined by computer selection of bursts, as defined according to the criteria indicated in METHODS. The degree of bicuculline-induced blockade of bursts varied. In one neuron (depicted in Fig. 10*A*), the burst occurrence was reduced to half, compared with control and recovery periods; in the two other neurons, the rates of bursts during control and recovery periods were 20 times (Fig. 10*B*) or 9 times higher than during the effect of bicuculline. The structure of bursts that survived during the bicuculline period was, however, very similar to that of bursts recorded before and during the recovery period.

DISCUSSION

The disconnection from the remaining thalamic nuclei was histologically complete in the experiments reported here. We recorded in the rostral pole of RE nucleus <0.5 mm in front of the thalamic transection (Figs. 1 and 2, *A* and *B*) or at a distance of ~1 mm (Fig. 2, *C* and *D*). The disconnection from cortically projecting thalamic nuclei was further indicated by abolition of spindles in the ipsilateral cortical EEG after each transection. The difficulty of recording at 0.5–1 mm apart from a cut cannot be emphasized enough, and it explains the small number of cells in stable conditions that were used for quantitative analyses. The persistence of spindle oscillations in the RE nucleus after total disconnection from the other thalamic nuclei, with the consequence of abolishing spindles in cortical EEG, would be sufficient to ascertain a pacemaker role of RE nucleus in spindling, especially since cortical transections were added in nine animals. Nonetheless, we evaluate in what follows the possible role of other surviving structures in the triangular islands depicted in Fig. 2: *1*) there is no available evidence for connections between caudate nucleus or putamen and RE nucleus. As to the caudate, the connections with RE nucleus were denied in an autoradiographic study (9). The well-known propensity to elicit spindles in relay thalamic nuclei by electrical stimulation of the caudate nucleus is best explained by antidromic invasion of intralaminar neurons projecting to the striatum, with axon-reflex excitation of RE neurons and subsequent phasic inhibition in cortically projecting neurons. In some experiments, we mistakenly inserted the microelectrodes anteriorly to RE nucleus and could not record any spindle oscillations in the caudate or in the putamen. In fact, spindles survive in central thalamic recordings not only after decortication (14) but also after more radical surgery in which, in addition to the cerebral cortex, the striatum and rhinencephalon were also removed (28); *2*) because of the high content of acetylcholinesterase in the RE nucleus (19), the possibility exists that, in addition to the pathways from the cholinergic Ch5 group of the caudal midbrain (see Refs. 8, 13, 29), the RE nucleus receives projections from the nucleus basalis of Meynert (Ch4 group). There is no evidence of spindle oscillations within nucleus basalis. Moreover, stimulation of another cholinergic group (Ch5) leads to blockade of oscillatory behavior in the perigeniculate part of RE nucleus (unpublished data).

Summing up, then, the disappearance of spindle rhythmicity in thalamic nuclei and cerebral cortex after selective lesions of RE nucleus by means of kainic acid (24) together with the preservation of both spindle-related rhythms in the disconnected RE nucleus

demonstrate that RE nucleus generates spindle rhythms. The isolation of RE nucleus in the present experiments is probably what could be done acutely in vivo.[1] At this point, we may only hope that RE neurons will be investigated in vitro and found to exhibit the oscillations described here. Studies in vitro are also needed to elucidate the ionic conductances that underly the complex burst patterns of RE neurons and their rhythmic oscillations. The RE neurons have been recorded in guinea-pig slices (6, 12). The lack of vesicle-containing presynaptic dendritic profiles in the rodent RE nucleus (17, 18) may require in vitro studies in cat, a species that shows dendrodendritic inhibitory synapses (1, 30) which are likely involved in the generation of rhythmic bursts in feline RE neurons (see below).

The burst structure in deafferented RE neurons is very similar to that of RE neurons in intact preparations. This sameness was also observed by comparing the burst features of RE-deprived thalamocortical neurons with those of intact thalamic relay cells (24). While the bursts of both thalamocortical and RE neurons are generated by their intrinsic cell properties (2, 6, 7, 12, 15), the spindle-related rhythmicity of bursts in thalamocortical neurons disappears after RE disconnection (24), whereas it is preserved in deafferented RE neurons (see Fig. 9). Again, this finding points to the pacemaker role of RE nucleus. Bursts of RE neurons were greatly reduced by bicuculline, which supports the suggestion that dendrodendritic interactions between GABAergic RE neurons play an essential role in the synchronization of oscillations (1). We assume that the dendritic hyperpolarization through dendrodendritic synapses of RE neurons (1, 30) would de-inactivate a low-threshold Ca^{2+} conductance with the consequence of triggering a Ca^{2+} spike, followed by GABA exocytosis and hyperpolarization of postsynaptic dendrites; hyperpolarization in the latter dendrites would then de-inactivate the Ca^{2+} conductance and thus hyperpolarize synaptically coupled dendrites. In this way, oscillations could start at any point in the network and spread to adjacent elements. It is, of course, difficult inferring GABA effects at the RE dendrodendritic synapses based only on the present results with bicuculline, without further dose-response curves and other analyses. The spatial organization of RE dendrites in tightly aggregated bundles (21) may explain why we found rhythmic bursts and/or spindle oscillations in some foci of the deafferented RE nucleus, presumably within highly concentrated dendritic bundles, but not in adjacent zones of RE nucleus.

The presence of spindle oscillations in the deafferented RE nucleus by no means excludes that, in the normal condition of an intact brain, other factors may be decisive in triggering the RE oscillator. During the onset of natural sleep, the discharge rates of rostrally projecting midbrain reticular neurons progressively slow down (26). This may lead to hyperpolarization through disfacilitation and consequently to burst discharges in their thalamic targets. Such events may be effective in setting into motion RE neurons by means of collaterals of thalamocortical neurons. Focal spindle oscillations in various thalamic foci would develop, however, into generalized and synchronous spindling in all thalamocortical systems only by spread of oscillations throughout the RE nuclear complex that, by virtue of its generalized thalamic projections, will induce rhythmic hyperpolarizations in almost all relay nuclei.

[1] Another type of experiment would involve total decortication and recording of RE neurons in chronic conditions, 5–6 mo or more after cortical ablation, to allow retrograde degeneration of thalamocortical neurons including their collaterals to RE nucleus. We did such experiments but, as yet, did not succeed in degenerating all thalamocortical neurons, especially in medial nuclei. Even 1 yr after ablation of visual cortex, 7% of lateral geniculate relay neurons are found intact (10), probably because of their collaterals to the perigeniculate nucleus. To complicate the matter, thalamic neurons that project only to RE nucleus, not by means of recurrent collaterals of cortically projecting axons, would not degenerate after chronic decortication.

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