INJECTIONS OF KAINIC ACID INTO THE AMYGDALOID COMPLEX OF THE RAT: AN ELECTROGRAPHIC, CLINICAL AND HISTOLOGICAL STUDY IN RELATION TO THE PATHOLOGY OF EPILEPSY

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Abstract—Kainic acid has been injected unilaterally into the amygdaloid complex of rats. Electroencephalographic and clinical changes have been studied in relation to subsequently demonstrated neuropathology using Fink-Heimer and Nissl stainings. Epileptiform electroencephalographic activity began (after 5-60 min) at the site of the injection and spread to the ipsilateral hippocampus, contralaterally and to the cortex. Motor signs of epilepsy occurred repetitively for 2-6 h; subsequently, irregular or regular spikes occurred continuously (for 4-30 h) without positive motor signs. Neuronal loss and gliosis was invariably noted at the injection site. In addition, neuronal loss and degenerative changes were present at other sites where lesions are found after status epilepticus; these included various hippocampal fields, the contralateral amygdala and claustrum and, bilaterally, the midline thalamic nuclei, lateral septum and various cortical areas. The first damage to appear (after 2 h of epileptiform activity) was in the ipsilateral CA3a hippocampal subfield. A correlation was found between the severity of the epileptiform activity in the ipsilateral hippocampus and the severity of pathological alterations. This, as well as other observations suggest that the distant brain damage is not a consequence of the diffusion (or intra-axonal transport) of kainic acid but is causally related to the epileptiform activity induced by the toxin.

Intra-amygdaloid injections of kainic acid thus provide a particularly suitable model for investigating the relationship between seizure activity and epileptic brain damage.

PATHOLOGICAL alterations are commonly found in post-mortem studies of patients having suffered from chronic temporal lobe epilepsy and status epilepticus. The pattern of brain damage, first described more than 150 years ago by Bouchet & Cazaubiel (1825), has been repeatedly confirmed (Blackwood & Corsellis, 1976; Falconer, 1970; Scholz, 1959). Thus, among patients with epilepsy in institutions, the commonest cerebral lesion is found in the hippocampus (Margerson & Corsellis, 1966): hippocampal neurons degenerate and are replaced by a proliferation of glial elements, hence the term 'mesial temporal sclerosis'. In addition to the hippocampal formation, brain damage is often found in other structures which are part of (or strongly interconnected with) the limbic system (Naughta, 1958), such as the amygdaloid complex, medial thalamic nuclei and various neocortical sites. A similar brain pathology, particularly involving the hippocampus, is also seen in infants following status epilepticus associated with febrile convulsions (Fowler, 1957).

Abbreviations: EEG, electroencephalographic.

The reason for this susceptibility of some brain structures to epilepsy is poorly understood. Thus, whether mesial temporal sclerosis is a cause or a consequence of epilepsy is not clearly established (Falconer, 1970; Scholz, 1959). Evidence derived from experiments utilizing convulsant drugs in baboons and rats suggest that local factors closely related to the seizure discharge may be of particular importance for the formation of the hippocampal lesions (Meldrum & Brierley, 1973). If seizures themselves can cause hippocampal sclerosis, it is important to characterize the physiological factors which may induce the brain damage and to examine whether specific pathways are uniquely involved in the propagation of epileptiform activity. To investigate these questions, a technique would be needed readily to reproduce status epilepticus of focalized origin. In this study, we report that intra-amygdaloid injections of kainic acid, the potent neurotoxic analogue of glutamic acid (Olney, Rhe and Ho, 1974), rapidly induce repetitive secondarily generalized convulsive seizures and subsequently a pattern of pathological alterations in various distant brain sites similar to that seen in man following status epi-
leptis (vide supra). In this and a parallel report (Ben-Ari, Tremblay, Ottersen & Meldrum, 1980) using this model various lines of evidence are presented which suggest that the distant brain damage may be a consequence of the epileptiform discharge induced by the toxin. Some of these results have been previously summarized elsewhere (Ben-Ari, Lagowska, Tremblay & Le Gal La Salle, 1979a).

EXPERIMENTAL PROCEDURES

One hundred and three Wistar rats (250-300 g) were used in these experiments. They had access to food and water ad libitum and were housed under diurnal lighting conditions with lights on from 0800 to 2000 h.

