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ORIENTING-LIKE REACTION AFTER IBOTENIC ACID INJECTIONS INTO THE THALAMIC CENTRE MÉDIAN NUCLEUS IN THE CAT

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INTRODUCTION

The centre médian nucleus (CM) of Luys is a member of the caudal group of the intralaminar complex of the thalamus, which has traditionally been considered a major target for ascending reticular activating afferents. In the cat, the CM is well differentiated and consists of a homogeneous population of small, densely packed cells located within the internal medullary lamina posteriorly, merging medially with the parafascicular nucleus (17). These neurons give rise to dense projections to the sensorimotor striatal territory (3, 22) have relatively restricted fields of termination in the sensorimotor cortex (16, 20, 21, 22), and some sparse projections to the midbrain reticular core (35). In addition to a collective input from the reticular formation (34), CM receives distinct projections from the entopeduncular nucleus (the subprimate homolog of the internal pallidal segment) (30), the subthalamic nucleus (42), the pars reticulata of the substantia nigra, the tectum, and the vestibular complex (23).

In the light of its hodology, it is not surprising that many different roles have been ascribed to the intralaminar CM. Besides the classical role in mediating the reticular activation of the cortical electroencephalogram (EEG) that characterizes both waking and REM states (8), a functional attribute for CM has been proposed in gaze control (40), visual orientation (13), orientation-related postural responses (23), mechanisms that mediate certain types of dyskinesia (40), and nociception (37). The ascending reticular activating concept, confirmed by structural and cellular data (see for rev. 41), influenced and stimulated research on the behavioral state control. Giuseppe Moruzzi's intuition, imagination and pioneering experiments (32) not only prepared the ground for a most productive area of research, but also began to dissect the brain stem subsystems involved in wake-sleep regulation (2, 24). Previous work from this laboratory has shown that the rostral group of the intralaminar complex, particularly the centralis lateralis nucleus (CL) has a role in REM sleep and its tonic (EEG desynchronization) and phasic (ocular movements and ponto-geniculo-occipital waves) events (26). Since the CL has

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different connectionai relationships (30), phylogenetically divergent evolution (33) and different neurochemical features (38) from the CM, the question arises as to the possible different functions of the rostral and caudal groups of the internal medullary lamina with respect to the various electrographic correlates of behavioral states.

The aim of the present study was to characterize further the functional role(s) of CM by investigating the immediate (excitatory) effects evoked by the bilateral injection, stereotaxically placed, in CM of the excitotoxic ibotenic acid, known to spare axons of passage and nerve terminals of extrinsic origin (9), on EEG, electrooculographic (EOG), pontogeniculooccipital (PGO), and electromyographic (EMG) activity in freely moving cats. Preliminary findings have been reported in brief (27).

METHODS

Preparation, recording and data analysis.

The experiments were carried out on seven adult cats weighing 2-3 kg. Under nembutal anesthesia (35mg/kg, i.p.), the animals were implanted with conventional electrodes for monitoring sleep-wake variables (screw electrodes for EEG and EOG, wires into neck muscles for EMG recordings). Teflon-coated stainless-steel tripoiar electrodes, dehinsulated for 1 mm (tip separation between each pole 1 mm and one slightly longer than the others) were stereotaxically implanted unilaterally in the lateral geniculate body at coordinates A 6.0, L 10.0, H +2, according to the atlas of Jasper and Ajmone-Marsan (14). The tripoiar electrodes increased the chances of obtaining high-amplitude PGO waves by recording between various electrodes combination.

Following recovery from surgery, cats underwent a period of habituation to an experimental sound-attenuated cage, equipped with a one-way mirror, whose temperature was maintained constant at 22-24 °C. EEG, EOG, EMG, PGO activity signals were filtered, amplified, and recorded on a Grass polygraph (Model 7D) for 6 h a day. After baseline recording, the cats received ibotenic acid (Sigma; 1.2-2.6 μl of 50μg/μl) bilaterally into the CM, under ketamine anesthesia (25mg/kg). This short-acting compound was used to avoid side-effects and to obtain short-lasting general anesthesia. The acid was dissolved immediately before use in 1 M phosphate buffer (pH 7.2) and slowly injected at target coordinates - A 6.5-7; L 2.5-3; H +1, +2 - (14), using a 5μl Hamilton microsyringe. The posterior portion of the CM was injected since it is particularly well defined in the cat at this level. Rectal temperature was closely monitored throughout recovery.

Videotapes were taken during the first 8 h post-injection to document changes in the cats' behavior. Continuous 24-h recordings were done in four cats before and after the injection. The polygraphic recordings were scored according to the traditional classification of states into wakefulness (W), stow wave sleep (SWS), and rapid eye movement (REM) sleep, by two investigators. The power spectra in EEG activity were computed on-line for 30 consecutive artifact-free 2-s epochs using a fast Fourier transform routine.

Histology.

After completion of experimental protocols, the cats were deeply anesthetized with nembutal and transcardially perfused with a saline rinse containing 25 IU/ml heparin, followed by 10% buffered formalin. After perfusion, the brains were removed, postfixed in the same fixative, then immersed for two to three days in 30% phosphate buffer sucrose solution (pH 7.4) at 4°C. After freezing into 50μm frontal sections, the portion containing the thalamus was cut. The serial sections were mounted on gelatin-coated slides and stained with cresyl-violet or thionin.

