

Research report

Brainstem-mediated locomotion and myoclonic jerks. I. Neural substrates

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Abstract

Eleven of 40 decerebrated cats were found to exhibit periods of spontaneous or sensory induced myoclonus and locomotion beginning 24 h after decerebration. Histological analysis showed that the cats generating myoclonus had hemorrhagic lesions in the retrorubral nucleus (RRN) and ventral mesopontine junction (vMPJ). However, animals with intact RRN and vMPJ never showed myoclonus. To verify that the lesions were responsible for myoclonus, 6 additional cats received *N*-methyl-D-aspartate (NMDA, 0.5 M/0.5 μ l) injections in the areas of RRN and vMPJ to produce bilateral lesions. Coordinated rhythmic leg movement (locomotion) or myoclonic twitches developed in all of these cats beginning 3 hours after NMDA injection. These NMDA lesion-induced movements appeared either spontaneously (5 out of 6 cats) or after sensory stimulation (1 cat). Four cats received saline control injections in the RRN and vMPJ and did not have spontaneous, or sensory stimulation-induced, myoclonic twitches during the 48 h observation period. These results indicate that the RRN and vMPJ have a suppressive effect on myoclonic twitches and rhythmic leg movement. Dysfunction of these regions could release motor activity into sleep and waking states.

Keywords: NMDA; Retrorubral nucleus; Atonia; Twitch; REM behavior disorder; Narcolepsy; Periodic leg movement

1. Introduction

“Myoclonus” is a sudden, brief and involuntary muscular contraction. It can occur unilaterally or bilaterally and may be symmetrical or asymmetrical. Myoclonus is observed in the head, neck, trunk, and limbs. Myoclonic jerks can occur while falling asleep (nocturnal myoclonus) and in patients with cofactor deficiency (biotin, pyridoxine), metal dysmetabolism (copper, lead, magnesium), central nervous system lesion, intoxications, and metabolic abnormalities [6,21,29,33].

The mechanism of myoclonus is unclear. Neural substrates related to myoclonus may include spinal cord, brainstem, and cortex [22,36]. However, myoclonus has been observed in patients with no known cause and no other neurologic abnormality, although rhythmic myoclonus is usually associated with some pathology of the brainstem or spinal cord [7]. Swanson et al. [34] and Denny-Brown [10] hypothesized that myoclonus is due to the release of the brainstem from forebrain inhibition. We have found that electrical stimulation of the ventral part of

the mesopontine junction (vMPJ) produces muscle tone suppression during stimulation and locomotion during the interstimulus interval with repetitive stimulation [18]. In the course of our studies we noted that damage to this region appeared to be associated with a dramatic increase in the incidence of spontaneous myoclonus or stepping-like activity. Therefore, we undertook a systematic study of the effect of damage to this area on myoclonus and spontaneous movement.

2. Materials and methods

2.1. Surgical preparations

Fifty-one cats, 18 males and 33 females, weighing 2.5–4.5 kg were used. Animals were decerebrated at the precollicular-postmammillary level. Tracheostomy, ligation of both carotid arteries, cannulation of right femoral artery and vein, and decerebration were performed under halothane-oxygen anesthesia as described previously [17]. Halothane anesthesia was discontinued after removal of the forebrain. The tentorium was removed to expose the brainstem and cerebellum for electrical stimulation and

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microinjection. Muscles in the neck (both sides of occipitoscapularis, splenius, and biventer cervicis), both forelimbs (triceps brachii), and left hindlimb (gastrocnemius) were dissected and implanted with stainless steel bipolar electrodes for electromyograph (EMG) recording. Blood pressure was measured from the right femoral artery through a Statham transducer and data were collected only from animals with mean arterial pressure above 80 mm Hg. Rectal temperature was maintained at $38 \pm 0.5^\circ\text{C}$ through a heating pad regulated by a thermoregulator. EMG activity and blood pressure were recorded by a polygraph (Grass, Model 78D).

