Dorsal Frontal, Orbital and Mesial Frontal Cortical Lesion and Amygdaloid Kindling in Cats

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SUMMARY: *Bilateral anteromesial or orbital cortical lesions do not affect sequential pattern of amygdaloid seizure development. However, orbital cortex lesions appear to significantly participate in the elaboration of a Stage 6 seizure pattern.*

Amygdaloid kindling ipsilateral to the side of anterodorsal cortical lesion or in animals with the same bilateral lesion appears to predispose them for the development of spontaneous, nonconvulsive (partial complex) seizures. It also significantly modifies clinical ictal patterns with practical omission of Stages 2, 3 and 5, and largely lateralizes AD propagation to the stimulated hemisphere.

The latter two features are strikingly reminiscent of the electroclinical manifestations of secondary site AM kindling in intact animals or AM kindling in animals with forebrain commissure bisection.

Nonconvulsive (partial complex) status epilepticus was readily arrested by placement of electrolytic lesions ipsilateral to the AM stimulation, suggesting that MRF is essential for the perpetuation of the recurrent spontaneous seizure.

Finally, the presence and absence of positive and negative aftereffects respectively, in animals with anterodorsal cortical lesion is consistent with the view that transfer and interference effects are mediated through the brain stem and forebrain commissures respectively.

RÉSUMÉ: *Des lésions anteromédianes bilatérales ou du cortex orbital n'affectent pas le réroulement séquentiel du développement des crises de l'amygdale. Cependant, les lésions du cortex orbital semblent participer significativement dans l'élaboration de la Phase 6 des convulsions.*

Le "kindling" amygdalien ipsilatéral au côté de la lésion corticale anterodorsale ou chez les animaux avec la même lésion bilatérale

Semble les prédisposer au développement d'attaques spontanées, non convulsives (complexes partiels)

Modifie significativement le mode ictal clinique avec en fait omission des Phases 2, 3 et 5

Latéralise largement la propagation de AD à l'hémisphère stimulé.

Les deux dernières caractéristiques rappellent remarquablement les manifestations électro-cliniques de kindling du site AM secondaire chez les animaux intacts ou de kindling AM chez les animaux avec une bisection de la commissure antérieure.

L'état de mal épileptique non-convulsif (complexe partiel) est facilement contrôlé en plaçant des lésions électrolytiques ipsilatérales à la stimulation AM, suggérant que le MRF est essentiel à la persévérance des attaques spontanées périodiques.

Finalement, aucune des lésions corticales créée ne produisait d'effet sur le transfert. Les résultats sont compatibles avec l'hypothèse voulant que le transfert et les effets d'interférence sont transmis à travers les commissures du tronc cérébral et du télencéphale respectivement.

In 1972 Tanaka reported that rhythmic sharp waves in the frontal (presumably including the sensorimotor) cortex were coincident with the evolution of clinical motor manifestations during amygdaloid kindling in rabbits. He concluded that the participation of the motor cortex is indispensable for the expression of kindled amygdaloid seizures. Our experience of amygdaloid kindling in cats and baboons also showed electrographic evidence of early participation of the frontal cortices. Indeed, in both species, the onset of focal ictal manifestations involving the contralateral body parts was coincident with the development of spike and sharp waves in the frontal-central cortical areas (Wada & Sato, 1974; Wada & Osawa, 1976). However, electroclinical manifestations of progressive seizure development resulting from frontal cortical kindling in cats and baboons were considerably different from those of amygdaloid kindling, suggesting that the frontal cortex participates in, but is not essential for amygdaloid seizure development (Wake & Wada, 1975; Wada, Osawa & Mizoguchi, 1975). Such an assumption was further supported by the effect of frontal cortical lesion upon amygdaloid kindling in rats (Corcoran, Urstad, McCaughran & Wada, 1975). In order to clarify the possible role of anterior neocortical areas in amygdaloid kindling, we have examined the effect of ablative cortical lesions upon amygdaloid seizure development in cats.

MATERIALS & METHODS

Sixteen male cats weighing 3.5 - 4.6 kg were used. Under nembutal anesthesia a sterile surgical lesion was created immediately preceding

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the implantation of a permanent electrode in 13 cats, while another cat received a combined frontal-cortical lesion and forebrain bisection under direct vision about two months prior to the electrode implantation. Bipolar recording electrodes were made by attaching a stainless steel wire 0.19 mm in diameter to No. 30 stainless steel tubing, insulated except at the tips with an interelectrode distance of 1 mm. The stimulating electrode was the same stainless steel wire, insulated except for 1 mm at the tip, and attached to the recording electrode. Electrodes were implanted bilaterally into the lateral amygdala (AM), hippocampus (HP), septum (SEP), pyriform cortex (PYR), nucleus centrum medianum (NCM), nucleus ruber (NR), and the midbrain reticular formation (MRF). A left dorsal cortical lesion was created in seven cats, one of which was also subjected to forebrain bisection as mentioned above Bilateral dorsal, mesial and orbital lesions were created in three cats each. The unilateral dorsal cortical lesion produced transient weakness of the contralateral extremity, but recovery appeared complete within one month. Recovery of bilateral lesioned animals was slow, and four cats, one from both the dorsal and mesial groups, and two from the orbital group, had to be discarded due to their unsatisfactory general physical condition. Particularly, the bilateral orbital lesion animals showed significant behavioral alteration with