In the first experimental series (‘acute’, n = 71), the animals were anaesthetized with equithesin (3 ml/kg, Jensen Salsbury) and placed in a stereotaxic frame, and kainic acid (0.4–2 μg dissolved in 0.1 to 0.4 μl phosphate buffer solution, pH 7.4) was unilaterally injected, under stereotaxic guidance, into the right amygdala. The neurotoxin was injected using a 1 μl Hamilton syringe at a constant rate for approx 2 min. In five additional rats, the vehicle solution was injected in similar volumes and conditions. Following the surgery, which generally lasted less than 30 min, each animal was placed in a plexiglass cylinder (30 cm dia., 130 cm height) and behaviour was continuously examined for periods of 2–8 h (and occasionally in the subsequent days) until they were killed. Recovery from the anaesthesia and surgical procedures usually occurred within less than 90 min from the onset of anaesthesia.

In the second experimental series (‘chronic’, n = 19), the animals were first unilaterally implanted under anaesthesia (stereotaxic guidance) with a stainless steel guide cannula (0.4 mm o.d.; 0.3 mm i.d.) whose tips were placed 1 mm above the right amygdala. In 11 out of 19 rats, a fine nichrome wire glued to the cannula and insulated except at its tip (1 mm below the tip of the cannula) enabled us to record the electrographic activity in the immediate vicinity of the injection site. In addition, cortical screws were implanted to record the electroencephalographic (EEG) and bipolar electrodes in various brain structures including usually the right and left dorsal hippocampi (in the CA1 fields according to Lorente de Nó, 1934). One week later kainic acid was locally applied without anaesthesia, via a stainless steel delivery cannula (0.28 mm o.d.; 0.2 mm i.d.) in similar concentrations and volumes as described above. The delivery cannula was 1 mm longer than the previously implanted guide cannula to just reach the amygdala. Four additional animals received the vehicle solution only. Following the injection, the electrographic activity was continuously monitored on an EEG pen recorder and behaviour noted for periods varying from 2 h to 6 days. The main electrographic features were evaluated by inspection of the records. Quantitative comparisons of the epileptic discharges were carried out in several cases; every second of the tracing was classified as one of the following: ‘normal EEG’, EEG with regular or irregular spikes, electrographic seizures either with or without motor events, and post-ictal depression (Table 1).

In both experimental series, one large dose of diazepam (valium, Roche, 20 mg/kg i.p.) was usually given after a few hours of generalized convulsive seizures to prevent the death of the rat due to status epilepticus. Following survival times between 2 h and 2 weeks, all experimental animals were deeply anaesthetized and intracardially perfused with saline followed by a 10%, formalin solution. Conventional histological procedures were then performed to identify the position of the electrodes and cannulae and also to map the degeneration and cell loss induced by kainic acid. These included alternate Nissl & Fink-Heimer (1967) staining of the frontal sections obtained from the entire brain.

RESULTS

Electrographic and motor effects of intra-amygdaloid kainic acid

Epileptiform activity, following an intra-amygdaloid injection of kainic acid, was first apparent at the site of injection (Fig. 1A). The delay between the application of kainic acid and the first amygdaloid epileptiform activity varied between 5 and 60 min in the unanaesthetized conditions. The sustained epileptiform activity rapidly propagated to the cortex and ipsilateral hippocampus (Fig. 1A and B) to the contralateral amygdala (not illustrated) and, with a longer delay, to the contralateral hippocampus (Fig. 1C). These seizures were accompanied by the following motor signs, in the order of appearance (Fig. 2): wet shakes (Blasig, Herz, Reinhold & Ziegllangberger, 1973; Calvino, Lagowska & Ben-Ari, 1979), masti-
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Table 1. Quantitative estimation (in s/h) of electrographic patterns in two hippocampi in two cases