2.2. Stimulation and lesion

The animals' heads were fixed in the stereotaxic frame and stabilized on the recording table for the entire period of the experiment to prevent labyrinthine modulation of posture [28]. The limbs and torso rested in a prone position on the stereotaxic table, located 15 cm below the earbars. Ten hours after decerebration, electrical stimulation (500 ms trains with 100 Hz, 0.2 ms, and 20–70 μA rectangular cathodal pulses) was applied through a stainless steel monopolar microelectrode (A-M Systems, Model 5710) to identify the areas of RRN and vMPJ [18]. These areas were located 2.5–0.5 mm anterior, 2.5–3.5 mm from the midline, and dorso-ventral at -5.0 , according to Berman's atlas [5]. In our previous study [18] we showed that electrical stimulation in these areas produced global muscle tone suppression during stimulation, while stepping-like activity occurred in between stimulations. After the area was located, 0.5 μl of 0.5 M NMDA was microinjected into the vMPJ, bilaterally through a 1 μl Hamilton micro-

syringe (25 sG, Model 7001) in 7 cats. The injection rate was 0.1 $\mu\text{l}/\text{min}$ and the needle was retained in position for an additional 15 min. Four cats received 0.5 μl of Ringer's saline in the areas of RRN and vMPJ, bilaterally. Neither NMDA lesion nor saline injection was made in the other 40 cats.

2.3. Data collection

The occurrence of muscle twitches was recorded by polygraph. However, visual observation was also used to assess the extent of muscle jerks in facial, trunk and right hindlimb musculature, in which EMG electrodes were not implanted.

2.4. Histology

Sodium pentobarbital 35 mg/kg (i.p.) was administered to the animal before thoracotomy to suppress reflexes, and then the cats were perfused intra-cardially with saline followed by buffered formalin solution. The brainstem was removed and sectioned in the coronal plane at 60 μm . Staining with neutral red was used to identify the lesion area.

3. Results

3.1. Motor phenomena

Motor phenomena seen in the decerebrate cats after lesion could be separated into two categories, coordinated

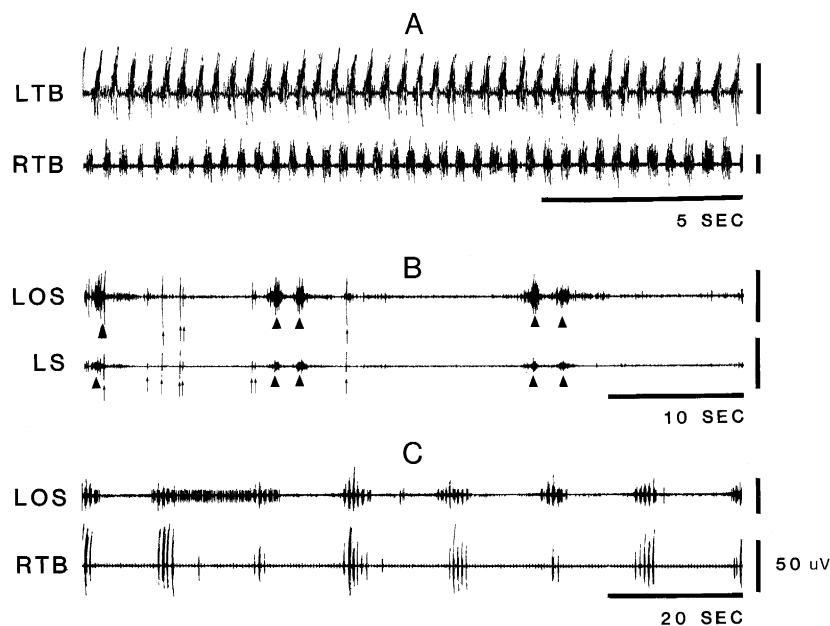


Fig. 1. Example of muscle hyperactivity in the decerebrate cat. Recordings were taken from 3 animals. A: stepping-like activity. B: a brief period of muscle twitches (arrow) and a longer tonic muscle contraction (arrowhead). C: "episode" of muscle twitches consisted of several muscle contractions at short intervals. LOS, left occipitoscapularis; LS, left splenius; LTB, left triceps brachii; RTB, right triceps brachii.