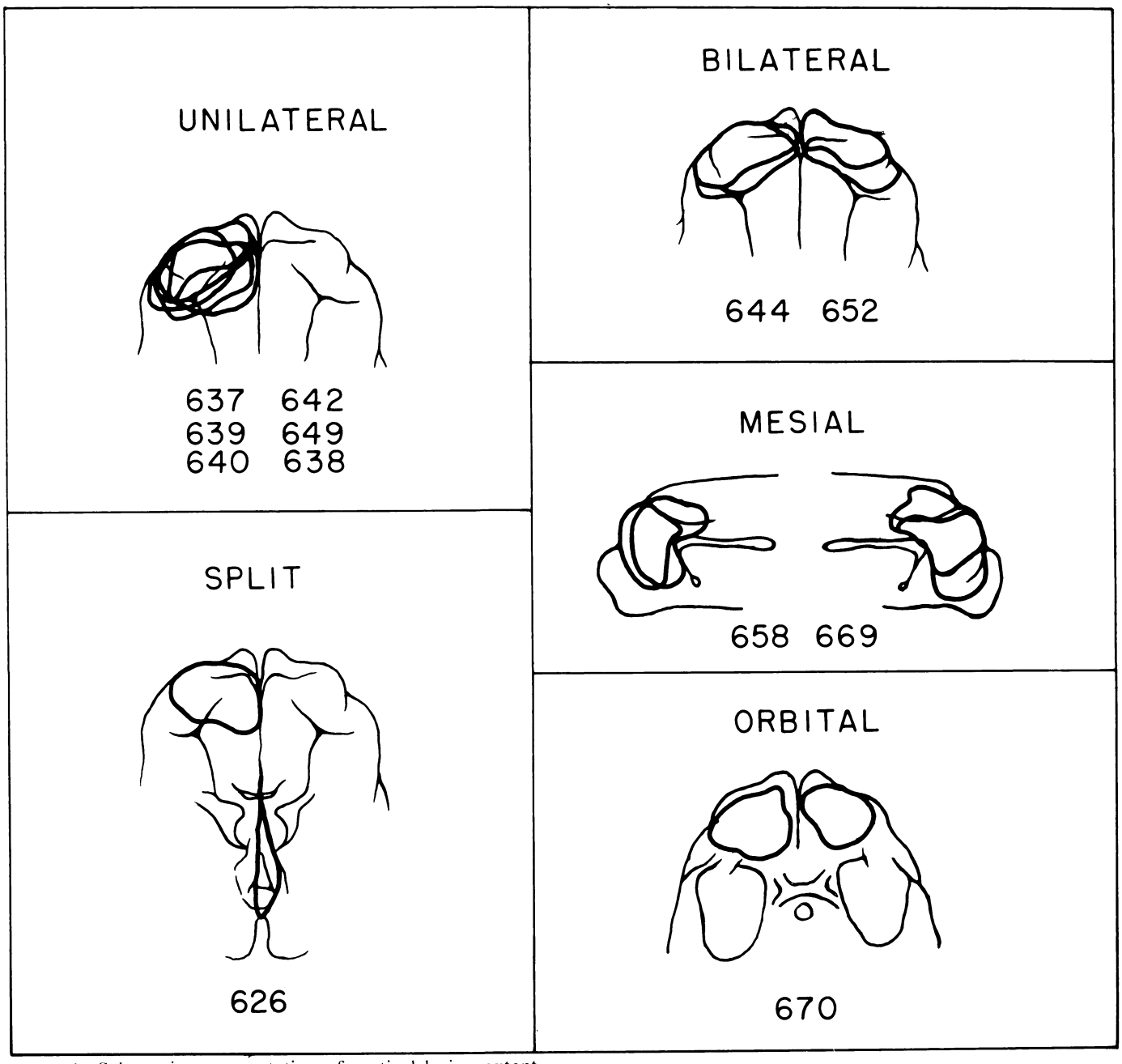

Figure 1—Schematic representation of cortical lesion extent.

hypokinesia and immobility and a progressive loss of weight in spite of a good appetite. The bilateral mesial lesion animals showed considerable taming and perseverative motor behavior. As shown in Fig. 1, the dorsal lesion group showed almost complete destruction, including Areas 4 and 6. Forebrain bisection was complete, involving corpus callosum, septum and the anterior commissure. The mesial lesion group showed destruction of Areas 12 and 32 as well as the anterior cingulate region. One month following electrode implantation, AM stimulation was delivered monopolarly once a day with 60 Hz sine waves lasting for one second. The intensity of the stimulus was regulated by a Grass constant current unit for one second. Stimulation began with 100 μ A initially, followed by 200 μ A and subsequent daily increases of 50 μ A steps until elicitation of an electrographic afterdischarge (AD) localized to the site of the stimulation. On each subsequent day, the stimulus intensity was set at 50 μ A less than that of the previous day until AD could no longer be elicited. The lowest intensity that produced afterdischarge was regarded arbitrarily as the afterdischarge threshold (ADT).