<table>
<thead>
<tr>
<th>Type of discharge</th>
<th>Side</th>
<th>1st hour</th>
<th>2nd hour</th>
<th>3rd hour</th>
<th>4th hour</th>
<th>1st hour</th>
<th>2nd hour</th>
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<tr>
<td>Normal</td>
<td>Ipsi</td>
<td>3196</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>308</td>
<td>0</td>
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<td></td>
<td>Contra</td>
<td>2918</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>64</td>
<td>170</td>
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<tr>
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<td>Ipsi</td>
<td>72</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1780</td>
<td>1406</td>
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<tr>
<td></td>
<td>Contra</td>
<td>6822</td>
<td>3254</td>
<td>2214</td>
<td>88</td>
<td>3100</td>
<td>1432</td>
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<tr>
<td>Electrographic seizures (without motor signs)</td>
<td>Ipsi</td>
<td>0</td>
<td>484</td>
<td>1318</td>
<td>3600</td>
<td>646</td>
<td>1608</td>
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<tr>
<td></td>
<td>Contra</td>
<td>0</td>
<td>264</td>
<td>1250</td>
<td>3512</td>
<td>212</td>
<td>1648</td>
</tr>
<tr>
<td>Electrographic seizures (with motor signs)</td>
<td>Ipsi</td>
<td>0</td>
<td>172</td>
<td>108</td>
<td>0</td>
<td>322</td>
<td>496</td>
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<tr>
<td></td>
<td>Contra</td>
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<td>70</td>
<td>70</td>
<td>0</td>
<td>172</td>
<td>342</td>
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<td>Post-ictal depression</td>
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<td>164</td>
<td>56</td>
<td>0</td>
<td>544</td>
<td>90</td>
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<td>12</td>
<td>0</td>
<td>0</td>
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</table>

Quantitative comparison of epileptic discharges in both hippocampi during the first 4 h after the injection of kainic acid in the right amygdala in cases EAK 16 and 15. The records were classified as ‘normal’, spikes (regular or irregular), and electrographic seizures without or with typical amygdaloid motor events, and post-ictal depression. The values are indicated in seconds per hour after the administration of kainic acid. Case EAK 15 showed after 2 h a continuous status epilepticus (also see Fig. 6), in both cases, kainic acid was injected in unanaesthetized conditions (chronic series).

catatory movements, myoclonus of the facial muscles and head nodding, rearing and tremor of the forepaws, full motor convulsion with loss of postural control (Fig. 2B-C). Since similar motor signs are present following daily electrical stimulation of the amygdala (i.e. ‘kindling’, GODDARD, McINTYRE & LEECH, 1969), we have adopted the rating on a five-point scale with respect to strength previously described by RACINE (1972). In addition to these signs, salivation and exophthalmos were often also present. At a longer latency, the convulsive seizures included barrel rotation (Fig. 2D-E), circling behaviour, intense agitation, vigorous jumps, similar to those seen during morphee withdrawal syndrome (see BLASIG et al., 1973 and CALVINO et al., 1979), and periods during which the animal was completely immobile.

Generalized seizures, such as those described in Figs 1 and 2, were observed at a variable frequency (often one per 2-10 min) for periods varying from 2 to 6 h. Regular spikes (Fig. 1D-E) or irregular spikes (see Fig. 6, case EAK 12) were continuously observed beginning 3-6 h after the injection and lasting 4-30 h in different animals; these spikes were usually not accompanied by motor manifestations. In several cases, a reduction in electrical activity was seen at the site of injection and in the ipsilateral hippocampus (Fig. 1E), possibly as a consequence of local neuronal loss (see below).

A similar sequence of events was observed in the ‘acute’ series (see Experimental Procedures), with the exception that the latency of the first motor seizure was often longer than in the chronic series. This difference is probably due to the anticonvulsant properties of the anesthetic agent (WOODBURY, 1969).

Pathological aspects of intra-amygdaloid kainic acid

At the site of injection: after very short survival times (e.g. 2 h) the neuronal somata near the centre of the injection were shrunken, triangular and darkly staining; often they showed scalloped edges and pycnotic nuclei. These pathological alterations were not fixation artifacts since the neurons of the contralateral amygdala were of normal size and appearance (not illustrated). During the subsequent few hours, the affected neurons became progressively fragmented and finally disappeared. The area of neuronal loss invariably showed extensive gliosis at survival times of 2–3 days (Fig. 3D-E). However, following the largest doses, neuronal and glial elements were absent from the central zone, and neuronal loss and gliosis were present in a more peripheral zone.

