THE ORIENTING REFLEX IN CATS WITH EXPERIMENTAL TEMPORAL LOBE EPILEPSY

Radu ROGOZEA and Viorica FLOREA-CIOCOIU

Institute of Neurology and Psychiatry
Bucharest, Romania

Abstract. Aluminum-induced temporal lobe epilepsy in 24 cats showed marked interictal intensification of somatic and EEG components of the orienting reaction and increase in their resistance to habituation. The greatest disturbances of the orienting response were noted in cases of bitemporal foci, of foci situated in the allocortex (hippocampus and amygdala) and of foci inducing generalized or generalized and partial seizures.

INTRODUCTION

In patients with temporal lobe epilepsy we found certain interictal changes in the orienting reflex and in its habituation (unpublished data). In the present work the modifications of the orienting reflex and of its habituation were studied in cats, using experimental temporal lobe epilepsy. To obtain experimental temporal lobe epilepsy we used metallic alumina powder which induces chronic epileptic states (5–7, 15, 18, 22) approximating human epilepsy.

Bearing in mind the well-known role played by the temporal neo- and allocortex in the pathogenesis of temporal lobe epilepsy, we applied the substance topically on the temporal neocortex and injected it in the allocortical structures (hippocampus or amygdala).

MATERIALS AND METHODS

Subjects. The investigations were performed in chronic experiments on 24 adult cats of either sex, weighing from 1.8 to 3.8 kg.
Surgery. Under strictly aseptic conditions and general anesthesia with sodium hexobarbital in each cat bipolar cortical and deep recording electrodes were implanted bilaterally. The cortical electrodes were applied epidurally at the level of middle ectosylvian and suprasylvian gyri; while the deep electrodes were implanted stereotaxically (12) in the dorsal hippocampus (F2-5, L5-7, P6.5-7), amygdaloid complex (F10-13, L9-10, P-5.5-6) and mesencephalic reticular formation (F2-4, L2-5, P-1-3). In 13 animals stainless steel cannulae 0.8 mm diameter provided with a piston for local introduction of convulsant substance was implanted unilaterally in the dorsal hippocampus or the amygdaloid complex. The cannula was located 2–3 mm from the homolateral intrahippocampal or intraamygdaloid electrode, permitting electrical recordings from the immediate vicinity of the epileptogenic focus.

After the animals' recovery and the electrographic control of their normal cerebral activity, the second stage of surgery was performed (25 to 30 days after the first) when the convulsant substance (sterile

![Diagram](https://example.com/diagram.png)

Fig. 1. Diagrammatic illustration of allo- and neocortical areas in which epileptogenic lesions were produced by topical application of aluminum powder. A, lesions in auditory area I; B, lesions in posterior ectosylvian area; C, lesions in dorsal hippocampus (the lesions extend between F2 and F5 according to Jasper and Ajmone Marsan's atlas). H, hippocampus; CS, colliculus superior; GC, griseum centrale; RM, substantia reticularis mesencephalica. D, lesions in the amygdaloid complex (the lesions extend between Fl0 and Fl3). Al, Abm and Abp, n. amygdaloideus lateralis and basalis (pars magnocellularis and parvocellularis). TO, tractus opticus; HL, hypothalamus lateralis; VA, VM and MD, n. ventralis anterior, ventralis medialis and medialis dorsalis.
Fig. 2. I: Neocortical lesion: Cat FE24 with epileptogenic chronic focus sited in the posterior ectosylvian area. A, macroscopic aspect of the lesion; B, aspect of the same lesion on a section stained for myelin (Spielmeyer); C and D, alterations in the aluminum-induced focus: central zone of necrosis with an intense glio-mesenchymal perifocal reaction (Spielmeyer, oc.7, ob.3 and oc.7, ob.6).

II: Allocortical lesion: Cat FE20 with intrahippocampal epileptogenic chronic focus. A, aspect of the lesion in right dorsal hippocampus on a section stained for myelin (Spielmeyer). The section is in F2; B, detail of the previous image; C and D, alterations in the aluminum-induced focus: central zone of necrosis with an intense glio-mesenchymal perifocal reaction (Spielmeyer, oc.7, ob.3 and oc.7, ob.6).
alumina powder) resulting in a chronic epileptogenic lesion was introduced. In 11 animals the alumina powder was topically applied on the temporal neocortex. For this, the cats were re-operated, a 2 × 2 mm filter-paper disk coated with 30 mg alumina powder being placed through a trephine hole over the anterior ectosylvian gyrus (auditory area I) in 6 animals (Fig. 1A) and over the posterior ectosylvian gyrus (posterior ectosylvian area) in 5 (Fig. 1B and 2IA). In the remaining 13 cats the substance was introduced through the cannulae fastened “à demeure” either into the dorsal hippocampus (7 animals) (Fig. 1C and 2IA) or into the amygdaloid complex (6 animals) (Fig. 1D). The amount of the substance introduced in these cases was 10 mg.