Table 1

The occurrence of muscle contractions and myoclonic twitches in 17 animals that had ventral mesopontine junction lesion

	<i>n</i>	%
Neck muscles	17	100
Shoulder	15	88
Forelimb		
Proximal end	14	82
Distal end	5	29
Unilateral forelimb	10	59
Bilateral forelimb	4	24
Hindlimb		
Unilateral hindlimb	6	35
Bilateral hindlimb	2	12
Facial muscles	11	65
Trunk	4	24

stepping-like behavior and rhythmic or non-rhythmic contractions of single muscles or muscle groups. Coordinated stepping-like activities (Fig. 1A) occurred in both forelimbs or in all four limbs. Rhythmic or non-rhythmic contractions could be subdivided into short muscle twitches of “myoclonus” and longer “tonic” contractions (Fig. 1B). Muscle contractions could occur repetitively in a short “episode” (Fig. 1C).

Myoclonus could be seen uni- or bilaterally in forelimbs and hindlimbs, uni- or bilaterally in the shoulder musculature or uni- or bilaterally in neck muscles. The most common location for myoclonus was in the neck muscles and the shoulder musculature, which occurred in 100% and 88% of the myoclonic episodes, respectively (Table 1). Tonic contractions were most commonly seen in the forelimbs. However, tonic contractions were also seen in the facial and trunk musculature (Table 1).

3.2. Spontaneous motor phenomena

On the second day after decerebration, 11 out of the 40 cats which did not receive any NMDA injections generated either spontaneous or mechanical/sensory stimulation-induced movement or myoclonic twitches. Of these 11 decerebrated animals, 8 exhibited spontaneous episodes of locomotion, 3 had auditory (finger snap, opening of sliding door to the recording room), tactile (light touching of the neck and back) and mechanical (electrode and needle penetration into the nucleus magnocellularis) stimulation-induced locomotion and/or myoclonic jerks, which persisted for 40 s to 10 min per stimulation. As shown in Fig. 2, insertion of a needle into the nucleus magnocellularis induced a decrease in muscle tone followed by locomotion. In all of these animals, it was found that the vMPJ and RRN were damaged bilaterally by blood penetration (Fig. 3C). In contrast, decerebrated animals with intact ventral mesopontine junctions never generated spontaneous locomotion or myoclonus ($n = 29$).

Hemorrhagic lesions in the dorsal part of the pons and/or dorsal midbrain were found in 8 of 40 cats without NMDA injection. Areas of neuronal degeneration included the superior colliculus, periaqueductal gray, dorsal mesencephalic reticular formation, and inferior colliculus (Fig. 3F). These cats never generated locomotion or myoclonus over the 5 day survival period.

3.3. Time course of motor activities induced by NMDA lesion

A high concentration of NMDA (0.5 M) injected into the rostral vMPJ produced a tonic suppression of tone in neck muscles contralateral to the injection site and both sides of forelimb muscles, 5 min (5.2 ± 0.38 min) after the