The pathological changes at the site of injection were in some cases confined to a single amygdaloid nucleus, whereas the entire complex was affected in other cases. After the largest doses were used, the gliotic zone often extended into the ventral striatum and pyriform cortex. Spread of kainic acid along the cannula track was evident in most of the ‘acute’ cases but could not be detected in any of the cases subjected to kainic acid injection via a chronically implanted cannula.

Outside the site of injection: at the shortest survival time used (2–4 h) cerebral pathological changes outside the site of injection were restricted to the ipsilat-
FIG. 2. Various clinical seizure types observed after unilateral injections of kainic acid in the right amygdala in case EAK 16 (same as preceding Figure). (A) Rearing, forepaw myoclonus, facial myoclonus, left sided exophthalmos, right-sided ptosis (stage 4, see Racine, 1972); (B) more pronounced rearing and forepaw tremor; (C) falling to one side, subsequent to rearing (stage 5); (D and E) barrel rotation, axial turning of head followed by trunk. Kainic acid was injected in unanaesthetized conditions ('chronic' series).
Fig. 3. Photomicrographs showing cerebral pathology subsequent to intra-amygdaloid injections of kainic acid. (A) Ipsilateral CA3 pyramidal neurons in rat EAK 29 (5 h survival, cf. Fig. 4C-E). The cells are shrunken and triangular. There is no glial proliferation (cresyl violet stain, mag. × 200). (B) Higher power view of dendrites of the neurons in A, in an adjacent section. Note the silver deposits in dendritic spines (arrow). (Fink–Heimer stain, mag. × 700). (C) Normal appearance of CA3 pyramidal neurons in the contralateral hippocampus of EAK 29 (cresyl violet stain, mag. × 200). (D) Low-power view of the injection site in rat EAK 16. Survival 4 days. ○ and △ denote the tracks of the guide cannula and recording electrode respectively. Note the almost total loss of neurons in the basolateral amygdala (cresyl violet stain, mag. × 16). (E) Higher magnification of the rectangle in D to show the extensive glial proliferation near the centre of the injection site (mag. × 100). (F) Degenerated neurons and fibres in the contralateral basolateral amygdala (rat K 002, survival 7 days) (Fink–Heimer stain, mag. × 100). (G) Bilateral neuronal loss in the mediodorsal nucleus of the thalamus (rat EAK 16, survival 4 days. cresyl violet stain, mag. × 13). (H) Higher magnification of the rectangle in G to show complete loss of neurons without significant glial proliferation. Cases EAK 29 and 26: kainic acid (1.2 μg dissolved in 0.3 μl solution) was injected in unanaesthetized conditions; case K002: kainic acid (1.5 μg dissolved in 0.15 μl solution) was injected in anaesthetized conditions (acute’ series).

Abbreviations: ABL, basolateral amygdala; AC, central nucleus of the amygdala; AM, medial nucleus of the amygdala; CP, caudate-putamen; CPF, piriform cortex; MD, mediodorsal nucleus of the thalamus (m and l: medial and lateral parts respectively); PV, paraventricular nucleus of the thalamus; RH, rhomboideus nucleus of the thalamus.
FIG. 4. Coronal sections through the septal one-third of the hippocampal formation in rats to show pathological changes after long (A and B) or short (C, D and E) intervals following an intra-amygdaloid injection of kainic acid (Fink-Heimer stain). (A) Strong argyrophyilia of all layers in the ipsilateral Ammon's horn (rat KA9, 48 h survival) due to degeneration of somata and dendrites of pyramidal cells and axons of hippocampal and extrahippocampal origin. The pyramidal cells are affected in CA1, CA3 and CA4 (mag. × 30). (B) Higher magnification of degenerated pyramidal cells in the ipsilateral CA3 (rat KA9); note the heavy terminal degeneration in the stratum oriens and the stratum radiatum. Also note the lack of staining of the granular cells of the fascia dentata (mag. × 110). (C) Intense staining (△) of apical dendrites of ipsilateral CA3 pyramidal neurons after a short survival period (rat EAK 29, 5 h survival). The 'vacuolization' is present in the stratum lucidum (see arrows) (mag. × 30). (D) Higher magnification of degenerating ipsilateral CA3 neurons (rat EAK 29) at a more caudal level than in C. Basal as well as apical dendrites are stained (mag. × 60). (E) Hippocampal CA3 pyramidal neurons from an adjacent section to that shown in D. Shrunken, triangular argyrophilic neurons are intermingled with apparently normal cells (arrows) (interference light, mag. × 300).