Apparatus. EEG recordings were taken with an 8-channel 111 RFT electroencephalograph, using bipolar leads for optimal registration of EPs and of EEG arousal reactions. EMG was recorded bipolarly from the nape muscles.

The auditory stimulus eliciting the orienting reflex and the intermittent light stimulus used for activation of epileptogenic foci were obtained from a Tur FS4 RFT phonophotostimulator. The tone was applied through a loudspeaker positioned 80 cm from the animal’s ears.

The behavioral and electrographic investigations were performed with the cats in a sound-proof, electrically screened cage with an observation window. During the recording sessions the animals were awake and unrestrained.

General procedure. A behavioral and electrographic study was performed in the prepared animals, which revealed in 19 of the 24 cats, 3 to 7 weeks after administration of the convulsant agent, occurrence of spontaneous epileptic seizures. In 5 cats the seizures could be elicited by intermittent light stimulation (1–25 flashes/s), and sudden auditory stimulation (claps).

After development of temporal lobe epilepsy all the animals were subjected to an electrographic investigation of the orienting reflex elicited by a repetitive auditory stimulus. The study consisted in simultaneous recording of the somatic component (EMG recorded from the nape muscles) and of the EEG component of the orienting reflex (acoustic evoked potential (EP) and EEG arousal reaction). Each animal was recorded in two recording sessions, the first before and the second after induction of the epileptogenic focus. The second recording was performed only when the electro-clinical checking disclosed no seizures for at least 6–7 h.

1 The terminology used for defining the auditory areas is that proposed by Rose and Woolsey (24): auditory area I (AI), auditory area II (AII) and posterior ectosylvian area (pE).
The orienting reflex was elicited under standard conditions by repetitive tones (800 cycle/s, 32 dB, 3 s duration and 30 s interstimulus intervals) maintained unchanged throughout the recording. Up to 150 stimuli were used during a recording session. The orienting reflex was considered habituated if absent during three successive applications of the stimulus. The number of tones required for habituation of the orienting reflex was taken as a quantitative index of the resistance to habituation (Fig. 6 and 8A–E).

The data obtained were elaborated statistically by Student’s “t” test.

Measurement of responses. 1. The acoustic EPs were measured in μV (10 mm = 100 μV).

2. The 50% reduction in the amplitude of brain waves corresponding with increase in their frequency following stimulus application was taken as the neocortical arousal reaction. At the level of the hippocampus both the fast low-voltage EEG responses (identical to the previously mentioned neocortical ones) and the slow, high-voltage reactions, namely the 4–7 cycle/s evoked theta activity, were taken as arousal reactions. The fast (15–25 cycle/s responses evoked by the stimulus were considered as the EEG arousal reaction at the level of the amygdaloid complex. The duration of these responses was measured in seconds (1 s = 1.5 cm).

3. The amplitude of EMG was measured in mV (10 mm = 1 mV) and its duration in seconds (1 s = 1.5 cm).

Anatomical verification

On completion of the experiments the animals were sacrificed and their brains were perfused with 10% formalin solution.

Location of cortical electrodes and delimitation of the cortical area over which the disk with alumina powder had been applied were performed by macroscopic examination of the brain (Fig. 2IA). Location of deep electrodes and of the cannulae used for administration of the convulsant substance as well as the estimation of the extent of neocortical, hippocampal and amygdaloid aluminum-induced epileptogenic lesions were carried out on serial sections stained for cells (Nissl), fibers (Spielmeyer) and collagen (van Gieson) (Fig. 2IA–D and IIA–D).