The animals were placed in an observation chamber (46 x 90 x 65 cm) with a one-way mirror. The electroencephalogram was recorded on either an 8 channel or 10 channel Grass machine, and stimulation delivered at least ten minutes after the animal assumed a resting posture, subsequent to the commencement of monitoring within the chamber. When a final Stage 6 convulsive seizure developed, the stimulation was repeated for five more days, then the stimulus intensity was gradually reduced until the animal ceased to respond with a generalized convulsive seizure. The stimulus intensity on the day before the disappearance of the behavioral convulsive response was designated as the generalized seizure triggering threshold (GST). The all-or-none property of the GST was ascertained by the observation that the intensity below the critical GST did not produce any electroclinical seizure manifestations. Secondary site kindling was performed in some animals fol-

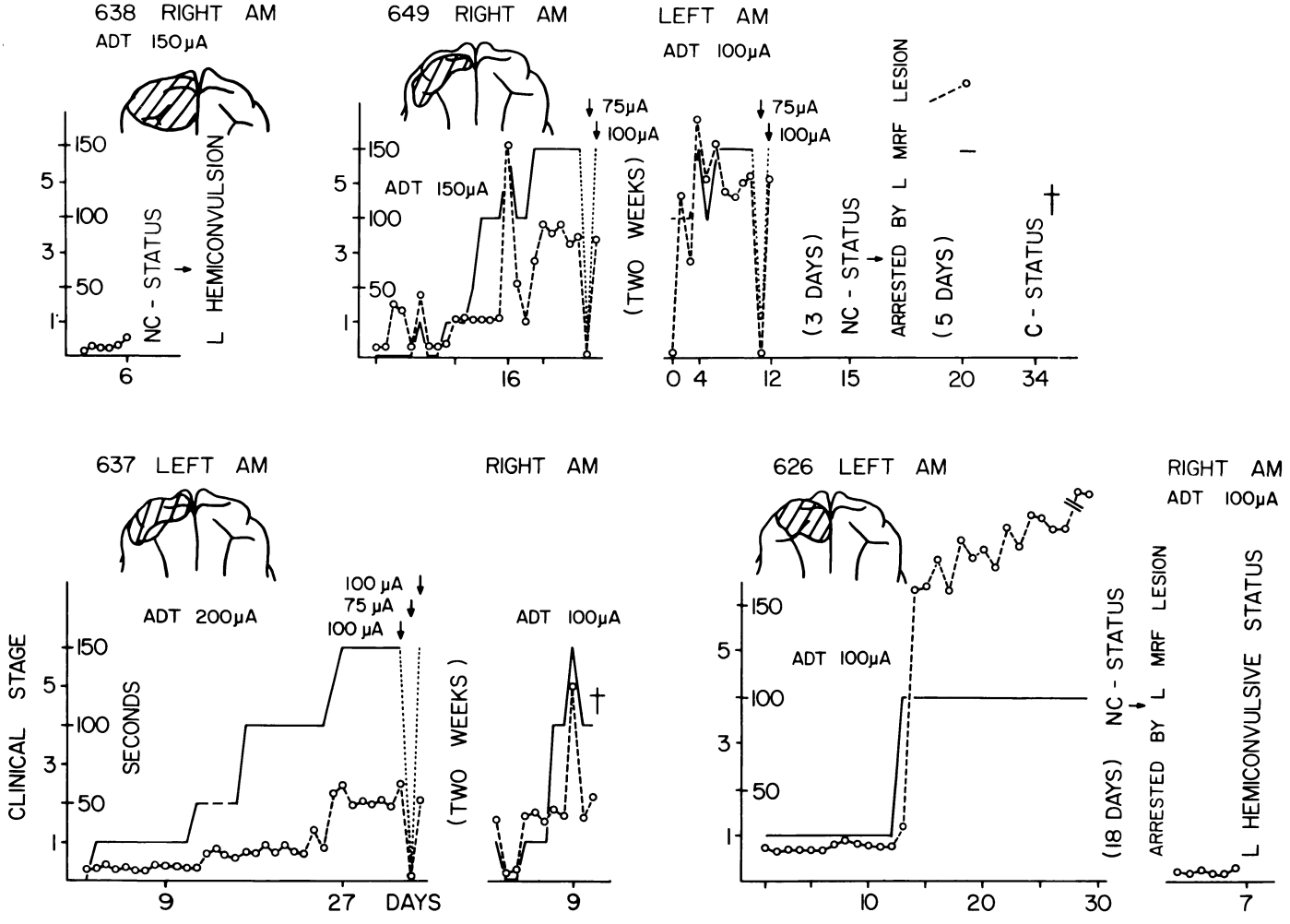

Figure 2—Profile of amygdaloid seizure development following ipsilateral (Cat 637, 626) and contralateral (Cat 638, 649) dorsal cortical lesion. Broken line of clinical Stage 2 indicates incomplete and atypical pattern. For explanation, see text.
NC — status: nonconvulsive (partial complex) status epilepticus; C — status: convulsive status epilepticus.

TABLE I

Summary of cortical lesion effect upon amygdaloid kindling

CORTICAL LESION	UNILATERAL (Left) ANTERIOR LESION							BILATERAL ANTERIOR		BILATERAL MESIAL		BILAT. ORB.
AM Stimulation	RIGHT			LEFT			Split	LEFT		RIGHT		RIGHT
Animal Number	638	640	649	637	639	642	626	644	652	658	669	670
AD Threshold (μa)	200	100	150	200	200	100	100	100	150	200	100	100
Number of Stimulations in each Stage 1		8	7	10	8	3	12	14	2	4	4	7
Number of Stimulations in each Stage 2		1	4	5	0	9	0	9	0	10	4	4
Number of Stimulations in each Stage 3		2	1	0	0	0	0	0	0	3	3	1
Number of Stimulations in each Stage 4		3	3	9	5	9	17	15	34	3	13	12
Stage 6 Seizure: Latency (day)		22	16	27	17	28		41		24	25	28
Stage 6 Seizure: Total number	6 *	2	8	17	20	19	29 **	11	37 **	6	8	7
GST (μa)			100	100	100	50		100		100	50	75
Status Epilepticus	NC(R)	?	C(R) NC(L)+		?		NC(L) C(R)+		?			