Abbreviations: G, granular layer, fascia dentata; LM, stratum lacunosum moleculare; O, stratum oriens; P, stratum pyramidale; R, stratum radiatum. Rat KA9: kainic acid (1.2 ng dissolved in 0.3 μl solution) was injected in anaesthetized conditions ('acute' series); rat EAK 29: (1.2 μg dissolved in 0.3 μl solution) was injected in unanaesthetized conditions ('chronic' series).
lateral CA3 hippocampal field (Figs 3A–B, 4C–D and E; for nomenclature of hippocampal subfields see LORENTE DE NÖ, 1934). They were most pronounced in the dorsal hippocampus at the level of the habenula. With Fink–Heimer staining, the most intense coloration was seen in the stratum radiatum and stratum lacunosum moleculare of CA3 (Fig. 4C). Using high magnification, the silver deposits were found to be located in dendrites and dendritic spines (Fig. 3B). The CA3 pyramidal perikarya were shrunken and distorted (Fig. 3A) but less argyrophilic than their apical dendrites. It was often impossible to trace those dendrites through the stratum lucidum, due to the 'vacuolization' present in the latter fibre layer. It should be noted that these early lesions were caudal to the cannula track, being separated from it by a zone devoid of neuronal degeneration. It is also worth noting that following short survival times, there were no pathological alterations in the contralateral Ammon's horn (see Fig. 3C and below).

At longer survival times, the ipsilateral hippocampal lesions proceeded to a complete necrosis of CA3, CA1 and CA4 (usually in that order of progression). CA2 neurons were seldom pathologically altered. The degenerative process spread progressively along the septotemporal axis of the hippocampus, reaching the temporal pole after approx 24 h. In parallel with the necrosis of neuronal somata, there was an increasing argyrophilia of dendrites and axons in all fibre layers, viz. the stratum oriens, radiatum and lacunosum moleculare (Fig. 4A and B). After 4 days survival, secondary lesions were found in both hippocampi and in several extra-hippocampal structures (Fig. 3F, G and H). The pattern of cerebral damage in a representative case is shown in Fig. 5 (EAK 16). In the hippocampus, degenerated neurons associated with a partial cell loss were found ipsilaterally in CA3 and bilaterally in CA1. In the thalamus, neuronal cell loss was seen bilaterally in medial structures, i.e. the parataenial, anteromedial, reuniens, mediiodorsal, postero medial and parafascicular nuclei as well as in the ventromedial complex. Neuronal necrosis was also found in the contralateral amygdala, predominantly in the dorsal nuclei and bilaterally in the chiasmatic, cingulate cortex and neocortex (layers 3, 5 and 6) dorsal to the rhinal sulcus. Terminal fibre degeneration often occurred in the areas also showing degeneration of neuronal somata (e.g. see Fig. 3F). The Purkinje cells of the cerebellum were not degenerated.

The histological appearance of the lesions distant
to the injection site differed from that of the lesion at the injection site itself. Thus, following intermediate survival times (2–8 days), there was invariably an extensive gliosis at the site of the application of kainic acid, whereas at the distant foci, gliosis was either absent (e.g. mediodorsal nucleus, Fig. 3H) or very modest (e.g. hippocampus). This difference could not be attributed to the later appearance of pathological changes in the secondary as compared with the primary structures. Thus, in the mediodorsal thalamus, neuronal degeneration was already evident 4–5 h after the intra-amygdaloid injection of kainic acid. In the animals that received an injection of the vehicle solution only, no cerebral lesions, apart from the cannula and electrode traces, were found.