Abbreviations:

EEG, electroencephalogram; EMG, electromyogram; EOG, electrooculogram; CM, centre median nucleus; CL, centralis lateralis nucleus; REM, rapid eye movements; PGO, pontogeniculooccipital waves.

RESULTS

1. *Assessment of the injection site.* - Since the animals were killed at least 30 days after the injections, the location and extent of the injection sites were assessed on the basis of cell damage. In all cases the posterior portion of CM was damaged.

Fig. 1B shows the typical aspect of the lesion on a frontal section through the thalamus at level A7.-7.5 The needle track and the reactive gliosis are clearly seen. The region of cell loss - reasonably restricted - is within the limits of the CM. The dorsomedial portion and the portion near the tractus habenulo-peduncularis (fasciculus retroflexus, fr) is more damaged, with parafascicular (Pf) loss of cells too, while the ventral part of CM is spared. Note that the sectors surrounding the fr are the part of the thalamic territory projecting densely upon the striatum (22).

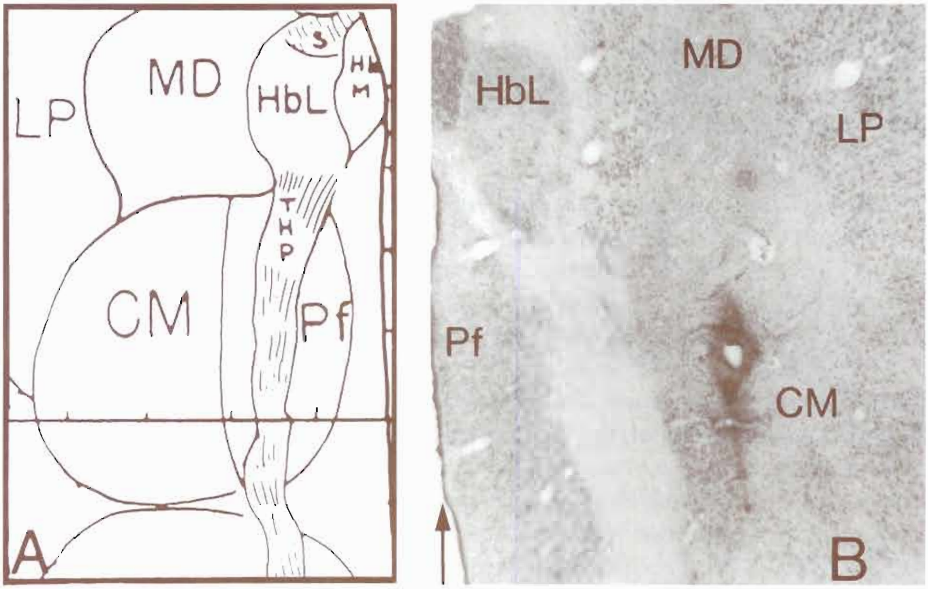

Fig 1 - *Histological aspect of a representative ibotenic acid lesion of the centre médian nucleus of the thalamus (CM).*

In A the level A7 from Jasper and Ajmone-Marsan's atlas is shown. In B cresyl-violet stained frontal section. Animal sacrificed 40 days after the ibotenic acid injection.

2. *Immediate effects of ibotenic acid injection in the CM on electrographic correlates of behavioral states.* - Fig. 2 shows the immediate (excitatory) effects induced by the bilateral injections of ibotenic acid into CM on EEG activity, EOG and EMG activity. The typical EEG activity of ketamine-sedated cats (sharp-slow wave complexes superimposed on beta wave activity) (5) was replaced by low-voltage desynchronized patterns. Series of spontaneous nystagmiform ocular movements and prominent neck muscle tone were observed. In the following, the effects on behavior, EEG patterns, muscle tone, and eye movements will be detailed.

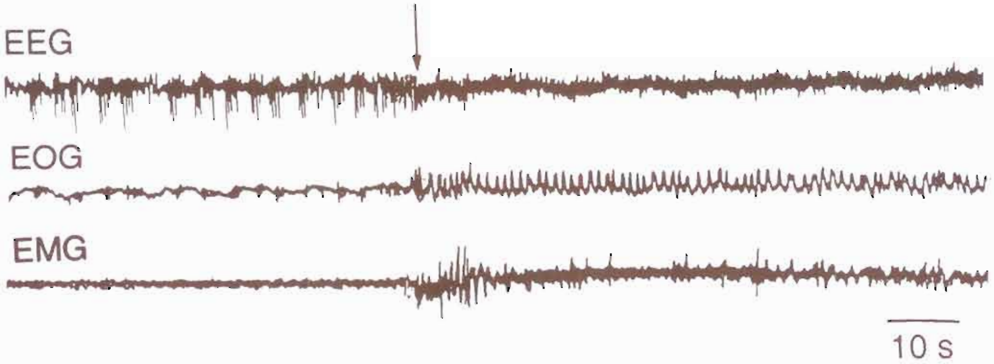

Fig. 2 - *Early electrographic signs induced by bilateral ibotenic acid injections in the centre médian (CM) of a chronically implanted cat.*

The traces depict, from top to bottom: EEG waves, ocular movements (EOG) and electromyogram of neck muscles (EMG). Note the low-voltage desynchronized EEG patterns, the series of spontaneous nystagmiform ocular movements, and the prominent neck muscle tone. The arrow indicates the time of the injection.