* = Stage 0 only
** = Stage 4 only
( ) Side of AD origin
R = Right
L = Left
AD Afterdischarge
C = Convulsive
NC = Non-convulsive
GST Generalized seizure triggering threshold
AM = amygdaloid
\+ = following secondary site AM stimulation
? circumstantial evidence of spontaneous seizures

lowing the completion of primary site kindling, usually within a two-week interval unless otherwise specified. Upon completion of this study all the animals were sacrificed under deep pentobarbital anesthesia. The extent of their cortical lesions is summarized in Fig. 1. Their brains were embedded in paraffin, serially sectioned (15 μ A), and stained with cresyl violet. Histological examination showed the stimulating and recording electrodes to be in the intended structures.

RESULTS

Findings are summarized in Table 1. Representative profiles of seizure development are shown in Fig. 2 & 3 and details are given below.

A) Dorsal Cortical Lesion

1) Contralateral AM kindling in animals with left cortical lesion (Cats 638, 640 & 649)

With daily stimulation, both 640 and 649 reached Stage 6 in 16-22 days with progressive recruitment of seizure manifestations as in intact animals. Briefly, initial facial twitching occurred ipsilateral to the stimulating site (Stage 1), then gradually became bilateral (Stage 2); head-nodding developed (Stage 3) followed by tonic extension of the contralateral forepaw associated with contralateral head-turning and rapid circling (Stage 4), clonic jumping while standing (Stage 5), and then falling down with generalized tonic-clonic convulsion (Stage 6). The only significant deviation from the usual pattern of seizure development was that, in Stage 3, head-nodding changed to side-to-side head-rolling without the usual rhythmic neck extension. Similarly, Stage 5 was practically missed since the animals fell down as soon as the jumping started and went into a Stage 6 generalized convulsion.

The pattern of AD dissemination was identical to that elicited in intact animals, with early generalization in Stage 2, development of independent AD into the hippocampus in Stage 2 and midbrain reticular formation in Stage 3, with subsequent propagation into the contralateral midbrain reticular formation. Further propagation into the contralateral amygdala was coincident with the progressive recruitment of clinical seizure manifestations to reach the Stage 6 seizure. The AD pattern which developed during this seizure is shown in Fig. 4 (Cat 640 — top row).

Cat 638 was stimulated at an ADT of 200 μ A for seven days with AD duration of 4-11 seconds without any clinical seizure development. Twenty-four hours after the last stimulation, this animal was found to have prolonged episodes of sniffing, visual searching, running and circling towards the right or left with profuse salivation and maximally dilated pupils. Electrographic monitor-