**Relationship between seizure discharge and subsequent hippocampal pathology**

As already noted, the hippocampus ipsilateral to the site of injection was by far the most susceptible to the epileptogenic actions of kainic acid. Inspection of the EEG records also showed a difference in the epi-

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**Fig. 6.** Relationship between epileptiform activity and pathology in the dorsal hippocampus ipsilateral to the site of injection of kainic acid (right amygdala) in four cases. The records were visually classified according to its patterns. (A) The 'normal' and depressed (post-ictal depression), electrographic activity of the right hippocampus is indicated as a percent of the first 4 h following the injection of kainic acid in the right amygdala (case EAK 9: 1 µg in 0.25 µl, remaining cases: 1.2 µg in 0.3 µl). The number of generalized motor seizures during the same period is indicated. (B) Histogram indicates duration (in percent) of the epileptiform activity in the hippocampus, without (open columns) or with (hatched columns) generalized motor seizures during each hour following intra-amygdaloid administration of kainic acid. (C) Histogram indicates duration (in percent) of hippocampal spike activity. (D) Diagram shows ipsilateral hippocampal fields according to LORENTE DE NÓ (1934) with regions of degeneration and neuronal loss indicated by black bands. Case EAK 15 displayed a generalized status epilepticus in particular during the third and fourth hours (C, filled circles). This rat died during the first night in spite of the large dose of diazepam given 5 h after the administration of kainic acid; therefore, the degeneration areas refers to pycnotic neuronal changes as revealed by Nissl stain. Survival times were 3 days for EAK 9 and EAK 13, and 4 days for EAK 16. Kainic acid was injected in anaesthetized conditions ('chronic' series).
The regional distribution of neuronal necrosis and loss is comparable to that observed after status epilepticus in man (see introduction) or experimental animals (MELDRUM & BRIERLEY, 1973). The common anatomical denominator of the degenerating structures is that they are part of (or interconnected with) the so-called limbic system (see NAUTA [1958] for discussion). They are, as such, strongly interconnected. Thus, the medial thalamic structures containing degenerated neurons in the present study, perhaps with the exception of the mediadorsal nucleus (see OTTERSEN & BEN-ARI, 1978; 1979), all project to the amygdala: the mediadorsal nucleus, however, receives amygdalofugal fibres (KRETEK & PRICE, 1977). It is worth stressing that, apart from the interanteromedial nucleus (OTTERSEN & BEN-ARI, 1979; 1979) these thalamoamygdaloid projections are strictly ipsilateral whereas the degeneration was bilateral following kainic acid (see below). The amygdala is also reciprocally interconnected with the cingulate cortex (NAUTA, 1961; PANDEYA, VAN HOESEN & DOMESECK, 1973) and experiments performed in cats (DRUGA, 1969), as well as monkeys (WHITLOCK & NAUTA, 1956) have shown that cortical areas probably corresponding to the parts of neocortex affected by intra-amygdaloid kainic acid emit fibres terminating in the amygdala. Similarly the two amygdalae are interconnected (LAMMERS, 1972) and the bed nucleus of the stria terminalis is a recipient of numerous amygdalofugal fibres (ibid.).

In contrast, direct connections between the central amygdala and Ammon’s horn have not been demonstrated. Impulses from the amygdala can, however, be relayed to the hippocampus via an amygdalofugal pathway terminating in the lateral part of the entorhinal cortex (KRETEK & PRICE, 1977) which in turn projects to Ammon’s horn via the perforant path (HJORTH-SIMONSEN, 1972). In fact, several observations suggest that the perforant path may be a particularly suitable candidate to mediate the epileptiform discharge from the amygdala to the hippocampus (BEN-ARI et al., 1980). The CA3 pyramidal neurons receive impulses from the perforant path both directly, via fibres terminating on the distal part of the apical dendrites (Hjorth-Simonsen, 1972) and indirectly via the granule cells and their mossy fibres terminating more proximally on the same dendrites (BLACKSTAD, BRINK, HEM & JHINNE, 1970). The fact that the stratum lucidum and the apical dendrites displayed the earliest pathological changes is in accordance with the hypothesis that the perforant path may play an important role in the pathogenesis of early hippocampal lesions. Further support for this hypothesis is derived from experiments in which kainic acid was injected in the amygdala of rats after a transection of the perforant path; both the epileptic discharge and the hippocampal lesions were consider-
ably reduced by the transection (Ben-Ari, Tremblay & Ottersen, 1979b; Ben-Ari et al., 1980).