3. *Behavior and EEG effects.* - Immediately after the CM injection, during the early excitatory phase, the animals displayed highly aroused behavior that was similar to that seen after CL chemical excitation (26). Pupillary dilatation was also observed. Three cats out of seven had difficulty in respiration. Forelimbs were extended and hypertonic, the hindlimbs more relaxed. The cats often raised their heads and appeared to be over-alert but they did not show any interaction with the environment. Their behavior did not mimic the normal arousal behavior completely in that activation of the cholinergic-thalamic system and not of the basal forebrain-cortex may be not sufficient. This "orienting-like" behavior was associated with desynchronized EEG patterns alternating with rare paroxysmal waves (sporadic spikes sometimes followed by a slow wave) (Fig. 3A). An electrographic picture similar to the recruiting response was never seen probably because we always injected the posterior part of the nucleus (as can be seen in Fig. 1) whereas recruiting responses were obtained after stimulation of the rostral pole of CM (15). EEG power spectra analysis showed an increase in activity in all the frequency bands (Fig. 3B), significant ($2P<0.05$) in the 4-7 Hz band, as compared to natural SWS before the injection (Fig. 3C).

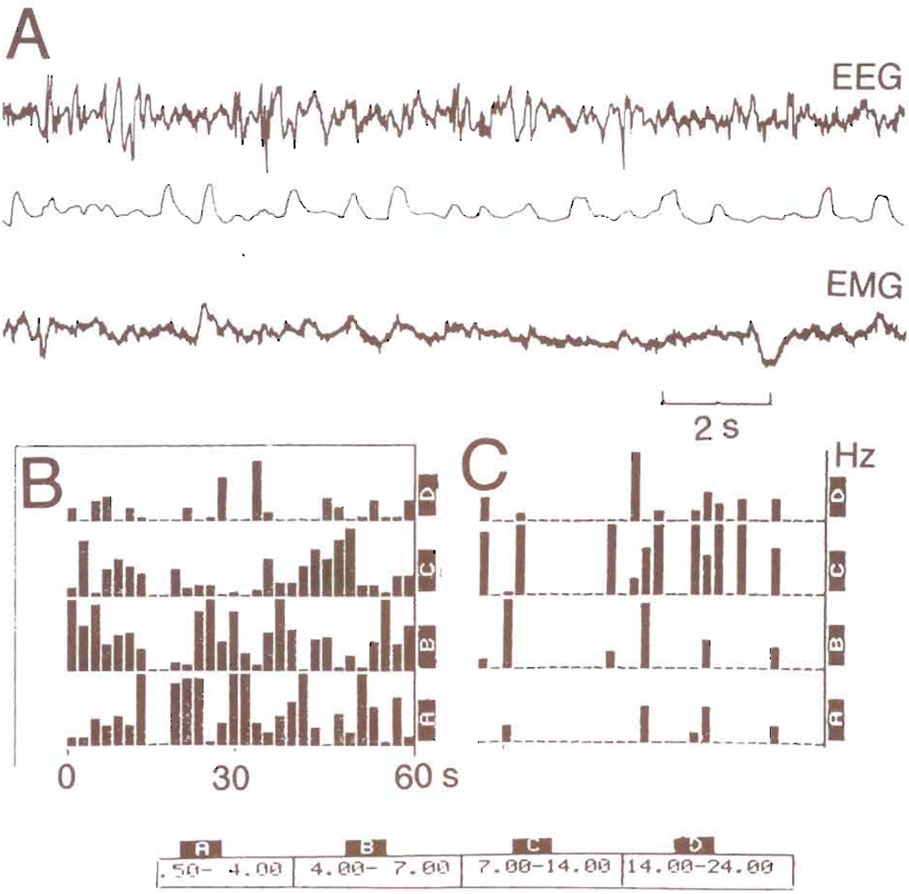

Fig. 3 - *EEG effects of ibotenic acid injection in the CM.*

A: Low voltage desynchronized EEG patterns alternating with short bursts of several spikes, followed by one or more rhythmic slow wave. B: percent band distribution of evolutive spectra 20 min after the ibotenic injection. The serial histograms are computed by 2 s epochs. Note the increase in the activity of all the frequency bands as compared to the activity during control slow wave sleep (C).

4. *Effects on EMG activity.* - The highly aroused postoperative behavior was associated with prominent muscle tone. Spontaneous, stereotyped twitches gradually started in neck muscles and forelimbs, and were fully developed 2-3h post-injection. The myoclonic jerks resembled spontaneous repetitive stretch reflexes at 3/30 Hz (Fig. 4A). EMG activity as single, doublets, and triplets quasi-periodic discharges was recorded in neck muscles and appeared sometimes to be linked to eye movements even though they were not consistently present at every eye movement (Fig. 4A). The sustained (intensity #2 in Slater and Dickinson's scale) myoclonias occurred every 5-10 s during waking, but their frequency and amplitude decreased (every 10-20 s) when the EEG became synchronized (Fig. 4B), and