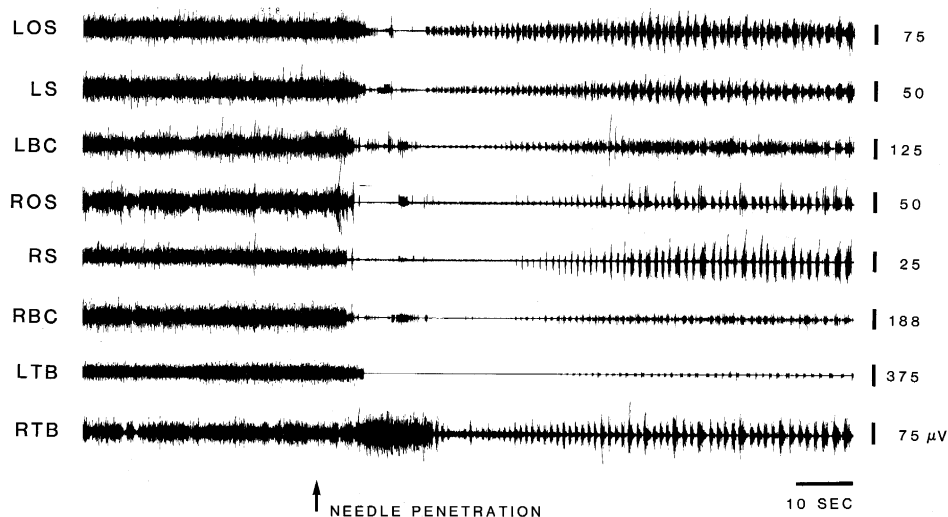
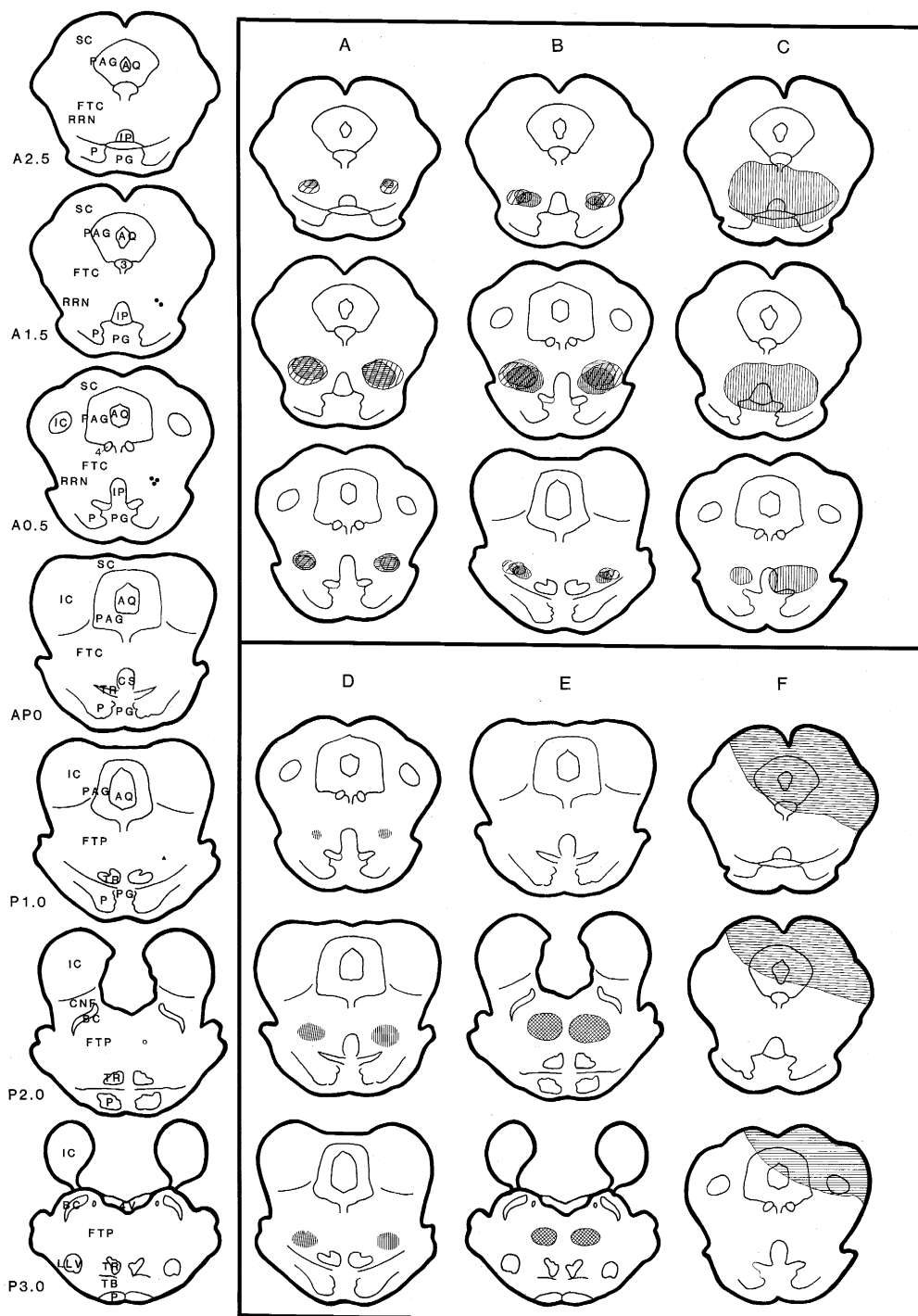