On the basis of these observations, it is tempting to speculate that the development of neuronal necrosis in the ipsilateral hippocampus is intimately associated with the local epileptic discharge itself and not merely a consequence of the systemic correlates of the motor seizures. The correlation between the local seizure activity during the first few hours following the injection and the severity of secondary pathology in the ipsilateral Ammon’s horn is in accordance with this hypothesis. Also, the different EEG patterns seen in both hippocampi in the early period may provide some indication of the characteristics of the degeneration that induces epileptiform discharge. In particular it focuses attention to the post-ictal depressions and the seizures associated with motor events. In focus is the post-ictal depression and the generalized seizures associated with motor events. In contrast, the spikes (regular or irregular) as well as the seizures not associated with motor events do not appear to play a major role in hippocampal damage. It is noteworthy that Blenow, Brierley, Meldrum & Siesjo (1978) have recently provided evidence which suggests that systemic 'metabolic' factors may play a role in cerebellar damage, but that local factors, clearly related to the seizure discharge, are of particular importance for the hippocampal lesions.

In regard to the distant lesions outside the ipsilateral hippocampus, it is not possible from the present results to evaluate whether the regional selectivity of the damage is attributable to locally enhanced seizure activity or other factors. Further experiments, including focal recordings from thalamic structures and various cortical areas should provide information in that respect. It is possible that systemic factors during the seizures are more important in the pathogenesis of these lesions than in the early degenerations seen in the ipsilateral hippocampus (Meldrum & Brierley, 1973).

What is the cause of the lesions outside the injection area? Obviously, the possibility that distant brain damage is not related to the epileptic activity must be considered. It is worth noting in that respect that the cerebral lesions outside the injection site are not attributable to the destruction of the amygdala per se, since they are not seen after an electrolytic destruction of the entire amygdaloid complex (unpublished observations). Furthermore, the pattern of focal degeneration neither correlates with the distribution of amygdalofugal connections nor with the sources of amygdalopetal fibers (see above) eliminating a pathogenic role of anterograde trans-synaptic or retrograde degeneration mechanisms. These, as well as other lines of evidence (Ben-Ari et al., 1979b; Ben-Ari, Tremblay, Ottersen & Naquet, 1979c; Ben-Ari et al., 1980) suggest that the possibility of uptake of the toxin and release at distant sites is unlikely (but see Schwab, Fuller & Price, 1978).

However, the most serious pitfall would be to disregard the possibility of a direct action of the toxin at the structures outside the injection site which show neuronal necrosis (Nadler, Perry & Cotman, 1978; Wuerthele, Lovell, Jones & Moore, 1978). The strongest argument against this alternative explanation is derived from the present experimental paradigm is derived from earlier studies showing that the repeated administration of a potent anticonvulsant in the postoperative period, considerably reduces the secondary brain damage without affecting the local (primary) lesions (Ben-Ari et al., 1979c). Furthermore, the pattern of cerebral lesions can hardly be explained on the basis of a local toxic effect of kainic acid. Thus, the rostral dorsal hippocampus was affected long before the caudal ventral hippocampus, which is adjacent to the injection site; also, in most cases the thalamic degeneration was bilateral, often being more pronounced contralaterally to the injected amygdala. The morphological differences between primary and secondary lesions in terms of the extent of the gliosis deserve particular emphasis; they may suggest that different aetiological factors are involved. When the results obtained from experiments in which the perforant path was transected are also taken into account (Ben-Ari et al., 1979b; 1980), we can conclude that in the absence of excessive spread of kainic acid along the track a direct toxic effect of kainic acid does not play a primary role in the pathogenesis of the distant lesions. We suggest that the damage inflicted upon the brain by intracerebral kainic acid has a twofold etiology: (1) a direct toxic effect of kainic acid at the site of the injection, and (2) a distant pathological damage which is related to the epileptogenic effects of the drug.

Acknowledgements—The authors are indebted to Drs K. Kneiević, R. Naquet and C. Hammond for criticism of the manuscript. The expert technical assistance of G. Chariton, B. Riber, G. Ghilini and J. P. Bouilot was appreciated, and Mrs Phyllis Byone for typing the manuscript. We also thank the E.T.P. (Twinning Grant) and C.N.R.S. (A.T.P. internationale) and D.G.R.S.T. for financial support. E. Tremblay is a member of the INSERM.

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Kainic acid, epilepsy and brain damage


(Accepted 25 October 1979)