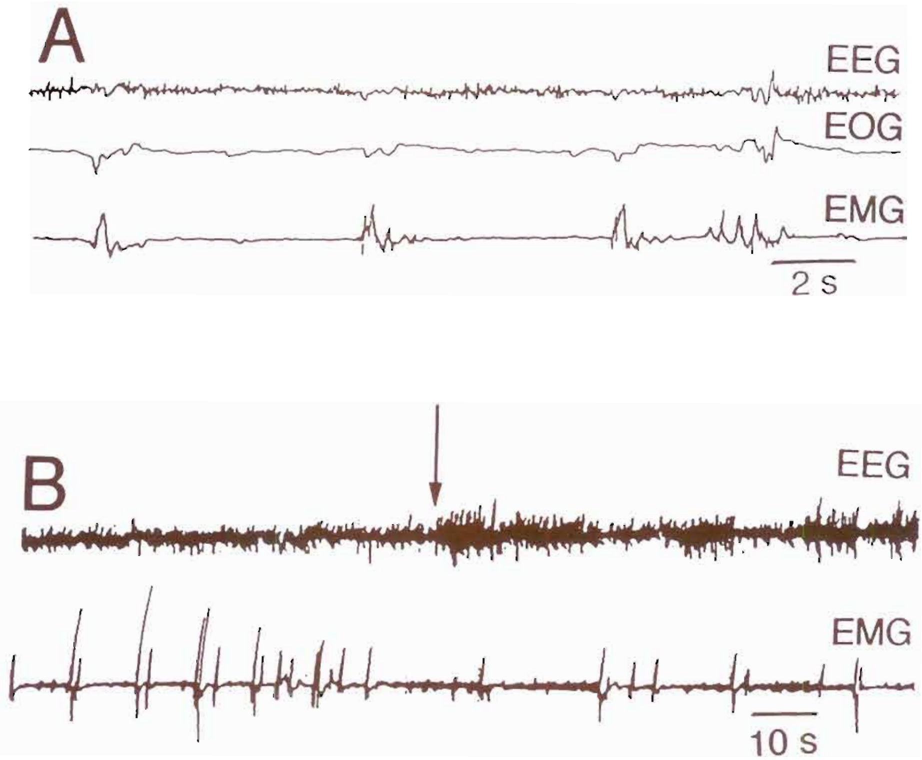

Fig. 4. - *Examples of spontaneous quasi-periodic myoclonic jerkings occurring during wake recorded in neck muscles.*

A illustrates that EMG activity occurred as single, doublets, and triplets quasi-periodic discharges and appeared to be sometimes linked to eye movements even though they were not consistently present at every eye movement. The sustained myoclonias occurred every 5-10 s during wake, but their frequency and amplitude decreased (every 10-20 s) when EEG became synchronized and disappeared at deeper levels of sleep when the EEG became persistently synchronized (B). Note that the myoclonias have no concomitant EEG correlates.

disappeared at deeper levels of sleep when the EEG became persistently synchronized (not illustrated).

Spectral analysis revealed that during SWS, each myoclonic jerk was concomitant with a short EEG desynchronized episode (Fig. 5A,B). The myoclonic jerkings preceded the desynchronization by approximately 250ms. Sometimes the jerk occurred at the transition from SWS to W (Fig.6), closely resembling the hypnic jerks described in man. These jerkings were never associated with paroxysmal EEG activity suggestive of epilepsy.

5. *Effects on eye movements.* - Series of spontaneous nystagmiform ocular movements at a frequency of 0.5-1 Hz, with quick and slow components, were recorded on the EOG as regular horizontal oscillations immediately after the injection. These movements were present also in the dark. The "floaty" saccades

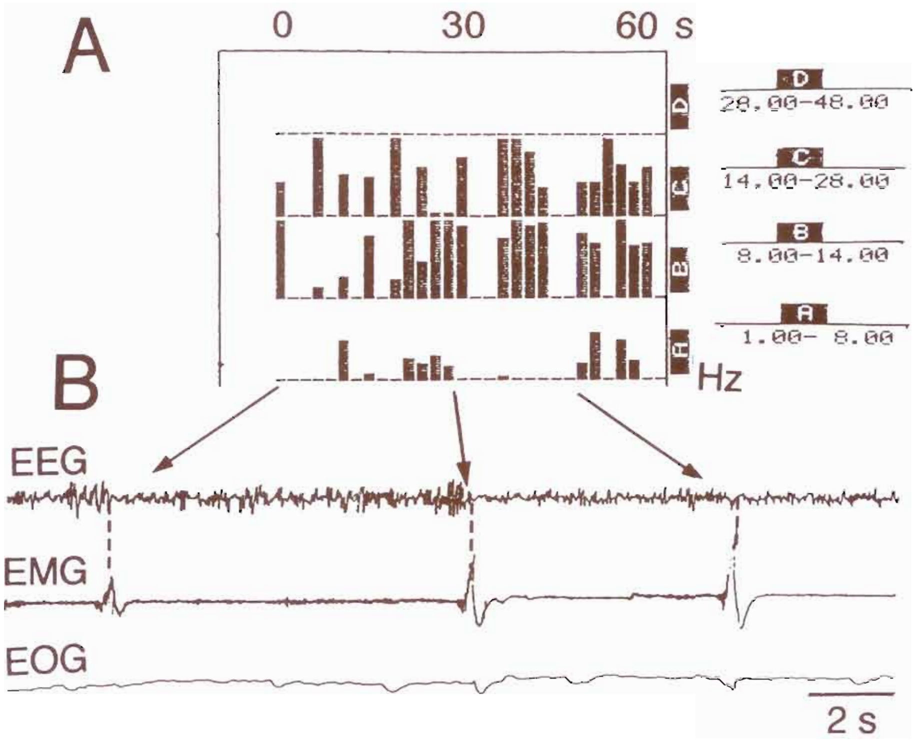

Fig. 5 - *Slow wave sleep.*

A: spectral analysis made after the ibotenic injection during slow wave sleep showing that each myoclonic jerk was concomitant with a short EEG desynchronized episode. B: the records show that the myoclonic jerkings precede the desynchronization for 250ms approximately.