RESULTS

The behavioral and EEG investigations showed that in all cats with aluminum-induced neocortical (AI or pE) or allocortical (amygdala or hippocampus) temporal foci, a chronic epileptic state developed progressively. In 19 animals spontaneous epileptic seizures occurred. In 5 an
Fig. 3. Electrographic aspect of seizures induced by the temporal epileptogenic foci. A, neocortical focal seizure clinically accompanied by slight changes in affective behavior (fear), induced by an aluminum lesion in the right anterior ectosylvian area in cat FE31. B, allocortical focal seizure without clinical manifestations, induced by a right intrahippocampal aluminum lesion in cat FE20. C, allocortical focal seizure clinically accompanied by autonomic manifestations (mydriasis, polypnea, salivation), induced by a right intra-amygdaloid aluminum focus in cat FE35; D, generalized electrical seizure clinically accompanied by facial myoclonic jerks in cat FE32, in consequence to discharge propagation from the intraamygdaloid aluminum focus to other cerebral structures. In this Figure and the next one: RmE and LmE, right and left middle ectosylvian gyrus; RmS, right middle suprasylvian gyrus; RDH and LDH, right and left dorsal hippocampus; RA and LA, right and left amygdaloid complex; MRF, mesencephalic reticular formation; EMG, electromyogram. Bipolar recordings. Calibration: for EEG, 100 μV, 1 s; for EMG, 2 mV, 1 s.
increased epileptogenic reactivity permitted seizures to be elicited by common activation methods.

The experimental epilepsy obtained evolved so that the seizures be-

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fig. 4. Interictal electrographic pattern of the orienting reflex elicited by a repetitive auditory stimulus in cats with chronic temporal epileptogenic foci. I: Cat FE37 with right intrahippocampal epileptogenic focus and with generalized electrical seizures accompanied by clinical manifestations of the myoclonic type. A, orienting reflex in the control experiment. B, after production of chronic epileptogenic focus a marked interictal intensification of the somatic and EEG components of the reaction is noted. II: Cat FE20 with right intrahippocampal epileptogenic focus and with focal electrical seizures devoid of clinical correlates. A, orienting reflex in the control experiment; B, after development of the chronic epileptogenic focus an interictal intensification of the two components of the reaction is noted. S, stimulus; the figure under the stimulus indicates the number of its repetitive applications; EsmR and EsmL, right and left middle ectosylvian gyrus; SsmR and SsmL, right and left middle suprasylvian gyrus; HDL and HDR, left and right dorsal hippocampus.
came more and more frequent, occasionally developing into a true status epilepticus, with remission periods during which the seizures sometimes disappeared for a time. This condition tended to worsen, and shortening of remission periods was noted.

Three types of seizures were differentiated: (i) partial seizures (in 11 cats) characterized electrically by focal discharges of fast (15–20 cycle/s) spikes or sharp waves (4–6 or 10–12 cycle/s) in the allo- and/or neocortex depending on the site of the aluminum-induced lesion (Fig. 3A–C), and clinically by anxiety, polypnea, mydriasis, facial myoclonic jerks, masticatory and sniffing motions, salivation, in four cases; (ii) generalized seizures (in 8 cats) as a consequence of the fast propagation of electrical discharges from the aluminum focus to the other cerebral structures (Fig. 3D), which were characterized clinically either by “absences” of the stuporous arrest reactions or, on the contrary, by localized or generalized motor convulsions of the myoclonic type; (iii) generalized plus focal seizures (in 5 cats) of the type mentioned above.

Development of the chronic epileptic state caused in the interictal period an intensification of both somatic and EEG components of the orienting reaction expressed by an increase in the amplitude and duration of EMG discharges as well as by an increase in the amplitude of acoustic EPs and the duration of EEG arousal (Fig. 4 and 5).

The investigation revealed an increase in the resistance to habituation of the somatic and EEG components of the orienting reaction, which required a significantly larger number of stimuli to become habituated (Fig. 6).

Fig. 5. Interictal changes in the amplitude and duration of the components of the orienting reflex elicited by a repetitive auditory stimulus in cats with chronic temporal epileptogenic foci (mean values calculated on first application of the stimulus). In this Figure and the next ones: white bars indicates values obtained in the group of animals before production of the chronic temporal epileptogenic focus (control); black bars indicates values obtained in the same group of animals after production of epileptogenic foci; EMG, electromyogram; EP, evoked potential; EEG-AR, arousal reaction; No, number of cats.
Peculiarities related to the site of the epileptogenic focus

The changes in the intensity of the orienting reaction and its habituation were significantly more marked in cats with epileptogenic foci situated in the temporal allocortex as compared with those in the temporal neocortex \((P < 0.05)\) (Fig. 7A and 8A). No statistically significant differences were noted between the changes induced by amygdaloid or hippocampal foci. Neocortical foci caused more marked changes when they were located in AI than in eP \((P < 0.05)\) (Fig. 7A and 8A). It was also noted that the changes were more marked when, in addition to the primary neo- or allocortical epileptogenic focus, secondary contralateral foci subsequently developed \((P < 0.05)\) (Fig. 7B and 8B). No differences were encountered between epileptogenic foci in the left and right temporal lobes (Fig. 7C and 8C).