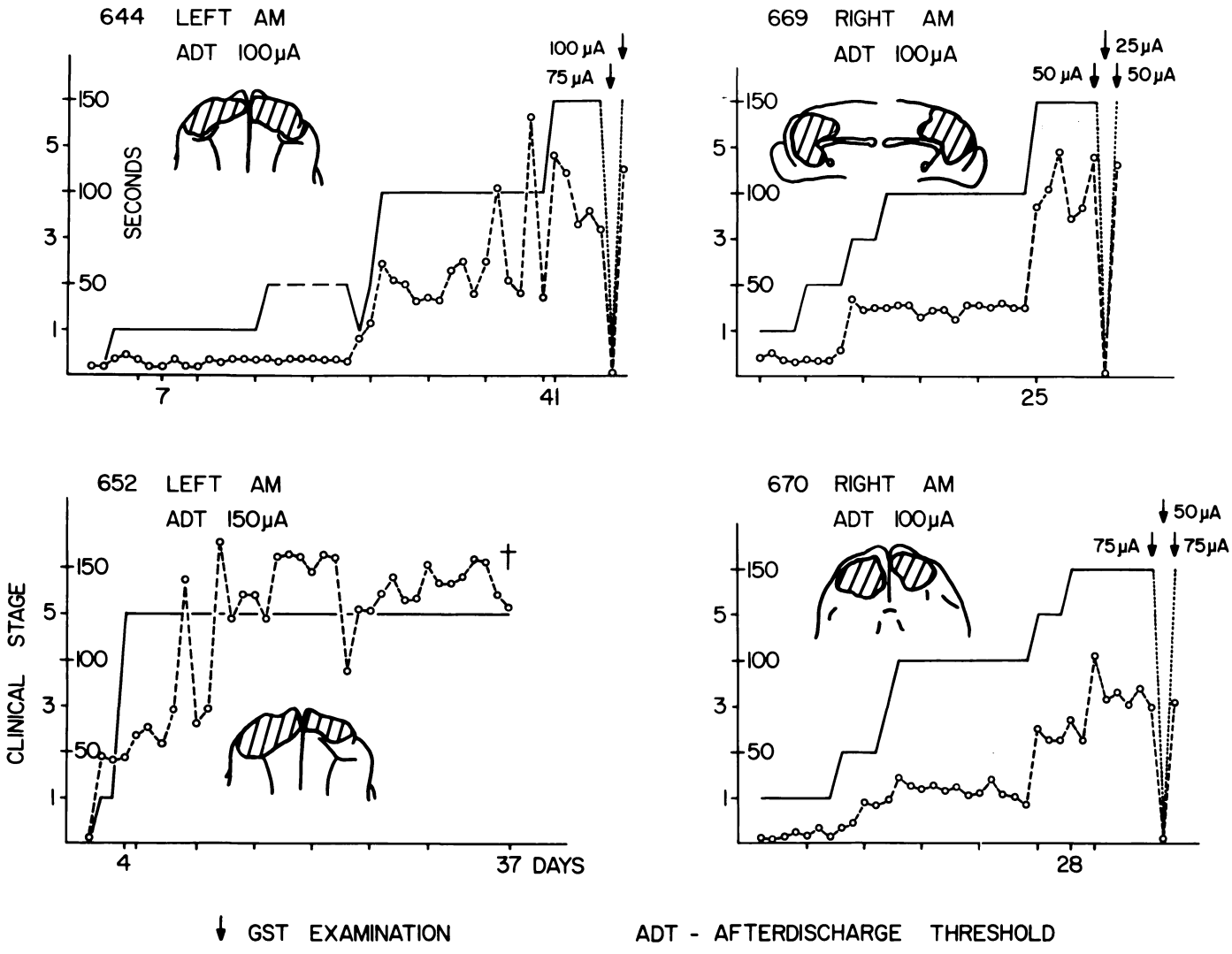

Figure 3—Profile of amygdaloid seizure development following bilateral dorsal (Cats 644, 652), mesial (Cat 669) and orbital (670) lesions. Note extremely prolonged process of seizure development in dorsal lesion groups in contrast to relatively normal pattern of development in mesial (Cat 669) and orbital (Cat 670) animals. Broken line in clinical Stage 2 Cat 644 indicates atypical and incomplete pattern.

ing showed the origin of the seizure to be within the right limbic structures, with ready propagation to the basal ganglia and the midbrain reticular formation. When it finally developed a clonic seizure involving the left extremities, there was widespread AD propagation over the right hemisphere involving the anterior neocortical areas. Repeated administration of taurine up to 2 gm/kg was without effect.

Cat 649 was subjected to secondary site kindling following the termination of right-side kindling. Stage 6 seizure was reached in four days with a pattern of seizure identical to that of ipsilateral kindling with a left cortical lesion to be described below. Three days following the determination of GST, this animal developed non-convulsive status epilepticus with profound salivation, pupillary dilatation, licking, chewing, rhythmic tongue protrusion with frequent head-turning to the right. Continuous electrographic discharge was observed, largely within the left hemispheric structures. Placement of an electrolytic lesion in the left MRF aborted the electroclinical status. However, when the left AM was stimulated at the GST of 100 μ A, five days later, this animal responded with a Stage 6 seizure. Two weeks later this animal developed another spontaneous episode of copious salivation, licking, chewing and circling to the left with the eventual development of Stage 6 convulsive seizure. Onset of clinical seizure was coincident with the emergence of sustained electrographic discharge within the right hemispheric structures, maximal at AM, HIPP, PYR and GP with ready propagation to the MRF.

2) Ipsilateral AM kindling in animals with left cortical lesion (Cats 637, 639, 642)

These animals developed the final

stage seizure within 17-28 days. However, there was a significant alteration in the pattern of clinical seizure development, with modification of all the seizure stages except for Stage 1. During Stage 2, the animals showed only irregular and slow blinking of the right eyelid in contrast to rhythmic ipsilateral facial twitching. The pattern of Stage 3 was characterized by atypical side-to-side head-rolling without the usual neck extension. During Stage 4, the animal showed contralateral head-turning and circling, but unlike the rapid tight circling in intact animals, lesioned animals made a frequently interrupted and loose pattern of circling while displaying profuse salivation, mastication, licking and sniffing. With the commencement of clonic jerking (in contrast to the tonic extension in intact animals) of the contralateral forepaw, the direction of head-turning changed ipsilaterally, with the subsequent development of severe clonic jerking in the ipsilateral extremity and the inability to stand up, followed by a Stage 6 generalized convulsion, which lacked a clear tonic component.

In contrast to the contralateral kindling group, the AD pattern was largely lateralized to the stimulated hemisphere. Propagation within the stimulated hemisphere was considerably restricted and the emergence of a unique independent afterdischarge in the midbrain reticular formation was not observed (Fig. 4 — bottom row). AD propagation to the contralateral amygdala was delayed until well beyond Stage 4. Emergence of independent AD in the contralateral amygdala in Stage 6 was coincident with the development of predominantly left-sided generalized convulsion. When compared with the contralateral group, there was less prominent fast spike discharge during Stage 6 seizure.

Cat 637 was subjected to secondary site kindling after the termination of left amygdaloid kindling. The animal developed Stage 6 seizure on the eighth day [which is within the normal range of 1-10 days (Wake & Wada, 1976)] but regressed to Stage 4 on the following two days. Unlike