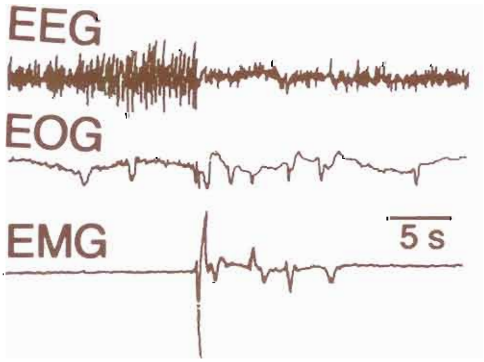

Fig. 6 - *Transition from slow wave sleep to wake.*

The record illustrates the occurrence of the jerk, closely resembling the hypnic jerks described in man.

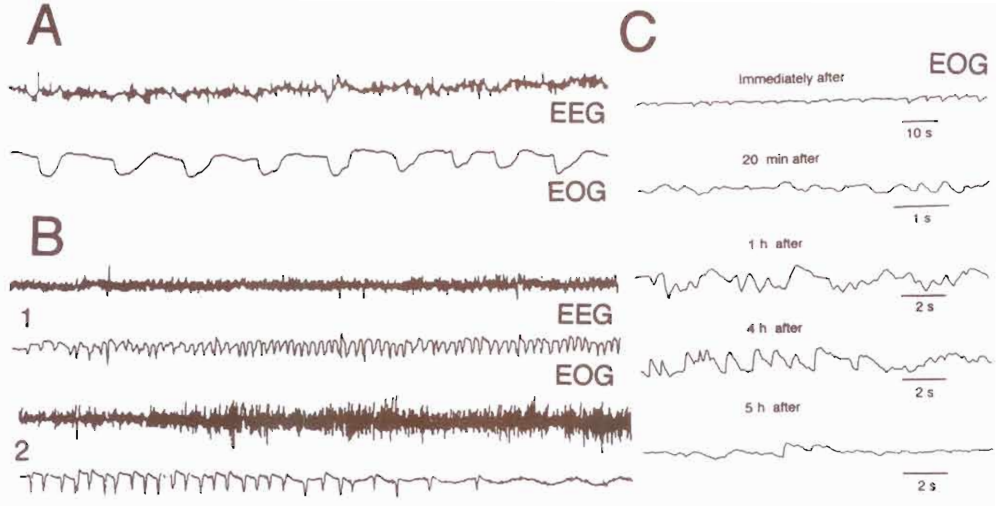

Fig. 7 - *Examples of series of saccades induced by chemical stimulation of the centre médian (CM) recorded from 3 animals immediately after the ibotenic CM-injection.*

A: note that ocular movements are accompanied by compensatory periods, most probably of vestibular origin. Also note the concomitant EEG desynchronization. The nystagmiform ocular movements occurred in waking and were reduced in amplitude and frequency and often disappeared when the EEG became synchronized (B). In C the dynamism of the effect on eye movement is shown, illustrating progressively more severe effects.

were accompanied by compensatory periods, most probably of vestibular origin (Fig. 7A and C). The dynamism of the effect of CM injection on eye movements is shown in Fig. 7C, illustrating progressively more marked effects. These deflections lasted several hours but they became smaller in amplitude and disappeared when the EEG became persistently synchronized (Fig. 7B) The state-dependent changes were very similar to the nystagmus induced by unilateral labyrinthectomy (1). Several days after the injections the rapid eye movements during episodes of REM sleep were still profoundly modified (not illustrated).

6. *Effects on lateral geniculate ponto-geniculo-occipital waves (LG-PGO).* - The excitotoxin also elicited a dramatic onset of single or clustered spontaneous large amplitude PGO waves in the lateral geniculate nucleus (Fig. 8), when the cats recovered from anesthesia, reaching a peak 5-6 h after the injections. These field potentials were continuous PGO activity for approximately 180 sec (1.6 per sec) (Fig. 8A) or grouped in clusters (3-4 per sec) (Fig. 8B and C). They occurred outside REM sleep, dissociated from the other signs of paradoxical sleep (Fig. 8A) in a state-independent manner. PGO waves were not in close time relation with ocular saccades.