Fig. 2. Mechanical stimulation in the brainstem-induced locomotion. Needle penetration (arrow) into the nucleus magnocellularis of the medulla on day 2 post-decerebration produced decreases in muscle tone and followed by locomotion. LBC and RBC, left and right biventer cervicis.

start of the injection (5 cases, Fig. 4), while caudal vMPPJ injection (2 cases) did not change muscle tone. Starting 6 min (6.7 ± 0.92 min) after injection onset, contralateral forelimb extension accompanied by ipsilateral forelimb flexion (Fig. 4C) was visually and polygraphically observed in all cases studied and lasted for 70 min (65–80 min). Needle penetration into the contralateral rostral vMPPJ blocked forelimb extension and flexion (Fig. 4D) in 5 of 7 cases. If this introduced needle was then used to inject NMDA, the forelimb extension and flexion were reinstated

(Fig. 4E) at a 5 min (5.6 ± 0.87 min) latency. The frequency of these muscle contraction episodes reached a maximum 40 min after the second injection into vMPPJ with the episodes recurring with a mean frequency of 5.2/min (5.2 ± 0.21 /min; based on 5 cases). Ninety minutes after injection onset, a mixture of tonic contraction episodes and myoclonus was seen in the neck and forelimb muscles (Fig. 4F). By 2 h after injection, this pattern was replaced by a regular coordinated stepping-like activity in 4 of 7 cases. Spontaneous myoclonic twitching was found