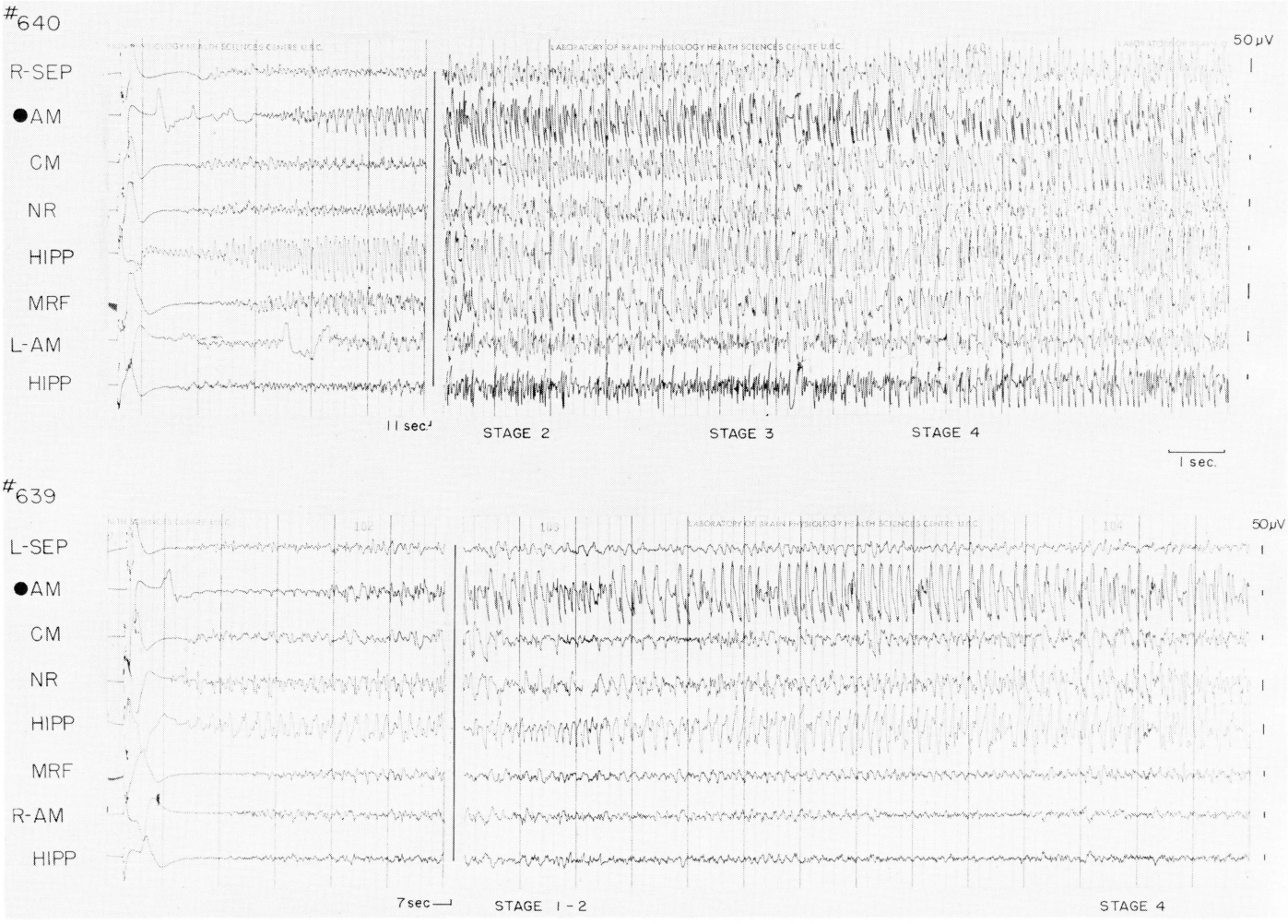

Figure 4—Electrographic feature of amygdaloid seizure development. Top Row: AM stimulation contralateral to dorsal cortical lesion results in early AD generalization and sequential ictal clinical development. Bottom Row: AM stimulation ipsilateral to dorsal cortical lesion. Note largely lateralized AD and poverty of MRF involvement. Clinical Stage 2 was atypical and inconspicuous.

the primary site kindling, the electroclinical pattern of developing and developed seizure of secondary site kindling was identical to that of contralateral AM kindling with left cortical lesion (modification of Stage 3 and omission of Stage 5). Thus, this animal lacked the unique secondary site kindling feature of missing Stages 2, 3 & 5, which was evident in intact animals (Wada & Sato, 1974) suggesting the critical importance of the anterior dorsal neocortex for the phenomenon of post-transfer interference.

3) Ipsilateral AM kindling in an animal with left cortical lesion and forebrain bisection (Cat 626)

This animal reached Stage 4 seizure on the 13th day (Fig. 2). During the subsequent 29 days, the animal continued to display extremely prolonged Stage 4 seizure pattern, often lasting for more than four minutes. The Stage 4 contained 'normal' Stage 1, but incomplete and modified Stage 2 & 3 patterns, as in the case of ipsilateral kindling described above. About one hour after the last stimulation which resulted in Stage 4 seizure, this animal developed status epilepticus with constant sniffing, licking, chewing and copious salivation and intermittent running towards the right. Since this condition was not significantly changed by repeated administration of a large quantity of taurine and only a transient effect could be obtained by giving phenobarbital or diazepam, an electrolytic lesion was placed in the left midbrain reticular formation through an acutely-inserted lesion electrode about 23 hours following the onset of the partial complex status epilepticus. This MRF lesioning aborted the electroclinical seizure. Curiously, there was an emergence of some spike activity in the right amygdala which gradually disappeared within 24 hours. Subsequently, there was a re-emergence of intermittent "Jack-in-the-box' electrographic sustained discharge within the left hemispheric structures which gradually dissipated over the next three weeks. There were no overtly apparent behavioral correlates of such a sustained electrographic discharge. Twenty-one days later, after the uneventful clinical recovery of this animal, secondary site kindling began with 100 μA stimulation with resultant AD lasting for two to three seconds. There was no clinical seizure development for six days. Approximately 20 hours following the sixth stimulation, this animal was found to be hissing, non-responsive to environmental stimuli, and subsequently developed a primarily left-sided clonic convulsion. Electrographic discharge was largely lateralized to the right hemispheric structures, with some recurrence of previously noted left-sided and independent sustained discharge. The repeated administration of taurine up to 2 gm/kg was ineffective.