Fig. 9 illustrates PGO and EOG recordings during four episodes of REM sleep, the potentiation of the amplitude and frequency of PGO waves in the early post-injection period (Fig. 9B), the obliteration when the drug had completely killed the

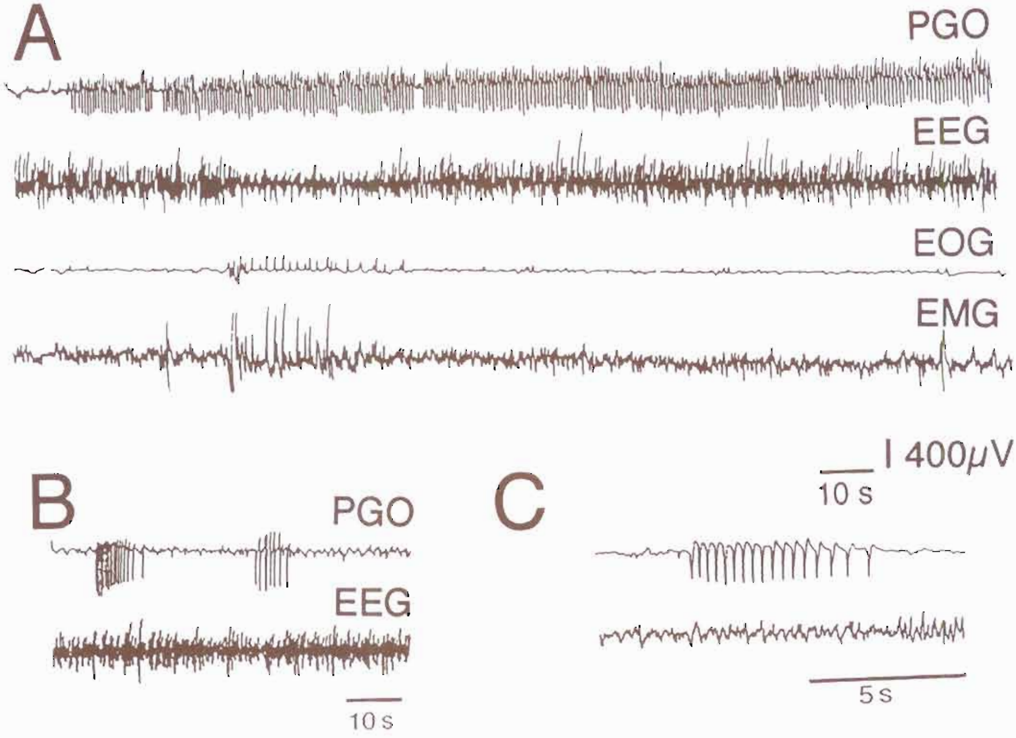

Fig. 8 - *Examples of lateral geniculo-ponto-occipital (PGO) waves recorded outside REM sleep episodes at different time-scales.*

Note that the large amplitude clusters are not in close time relation with ocular saccades.

somata, 10 days after the injection (Fig. 9C), and the reappearance of the events, 30 days after the injection (Fig. 9D) compared to the control (Fig. 9A).

7. *Alterations in the sleep-wake cycle.* - REM sleep was obliterated during the 24-h observation period after the injection (Fig. 10). During the night after the injection the EEG showed fully synchronized activity alternating with brief epochs of desynchronization. The latter were associated with floating, not rapid eye movements and sustained muscle tone with superimposed myoclonic jerking and were thus identified as waking. In some cases there was a slight rebound of REM sleep on day 1 post-injection which we ascribe to its suppression for 24 h.

8. *Recovery.* - The ibotenic acid injected into the CM immediately changed the electrographic correlates of the activated behavioral state, but only transiently. The ocular movements, PGO potentiation, and motor dyskinesia gradually faded away within two days.

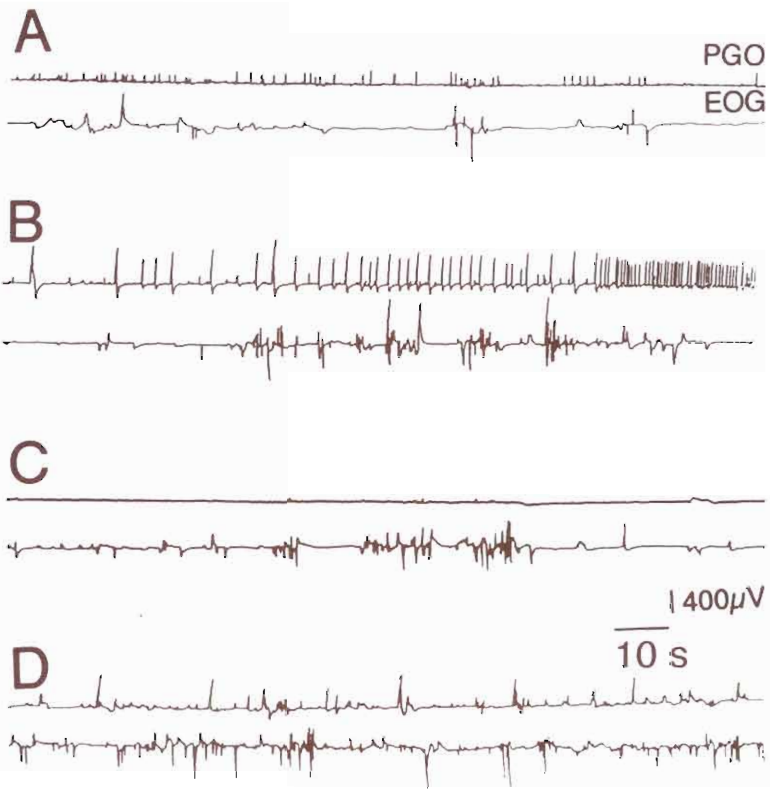

Fig. 9 - *Biphasic effect on PGO waves.*

PGO and EOG recordings during four episodes of REM sleep: before the injection (A); early post-injection period (B); 10 days after the injection, period corresponding to the complete loss of the somata. Note the obliteration of PGO activity (C); 30 days post-operation. Note the reappearance of the PGO (D).