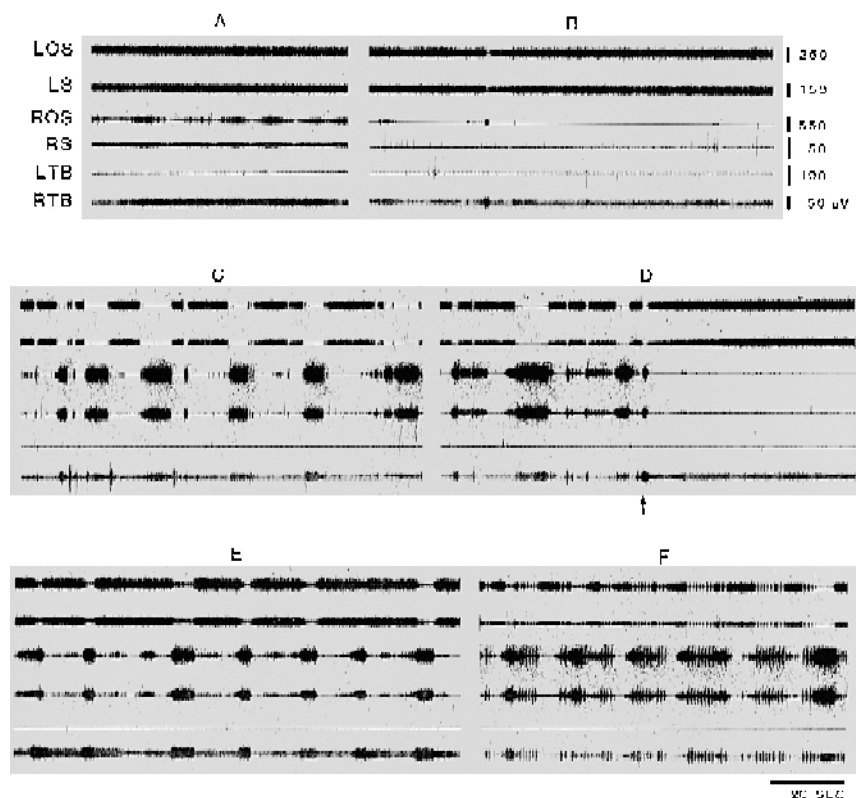


Fig. 4. NMDA effect on muscle activity. One half microliter of 0.5 M NMDA was injected into the ventral part of the mesopontine junction (vMPJ). A: baseline level of muscle activity. B: muscle tone slightly decreased 2 min after the end of NMDA injection into the left side of vMPJ. C: combination of short, brief muscle twitches with prolonged muscle contraction appeared 15 min after NMDA injection into the left side of RRN and vMPJ. D: injection needle inserted into the right side (arrowhead) of the vMPJ induced a cessation of muscle hyperactivity. E: hyperactivity reappeared 7 min after the second NMDA injection into right side of the vMPJ. F: a combination of myoclonus with prolonged muscle contraction reappeared 12 min after the second NMDA injection. ROS, right occipitospularis; RS, right splenius.

in 1 of the 7 cats. Histology showed that lesions in these 5 cats were localized to the vMPJ including the caudal portion of the ventral mesencephalic reticular formation, retrorubral nucleus, and ventral mesopontine junction (Fig. 3 and Fig. 5).

Of the other 2 NMDA injected cats, one developed muscle twitches in response to auditory stimulation and gentle touching the skin. This cat had a small lesion including vMPJ and adjacent regions of the paralemnisal tegmental field (Fig. 3D). Neither muscle twitches nor locomotion were found in another cat in which the lesioned area was located in the medial pons (Fig. 3E).

Saline injection in the vMPJ ($n = 4$) did not generate motor activity.

3.4. Histology

A high concentration (0.5 M) of NMDA produced neuronal degeneration during the 5 day duration of the experiment (Fig. 5). The lesion size produced by 0.5 μ l of 0.5 M NMDA was approximately 2.5 mm in diameter. The areas of neuronal degeneration which produced locomotion or muscle jerks were localized to the ventral part of the paralemnisal tegmental field, retrorubral nucleus, and

Fig. 3. Histological mapping showing lesions induced by either NMDA injection or blood penetration. Serial coronal sections shown on the left side of the figure represent the location of the center of the NMDA injection in each animal. Filled circles represent the cats that received an NMDA injection centered in the rostral ventral mesopontine junction and exhibited spontaneous movement. Filled triangle represents the cat that received NMDA injections in the middle portion of the vMPJ and produced sensory induced movement. However, no movement was found in the cat which received an NMDA injection in the mid-pons (open circle). A, B, D and E: shaded areas represent regions of neuronal degeneration induced by NMDA injections. A was taken from two cats that received NMDA injection at the A1.5 level; B was taken from 3 cats that received NMDA injections at the level of A0.5; D was taken from one cat which received NMDA injections at the P1.0 level; E was taken from one cat which received NMDA injections at the P2.0 level. C and F represent areas damaged by penetration of blood. Cats produced spontaneous movement when damaged areas included the vMPJ (C), while no movement was found when the damaged area was located in the dorsal part of the brainstem (F). AQ, aqueduct; BC, brachium conjunctivum; CNF, nucleus cuneiformis; CS, superior central nucleus; FTC, mesencephalic reticular formation; FTP, paralemnisal tegmental field; IC, inferior colliculus; IP, interpeduncle nucleus; LLV, ventral nucleus of the lateral lemniscus; P, pyramidal tract; PAG, periaqueductal gray; PG, pontine gray; RRN, retrorubral nucleus; TB, trapezoid body; TR, tegmental reticular nucleus; SC, superior colliculus; 3, oculomotor nucleus; 4, trochlear nucleus.