4) Left AM kindling in animals with bilateral cortical lesions Cats 644 & 652

Cat 644 reached the final Stage 6 on the 41st day, while 652 reached Stage 4 on the fourth day and continued to display a Stage 4 pattern until the 37th day. Except for the complete omission of Stage 3 in this group, the pattern of clinical seizure development was identical to that of ipsilateral kindling described above. During Stage 4, the animals displayed a minimal tendency to circle with profuse salivation, sniffing, chewing, licking and marked pupillary dilatation. Contralateral head turning was present but tonic extension of the contralateral forepaw was replaced by clonic jerking. This was followed by the development of contralateral hemiconvulsion or feeble and contralaterally-dominant bilateral clonic seizure without tonic component. The sequence of electrographic events was identical to the ipsilateral kindling except for the fact that the amount of fast spikes during Stage 6 was the least conspicuous among all the groups studied.

About 20 hours following the 37th stimulation which resulted in Stage 4 seizure, Cat 652 was found immobile with pupillary dilatation and urinary incontinence and was almost entirely oblivious to painful stimuli. There was a significantly increased rate of interictal spike discharge diffusely, particularly within the left hemispheric structures, but no sustained afterdischarge was present. Repeated administration of taurine 2 gm/kg was ineffective.

B) Bilateral Mesial Cortical Lesion (Cats 658 & 669)

Both the animals reached the final Stage 6 on the 24th day and the 25th day of stimulation, which is close to the normal mean of 25.5 days (Wada & Sato, 1974). The pattern of electroclinical seizure development and the developed seizure was identical to that of intact animals.

C) Bilateral Orbital Lesion (Cat 670)

This animal reached the final Stage 6 on the 28th day of stimulation. The sequence and the pattern of clinical ictal events were identical to those of intact animals, except for the final Stage 6 generalized convulsion, which was often abortive with irregular clonic jerking only, as in the case of bilateral dorsal cortical lesioned animals. The pattern of electrographic seizure development was significantly different from that of intact animals, with a tendency for lateralized discharge within the stimulated hemisphere, an absence of emergence of independent MRF discharge, and a striking poverty of fast spikes during Stage 5 convulsion.

D) Afterdischarge Threshold and GST

As shown in Table 1, ranges of AD threshold and GST were 100-200 μA and 50-100 μA respectively. This finding is comparable to that observed in intact animals (Wada & Sato, 1974).

DISCUSSION

Among all the lesioned groups studied, mesial cortical lesion had no significant effect upon the electroclinical pattern of seizure development or developed seizures, suggesting that this area does not participate in the process of amygdaloid kindling. Although findings in the dorsal cortical lesioned animals were all

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similar, there was a considerable variation depending on the laterality of the amygdaloid kindling with respect to the side of the cortical lesion, with or without forebrain bisection or with bilateral lesion. Presumably, the interruption of commissural pathways in the forebrain bisected animal (Cat 626) is comparable to bilateral cortical lesion in that there was no direct commissural access to the contralateral homologous cortical areas in the former. Except for the contralateral kindling group, all the animals showed an incomplete Stage 2 pattern, with obscure ictal involvement of the contralateral facial muscles, a modified Stage 3 pattern with head-rolling, and the omission of Stage 5 pattern. All of these manifestations are strikingly similar to those of secondary site kindling in intact animals (Wake & Wada, 1976). In addition, significantly modified and reduced motor components of a prolonged Stage 4 seizure pattern as well as markedly diminished Stage 6 motor seizure intensity were noted in animals with bilateral dorsal lesion, or ipsilateral kindling with dorsal lesion and forebrain bisection. The electrographic features of the predominantly lateralized afterdischarge, the lack of or poor development of independent MRF discharge, the delayed ictal involvement of the contralateral AM, and the reduced fast spike discharge during Stage 6 are all consistent with the assumption that the ipsilateral dorsal cortex plays a role in the generalization of AD originating from the AM and its propagation into the brainstem. This is not surprising since preferential propagation of AD into the sensory motor cortex was reported to occur following basal AM stimulation in cats (Goodfellow & Niemer, 1961). More recently, the frontal cortex has been shown to receive direct projections from the amygdala (Kretteck & Price, 1974; Jacobsen and Trojanowski, 1975).

Although the bilateral orbital lesioned animals showed a normal seizure development except for the significantly diminished Stage 6 seizure intensity, the pattern of electrographic seizure development was similar to that of the bilateral dorsal cortical lesioned animals. This finding suggests that orbital cortical areas are not essential for sequential ictal clinical development, but they participate significantly in the elaboration of a Stage 6 seizure pattern, probably in part through the common (forebrain-brainstem?) mechanism shared with the dorsal cortical areas.

On the other hand, the absence or significant alteration of the Stage 3 and 5 pattern in dorsal cortical lesioned animals, regardless of the side of kindling, suggests that the dorsal cortex of both hemispheres participates in the patterning of Stage 3 & 5. Similarly, the preservation and modification of the Stage 2 pattern in the contralateral and ipsilateral kindling groups, respectively, suggests that the rhythmic contralateral facial twitching of Stage 2 may be primarily due to the activation of the ipsilateral dorsal cortex. However, our previous observations of normal Stage 2 patterns in animals with bisected corpus callosum, but intact anterior commissures, suggest that the AM can also contribute to the Stage 2 seizure pattern. The lack of tonic extension in Stage 4 and the predominantly asymmetrical or reduced intensity of Stage 6 in the ipsilateral kindling group further corroborates the significance of ipsilateral dorsal cortical participation in the elaboration of clinical seizure pattern.