Fig. 6. Interictal resistance to habituation of the somatic and EEG components of the orienting reflex elicited by a repetitive auditory stimulus in animals with chronic temporal epileptogenic foci (mean number of repetitive auditory stimulations required for habituation). S, somatic component of the reflex; EEG, electroencephalographic component.

Fig. 7. Changes in the intensity of the orienting reaction and its habituation in animals with epileptogenic foci in the temporal lobes.

Peculiarities related to the form of seizures

The most marked changes in the intensity of the orienting reflex and its resistance to habituation were noted in animals in which the temporal aluminum focus had induced generalized seizures as well as in animals exhibiting generalized plus partial seizures \((P < 0.05)\) (Fig. 7D and 8D). If the temporal epileptogenic focus induced only focal seizures, the statistically significant reactivity changes \((P < 0.05)\) were less marked (Fig. 7D and 8D); in this case, the interictal reactivity disturbances were more conspicuous in animals with allocortical than with neocortical focal seizures (Fig. 7E and 8E).
Fig. 7. Relation between the interictal changes in the intensity of the orienting reflex components elicited by a repetitive auditory stimulus in cats with experimental temporal lobe epilepsy and the site of the epileptogenic focus (I, II, III) or the electro-clinical form of seizures (IV, V) (mean values calculated on first application of the stimulus). In this Figure and the next one: C, control values obtained before production of temporal epileptogenic focus; H, animals with intrahippocampal foci; A, animals with intramygdaloid foci; AI, animals with anterior ectosylvian foci (auditory area I); pE, animals with posterior ectosylvian foci; PF, primary foci; P + SF, primary + secondary foci; LF, left foci; RF, right foci; G, generalized seizures; G + P, generalized + partial seizures; P, partial seizures; NF, neocortical focal seizures: AF, allocortical focal seizures.
Fig. 8. Relation between the interictal changes in the resistance to habituation of the components of the orienting reflex elicited by a repetitive auditory stimulus in cats with experimental temporal lobe epilepsy and the site of the epileptogenic focus (A, B, C) or the electro-clinical form of seizures (D, E) (mean number of repetitive auditory stimulations required for habituation); solid line, habituation of the somatic component of the orienting reflex; dashed line, habituation of the EEG component.

DISCUSSION

The interictal changes in the orienting reflex and its resistance to habituation, found in aluminum-induced temporal epilepsy, point to the significant reactivity disturbances that should be attributed (23) to diffuse excitability changes caused in the nervous system by the influence of the epileptogenic aluminum focus upon the pathways and neural structures involved in the transmission and integration of the sensory messages and implicitly in the elaboration and control of the orienting reflex.
The difference in the reactivity alterations induced by the allo- and neocortical temporal foci should be related to their different capacity to determine interictal disturbances in diffuse excitability. Thus, the excessive reactivity of the temporal allocortex, expressed by longlasting discharges (2, 8, 9, 16, 19) as well as the richness of its connections (10, 14) may explain why the reactivity disturbances induced by hippocampal and amygdaloid foci are stronger than those induced by the neocortical ones.

The cortico-cortical activating influence exerted by the auditory area I particularly upon the auditory II and the posterior ectosylvian areas (1, 3, 4, 17) may explain both the more severe reactivity disturbances noted in cases of foci situated in AI and the less marked disturbances for foci located in pE, which is functionally dependent on AI.

The significantly more marked reactivity disturbances found if a contralateral secondary foci was developed during the evolution of the primary epileptogenic focus indicates that the simultaneous activity of two independent temporal foci has more marked repercussions on the diffuse excitability, and implicitly, on the orienting reflex and its habituation.

The interictal cerebral reactivity is affected more severely in case of generalized than of focal seizures because more profound excitability disturbances occur following focal discharges that propagate quickly throughout the whole brain than after discharges involving only a limited number of cerebral formations.

Taking into account that habituation of the orienting reflex is an elementary process of negative learning (11, 13), the interictal impairment of habituation, which we have noted in experimental temporal lobe epilepsy corroborates the experimental and clinical observations concerning the role played by the temporal neo- and allocortex in learning and memory (20, 21, 25).

REFERENCES


23. ROGOZEA, R. and FLOREA-CIOCOIU, V. 1973. The orienting reflex in epilepsy. Electrographic data concerning the ictal and interictal peculiarities of the orienting reflex as a function of the electro-clinical form of the


Accepted 20 August 1975

Radu ROGOZEA and Viorica FLOREA-CIOCOIU, Institute of Neurology and Psychiatry of the Academy of Medical Sciences, Str. Povernei No. 42, Bucharest I, Romania.