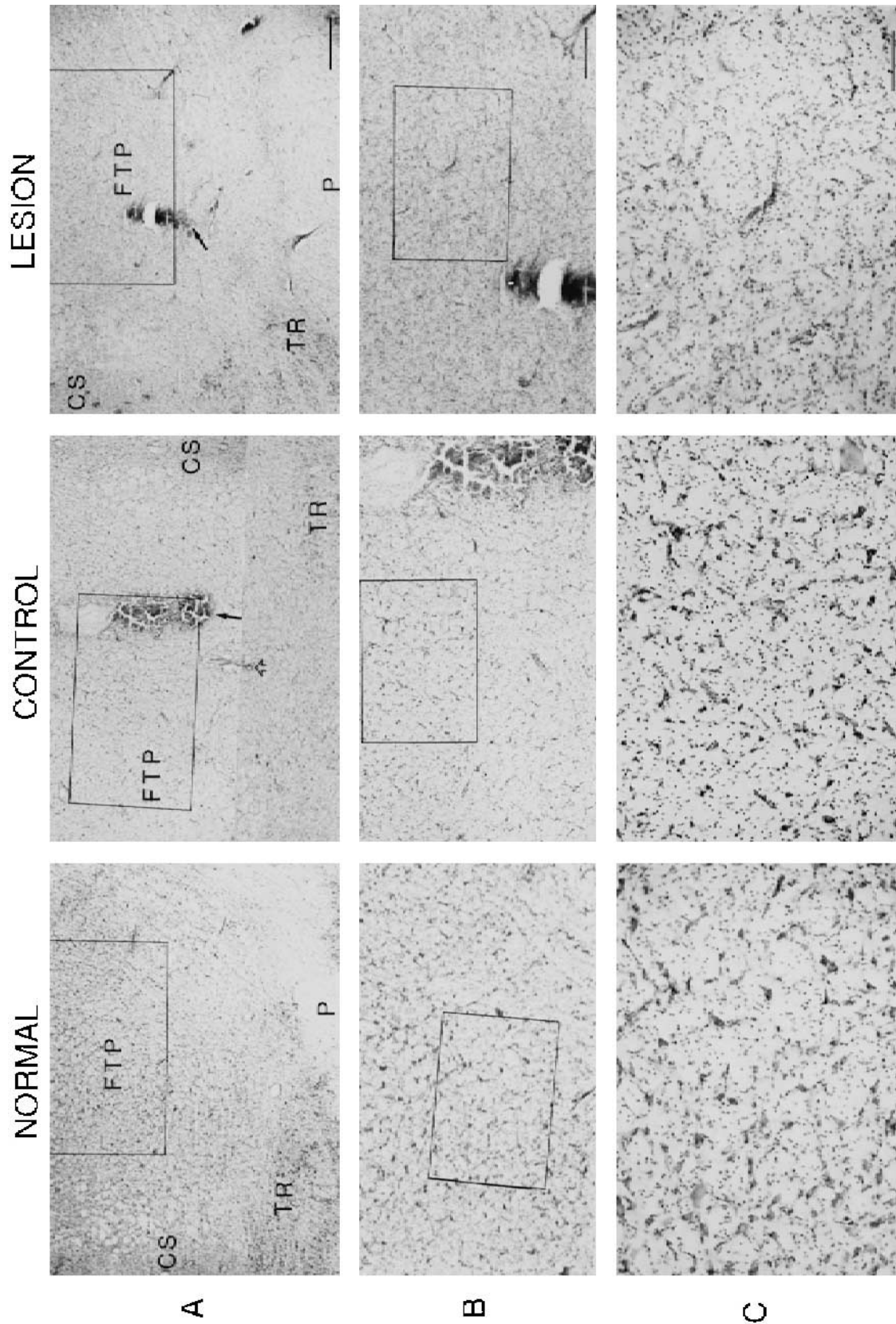


Fig. 5. Microphotographs showing neuronal degeneration induced by NMDA injection. The normal and control sections of the microphotograph were taken from the unoperated and saline injection cats, respectively. Solid and open arrows represent NMDA injection center and electrical stimulation site, respectively. A: low magnification microphotograph taken from the ventral portion of the mesopontine junction shows lesion area. B: a higher magnification of the rectangular areas of A. C: higher magnification of the rectangular areas of B. No neurons were seen in the lesioned animal. CS, superior central nucleus; FTP, paralemniscal tegmental field; TR, tegmental reticular nucleus. Calibration: A = 500 μm ; B = 250 μm ; C = 100 μm .

caudo-ventral mesencephalic reticular formation (Fig. 3A, B, D). However, cats which had lesions localized in the medial paralemniscal tegmental field never generated muscle hyperactivity (Fig. 3E).