DISCUSSION

The immediate effects of ibotenic acid bilaterally injected into the anterior group of the intralaminar complex (in particular the centralis lateralis, CL) were to induce a highly aroused state with EEG desynchronization (26). The main finding in the present study was that bilateral ibotenic acid injection into the posterior intralaminar group (particularly the CM) also induced a syndrome of highly aroused behavior, with activated EEG. This over-aroused behavior was similar to the "hallucinatory-type" behavior following kainic acid injections into the midbrain reticular core (18), thus confirming that the intralaminar complex is involved in the ascending activating system.

The syndrome may well be due to cellular excitation since the effects occurred immediately after the injection of the excitotoxin which has been shown to induce slowly developing degeneration (29).

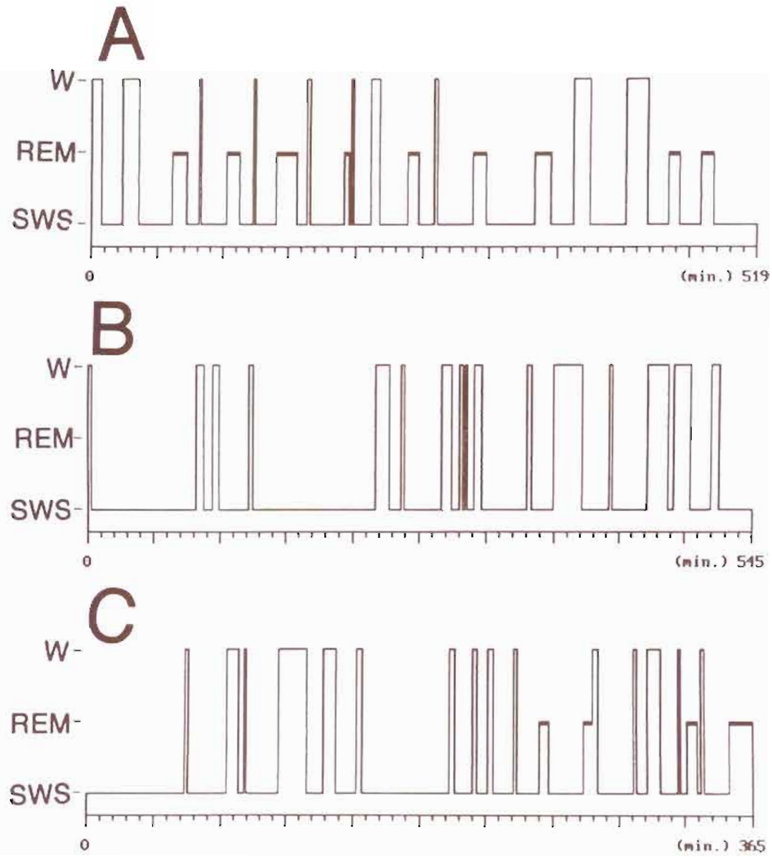

Fig. 10 - *Hypnograms of a representative case showing the profiles of waking (W), slow wave sleep (SWS), and REM sleep before (A), one day (B), and two days after the injection (C).*

Note that REM sleep was obliterated during the 24h observation period after the injection and that recovered 2 days post-operation.

Cortical activation as well as the other electrographic correlates of the activated behavioral state induced by CM injection (ocular movements, myoclonic jerks and PGO) are aspects of the orientation reaction. Eye movements are a form of attention, particularly in cats in whom states of alertness, in response to a novel stimulus, are independent of gross bodily movement. Myoclonic jerks are typical phasic orienting reflexes. PGO waves may be considered as components of an orienting or startle reflex (4). The associated eye-head events are typical orienting responses and indicate CM participation in the control of synergic eye and head movements during orienting, possibly through descending connections that may activate the tectoreticulospinal neurons known to be responsible for the generation of slow, postsaccadic eye movements as well as the accompanying neck EMG activity (10). Based on anatomical data, it has been proposed that "CM plays an important role in funneling to the neostriatum sensory activities which are related to the initiation, organization and execution of orientation-related postural responses" (23). As outlined in the introduction, CM projects to the sensorimotor and premotor cortices and has a striking anatomical relationship to the striatal structures (3, see also 20). Because of this anatomical organization, this thalamic cell population may play a role in bringing the basal ganglia-thalamocortical system to a higher level of activity, i.e. to a state of alertness. The privileged links with the striatum, known to be involved in experimental myoclonus (36), may also mediate the spontaneous myoclonic jerkings in the forelimbs and neck muscles, subsequent to bilateral ibotenic acid injections in the CM, but not observed after the CL injections.