The predominantly lateralized AD and the lack of independent MRF discharge in those animals with ipsilateral dorsal, bilateral dorsal or orbital lesions (in contrast to contralateral dorsal lesions) suggest that the dorsal and orbital cortex contribute significantly in the horizontal as well as the vertical dissemination of AD. That the horizontal (cortico-cortical) ictal transmission through the callosal pathway may be responsible for the phenomenon of post-transfer interference is suggested by a lack of electroclinical evidence of such interference during the secondary site kindling in the animals with unilateral dorsal lesion regardless of its laterality. This finding is in contrast to the development of clear positive aftereffect; that is, transfer regardless of whether the lesion side or the intact side was kindled first. These findings are consistent with the assumption that transfer and interference effects are mediated through the brainstem and the forebrain commissures, respectively (McIntyre et al., 1975; McCaughran, 1976).

Delay of the onset of Stage 6 convulsion in animals with bilateral dorsal cortical lesions requires some comment. One animal reached Stage 6 on the 41st day and another animal remained in Stage 4 until the 37th day when it developed partial complex status epilepticus: these latencies are beyond the normal range of 15-36 days for completion of amygdaloid kindling (Wada & Sato, 1974). In addition, the forebrain bisected animal developed nonconvulsive partial complex status epilepticus on the 29th day with a modified pattern of seizure Stage 4. The latter finding is in contrast to a significantly accelerated amygdaloid seizure development in animals with an intact dorsal cortex but with forebrain bisection (Wada & Sato, 1975a). The fact that the animal with the bilateral lesion can reach the final Stage 6 suggests that the anterior neocortex is not essential for the evolution of the final Stage 6 seizure. However, the present findings clearly indicate that the anterior dorsal neocortex has a significant role to play in the process of sequential motor seizure development during amygdaloid kindling.

Among more than 150 cats used for amygdaloid kindling in this laboratory so far, nonconvulsive status epilepticus was observed only in the present series of experiments. Of three animals with verified status epilepticus, two developed a nonconvulsive partial complex status epilepticus from stimulation of the amygdala with ipsilateral dorsal neocortical lesion (Cats 626 & 649). The same two animals developed convulsive status epilepticus coincident with the onset of electrographic seizure discharge from the intact

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hemisphere. This finding implies the significance of the dorsal neocortex in the development of convulsive status epilepticus following AM kindling which seems relevant to our understanding of the seizure patterns of human epilepsy. We are all familiar with the fact that patients with epileptogenic focus in the temporal lobe may manifest a variety of nonconvulsive seizures, convulsive seizures, or both, although the presence of generalized convulsive seizure may be conceived as a reflection of more severe, generalized propagation of epileptic discharge (Brazier) Crandall & Walsh, 1976). The reason for such variation in the pattern of seizure is not well understood when EEG examination may show a localized focus in the temporal region. If we exclude cases with multifocal abnormalities, it is possible that convulsive seizures of temporal lobe origin reflect pathologically facilitated ictal linkage, based upon genetic, acquired or combined factors between the limbic system and the anterodorsal neocortical areas. One of our animals, Cat 638, developed nonconvulsive partial complex status after only six AM stimulations which did not produce any clinical seizure. No explanation is available at this time, since all the status epilepticus we have observed occurred following the development of Stage 4 or Stage 6 seizure. It is possible that this animal had an epileptogenic predisposition on a genetic basis, or alternatively, cortical lesioning may have conferred an acquired predisposition by some mechanism. Among seven animals with unilateral neocortical lesion, three animals developed verified status epilepticus (Table 1). The reason for this unusually high incidence is not clear, but it raises the possibility that unilateral anterior neocortical lesion increases the chance of developing status epilepticus upon amygdaloid stimulation, possibly due to denervation hypersensitivity of some distant structures.

Placement of electrolytic lesion in the MRF on the side of the electrographic seizure discharge aborted both the clinical manifestation of status epilepticus (Cat 629) and the electroclinical seizure manifestation (Cat 649). The former animal continued to display sustained electrographic seizure of the "will-o'-the-wisp' type, suggesting that MRF lesion must have interrupted the pathway linking the forebrain and the brain stem mechanisms essential for the evolution of clinical seizure. Failure to elicit even electrographic AD by stimulation of the amygdala with a much higher intensity (200 μ A) in this animal (620) is consistent with our previous assumption that the MRF must exert tonic ascending influence for the maintenance of amygdaloid excitability (Wada & Sato, 1975b). Such an assumption may appear contradictory to our finding in animal 649, where a small MRF lesion promptly aborted electroclinical seizure manifestations of status epilepticus, but subsequent stimulation of the AM at GST produced a Stage 6 convulsion. This finding suggests that the MRF lesion, at least in this animal, did not interrupt the established pathway directly involved for the ictal linkage between the stimulated amygdala and the lower brain stem. Rather, MRF lesion led to a transient yet significant reduction of the tonic ascending influence to a degree insufficient to sustain the process of status epilepticus. Our findings not only support our previous assumption that the MRF is an integral part of the neural circuit responsible for the elaboration of the AM kindled seizure, but also suggest that it is essential for the perpetuation of the recurrent seizure state. However, in what manner the MRF may be involved in the process of the AM kindling remains to be elucidated.

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