4. Discussion

In the present study, we found that lesion of the RRN and vMPJ produced myoclonus and spontaneous locomotion in the decerebrate cat. Cats transected at the precollicular-postmammillary level with an intact brainstem or with dorsal brainstem lesions never generated this pattern of motor hyperactivity over the 5 day period of the experiment. However, animals prepared in the same way developed myoclonus and spontaneous locomotion if their ventral mesopontine junction was damaged by either chemical or hemorrhagic lesion. In these animals, myoclonus and locomotion could be elicited by sensory input, such as touching, tapping, and auditory stimulation.

In most cases, we saw a decrease in muscle tone immediately before the occurrence of locomotion and/or muscle jerks. Mori et al. [26], as well as our previous study [18], had found that an optimal level of muscle tone was necessary to generate locomotion. Clinically, muscle atonia occurring immediately before leg jerks has been reported in patients with periodic leg movement [22].

As early as 1922, Bazett and Penfield [2] found that cats transected at the level of mid-pons ventrally had spontaneous movement 2–4 days after decerebration. Similar results were also found in dogs by Keller [16] who reported that spontaneous running behavior developed in animals transected at the level of the rostral one-third of the pons. Cats transected at the mid-collicular level were reported to have rhythmic muscle jerks [8,32]. Cats generating myoclonus and locomotion in the present study had a common lesion in the area of the ventral mesopontine junction. In contrast, our precollicular-postmammillary decerebrate cats with either intact ventral mesopontine reticular formation or damage at the dorsal mesopontine junction never generated spontaneous or stimulus-induced movements over as long as 5 survival days. These results indicate that an intact vMPJ is critical to the control of muscle activity.

Clinically, the brainstem has been implicated in myoclonus. All posthypoxic or post-methyl bromide intoxication-induced myoclonic patients reported by Hauw et al. [14] had a pathological change in the mesencephalic reticular formation. Pathophysiological changes in the pontine reticular formation were also found in myoclonic patients with magnetic resonance imaging (MRI) [13] or CT scanning [27].

The retrorubral nucleus, A8 group of monoaminergic neurons [9], and ventral mesopontine junction contain dopaminergic [15,35] and glutamatergic neurons [19]. Retrograde transport of HRP combined with immunohisto-

chemical and fluorescence studies have shown that glutamatergic neurons project to the pontine reticular formation [19] and nucleus magnocellularis of the medulla [20], while dopaminergic neurons project to the caudate-putamen [11]. Clinically L-DOPA, which is a dopaminergic agonist, has been found to be the most potent pharmacological treatment for periodic leg movement (PLM) in sleep [3,23,24], suggesting that a dopaminergic mechanism is involved in PLM [25]. The present finding that lesion in the areas of RRN and vMPJ induces motor hyperactivity leads us to suggest that these areas participate in the control of periodic motor activity.

Our previous study [18] found that repetitive stimulation of the ventral part of the mesopontine junction produced muscle tone suppression. However, with repetitive stimulations, “spontaneous” locomotion appeared between stimulations when basal muscle tone was low. A similar phenomenon is also found in normal REM sleep in which phasic muscle twitches are superimposed on muscle atonia. Clinically, narcoleptic patients have a higher level of phasic muscle activities during REM sleep [12,31] and increased body movement in sleep [1,4], as well as increased occurrence of nocturnal myoclonus (periodic leg movement) and REM sleep behavior disorder. In REM sleep behavior disorder, abnormal motor activity and “dream re-enactment” occur during sleep. Muscle twitches persist in either slow wave sleep or REM sleep in affected patients when the basal muscle tone is low. Neuropathological studies have been negative in most of these cases. However, dysfunction of the pontomesencephalic region was found in some REM sleep behavior disorder patients [30]. Our present finding, that lesion of the RRN and vMPJ produces motor hyperactivity, suggests that degeneration or hypoactivity of this region may contribute to some movement disorders in waking and sleep.

Acknowledgements

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