Human neuropathological material led Schulman (40) to postulate a critical role of CM in the mechanisms of certain dyskinesias. That the mesial thalamic nuclei may play a central role in the genesis of myoclonic discharges was also suggested by Milhorat (31) on the basis of lesion experiments in the monkey. The fact that no EEG epileptic abnormalities preceded the myoclonic jerk suggests that a subcortical motor system could be primarily responsible for this manifestation of instability in the peripheral control system (dyskinetic movements). The bilateral ibotenate injections may have facilitated the appearance of the symptom since these nuclei do not connect with the contralateral counterparts (17).

Myoclonias and their EEG correlates induced by experimental chemical CM lesions in the cat have some resemblance to human nocturnal myoclonus. Brief, jerky contractions of a muscle or groups of muscles (so-called hypnic jerks) are normal in the course of falling asleep. The preferential targeting of CM to the striatum and other structures involved in the control of movements (e.g. subthalamic nucleus) suggests myoclonic discharges are involved in the control circuit, but the role of CM in movement-related activities merits further investigation. The loop system linking CM with the basal ganglia receives its most direct sensory input from structures such as tectum and vestibular complex, entopeduncular nucleus and pars reticulata of substantia nigra concerned with the organization and elaboration of orienting responses, particularly gaze shifts. The CM connections with the rostral mesencephalic tegmentum (35), known to contain a number of preoculomotor nuclei, may be the appropriate anatomical substrate for processing eye movements. That the intralaminar system is involved in processing visual information has long been proposed (39).

The anatomical location of cells whose activity was time-locked to saccades corresponds well with our injection. The eye movements occurred in waking and underwent the same state-dependent changes as nystagmus induced by vestibular lesion (1). Their amplitude became smaller and they often disappeared when the EEG became synchronized, and were profoundly modified during episodes of REM sleep. The concept that vestibular nystagmus can be elicited only during wakefulness had emerged from early studies in sleeping children (6).

The view of the intralaminar thalamus role in gaze mechanisms seems to contrast markedly with the traditional concept that the intralaminar system mediates activation of the cortical EEG. The present results support the role of the CM in processing eye movements and in cortical activation. Possibly CM exerts a double control: in the cortex (activation of frontal areas) and the basal ganglia (activation of structures involved in eye movements and myoclonus). CM neurons, while setting the appropriats cortical excitability, may create the readiness to respond and concomitantly participate in organizing ocular movements.

One possible interpretation of this effect can be proposed on the basis of elegant recording experiments in monkeys. Galletti *et al.* (7) suggested that since V3A gaze-dependent neurons appeared to show the same activities as seen in intralaminar neurons, the intralaminar system may be the best candidate as the source of eye position input for gaze-dependent cortical cells, and objective spatial maps may be present in the intralaminar nuclei. In normal conditions, the map would remain unchanged and the animal would perceive a stable visual environment, but when the cell excitability is strongly enhanced, for example, after infusion of ibotenic acid, the internal map would change and a sensation of object movement will be perceived. Hence eye movements would arise.

PGO waves released after ibotenic acid injection in the CM are similar to those induced by CL injection (26) and connections with the brainstem mesopontine structures (35) may be the anatomical substrate for their genesis, although they had different temporal distribution within the states. The release of clusters of PGO waves outside REM sleep dissociated from the other signs of paradoxical sleep is an example of state component dissociations reminiscent of human state dissociation syndromes. This question may be of clinical relevance since new clinical syndromes have been described (REM sleep disorders, status dissociatus (25), nocturnal periodic clonias (19) that challenge the association of the three cardinal physiological correlates: brain wave activity, eye movements, and muscle tone that no longer appear to label the behavioral states so constantly. PGO signals are not merely corollary discharges of eye movements, but are the central correlates of orientation reactions to stimuli from the outside world during waking, or to internal drives during REM sleep (4, 12).

The obliteration of REM during the first 24 h after the CM-injection was unexpected since it contrasts with the potentiation of REM after CL-injection. There may be an anatomical interpretation (28). Injection of a highly sensitive anterograde marker (biocytin) into the caudal intralaminar group of rats resulted in labeling of descending fibers in the brain stem and termination fields in the raphe system. If homology exists between rodents and felines in this system, the descending thalamus-raphe projections may mediate the obliteration of REM since the raphe cells are permissive of REM sleep (11).

The symptoms regarding the electrographic correlates of the activated state after CM injection also differed in several respects from those after CL injection, so it is tempting to speculate that the two intralaminar nuclei may exert a concerted action to regulate both the activated states and their electrographic correlates.

SUMMARY

1. The excitotoxin ibotenic acid was injected bilaterally into the intralaminar

centre médian nucleus of chronically implanted cats in order to study the effects of early excitation of centre médian population on electrographic correlates of behavioral states and to compare them to those induced by injection into intralaminar centralis lateralis nucleus, previously shown.

2. Immediately and during the first 24h after injection, highly aroused behavior with electrocortical activation, myoclonic jerks, enhancement of ocular movements and ponto-geniculo-occipital waves were observed.

3. Surprisingly, in contrast to the increase of REM sleep episodes in centralis lateralis cases, REM sleep was obliterated.

4. The injection sites were histologically confirmed. The different connectional properties of the two intralaminar population may explain the differential results.

5. In conclusion, the present behavioral observations and electrographic findings taken together with the known afferent and efferent projections suggest that the caudal group of intralaminar nuclei is involved in orienting-like behavior.

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